Early  Vaccine- Monitor

Final Report

Cohort monitoring of Adverse Events of Special Interest and COVID-19 diagnoses prior to and after COVID-19 vaccination

V1.0

Early safety monitoring of SARS-CoV-2 vaccines in European Member States
Specific Contract 05 implementing FWC No EMA/2018/28/PE
Deliverable 4

Authors:
Miriam Sturkenboom[1], Davide Messina[2], Olga Paoletti[2] , Airam de Burgos[3], Patricia Garcia[3], Consuelo Huerta[3], Ana Llorente[3], Olaf Klungel[5], Mar Martin[3], Maria Martinez[3], Ivonne Martin[1], Jetty Overbeek[4], Patrick Souverein[5], Karin Swart[4], Rosa Gini[2]

Document history

Version	Date	Authors	Comments
0.1	January 17	Miriam Sturkenboom (UMC)	First draft report
	January 24	Rosa Gini, Davide Messina, Olaf Klungel, Mar Martin, Ivonne Martin	Comments, creation of graphs and tables
0.2	January 31	Miriam Sturkenboom	Inclusion of graphics, tables & result description
		Rosa Gini, Mar Martin, Patricia Garcia, Oaf Klungel	Review
0.9	February 2	Miriam Sturkenboom	Finalization draft deliverable for submission to EMA
1.0	June 8, 2022	Miriam Sturkenboom	Final lay-out following second review by EMA of v0.9

Acknowledgment and disclaimer

The research leading to these results was conducted as part of the activities of the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network (led by Utrecht University) with collaboration from the Vaccine Monitoring Collaboration for Europe network (VAC4EU). Scientific work for this project was coordinated by the University Medical Center Utrecht. The project has received support from the European Medicines Agency under the Framework service contract nr EMA/2018/28/PE.

This document expresses the opinion of the authors, and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

The authors from BIFAP would like to acknowledge the excellent collaboration of the primary care practitioners and pediatricians, and also the support of the regional authorities participating in the database.

List of abbreviations

ACCESS	vACCine covid-19 monitoring readinESS
ADVANCE	Accelerated Development of VAccine beNefit-risk Collaboration in Europe
AESI	Adverse Event of Special Interest
ARDS	Acute respiratory distress requiring ventilation
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDM	Common Data Model
CI	Confidence interval
DAP	Data Access Provider
DRE	Digital Research Environment
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
ETL	Extract, Transform, and Load
EU PAS	The European Union electronic Register of Post-Authorisation Studies
GDPR	General Data Protection Regulation
GP	General Practitioner
GPP	Good Participatory Practice
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IMI	Innovative Medicines Initiative
MIS-C	Multisystem Inflammatory Syndrome in children
mRNA	messenger Ribonucleic acid
NHS	National Health Service
QC	Quality Control
RNA	Ribonucleic acid
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SPEAC	Safety Platform for Emergency vACcines
VAC4EU	Vaccine monitoring Collaboration for Europe

Table of Contents

List of Tables

List of Figures

Executive summary

Title:
Cohort monitoring of Adverse Events of Special Interest and COVID-19 diagnoses prior to and after COVID-19 vaccination

Primary objectives

- To monitor and estimate the incidence rates of adverse events of special interest (AESI) in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-October 31st 2021 by brand and dose of vaccine and age of the population.
- To monitor and estimate the incidence rates of diagnosed COVID-19 in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-October 31st 2021 by brand and dose of vaccine as well as age.
- To monitor exposure and coverage to COVID-19 vaccines by brand and dose of vaccine as well as age.

Secondary objectives

- To compare the incidence rates of AESIs in the risk window of 28 days after vaccination with dose 1 and/or dose 2 with the incidence rates of AESIs in 2020.
- To monitor and estimate vaccine exposure, incidence rates of adverse events of special interest. (AESI) and of COVID-19 in vaccinated and non-vaccinated persons over the period January 1st 2020-October 31st 2021 in the at-risk population for developing severe COVID-19 by data source, brand and dose of vaccine as well as age.

Methods

We use a retrospective cohort design, in 4 electronic health care databases, with periodic updates of the data during the study period (January 2020 -September 2021). Persons enter the cohort on 1/1/2020 and exit upon latest data extraction, death, moving out or the specific events of interest. Person-time after cohort entry was divided in non-exposed person-time, and person-time following vaccination by specific brands, labelled by dose and distance since last vaccination (-1, -2, -3 weeks etc).
The source population included all individuals observed in one of the participating data sources for at least one day during the study period (01 January 2020 - last data availability) and who have at least 1 year of data availability before cohort entry, except for individuals with data available since birth.

Per event, for calculation of incidence, individuals were followed from cohort entry and contribute to person-time in month (prior to vaccination) and in weeks after vaccination plus specific vaccine exposure (brand & dose) category. Follow-up was censored upon the earliest of date of the event (except for recurrent events), death, exiting the data source, or last data draw-down. For comparison of post-vaccination rates follow-up ended 28 days after each of the vaccine doses, if they had a 2nd dose the intervals post-dose stopped at the date of vaccination with the second. Incidence rates were calculated for 2020 (non-exposed), and after vaccination by vaccine brand, dose and data source. Incidence rates were standardised directly to the Eurostat population and standardised rate differences were calculated using R. Following results of the interim analysis in July 2021, Poisson regression was added to the amended protocol to adjust for measured covariates that were related to the chance of exposure to certain vaccines (age, sex, risk factors for severe covid and prior covid-19). We did not design to adjust for covariates related to the specific outcomes and this study was not designed for causal inference but for monitoring safety. This means that residual confounding may remain, which is why we pre-stated that we classify an association as 'disproportional' if the IRR was above 2.

Results

This study comprised a total of 25,720,158 subjects. We count only the largest population for BIFAP for the total, as the regions with hospital linkage are a subset of the primary care populations. The largest population included was from CPRD with more than 14 million participants. Data locks differed per site: June 30, 2021 in Tuscany, August 31st for BIFAP, August 1st 2021 for PHARMO and May 2021 for CPRD Aurum. At the start of the study 1/1/2020, 34% of the Tuscany population had one or more risk factors for severe COVID-19 disease, and this was around 25% in each of the other data sources (table 2). Median age was highest in Tuscany region (49) and BIFAP-HOSP regions (49).
Overall, 12,117,458 persons received a first dose of a Covid-19 vaccine (47.1%) (excluding unknown vaccines manufacturers). Percentage was highest in BIFAP (68.7%). In BIFAP the majority of persons also had received a second dose for each of the vaccine brands. Percentage of full primary regimen of 2-dose primary regimens were lower in other data sources, in particular for AstraZeneca in CPRD, as this vaccine also had the highest distance between dose 1 and 2 in each data source. mRNA vaccines had a short distance between dose 1 and 2 in all sites

except for CPRD, where Pfizer also had a mean of 76 days between dose 1 and 2, but only 28 days for Moderna vaccine. In this data instance heterologous schedules were very rare.
Vaccination coverage data reflected well the regional/national data for ARS and BIFAP, but were lower for CPRD and PHARMO, probably due to delays in automated feedback on vaccination from immunization registers.
We studied the 2020 rates of different AESI. Most AESI were very rare, only the coagulation disorders were more common. We monitored the occurrence of AESI using cumulative weekly rates, and by censoring at 28-day intervals after each dose. The latter was used to compare against background, which was done using age standardized incidence rate differences, and subsequent Poisson analysis adjusting (where possible for age, sex, prior covid-19 and any risk factors for COVID). The table below shows the key results. For most AESI no excess risk was observed following vaccination, 30 event/vaccine/dose combinations showed excess age standardized rate differences and associations in the Poisson analyses (see table below), however after adjustment for factors associated with vaccine roll out, only 10 significant associations of pooled incidence rate ratios remained based on dose 1 and 2 combined. These comprised anaphylaxis after AstraZeneca, TTS after both AstraZeneca and Janssen vaccine, erythema multiforme after Moderna, GBS after Janssen vaccine, SOCV after Janssen vaccine, thrombocytopenia after Janssen and Moderna vaccine and venous thromboembolism after Moderna and Pfizer vaccines. The risk was more than two-fold increased for TTS, SOCV and thrombocytopenia.

AESI	Vaccine	Dose-Background	Age standardized RD*	95%CI LL	95%CI UL	#. Events	Pooled Crude Random effects IRR	Pooled IRR adj random
Acute disseminated encephalomyelitis	AZ	Dose1	1.41	-0.68	3.51			
	AZ	Dose12	0.67	-0.82	2.15			
	AZ	Dose2	-1.05	-1.17	-0.92	8	1.53 (0.75,3.09)	1.22 (0.60,2.47)
	JJ	Dose1	-1.05	-1.17	-0.92	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-1.05	-1.17	-0.92			
	Moderna	Dose12	-1.05	-1.17	-0.92	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-1.05	-1.17	-0.92			
	Pfizer	Dose1	0.71	-0.72	2.14			
	Pfizer	Dose12	0.14	-0.80	1.08	7	1.70 (0.62,4.64)	2.32 (0.32,16.77)
	Pfizer	Dose2	-0.73	-1.37	-0.09			
	None	**Background**	1.05	0.92	1.18			
Acute kidney injury	AZ	Dose1	**77.33**	**56.42**	**98.23**			
	AZ	Dose12	**56.77**	**39.86**	**73.68**	975	0.82 (0.31,2.13)	0.45 (0.18,1.13)
	AZ	Dose2	11.34	-13.25	35.93			
	JJ	Dose1	149.02	-174.82	472.86	15	0.67 (0.27,1.62)	0.54 (0.10,2.87)
	Moderna	Dose1	-12.17	-41.06	16.72			
	Moderna	Dose12	6.67	-16.18	29.53	138	**1.59 (1.34,1.88)**	1.22 (0.79,1.88)
	Moderna	Dose2	26.74	-9.61	63.09			
	Pfizer	Dose1	7.16	-2.37	16.69			
	Pfizer	Dose12	1.29	-5.74	8.32	1979	**2.26 (1.87,2.73)**	1.15 (0.81,1.62)
	Pfizer	Dose2	-7.89	-17.66	1.88			
	None	**Background**	132.18	130.80	133.58			
Acute liver injury	AZ	Dose1	-2.10	-4.53	0.34			
	AZ	Dose12	-2.25	-4.43	-0.07	41	1.27 (0.93,1.73)	0.78 (0.57,1.07)
	AZ	Dose2	-1.45	-7.20	4.30			
	JJ	Dose1	-8.45	-8.81	-8.09	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-0.77	-7.81	6.26			
	Moderna	Dose12	2.49	-3.92	8.89	11	1.53 (0.84,2.78)	1.20 (0.66,2.17)
	Moderna	Dose2	4.37	-5.23	13.98			
	Pfizer	Dose1	-0.62	-3.19	1.96			
	Pfizer	Dose12	-1.35	-3.22	0.51	71	1.20 (0.95,1.53)	0.78 (0.61,0.98)
	Pfizer	Dose2	-2.75	-5.11	-0.38			
	None	**Background**	8.45	8.10	8.82			
Anaphylaxis	AZ	Dose1	13.43	6.81	20.06			
	AZ	Dose12	11.00	5.33	16.67	98	1.33 (0.65,2.70)	**1.68 (1.37,2.06)**
	AZ	Dose2	1.79	-8.61	12.20			
	JJ	Dose1	-11.69	-12.11	-11.27	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-3.42	-10.27	3.42			
	Moderna	Dose12	-3.53	-9.03	1.98	9	1.60 (0.62,4.11)	1.77 (0.83,3.78)
	Moderna	Dose2	-3.35	-12.90	6.19			
	Pfizer	Dose1	1.67	-2.23	5.57			
	Pfizer	Dose12	-0.81	-3.73	2.11	78	0.95 (0.54,1.67)	1.07 (0.73,1.55)
	Pfizer	Dose2	-5.29	-8.69	-1.89			
	None	**Background**	11.69	11.28	12.11			
Anosmia	AZ	Dose1	-15.69	-25.98	-5.41			
	AZ	Dose12	-22.06	-30.86	-13.26	196	0.63 (0.55,0.73)	0.53 (0.46,0.61)
	AZ	Dose2	-56.69	-65.05	-48.32			
	JJ	Dose1	-71.34	-72.54	-70.14	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-66.08	-73.46	-58.69			
	Moderna	Dose12	-67.50	-72.95	-62.06	<5	0.69 (0.17,2.74)	0.58 (0.14,2.31)
	Moderna	Dose2	-71.34	-72.54	-70.14			
	Pfizer	Dose1	-12.24	-23.18	-1.31			
	Pfizer	Dose12	-23.25	-31.59	-14.91	204	1.01 (0.65,1.58)	0.86 (0.52,1.43)
	Pfizer	Dose2	-47.43	-56.59	-38.26			
	None	**Background**	71.34	70.14	72.55			
Acute respiratory distress	AZ	Dose1	-25.47	-28.50	-22.44			
	AZ	Dose12	-26.94	-29.38	-24.49	92	0.82 (0.66,1.03)	0.49 (0.37,0.65)
	AZ	Dose2	-28.22	-34.06	-22.38			
	JJ	Dose1	226.77	-94.70	548.25	9	0.74 (0.38,1.44)	0.53 (0.10,2.78)
	Moderna	Dose1	24.13	**3.17**	**45.09**			
	Moderna	Dose12	21.79	**6.30**	**37.28**	59	1.12 (0.86,1.44)	0.93 (0.72,1.20)
	Moderna	Dose2	15.53	-5.59	36.66			
	Pfizer	Dose1	11.32	**5.66**	**16.99**			
	Pfizer	Dose12	10.06	**5.55**	**14.56**	696	1.54 (0.82,2.88)	0.83 (0.33,2.08)
	Pfizer	Dose2	11.61	**1.93**	**21.30**			
	None	**Background**	37.86	37.12	38.61			
Arrhythmia	AZ	Dose1	139.79	**97.81**	**181.77**			
	AZ	Dose12	128.41	**93.14**	**163.69**	3975	1.33 (0.88,2.01)	0.78 (0.52,1.18)
	AZ	Dose2	133.10	**77.79**	**188.41**			
	JJ	Dose1	191.83	-170.56	554.22	123	0.89 (0.61,1.28)	0.81 (0.36,1.82)
	Moderna	Dose1	**99.79**	**30.28**	**169.30**			
	Moderna	Dose12	**194.60**	**138.99**	**250.21**	741	**1.45 (1.35,1.56)**	1.25 (0.93,1.68)
	Moderna	Dose2	**329.35**	**219.50**	**439.20**			
	Pfizer	Dose1	**160.23**	**135.91**	**184.54**			
	Pfizer	Dose12	**128.74**	**110.00**	**147.49**	9256	**1.99 (1.56,2.54)**	1.12 (0.94,1.34)
	Pfizer	Dose2	**75.13**	**48.28**	**101.99**			
	None	**Background**	598.35	595.47	601.24			
Thrombotic Thrombocytopenia syndrome	AZ	Dose1	**2.08**	**0.46**	**3.69**			
	AZ	Dose12	**1.57**	**0.25**	**2.90**	13	**5.17 (2.91,9.18)**	**2.98 (1.67,5.31)**
	AZ	Dose2	-0.56	-0.65	-0.47			
	JJ	Dose1	5.84	-6.70	18.39	<5	**65.57 (7.89,Inf)**	**89.99 (10.30,Inf)**
	Moderna	Dose1	-0.56	-0.65	-0.47			
	Moderna	Dose12	0.52	-1.60	2.64	<5	3.22 (0.45,23.24)	2.19 (0.30,15.83)
	Moderna	Dose2	1.80	-2.82	6.43			
	Pfizer	Dose1	-0.56	-0.65	-0.47			
	Pfizer	Dose12	-0.29	-0.59	0.00	<5	1.32 (0.48,3.62)	0.72 (0.26,1.99)
	Pfizer	Dose2	0.01	-0.63	0.65			
	None	**Background**	0.56	0.47	0.66			
Bell's Palsy	AZ	Dose1	-1.20	-16.24	13.83			
	AZ	Dose12	-3.46	-14.31	7.38	44	**1.34 (1.00,1.81)**	1.15 (0.86,1.55)
	AZ	Dose2	-2.16	-21.19	16.86			
	JJ	Dose1	94.25	-123.94	312.45	6	1.19 (0.50,2.83)	1.08 (0.45,2.60)
	Moderna	Dose1	-4.70	-17.20	7.80			
	Moderna	Dose12	-3.07	-13.17	7.04	27	1.14 (0.77,1.67)	0.99 (0.68,1.45)
	Moderna	Dose2	-2.08	-18.46	14.31			
	Pfizer	Dose1	-6.11	-11.67	-0.55			
	Pfizer	Dose12	-4.11	-8.59	0.38	149	1.03 (0.81,1.32)	0.87 (0.69,1.10)
	Pfizer	Dose2	-2.37	-9.27	4.53			

	None	**Background**	29.11	28.20	30.03			
Acute coronary artery disease	AZ	Dose1	9.61	-2.25	21.47			
	AZ	Dose12	-2.63	-11.85	6.58	894	**1.43 (1.01,2.01)**	0.79 (0.62,1.00)
	AZ	Dose2	-20.22	-37.88	-2.57			
	JJ	Dose1	-30.00	-74.19	14.20	23	1.11 (0.74,1.67)	0.82 (0.32,2.05)
	Moderna	Dose1	-12.05	-40.01	15.91			
	Moderna	Dose12	0.34	-20.90	21.58	138	**1.45 (1.22,1.71)**	1.21 (0.91,1.60)
	Moderna	Dose2	16.72	-16.07	49.50			
	Pfizer	Dose1	-4.17	-12.81	4.47			
	Pfizer	Dose12	-11.82	-18.18	-5.46	1564	**1.62 (1.30,2.03)**	0.89 (0.84,0.94)
	Pfizer	Dose2	-22.22	-31.32	-13.11			
	None	**Background**	128.53	127.21	129.86			
Chilblain like lesions	AZ	Dose1	**14.95**	**8.14**	**21.77**			
	AZ	Dose12	**11.16**	**5.41**	**16.91**	148	1.09 (0.30,4.00)	1.03 (0.30,3.58)
	AZ	Dose2	-1.57	-12.23	9.09			
	JJ	Dose1	-17.14	-17.64	-16.64	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-13.09	-18.73	-7.46			
	Moderna	Dose12	-15.10	-17.97	-12.22	<5	0.07 (0.01,0.48)	0.07 (0.01,0.48)
	Moderna	Dose2	-17.14	-17.64	-16.64			
	Pfizer	Dose1	**6.48**	**1.78**	**11.17**			
	Pfizer	Dose12	**1.15**	**-2.21**	**4.52**	185	0.95 (0.19,4.82)	0.87 (0.19,4.02)
	Pfizer	Dose2	-6.92	-10.53	-3.32			
	None	**Background**	17.14	16.65	17.65			
Death (any cause)	AZ	Dose1	**251.46**	**211.27**	**291.66**			
	AZ	Dose12	**66.56**	**38.67**	**94.46**	3666	0.23 (0.04,1.43)	0.12 (0.02,0.68)
	AZ	Dose2	-200.42	-237.15	-163.68			
	JJ	Dose1	746.33	-31.40	1524.05	24	0.13 (0.05,0.32)	0.11 (0.02,0.67)
	Moderna	Dose1	-356.89	-408.20	-305.59			
	Moderna	Dose12	-358.54	-395.55	-321.53	332	0.47 (0.12,1.89)	0.37 (0.12,1.10)
	Moderna	Dose2	-351.19	-406.32	-296.07			
	Pfizer	Dose1	-251.16	-266.25	-236.08			
	Pfizer	Dose12	-325.71	-336.09	-315.33	7244	**1.31 (1.03,1.66)**	0.62 (0.48,0.80)
	Pfizer	Dose2	-396.06	-411.35	-380.77			
	None	**Background**	721.10	717.95	724.26			
Disseminated Intravascular Coagulation	AZ	Dose1	-0.08	-0.46	0.30			
	AZ	Dose12	-0.15	-0.40	0.11	<5	2.26 (0.31,16.39)	1.44 (0.20,10.50)
	AZ	Dose2	-0.27	-0.33	-0.21			
	JJ	Dose1	-0.27	-0.33	-0.21	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-0.27	-0.33	-0.21			
	Moderna	Dose12	-0.27	-0.33	-0.21	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-0.27	-0.33	-0.21			
	Pfizer	Dose1	-0.27	-0.33	-0.21			
	Pfizer	Dose12	-0.12	-0.36	0.13	<5	1.27 (0.31,5.23)	0.74 (0.18,3.08)
	Pfizer	Dose2	0.08	-0.48	0.64			
	None	**Background**	0.27	0.21	0.34			
Erythema multiforme	AZ	Dose1	-1.98	-3.65	-0.30			
	AZ	Dose12	-2.18	-3.59	-0.78	17	0.83 (0.51,1.34)	0.90 (0.56,1.46)
	AZ	Dose2	-3.37	-5.14	-1.60			
	JJ	Dose1	-4.81	-5.09	-4.53	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	9.07	-0.70	18.85			
	Moderna	Dose12	5.16	-1.47	11.79	7	**2.45 (1.16,5.20)**	**2.64 (1.25,5.60)**
	Moderna	Dose2	-1.93	-7.59	3.72			
	Pfizer	Dose1	-2.19	-3.95	-0.43			
	Pfizer	Dose12	-1.96	-3.52	-0.39	21	0.77 (0.43,1.37)	0.79 (0.51,1.23)
	Pfizer	Dose2	-2.00	-4.17	0.17			
	None	**Background**	4.81	4.54	5.10			
GBS	AZ	Dose1	0.70	-0.65	2.05			
	AZ	Dose12	0.46	-0.69	1.62	15	**2.00 (1.19,3.35)**	1.43 (0.85,2.40)
	AZ	Dose2	-0.99	-2.04	0.05			
	JJ	Dose1	7.05	-5.98	20.08	2	**6.74 (1.67,27.18)**	**5.65 (1.40,22.83)**
	Moderna	Dose1	-1.74	-1.90	-1.58			
	Moderna	Dose12	-1.74	-1.90	-1.58	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-1.74	-1.90	-1.58			
	Pfizer	Dose1	0.55	-0.95	2.04			
	Pfizer	Dose12	0.06	-0.95	1.07	16	1.52 (0.81,2.85)	1.10 (0.56,2.15)
	Pfizer	Dose2	-0.79	-1.75	0.17			
	None	**Background**	1.74	1.59	1.91			
Generalized convulsions	AZ	Dose1	**204.25**	**152.97**	**255.53**			
	AZ	Dose12	**177.05**	**131.03**	**223.08**	881	0.66 (0.30,1.47)	0.65 (0.31,1.39)
	AZ	Dose2	**73.87**	**-34.61**	**182.36**			
	JJ	Dose1	-16.03	-234.13	202.08	4	0.27 (0.10,0.73)	0.32 (0.12,0.84)
	Moderna	Dose1	-52.01	-75.93	-28.09			
	Moderna	Dose12	-53.58	-71.78	-35.39	81	1.18 (0.59,2.39)	1.29 (0.83,1.99)
	Moderna	Dose2	-52.42	-82.13	-22.70			
	Pfizer	Dose1	-23.53	-34.28	-12.77			
	Pfizer	Dose12	-33.41	-42.04	-24.78	919	1.10 (0.89,1.37)	1.05 (0.93,1.20)
	Pfizer	Dose2	-39.82	-58.96	-20.69			
	None	**Background**	135.40	133.99	136.82			
Hemorrhagic stroke	AZ	Dose1	6.12	-0.37	12.60			
	AZ	Dose12	4.08	-0.98	9.13	164	1.10 (0.59,2.05)	0.63 (0.36,1.09)
	AZ	Dose2	7.89	-4.83	20.62			
	JJ	Dose1	-25.14	-25.72	-24.56	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-9.39	-19.87	1.09			
	Moderna	Dose12	-9.94	-17.48	-2.41	13	0.62 (0.29,1.32)	0.50 (0.19,1.33)
	Moderna	Dose2	-10.65	-21.43	0.12			
	Pfizer	Dose1	-3.50	-6.81	-0.20			
	Pfizer	Dose12	-4.12	-6.60	-1.63	354	**1.84 (1.65,2.04)**	0.99 (0.77,1.27)
	Pfizer	Dose2	-4.28	-8.29	-0.27			
	None	**Background**	25.14	24.56	25.72			
Heart failure	AZ	Dose1	**43.53**	**24.43**	**62.63**			
	AZ	Dose12	**28.17**	**13.63**	**42.70**	1322	0.89 (0.35,2.26)	0.44 (0.20,0.96)
	AZ	Dose2	6.31	-17.24	29.85			
	JJ	Dose1	11.46	-227.16	250.08	19	0.38 (0.23,0.61)	0.57 (0.10,3.15)
	Moderna	Dose1	**71.71**	**26.54**	**116.88**			
	Moderna	Dose12	**80.96**	**47.84**	**114.07**	267	**1.24 (1.10,1.40)**	1.09 (0.78,1.54)
	Moderna	Dose2	**90.82**	**42.14**	**139.49**			

	Pfizer	Dose1	**35.06**	**24.36**	**45.77**			
	Pfizer	Dose12	**35.00**	**27.15**	**42.86**	4380	**2.47 (1.99,3.06)**	1.16 (0.96,1.40)
	Pfizer	Dose2	**33.75**	**22.25**	**45.26**			
	None	**Background**	209.76	208.11	211.43			
Ischemic Stroke	AZ	Dose1	**22.17**	**9.20**	**35.14**			
	AZ	Dose12	9.91	0.04	19.77	817	1.16 (0.81,1.67)	0.64 (0.47,0.85)
	AZ	Dose2	-4.95	-23.02	13.13			
	JJ	Dose1	183.03	-134.56	500.62	20	0.78 (0.50,1.21)	0.69 (0.30,1.60)
	Moderna	Dose1	9.67	-20.54	39.89			
	Moderna	Dose12	5.96	-15.49	27.41	110	1.06 (0.87,1.27)	0.88 (0.73,1.07)
	Moderna	Dose2	3.35	-27.47	34.17			
	Pfizer	Dose1	**14.82**	**6.38**	**23.26**			
	Pfizer	Dose12	**8.37**	**2.23**	**14.51**	1954	**2.09 (1.73,2.53)**	1.09 (0.94,1.25)
	Pfizer	Dose2	-0.25	-8.99	8.49			
	None	**Background**	117.11	115.86	118.36			
Meningo-encephalitis	AZ	Dose1	1.48	-1.45	4.40			
	AZ	Dose12	-0.23	-2.30	1.85	23	1.19 (0.79,1.80)	0.88 (0.58,1.33)
	AZ	Dose2	-4.37	-4.61	-4.12			
	JJ	Dose1	-1.63	-6.99	3.73	<5	1.63 (0.23,11.59)	1.97 (0.28,14.06)
	Moderna	Dose1	0.25	-5.22	5.71			
	Moderna	Dose12	1.15	-3.37	5.67	6	1.92 (0.85,4.34)	1.72 (0.77,3.85)
	Moderna	Dose2	2.14	-5.28	9.55			
	Pfizer	Dose1	0.30	-1.77	2.38			
	Pfizer	Dose12	-0.17	-1.66	1.32	43	**1.43 (1.02,1.99)**	1.01 (0.66,1.54)
	Pfizer	Dose2	-1.15	-2.84	0.54			
	None	**Background**	4.37	4.12	4.62			
Microangiopathy	AZ	Dose1	0.17	-0.57	0.92			
	AZ	Dose12	0.01	-0.56	0.57	7	3.93 (0.40,39.03)	2.48 (0.16,37.88)
	AZ	Dose2	-0.38	-1.08	0.33			
	JJ	Dose1	-0.73	-0.84	-0.63	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-0.73	-0.84	-0.63			
	Moderna	Dose12	-0.73	-0.84	-0.63	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-0.73	-0.84	-0.63			
	Pfizer	Dose1	0.18	-0.65	1.02			
	Pfizer	Dose12	-0.05	-0.60	0.49	7	2.74 (1.28,5.84)	1.05 (0.49,2.25)
	Pfizer	Dose2	-0.46	-0.85	-0.08			
	None	**Background**	0.73	0.63	0.85			
Multi-Inflammatory syndrome	AZ	Dose1	-0.83	-0.95	-0.71			
	AZ	Dose12	-0.83	-0.95	-0.71	0	NA (NA,NA)	NA (NA,NA)
	AZ	Dose2	-0.83	-0.95	-0.71			
	JJ	Dose1	-0.83	-0.95	-0.71	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-0.83	-0.95	-0.71			
	Moderna	Dose12	-0.83	-0.95	-0.71	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-0.83	-0.95	-0.71			
	Pfizer	Dose1	-0.83	-0.95	-0.71			
	Pfizer	Dose12	-0.83	-0.95	-0.71	0	NA (NA,NA)	NA (NA,NA)
	Pfizer	Dose2	-0.83	-0.95	-0.71			
	None	**Background**	0.83	0.71	0.96			
Myo/pericarditis	AZ	Dose1	-2.66	-7.32	2.00			
	AZ	Dose12	-1.48	-5.71	2.75	64	1.15 (0.90,1.47)	0.87 (0.68,1.12)
	AZ	Dose2	2.98	-7.14	13.09			
	JJ	Dose1	-3.58	-17.75	10.59	<5	0.94 (0.30,2.93)	0.74 (0.24,2.29)
	Moderna	Dose1	7.97	-4.78	20.73			
	Moderna	Dose12	7.91	-2.26	18.08	21	**1.62 (1.01,2.60)**	1.29 (0.68,2.46)
	Moderna	Dose2	5.35	-8.91	19.60			
	Pfizer	Dose1	3.30	-1.48	8.08			
	Pfizer	Dose12	**5.97**	**1.75**	**10.18**	128	**1.23 (1.02,1.50)**	0.96 (0.78,1.19)
	Pfizer	Dose2	**9.05**	**1.84**	**16.27**			
	None	**Background**	14.70	14.23	15.19			
Myocarditis	AZ	Dose1	-0.36	-3.40	2.67			
	AZ	Dose12	-0.75	-3.27	1.76	13	1.06 (0.61,1.83)	0.87 (0.44,1.69)
	AZ	Dose2	-1.49	-5.30	2.32			
	JJ	Dose1	1.99	-9.89	13.87	<5	4.01 (0.56,28.79)	3.21 (0.45,23.10)
	Moderna	Dose1	-0.75	-5.84	4.33			
	Moderna	Dose12	0.05	-5.21	5.31	<5	3.13 (0.99,9.86)	2.86 (0.90,9.05)
	Moderna	Dose2	-0.05	-7.93	7.82			
	Pfizer	Dose1	-0.63	-2.38	1.13			
	Pfizer	Dose12	1.31	-0.63	3.25	35	1.34 (0.94,1.92)	1.09 (0.69,1.71)
	Pfizer	Dose2	**5.19**	**0.37**	**10.01**			
	None	**Background**	4.07	3.83	4.32			
Narcolepsy	AZ	Dose1	-0.50	-1.12	0.12	7	1.92 (0.32,11.38)	1.83 (0.31,10.78)
	AZ	Dose12	0.35	-0.85	1.54			
	AZ	Dose2	3.07	-2.34	8.47			
	JJ	Dose1	1.13	-3.05	5.31	<5	5.54 (0.77,39.88)	4.66 (0.65,33.73)
	Moderna	Dose1	-1.00	-1.13	-0.88			
	Moderna	Dose12	-1.00	-1.13	-0.88	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-1.00	-1.13	-0.88			
	Pfizer	Dose1	0.03	-1.30	1.36			
	Pfizer	Dose12	-0.13	-1.23	0.97	<5	1.10 (0.16,7.63)	1.06 (0.14,8.01)
	Pfizer	Dose2	-0.73	-1.28	-0.18			
	None	**Background**	1.00	0.88	1.14			
Single Organ Cutaneous Vasculitis	AZ	Dose1	-2.07	-3.85	-0.30			
	AZ	Dose12	-2.65	-3.99	-1.32	19	1.28 (0.43,3.83)	1.65 (0.64,4.24)
	AZ	Dose2	-4.26	-5.55	-2.98			
	JJ	Dose1	-0.20	-7.37	6.97	<5	3.00 (0.75,12.07)	**4.39 (1.09,17.71)**
	Moderna	Dose1	-5.37	-5.66	-5.07			
	Moderna	Dose12	-3.25	-6.20	-0.29	<5	0.78 (0.19,3.13)	0.92 (0.23,3.69)
	Moderna	Dose2	-0.92	-7.10	5.27			
	Pfizer	Dose1	-2.58	-4.19	-0.96			
	Pfizer	Dose12	-1.68	-3.34	-0.02	31	0.73 (0.26,2.06)	0.96 (0.42,2.21)
	Pfizer	Dose2	1.90	-5.48	9.27			
	None	**Background**	5.37	5.07	5.67			
Stress Cardiomyopathy	AZ	Dose1	0.92	-0.69	2.53			
	AZ	Dose12	0.31	-0.85	1.47	18	2.24 (0.51,9.73)	1.27 (0.28,5.81)
	AZ	Dose2	-1.28	-2.31	-0.26			
	JJ	Dose1	-2.01	-2.19	-1.84	0	NA (NA,NA)	NA (NA,NA)

	Moderna	Dose1	-2.01	-2.19	-1.84			
	Moderna	Dose12	-1.11	-2.89	0.66	<5	0.75 (0.10,5.31)	0.64 (0.09,4.55)
	Moderna	Dose2	-0.20	-3.76	3.37			
	Pfizer	Dose1	-0.14	-1.15	0.88			
	Pfizer	Dose12	-0.27	-0.98	0.43	30	**2.45 (1.47,4.06)**	1.09 (0.75,1.57)
	Pfizer	Dose2	-0.47	-1.39	0.45			
	None	**Background**	2.01	1.84	2.19			
thrombotic microangiopathy	AZ	Dose1	0.00	-0.55	0.55			
	AZ	Dose12	-0.01	-0.47	0.44	<5	2.56 (0.54,12.13)	1.91 (0.30,12.01)
	AZ	Dose2	-0.12	-0.82	0.59			
	JJ	Dose1	-0.47	-0.56	-0.39	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-0.47	-0.56	-0.39			
	Moderna	Dose12	-0.47	-0.56	-0.39	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-0.47	-0.56	-0.39			
	Pfizer	Dose1	-0.26	-0.68	0.15			
	Pfizer	Dose12	-0.28	-0.57	0.01	<5	0.73 (0.18,2.96)	0.50 (0.12,2.05)
	Pfizer	Dose2	-0.34	-0.61	-0.06			
	None	**Background**	0.47	0.39	0.57			
Thrombocytopenia	AZ	Dose1	**35.47**	**20.93**	**50.01**			
	AZ	Dose12	**32.58**	**20.06**	**45.11**	301	2.60 (0.85,7.99)	1.68 (0.57,4.97)
	AZ	Dose2	**21.66**	**4.45**	**38.86**			
	JJ	Dose1	7.82	-15.24	30.89	12	**2.17 (1.20,3.92)**	**2.27 (1.25,4.10)**
	Moderna	Dose1	13.66	-2.57	29.88			
	Moderna	Dose12	**12.03**	**0.16**	**23.90**	43	**2.20 (1.10,4.43)**	**1.84 (1.07,3.17)**
	Moderna	Dose2	8.19	-8.24	24.61			
	Pfizer	Dose1	**11.00**	**5.45**	**16.54**			
	Pfizer	Dose12	**12.70**	**8.22**	**17.18**	463	**1.92 (1.20,3.07)**	1.21 (0.71,2.07)
	Pfizer	Dose2	**13.54**	**6.76**	**20.31**			
	None	**Background**	27.02	26.41	27.64			
Transverse myelitis	AZ	Dose1	0.35	-1.19	1.88			
	AZ	Dose12	-0.20	-1.15	0.76	5	1.18 (0.48,2.87)	0.90 (0.37,2.21)
	AZ	Dose2	-1.20	-1.37	-1.04			
	JJ	Dose1	-1.20	-1.37	-1.04	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose1	-1.20	-1.37	-1.04			
	Moderna	Dose12	-1.20	-1.37	-1.04	0	NA (NA,NA)	NA (NA,NA)
	Moderna	Dose2	-1.20	-1.37	-1.04			
	Pfizer	Dose1	2.49	-0.75	5.72			
	Pfizer	Dose12	1.54	-0.69	3.76	9	2.48 (0.50,12.18)	1.88 (0.37,9.60)
	Pfizer	Dose2	-0.80	-1.41	-0.18			
	None	**Background**	1.20	1.04	1.38			
Venous thromboembolism (DVT/PE)	AZ	Dose1	**40.52**	**25.71**	**55.33**			
	AZ	Dose12	**34.83**	**22.38**	**47.28**	968	**1.54 (1.14,2.07)**	0.93 (0.74,1.18)
	AZ	Dose2	17.65	-6.43	41.73			
	JJ	Dose1	-38.78	-71.83	-5.72	28	0.94 (0.55,1.62)	0.77 (0.32,1.88)
	Moderna	Dose1	**74.16**	**37.22**	**111.11**			
	Moderna	Dose12	**79.89**	**52.08**	**107.69**	213	**1.75 (1.11,2.76)**	**1.60 (1.40,1.84)**
	Moderna	Dose2	**83.87**	**41.82**	**125.93**			
	Pfizer	Dose1	**21.33**	**11.13**	**31.52**			
	Pfizer	Dose12	**18.70**	**10.97**	**26.43**	1858	**1.87 (1.63,2.15)**	**1.11 (1.00,1.24)**
	Pfizer	Dose2	**18.73**	**3.91**	**33.55**			
	None	**Background**	129.97	128.64	131.31			

Conclusions

This study has provided many lessons

1) It showed that we could monitor a large number of AESI and COVID-19 across 4 data sources in four countries based on the ConcePTION common data model, and common analytics pipeline, and that semantic harmonization was possible across the different disease terminologies
2) Monitoring could start very early in the vaccination campaign, and repeated updates were possible
3) The same population and data sources were used both to compute background rates, and to retrieve observed events after vaccination. This design avoids a limitation of using, on the one hand, real-world data to assess background rates, and, on the other, spontaneous reporting to assess observed cases: underestimation, if any, is more likely to affect the two periods is a uniform way, thus improving the validity of comparison.
4) Underestimation of an AESI can be discussed, based on the characteristics of the data source in relation with the AESI. For example, ICPC codes do not allow for studying the majority for rare AESI, which affected the ability of PHARMO of monitoring such AESI; or, events that do not require hospitalisation or access to emergency room cannot be studied in the ARS data source.
5) COVID-19 vaccines had very different user patterns across the countries in terms of type, distance between dose 1 and 2 and the populations targeted. We observed strong channelling of the different vaccines that differed across countries
6) AESI incidence rates were mostly very low, especially for neurological, immunological and haematological events. Coagulations disorders and cardiac disorders were more frequent, at the same time such events were those with stronger confounding

7) For several AESI we observed disproportionalities between post-vaccination observed and expected rates. Most of these events had been the topic of regulatory discussions, based on public records such as the haematological events, neurological events and erythema multiforme.
8) In spite of the large numbers of vaccinees, power is limited for the events that are very rare <10/100,000 PY and continuous monitoring and scaling up (across countries and over time) is required.
9) This study was for monitoring purposes and not for testing signals, if this needs to be done, proper pharmacoepidemiological designs (such as matching/restriction) should be applied to deal with confounding.

Marketing authorisation holder

Not applicable
This protocol has been developed by the EU PE&PV research network as a deliverable of the Specific Contract 05 implementing the Framework contract No EMA/2018/28/PE with the European Medicines Agency.

Responsible parties

University Medical Center Utrecht, The Netherlands, Utrecht University, The Netherlands
ARS Toscana, Italy
Miriam Sturkenboom, PhD, professor
Olaf Klungel, PhD, professor
Rosa Gini, PhD

Sponsor: University Medical Center Utrecht, The Netherlands Address: Heidelberglaan 100, Utrecht The Netherlands
Miriam Sturkenboom, PhD, professor, department head
Ivonne Martin, PhD, statistician
Rene Eijkemans, PhD, professor, statistician
Sandor Schmikli, MSc senior data management
Marc Padros Goossens, MSc, senior data management

Collaborating Institutions (by alphabetical order)	Study Sites	Key persons
Agenzia Regionale di Sanita Toscana (ARS)	Italy	Rosa Gini, Claudia Bartolini, Davide Messina, Olga Paoletti
Spanish Agency of Medicines and Medical Devices (AEMPS)	Spain	Consuelo Huerta, Mar Martín-Pérez, Patricia García-Poza
PHARMO/STIZON	The Netherlands	Jetty Overbeek, Karin Swart-Polinder, Ron Herings
Utrecht University	The Netherlands	Olaf Klungel, Helga Gardarsdottir, Patrick Souverein, Satu Siiskonen
RTI-Health Solutions	Spain	Susana Perez-Gutthann, Alejandro Arano
VAC4EU secretariat	Belgium	Patrick Mahy, Daniel Weibel

1. Rationale and Background

1.1 Background

Coronavirus disease 2019 (COVID-19)[1]. The landscape for COVID-19 vaccines is characterized by a wide range of technology platforms including nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus and inactivated virus approaches.

On December 21st, 2020, EMA has recommended granting a conditional marketing authorisation for the vaccine Comirnaty, developed by BioNTech and Pfizer, to prevent COVID-19 in people from 16 years of age[2]. On January 6, 2021, EMA has recommended granting a conditional marketing authorisation for COVID-19 Vaccine Moderna to prevent Coronavirus disease COVID-19 in people from 18 years of age. This was the second COVID-19 vaccine that EMA has recommended for authorisation[3]. Other vaccines from AstraZeneca and Janssen followed (see table 1).

Table 1 Overview of COVID-19 products with market access in Europe (March 30, 2021)

product	excipients	dosing	formulation
Comirnaty 1 vial (0.45 mL) contains 5 doses of 30 micrograms of BNT162b2 RNA (embedded in lipid nanoparticles). **Licensed** EMA: Dec 21, 2020 EUL: UK Dec 2, 2020 WHO: 31 December 2020	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315) 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159) 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC) Cholesterol Potassium chloride Potassium dihydrogen phosphate Sodium chloride Disodium phosphate dihydrate Sucrose Water for injections	Comirnaty is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart	This is a multidose vial and must be diluted before use. One vial (0.45 mL) contains 5 doses of 0.3 mL after dilution. 1 dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
Moderna Covid-19 vaccine One dose (0.5 mL) contains 0.10 mg of mRNA (embedded in lipid nanoparticles) **Licensed** EMA: Jan 6, 2021 EUL: UK Jan 8, 2021 USA: Dec.18, 2020	Lipid SM-102 Cholesterol 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG) Tromethamol hydrochloride Acetic acid Sodium acetate trihydrate Sucrose Water for injections	COVID-19 Vaccine Moderna is administered as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose	This is a multidose vial which contains 10 doses of 0.5 mL. One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles). The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days. Once thawed the vaccine should not be re-frozen. The unopened vaccine may be stored at 8°C to 25°C up to 12 hours after removal from refrigerated conditions. Vial should not be shaken
AstraZeneca (Vaxzevria) One dose (0.5 ml) contains: COVID 19 Vaccine (ChAdOx1-S* recombinant) 5 × 10^10 viral particles where ChAdOx1-S means the recombinant,	L-histidine L-histidine hydrochloride monohydrate magnesium chloride hexahydrate polysorbate 80 ethanol sucrose sodium chloride disodium edetate dihydrate	COVID-19 Vaccine AstraZeneca is injected into a muscle (usually in the upper arm).	Pack sizes 10 dose vial (5 ml) in packs of 10 vials 8 dose vial (4 ml) in packs of 10 vials Store in a refrigerator (2°C to 8°C). Do not freeze. Keep vials

[1] Le, T. Thanh, et al. "The COVID-19 vaccine development landscape." *Nat Rev Drug Discov* 19.5 (2020): 305-6.
[2] https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu
[3] https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu

replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein **Licensed** EMA: 29/01/2021 EUL UK: Dec 29, 2020 Argentina (30 Dec 2020) and India (03 Jan 2021) Mexico (04 Jan 2021)	water for injections	Persons will receive 2 injections. The second injection can be given between 4 and 12 weeks after the first injection.	in outer carton to protect from light. The vaccine does not contain any preservative and should be administered by a healthcare professional. After the first dose is withdrawn, the vaccine should be used as soon as practically possible and within 6 hours. During use it can be stored from 2°C to 25°C.
Janssen One dose (0.5 mL) contains: Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein* (Ad26.COV2-S), not less than 8.92 log10 infectious units (Inf.U). * Produced in the PER.C6 TetR Cell Line and by recombinant **Licensed** EMA: 11/03/2021 FDA: EUL: February 27, 2021	2-hydroxypropyl-β-cyclodextrin (HBCD) Citric acid monohydrate Ethanol Hydrochloric acid Polysorbate-80 Sodium chloride Sodium hydroxide Trisodium citrate dihydrate Water for injections	COVID-19 Vaccine Janssen is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.	The Janssen vaccine is packaged as a multi-dose vial which contains 5 doses of 0.5 mL.

1.2 Monitoring COVID-19 vaccines in EU

In line with the EU's safety monitoring plan for COVID-19 vaccines[4], COVID-19 vaccines are closely monitored and subject to several activities that apply specifically to COVID-19 vaccines. Although large numbers of people have received COVID-19 vaccines in clinical trials, certain side effects may only emerge when millions of people are vaccinated. This report is part of the European Medicines Agency (EMA) activities to monitor the COVID-19 vaccines.

[4] https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf

1.3 Research question and objectives

These research questions and objectives are based on the ECVM protocol v.1.5 as posted on the EUPAS register (EUPAS 40404)

Primary objectives

- To monitor and estimate the incidence rates of adverse events of special interest (AESI) in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-August 31st 2021by brand and dose of vaccine and age of the population
- To monitor and estimate the incidence rates of diagnosed COVID-19 in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-August 31st 2021 by brand and dose of vaccine as well as age
- To monitor exposure and coverage to COVID-19 vaccines by brand and dose of vaccine as well as age

Secondary objectives

- To compare the incidence rates of AESIs in the risk window of 28 days after vaccination with dose 1 and/or dose 2 with the incidence rates of AESIs in 2020.
- To monitor and estimate vaccine exposure, incidence rates of adverse events of special interest (AESI) and of COVID-19 in vaccinated and non-vaccinated persons over the period January 1st 2020-August 31st 2021 in the at-risk population for developing severe COVID-19 by data source, brand and dose of vaccine as well as age

2. Research methods

2.1 Study design

We use a retrospective cohort design, in 4 electronic health care databases, with periodic updates of the data during the study period (January 2020-September 2021). Persons enter the cohort on 1/1/2020 and exit upon latest data extraction, death, moving out or the specific events of interest.
Person-time after cohort entry was divided in non-exposed person-time, and person-time following vaccination by specific brands, labelled by dose and distance since last vaccination (-1, -2, -3 weeks etc).
The source population included all individuals observed in one of the participating data sources for at least one day during the study period (01 January 2020 - last data availability) and who have at least 1 year of data availability before cohort entry, except for individuals with data available since birth.

Per event, for calculation of incidence, individuals were followed from cohort entry and contribute to person-time in month (prior to vaccination) and in weeks after vaccination plus specific vaccine exposure (brand & dose) category. Follow-up was censored upon the earliest of date of the event (except for recurrent events), death, exiting the data source, or last data draw-down.

Comparisons of incidence rates of AESIs was conducted between the following sub-cohorts of vaccinated persons and non-exposed cohort from 2020 comprising person time prior to vaccination in 2020.

- 1a. Sub-cohort of vaccinated persons with Pfizer Dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 2 of the vaccine, whichever is earliest
- 1b. Sub-cohort of vaccinated persons with Pfizer Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest
- 1c. Sub-cohort of vaccinated persons with Pfizer Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest
- 1d. Sub-cohort of vaccinated persons with J&J dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest
- 1e. Sub-cohort of vaccinated persons with AstraZeneca dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 2 of the vaccine, whichever is earliest
- 1f. Sub-cohort of vaccinated persons with AstraZeneca Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest
- 1g. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 & 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest
- 1h. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 and mRNA vaccine dose 2 followed from 1st dose of vaccination until a maximum of 4 weeks after 2nd dose or end of follow-up, whichever is earliest.

- 1i. Sub-cohort of vaccinated persons with Moderna dose 1 followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 2 of the vaccine, whichever is earliest
- 1j. Sub-cohort of vaccinated persons with Moderna dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest
- 1k. Sub-cohort of vaccinated persons with Moderna Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after that 2nd dose or end of follow-up, whichever is earliest

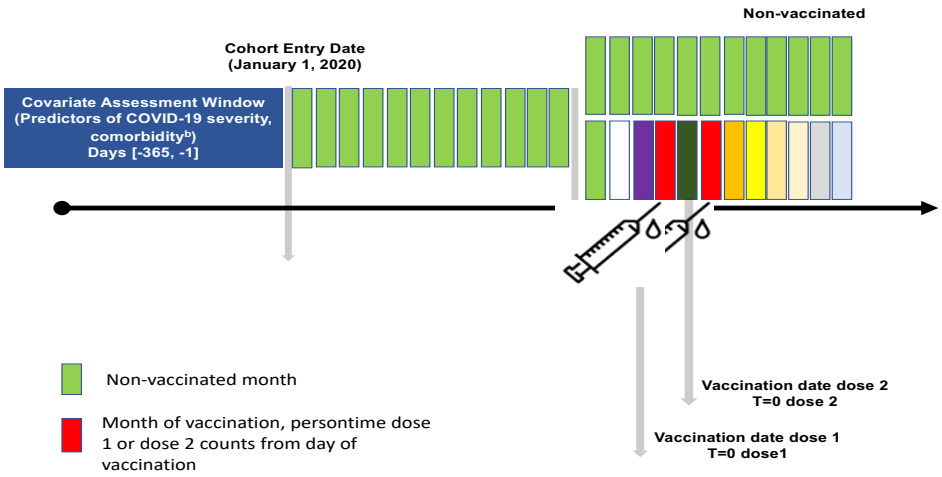


Figure 1 Study design

Study period from January 1st 2020 until last data collected (last possible August 2021), the year 2019 is a run-in period and is used to calculate background rates. Censoring occurs at event date (except for anaphylaxis and generalized convulsions), last data collected, last data draw-down, or death, whichever occurs first.

2.2 Setting

The study results include data from 4 data sources in 4 European countries, comprising more than 25 million individuals (Table 2). Data sources are described in section 2.4.

Table 2 Overview of data sources to be used for the study

Country	Data Access Provider	Name Data source	Active population	Data banks available in nearly real-time	Types of encounters for diagnoses of acute events
Netherlands	PHARMO	NL-PHARMO	2.5 million	Primary care medical records	Primary care medical records
Spain	AEMPS	ES-BIFAP-PC	6.9 million*	Primary care medical records, COVID Registry	Primary care medical records, COVID registry
	AEMPS	ES-BIFAP-HOSP-PC		Primary care medical, hospitalization records, COVID	Primary care Discharge diagnoses
Italy	ARS	IT-ARS	3.6 million	Inhabitant registry, Hospitalisations, Hospital Emergency visits, COVID registry, Vaccines, Dispensings of medicines, Exemptions from copayment	Hospitalisations, Hospital Emergency visits, COVID registry
United Kingdom	Utrecht University	UK-CPRD Aurum	16 million	Primary care medical records	Primary care medical records

GP: General practitioner
*For a subset of 4 out of the 8 regions participating in BIFAP, for which data is available for 2021.

Data sources were chosen from those that have been able to prepare for monitoring COVID-19 vaccines in the ACCESS project, and have the ability to have short delays, access to COVID-19 vaccine data and 3 monthly updates.

2.3 Variables

Variables of interest are those relevant for creation of:

- Person-time: period of follow-up, e.g. date of birth and death dates as well as periods of observation within different databanks, vaccination and occurrence of events
- Events: dates of medical and/or procedure and/or prescription/dispensing codes to identify AESI, at-risk medical conditions or COVID-19
- Vaccinations: date, brand and dose of vaccination

2.3.1 Person-time & Follow-up

For incidence rates of AESI & COVID-19, cohort entry started on 1st January 2020, for those who have at least one year of data (registered on January 1st, 2019) or are born in 2019.
End of follow-up is defined per event as the earliest of date of event (except for anaphylaxis & generalized convulsions), death, last data draw-down, or exiting the data source. Individual person-time varies according to the event under evaluation. One person can contribute time to non-vaccinated category as well as to vaccinated category as displayed in figure 1. Within the vaccinated persons, person-time is counted by brand and dose of vaccine (dose 1 or 2), and by distance (in weeks and then aggregated in months) to last vaccination in months. Exposure date (t=0) is the date of vaccination, and is calculated as exposed. Whenever a person switches from non-vaccinated to vaccinated or between doses, contribution of person time is halted in the prior category.

2.3.2 AESI, At-risk medical conditions & Operationalization

2.3.2.1 Events

Events to be monitored comprise diagnosed COVID-19 and Adverse events of special interest (table 3). Definitions and code lists for each of these events have been made available through the ACCESS project and are listed on Zenodo VAC4EU community https://zenodo.org/communities/vac4eu/?page=1&size=20. In addition to the definitions in ACCESS, Bell's palsy was added.

The date of an event is the first occurrence of a record of a diagnostic code for such an event during follow-up. We do not consider recurrent events, except for anaphylaxis and generalized convulsion, where recurrence after 30 days are permitted.

According to the data source, diagnoses may have been recorded in different data banks. Two data sources (NL-PHARMO, UK-CPRD) have only primary care medical records in a real-time manner. One data source (ES-BIFAP) can link also a Covid registry of Covid tests. The last data source (IT-ARS) does not have primary care medical records, and to detect the AESI uses hospitalisations, access to hospital emergency visits, and COVID registry. CPRD, 4 of the 5 regions of BIFAP both include positive and negative tests.

Table 3 List of events

Event	Recurrence allowed#	In initial ACCESS AESI list	Naïve period
COVID disease*	No	Yes	365 days
Multisystem inflammatory syndrome	No	Yes	365 days
Acute respiratory distress syndrome	No	Yes	365 days
Acute cardiovascular injury, including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis	No	Yes	365 days
Coagulation disorders, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease, thrombotic thrombocytopenia syndrome	No	Yes (have been isolated now because of issues seen in AZ vaccine)	365 days
Generalised convulsion	Yes	Yes	30 days
Guillain Barré Syndrome	No	Yes	365 days
Diabetes (type 1 and unspecified type)	No	Yes	365 days
Acute kidney injury	No	Yes	365 days
Acute liver injury	No	Yes	365 days
Anosmia, ageusia	No	Yes	365 days
Chilblain-like lesions	No	Yes	365 days
Single organ cutaneous vasculitis	No	Yes	365 days
Erythema multiforme	No	Yes	365 days
Anaphylaxis	Yes	Yes	30 days
Death	No	Yes	365 days
Sudden death	No	Yes	365 days
Acute aseptic arthritis	No	Yes	365 days
Meningoencephalitis	No	Yes	365 days
Acute disseminated encephalomyelitis (ADEM)	No	Yes	365 days
Narcolepsy	No	Yes	365 days
Thrombocytopenia	No	Yes	365 days

Transverse myelitis	No	Yes but isolated now because of trial data	365 days
Bells' palsy	No	No, but included because of issues in trials	365 days

Covid was measured in 5 levels according to the WHO classification: level 1: asymptomatic, level 2: symptomatic not hospitalized, level 3: symptoms requiring hospitalization, level 4 ICU level 5: death. In the analysis, severity levels were pooled hyerarchically (e.g, level 3 or worse includes all hospitalised, all admitted to ICU, and all dead)
Recurrence is allowed if an event is acute and may re-occur and can be distinguished from prior event

Using information contained in event definition forms together with data access provider experience, broad and narrow algorithms for definition of each AESI have been defined in the ACCESS project, only narrow codes (specific for the event) were applied for this study to avoid misclassification.

2.3.2.2 At-Risk to develop severe COVID-19 due to Medical Conditions

Medical conditions putting individuals at risk for severe COVID-19 disease were obtained from the CDC website[5] This website is updated regularly and provide a classification of at-risk conditions for developing severe COVID-19 based on level of evidence.

Medical codes and associated dates for at-risk medical conditions characterizing at-risk groups for developing severe COVID-19 as well as prescription and/or dispensing records for drug exposures which may be used as proxies for their identification. At-risk groups were created for each of the at-risk medical conditions listed in Table 4. Multi-morbidity was considered (subjects may belong to more than one at-risk group).

Table 4 Comorbid conditions with evidence of increased COVID-19 severity

At-risk medical conditions identified by diagnosis codes (see code sheets)	Medicinal product proxy(ies) (ATC code)
Cancer (with chemo/immuno/radio-therapy, cancer treatment, immunosuppressant; targeted cancer treatment (such as protein kinase inhibitors or PARP inhibitors); blood or bone marrow cancer (such as leukemia, lymphoma, myeloma))	Alkylating agents (L01A) Antimetabolites (L01B) Plant alkaloids and other natural products (L01C) Cytotoxic antibiotics and related substances (L01D) Other antineoplastic agents (L01X) Hormones and related agents (L02A) Hormone antagonists and related agents (L02B) Immuno-stimulants (L03) Immunosuppressants (L04)
Type 1& 2 Diabetes	Blood glucose lowering drugs A10A & A10B
Obesity (BMI > 30)	Peripherally acting anti-obesity products (A08AB) Centrally acting anti-obesity products (A08AA)
Cardiovascular disease/ Serious heart conditions including heart failure, coronary artery disease, and myocarditis/pericarditis	Antiarrhythmics, class I and III (C01B) Cardiac stimulants excl. Cardiac glycosides (C01C) Vasodilators used in cardiac diseases (C01D) Other cardiac preparations (C01E) Antithrombotic agents (B01A) B01A*
Chronic lung disease including COPD, asthma	Drugs for obstructive airway diseases (R03) Lung surfactants (R07AA) Respiratory stimulants (R07AB)
Chronic kidney disease	Erythropoietin (B03XA01)
HIV	Protease inhibitors (J05AE) Combinations to treat HIV (J05AR) NRTI (J05AF) NNRTI (J05AG)
Immunosuppression	Immunosuppressants (L04A) Corticosteroids (H02)
Sickle Cell Disease	Hydroxyurea (L01XX05) Other hematological agents (B06AX)
Hypertension	anti-hypertensive drugs (C02, C03, C07, C08, C09)

2.3.2.3 Operationalization & validation

For each of the events of interest, event definition forms have been created in the ACCESS project comprising the following chapters:

1. Event definition: using the Brighton Collaboration definitions if available and otherwise definitions from European learned societies
2. Synonyms / lay terms used for the event: these show how an event may be described/called in free text

[5] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

3. Laboratory tests done specific for event (may be used as confirmation)
4. Diagnostic tests done specific for event (may be used as confirmation in building algorithms)
5. Drugs used to treat event (may be used as confirmation in building algorithms)
6. Procedures used specific for event treatment (may be used as confirmation in building algorithms)
7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently diagnosed
8. Diagnosis codes or algorithms used in different papers to identify the events in Europe/USA
9. Experience of participating data sources to identify or validate the events (to be completed by each data source)
10. Proposed codes by Codemapper (Becker et al., 2017)
11. Algorithm proposal for event identification
12. References

Proposed codelists were reviewed by the data access providers. Codelists for each of the included events and the co-variates is included in the VAC4EU community Zenodo repository (https://www.zenodo.org/communities/vac4eu/?page=1&size=20).
Events were not validated for this monitoring study as it is for monitoring purposes only.

2.3.3 Exposure to COVID-19 vaccinations

Exposure is based on recorded receipt of any of the COVID-19 vaccines. Vaccine brand and date of vaccination were obtained from general practice records in all data sources except IT-ARS, where the immunization register was used. As the Pfizer BioNTech, Moderna and Oxford/AstraZeneca COVID-19 vaccines are all licensed as a two-dose vaccine series, multiple vaccinations per person were identified. Exposure to these vaccines is classified by brand and dose and calendar month of administration and counted for exposure monitoring.

In PHARMO, multiple recordings of the same dose were found in the primary care medical records, referring to different aspects of the immunization procedure: scheduling of the appointment, injection at the primary care practice or at another site, invoice of the procedure, etc. An algorithm was developed to identify uniquely each dose. For quality purposes, repeated vaccine entries within 14 days were discarded between dose 1 and 2.

Exposure windows for event monitoring
Person time of follow up in the cohort was categorized as at risk (vaccinated) and non-vaccinated periods. Person time was not stopped at the occurrence of a vaccination. The vaccination day and monthly (28 days) risk-windows after vaccination was classified as risk periods with increasing months of distance since last dose of vaccination. To keep track of dose, these periods were also be labelled by the number of previous COVID-19 containing vaccinations.

For comparisons of incidence rates, we limited post-vaccination rates to 28 days risk windows post-dose 1 and post-dose 2 to avoid misclassification.

2.3.4 Other variables

- Demographic characteristics: dates of birth and death, sex, country & data source.

In those data sources in which full date of birth is not available for privacy reasons, date of birth was derived as follows:

- Date of birth is defined as the 15th of the birth month and birth year. If the birth month and date are missing, the birth date is be defined as the 30th June of the birth year.

2.4 Data sources

2.4.1 Description of data sources participating in this protocol

The below mentioned data sources have indicated to be able to participate, have relatively short lag times on their outcomes and able to provide information on vaccination.

2.4.1.1 Netherlands: PHARMO Database Network

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymization of the data is performed by STIZON. STIZON is an independent, ISO/IEC 27001 certified foundation, which acts as a Trusted Third Party between the data sources and the PHARMO Institute. The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 9 million persons of a well-defined population in the Netherlands for an average of twelve years. For the ECVM study only the General Practitioner databank was used comprising data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO ATC Classification System [www.whocc.no]. Diagnoses and symptoms are coded according to the International Classification of Primary Care - ICPC [www.nhg.org], which can be mapped to the International Classification of Diseases - ICD codes, but can also be entered as free text. GP data cover a catchment area representing 3.2 million residents (~20% of the Dutch population).

2.4.1.2 Spain: BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerized database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). The project started in 2001 and current complete version of the database with information until December 2019 includes clinical information of 10.153 of primary care physicians (PCPs) and paediatricians. Nine participant autonomous regions send their data to BIFAP every year. BIFAP database currently includes anonymized clinical and prescription/dispensing data from around 20 million (17 active population) patients representing 92% of all patients of those regions participating in the database, and 32% of the Spanish population. Mean duration of follow-up in the database is 9 years. Information collected by PCPs includes administrative, socio-demographic, lifestyle, and other general data, clinical diagnosis and health problems, results of diagnostic procedures, interventions, and prescriptions/dispensations. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2, ICD-9CM and SNOMEDCT system, and a variable proportion of clinical information is registered in "medical notes" in free text fields in the EMR. Additionally, information on hospital discharge diagnoses coded in ICD-10 terminology is linked to patients included in BIFAP for a subset of periods and regions participating in the database. All information on prescriptions of medicines by the PCP is incorporated and linked by the PCP to a health problem (episode of care), and information on the dispensation of medicines at pharmacies is extracted from the e-prescription system that is widely implemented in Spain. The BIFAP database was characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment[6]. BIFAP has been linked to a COVID registry for COVID monitoring.

2.4.1.3 Italy: ARS database

The Italian National Healthcare System is organized at regional level: the national government sets standards of assistance and a tax-based funding for each region, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. The Agenzia Regionale di Sanita' della Toscana (ARS) is a research institute of the Tuscany Region. The ARS data source comprises all data banks that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects data from regional initiatives. All the data in the ARS data source can be linked one another at the individual level, through a pseudo-anonymous identifier. The ARS data banks include dispensing of drugs for outpatient, ambulatory, and, in part, inpatientuse, hospital administrative records, admissions to emergency care, exemptions from co-payment, administration of diagnostic tests and procedures, causes of death, mental health services registry, birth registry, spontaneous abortion registry, induced terminations registry, COVID registry. A pathology registry is available, mostly recorded in free text, but with morphology and topographic Snomed codes. Vaccine data is available since 2016 for children and since 2019 for adults. The ARS

[6] Sturkenboom M et al. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations. Vaccine (2020).

data source was characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment when using the new vaccine registry (from 2019)[11]

2.4.1.4 United Kingdom: CPRD

The Clinical Practice Research Datalink (CPRD) from the UK collates the computerized medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals, and hospitalizations. GPs act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care as necessary. Secondary care teams also feedback information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. The majority of the data are coded in Read Codes. Validation of data with original records (specialist letters) is also available.
The dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage. There are currently approximately 50 million patients (acceptable for research purposes) – of which 16 million are active (still alive and registered with the GP practice) – in approximately 1,700 practices (https://cprd.com/Data). Data include demographics, all GP/healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments, including all prescriptions, all data referrals to other care, hospital discharge summary (date and Read codes), hospital clinic summary, preventive treatment and immunizations, death (date and cause). CPRD is listed under the ENCePP resources database, access was provided by the Utrecht University. The CPRD was not yet characterized in the ADVANCE project, where the UK THIN and RCGP databases were used, but has been widely used in vaccine studies. COVID-19 vaccine administration is obtained in from the national registry and may be slightly delayed.

2.5 Study size

The study population included all individuals registered with at least one year of data prior to the start of the study period (January 1st 2020) or follow-up from birth.

2.6 Data management

This study is conducted in a distributed manner using a common protocol, common data model (CDM), and common analytics programs (Figure 3). The data pipeline has been developing from the EU-ADR to the IMI-ADVANCE project and was further improved in the IMI-ConcePTION project (https://www.imi-conception.eu/) and used to generate background rates in the ACCESS project[7]. This process maximizes the involvement of the data providers in the study by utilizing their knowledge on the characteristics and the process underlying the data collection which makes analysis more efficient. Moreover, semantic harmonization is conducted as part of the data transformation pipeline which makes it faster and more transparent.

2.6.1 Data extraction

Each database access provider (DAP) creates ETL specifications using the standard ConcePTION ETL design template. The current version for this analysis is version 2.2 of the ConcePTION CDM. Details on the ConcePTION CDM are described in the paper by Thurin et al.[8]

[7] https://vac4eu.org/covid-19-tool/

[8] Thurin NH, Pajouheshnia R, Roberto G, Dodd C, Hyeraci G, Bartolini C, Paoletti O, Nordeng H, Wallach-Kildemoes H, Ehrenstein V, Dudukina E, MacDonald T, De Paoli G, Loane M, Damase-Michel C, Beau AB, Droz-Perroteau C, Lassalle R, Bergman J, Swart K, Schink T, Cavero-Carbonell C, Barrachina-Bonet L, Gomez-Lumbreras A, Giner-Soriano M, Aragón M, Neville AJ, Puccini A, Pierini A, Ientile V, Trifirò G, Rissmann A, Leinonen MK, Martikainen V, Jordan S, Thayer D, Scanlon I, Georgiou ME, Cunnington M, Swertz M, Sturkenboom M, Gini R. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clin Pharmacol Ther. 2022 Jan;111(1):321-331. doi: 10.1002/cpt.2476.

Following completion of the ETL template and review with study statisticians and principal investigators, each DAP extracts the relevant study data locally using their software (eg Stata, SAS, R, Oracle). This data is loaded into the CDM structure in csv format. These data remain local (Figure 3).

2.6.2 Description of data transformation & quality and analysis pipeline

This study uses data that is already collected for analysis and available in electronic health care data sources in 4 EU countries and follow the following principles.

First, to harmonize the structure of the data sets held by each partner, a shared syntactic foundation is utilized, we use the common data model that was developed in the IMI-ConcePTION project (annex 1). In this common data model, data is represented in a common structure but the content of the data remain in their original format.

To reconcile differences across terminologies a shared semantic foundation is built for the definition of events under study by collecting relevant concepts in a structured fashion using a standardised event definition template. The Codemapper tool (https://vac4eu.org/codemapper/) was used to create diagnosis code lists based upon completed event definition templates for each event and comorbid risk condition in the ACCESS-BGR protocol and for Bell's palsy (see Zenodo)
Based on the relevant diagnostic medical codes, as well as other relevant concepts (e.g. medications), algorithms were constructed to operationalize the identification and measurement of each event. These algorithms may differ per data source, as the components that go into the study variable may differ. Wherever possible the event definition sheet specifies prior validation of algorithms and codes for benchmarking. Scripts for semantic harmonization are created centrally and provided in R and distributed to data access providers for local deployment. This resulted in a set of study variables which are both semantically and syntactically harmonized.

The extraction, transform, and load (ETL) design is made available on paper and currently on the VAC4EU Molgenis FAIR catalogue which was designed and piloted in the ConcePTION and MINERVA projects.

Quality control of the ETL process was assessed using Level 1 (completeness) and Level 2 (logical consistency) verifications that have been developed as part of the IMI-ConcePTION project. These level 1[9] and 2[10] checks are publicly available R-scripts that are run against the CDM v2.2. The scripts can be downloaded from the Github by the DAP and run locally. They produce an R- mark down report that is shared on the DRE and evaluated by the study team and the data access provider.

To harmonize study variable sets, publicly available R scripts for creation of analytical datasets were developed on GitHub and distributed to data access providers for local deployment. The R script is available with documentation in the GitHub repository https://github.com/ARS-toscana/ECVM.
The aggregated results produced by these R scripts were then be uploaded to the Digital Research Environment (DRE) for pooled analysis of incidence and visualization (see Figure 2). The DRE is a cloud based, globally available research environment where data is stored and organized securely and where researchers can collaborate (https://www.andrea-consortium.org/azure-dre/).

All final statistical computations were performed on the DRE using R. Data access providers had access to the project workspace for verification of the results.

Within the DRE, each project-specific area consists of a separate, secure folder, called a 'workspace'. Each workspace is completely secure, so researchers are in full control of their data. Each workspace has its own list of users, which is managed by its administrators. The architecture of the DRE allows researchers to use a solution within the boundaries of data management rules and regulations. Although General Data Protection Regulation (GDPR) and Good (Clinical) Research Practice still rely on researchers, the DRE offers tools to more easily control and monitor which activities take place within projects. All researchers who need access to DRE are granted access to study-specific secure workspaces through VAC4EU. Access to this workspace is only possible with double authentication using an ID and password together with the user's mobile phone for authentication. Upload of files is possible for all researchers with access to the workspace within the DRE. Download of files is only possible after requesting and receiving permission from a workspace member with an 'owner' role.

[9] https://github.com/IMI-ConcePTION/Level-1-checks
[10] https://github.com/IMI-ConcePTION/Level-2-checks

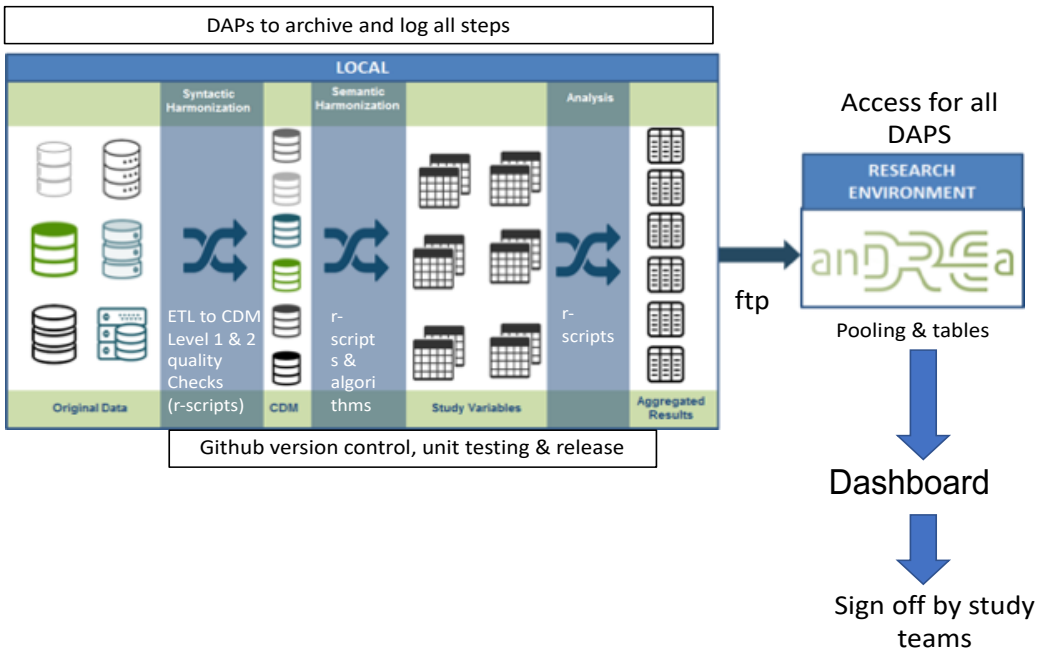


Figure 2 Data transformation and flow

2.6.3 Data processing and analysis

A detailed statistical analysis plan was created and delivered to EMA in April 2021.
In March 2021, a baseline data extraction was requested from the DAPs. This created a baseline instance of the data source. This was ETL'ed into the ConcePTION CDM and formed the baseline instance of the CDM. In June and in October, DAPs were requested to reperform the extraction of the new data, which constituted a new instance of their data source. Each instance of the data source was ETL'ed to the ConcePTION CDM, was quality assessed and processed and analysed using the same R script available in a GitHub repository (https://github.com/ARS-toscana/ECVM). R- and Stata scripts pooling data from multiple data sources, executing the Poisson analysis, and generating tables and figures were executed on the DRE. R-code and Stata code for the calculation of standardised incidence rate differences and Poisson analysis and the creation of the tables and figures is included in the ECVM script repository.

2.6.4 Data visualization & dashboard

After pooling of the incidence rate data from the various DAPs on the DRE they were transferred to a POWERBI platform (https://powerbi.microsoft.com/en-us/for visualization) by UMC Utrecht.
PowerBI runs on the UMCU Datawarehouse. EMA and PRAC were provided with access to the POWERBI platform to monitor incidence rates of events.
Access to the visuals can be provided to selected groups at the moment, until EMA agrees to release them to a larger group.

2.6.5 Archiving and record retention

DAPs are responsible locally to archive each data source instance that is used for the study. The DAP has the obligation to archive the data source instances, the ETL scripts, the R-scripts that were used and the results that were uploaded to the DRE, locally.

Aggregated results from DAPs are stored in the DRE for inspection by the study sponsor for at least five years. The final study aggregated results sets and statistical programs to pool and visualize are made publicly available through Github.
Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with GPP guidelines. Study records or documents may also include the analyses files, syntaxes (usually stored at the site of the database), ETL specifications, and output of data quality checks.

After 5 years all materials from the DRE will be retained for at an additional maximum of 10 years on a UMCU secure drive in line with local procedures. The final study protocol and possible amendments, the final statistical report, statistical programs and output files will be archived on the UMCU secure drive according to Julius Center standard operating procedures.

2.7 Data analysis

2.7.1 Analysis of Demographics and Baseline Characteristics

Demographic characteristics (age at cohort entry and sex) and baseline characteristics such as at-risk medical conditions were summarized for each data source using descriptive statistics.

Frequency tables including numbers and percentages were generated for categorical variables (age at study entry in categories, sex, and presence of at-risk medical conditions at start of cohort entry and at the time of first vaccination by vaccine brand. Baseline characteristics at first vaccination were compared between the vaccination brands. Mean, standard error, median and range were provided for continuous variables.

2.7.2 Hypotheses

This study was not designed for causal inference, but is descriptive in nature, rates are provided in non-vaccinated and post vaccination. Since the availability of incidence rates, draws one to comparisons, which may be confounded due to heavy channelling in the roll out of the vaccination campaign that was witnessed in the interim report, we amended the protocol in October 2021, and added as a secondary objective that we would adjust for measurable confounding, and explore presence of effect modification for age (<60, 60 and older), gender, prior COVID-19 disease and any risk factor for severe COVID disease, based on the data that has been collected through the original monitoring protocol.

As secondary objective we provide statistical analyses, based on the initial design, to try to address confounding as far as possible with the measured variables as this provides more accurate estimates than a comparison of crude or age standardised rates.
We will consider the relative risk to be meaningfully elevated if the RR is above 2 (to acknowledge that there may be residual confounding as we do not adjust for risk factors for the different AESI, only for exposure) and the lower limit of the 95% confidence interval of the relative risk is above 1.

2.7.3 Statistical Methods

Incidence rates of all events listed in table 3 were estimated in 2020 by age band and week in the non-vaccinated time dividing the number of incident cases (not in run-in year) (numerator) by the total person-time at risk (denominator). Incidence rates of events in vaccinated subjects were calculated by vaccine brand and dose and the week since last vaccination, cumulation was conducted due to low counts, except in the case of COVID. A 95%CI was computed using the exact method[11].

To monitor COVID-19 vaccination exposure, the counts of administered doses of a first or second dose of any specific type of COVID-19 vaccine was recorded and counted on the dashboard by calendar week. Weekly estimates of coverage were calculated by summing those vaccinated with any or specific COVID-19 vaccine,

[11] https://www.statsdirect.com/help/rates/poisson_rate_ci.html

and still included in the study population, divided by the number of persons in the study population in the same week.

For estimation of incidence rate differences we used direct standardization, using the incidence rates of the background rates for each data sources in each of the gender and age strata and the person-time in the corresponding post-vaccination age strata to estimate the age adjusted standardised rate[12].

2.7.4 Statistical Analysis

2.7.4.1 Vaccination exposure monitoring & coverage

For every data source, summary tables with number of administered doses per vaccine brand within the primary series (dose 1 and dose 2) by calendar time (in weeks) over the follow-up period were created. The following data transformation steps were performed:

Calculation of time by week and birthyear
The number of administered COVID-19 vaccine doses of specific brand by calendar time x age (birthyears) and dose. This table is used as input to the vaccination exposure component of the dashboard. Bar charts are created with weekly number of administered doses in the observed population.

For every data source, summary tables were created, with the number of persons of a given birth year who are present in the study cohort on January 1, 2021. The total number of persons as well as the persons vaccinated with dose 1, and dose 1 & dose 2 are obtained by brand of vaccine. This table is used as input to the COVID-19 vaccination coverage component of the dashboard. A separate and similar calculation was done for persons with an at-risk medical condition.

We calculated vaccination coverage by dose 1 and 1+2 over time. The coverage at week i was calculated by dividing the number of vaccinated subjects n_ij by the total number of subjects under follow-up at week i (N_ij), expressed as a percentage.

2.7.4.2 Benefits: plots with COVID-19 incidence rates

The weekly incidence (/100.000 person-years) of COVID-19 disease was calculated as the number of COVID-19 events (diagnoses or positive tests) divided by the total person-time at risk multiplied with 100.000, in each calendar week, prior to vaccination and following dose 1 and 2 of a specific vaccine. Exact Poisson 95% confidence intervals were calculated using the method of Ulm[13].

2.7.4.3 Risks: plots with incidence of AESI

The incidence rate (per 100,000 PY) for each AESI is stratified prior to vaccination in 2020, and calculated per month and after vaccination by brand, dose and week since vaccination. Numerator is the number of cases within the defined category and the denominator is the number of person years. Exact Poisson 95% confidence intervals are calculated using Ulm's method.

This study is not designed for causal inference but was descriptive in nature with the purpose of monitoring of safety, which typically comprises disproportionality or observed/expected analyses. In this study the incidence in non-vaccinated and post-vaccination are generated directly from the same data and can be used to investigate observed/expected. Due to the heavy initial channelling of COVID-19 vaccines to elderly and certain at-risk groups, confounding was very strong in the early stages of the vaccination campaign.

Based on the interim report, which showed very strong confounding, we further explored risk in the first 28 days after vaccination while trying to deal (as far as possible) with confounding.

[12] http://www.epidemiolog.net/evolving/Standardization.pdf Accessed January 15, 2022
[13] https://www.statsdirect.com/help/rates/poisson_rate_ci.htm

In each data source, crude and age-standardised incidence rates of each AESI (per 100,000 PYs) were calculated both in the unvaccinated population in 2020 (background rates), and in the vaccinated cohorts, per vaccine and dose, using person time within 28 days after dose 1 and 2. Confidence intervals for the direct standardised rates were estimated using the formula from Fay and Feuer[14]. In addition, we calculated the difference between the standardised incidence rate post-vaccination with the background rates. The computation for the standardised incidence rates and their differences were done in R version 4.0.5 using the R package dsr version 0.2.2[15].
The standard population was the European Standard Population, 2013 Edition, reshaped to fit our age bands.

To address residual confounding as far as possible (acknowledging we are not testing a hypothesis) with the covariate data we had available (which may not be able to deal with all confounding) we used a multivariate Poisson regression adjusting concurrently for the four confounding factors that were included in the original monitoring protocol (age, gender, any risk factor for covid severity, and previous Sars-Cov-2 infection). The log person-days in each risk or comparison interval were included in the regression model as the offset. Incidence rate ratios – estimating the ratio of outcome incidence in the risk interval divided by outcome incidence in the comparison interval are reported with 95% confidence intervals. converge The negative binomial regression model did not converge for most AESI and when they do converge, the Poisson model fits the data better. This indicates that overdispersion does not exist, thus the estimated standard errors from the Poisson regression were used to calculate the approximate confidence interval. IRR were pooled using both fixed and random effects using the R package meta.

For statistically significantly elevated incidence rate ratios we explored presence of effect modification when there were enough cases.
Interaction was tested on a multiplicative scale using the likelihood ratio (LR) test, we first built a model without interaction, and subsequently a model with potential interaction terms for age (<60, 60 years and older), sex, any history of comorbidities that may increase the risk of severe COVID-19 and prior COVID-19 (for those vaccinated).. This LR test served as a global test whether there is evidence of any interaction (effect modification). Effect modification was also assessed for each of the four factors separately.

Specific analyses were conducted for each brand and dose of COVID-19 vaccine against the non-exposed. For each 2-dose vaccine, we conducted analyses for each of three types of 28-day risk interval: the 28 days following Dose 1, the 28 days following Dose 2, and the days that are summed in the 28 days after either dose (total of up to 56 days).
For each of these risk intervals, the comparator was the background rates in non-vaccinated persons in 2020.

Non-vaccinated: 2020 monthly incidence rates by age, sex, history of co-morbidity that increases COVID-19 severity
Exposure groups and time at risk for the Vaccinated with:

- Pfizer:
  1a. Sub-cohort of vaccinated persons with Pfizer Dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 2 of the vaccine, whichever is earliest
  1b. Sub-cohort of vaccinated persons with Pfizer Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest
  1c. Sub-cohort of vaccinated persons with Pfizer Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest
- J&J
  1d. Sub-cohort of vaccinated persons with J&J dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest
- AZ:
  1e. Sub-cohort of vaccinated persons with AstraZeneca dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest
  1f. Sub-cohort of vaccinated persons with AstraZeneca Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest

[14] Fay MP, Feuer EJ. Confidence Intervals for Directly Standardised Rates: A Method Based on The Gamma Distribution. Stat Methods Med Res. 1997 VOL. 16, 791—801.)
January 23, 2022, 7:12 PM

[15] https://github.com/cran/dsr.

1g. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 & 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest

1h. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 and mRNA vaccine dose 2 followed from 1st dose of vaccination until a maximum of 4 weeks after 2nd dose or end of follow-up, whichever is earliest.

- Moderna:

1i. Sub-cohort of vaccinated persons with Moderna dose 1 followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest

1j. Sub-cohort of vaccinated persons with Moderna dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest

1k. Sub-cohort of vaccinated persons with Moderna Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after that 2nd dose or end of follow-up, whichever is earliest

2.7.5 Missing data

Since the underlying data represent attended medical care, we do assume that absence of information of clinical events means absence of that condition. Imputations were done for missing dates of births or incomplete dates of birth as well as missing doses of vaccines. Vaccine dose was imputed based on chronological order of COVID-19 vaccines.

2.7.6 Ethics and governance

For this analysis, we used CPRD Aurum (June2021).Use of CPRD data for this project was approved by CPRD's Research Data Governance (RDG) Process (protocol no. 21_000429) The use of PHARMO data was approved by the Institutional Review Board of 'Stichting Informatie voor Zorg en Onderzoek'(STIZON, ID CC2021-21). Use of BIFAP data for this project was approved by the Scientific Committee of BIFAP (protocol reference: 01/2021) and an Ethics Committee (Comité de Ética de La Investigación con Medicamentos del Hospital Universitario de la Princesa)

3. Results

3.1 Descriptives

This study comprised a total of 25,720,158 subjects (table 5). We count only the largest population for BIFAP for the total, as the regions with hospital linkage are a subset of the primary care populations. The largest population included was from CPRD with more than 14 million participants. Data locks differed per site, the recommended end date to use the data was June 30, 2021 in Tuscany, August 31st for BIFAP, August 1st 2021 for PHARMO and May 2021 for CPRD Aurum (see figure 3.)

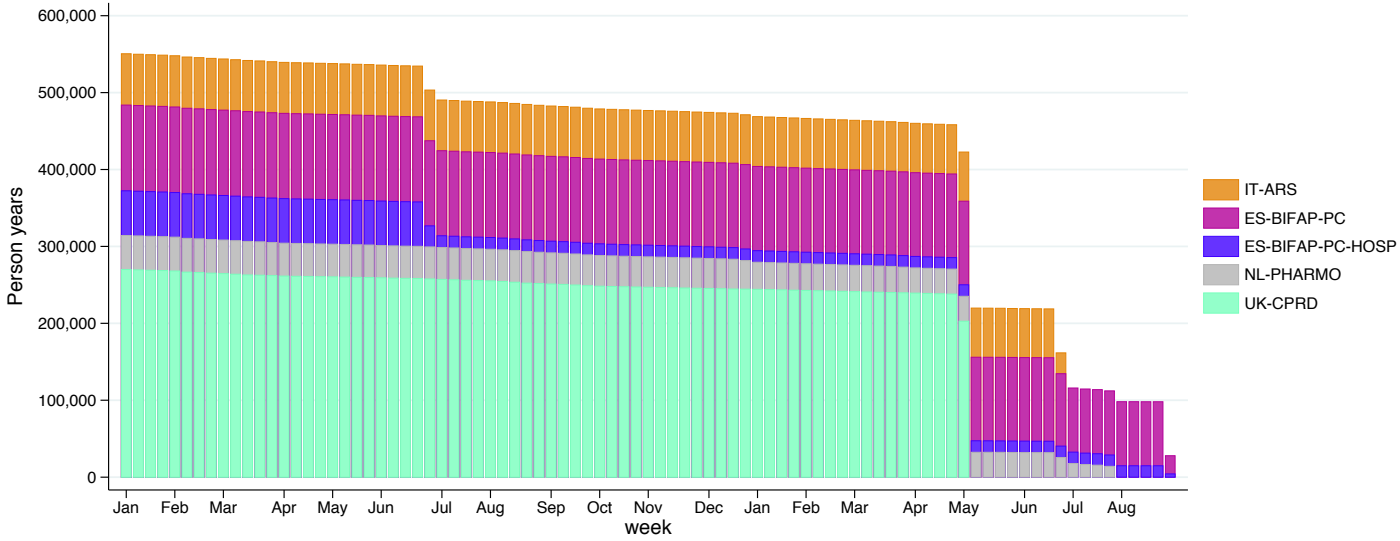


Figure 3 Person years of follow-up from 1/1/2020 till end of data by data source

Table 5 Attrition diagram 1: subjects included in the instance of the data source having insufficient data or not being in the data source at study start

Condition	ARS	BIFAP_PC	BIFAP_PC_HOSP	PHARMO	CPRD
Type of datasource	Record linkage of multiple data banks	Primary care medical records	Primary care medical records linked to hospital administrative records	Primary care medical records	Primary care medical records
Recommended end date	30jun2021	31aug2021	31aug2021	01aug2021	09may2021
Coding systems for diagnoses	ICD9CM	SNOMED, ICD9CM	I, ICD10CM	ICPC	SNOMED, RCD2
Attrition					
Persons in the instance of the data source	3,780,912	7,780,289	7,780,289	2,343,154	17,235,828
Sex or birth date missing or absurd, no dates of entry or exit	0	10	10	7	2,466
Death before study start	49,071	550,903	550,903	0	0
Exit from the data source before study start	201,310	1,283,926	4,143,292	1,446	1,862,872
Persons in the data source at study start	**3,530,531**	**5,945,450**	**3,086,084**	**2,341,701**	**15,370,491**
Less than 365 days history at 1//1/2020	40,908	128,895	51,158	29,247	1,268,965
Study population	**3,489,623**	**5,816,555**	**3,034,926**	**2,312,454**	**14,101,526**

Data sources used different vocabularies for diagnoses. In BIFAP-PC_HOSP many persons were excluded as the period for updated hospital data ended prior to study start, and a large share of persons were censored during the study period when updated hospital data ended.

Table 6 shows the characteristics of the study population at the start of the study. Median age at study start was highest in Tuscany (49 years), which may also explain the higher prevalence of at-risk conditions for severe COVID-19. Prevalence of risk factors and co-morbidities was quite similar for other conditions, although immunocompromised and cardiovascular disease status was highest in Tuscany.

At the start of the study 1/1/2020, 34% of the Tuscany population had one or more risk factors for severe COVID-19 disease, and this was around 25% in each of the other data sources (table 6). Median age was highest in Tuscany region (49) and BIFAP-HOSP regions (49).

Table 6 **Cohort characteristics at start of study (1/1/2020)**

Variable	Values	ARS		BIFAP_PC		BIFAP_PC_HOSP		PHARMO		CPRD	
Study population	N	3,489,623		5,816,555		3,034,926		2,312,454		14,101,526	
follow-up (years)	PY	5,103,641		9,336,755		2,422,922		3,117,555		17,825,614	
Age in years	Min	0		0		0		0		0	
	P25	29		27		30		23		23	
	P50	49		46		49		44		40	
	Mean	47		45		47		43		41	
	P75	66		63		65		61		58	
	Max	119		113		113		120		120	
Age in categories	0-4	113,669	3.3%	220,670	3.8%	97,779	3.2%	98,505	4.3%	698,613	5%
	5-11	211,885	6.1%	385,632	6.6%	174,324	5.7%	169,465	7.3%	1,137,333	8.1%
	12-17	185,910	5.3%	335,254	5.8%	154,293	5.1%	159,050	6.9%	914,983	6.5%
	18-24	212,915	6.1%	365,851	6.3%	174,301	5.7%	193,115	8.4%	1,124,457	8%
	25-29	155,684	4.5%	278,046	4.8%	133,298	4.4%	136,145	5.9%	958,862	6.8%
	30-39	359,062	10.3%	711,513	12.2%	346,769	11.4%	270,731	11.7%	2,075,853	14.7%
	40-49	521,342	14.9%	939,792	16.2%	473,541	15.6%	295,905	12.8%	1,940,625	13.8%
	50-59	562,496	16.1%	880,812	15.1%	482,679	15.9%	349,615	15.1%	1,965,633	13.9%
	60-69	448,863	12.9%	702,145	12.1%	412,271	13.6%	302,116	13.1%	1,446,722	10.3%
	70-79	401,694	11.5%	531,479	9.1%	312,825	10.3%	226,903	9.8%	1,129,563	8%
	80+	316,103	9.1%	465,361	8%	272,846	9%	110,904	4.8%	708,882	5%
	60+	1,166,660	33.4%	1,698,985	29.2%	997,942	32.9%	639,923	27.7%	3,285,167	23.3%
Person years across sex	Male	2,657,824	52.1	4,767,360	51.1	1,255,552	51.8	1,580,705	50.7	8,887,890	49.9
	Female	2,445,817	47.9	4,569,396	48.9	1,167,370	48.2	1,536,850	49.3	8,937,724	50.1
At risk population at January 1-2020	Cardiovascular disease	969,895	27.8%	1,107,931	19%	582,132	19.2%	452,131	19.6%	2,263,129	16%
	Cancer	84,142	2.4%	67,793	1.2%	55,848	1.8%	51,417	2.2%	165,691	1.2%
	Chronic lung disease	195,898	5.6%	248,979	4.3%	153,744	5.1%	144,273	6.2%	931,935	6.6%
	HIV	8,728	0.3%	702	0%	407	0%	2,519	0.1%	3,923	0%
	Chronic kidney disease	17,536	0.5%	16,539	0.3%	8,804	0.3%	13,093	0.6%	23,076	0.2%
	Diabetes	193,969	5.6%	323,509	5.6%	173,341	5.7%	110,086	4.8%	650,872	4.6%
	Severe obesity	5,391	0.2%	47,823	0.8%	31,973	1.1%	3,703	0.2%	87,926	0.6%
	Sickle cell disease	3,560	0.1%	2,882	0%	2,084	0.1%	827	0%	2,230	0%
	Use of immunosuppressants	207,855	6%	70,646	1.2%	45,631	1.5%	68,202	2.9%	53,977	0.4%
	Any risk factors	1,200,345	34.4%	1,392,185	23.9%	762,800	25.1%	605,829	26.2%	3,111,051	22.1%

*Based on diagnosis codes or proxy medicines as specified in the methods

Table 7 describes the characteristics at cohort entry of first dose of COVID-19 vaccine for IT-ARS. In ARS Tuscany, the Pfizer vaccine recipients had median age of 59 years, 49.8% was above 60 years, 21.9% above 80, 1.1% was between 12-17, 55% was female, more than 50% (56%) had any risk factor for sever covid-19 disease. Moderna vaccine recipients had median age 57 years, 0.7% was above 80, and 31.2% above 60, only 0.1% were between 12-17 years, 48.3% was female, 51.4% had any risk factor for severe covid-19. For AstraZeneca median age of recipients at first dose was 69 years, 71.6% was above 60 years of age and 0% above 80, most persons were between 60 and 79%, 56.7% were female. For Janssen vaccine recipients median age was 62, 86.7% was above 60, but only 0.3% was above 80. Most of the vaccine was administered in May-June 2021, 57% of people had a risk factor for severe covid-19.

Table 7 Cohort characteristics at study start 1/1/2020, and first dose of any COVID-19 vaccine in IT-ARS

Variable	Values	Baseline 1/1/2020 total population		Pfizer 1st dose		Moderna 1st dose		**AstraZeneca** 1st dose		Janssen 1st dose	
Persons 1st dose	N			1,320,326	69.6%	184,013	9.7%	332,872	17.6%	58,513	3.1%
follow-up 1st-2nd dose	PY			87,593	50.5%	13,726	7.9%	66,133	38.1%	6,140	3.5%
Month 1st vaccination				12		1		2		3	
2021 January	N			62,665	4.7%	2,984	1.6%	0	0%	0	0%
2021 February	N			68,773	5.2%	5,938	3.2%	48,174	14.5%	0	0%
2021 March	N			117,022	8.9%	28,654	15.6%	89,203	26.8%	1	0%
2021 April	N			248,304	18.8%	26,011	14.1%	110,435	33.2%	10,250	17.5%
2021 May	N			338,400	25.6%	60,291	32.8%	82,873	24.9%	24,871	42.5%
2021 June	N			483,579	36.6%	60,135	32.7%	2,187	0.7%	23,391	40%
2020 December	N			1,583	0.1%	0	0%	0	0%	0	0%
Age in years	Min			11		9		1		18	
	P25	29		48		39		57		60	
	P50	49		59		57		69		62	
	Mean	47		60		52		63		65	
	P75	66		76		64		74		69	
	Max	119		108		103		91		102	
Age in categories	0-4			0	0%	0	0%	1	0%	0	0%
	5-11	211,885	6.1%	1	0%	2	0%	1	0%	0	0%
	12-17	185,91	5.3%	13,924	1.1%	120	0.1%	0	0%	0	0%
	18-24	212,915	6.1%	61,759	4.7%	13,613	7.4%	2,004	0.6%	58	0.1%
	25-29	155,684	4.5%	37,391	2.8%	4,497	2.4%	5,606	1.7%	78	0.1%
	30-39	359,062	10.3%	103,599	7.8%	30,177	16.4%	15,756	4.7%	206	0.4%
	40-49	521,342	14.9%	148,244	11.2%	27,111	14.7%	34,948	10.5%	434	0.7%
	50-59	562,496	16.1%	297,275	22.5%	51,110	27.8%	36,370	10.9%	7,014	12%
	60-69	448,863	12.9%	216,806	16.4%	33,056	18%	79,766	24%	37,411	63.9%
	70-79	401,694	11.5%	152,143	11.5%	23,050	12.5%	158,292	47.6%	13,162	22.5%
	80+	316,103	9.1%	289,184	21.9%	1,277	0.7%	128	0%	150	0.3%
	60+	1,166,660	33.4%	658,133	49.8%	57,383	31.2%	238,186	71.6%	50,723	86.7%
Person years across sex	Female	2,657,824	52.1%	48,204	55%	6,628	48.3%	37,505	56.7%	3,244	52.8%
	Male	2,445,817	47.9%	39,389	45%	7,098	51.7%	28,628	43.3%	2,896	47.2%
At risk population at date of vaccination	Cardiovascular disease	969,895	27.8%	620,684	47%	70,923	38.5%	162,002	48.7%	28,471	48.7%
	Cancer	84,142	2.4%	57,368	4.3%	20,967	11.4%	8,821	2.6%	1,344	2.3%
	Chronic lung disease	195,898	5.6%	123,168	9.3%	16,360	8.9%	25,816	7.8%	4,191	7.2%
	HIV	8,728	0.3%	4,228	0.3%	1,779	1%	389	0.1%	78	0.1%
	Chronic kidney disease	17,536	0.5%	15,140	1.1%	4,210	2.3%	877	0.3%	120	0.2%
	Diabetes	193,969	5.6%	134,732	10.2%	19,235	10.5%	18,690	5.6%	3,254	5.6%
	Severe obesity	5,391	0.2%	5,101	0.4%	1,057	0.6%	589	0.2%	125	0.2%
	Sickle cell disease	3,56	0.1%	2,504	0.2%	603	0.3%	185	0.1%	19	0%
	Use of immunosuppressants	207,855	6%	192,122	14.6%	33,640	18.3%	42,622	12.8%	7,761	13.3%
	Any risk factors	1,200,345	34.4%	739,700	56%	94,645	51.4%	188,759	56.7%	33,550	57.3%

Table 8 describes characteristics at cohort entry of the cohort with a first dose of COVID-19 vaccine for the 4 regions of BIFAP-PC data. The majority of persons with first dose received Pfizer vaccine (70.3%) followed by Astrazeneca (13.4%) and Moderna (11.2%). The Pfizer vaccine recipients had median age of 51 years, 34.8% was above 60 years, 12.3% above 80, 6% was between 12-17, 52.5% was female, more than 38.3% had any risk factor for severe covid-19 disease. Moderna vaccine recipients had median age 49 years, 6.6% was above 80, and 23% above 60, only 5.6% were between 12-17 years, 52.2% was female, 32% had any risk factor for severe covid-19. For AstraZeneca median age of recipients at first dose was 61 years, 71.1% was above 60 years of age and 0% above 80, most persons were between 60 and 69, 54.8% were female and 41.7% had a risk factors for severe covid-19 disease. For Janssen vaccine recipients median age was 49, 18.1% was above 60, but only 0.2% was above 80. Most of the vaccine was administered in May-June 2021, 28% of people had a risk factor for severe covid-19. There were 233 vaccines without known brand. Comparison with population at baseline shows that the vaccinated population was older, and had more risk factors for severe covid-19 and more often female.

Table 8 Cohort characteristics at study start 1/1/2020, and first dose of any COVID-19 vaccine in ES- BIFAP-PC

Variable	Values	All population at 1/1/2020		Pfizer		Moderna		AstraZeneca		Janssen		Unknown brand	
Persons 1st dose	N			2,808,700	70.3%	447,401	11.2%	537,122	13.4%	201,543	5%	233	0%
follow-up 1st-2nd dose	PY			176,483	47.9%	36,474	9.9%	115,480	31.3%	40,061	10.9%	30	0%
Month of first vaccination				12		1		1		2		12	
2021 January	N			165,885	5.9%	4,263	1%	2	0%	0	0%	33	14.2%
2021 February	N			103,859	3.7%	18,075	4%	23,169	4.3%	2	0%	29	12.4%
2021 March	N			191,809	6.8%	26,920	6%	100,409	18.7%	4	0%	40	17.2%
2021 April	N			520,783	18.5%	50,584	11.3%	230,122	42.8%	14,564	7.2%	29	12.4%
2021 May	N			351,643	12.5%	129,507	28.9%	150,394	28%	37,012	18.4%	47	20.2%
2021 June	N			763,483	27.2%	51,301	11.5%	18,876	3.5%	110,723	54.9%	25	10.7%
2021 July	N			382,209	13.6%	103,590	23.2%	13,075	2.4%	34,312	17%	21	9%
2021 August	N			316,591	11.3%	63,161	14.1%	1,075	0.2%	4,926	2.4%	5	2.1%
2020 December	N			12,438	0.4%	0	0%	0	0%	0	0%	4	1.7%
Age in years	Min	0		2		3		5		9		13	
	P25	27		39		30		59		42		30	
	P50	46		51		49		61		49		47	
	Mean	45		53		47		58		50		50	
	P75	63		71		58		64		56		64	
	Max	113		112		103		101		102		102	
Age in categories	0-4	220,67	3.8%	10	0%	2	0%	0	0%	0	0%	0	0%
	5-11	385,632	6.6%	1,550	0.1%	278	0.1%	3	0%	1	0%	0	0%
	12-17	335,254	5.8%	168,143	6%	25,117	5.6%	102	0%	59	0%	4	1.7%
	18-24	365,851	6.3%	142,276	5.1%	53,718	12%	11,704	2.2%	5,049	2.5%	37	15.9%
	25-29	278,046	4.8%	109,504	3.9%	27,754	6.2%	11,452	2.1%	3,250	1.6%	15	6.4%
	30-39	711,513	12.2%	315,236	11.2%	65,785	14.7%	28,665	5.3%	12,150	6%	33	14.2%
	40-49	939,792	16.2%	566,889	20.2%	53,176	11.9%	39,664	7.4%	85,463	42.4%	32	13.7%
	50-59	880,812	15.1%	526,549	18.7%	119,088	26.6%	63,424	11.8%	59,002	29.3%	41	17.6%
	60-69	702,145	12.1%	197,008	7%	36,512	8.2%	381,833	71.1%	25,465	12.6%	22	9.4%
	70-79	531,479	9.1%	435,772	15.5%	36,625	8.2%	241	0%	10,614	5.3%	11	4.7%
	80+	465,361	8%	345,763	12.3%	29,346	6.6%	34	0%	490	0.2%	38	16.3%
	60+	1,698,985	29.2%	978,543	34.8%	102,483	23%	382,108	71.1%	36,569	18.1%	71	30.4%
Person years across sex	Female	4,767,360	51.1	92,692	52.5%	19,026	52.2%	63,238	54.8%	18,408	45.9%	19	63.3%
	Male	4,569,396	48.9	83,791	47.5%	17,448	47.8%	52,241	45.2%	21,653	54.1%	11	36.7%
At risk population at date of vaccination	Cardiovascular disease	1,107,931	19%	851,851	30.3%	105,818	23.7%	174,031	32.4%	38,866	19.3%	64	27.5%
	Cancer	67,793	1.2%	66,405	2.4%	13,867	3.1%	11,595	2.2%	3,158	1.6%	1	0.4%
	Chronic lung disease	248,979	4.3%	224,775	8%	30,356	6.8%	38,438	7.2%	12,181	6%	21	9%
	HIV	702	0%	749	0%	238	0.1%	131	0%	64	0%	0	0%
	Chronic kidney disease	16,539	0.3%	22,730	0.8%	2,447	0.5%	2,169	0.4%	536	0.3%	0	0%
	Diabetes	323,509	5.6%	252,396	9%	31,789	7.1%	56,447	10.5%	12,571	6.2%	12	5.2%
	Severe obesity	47,823	0.8%	49,821	1.8%	6,567	1.5%	10,447	1.9%	3,835	1.9%	2	0.9%
	Sickle cell disease	2,882	0%	2,373	0.1%	413	0.1%	312	0.1%	113	0.1%	0	0%
	Use of immunosuppressants	70,646	1.2%	84,441	3%	13,704	3.1%	14,889	2.8%	4,831	2.4%	4	1.7%
	Any risk factors	1,392,185	23.9%	1,076,081	38.3%	143,137	32%	223,772	41.7%	56,637	28.1%	80	34.3%

The BIFAP-PC-Hosp population is a subpopulation of the PC population, and is limited to the regions who can link data, follow-up stops earlier, because of lack of hospitalization data updates. Table 9 describes the characteristics of the population, the majority of vaccinated persons received Pfizer vaccine (65.7%)

Table 9 Cohort characteristics at study start 1/1/2020, and first dose of any COVID-19 vaccine in ES- BIFAP-PC HOSP

Variable	Values	Total Population at 1/1/2020		Pfizer		Moderna		AstraZeneca		Janssen	
Persons with a first dose	N			353,509	65.7%	74,275	13.8%	78,602	14.6%	31,993	5.9%
Person-years of follow-up between first and second dose	PY			22,816	44.6%	5,570	10.9%	16,142	31.5%	6,670	13%
Month of first vaccination				12		1		2		4	
2021 January	N			9,550	2.7%	1,002	1.3%	0	0%	0	0%
2021 February	N			7,352	2.1%	2,528	3.4%	714	0.9%	0	0%
2021 March	N			9,350	2.6%	5,853	7.9%	2,731	3.5%	0	0%
2021 April	N			55,960	15.8%	10,935	14.7%	26,217	33.4%	1,472	4.6%
2021 May	N			62,043	17.6%	26,470	35.6%	31,451	40%	5,043	15.8%
2021 June	N			109,695	31%	2,240	3%	9,824	12.5%	18,071	56.5%
2021 July	N			57,152	16.2%	12,745	17.2%	7,523	9.6%	5,421	16.9%
2021 August	N			41,275	11.7%	12,502	16.8%	142	0.2%	1,986	6.2%
2020 December	N			1,132	0.3%	0	0%	0	0%	0	0%
Age in years	Min	0		4		11		16		15	
	P25	30		35		29		60		43	
	P50	49		47		52		63		50	
	Mean	47		48		49		62		52	
	P75	65		61		67		65		61	
	Max	113		105		103		85		102	
Age in categories	0-4	97,779	3.2%	1	0%	0	0%	0	0%	0	0%
	5-11	174,324	5.7%	1,347	0.4%	267	0.4%	0	0%	0	0%
	12-17	154,293	5.1%	23,562	6.7%	5,447	7.3%	1	0%	1	0%
	18-24	174,301	5.7%	21,312	6%	8,955	12.1%	303	0.4%	107	0.3%
	25-29	133,298	4.4%	16,087	4.6%	4,109	5.5%	493	0.6%	98	0.3%
	30-39	346,769	11.4%	53,347	15.1%	6,503	8.8%	1,456	1.9%	1,591	5%
	40-49	473,541	15.6%	83,748	23.7%	5,288	7.1%	2,043	2.6%	13,711	42.9%
	50-59	482,679	15.9%	64,638	18.3%	23,882	32.2%	7,807	9.9%	7,457	23.3%
	60-69	412,271	13.6%	19,174	5.4%	3,758	5.1%	66,474	84.6%	6,461	20.2%
	70-79	312,825	10.3%	53,033	15%	9,382	12.6%	23	0%	2,408	7.5%
	80+	272,846	9%	17,260	4.9%	6,684	9%	2	0%	159	0.5%
	60+	997,942	32.9%	89,467	25.3%	19,824	26.7%	66,499	84.6%	9,028	28.2%
Person years across sex	Female	1,255,552	51.8	11,810	51.8%	2,981	53.5%	8,623	53.4%	3,172	47.5%
	Male	1,167,370	48.2	11,007	48.2%	2,589	46.5%	7,519	46.6%	3,499	52.5%
At risk population at date of vaccination	Cardiovascular disease	582,132	19.2%	86,275	24.4%	20,046	27%	30,992	39.4%	7,280	22.8%
	Cancer	55,848	1.8%	10,030	2.8%	2,112	2.8%	2,825	3.6%	748	2.3%
	Chronic lung disease	153,744	5.1%	29,729	8.4%	5,495	7.4%	6,762	8.6%	2,384	7.5%
	HIV	407	0%	123	0%	71	0.1%	34	0%	17	0.1%
	Chronic kidney disease	8,804	0.3%	2,070	0.6%	577	0.8%	448	0.6%	114	0.4%
	Diabetes	173,341	5.7%	25,232	7.1%	5,615	7.6%	9,978	12.7%	2,249	7%
	Severe obesity	31,973	1.1%	3,004	0.8%	634	0.9%	662	0.8%	304	1%
	Sickle cell disease	2,084	0.1%	255	0.1%	78	0.1%	79	0.1%	17	0.1%
	Use of immunosuppressants	45,631	1.5%	9,859	2.8%	1,741	2.3%	2,576	3.3%	875	2.7%
	Any risk factors	762,8	25.1%	118,339	33.5%	25,906	34.9%	38,757	49.3%	10,208	31.9%

Table 10 describes characteristics at cohort entry of the cohort with a first dose of COVID-19 vaccine for PHARMO-PC data. The majority of persons with first dose received Pfizer vaccine (67.6%) followed by Astrazeneca (8.2%) and Moderna (8.1%), Janssen was only used by 2.7% of vaccinated, 13.5% of vaccines had unknown brand. The Pfizer vaccine recipients had median age of 56 years, 40.9% was above 60 years, 6.4% above 80, 4.6% was between 12-17, 51.5% was female, 44.2% had any risk factor for severe covid-19 disease. Moderna vaccine recipients were much younger than Pfizer recipients and had median age 47 years and concentrated in middle ages, 1.2% was above 80, and 4.5% above 60, only 0.2% were between 12-17 years, 48% was female, only 28.8% had any risk factor for severe covid-19.
For AstraZeneca median age of recipients at first dose was high at 62 years, 89.2%% was above 60 years of age and only 1.9% above 80, most persons were between 60 and 79, 59.5% were female and 54% had a risk factors for severe covid-19 disease. For Janssen vaccine recipients median age was very young at 26, 1.4% was above 60, but only 0.1% was above 80. Most of the Janssen vaccine was administered in June and July 2021, 9% of people had a risk factor for severe covid-19.

Table 10 Cohort characteristics at study start 1/1/2020, and first dose of any COVID-19 vaccine in NL-PHARMO

Variable	Values	total population at 1/1/2020		Pfizer		Moderna		AstraZeneca		Janssen		Unknown manufacturer	
Persons with a first dose	N			568,119	67.6%	67,689	8.1%	68,655	8.2%	22,455	2.7%	113,201	13.5%
Person-years of follow-up 1st and 2nd dose	PY			59,305	59.3%	5,551	5.6%	14,211	14.2%	1,603	1.6%	19,309	19.3%
Month of first vaccination				1		1		1		1		1	
2021 January	N			465	0.1%	415	0.6%	8	0%	1	0%	1,113	1%
2021 February	N			1,570	0.3%	520	0.8%	5,769	8.4%	1	0%	7,132	6.3%
2021 March	N			29,649	5.2%	991	1.5%	13,291	19.4%	7	0%	14,735	13%
2021 April	N			106,777	18.8%	876	1.3%	21,970	32%	123	0.5%	34,916	30.8%
2021 May	N			139,336	24.5%	21,236	31.4%	19,590	28.5%	339	1.5%	30,832	27.2%
2021 June	N			185,136	32.6%	20,465	30.2%	7,006	10.2%	12,863	57.3%	18,977	16.8%
2021 July	N			104,323	18.4%	23,152	34.2%	1,021	1.5%	9,116	40.6%	5,493	4.9%
2021 August	N			863	0.2%	34	0.1%	0	0%	5	0%	3	0%
Age in years	Min	0		2		15		7		17		1	
	P25	23		37		36		60		21		53	
	P50	44		56		47		62		26		62	
	Mean	43		54		45		61		32		59	
	P75	61		71		54		63		45		66	
	Max	120		105		108		103		95		105	
Age in categories	0-4	98,505	4.3%	1	0%	0	0%	0	0%	0	0%	8	0%
	5-11	169,465	7.3%	16	0%	0	0%	2	0%	0	0%	18	0%
	12-17	159,05	6.9%	25,858	4.6%	140	0.2%	18	0%	298	1.3%	866	0.8%
	18-24	193,115	8.4%	35,607	6.3%	7,299	10.8%	500	0.7%	10,136	45.1%	4,927	4.4%
	25-29	136,145	5.9%	26,007	4.6%	3,769	5.6%	370	0.5%	2,870	12.8%	2,863	2.5%
	30-39	270,731	11.7%	66,433	11.7%	9,351	13.8%	1,011	1.5%	2,665	11.9%	6,036	5.3%
	40-49	295,905	12.8%	71,856	12.6%	19,666	29.1%	1,821	2.7%	1,456	6.5%	8,457	7.5%
	50-59	349,615	15.1%	109,862	19.3%	24,485	36.2%	3,617	5.3%	4,697	20.9%	16,101	14.2%
	60-69	302,116	13.1%	73,675	13%	1,530	2.3%	59,144	86.1%	230	1%	52,002	45.9%
	70-79	226,903	9.8%	122,296	21.5%	662	1%	841	1.2%	70	0.3%	14,239	12.6%
	80+	110,904	4.8%	36,508	6.4%	787	1.2%	1,331	1.9%	33	0.1%	7,684	6.8%
	60+	639,923	27.7%	232,479	40.9%	2,979	4.5%	61,316	89.2%	333	1.4%	73,925	65.3%
Person years across sex	Female	1,580,705	50.7	30,548	51.5%	2,667	48%	7,032	49.5%	627	39.1%	10,863	56.3%
	Male	1,536,850	49.3	28,758	48.5%	2,884	52%	7,179	50.5%	976	60.9%	8,446	43.7%
At risk population at date of vaccination	Cardiovascular disease	452,131	19.6%	190,844	33.6%	11,025	16.3%	28,541	41.6%	1,177	5.2%	39,949	35.3%
	Cancer	51,417	2.2%	29,099	5.1%	2,527	3.7%	4,040	5.9%	165	0.7%	6,168	5.4%
	Chronic lung disease	144,273	6.2%	60,974	10.7%	6,081	9%	8,882	12.9%	547	2.4%	12,633	11.2%
	HIV	2,519	0.1%	1,076	0.2%	193	0.3%	189	0.3%	16	0.1%	185	0.2%
	Chronic kidney disease	13,093	0.6%	9,155	1.6%	278	0.4%	1,041	1.5%	16	0.1%	2,494	2.2%
	Diabetes	110,086	4.8%	48,399	8.5%	3,438	5.1%	7,864	11.5%	237	1.1%	9,977	8.8%
	Severe obesity	3,703	0.2%	3,015	0.5%	385	0.6%	1,025	1.5%	57	0.3%	672	0.6%
	Sickle cell disease	827	0%	242	0%	46	0.1%	28	0%	2	0%	52	0%
	Use of immunosuppressants	68,202	2.9%	37,848	6.7%	3,403	5%	5,468	8%	238	1.1%	9,039	8%
	Any risk factors	605,829	26.2%	251,069	44.2%	19,526	28.8%	37,119	54.1%	2,103	9.4%	54,226	47.9%

Table 11 describes characteristics at cohort entry of the cohort with a first dose of COVID-19 vaccine for CPRD data, which was updated until may 2021. The majority of persons with first dose received AstraZeneca vaccine (66.8%) followed by Pfizer (32.8%) and Moderna (0.5%), there was no use of Janssen vaccine. The Pfizer vaccine recipients had median age of 65 years, 59% was above 60 years, 20.1 % above 80, 0.7% was between 12-17, 58% was female, 59% had any risk factor for severe covid-19 disease. Moderna vaccine recipients were much younger than Pfizer recipients and had median age 46 years and concentrated in ages 40-49, 0% was above 80, and 0.7% above 60, only 0.1% were between 12-17 years, 45% was female, only 13% had any risk factor for severe covid-19.
For AstraZeneca median age of recipients at first dose was high at 56 years, 39.1% was above 60 years of age and only 3.9% above 80, most persons were between 60 and 79, 52.7% were female and 42% had a risk factors for severe covid-19 disease.

Table 11 Cohort characteristics at study start 1/1/2020, and first dose of any COVID-19 vaccine in UK-CPRD

Variable	Values	Total population at 1/1/2020		Pfizer		Moderna		AstraZeneca	
Persons with a first dose	N			1,801,355	32.8%	27,023	0.5%	3,671,672	66.8%
Person-years of follow-up between first and second dose	PY			351,696	37.2%	1,172	0.1%	592,811	62.7%
Month of first vaccination				12		1		12	
2021 January	N			855,054	47.5%	10	0%	508,269	13.8%
2021 February	N			649,482	36.1%	9	0%	1,077,156	29.3%
2021 March	N			71,747	4%	9	0%	1,669,343	45.5%
2021 April	N			32,454	1.8%	22,981	85%	326,638	8.9%
2021 May	N			7,684	0.4%	4,014	14.9%	90,114	2.5%
2020 December	N			184,934	10.3%	0	0%	152	0%
Age in years	Min	0		1		16		4	
	P25	23		50		44		47	
	P50	40		65		46		56	
	Mean	41		62		45		56	
	P75	58		77		48		66	
	Max	120		111		92		110	
Age in categories	0-4	698,613	5%	10	0%	0	0%	1	0%
	5-11	1,137,333	8.1%	17	0%	0	0%	13	0%
	12-17	914,983	6.5%	12,412	0.7%	25	0.1%	3,843	0.1%
	18-24	1,124,457	8%	47,584	2.6%	551	2%	88,712	2.4%
	25-29	958,862	6.8%	50,177	2.8%	532	2%	84,502	2.3%
	30-39	2,075,853	14.7%	134,641	7.5%	531	2%	277,494	7.6%
	40-49	1,940,625	13.8%	199,681	11.1%	24,619	91.1%	713,969	19.4%
	50-59	1,965,633	13.9%	294,015	16.3%	564	2.1%	1,064,781	29%
	60-69	1,446,722	10.3%	322,598	17.9%	155	0.6%	771,523	21%
	70-79	1,129,563	8%	378,051	21%	35	0.1%	522,022	14.2%
	80+	708,882	5%	362,169	20.1%	11	0%	144,812	3.9%
	60+	3,285,167	23.3%	1,062,818	59%	201	0.7%	1,438,357	39.1%
Person years across sex	Female	8,887,890	49.9	204,369	58.1%	526	44.9%	312,481	52.7%
	Male	8,937,724	50.1	147,327	41.9%	646	55.1%	280,330	47.3%
At risk population at date of vaccination	Cardiovascular disease	2,263,129	16%	851,748	47.3%	1,856	6.9%	1,137,992	31%
	Cancer	165,691	1.2%	94,608	5.3%	139	0.5%	110,744	3%
	Chronic lung disease	931,935	6.6%	281,204	15.6%	1,494	5.5%	452,459	12.3%
	HIV	3,923	0%	1,504	0.1%	5	0%	2,614	0.1%
	Chronic kidney disease	23,076	0.2%	15,143	0.8%	1	0%	13,872	0.4%
	Diabetes	650,872	4.6%	255,170	14.2%	138	0.5%	327,116	8.9%
	Severe obesity	87,926	0.6%	34,650	1.9%	239	0.9%	60,182	1.6%
	Sickle cell disease	2,23	0%	1,065	0.1%	0	0%	1,066	0%
	Use of immunosuppressants	53,977	0.4%	26,324	1.5%	46	0.2%	37,658	1%
	Any risk factors	3,111,051	22.1%	1,068,639	59.3%	3,600	13.3%	1,547,474	42.1%

3.2 Vaccinations and coverage in the population

Table 12 describes the vaccine recipients in each data source by dose. Overall, 12,117,458 persons received a first dose of a covid-vaccine (47.1%) (excluding unknown vaccines manufacturers). Percentage was highest in BIFAP (68.7%). In BIFAP the majority of persons also had received a second dose for each of the vaccine brands. Percentage of full primary regimen of 2-dose primary regimens were lower in other data sources, in particular for AstraZeneca in CPRD, as this vaccine also had the highest distance between dose 1 and 2 in each data source. mRNA vaccines had a short distance between dose 1 and 2 in all sites except for CPRD, where Pfizer also had a mean of 76 days between dose 1 and 2, but only 28 days for Moderna vaccine. In this data instance heterologous schedules were very rare.

Table 12 Vaccine regimens by dose, data source and brand

Dose	Measure	ARS		BIFAP_PC		BIFAP_PC_HOSP		PHARMO		CPRD		Total	
Study population	N	3489623		5816555		3034926		2312454		14101526		25720158	
AstraZeneca dose 1, % of total population	Persons	332872	9,5%	537122	9,2%	78602	2,6%	68655	3,0%	3671672	26,0%	4610321	17,9%
AstraZeneca dose 2, % of 1st dose	Persons	187052	56%	397186	74%	59342	75%	28779	42%	1172745	32%	1785762	39%
Other vaccine dose 2, % of first dose	Persons	7150	2%	7298	1%	368	0%	0	0%	3113	0%	17561	0%
Amongst persons with AstraZeneca dose 2 distance	Min	20		14		21		70		14			
Amongst persons with AstraZeneca dose 2 distance	P25	84		71		70		76		70			
Amongst persons with AstraZeneca dose 2 distance	P50	84		82		76		77		77			
Amongst persons with AstraZeneca dose 2 distance	P75	84		84		84		84		78			
Amongst persons with AstraZeneca dose 2 distance	Max	126		193		166		155		127			
Janssen dose 1, % of total population	Persons	58513	1,7%	201543	3,5%	31993	1,1%	22455	1,0%			282511	1,1%
Janssen dose 2, % of 1st dose	Persons	0		0		0		0				0	
Other vaccine dose 2, % of 1st dose	Persons	0		63	0,0%	11	0,0%	15	0,1%			78	0,0%
Moderna dose 1, % of total population	Persons	184013	5,3%	447401	7,7%	74275	2,4%	67689	2,9%	27023	0,2%	726126	2,8%
Moderna dose 2, % of 1st dose	Persons	100673	54,7%	363226	81,2%	60459	81,4%	25638	37,9%	<5		489540	67,4%
Other vaccine dose 2, % of 1st dose	Persons	125	0,1%	590	0,1%	37	0,0%	0	0,0%	9	0,0%	718	0,1%
Amongst persons with Moderna dose 2 distance	Min	16		14		14		21		28			
Amongst persons with Moderna dose 2 distance	P25	28		28		28		35		28			
Amongst persons with Moderna dose 2 distance	P50	28		28		28		35		28			
Amongst persons with Moderna dose 2 distance	P75	28		28		28		35		44			
Amongst persons with Moderna dose 2 distance	Max	124		224		224		160		91			
Pfizer dose 1, % of total population	Persons	1320326	37,8%	2808700	48,3%	353509	11,6%	568119	24,6%	1801355	12,8%	6498500	25,3%
Pfizer dose 2, % of 1st dose	Persons	653580	49,5%	2372395	84,5%	308848	87,4%	232351	40,9%	1332285	74,0%	4590611	70,6%
Other vaccine dose 2, % of 1st dose	Persons	138	0,0%	1179	0,0%	30	0,0%	0	0,0%	6226	0,3%	7543	0,2%
Amongst persons with Pfizer dose 2 distance	Min	14		14		14		21		14			
Amongst persons with Pfizer dose 2 distance	P25	21		21		21		35		70			
Amongst persons with Pfizer dose 2 distance	P50	21		21		21		35		76			
Amongst persons with Pfizer dose 2 distance	P75	21		21		21		36		78			
Amongst persons with Pfizer dose 2 distance	Max	174		244		210		169		147			
Total first doses , % of total population	**Persons**	**1895724**	**54,3%**	**3994766**	**68,7%**	**538379**	**17,7%**	**726918**	**31,4%**	**5500050**	**39,0%**	**12117458**	**47,1%**

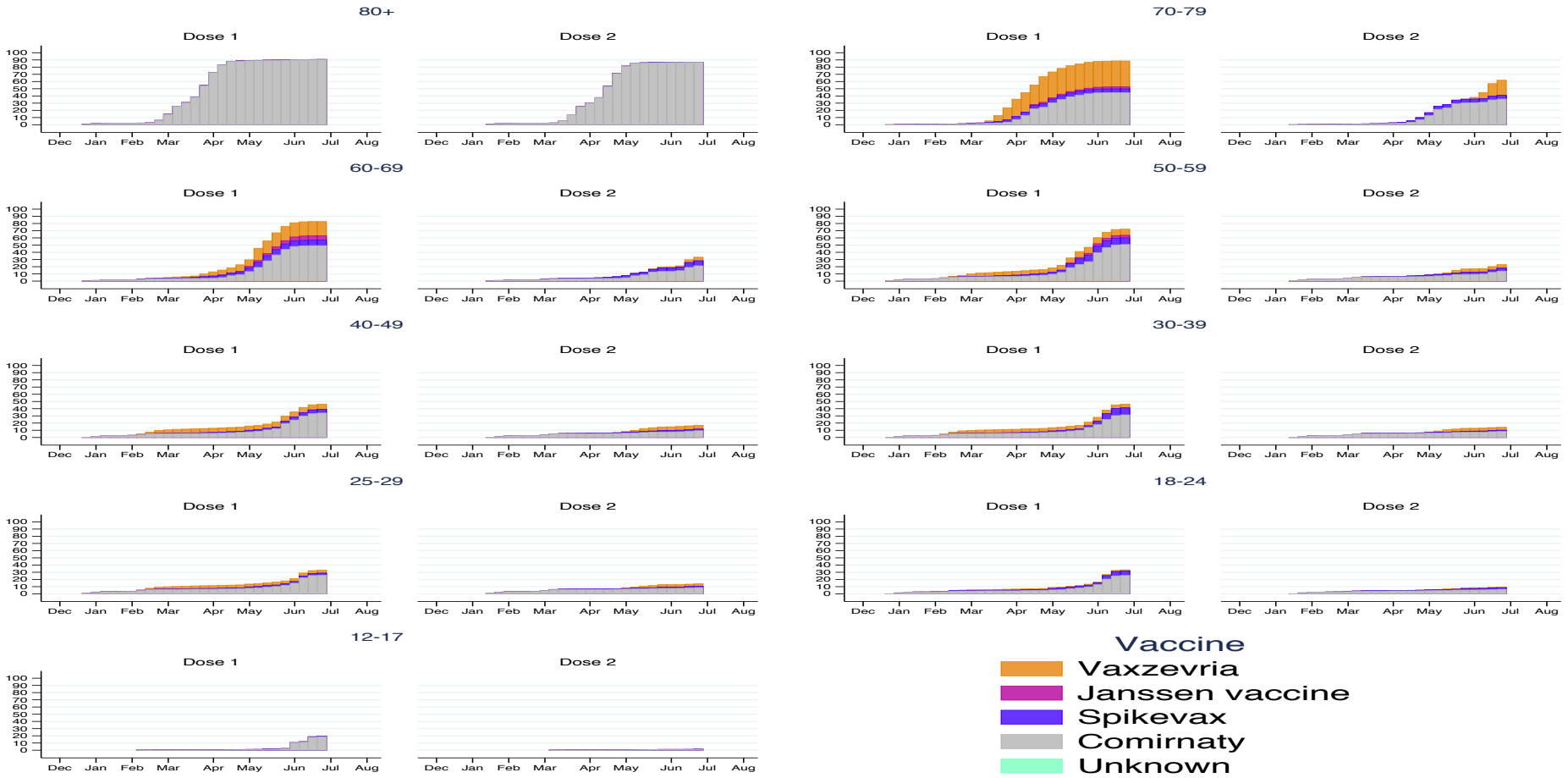


Figure 4 Overall Uptake of COVID-19 vaccines dose 1 and 2 in ARS Tuscany by age and dose

Figure 4 shows the cumulative coverage of covid-19 vaccines by age and dose in Tuscany, it shows the early roll out of Pfizer vaccine to 80+, and subsequent targeting of younger age groups, Vaxzevria was used mostly in 60-79. Dose 2 was highest in older people and low in the younger age groups.

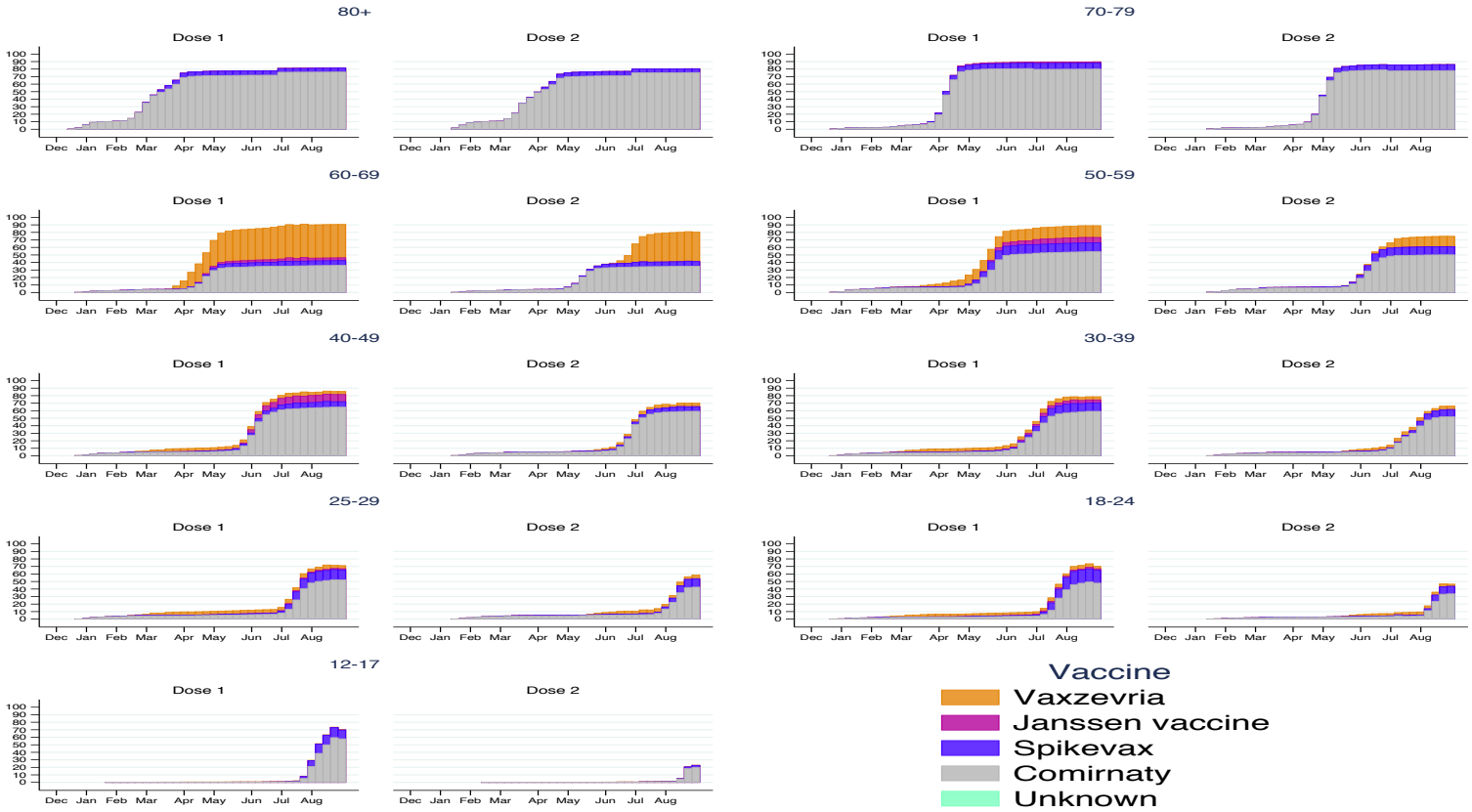


Figure 5 Overall Uptake of COVID-19 vaccines dose 1 and 2 in BIFAP PC by age and dose

Figure 5 shows the cumulative coverage of covid-19 vaccines by age and dose in BIFAP PC, it shows the early roll out of Pfizer vaccine to 80+, and subsequent targeting of younger age groups, Vaxzevria was used mostly in 60-69. Dose 2 coverage was highest in older people and became gradually higher in the younger age groups.

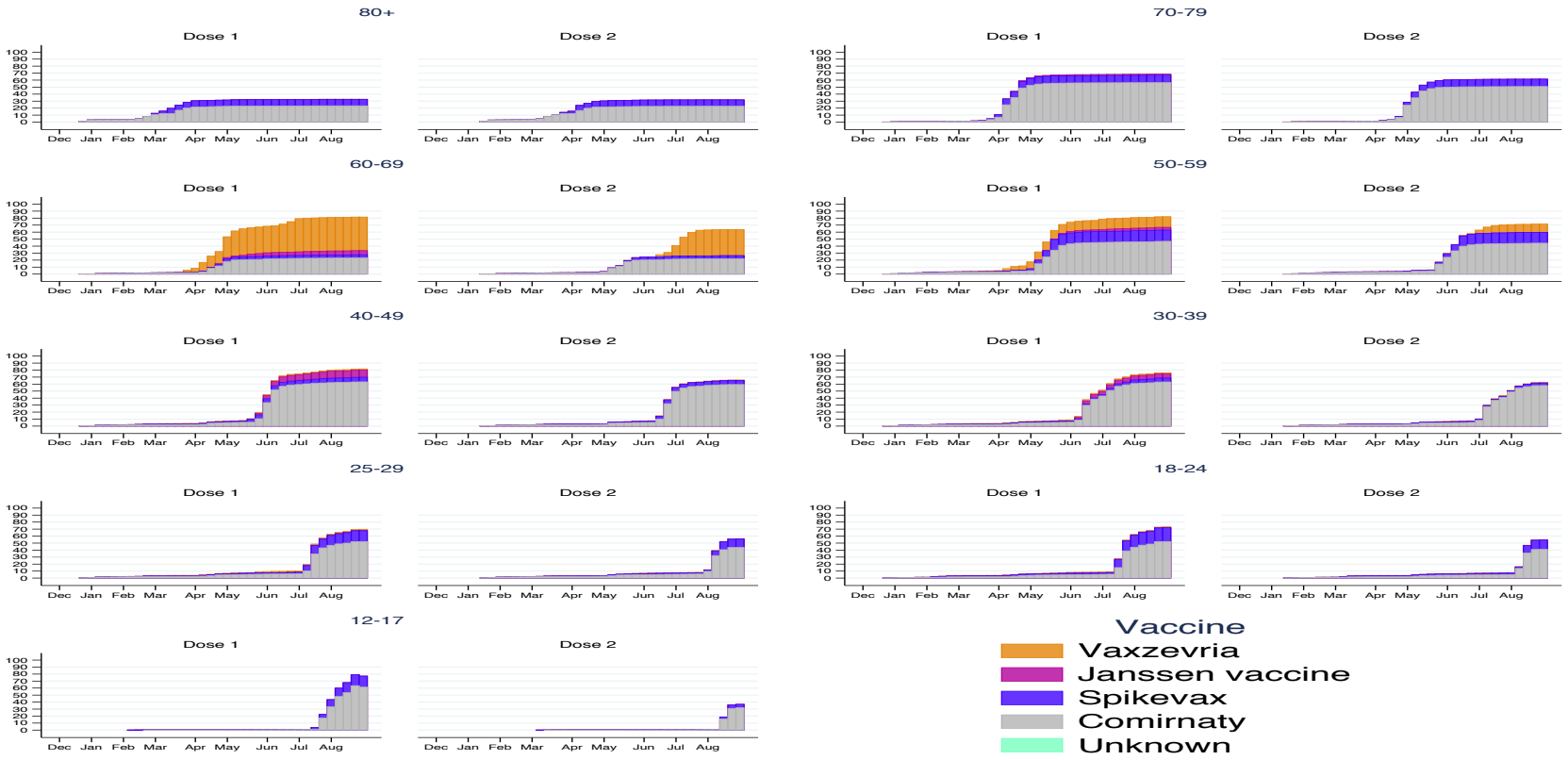


Figure 6 Overall Uptake of COVID-19 vaccines dose 1 and 2 in BIFAP PC-HOSP by age and dose

Figure 6 shows the cumulative coverage of covid-19 vaccines by age and dose in BIFAP PC-HOSP, it shows relatively low coverage in the 80+ which is an error that will be corrected for a manuscript (lack of inclusion of vaccines given in frail elderly in one region), and subsequent targeting of younger age groups, Vaxzevria was used mostly in 60-69. Dose 2 was highest in older people and lower in the younger age groups.

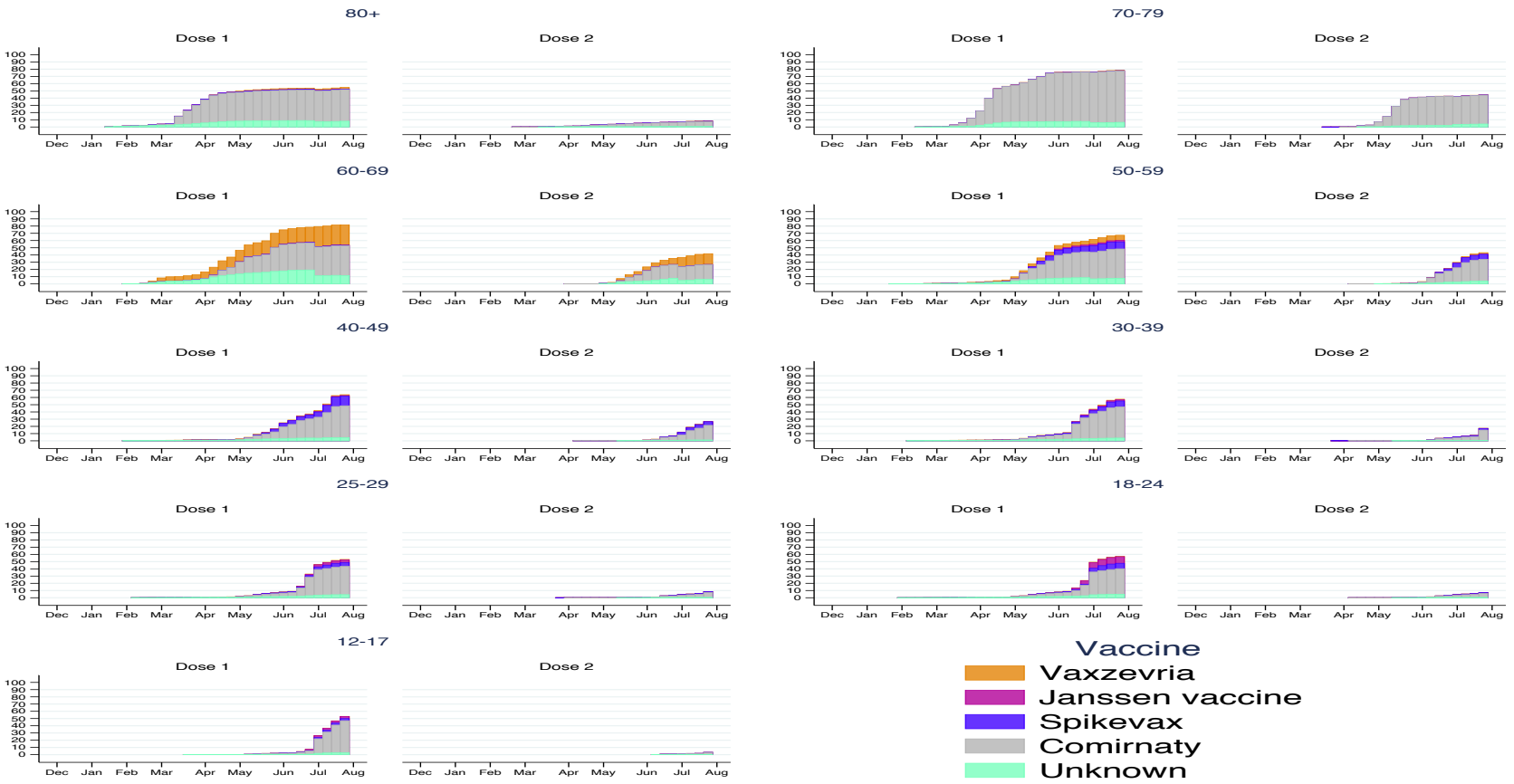


Figure 7 Overall Uptake of COVID-19 vaccines dose 1 and 2 in PHARMO by age and dose

Figure 7 shows the cumulative coverage of covid-19 vaccines by age and dose in PHARMO, it shows relatively moderate coverage in the 80+ with very little information on dose 2, most of these vaccines were provided in long term care facilities in frail elderly and may not have been sent to GPs. Coverage in other age groups is consistent with roll out of the campaign and use of vaccines and subsequent targeting of younger age groups, dose 2 information was still very low. Unknown vaccine brands were most prevalent in older age groups.

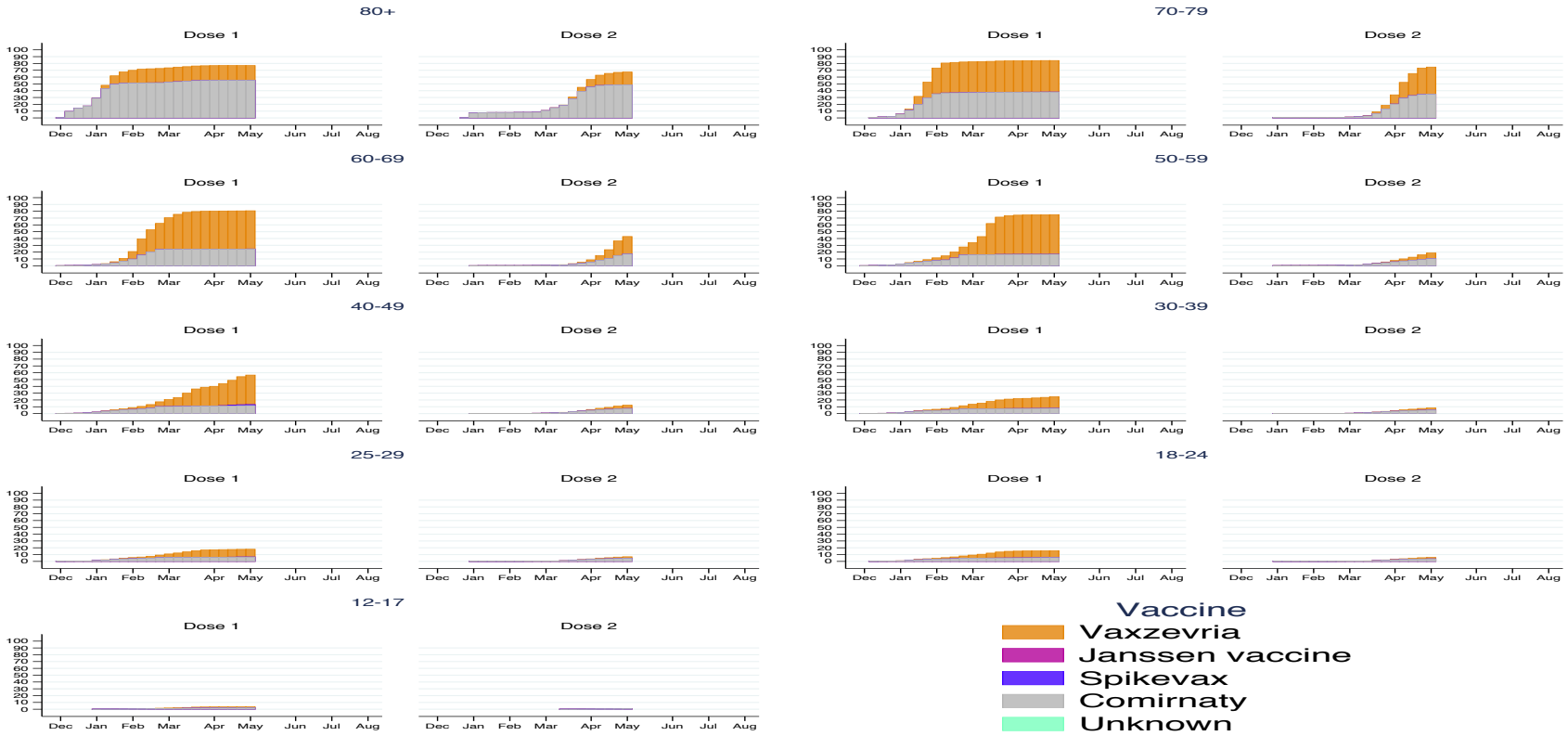


Figure 8 Overall Uptake of COVID-19 vaccines dose 1 and 2 in CPRD by age and dose

Figure 8 shows the cumulative coverage of covid-19 vaccines by age and dose in CPRD, it shows high coverage older age groups, and the distribution of different brands. Coverage in other age groups is consistent with roll out of the campaign and use of vaccines and subsequent targeting of younger age groups, dose 2 information was still very low.

3.3 Cases

Table 13 shows the number of incident cases recorded in both 2020 and 2021. AESIs for which no ICPC code exist are not estimated (n.e). ICD9/10, SNOMED and ICPC code counts and the provenance of the code are listed in annex 1.

Table 13 Number of incident cases during study period by calendar year and data source

system	AESI	year	ARS	BIFAP_PC	BIFAP_PC_HOSP	PHARMO	CPRD
Auto-immune diseases	Guillain Barre Syndrome	2020	150	78	64	28	653
	Guillain Barre Syndrome	2021	56	51	15	14	223
	Acute disseminated myelitis	2020	7	31	16	n.e	568
	Acute disseminated myelitis	2021	<5	20	<5	n.e	218
	Narcolepsy	2020	5	79	17	n.e	603
	Narcolepsy	2021	<5	39	6	n.e	163
	Acute Aseptic Arthritis	2020	0	0	0	n.e	0
	Acute Aseptic Arthritis	2021	0	0	0	n.e	0
	Thrombocytopenia	2020	1,182	2,112	760	70	8,745
	Thrombocytopenia	2021	577	2,113	251	53	3,488
Cardiovascular system	Microangiopathy	2020	13	12	8	n.e	321
	Microangiopathy	2021	7	16	8	n.e	95
	Heart failure	2020	36,087	13,302	9,219	3,692	74,856
	Heart failure	2021	17,763	11,168	3,626	1,898	27,653
	Stress Cardiomyopathy	2020	266	8	17	n.e	579
	Stress Cardiomyopathy	2021	99	5	<5	n.e	177
	Coronary artery disease	2020	13,359	5,557	3,936	3,297	43,515
	Coronary artery disease	2021	5,644	3,740	1,179	1,589	14,150
	Arrhythmia	2020	52,779	36,695	15,710	20,630	202,129
	Arrhythmia	2021	24,390	28,956	5,168	10,742	66,870
	Myocarditis or pericarditis	2020	1,437	912	464	362	3,073
	Myocarditis or pericarditis	2021	612	654	145	156	1,073
	Myocarditis	2020	230	109	65	362	831
	Myocarditis	2021	106	79	19	156	263
	Pericarditis	2020	1,207	802	412	0	2,269
	Pericarditis	2021	506	576	131	0	832
Blood	Disseminated intravascular coagulation	2020	46	10	0	n.e	16
	Disseminated intravascular coagulation	2021	16	6	0	n.e	6
	Venous thromboembolism	2020	8,752	8,847	4,962	3,717	32,997
	Venous thromboembolism	2021	4,677	6,891	1,310	1,910	11,118
	Thrombotic microangiopathy	2020	13	32	9	n.e	180
	Thrombotic microangiopathy	2021	7	19	6	n.e	66
	Hemorrhagic stroke	2020	4,140	1,150	841	184	6,467
	Hemorrhagic stroke	2021	1,762	854	312	137	2,012
	Ischemic stroke	2020	11,718	8,450	5,401	896	38,600
	Ischemic stroke	2021	5,463	6,149	1,901	391	12,440
	Cerebral venous sinus thrombosis	2020	40	18	14	n.e	58
	Cerebral venous sinus thrombosis	2021	13	5	<5	n.e	34
	Single Organ Cutaneous Vasculitis	2020	189	271	121	n.e	1,841
	Single Organ Cutaneous Vasculitis	2021	68	214	13	n.e	442

system	AESI	year	ARS	BIFAP_PC	BIFAP_PC_HOSP	PHARMO	CPRD
Hepato-gastrointestinal and renal system	Acute Liver Injury	2020	806	446	293	n.e	1,588
	Acute Liver Injury	2021	311	346	69	n.e	458
	Acute Kidney Injury	2020	12,281	4,174	1,929	n.e	39,453
	Acute Kidney Injury	2021	5,161	3,612	463	n.e	16,513
Nerves and central nervous system	Generalized convulsions	2020	8,437	2,834	1,779	447	31,848
	Generalized convulsions	2021	3,666	1,739	479	153	10,069
	Meningoencephalitis	2020	257	255	153	31	1,420
	Meningoencephalitis	2021	101	200	34	13	504
	Transverse myelitis	2020	42			n.e	467
	Transverse myelitis	2021	32			n.e	169
	Bell's palsy	2020	1,005	1,894	707	672	0
	Bell's palsy	2021	505	1,159	264	349	0
Respiratory system	Acute respiratory distress	2020	3,077	4,043	1,987	n.e	2,052
	Acute respiratory distress	2021	2,906	3,165	196	n.e	537
Skin and mucous membrane, bone and joints system	Erythema multiforme	2020	156	239	94	n.e	1,154
	Erythema multiforme	2021	66	135	13	n.e	315
	Chilblain	2020	7	1,569	533	653	2,318
	Chilblain	2021	8	2,109	524	872	3,385
Other systems	Anosmia/dysgeusia	2020	<5	n.e	n.e	1,149	26,552
	Anosmia/dysgeusia	2021	<5	n.e	n.e	627	3,596
	Anaphylaxis	2020	613	369	147	157	2,069
	Anaphylaxis	2021	347	329	9	74	884
	Sudden death	2020	61	75	5	n.e	10,079
	Sudden death	2021	26	49	0	n.e	1,293
	Death	2020	45,542	41,405	15,813	n.e.	99,866
	Death	2021	21,770	28,897	6,704	N.e.	33,480

3.4 Incidence rates, rate differences and incidence rate ratios

Background rates for each of the AESI are listed in excel format annexes 2, by age. In section 3.4 we provide an event-based approach, alphabetically ordered. Rates are classified by a modification of the Council of International Organization of Medical Sciences frequency classification as extremely rare <1/100,000 PY, very rare 1- 100/100,000 PY, uncommon: between 1/1000 and 1/100 PY.
Rates of events post-vaccinated are calculated for dose 1 and 2, within a maximum of 28 days after vaccination.

3.4.1 Acute Aseptic Arthritis

No cases were observed for acute aseptic arthritis as there were no narrow codes in any of the vocabularies.

3.4.2 Acute disseminated myelitis (ADEM)

ADEM is extremely rare (<1/100,000 PY) in each of the data sources, except in CPRD where it is very rare 1.6/100,000 PY, in PHARMO no ICPC codes were available (Table 14). No significant association was found for Pfizer vaccine or AstraZeneca vaccine and ADEM, only very few cases were observed.

Table 14 Incidence rates and rate differences (when there >0 cases) (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine, rate difference with 2020 background rates for ADEM

Type vaccine	Dose	Estimates	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	0.1 (0.0;0.2)	0.5 (0.3;0.7)	0.7 (0.4;1.2)	1.6 (1.4;1.8)	
None		Background age-standardised incidence rate	0.1 (0.0;0.3)	0.5 (0.3;0.7)	0.8 (0.4;1.3)	1.6 (1.4;1.8)	
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	.
Comirnaty	1	Expected cases	0	1	0	<5	.
Comirnaty	1	Observed cases	1	1	1	<5	.
Comirnaty	1	Age-standardised incidence rate	3.5 (0.1;19.4)	0.5 (0.0;2.7)	3.9 (0.1;21.9)	2.9 (0.7;7.6)	
Comirnaty	1	Age-standardised rate difference	3.4 (-3.4;10.2)	-0.0 (-1.0;1.0)	3.2 (-4.6;10.9)	1.3 (-1.6;4.2)	
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	.
Comirnaty	2	Expected cases	0	1	0	<5	.
Comirnaty	2	Observed cases	0	1	0	0	.
Comirnaty	2	Age-standardised incidence rate		0.6 (0.0;3.5)			
Comirnaty	2	Age-standardised rate difference		0.1 (-1.1;1.4)			
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	.
Vaxzevria	1	Expected cases	0	0	0	5	.
Vaxzevria	1	Observed cases	0	0	0	8	.
Vaxzevria	1	Age-standardised incidence rate				2.9 (1.0;6.4)	
Vaxzevria	1	Age-standardised rate difference				1.3 (-1.1;3.7)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	.
Vaxzevria	2	Expected cases	0	0	0	<5	.
Vaxzevria	2	Observed cases	0	0	0	0	.
Vaxzevria	2	Age-standardised incidence rate					
Vaxzevria	2	Age-standardised rate difference					
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	.
Spikevax	1	Expected cases	0	0	0	0	.
Spikevax	1	Observed cases	0	0	0	0	.
Spikevax	1	Age-standardised incidence rate					
Spikevax	1	Age-standardised rate difference					
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	.
Spikevax	2	Expected cases	0	0	0	0	.
Spikevax	2	Observed cases	0	0	0	0	.
Spikevax	2	Age-standardised incidence rate					
Spikevax	2	Age-standardised rate difference					
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	.
Janssen	1	Expected cases	0	0	0	.	.
Janssen	1	Observed cases	0	0	0	.	.
Janssen	1	Age-standardised incidence rate					
Janssen	1	Age-standardised rate difference					
Unknown	1	Observed person-years after vaccination		16			
Unknown	1	Expected cases		0			
Unknown	1	Observed cases		0			
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			
Unknown	2	Expected cases		0			
Unknown	2	Observed cases		0			
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

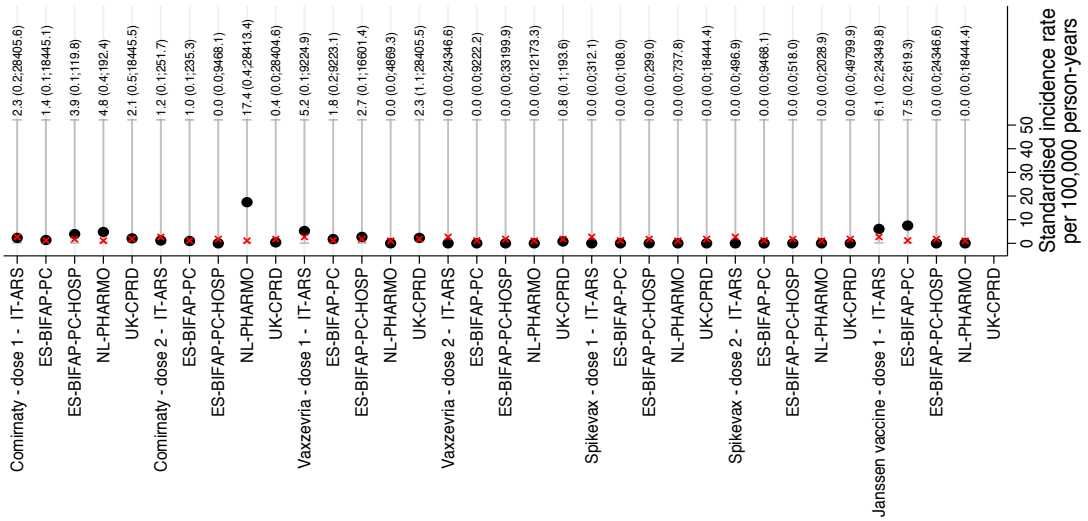


Figure 9 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for ADEM**

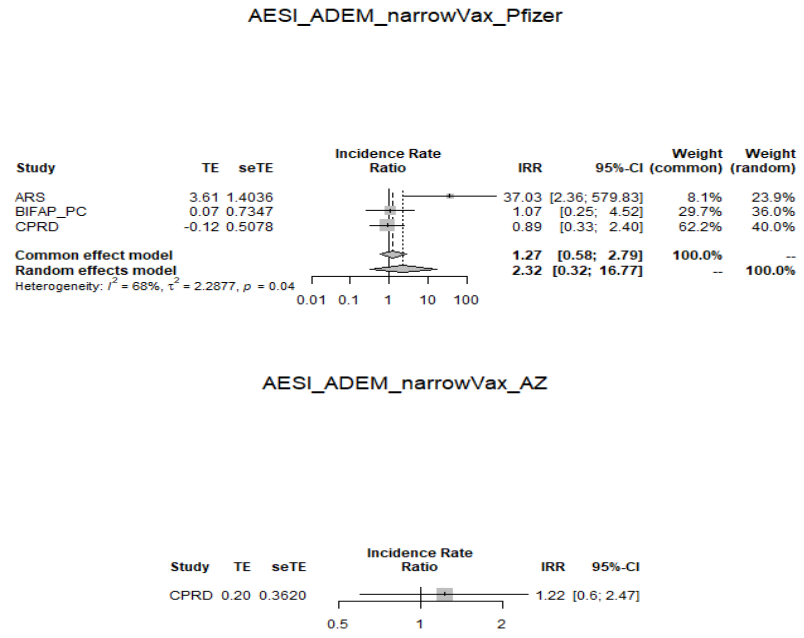


Figure 10
Partially adjusted incidence rate ratio for ADEM between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19 disease.

Figure 10 shows a relatively high estimate for ARS with Comirnaty however this is based on one case only and may well be a spurious finding in isolation.

3.4.3 Acute Kidney Injury (AKI)

AKI is an uncommon event, incidence rates are displayed in table 15, figure 12 shows no association between vaccination and AKI. Rates are lower for BIFAP than ARS and CPRD. In PHARMO there were no narrow ICPC codes. Incidence rate differences show excess for Comirnaty dose 1 and 2 in BIFAP-PC but not PC-HOSP, and for Spikevax dose 1 (BIFAP PC) and dose 2. The meta-analysis of adjusted IRR showed no association.

Table 15 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Standardised rate difference post-vaccination dose 1 (28 days) or 2 (28 days) with 2020 background rates for AKI (empty means no cases were observed post-vaccination)

Type vaccine	Dose	Estimates	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
	none	Background crude incidence rate	252.9 (247.6;258.3)	70.0 (67.8;72.2)	92.4 (88.1;96.8)	155.9 (153.8;158.1)	
		Background age-standardised incidence rate	174.3 (170.6;178.1)	58.6 (56.7;60.4)	68.8 (65.5;72.2)	164.1 (161.9;166.3)	
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	.
Comirnaty	1	Expected cases	345	149	15	480	.
Comirnaty	1	Observed cases	267	266	7	501	.
Comirnaty	1	Age-standardised incidence rate	143.0 (124.4;163.6)	102.5 (89.6;116.7)	36.6 (13.9;77.9)	214.1 (186.7;244.5)	
Comirnaty	1	Age-standardised rate difference	-31.3 (-50.9;-11.7)	**43.9 (30.4;57.3)**	-32.3 (-60.9;-3.7)	50.0 (21.6;78.5)	
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	.
Comirnaty	2	Expected cases	364	185	18	368	.
Comirnaty	2	Observed cases	296	294	13	355	.
Comirnaty	2	Age-standardised incidence rate	158.2 (132.6;187.3)	91.9 (80.7;104.2)	48.7 (25.3;84.7)	184.3 (158.2;213.4)	
Comirnaty	2	Age-standardised rate difference	-16.1 (-43.1;10.9)	**33.3 (21.6;45.1)**	-20.1 (-47.6;7.4)	20.2 (-7.0;47.4)	
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	.
Vaxzevria	1	Expected cases	76	27	5	564	.
Vaxzevria	1	Observed cases	27	25	6	694	.
Vaxzevria	1	Age-standardised incidence rate	33.8 (19.6;54.4)	18.0 (11.0;27.7)	26.2 (7.6;65.3)	232.1 (209.8;256.2)	
Vaxzevria	1	Age-standardised rate difference	-140.5 (-157.1;-123.8)	-40.6 (-48.7;-32.5)	-42.6 (-67.7;-17.5)	68.0 (45.0;91.0)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	.
Vaxzevria	2	Expected cases	15	19	4	225	.
Vaxzevria	2	Observed cases	1	19	0	209	.
Vaxzevria	2	Age-standardised incidence rate	4.9 (0.1;27.3)	20.9 (11.8;34.3)		206.3 (164.3;255.8)	
Vaxzevria	2	Age-standardised rate difference	-169.4 (-179.7;-159.1)	-37.7 (-48.3;-27.0)		42.2 (-2.2;86.7)	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	.
Spikevax	1	Expected cases	19	21	5	1	.
Spikevax	1	Observed cases	35	33	1	1	.
Spikevax	1	Age-standardised incidence rate	268.5 (123.1;508.8)	91.1 (61.6;129.7)	11.8 (0.3;65.5)	383.6 (9.7;2137.2)	
Spikevax	1	Age-standardised rate difference	94.2 (-80.7;269.2)	**32.5 (0.1;64.9**)	-57.1 (-80.3;-33.8)	219.5 (-532.3;971.3)	
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	.
Spikevax	2	Expected cases	14	19	5	0	.
Spikevax	2	Observed cases	34	36	8	0	.
Spikevax	2	Age-standardised incidence rate	501.2 (247.1;904.4)	107.3 (74.5;149.7)	116.3 (44.8;245.8)		
Spikevax	2	Age-standardised rate difference	**326.8 (26.2;627.5)**	**48.8 (12.8;84.7)**	47.5 (-41.9;136.9)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	.
Janssen	1	Expected cases	9	6	1	.	.
Janssen	1	Observed cases	4	10	2	.	.
Janssen	1	Age-standardised incidence rate	45.4 (11.8;119.1)	229.6 (20.0;925.9)	568.1 (18.9;2976.6)		
Janssen	1	Age-standardised rate difference	-128.9 (-174.8;-83.0)	171.0 (-178.9;521.0)	499.3 (-565.0;1563.6)		
Unknown	1	Observed person-years after vaccination		16			
Unknown	1	Expected cases		0			
Unknown	1	Observed cases		0			
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			
Unknown	2	Expected cases		0			
Unknown	2	Observed cases		0			
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

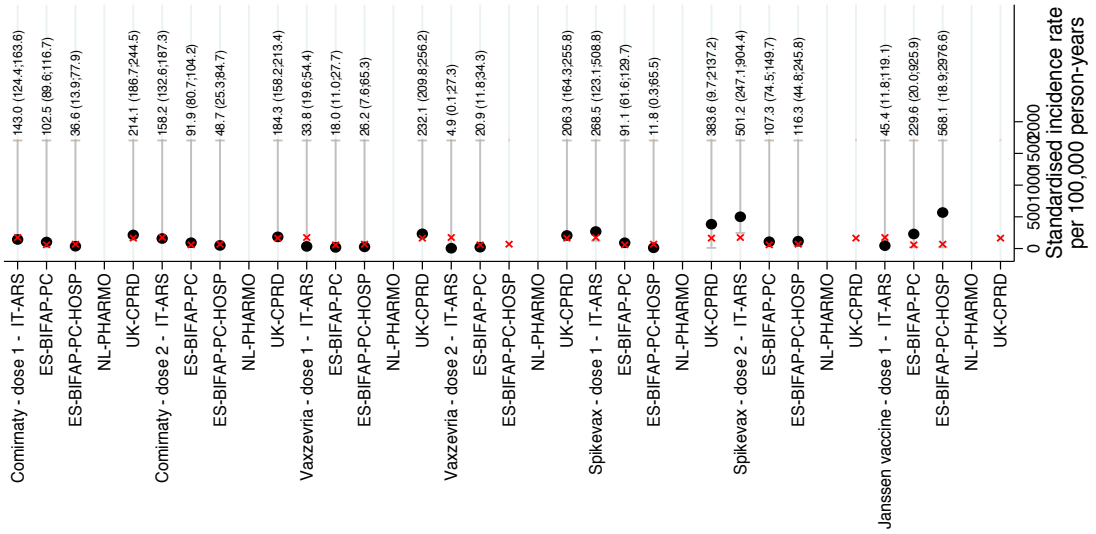
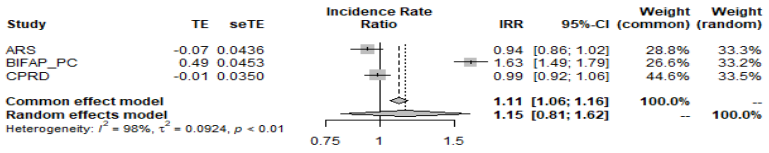
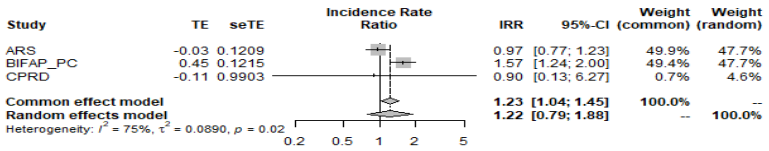


Figure 11 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for acute kidney injury**

AESI_AKI_narrowVax_Pfizer



AESI_AKI_narrowVax_Moderna



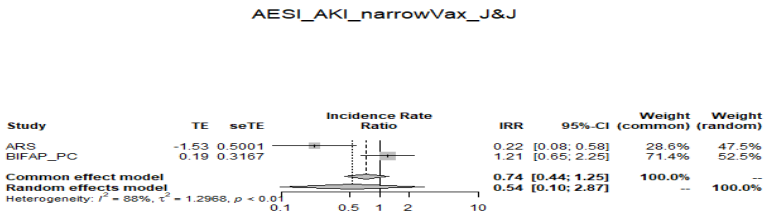


Figure 12 Partially adjusted incidence rate ratio for AKI between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19

3.4.4 Acute Liver Injury

Acute liver injury is very rare, we observed a significant reduction in the rate of ALI after Comirnaty (Pfizer) vaccination and a non-significant reduction after Vaxzevria (Table 16, figure 13).

Table 16 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for acute liver injury

Vaccine	Dose	Esitimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	16.9 (15.5;18.3)	7.2 (6.6;8.0)	11.7 (10.2;13.3)	7.0 (6.6;7.5)	
None		Background age-standardised incidence rate	14.2 (13.1;15.5)	6.8 (6.1;7.4)	10.3 (9.0;11.8)	7.2 (6.7;7.7)	
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	.
Comirnaty	1	Expected cases	18	13	<5	14	.
Comirnaty	1	Observed cases	15	15	<5	10	.
Comirnaty	1	Age-standardised incidence rate	11.6 (6.2;19.9)	9.1 (4.9;15.5)	16.9 (3.3;51.0)	4.5 (2.1;8.5)	
Comirnaty	1	Age-standardised rate difference	-2.6 (-9.0;3.8)	2.4 (-2.6;7.3)	6.6 (-13.2;26.4)	-2.7 (-5.6;0.3)	
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	.
Comirnaty	2	Expected cases	13	15	<5	9	.
Comirnaty	2	Observed cases	13	10	0	8	.
Comirnaty	2	Age-standardised incidence rate	23.5 (9.6;48.0)	3.8 (1.7;7.3)		5.6 (1.6;13.8)	
Comirnaty	2	Age-standardised rate difference	9.3 (-7.9;26.5)	**-3.0 (-5.6;-0.4)**		-1.6 (-6.8;3.7)	
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	.
Vaxzevria	1	Expected cases	6	5	<5	29	.
Vaxzevria	1	Observed cases	<5	7	<5	25	.
Vaxzevria	1	Age-standardised incidence rate	0.8 (0.0;4.7)	18.6 (5.4;46.2)	3.1 (0.1;17.4)	5.9 (3.7;8.9)	
Vaxzevria	1	Age-standardised rate difference	**-13.4 (-15.4;-11.3)**	11.9 (-5.7;29.5)	-7.2 (-13.4;-0.9)	-1.3 (-3.8;1.2)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	.
Vaxzevria	2	Expected cases	<5	<5	<5	7	.
Vaxzevria	2	Observed cases	<5	<5	0	5	.
Vaxzevria	2	Age-standardised incidence rate	15.9 (1.9;57.6)	2.1 (0.1;12.0)		7.0 (1.5;20.3)	
Vaxzevria	2	Age-standardised rate difference	1.7 (-20.4;23.9)	-4.6 (-8.9;-0.3)		-0.2 (-8.1;7.7)	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	.
Spikevax	1	Expected cases	<5	<5	<5	0	.
Spikevax	1	Observed cases	<5	<5	0	0	.
Spikevax	1	Age-standardised incidence rate	8.7 (0.2;48.7)	9.5 (2.2;26.2)			
Spikevax	1	Age-standardised rate difference	-5.5 (-22.7;11.7)	2.8 (-7.4;12.9)			
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	.
Spikevax	2	Expected cases	<5	<5	<5	0	.
Spikevax	2	Observed cases	<5	<5	<5	0	.
Spikevax	2	Age-standardised incidence rate	25.5 (4.8;77.4)	10.7 (2.2;31.5)	14.5 (0.4;80.7)		
Spikevax	2	Age-standardised rate difference	11.3 (-18.7;41.3)	3.9 (-8.3;16.2)	4.2 (-24.2;32.6)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	.
Janssen	1	Expected cases	<5	<5	0	.	.
Janssen	1	Observed cases	0	0	0	.	.
Janssen	1	Age-standardised incidence rate					
Janssen	1	Age-standardised rate difference					
Unknown	1	Observed person-years after vaccination		16			
Unknown	1	Expected cases		0			
Unknown	1	Observed cases		0			
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			
Unknown	2	Expected cases		0			
Unknown	2	Observed cases		0			
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

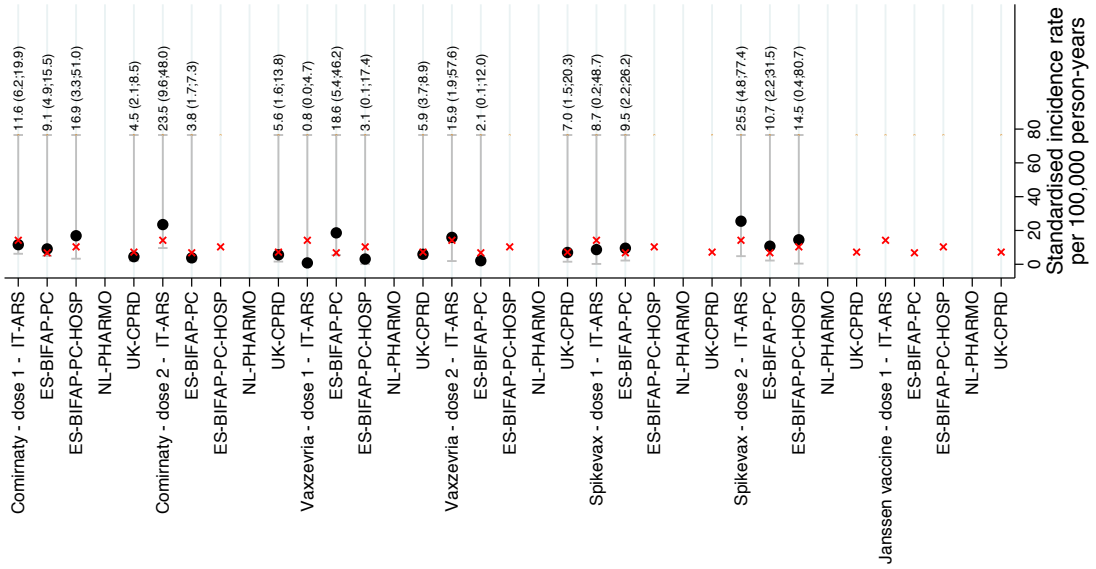
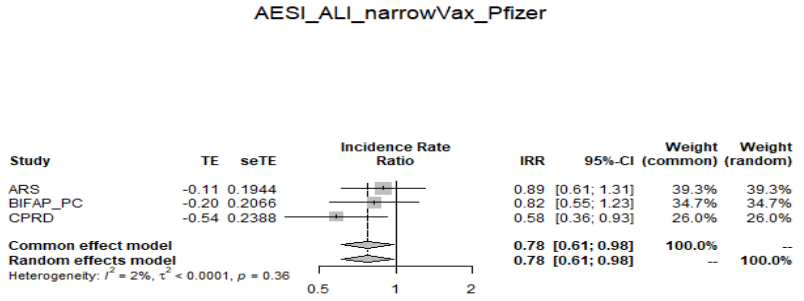
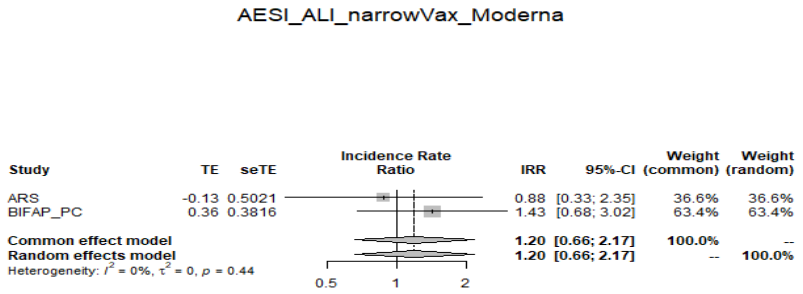


Figure 13 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for acute liver injury**





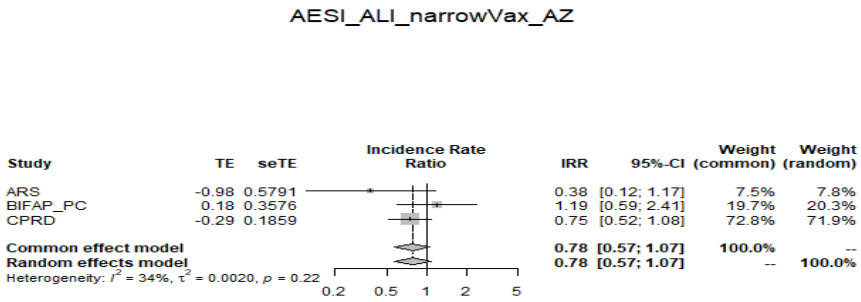


Figure 14 **Partially adjusted incidence rate ratio for acute liver injury between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.5 Anaphylaxis

Anaphylaxis is a very rare event, we observe significant standardised rate differences for Vaxzevria (reduced) in ARS and (increased) in CPRD. The meta-analysis of partially adjusted IRR showed an increased risk of anaphylaxis following Vaxzevria, but the IRR was below 2 (1.68).

Table 17 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for anaphylaxis

Vaccine	Dose	Esitimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	17.3 (15.9;18.8)	6.2 (5.6;6.9)	7.1 (6.0;8.4)	13.5 (12.9;14.1)	7.0 (6.0;8.2)
none		Background age-standardised incidence rate	21.0 (19.4;22.8)	6.5 (5.8;7.2)	8.3 (6.9;9.9)	13.5 (12.9;14.1)	6.9 (5.9;8.1)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	6	8	<5	17	<5
Comirnaty	1	Observed cases	5	19	0	30	<5
Comirnaty	1	Age-standardised incidence rate	12.2 (2.9;33.8)	10.8 (6.2;17.4)		26.8 (14.8;44.6)	8.6 (1.6;26.1)
Comirnaty	1	Age-standardised rate difference	-8.8 (-21.9;4.4)	4.3 (-0.9;9.6)		13.3 (-0.5;27.1)	1.7 (-8.5;11.8)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	<5	8	<5	11	<5
Comirnaty	2	Observed cases	<5	11	0	6	0
Comirnaty	2	Age-standardised incidence rate	3.6 (0.9;9.8)	6.9 (3.2;12.9)		7.5 (1.7;21.4)	
Comirnaty	2	Age-standardised rate difference	-17.4 (-21.6;-13.2)	0.4 (-4.0;4.8)		-5.9 (-14.2;2.4)	
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	<5	<5	0	34	0
Vaxzevria	1	Observed cases	<5	<5	<5	80	0
Vaxzevria	1	Age-standardised incidence rate	3.4 (0.6;10.7)	4.4 (1.1;11.7)	10.6 (0.3;59.0)	28.9 (21.6;37.8)	
Vaxzevria	1	Age-standardised rate difference	**-17.6 (-22.1;-13.1)**	-2.1 (-6.7;2.4)	2.3 (-18.5;23.1)	**15.4 (7.6;23.2)**	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	<5	<5	0	7	0
Vaxzevria	2	Observed cases	0	<5	0	9	0
Vaxzevria	2	Age-standardised incidence rate		3.0 (0.3;11.9)		25.1 (8.5;57.5)	
Vaxzevria	2	Age-standardised rate difference		-3.5 (-8.1;1.0)		11.7 (-9.8;33.2)	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	<5	<5	0	0	0
Spikevax	1	Observed cases	<5	<5	0	0	<5
Spikevax	1	Age-standardised incidence rate	9.7 (1.1;36.1)	4.9 (0.5;18.7)			26.6 (3.2;96.2)
Spikevax	1	Age-standardised rate difference	-11.3 (-25.3;2.6)	-1.6 (-8.8;5.6)			19.7 (-17.2;56.6)
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	0	<5	0	0	0
Spikevax	2	Observed cases	<5	<5	0	0	0
Spikevax	2	Age-standardised incidence rate	26.7 (2.4;106.8)	4.1 (0.1;22.6)			
Spikevax	2	Age-standardised rate difference	5.6 (-34.8;46.1)	-2.4 (-10.4;5.6)			
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	0	<5	0	.	0
Janssen	1	Observed cases	0	0	0	.	0
Janssen	1	Age-standardised incidence rate					
Janssen	1	Age-standardised rate difference					
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			<5
Unknown	1	Observed cases		0			<5
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			0
Unknown	2	Observed cases		0			0
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

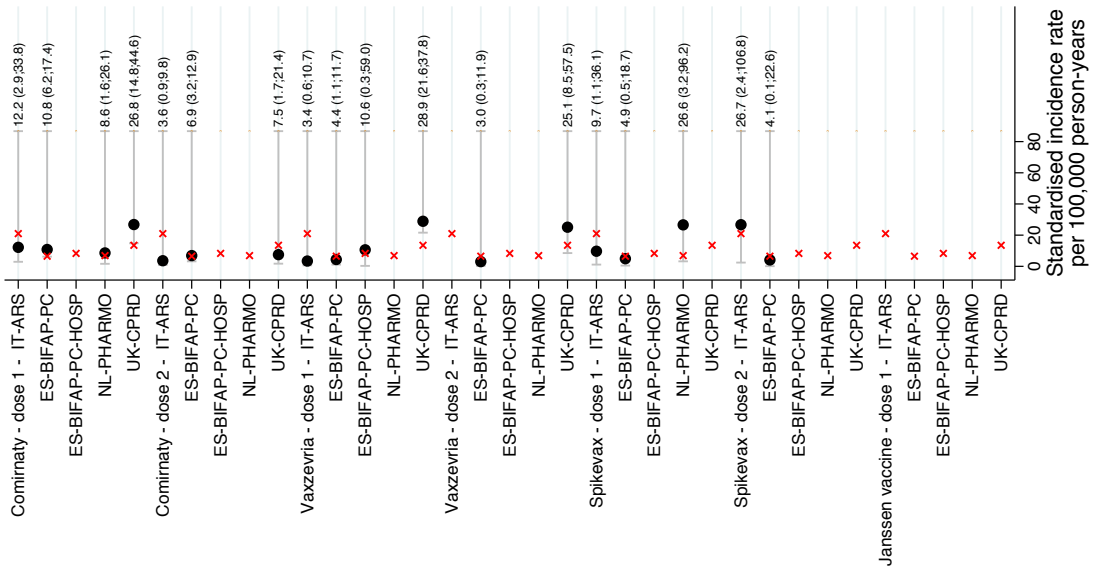
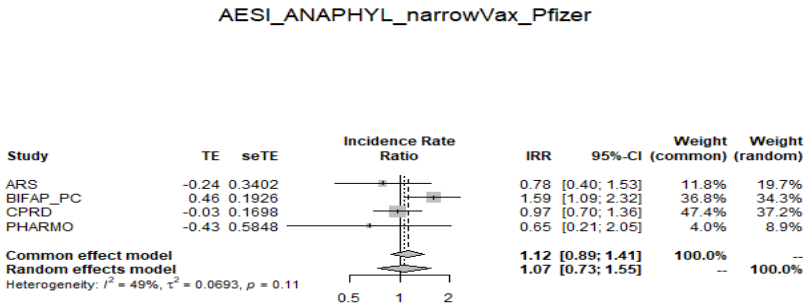
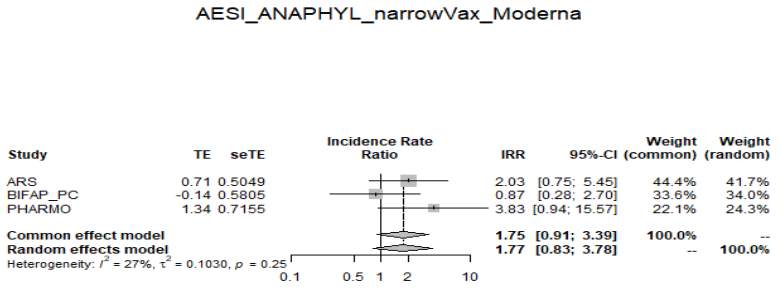


Figure 15 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for anaphylaxis**





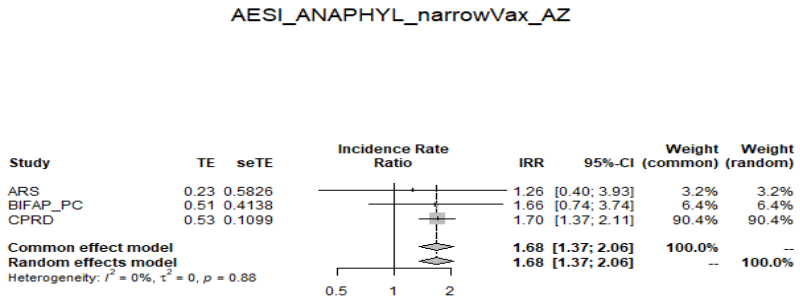


Figure 16 **Partially adjusted incidence rate ratio for anaphylaxis between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

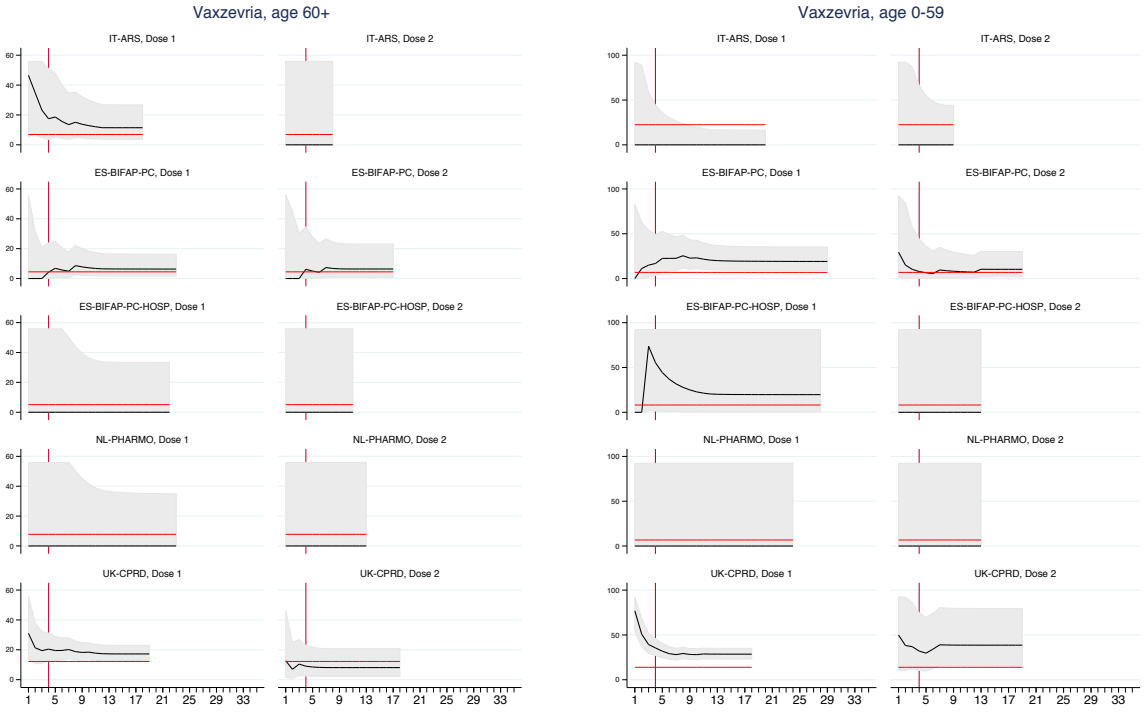


Figure 17 **Monitoring of Anaphylaxis over time (x-axis weeks), y-axis IR/100,000 PY following Vaxzevria**

Figure 17 shows that anaphylaxis was elevated especially during the first days after Vaxzevria administration for the first dose. This was observed in BIFAP, CPRD and IT-ARS but not in PHARMO.

3.4.6 Anosmia/ageusia

Anosmia/dysgeusia is uncommon and cannot be measured in hospital (ARS), also BIFAP did not extract the codes, which limited the analysis to PHARMO and CPRD. We do not observe an association or increased rate after any of the covid-19 vaccines. Vaccination reduced the rate of anosmia/ageusia, most likely since it reduced covid-19.

Table 18 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for anosmia/dysgeusia

Vaccine	Dose	Estimate	CPRD	PHARMO
		Background crude incidence rate	93.0 (91.4;94.6)	51.9 (48.9;55.0)
		Background age-standardised incidence rate	92.6 (91.0;94.2)	51.3 (48.3;54.4)
Comirnaty	1	Observed person-years after vaccination	135,464	37,990
Comirnaty	1	Expected cases	124	22
Comirnaty	1	Observed cases	139	26
Comirnaty	1	Age-standardised incidence rate	94.2 (76.3;115.0)	58.3 (36.5;88.2)
Comirnaty	1	Age-standardised rate difference	1.6 (-17.3;20.5)	6.9 (-17.6;31.5)
Comirnaty	2	Observed person-years after vaccination	85,610	13,856
Comirnaty	2	Expected cases	75	8
Comirnaty	2	Observed cases	30	9
Comirnaty	2	Age-standardised incidence rate	30.5 (19.0;46.5)	64.6 (21.8;147.4)
Comirnaty	2	Age-standardised rate difference	**-62.1 (-75.1;-49.0)**	13.3 (-41.8;68.4)
Vaxzevria	1	Observed person-years after vaccination	268,652	5,172
Vaxzevria	1	Expected cases	269	3
Vaxzevria	1	Observed cases	177	1
Vaxzevria	1	Age-standardised incidence rate	60.1 (49.7;72.1)	13.4 (0.3;74.4)
Vaxzevria	1	Age-standardised rate difference	**-32.5 (-43.5;-21.4)**	**-37.9 (-64.3;-11.6)**
Vaxzevria	2	Observed person-years after vaccination	59,921	1,779
Vaxzevria	2	Expected cases	52	1
Vaxzevria	2	Observed cases	17	1
Vaxzevria	2	Age-standardised incidence rate	17.4 (8.2;32.2)	9.0 (0.2;50.1)
Vaxzevria	2	Age-standardised rate difference	**-75.2 (-86.3;-64.2)**	**-42.3 (-60.2;-24.4)**
Spikevax	1	Observed person-years after vaccination	1,168	4,208
Spikevax	1	Expected cases	1	2
Spikevax	1	Observed cases	0	2
Spikevax	1	Age-standardised incidence rate		20.0 (2.4;72.1)
Spikevax	1	Age-standardised rate difference		**-31.3 (-59.2;-3.5)**
Spikevax	2	Observed person-years after vaccination	30	1,397
Spikevax	2	Expected cases	0	1
Spikevax	2	Observed cases	0	0
Spikevax	2	Age-standardised incidence rate		
Spikevax	2	Age-standardised rate difference		
Janssen vaccine	1	Observed person-years after vaccination	.	1,282
Janssen vaccine	1	Expected cases	.	1
Janssen vaccine	1	Observed cases	.	0
Janssen vaccine	1	Age-standardised incidence rate		
Janssen vaccine	1	Age-standardised rate difference		
Unknown	1	Observed person-years after vaccination		8,282
Unknown	1	Expected cases		5
Unknown	1	Observed cases		6
Unknown	1	Age-standardised incidence rate		
Unknown	1	Age-standardised rate difference		
Unknown	2	Observed person-years after vaccination		2,044
Unknown	2	Expected cases		1
Unknown	2	Observed cases		0
Unknown	2	Age-standardised incidence rate		
Unknown	2	Age-standardised rate difference		

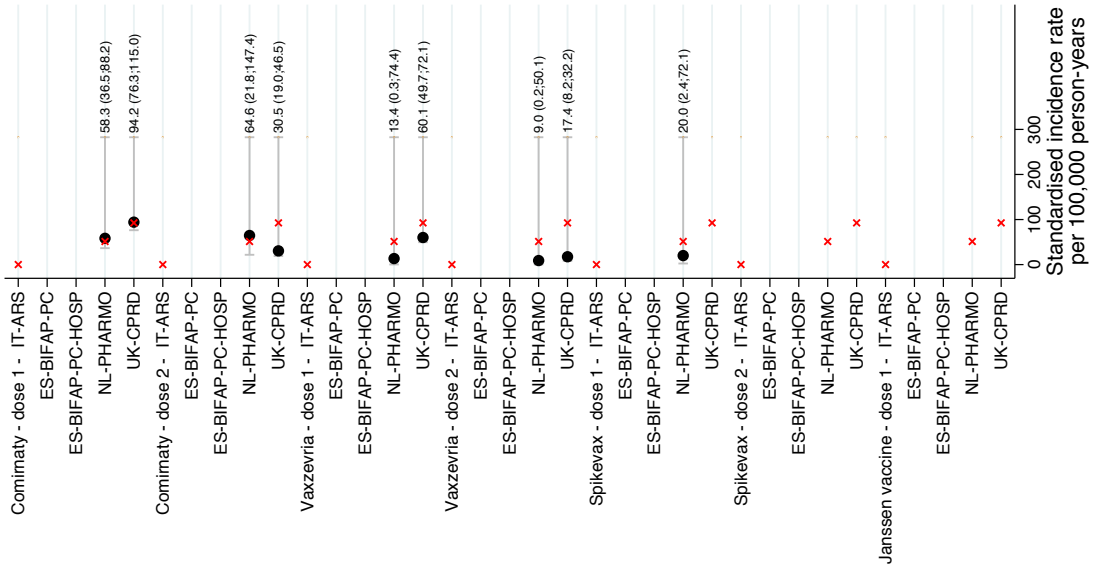
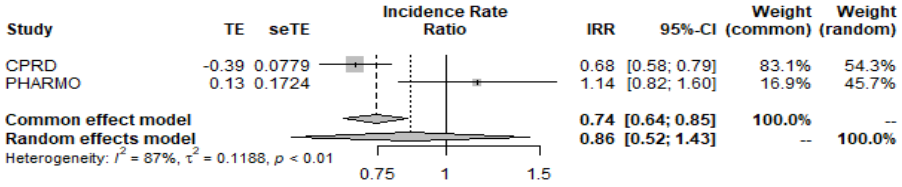
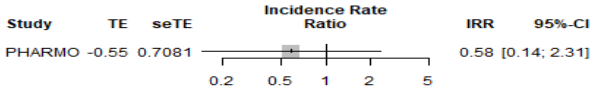


Figure 18 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for anosmia/ageusia**

AESI_ANOSMIA_narrowVax_Pfizer



AESI_ANOSMIA_narrowVax_Moderna



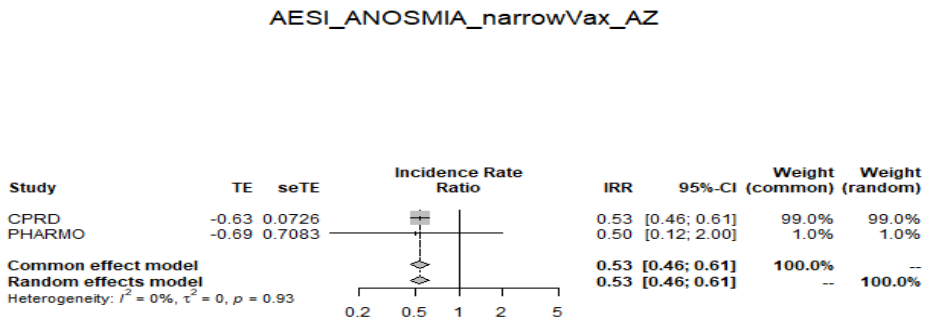


Figure 19 **Partially adjusted incidence rate ratios for anosmia/ageusia between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.7 Acute respiratory distress

Acute respiratory distress is a very rare event, which is a complication of COVID-19. It is not associated with any of the vaccines as shown in figures and table below. Rates were much lower in CPRD as this is mostly an event diagnosed in hospital and there may be a lagtime in reporting back to GPs. It could not be extracted in PHARMO due to lack of specific ICPC codes.

Table 19 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for acute respiratory distress

ordvac	Dose	namelong	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	85.3 (82.3;88.5)	65.4 (63.4;67.6)	97.7 (93.3;102.3)	11.8 (11.2;12.4)
None		Background age-standardised incidence rate	63.8 (61.4;66.2)	54.4 (52.7;56.3)	76.2 (72.6;79.9)	12.4 (11.8;13.0)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	104	135	16	31
Comirnaty	1	Observed cases	154	215	9	14
Comirnaty	1	Age-standardised incidence rate	84.2 (69.7;100.9)	79.5 (68.3;92.0)	37.9 (16.4;74.7)	10.2 (2.3;28.5)
Comirnaty	1	Age-standardised rate difference	**20.5 (5.0;35.9)**	**25.0 (13.3;36.8)**	**-38.3 (-64.8;-11.7)**	-2.2 (-13.2;8.9)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	94	164	19	23
Comirnaty	2	Observed cases	43	264	9	6
Comirnaty	2	Age-standardised incidence rate	32.4 (19.4;50.8)	88.4 (72.5;106.6)	31.8 (14.3;61.1)	4.6 (1.1;12.8)
Comirnaty	2	Age-standardised rate difference	**-31.4 (-46.3;-16.5)**	**33.9 (17.2;50.6)**	**-44.3 (-65.8;-22.9)**	-7.8 (-12.8;-2.8)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	31	22	5	44
Vaxzevria	1	Observed cases	30	19	<5	25
Vaxzevria	1	Age-standardised incidence rate	32.9 (20.9;49.4)	13.4 (7.5;22.0)	3.1 (0.1;17.4)	5.6 (3.5;8.4)
Vaxzevria	1	Age-standardised rate difference	**-30.8 (-44.5;-17.2)**	**-41.1 (-48.0;-34.1)**	**-73.0 (-80.1;-65.9)**	**-6.8 (-9.2;-4.4)**
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	7	15	<5	16
Vaxzevria	2	Observed cases	0	14	0	4
Vaxzevria	2	Age-standardised incidence rate		17.8 (6.0;40.8)		5.7 (0.8;19.5)
Vaxzevria	2	Age-standardised rate difference		**-36.6 (-52.0;-21.3)**		-6.7 (-14.3;0.8)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	9	19	5	0
Spikevax	1	Observed cases	13	21	<5	0
Spikevax	1	Age-standardised incidence rate	67.0 (34.8;116.5)	62.8 (38.3;96.9)	11.7 (0.3;65.4)	
Spikevax	1	Age-standardised rate difference	3.2 (-34.5;40.9)	8.3 (-19.2;35.9)	**-64.4 (-87.7;-41.2)**	
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	6	17	5	0
Spikevax	2	Observed cases	7	18	<5	0
Spikevax	2	Age-standardised incidence rate	64.1 (24.9;135.1)	54.1 (31.1;87.5)	26.4 (3.1;95.8)	
Spikevax	2	Age-standardised rate difference	0.3 (-48.8;49.5)	-0.4 (-26.7;26.0)	**-49.8 (-86.7;-12.9)**	
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	<5	5	<5	.
Janssen	1	Observed cases	<5	8	<5	.
Janssen	1	Age-standardised incidence rate	7.0 (0.2;39.0)	241.0 (25.2;915.7)	538.9 (13.6;3002.7)	
Janssen	1	Age-standardised rate difference	**-56.8 (-70.7;-42.8)**	186.5 (-162.6;535.7)	462.8 (-593.5;1519.1)	
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

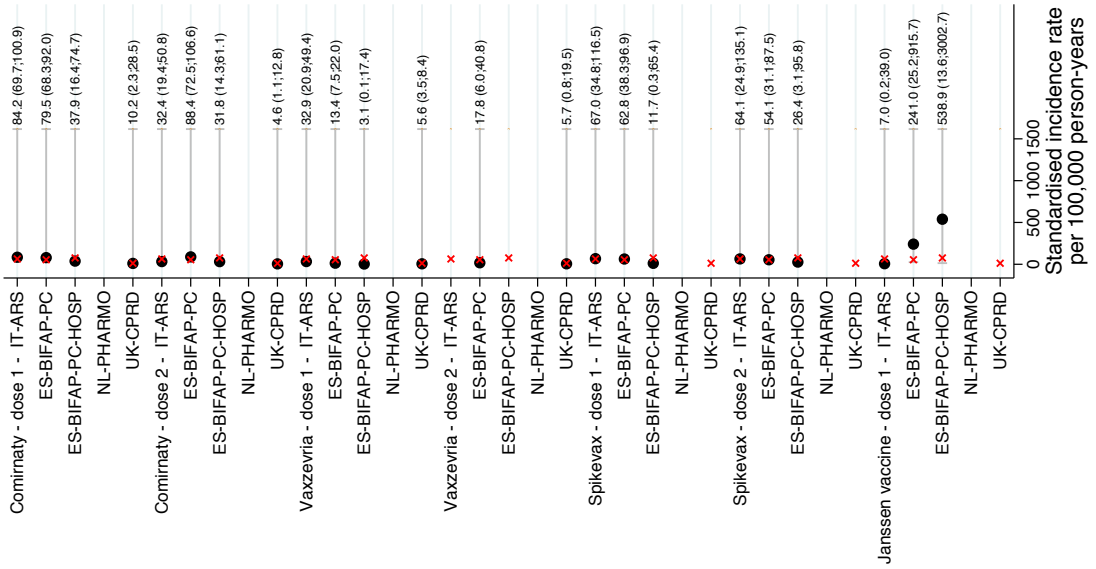
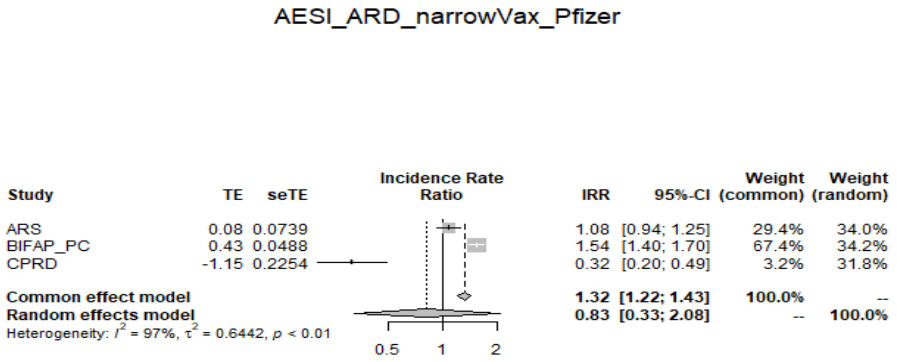
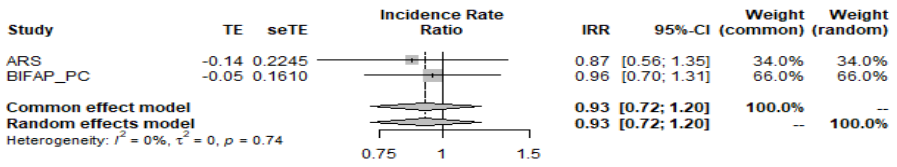


Figure 20 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for acute respiratory distress**





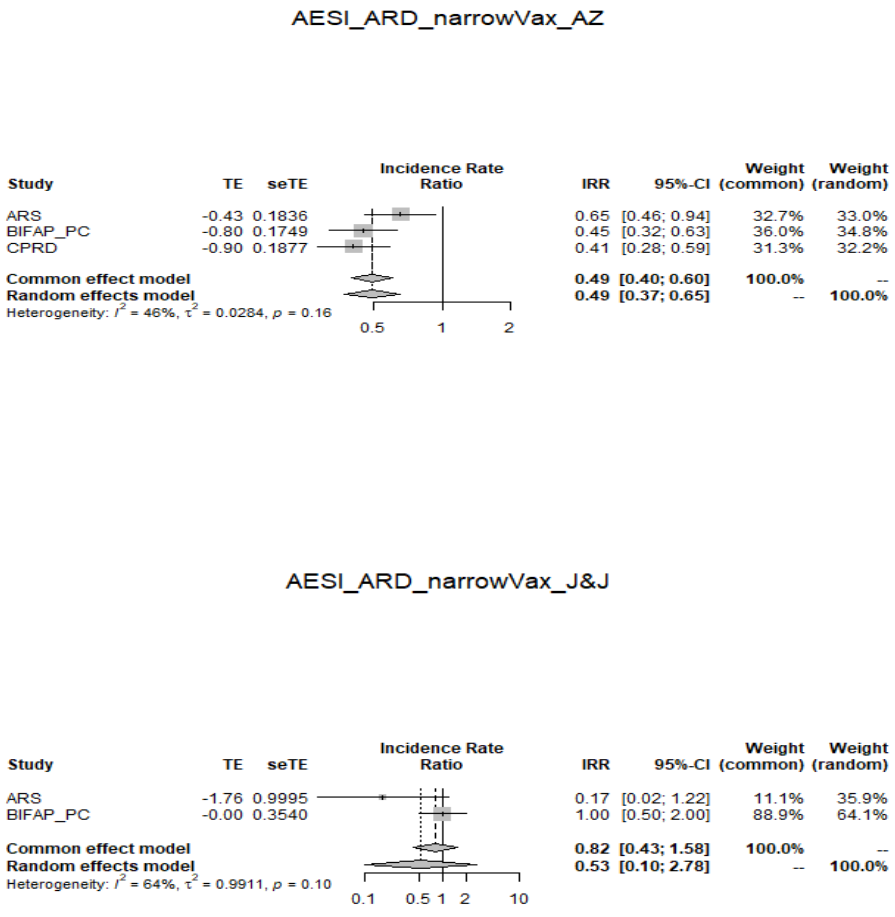


Figure 21 **Partially adjusted incidence rate ratio for acute respiratory distress between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

Figure 21 shows that the rate of ARD was reduced following each of the vaccines, which is an indicator of vaccine effectiveness and not showing vaccine associated enhanced disease.

3.4.8 Arrhythmia

Arrhythmia was an uncommon event, with very comparable rates across data sources. Age standardised rate difference showed an excess risk, however adjustment for age, gender, prior covid and any risk factor for covid-disease showed that the rates were confounded. No significant association remained.

Table 20 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for arrhythmia

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	860.6 (850.7;870.5)	545.5 (539.5;551.6)	659.7 (648.1;671.3)	564.7 (560.6;568.7)	884.5 (872.0;897.2)
none		Background age-standardised incidence rate	632.7 (625.3;640.1)	485.6 (480.1;491.1)	534.6 (524.9;544.3)	615.9 (611.5;620.3)	865.9 (853.6;878.4)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	1,147	1,112	119	1,912	442
Comirnaty	1	Observed cases	957	1,622	146	1,951	502
Comirnaty	1	Age-standardised incidence rate	620.4 (574.6;668.8)	730.1 (691.4;770.4)	712.3 (595.4;845.5)	814.9 (765.9;866.2)	1059.2 (959.9;1166.1)
Comirnaty	1	Age-standardised rate difference	-12.3 (-59.5;34.9)	**244.5 (204.9;284.1)**	**177.7 (55.2;300.3)**	**199.0 (149.0;248.9)**	**193.3 (90.7;295.9)**
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	1,156	1,321	139	1,484	180
Comirnaty	2	Observed cases	859	1,801	135	1,375	189
Comirnaty	2	Age-standardised incidence rate	629.7 (565.9;698.8)	677.9 (639.8;717.7)	527.1 (431.3;637.9)	656.9 (611.0;705.3)	1009.9 (784.8;1279.5)
Comirnaty	2	Age-standardised rate difference	-2.9 (-68.9;63.0)	**192.3 (153.3;231.4**)	-7.4 (-108.6;93.7)	41.0 (-5.9;87.9)	144.0 (-95.8;383.7)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	296	229	40	2,133	60
Vaxzevria	1	Observed cases	182	303	46	2,276	85
Vaxzevria	1	Age-standardised incidence rate	**248.7 (203.7;300.6)**	**359.3 (295.1;433.3)**	**358.9 (173.9;655.7)**	**758.2 (713.6;804.8)**	**1582.8 (883.0;2616.6)**
Vaxzevria	1	Age-standardised rate difference	-384.0 (-431.8;-336.3)	-126.3 (-193.9;-58.8)	-175.6 (-395.7;44.5)	142.3 (96.9;187.8)	716.8 (-88.0;1521.7)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	62	159	31	932	21
Vaxzevria	2	Observed cases	33	174	30	894	28
Vaxzevria	2	Age-standardised incidence rate	**259.8 (168.2;383.5)**	**382.8 (296.1;486.9)**	**182.9 (113.8;278.3)**	**771.6 (697.2;851.8)**	**1139.5 (175.0;3766.4)**
Vaxzevria	2	Age-standardised rate difference	-372.9 (-474.9;-270.8)	-102.8 (-195.2;-10.4)	-351.7 (-429.7;-273.7)	**155.7 (79.3;232.1)**	273.6 (-1182.1;1729.4)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	76	171	36	<5	35
Spikevax	1	Observed cases	115	211	33	<5	55
Spikevax	1	Age-standardised incidence rate	**1076.7 (707.6;1569.9)**	**600.2 (519.2;690.2)**	**525.3 (350.3;757.0)**	**30.0 (3.6;108.4)**	**1767.9 (1074.1;2741.5)**
Spikevax	1	Age-standardised rate difference	**444.0 (35.4;852.5)**	**114.6 (30.5;198.7)**	-9.3 (-202.5;184.0)	-585.9 (-627.7;-544.1)	**901.9 (119.6;1684.3)**
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	56	148	33	<5	12
Spikevax	2	Observed cases	101	234	57	<5	25
Spikevax	2	Age-standardised incidence rate	1599.7 (1090.3;2264.9)	838.1 (680.0;1021.8)	949.0 (680.6;1288.3)	3240.0 (82.0;18052.0)	1771.4 (774.2;3463.0)
Spikevax	2	Age-standardised rate difference	**967.0 (407.9;1526.1)**	**352.5 (186.0;518.9)**	**414.5 (123.2;705.7)**	2624.1 (-3726.2;8974.3)	905.4 (-307.3;2118.1)
Janssen vaccine	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	37	59	11	.	9
Janssen	1	Observed cases	22	88	15	.	10
Janssen	1	Age-standardised incidence rate	213.2 (130.9;328.0)	710.6 (371.9;1230.3)	1086.8 (245.0;3049.8)		797.0 (299.1;1712.0)
Janssen	1	Age-standardised rate difference	-419.5 (-512.4;-326.6)	225.0 (-170.4;620.5)	552.2 (-626.5;1730.9)		-68.9 (-695.3;557.5)
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			98
Unknown	1	Observed cases		0			122
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			24
Unknown	2	Observed cases		0			27
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

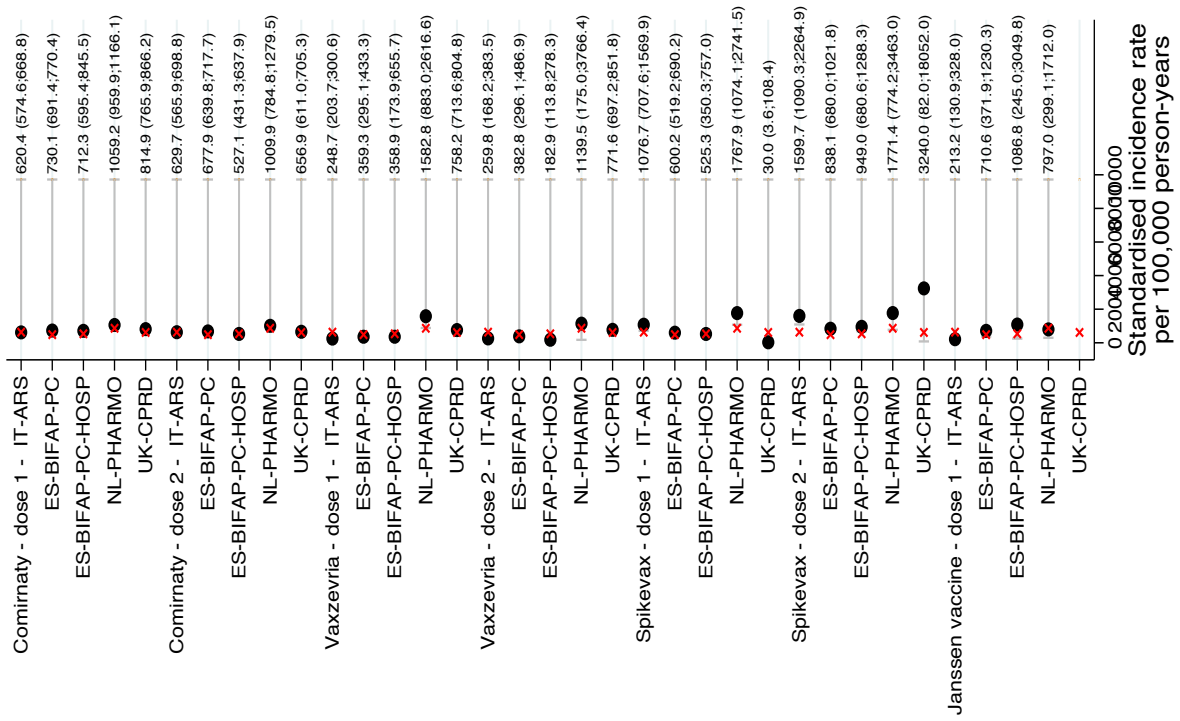
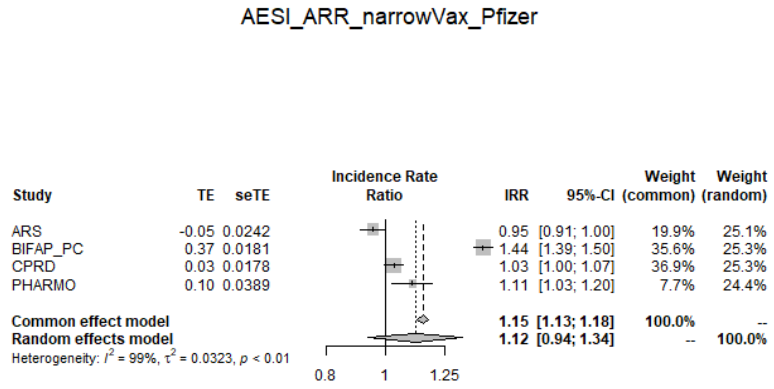
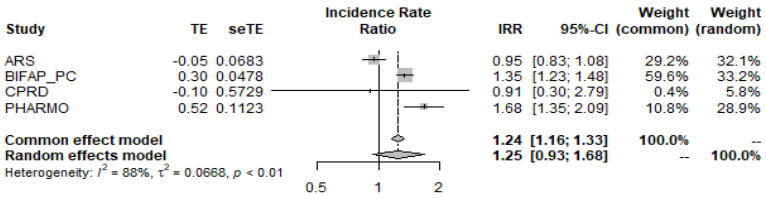


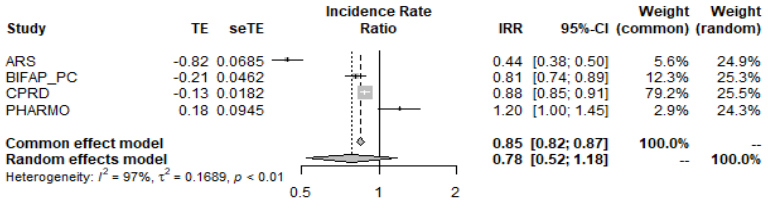
Figure 22 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for arrhythmia**



AESI_ARR_narrowVax_Moderna



AESI_ARR_narrowVax_AZ



AESI_ARR_narrowVax_J&J

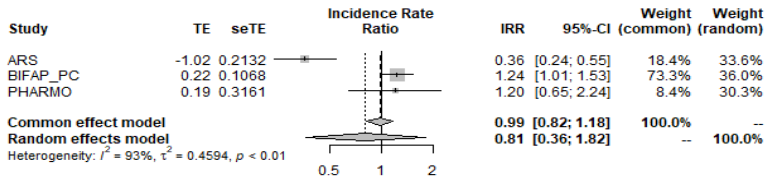


Figure 23 Incidence rate ratio for arrhythmia between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19

3.4.9 Bell's Palsy (BP)

Bell's palsy is a very rare disease, our rates were quite consistent, but were not retrieved in CPRD (error in ETL). We observed no excess risk of BP within 28 days after any of the covid-19 vaccine brands and doses.

Table 21 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for arrhythmia

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	27.0 (25.3;28.8)	31.1 (29.7;32.6)	34.2 (31.6;36.9)		30.2 (28.0;32.6)
None		Background age-standardised incidence rate	25.4 (23.7;27.1)	30.3 (28.9;31.7)	32.2 (29.7;34.9)		29.6 (27.4;32.0)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	.	37,990
Comirnaty	1	Expected cases	24	54	7	.	13
Comirnaty	1	Observed cases	25	39	5	0	11
Comirnaty	1	Age-standardised incidence rate	24.1 (14.2;38.1)	20.6 (14.3;28.9)	22.4 (6.8;54.3)		28.1 (13.2;52.5)
Comirnaty	1	Age-standardised rate difference	-1.3 (-12.6;10.0)	-9.6 (-16.8;-2.5)	-9.8 (-30.5;11.0)		-1.5 (-19.5;16.5)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	.	13,856
Comirnaty	2	Expected cases	14	57	8	.	5
Comirnaty	2	Observed cases	17	53	10	0	<5
Comirnaty	2	Age-standardised incidence rate	27.5 (12.7;52.0)	26.5 (18.8;36.4)	44.7 (19.9;86.3)		29.3 (4.2;98.9)
Comirnaty	2	Age-standardised rate difference	2.2 (-15.8;20.1)	-3.8 (-12.3;4.8)	12.5 (-17.7;42.6)		-0.4 (-38.6;37.9)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	.	5,172
Vaxzevria	1	Expected cases	8	16	3	.	2
Vaxzevria	1	Observed cases	9	19	<5	0	<5
Vaxzevria	1	Age-standardised incidence rate	21.9 (8.1;47.5)	23.1 (8.8;49.2)	141.2 (5.3;717.8)		3.3 (0.1;18.4)
Vaxzevria	1	Age-standardised rate difference	-3.5 (-21.0;14.1)	-7.2 (-25.2;10.8)	109.0 (-149.6;367.7)		-26.3 (-33.2;-19.4)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	.	1,779
Vaxzevria	2	Expected cases	<5	11	<5	.	1
Vaxzevria	2	Observed cases	<5	9	<5	0	<5
Vaxzevria	2	Age-standardised incidence rate	27.4 (4.6;87.7)	17.0 (3.7;48.7)	18.8 (1.4;79.2)		26.9 (5.6;78.7)
Vaxzevria	2	Age-standardised rate difference	2.0 (-32.0;36.0)	-13.3 (-32.2;5.6)	-13.4 (-43.2;16.4)		-2.7 (-33.3;27.9)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	.	4,208
Spikevax	1	Expected cases	<5	11	<5	.	1
Spikevax	1	Observed cases	<5	10	<5	0	<5
Spikevax	1	Age-standardised incidence rate	13.4 (2.7;39.3)	26.6 (12.4;50.0)	15.8 (0.4;88.3)		20.0 (2.4;72.1)
Spikevax	1	Age-standardised rate difference	-12.0 (-27.3;3.3)	-3.7 (-20.8;13.5)	-16.4 (-47.5;14.8)		-9.7 (-37.4;18.1)
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	.	1,397
Spikevax	2	Expected cases	<5	8	<5	.	1
Spikevax	2	Observed cases	5	7	0	0	0
Spikevax	2	Age-standardised incidence rate	93.8 (20.7;266.0)	22.1 (8.1;48.0)			
Spikevax	2	Age-standardised rate difference	68.4 (-34.5;171.3)	-8.2 (-25.9;9.5)			
Janssen vaccine	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen vaccine	1	Expected cases	<5	5	<5	.	0
Janssen vaccine	1	Observed cases	<5	<5	0	.	<5
Janssen vaccine	1	Age-standardised incidence rate	22.6 (2.7;81.5)	12.3 (2.2;38.0)			4355.2 (110.3;24265.6)
Janssen vaccine	1	Age-standardised rate difference	-2.8 (-34.1;28.5)	-18.0 (-32.8;-3.2)			4325.6 (-4210.5;12861.6)
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			3
Unknown	1	Observed cases		0			<5
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			1
Unknown	2	Observed cases		0			<5
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

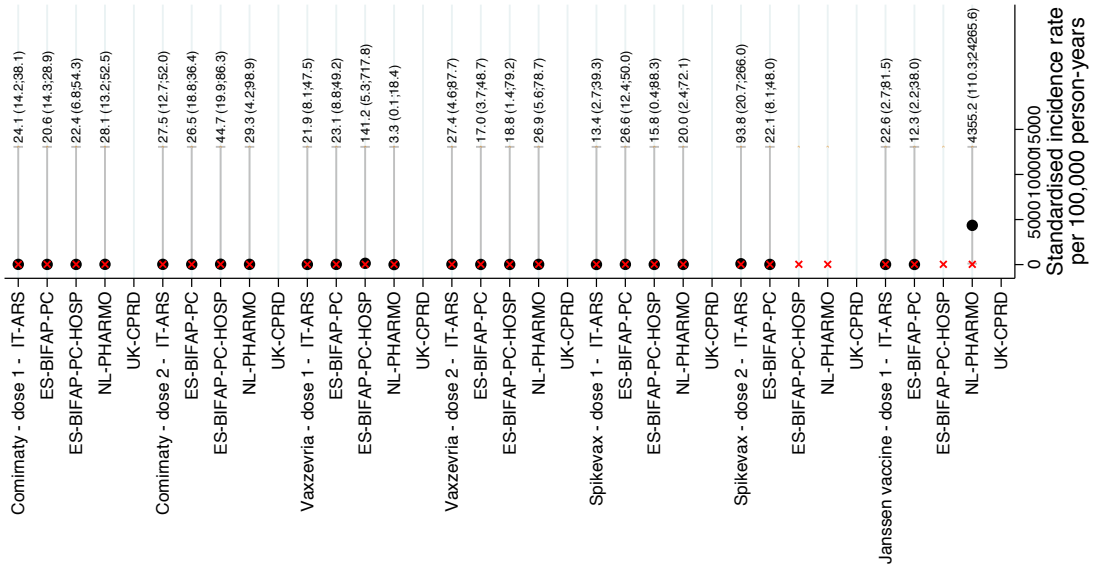
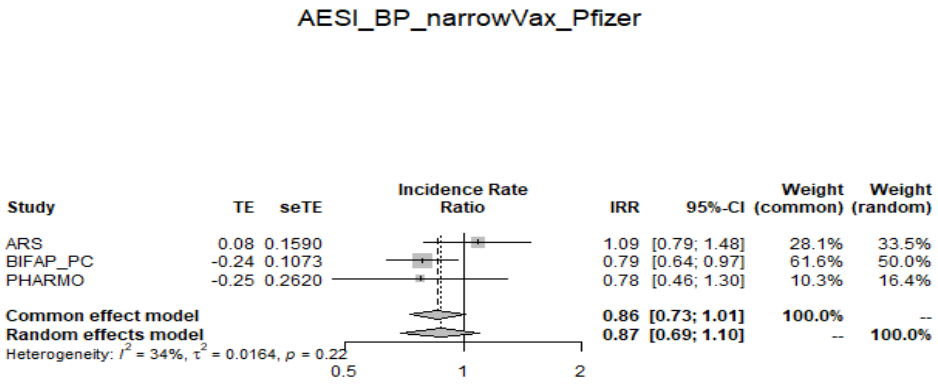
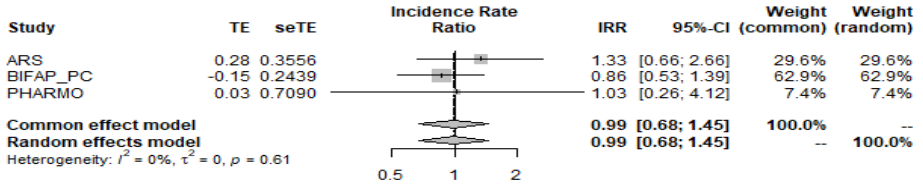


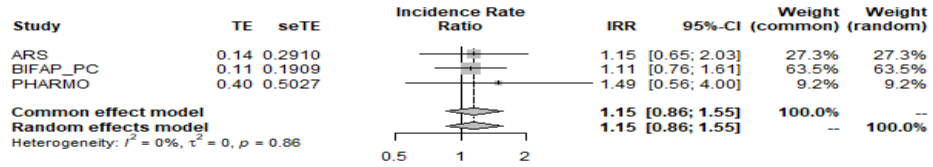
Figure 24 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for Bell's Palsy**



AESI_BP_narrowVax_Moderna



AESI_BP_narrowVax_AZ



AESI_BP_narrowVax_J&J

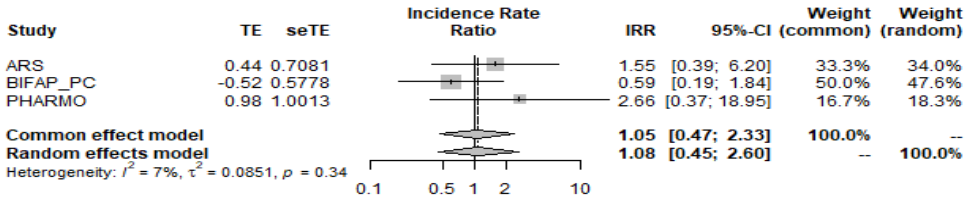


Figure 25 Incidence rate ratio for Bell's palsy between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19

3.4.9 Chilblain like lesions

Chilblains could not be identified in ARS, as this is a condition captured in primary care. Age standardised rates were comparable across data sources. Rate differences varied, from being reduced to being elevated (CPRD) both after Comirnaty and Vaxzevria and the meta-analysis showed strong heterogeneity. Partial adjustment for the variables measured in the study showed that no association remained after pooling in the random effects model.

Table 22 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for chilblain

Vaccine	Dose	Estimate	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
none		Background crude incidence rate	26.4 (25.1;27.8)	27.5 (25.2;29.9)	13.9 (13.3;14.6)	29.8 (27.5;32.2)
none		Background age-standardised incidence rate	27.1 (25.7;28.5)	28.0 (25.6;30.6)	14.0 (13.4;14.7)	29.3 (27.1;31.7)
Comirnaty	1	Observed person-years after vaccination	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	43	6	21	12
Comirnaty	1	Observed cases	18	<5	109	7
Comirnaty	1	Age-standardised incidence rate	8.5 (4.8;13.8)	8.9 (1.0;33.2)	71.1 (51.5;95.8)	10.9 (3.1;27.6)
Comirnaty	1	Age-standardised rate difference	**-18.6 (-23.0;-14.2)**	**-19.2 (-32.1;-6.3)**	**57.1 (35.9;78.4)**	**-18.4 (-29.1;-7.6)**
Comirnaty	2	Observed person-years after vaccination	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	41	6	14	<5
Comirnaty	2	Observed cases	14	<5	37	0
Comirnaty	2	Age-standardised incidence rate	5.1 (2.6;9.0)	9.6 (1.1;35.7)	30.4 (18.1;48.0)	
Comirnaty	2	Age-standardised rate difference	**-22.0 (-25.2;-18.7)**	**-18.5 (-32.3;-4.6)**	**16.4 (2.4;30.4)**	
Vaxzevria	1	Observed person-years after vaccination	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	8	<5	37	<5
Vaxzevria	1	Observed cases	6	0	122	<5
Vaxzevria	1	Age-standardised incidence rate	20.0 (5.4;51.3)		37.1 (29.7;45.8)	3.3 (0.1;18.5)
Vaxzevria	1	Age-standardised rate difference	-7.1 (-26.8;12.6)		**23.1 (15.3;30.9)**	**-26.0 (-32.9;-19.1)**
Vaxzevria	2	Observed person-years after vaccination	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	6	<5	10	<5
Vaxzevria	2	Observed cases	<5	<5	17	<5
Vaxzevria	2	Age-standardised incidence rate	0.8 (0.0;4.6)	4.3 (0.1;23.9)	26.3 (9.7;57.0)	9.0 (0.2;50.0)
Vaxzevria	2	Age-standardised rate difference	**-26.2 (-28.4;-24.1)**	**-23.7 (-32.5;-15.0)**	12.3 (-8.7;33.2)	**-20.3 (-38.1;-2.6)**
Spikevax	1	Observed person-years after vaccination	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	9	<5	0	<5
Spikevax	1	Observed cases	<5	<5	0	0
Spikevax	1	Age-standardised incidence rate	2.6 (0.1;14.7)	11.7 (0.3;65.3)		
Spikevax	1	Age-standardised rate difference	**-24.4 (-29.8;-19.1)**	-16.3 (-39.4;6.8)		
Spikevax	2	Observed person-years after vaccination	23,386	4,095	30	1,397
Spikevax	2	Expected cases	6	<5	0	0
Spikevax	2	Observed cases	0	0	0	0
Spikevax	2	Age-standardised incidence rate				
Spikevax	2	Age-standardised rate difference				
Janssen	1	Observed person-years after vaccination	14,667	2,404	.	1,282
Janssen	1	Expected cases	<5	<5	.	0
Janssen	1	Observed cases	0	0	.	0
Janssen	1	Age-standardised incidence rate				
Janssen	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination	16			8,282
Unknown	1	Expected cases	0			<5
Unknown	1	Observed cases	0			<5
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination	9			2,044
Unknown	2	Expected cases	0			<5
Unknown	2	Observed cases	0			<5
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

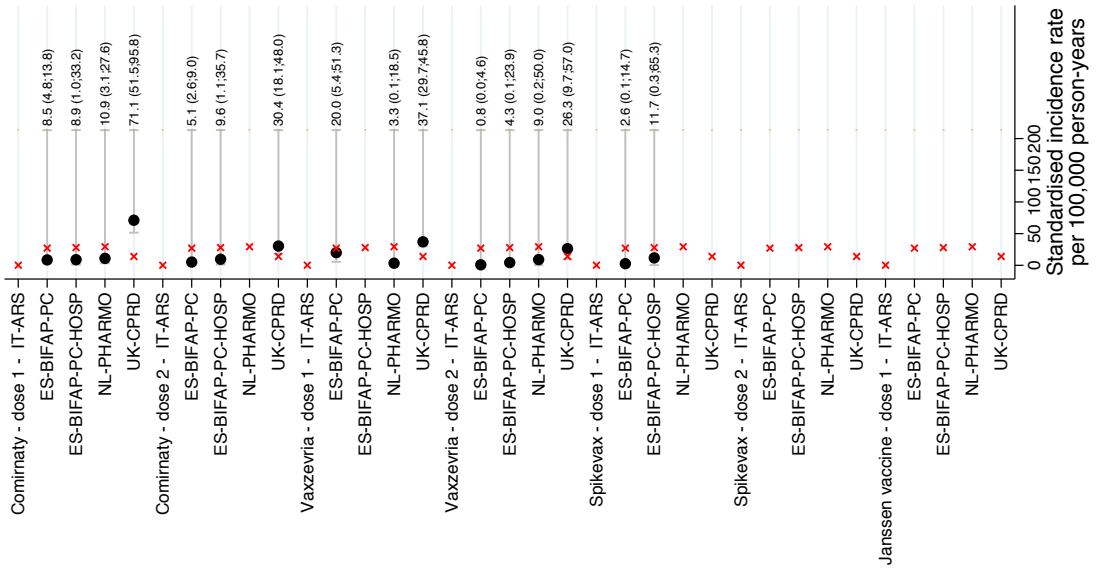
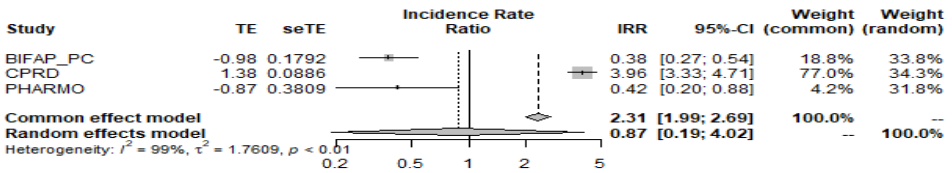
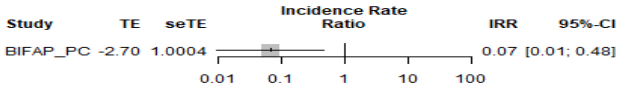


Figure 26 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for chilblain**

AESI_CHILBLAIN_narrowVax_Pfizer



AESI_CHILBLAIN_narrowVax_Moderna



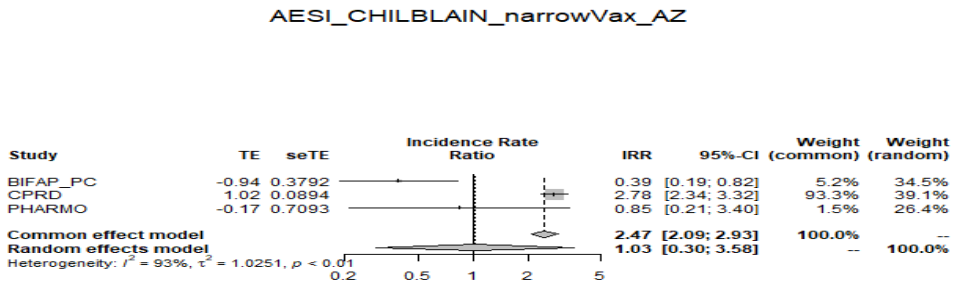


Figure 27 Incidence rate ratio for chilblain between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19

3.4.10 Death

Death is a common event, crude rates showed both elevations and reductions. Partial adjustment for the covariates we could measure showed that none of the vaccines was associated with death. In PHARMO level checks showed that death data were not complete and therefore not included in this analysis.

Table 23 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for all cause death

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	1330.1 (1317.9;1342.3)	725.5 (718.5;732.4)	845.0 (832.0;858.1)	746.2 (741.6;750.8)
None		Background age-standardised incidence rate	870.6 (862.5;878.8)	546.6 (541.3;552.0)	559.9 (551.0;568.8)	790.7 (785.8;795.6)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	1,904	1,612	116	2,910
Comirnaty	1	Observed cases	1,264	1,412	166	1,562
Comirnaty	1	Age-standardised incidence rate	608.5 (572.0;646.7)	446.1 (421.9;471.3)	834.1 (709.2;974.6)	434.4 (410.2;459.6)
Comirnaty	1	Age-standardised rate difference	**-262.2 (-300.1;-224.3)**	**-100.5 (-125.7;-75.4)**	**274.2 (144.0;404.4)**	**-356.3 (-381.3;-331.3)**
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	2,119	2,030	142	2,384
Comirnaty	2	Observed cases	1,188	1,028	107	790
Comirnaty	2	Age-standardised incidence rate	720.4 (567.6;901.7)	264.9 (247.6;283.0)	453.0 (369.4;549.8)	257.9 (235.8;281.6)
Comirnaty	2	Age-standardised rate difference	-150.2 (-312.4;12.0)	**-281.8 (-300.1;-263.4)**	**-106.9 (-195.2;-18.6)**	**-532.8 (-555.9;-509.6)**
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	301	161	28	2,473
Vaxzevria	1	Observed cases	41	22	12	2,747
Vaxzevria	1	Age-standardised incidence rate	52.0 (34.4;75.5)	20.9 (7.5;46.2)	45.0 (20.8;84.7)	1036.8 (995.6;1079.1)
Vaxzevria	1	Age-standardised rate difference	**-818.6 (-839.7;-797.5)**	**-525.7 (-543.6;-507.8)**	**-514.9 (-545.3;-484.6)**	**246.0 (204.2;287.9)**
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	61	111	22	1,256
Vaxzevria	2	Observed cases	3	19	8	834
Vaxzevria	2	Age-standardised incidence rate	17.6 (3.4;52.9)	19.5 (11.0;31.9)	34.3 (14.8;67.6)	578.5 (535.6;623.9)
Vaxzevria	2	Age-standardised rate difference	**-853.0 (-875.1;-831.0)**	**-527.1 (-538.2;-516.0)**	**-525.6 (-550.9;-500.2)**	**-212.2 (-256.2;-168.3)**
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	76	197	44	2
Spikevax	1	Observed cases	118	59	24	0
Spikevax	1	Age-standardised incidence rate	1612.1 (1101.7;2277.3)	158.7 (120.2;205.7)	294.6 (188.0;439.5)	
Spikevax	1	Age-standardised rate difference	**741.4 (181.7;1301.2)**	**-387.9 (-429.5;-346.3)**	**-265.3 (-384.4;-146.3)**	
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	59	189	44	1
Spikevax	2	Observed cases	120	35	26	0
Spikevax	2	Age-standardised incidence rate	2056.5 (1461.5;2812.6)	101.4 (69.9;142.3)	388.4 (241.2;592.4)	
Spikevax	2	Age-standardised rate difference	**1185.8 (539.3;1832.3)**	**-445.2 (-480.1;-410.3)**	**-171.4 (-336.8;-6.0)**	
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	36	35	7	.
Janssen	1	Observed cases	4	19	12	.
Janssen	1	Age-standardised incidence rate	34.5 (8.6;92.5)	1173.0 (488.8;2363.6)	3570.5 (1472.2;7242.7)	
Janssen	1	Age-standardised rate difference	**-836.1 (-872.6;-799.6)**	626.3 (-214.6;1467.3)	3010.6 (425.5;5595.8)	
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

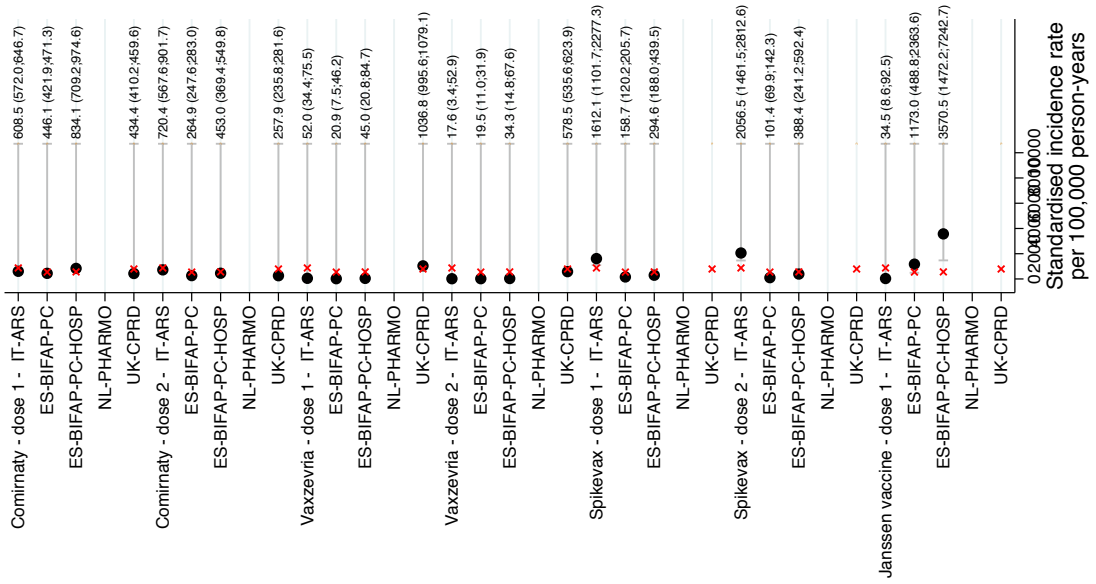
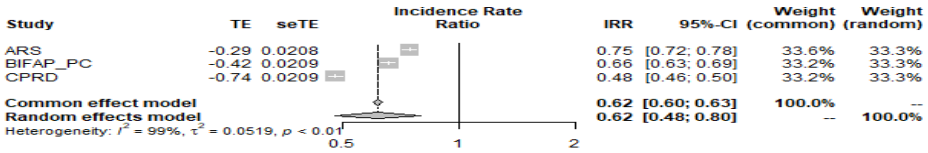
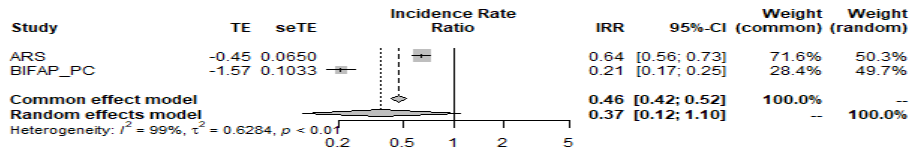


Figure 28 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for all cause death**

AESI_DEATHVax_Pfizer



AESI_DEATHVax_Moderna



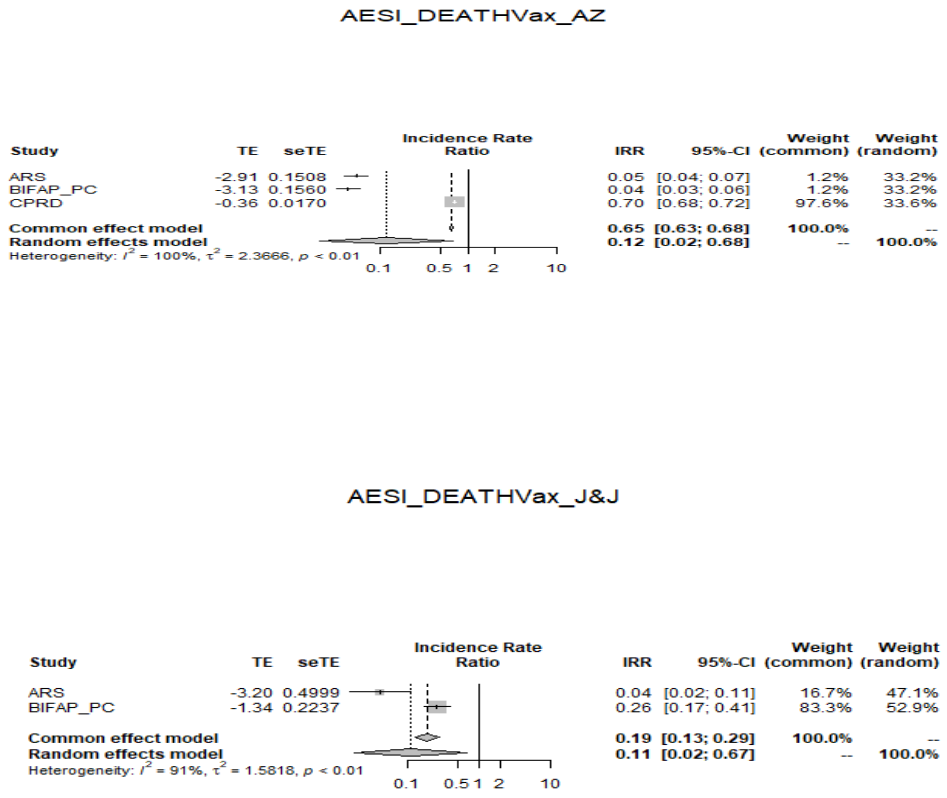


Figure 29 **Incidence rate ratio for all cause death between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

Table 24 Crude incidence rate ratios of death comparing post-vaccination dose 1 and 2 (28 days) with non-vaccinated (2020)

vaccine	Cases ARS	IRR crude ARS	Cases BIFAP PC	IRR crude BIFAP PC	Cases BIFAP-PC-HOSP	Crude IRR BIFAP PC-HOSP	Cases CPRD	Crude IRR CPRD
AZ	44	0.10 (0.07,0.13)	41	0.08 (0.06,0.11)	20	0.22 (0.14,0.35)	3581	1.46 (1.41,1.51)
J&J	4	0.07 (0.03,0.20)	20	0.19 (0.12,0.29)	12	0.59 (0.33,1.04)	0	0.00 (0.00,0.00)
Moderna	238	0.95 (0.84,1.08)	94	0.23 (0.19,0.28)	50	0.63 (0.47,0.83)	0	0.00 (0.00,Inf)
Pfizer	2452	1.53 (1.47,1.59)	2440	1.03 (0.99,1.08)	273	0.77 (0.68,0.87)	2352	1.42 (1.37,1.48)
Background rate	3937		403		403		4374	

Table 23 shows that the crude incidence rate ratios showed both elevation and reductions of risk, adjustment for factors we could measure (see figure 29) reversed this substantially, indicating strong confounding, and actual protection from death.

We tried to assess sudden death, but this was highly variable and not credible between data sources. We would recommend a dedicated study to assess this.

3.4.11 Erythema multiforme

Erythema multiforme is an extremely rare event, rates were very comparable across sites (PHARMO could not assess). In our data we do not find an association with covid vaccinations, except for Moderna vaccine (Spikevax), which showed a pooled IRR of 2.64 (1.25-5.60), based on seven events, in particular three observed in ARS.

Table 25 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for erythema multiforme

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	4.2 (3.5;4.9)	4.0 (3.5;4.6)	4.7 (3.8;5.8)	5.1 (4.8;5.5)
none		Background age-standardised incidence rate	4.0 (3.3;4.7)	4.3 (3.8;4.9)	5.5 (4.4;6.8)	5.1 (4.8;5.5)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	4	5	1	6
Comirnaty	1	Observed cases	6	3	0	3
Comirnaty	1	Age-standardised incidence rate	7.6 (2.4;18.3)	1.8 (0.3;5.7)		0.7 (0.1;2.2)
Comirnaty	1	Age-standardised rate difference	3.6 (-3.3;10.6)	-2.5 (-4.7;-0.2)		-4.4 (-5.3;-3.5)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	2	5	1	4
Comirnaty	2	Observed cases	1	4	0	4
Comirnaty	2	Age-standardised incidence rate	0.3 (0.0;1.8)	1.6 (0.4;4.5)		8.2 (2.1;21.4)
Comirnaty	2	Age-standardised rate difference	**-3.7 (-4.6;-2.8)**	**-2.7 (-4.5;-0.8)**		3.0 (-5.2;11.3)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	1	1	0	11
Vaxzevria	1	Observed cases	1	1	0	12
Vaxzevria	1	Age-standardised incidence rate	0.8 (0.0;4.7)	0.5 (0.0;2.7)		3.0 (1.5;5.4)
Vaxzevria	1	Age-standardised rate difference	**-3.2 (-4.9;-1.4)**	**-3.8 (-4.9;-2.7)**		**-2.1 (-4.0;-0.3)**
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	1	0	3
Vaxzevria	2	Observed cases	0	0	0	3
Vaxzevria	2	Age-standardised incidence rate				2.5 (0.5;7.3)
Vaxzevria	2	Age-standardised rate difference				-2.7 (-5.5;0.2)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	1	0	0
Spikevax	1	Observed cases	3	3	2	0
Spikevax	1	Age-standardised incidence rate	21.3 (3.9;65.7)	9.6 (1.9;28.6)	39.0 (4.5;143.5)	
Spikevax	1	Age-standardised rate difference	17.3 (-8.1;42.8)	5.3 (-5.8;16.4)	33.5 (-21.5;88.4)	
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	1	0	0
Spikevax	2	Observed cases	0	1	0	0
Spikevax	2	Age-standardised incidence rate		4.0 (0.1;22.5)		
Spikevax	2	Age-standardised rate difference		-0.3 (-8.2;7.7)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	0	0	.
Janssen	1	Age-standardised incidence rate				
Janssen	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

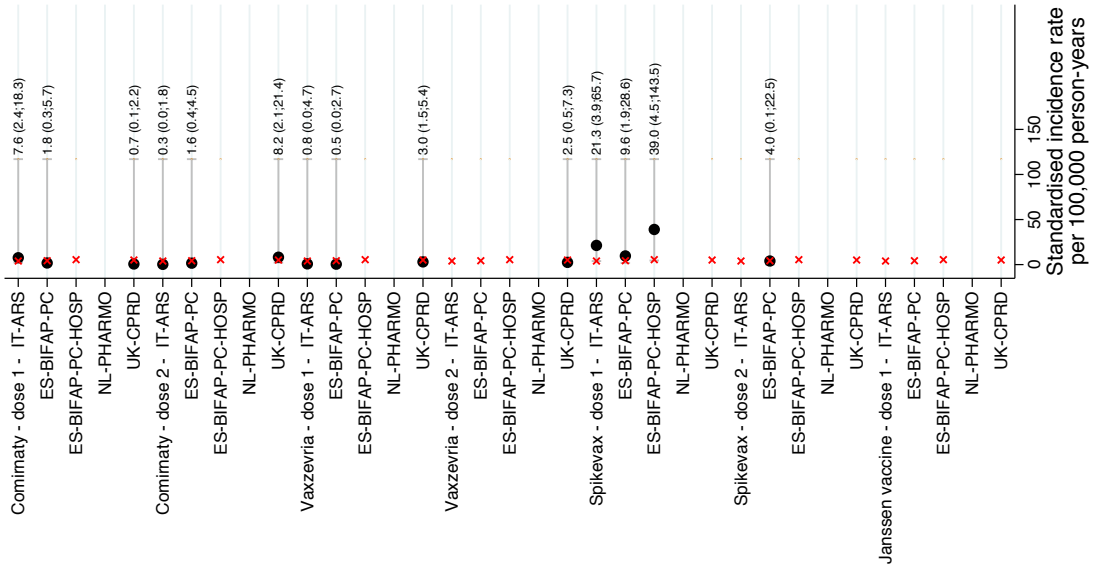
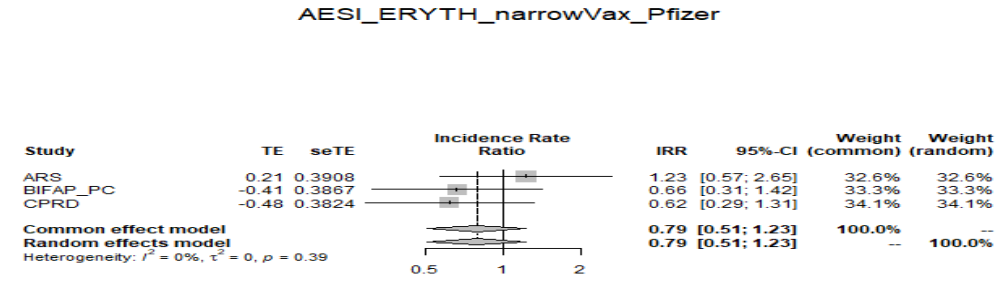
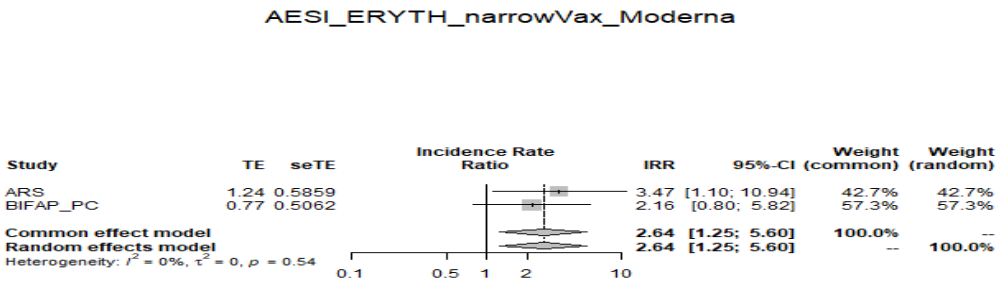


Figure 30 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for erythema multiforme**





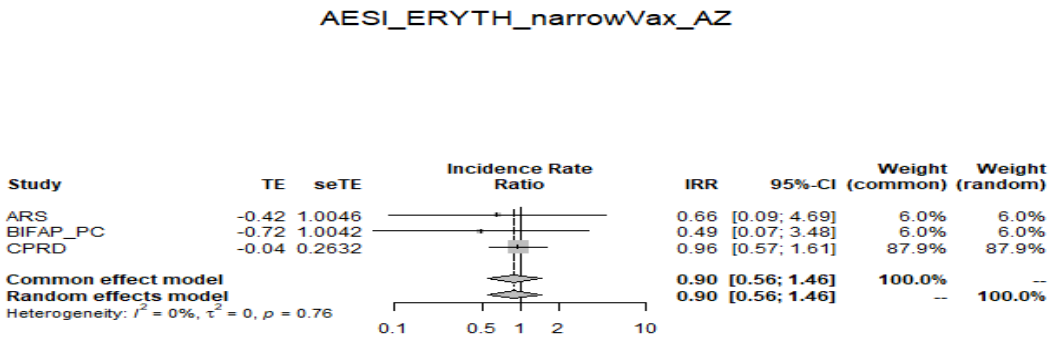


Figure 31 **Incidence rate ratio for erythema multiforme between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

Table 26 **Crude incidence rate ratios for erythema multiforme comparing post-vaccination dose 1+2 with non-vaccinated (2020)**

	ARS		BIFAP_PC		BIFAP_PC_HOSP		CPRD		PHARMO	
Vaccine	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)
AZ	1	0.71 (0.10,5.05)	1	0.36 (0.05,2.54)	0	0.00 (0.00,Inf)	15	0.89 (0.53,1.48)	0	0.00 (0.00,0.00)
J&J	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)	0	0.00 (0.00,0.00)	0	0.00 (0.00,0.00)
Moderna	3	**3.82 (1.22,11.99)**	4	1.76 (0.66,4.73)	2	**4.48 (1.10,18.17)**	0	0.00 (0.00,Inf)	0	0.00 (0.00,0.00)
Pfizer	7	1.39 (0.65,2.96)	7	0.54 (0.25,1.14)	0	0.00 (0.00,Inf)	7	0.62 (0.29,1.30)	0	0.00 (0.00,0.00)
Background	139		40		40		405		NA	

Figure 32 shows the monitoring of erythema multiforme over time following Moderna vaccination, the increase is visible especially in ARS and BIFAP, in young people after dose 1.

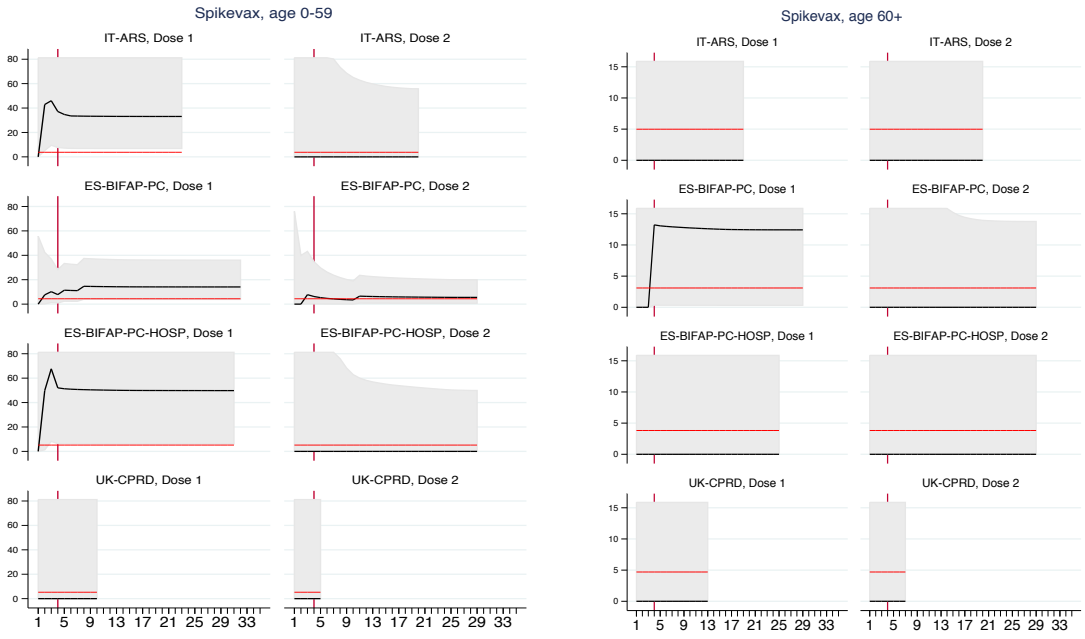


Figure 32: Monitoring graphics of erythema multiforme following Moderna vaccination over time (cumulative), black is post-vaccine, red is background rate in 2020

3.4.12 Guillain Barre Syndrome (GBS)

GBS is a very rare event, and the age standardised background rate was very comparable across sites. In our study we observed a significant association between Janssen vaccine and GBS, but only based on < 5 cases. In the crude analysis, also AstraZeneca was associated with an increased risk of GBS in CPRD and with Pfizer vaccine in PHARMO. Much of this was confounded and the relative risk (see forest plots) were lower, but remained significantly elevated for Janssen vaccine.

Table 27 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for GBS

Vaccine	Dose	namelong	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
		Background crude incidence rate	3.1 (2.5;3.7)	1.2 (0.9;1.5)	1.9 (1.3;2.6)	1.8 (1.5;2.0)	1.1 (0.7;1.7)
		Background age-standardised incidence rate	2.7 (2.2;3.3)	1.2 (0.9;1.5)	1.8 (1.2;2.5)	1.8 (1.6;2.1)	1.1 (0.7;1.6)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	<5	<5	0	<5	<5
Comirnaty	1	Observed cases	<5	<5	<5	<5	<5
Comirnaty	1	Age-standardised incidence rate	2.4 (0.3;9.1)	1.4 (0.1;5.2)	3.9 (0.1;21.9)	2.1 (0.5;5.9)	4.8 (0.4;20.5)
Comirnaty	1	Age-standardised rate difference	-0.3 (-3.8;3.2)	0.2 (-1.8;2.2)	2.2 (-5.6;9.9)	0.3 (-2.0;2.6)	3.7 (-4.0;11.4)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	<5	<5	0	<5	0
Comirnaty	2	Observed cases	<5	<5	0	<5	<5
Comirnaty	2	Age-standardised incidence rate	1.4 (0.1;6.0)	1.0 (0.1;3.8)		0.4 (0.0;2.1)	18.3 (0.5;101.8)
Comirnaty	2	Age-standardised rate difference	-1.3 (-3.6;1.0)	-0.2 (-1.7;1.3)		-1.4 (-2.2;-0.7)	17.2 (-18.6;53.0)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	<5	<5	0	7	0
Vaxzevria	1	Observed cases	<5	<5	<5	10	0
Vaxzevria	1	Age-standardised incidence rate	5.2 (0.1;28.7)	1.8 (0.2;7.2)	3.1 (0.1;17.4)	2.3 (1.1;4.2)	
Vaxzevria	1	Age-standardised rate difference	2.5 (-7.6;12.6)	0.6 (-2.1;3.3)	1.4 (-4.8;7.5)	0.4 (-1.0;1.9)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	0	0	0	<5	0
Vaxzevria	2	Observed cases	0	0	0	<5	0
Vaxzevria	2	Age-standardised incidence rate				0.8 (0.1;2.9)	
Vaxzevria	2	Age-standardised rate difference				-1.0 (-2.2;0.1)	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	0	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0	0
Spikevax	1	Age-standardised incidence rate					
Spikevax	1	Age-standardised rate difference					
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	0	0	0	0	0
Spikevax	2	Observed cases	0	0	0	0	0
Spikevax	2	Age-standardised incidence rate					
Spikevax	2	Age-standardised rate difference					
Janssen vaccine	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen vaccine	1	Expected cases	0	0	0	.	0
Janssen	1	Observed cases	<5	<5	0	.	0
Janssen	1	Age-standardised incidence rate	**7.0 (0.2;39.0)**	**7.9 (0.2;43.9)**			
Janssen	1	Age-standardised rate difference	4.3 (-9.4;18.0)	6.7 (-8.7;22.1)			
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			0
Unknown	1	Observed cases		0			2
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			0
Unknown	2	Observed cases		0			0
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

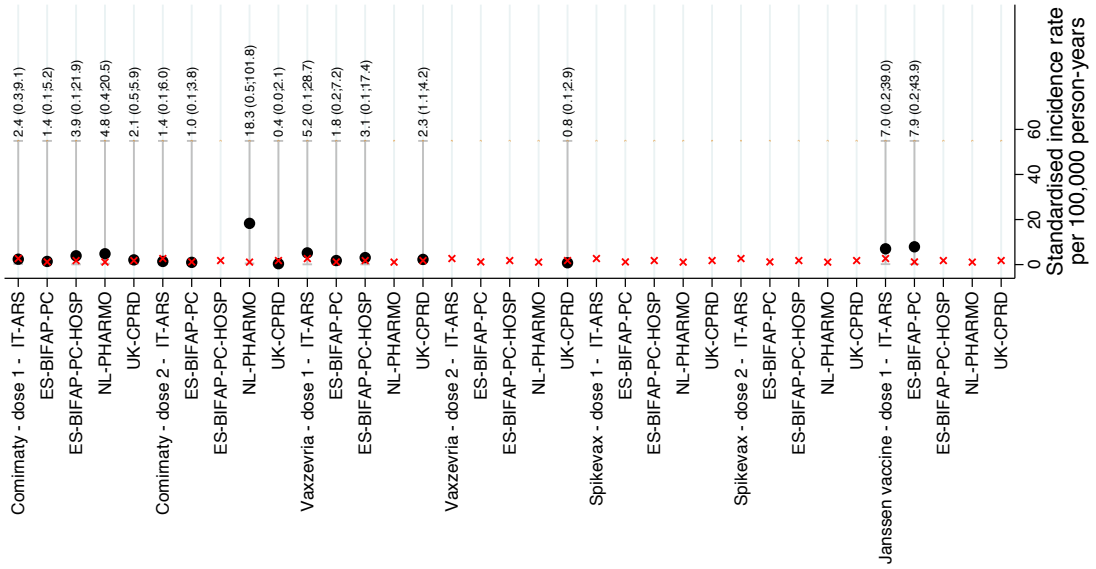


Figure 33 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for GBS**

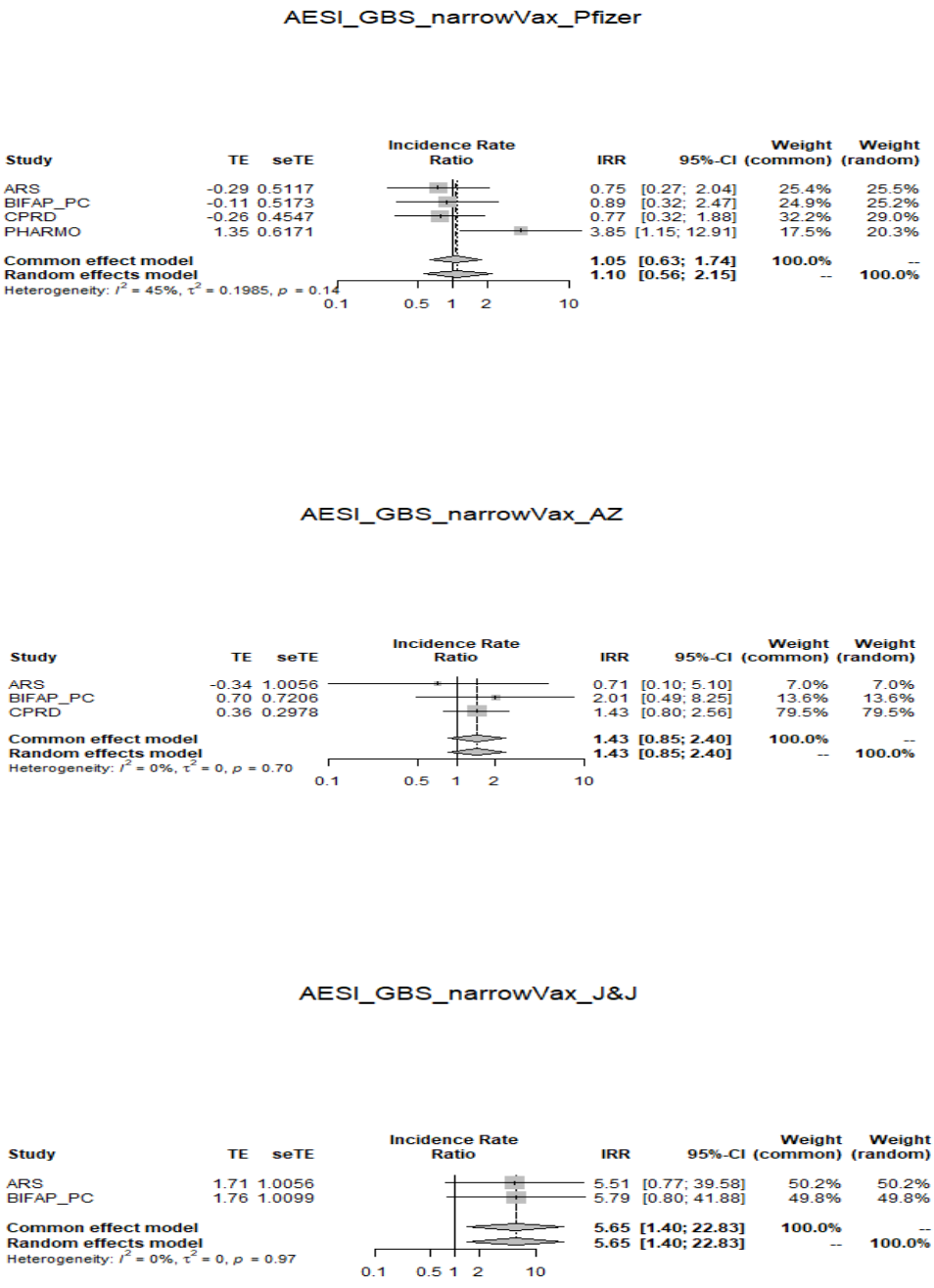


Figure 34 Incidence rate ratio for GBS between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19

Table 28 Crude incidence rate ratios for GBS comparing post-vaccination dose 1+2 with non-vaccinated (2020)

	ARS		BIFAP_PC		BIFAP_PC_HOSP		CPRD		PHARMO	
Vaccine	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)
AZ	1	0.96 (0.13,6.87)	2	2.40 (0.59,9.77)	1	5.01 (0.69,36.53)	12	**2.07 (1.16,3.69)**	0	0.00 (0.00,Inf)
J&J	1	**7.96 (1.11,Inf)**	1	5.70 (0.79,41.06)	0	0.00 (0.00,Inf)	0	0.00 (0.00,0.00)	0	0.00 (0.00,Inf)
Moderna	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)
Pfizer	4	1.08 (0.40,2.92)	4	1.03 (0.38,2.82)	1	1.26 (0.17,9.18)	5	1.28 (0.53,3.10)	3	**5.03 (1.52,16.66)**
Background	105		31		31		209		19	

Figure 33 shows a significant increased rate of GBS post-dose 1 of Janssen vaccine, table 27 shows that the crude results were much higher and adjustment lowered the rate ratios. Figure 35 shows the monitoring of GBS over time, it shows that the risk is elevated both in BIFAP and ARS post dose 1 of Janssen, especially in elderly.

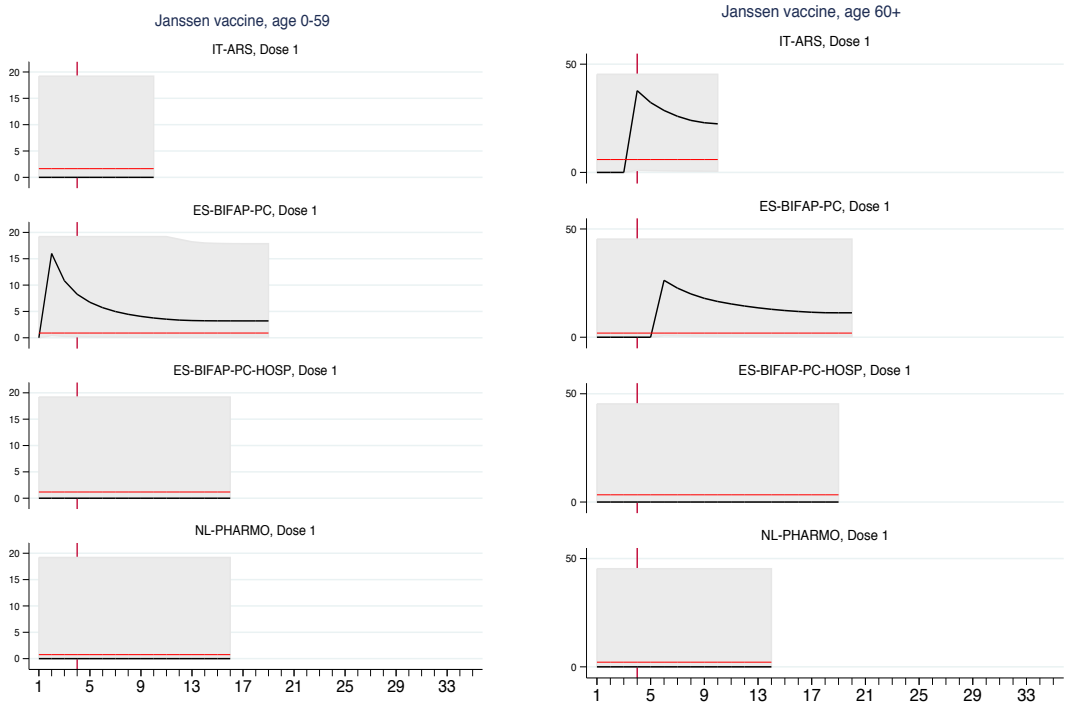


Figure 35 Monitoring of GBS incidence (y-axis per 100,000 PY) post-vaccination (cumulative) following Janssen (J&J) vaccination over time (cumulative weeks), black is post-vaccine, red is background rate in 2020

3.4.13 Generalized convulsions

Generalized convulsions are rare events, in this study AstraZeneca and Moderna Covid-19 vaccine showed small associations with generalized convulsions, comparison of the crude associations and the adjusted showed substantial change towards the null. No elevation of rates remains.

Table 29 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for generalized convulsions

Vaccine	Dose	namelong	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	192.6 (188.0;197.3)	45.9 (44.2;47.7)	80.4 (76.5;84.6)	182.9 (180.6;185.2)	20.3 (18.4;22.2)
None		Background age-standardised incidence rate	187.0 (182.3;191.8)	48.2 (46.3;50.1)	88.6 (84.0;93.4)	183.9 (181.6;186.2)	22.3 (20.3;24.5)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	157	58	11	252	4
Comirnaty	1	Observed cases	201	66	10	316	5
Comirnaty	1	Age-standardised incidence rate	198.2 (162.8;239.0)	33.9 (25.5;44.3)	46.2 (21.0;88.0)	267.0 (223.1;317.1)	12.3 (3.3;31.8)
Comirnaty	1	Age-standardised rate difference	11.2 (-26.2;48.6)	-14.2 (-23.5;-5.0)	-42.4 (-73.1;-11.7)	83.1 (37.1;129.1)	-10.0 (-22.4;2.4)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	125	62	12	167	1
Comirnaty	2	Observed cases	122	79	14	129	1
Comirnaty	2	Age-standardised incidence rate	335.3 (188.0;552.5)	42.0 (28.0;60.7)	73.6 (30.7;148.2)	175.0 (110.5;263.5)	4.6 (0.1;25.4)
Comirnaty	2	Age-standardised rate difference	148.3 (-21.0;317.7)	-6.1 (-21.8;9.5)	-15.0 (-67.9;37.9)	-8.9 (-81.1;63.2)	-17.7 (-26.9;-8.6)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	48	13	4	448	0
Vaxzevria	1	Observed cases	19	11	3	708	0
Vaxzevria	1	Age-standardised incidence rate	38.4 (16.9;74.6)	10.3 (3.0;25.8)	9.4 (1.9;27.4)	389.5 (335.0;450.2)	
Vaxzevria	1	Age-standardised rate difference	-148.6 (-175.1;-122.2)	-37.9 (-47.9;-27.8)	-79.2 (-90.8;-67.6)	205.6 (149.0;262.1)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	12	9	3	112	0
Vaxzevria	2	Observed cases	6	5	1	132	0
Vaxzevria	2	Age-standardised incidence rate	99.6 (18.7;303.4)	6.7 (1.9;17.2)	4.3 (0.1;23.9)	333.3 (190.0;542.4)	
Vaxzevria	2	Age-standardised rate difference	-87.4 (-205.0;30.2)	-41.4 (-48.3;-34.6)	-84.3 (-93.9;-74.7)	149.4 (-14.6;313.4)	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	17	10	3	2	0
Spikevax	1	Observed cases	35	12	2	0	0
Spikevax	1	Age-standardised incidence rate	209.5 (143.4;295.7)	40.2 (20.4;71.0)	28.7 (3.5;103.8)		
Spikevax	1	Age-standardised rate difference	22.5 (-50.2;95.2)	-8.0 (-31.3;15.3)	-59.8 (-99.9;-19.7)		
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	11	8	3	0	0
Spikevax	2	Observed cases	25	9	0	0	0
Spikevax	2	Age-standardised incidence rate	343.5 (195.4;559.8)	34.7 (15.5;67.1)			
Spikevax	2	Age-standardised rate difference	156.5 (-13.2;326.1)	-13.5 (-36.9;9.9)			
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	7	4	1	.	0
Janssen	1	Observed cases	2	2	0	.	0
Janssen	1	Age-standardised incidence rate	14.0 (1.7;50.6)	180.6 (5.6;961.7)			
Janssen	1	Age-standardised rate difference	-173.0 (-193.0;-153.0)	132.4 (-210.0;474.8)			
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			1
Unknown	1	Observed cases		0			1
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			0
Unknown	2	Observed cases		0			1

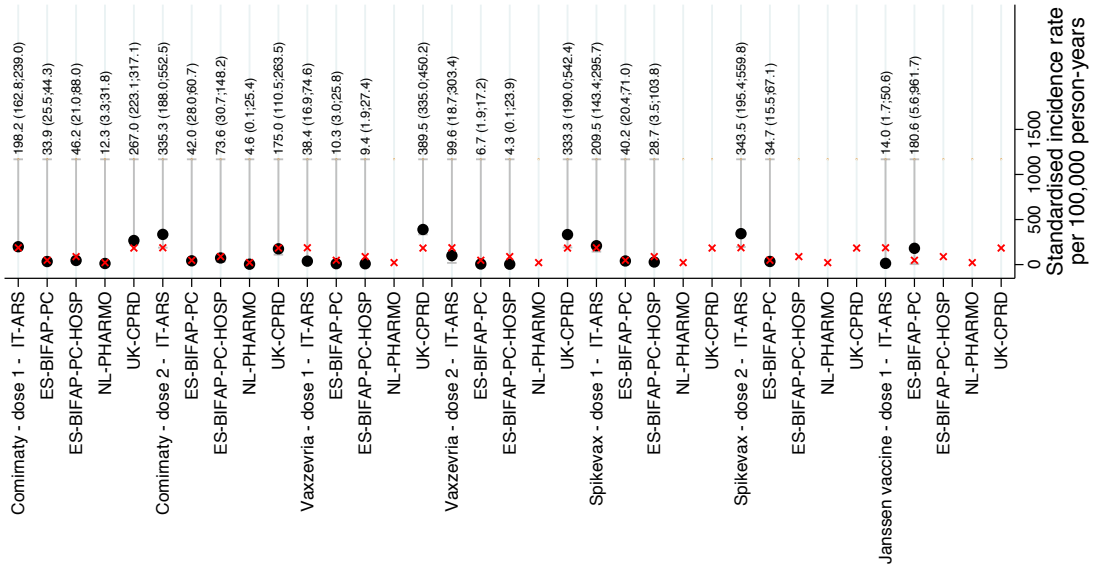
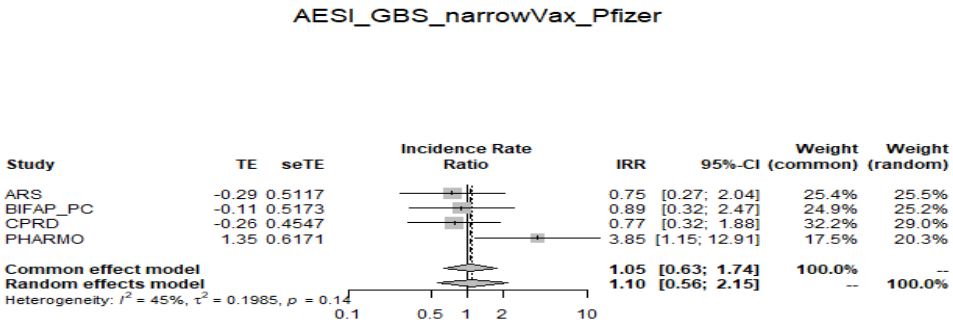
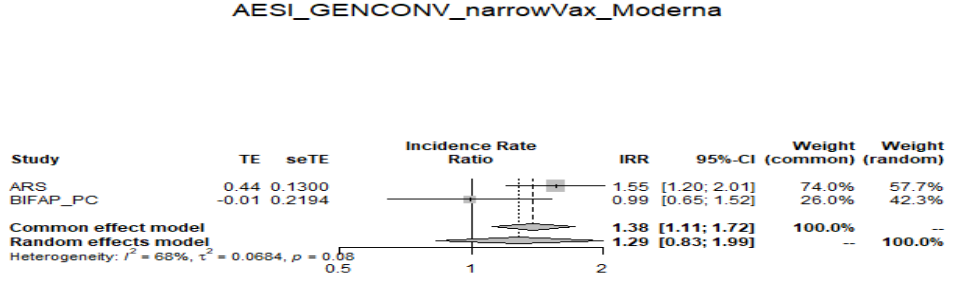


Figure 36 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for generalized convulsions**





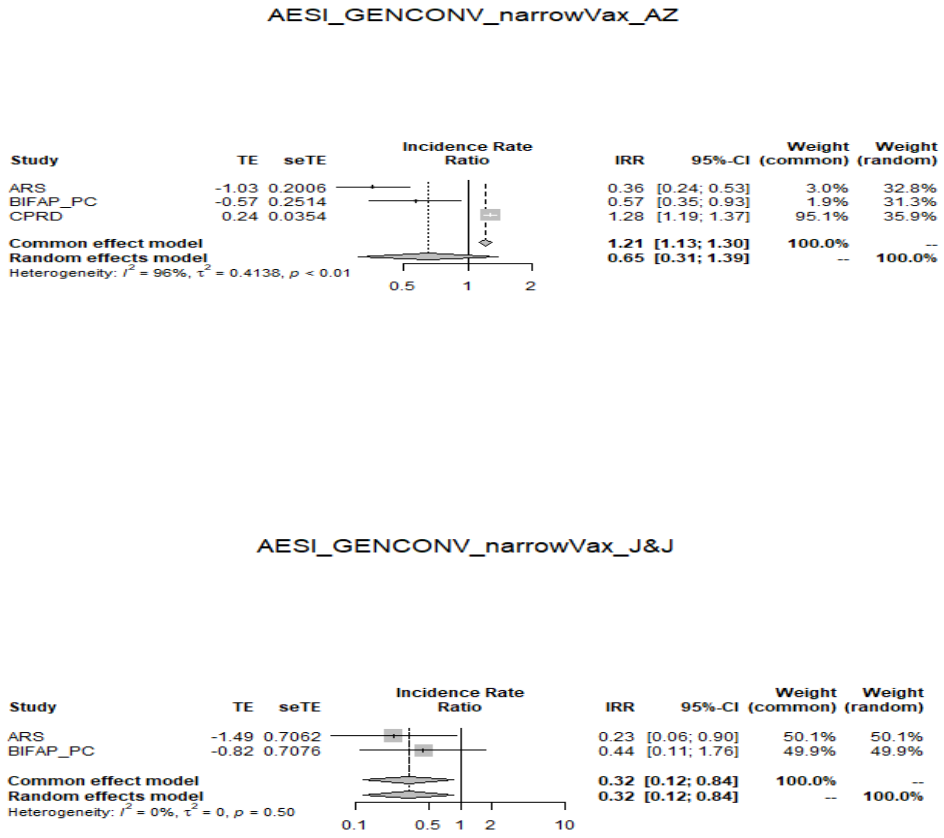


Figure 37 **Partially adjusted incidence rate ratios for generalized convulsions between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

Table 30 **Crude incidence rate ratios for generalized convulsions comparing post-vaccination dose 1+2 with non-vaccinated (2020)**

	ARS		BIFAP_PC		BIFAP_PC_HOSP		CPRD		PHARMO	
Vaccine	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)	Events	IRR (95%CI)
AZ	25	0.38 (0.26,0.57)	16	0.50 (0.30,0.81)	4	0.47 (0.18,1.26)	840	**1.40 (1.30,1.50)**	0	0.00 (0.00,Inf)
J&J	2	0.25 (0.06,1.02)	2	0.30 (0.07,1.18)	0	0.00 (0.00,Inf)	0	0.00 (0.00,0.00)	0	0.00 (0.00,Inf)
Moderna	60	**1.66 (1.29,2.14)**	21	0.81 (0.53,1.24)	2	0.26 (0.07,1.05)	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)
Pfizer	323	**1.39 (1.24,1.55)**	145	0.97 (0.82,1.15)	24	0.71 (0.47,1.06)	445	**1.10 (1.00,1.21)**	6	0.57 (0.25,1.28)
Background	3015	ref	240	ref	240	ref	4392	ref	108	**ref**

3.4.14 Heart failure

Heart failure is an uncommon event, it was not associated with any covid-19 vaccine in our study, although initially standardised rate differences were elevated for some vaccines.

Table 31 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Standardised rate difference with 2020 background rates for heart failure

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	513.1 (505.5;520.7)	198.9 (195.3;202.6)	319.9 (311.9;328.0)	177.2 (175.0;179.5)	155.4 (150.2;160.8)
None		Background age-standardised incidence rate	352.6 (347.3;357.9)	153.7 (150.8;156.6)	217.8 (212.3;223.5)	191.4 (189.0;193.8)	155.9 (150.6;161.2)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	730	457	47	683	96
Comirnaty	1	Observed cases	680	693	63	708	111
Comirnaty	1	Age-standardised incidence rate	352.1 (323.8;382.1)	243.8 (224.9;263.8)	312.4 (237.4;403.7)	215.6 (198.3;233.9)	199.3 (161.8;242.8)
Comirnaty	1	Age-standardised rate difference	-0.5 (-29.9;28.8)	**90.1 (70.6;109.6)**	**94.6 (14.1;175.1)**	**24.2 (6.4;41.9)**	**43.4 (3.7;83.2)**
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	789	578	57	551	36
Comirnaty	2	Observed cases	685	878	91	578	47
Comirnaty	2	Age-standardised incidence rate	389.6 (346.4;436.7)	238.1 (221.7;255.4)	383.2 (306.6;473.0)	200.5 (180.4;222.2)	377.8 (235.6;574.2)
Comirnaty	2	Age-standardised rate difference	37.0 (-7.8;81.7)	**84.4 (67.5;101.3)**	**165.3 (84.3;246.3)**	9.1 (-11.7;29.9)	**222.0 (62.5;381.4)**
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	148	40	9	636	8
Vaxzevria	1	Observed cases	62	37	<5	827	18
Vaxzevria	1	Age-standardised incidence rate	77.6 (56.2;104.6)	788.1 (24.4;4198.0)	9.4 (1.9;27.5)	268.3 (248.6;289.1)	629.9 (250.5;1306.6)
Vaxzevria	1	Age-standardised rate difference	-274.9 (-298.7;-251.2)	634.4 (-860.2;2129.0)	-208.4 (-220.5;-196.4)	76.9 (56.7;97.1)	474.0 (2.8;945.2)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	30	27	7	314	<5
Vaxzevria	2	Observed cases	5	18	<5	351	<5
Vaxzevria	2	Age-standardised incidence rate	44.6 (11.6;117.0)	17.4 (9.8;28.6)	37.7 (8.0;108.6)	237.7 (210.5;267.3)	594.1 (19.9;3108.9)
Vaxzevria	2	Age-standardised rate difference	-308.0 (-353.2;-262.7)	-136.3 (-145.5;-127.1)	-180.2 (-222.5;-137.8)	46.3 (18.2;74.3)	438.3 (-673.7;1550.3)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	35	54	17	0	<5
Spikevax	1	Observed cases	59	72	19	0	<5
Spikevax	1	Age-standardised incidence rate	521.8 (297.1;849.7)	213.9 (166.9;270.0)	268.0 (157.3;426.6)		343.0 (75.1;975.7)
Spikevax	1	Age-standardised rate difference	169.2 (-88.1;426.4)	60.2 (10.2;110.2)	50.1 (-75.8;176.1)		187.2 (-190.3;564.6)
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	28	53	17	0	<5
Spikevax	2	Observed cases	61	68	18	0	<5
Spikevax	2	Age-standardised incidence rate	1091.9 (639.8;1740.7)	205.2 (158.7;261.0)	245.4 (140.4;398.3)		751.9 (70.9;2958.0)
Spikevax	2	Age-standardised rate difference	**739.3 (225.1;1253.5)**	**51.5 (1.9;101.0)**	27.6 (-92.6;147.8)		596.0 (-526.4;1718.4)
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	17	9	<5	.	0
Janssen	1	Observed cases	5	13	<5	.	<5
Janssen	1	Age-standardised incidence rate	1295.1 (40.7;6873.3)	142.7 (68.2;263.1)	170.6 (18.6;639.2)		3660.4 (92.7;20394.4)
Janssen	1	Age-standardised rate difference	942.5 (-1507.0;3392.0)	-11.0 (-99.9;77.9)	-47.2 (-291.5;197.0)		3504.5 (-3669.7;10678.8)
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			19
Unknown	1	Observed cases		0			37
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			<5
Unknown	2	Observed cases		0			<5
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

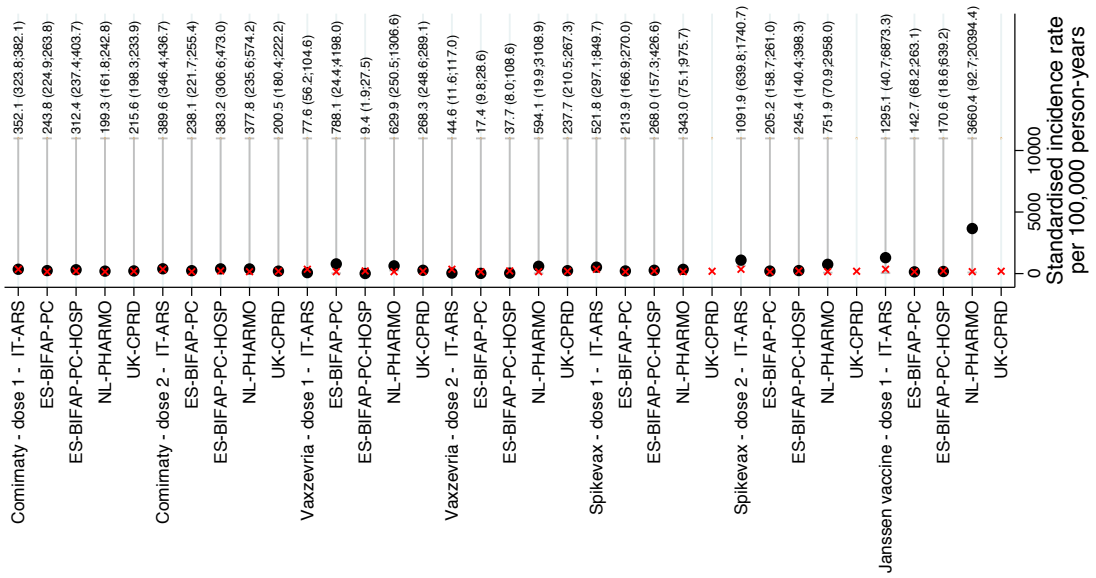
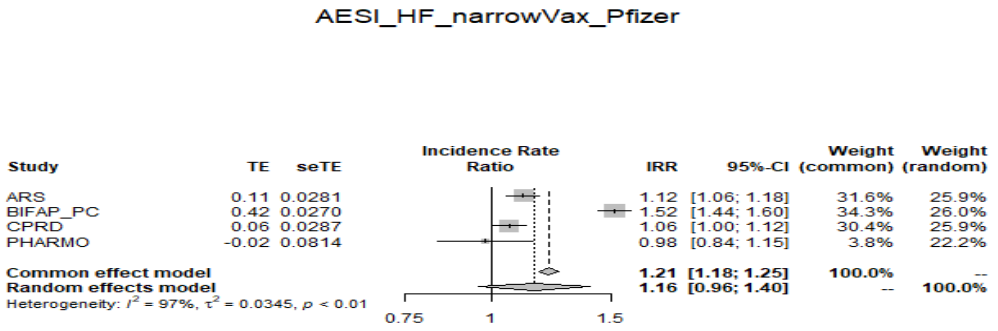
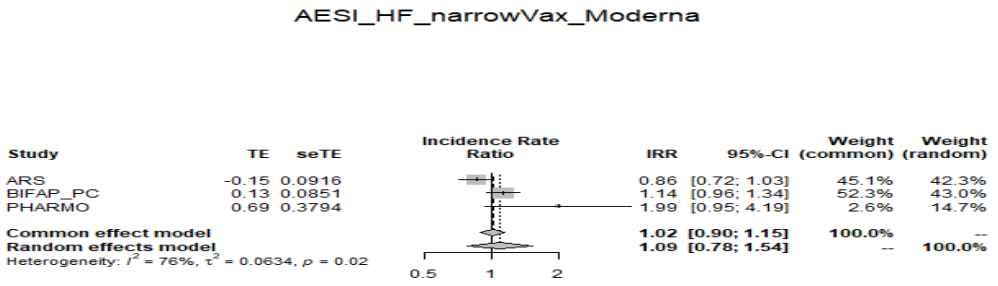


Figure 38 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for heart failure**





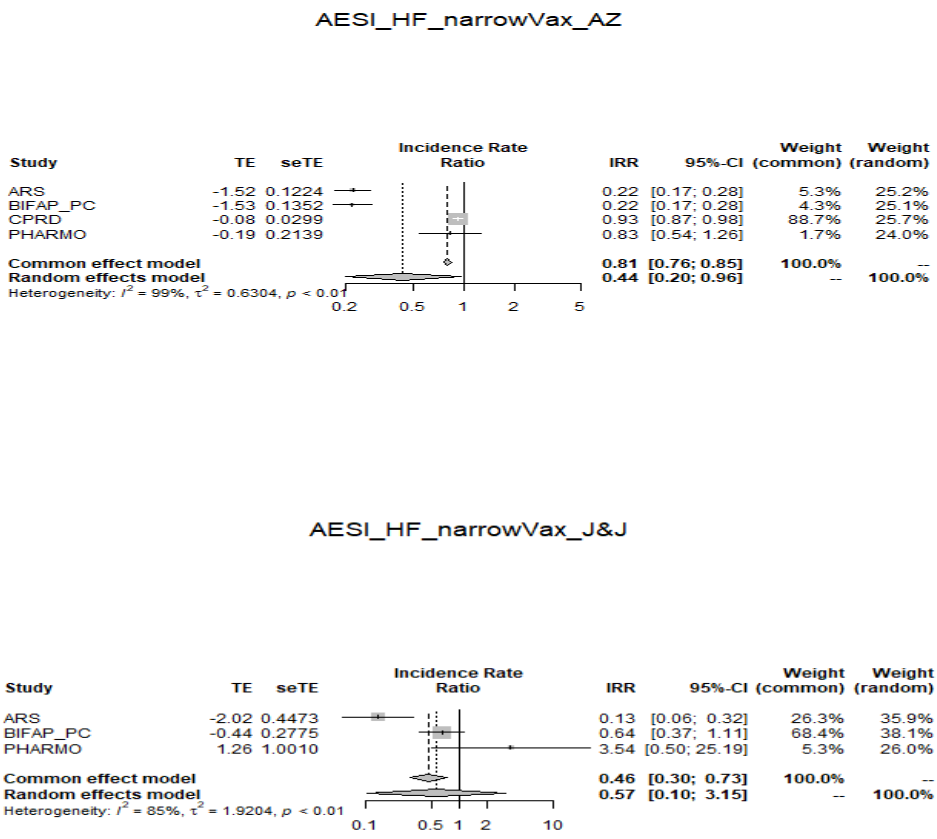


Figure 39 **Partially adjusted incidence rate ratio for heart failure between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.15 Meningoencephalitis

Meningo-encephahitis is an extremely rare event, it was not associated with any of the vaccines in our study, although point estimates were (non-significantly) elevated after Spikevax. PHARMO rates were lower than other datasources, and should only be used for internal comparisons.

Table 32 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for meningoencephalitis

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	5.5 (4.7;6.3)	4.2 (3.7;4.8)	6.9 (5.8;8.2)	4.5 (4.2;4.9)	1.4 (0.9;2.0)
None		Background age-standardised incidence rate	4.9 (4.2;5.7)	3.8 (3.3;4.3)	6.4 (5.3;7.7)	4.6 (4.2;5.0)	1.3 (0.9;1.9)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	5	8	<5	8	<5
Comirnaty	1	Observed cases	<5	10	<5	10	0
Comirnaty	1	Age-standardised incidence rate	9.3 (2.0;26.5)	4.0 (1.8;7.7)	3.9 (0.1;21.9)	6.3 (2.7;12.3)	
Comirnaty	1	Age-standardised rate difference	4.4 (-5.8;14.7)	0.3 (-2.4;3.0)	-2.5 (-10.3;5.3)	1.7 (-2.6;6.0)	
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	<5	10	<5	5	0
Comirnaty	2	Observed cases	<5	14	0	<5	0
Comirnaty	2	Age-standardised incidence rate	12.6 (1.6;44.6)	4.4 (2.3;7.7)		2.7 (0.3;10.2)	
Comirnaty	2	Age-standardised rate difference	7.7 (-9.5;24.9)	0.6 (-1.9;3.2)		-1.9 (-5.8;2.0)	
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	<5	<5	0	15	0
Vaxzevria	1	Observed cases	<5	<5	0	19	0
Vaxzevria	1	Age-standardised incidence rate	3.5 (0.4;12.6)	1.8 (0.2;7.2)		6.2 (3.4;10.5)	
Vaxzevria	1	Age-standardised rate difference	-1.4 (-6.3;3.5)	-2.0 (-4.7;0.8)		1.7 (-1.6;4.9)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	0	<5	0	<5	0
Vaxzevria	2	Observed cases	0	0	0	0	0
Vaxzevria	2	Age-standardised incidence rate					
Vaxzevria	2	Age-standardised rate difference					
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	1	1	0	0	0
Spikevax	1	Observed cases	2	1	0	0	0
Spikevax	1	Age-standardised incidence rate	9.7 (1.1;36.2)	4.0 (0.1;22.4)			
Spikevax	1	Age-standardised rate difference	4.8 (-9.0;18.6)	0.3 (-7.6;8.2)			
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	0	1	0	0	0
Spikevax	2	Observed cases	1	2	0	0	0
Spikevax	2	Age-standardised incidence rate	6.8 (0.2;38.0)	8.4 (1.0;30.5)			
Spikevax	2	Age-standardised rate difference	1.9 (-11.5;15.3)	4.7 (-7.0;16.4)			
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	0	0	0	.	0
Janssen	1	Observed cases	0	1	0	.	0
Janssen	1	Age-standardised incidence rate		6.0 (0.2;33.3)			
Janssen	1	Age-standardised rate difference		2.2 (-9.5;13.9)			
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			0
Unknown	1	Observed cases		0			0
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			0
Unknown	2	Observed cases		0			0
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

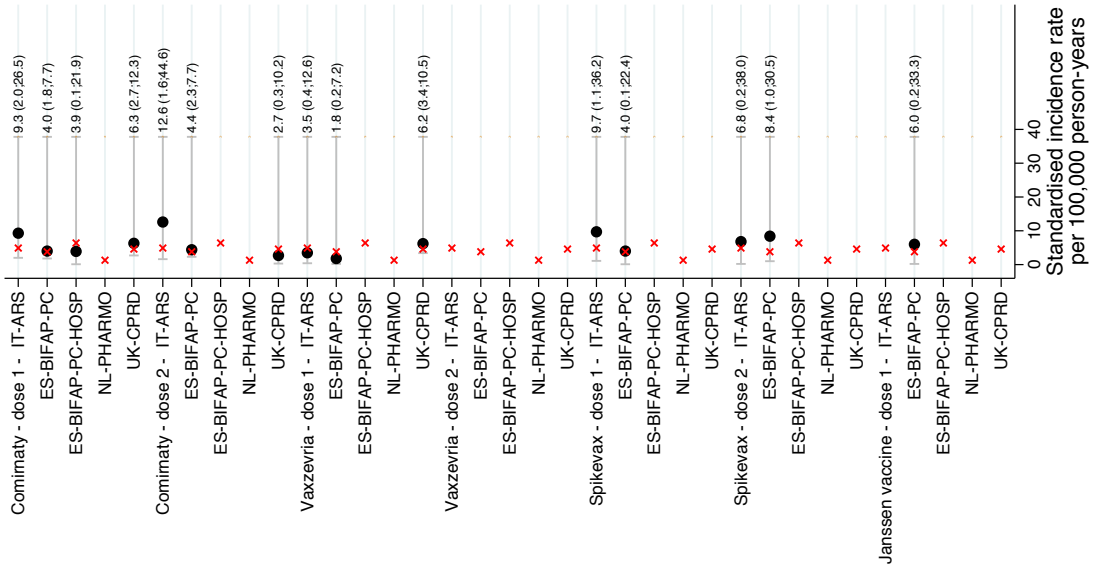
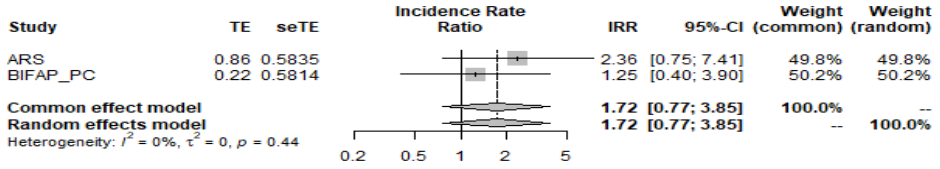
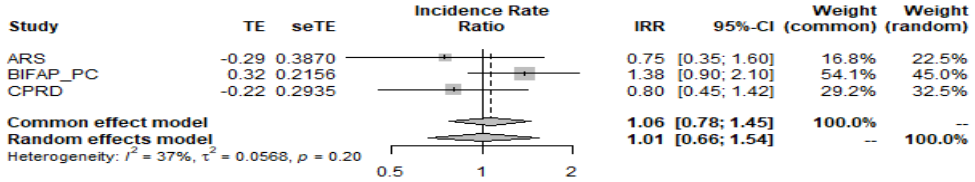


Figure 40 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for meningoencephalitis**

AESI_MENINGOENC_narrowVax_Moderna



AESI_MENINGOENC_narrowVax_Pfizer



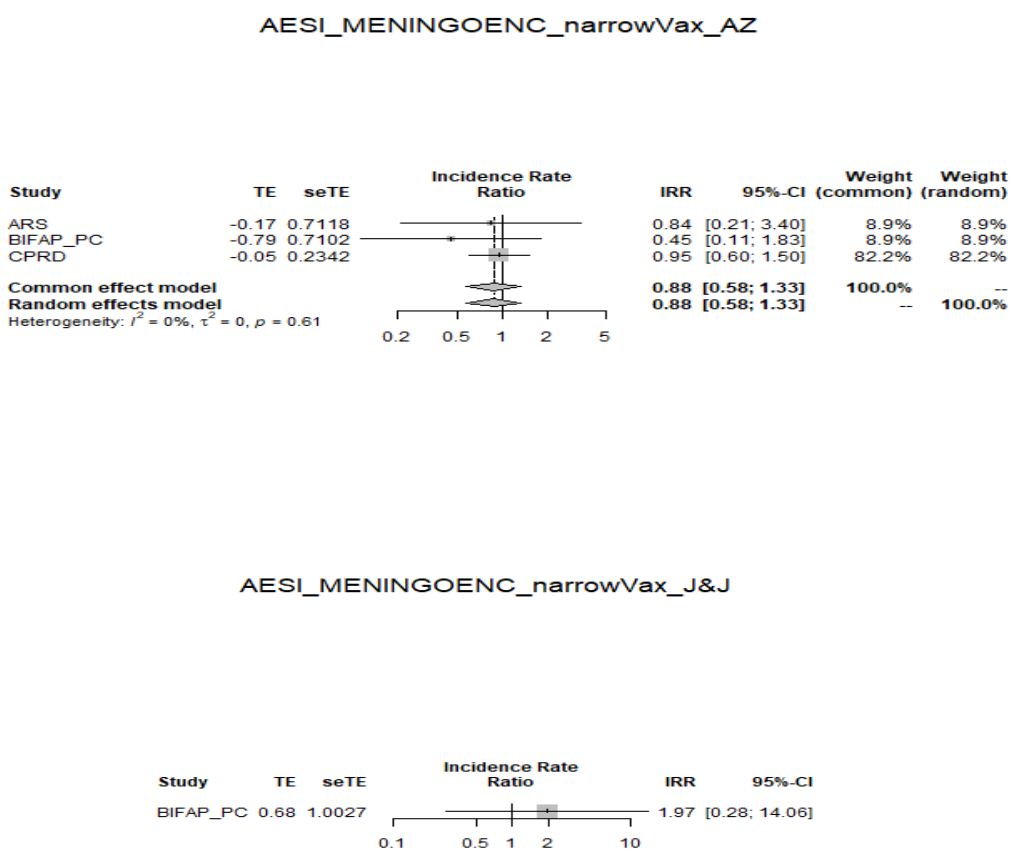


Figure 41 **Partially adjusted incidence rate ratio for meningoencephalitis between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.16 Multi-inflammatory syndrome (MISC)

MIS(C), is an extremely rare condition, no cases were observed within the 28 day risk intervals post-vaccination.

Table 33 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for MIS

Vaccine	Dose	namelong	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
none		Background crude incidence rate	0.6 (0.3;0.9)	0.3 (0.2;0.5)	0.7 (0.4;1.2)	1.0 (0.8;1.2)
none		Background age-standardised incidence rate	0.8 (0.5;1.3)	0.4 (0.2;0.6)	1.1 (0.6;1.8)	1.0 (0.8;1.1)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	0	0	0	0
Comirnaty	1	Observed cases	0	0	0	0
Comirnaty	1	Age-standardised incidence rate				
Comirnaty	1	Age-standardised rate difference				
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	0	0	0	0
Comirnaty	2	Observed cases	0	0	0	0
Comirnaty	2	Age-standardised incidence rate				
Comirnaty	2	Age-standardised rate difference				
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	0	0	0	0
Vaxzevria	1	Observed cases	0	0	0	0
Vaxzevria	1	Age-standardised incidence rate				
Vaxzevria	1	Age-standardised rate difference				
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	0
Vaxzevria	2	Observed cases	0	0	0	0
Vaxzevria	2	Age-standardised incidence rate				
Vaxzevria	2	Age-standardised rate difference				
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	0	0	0	0
Spikevax	2	Age-standardised incidence rate				
Spikevax	2	Age-standardised rate difference				
Janssen vaccine	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen vaccine	1	Expected cases	0	0	0	.
Janssen vaccine	1	Observed cases	0	0	0	.
Janssen vaccine	1	Age-standardised incidence rate				
Janssen vaccine	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

3.4.17 Myo/pericarditis

Myo/pericarditis is a very rare disease, rates were increased after Spikevax and Comirnaty dose 2 but not significantly.

Table 34 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Standardised rate difference with 2020 background rates for myo/pericarditis

ordvac	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
none		Background crude incidence rate	28.2 (26.4;30.0)	13.9 (12.9;14.9)	17.6 (15.8;19.6)	11.7 (11.1;12.3)	15.8 (14.2;17.6)
none		Background age-standardised incidence rate	25.1 (23.5;26.7)	13.8 (12.9;14.8)	17.2 (15.3;19.2)	11.7 (11.1;12.3)	
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	27	25	<5	19	8
Comirnaty	1	Observed cases	19	23	<5	28	<5
Comirnaty	1	Age-standardised incidence rate	20.5 (9.7;38.1)	14.6 (8.9;22.5)	18.0 (4.4;48.5)	19.5 (11.8;30.4)	
Comirnaty	1	Age-standardised rate difference	-4.5 (-17.6;8.5)	0.8 (-5.7;7.2)	0.9 (-17.9;19.6)	7.8 (-0.9;16.6)	
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	19	26	<5	11	<5
Comirnaty	2	Observed cases	17	30	10	11	<5
Comirnaty	2	Age-standardised incidence rate	43.6 (17.1;91.2)	22.0 (13.2;34.5)	42.6 (17.6;86.6)	12.7 (4.9;26.8)	
Comirnaty	2	Age-standardised rate difference	18.5 (-14.5;51.6)	8.2 (-1.8;18.2)	25.5 (-5.5;56.4)	1.0 (-8.8;10.8)	
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	10	6	<5	39	<5
Vaxzevria	1	Observed cases	<5	8	<5	34	<5
Vaxzevria	1	Age-standardised incidence rate	3.4 (0.6;10.7)	27.7 (8.3;67.4)	3.1 (0.1;17.4)	10.3 (6.4;15.9)	
Vaxzevria	1	Age-standardised rate difference	-21.6 (-26.1;-17.1)	13.8 (-11.7;39.4)	-14.1 (-20.5;-7.6)	-1.4 (-5.9;3.1)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	<5	<5	<5	8	0
Vaxzevria	2	Observed cases	<5	<5	<5	13	0
Vaxzevria	2	Age-standardised incidence rate	13.0 (1.4;48.5)	9.6 (0.9;37.9)	4.3 (0.1;23.9)	23.7 (9.3;49.5)	
Vaxzevria	2	Age-standardised rate difference	-12.1 (-30.7;6.5)	-4.2 (-18.6;10.2)	-12.9 (-21.5;-4.3)	12.0 (-5.9;29.9)	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	<5	<5	<5	0	<5
Spikevax	1	Observed cases	<5	11	1	0	0
Spikevax	1	Age-standardised incidence rate	3.7 (0.1;20.7)	29.0 (14.2;52.6)	14.4 (0.4;80.1)		
Spikevax	1	Age-standardised rate difference	-21.3 (-28.8;-13.9)	15.2 (-2.3;32.8)	-2.8 (-31.0;25.4)		
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	<5	<5	<5	0	0
Spikevax	2	Observed cases	5	<5	0	0	0
Spikevax	2	Age-standardised incidence rate	51.7 (14.4;131.1)	13.5 (3.1;37.5)			
Spikevax	2	Age-standardised rate difference	26.6 (-23.5;76.8)	-0.3 (-14.9;14.2)			
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	<5	<5	0	.	0
Janssen	1	Observed cases	<5	<5	0	.	0
Janssen	1	Age-standardised incidence rate	11.3 (0.3;62.8)	10.4 (0.8;43.1)			
Janssen	1	Age-standardised rate difference	-13.8 (-35.9;8.4)	-3.4 (-19.7;12.8)			
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			2
Unknown	1	Observed cases		0			1
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			0
Unknown	2	Observed cases		0			1
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

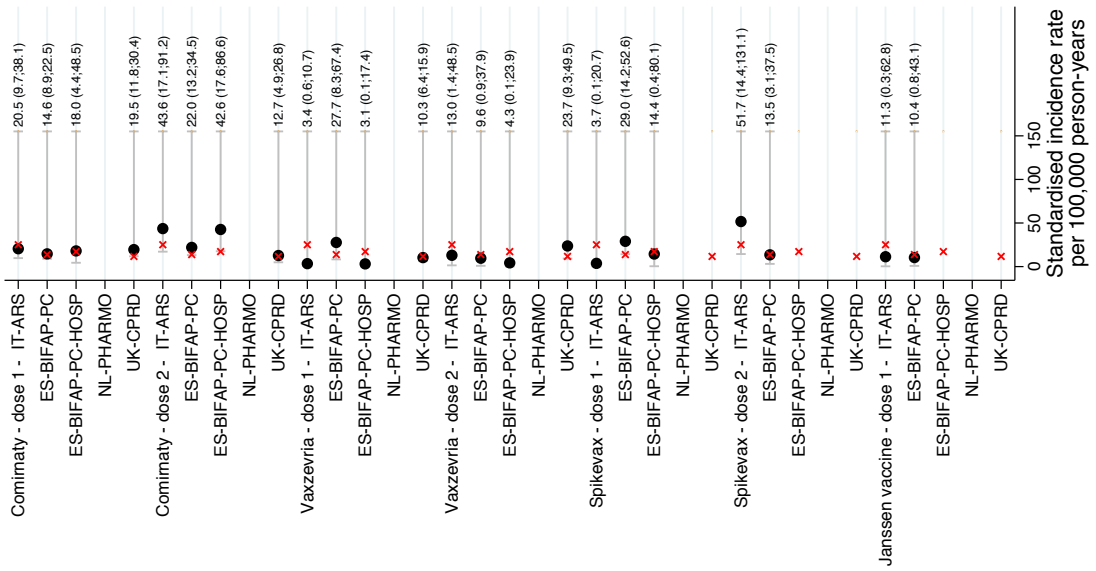
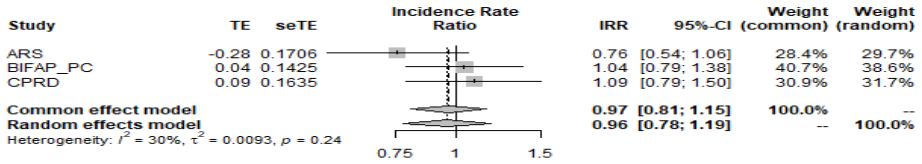
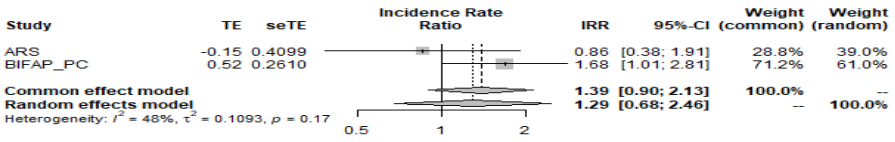


Figure 42 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for myo/pericarditis**

AESI_MYOCARD_narrowVax_Pfizer



AESI_MYOCARD_narrowVax_Moderna



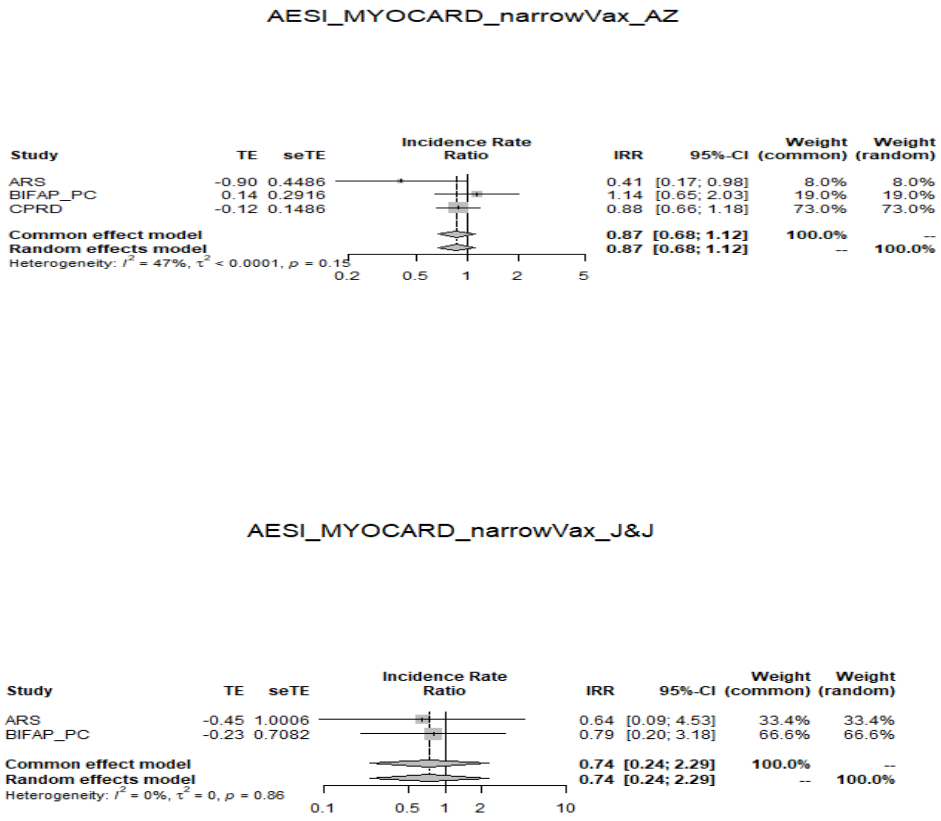


Figure 43 **Partially adjusted Incidence rate ratio for myo/pericarditis between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.18 Myocarditis alone

Myocarditis is a very rare disease. PHARMO data cannot be used since ICPC codes cannot distinguish between myocariditis and pericarditis. Standardised rate differences were higher in dose 2 Comirnaty and Spikevax dose 1 and 2 (only in BIFAP) but did not differ significantly, neither did the partially adjusted incidence rate ratio for dose 1 and 2 combined. Due to low numbers we did not explore effect modification by age.

Table 35 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Standardised rate difference with 2020 background rates for myocarditis

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	5.2 (4.4;6.0)	1.7 (1.4;2.1)	2.3 (1.7;3.1)	3.2 (3.0;3.6)
None		Background age-standardised incidence rate	5.2 (4.4;6.0)	1.8 (1.4;2.1)	2.5 (1.8;3.4)	3.3 (3.0;3.6)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	<5	<5	<5	5
Comirnaty	1	Observed cases	<5	<5	<5	7
Comirnaty	1	Age-standardised incidence rate	3.3 (0.6;10.0)	1.1 (0.1;4.1)	2.9 (0.1;16.3)	5.5 (2.0;12.2)
Comirnaty	1	Age-standardised rate difference	-1.9 (-5.8;2.1)	-0.7 (-2.3;1.0)	0.4 (-5.4;6.1)	2.3 (-2.2;6.8)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	<5	<5	<5	<5
Comirnaty	2	Observed cases	<5	8	<5	5
Comirnaty	2	Age-standardised incidence rate	18.7 (2.3;67.3)	7.7 (2.6;17.3)	11.9 (2.1;37.2)	7.4 (1.5;21.6)
Comirnaty	2	Age-standardised rate difference	13.5 (-12.3;39.4)	5.9 (-0.6;12.4)	9.4 (-5.0;23.8)	4.1 (-4.3;12.4)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	<5	<5	0	11
Vaxzevria	1	Observed cases	0	<5	0	7
Vaxzevria	1	Age-standardised incidence rate		14.0 (1.6;51.3)		2.4 (0.6;6.4)
Vaxzevria	1	Age-standardised rate difference		12.2 (-7.4;31.9)		-0.9 (-3.4;1.6)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	<5
Vaxzevria	2	Observed cases	0	0	0	<5
Vaxzevria	2	Age-standardised incidence rate				5.7 (0.6;21.5)
Vaxzevria	2	Age-standardised rate difference				2.4 (-5.8;10.6)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	<5	<5	0	0
Spikevax	1	Observed cases	0	<5	0	0
Spikevax	1	Age-standardised incidence rate		4.6 (0.5;17.6)		
Spikevax	1	Age-standardised rate difference		2.9 (-3.9;9.6)		
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	0	<5	0	0
Spikevax	2	Age-standardised incidence rate		5.5 (0.1;30.9)		
Spikevax	2	Age-standardised rate difference		3.8 (-7.1;14.6)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	<5	0	.
Janssen	1	Age-standardised incidence rate		7.9 (0.2;43.9)		
Janssen	1	Age-standardised rate difference		6.1 (-9.3;21.5)		
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

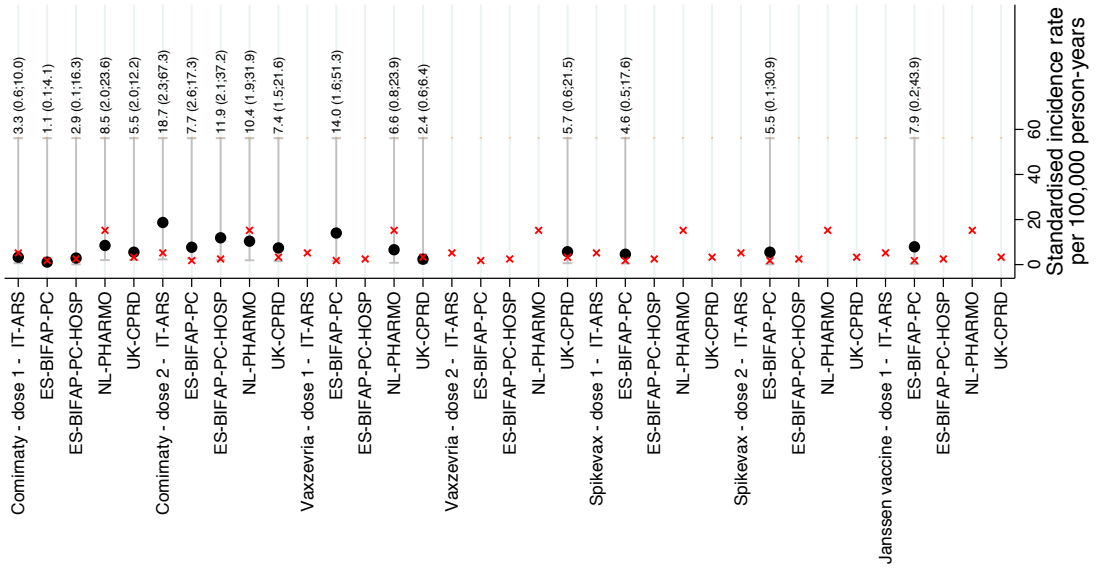
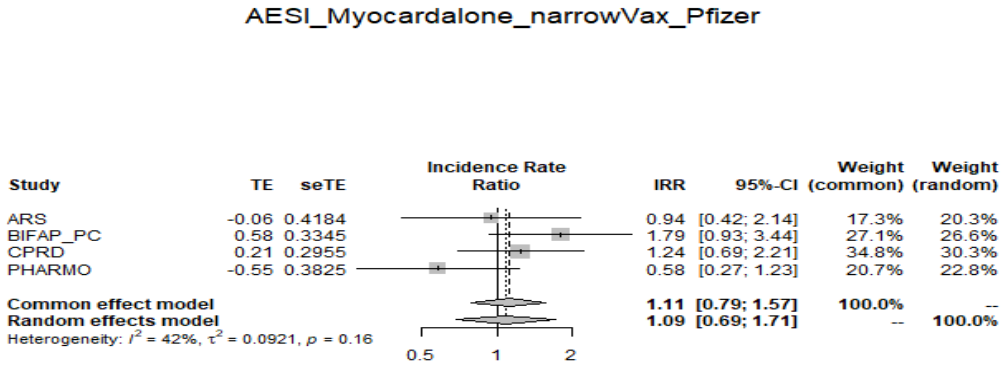


Figure 44 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for myocarditis**



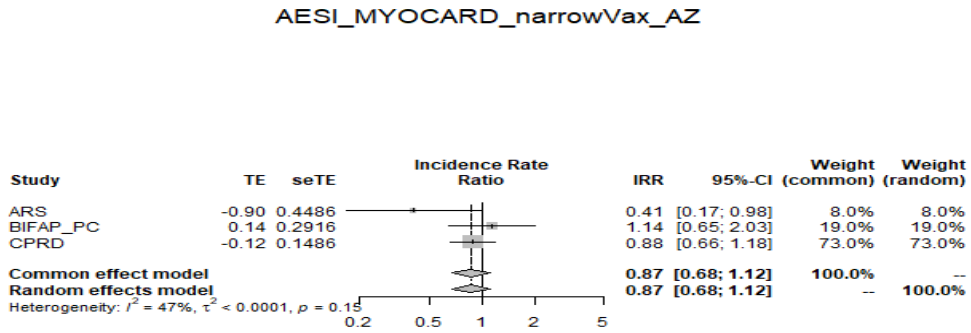


Figure 45 **Incidence rate ratio for myocarditis between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.19 Narcolepsy

Narcolepsy is an extremely rare disease. It is typically not diagnosed during hospitalization but in an outpatient setting. Very few cases were observed. In BIFAP there was a relatively strong association between Vaxzevria and narcolepsy, but upon pooling this disappeared. It is unlikely that narcolepsy would be diagnosed within four weeks after doses of vaccination, as it usually has a long lag time.

Table 36 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for narcolepsy

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	0.1 (0.0;0.3)	1.2 (1.0;1.5)	0.6 (0.3;1.0)	1.2 (1.0;1.4)
None		Background age-standardised incidence rate	0.1 (0.0;0.2)	1.2 (0.9;1.5)	0.6 (0.3;1.1)	1.2 (1.0;1.4)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	0	<5	0	<5
Comirnaty	1	Observed cases	<5	0	0	<5
Comirnaty	1	Age-standardised incidence rate	5.0 (0.1;28.0)			1.4 (0.1;5.3)
Comirnaty	1	Age-standardised rate difference	5.0 (-4.9;14.8)			0.2 (-1.8;2.2)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	0	<5	0	<5
Comirnaty	2	Observed cases	0	<5	0	0
Comirnaty	2	Age-standardised incidence rate		0.5 (0.0;2.5)		
Comirnaty	2	Age-standardised rate difference		-0.8 (-1.7;0.2)		
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	0	0	0	<5
Vaxzevria	1	Observed cases	0	<5	0	<5
Vaxzevria	1	Age-standardised incidence rate		1.0 (0.1;3.6)		0.3 (0.0;1.6)
Vaxzevria	1	Age-standardised rate difference		-0.2 (-1.6;1.2)		-0.9 (-1.5;-0.3)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	0
Vaxzevria	2	Observed cases	0	<5	0	2
Vaxzevria	2	Age-standardised incidence rate		9.9 (0.4;49.5)		1.1 (0.1;4.3)
Vaxzevria	2	Age-standardised rate difference		8.7 (-9.2;26.6)		-0.0 (-1.7;1.6)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	0	0	0	0
Spikevax	2	Age-standardised incidence rate				
Spikevax	2	Age-standardised rate difference				
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	1	0	.
Janssen	1	Age-standardised incidence rate		2.5 (0.1;14.0)		
Janssen	1	Age-standardised rate difference		1.3 (-3.6;6.2)		
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

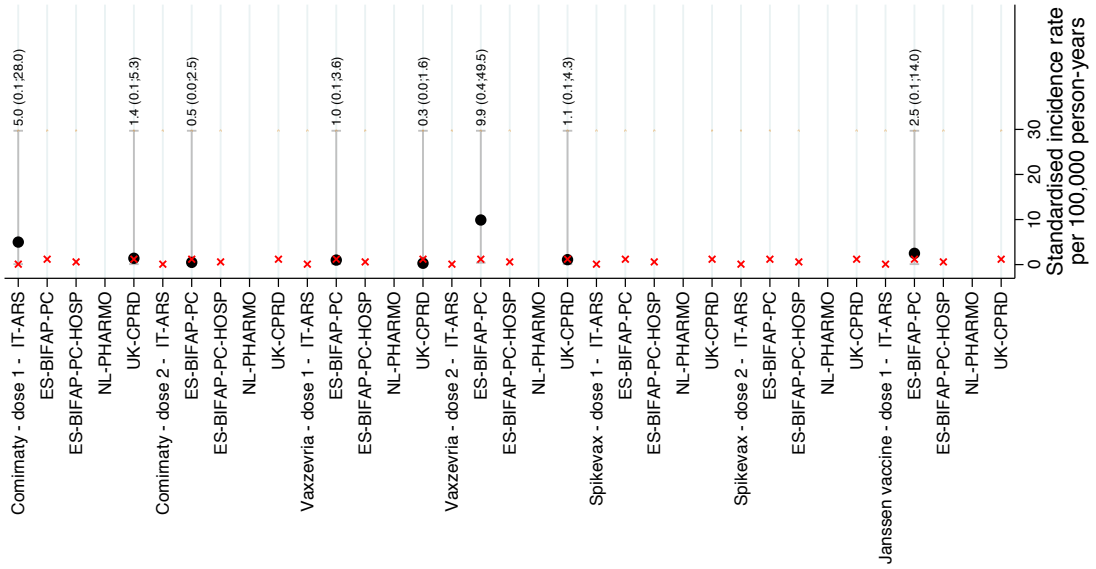
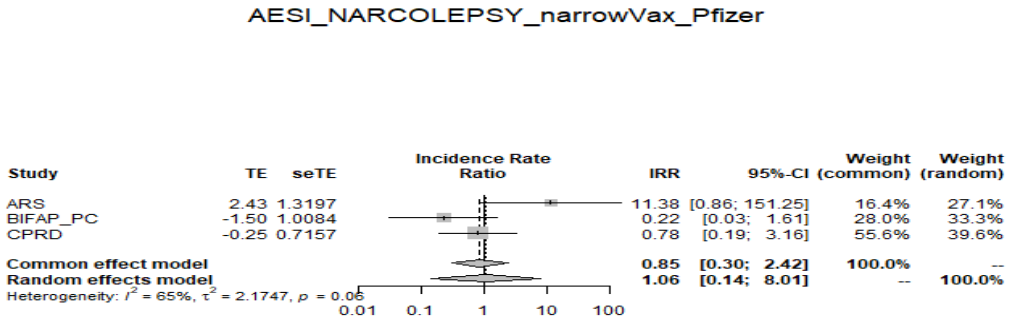


Figure 46 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for narcolepsy**



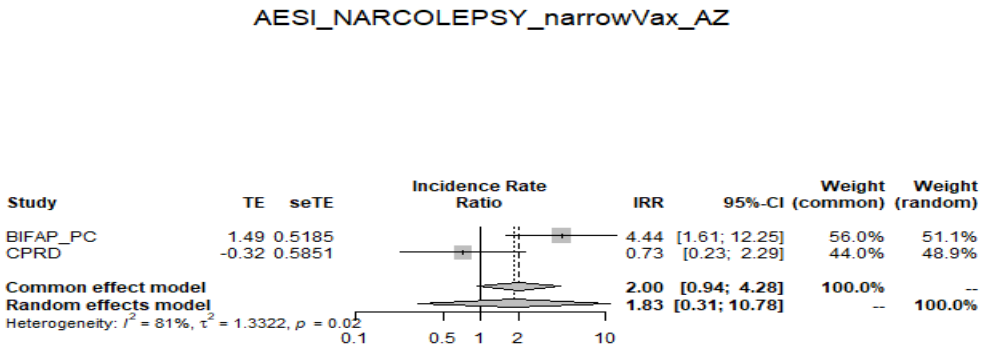


Figure 47 **Partially adjusted incidence rate ratio for narcolepsy between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.20 Single Organ Cutaneous Vasculitis (SOCV)

SOCV is a very rare event, but standardised incidence rates were very comparable. In BIFAP an association was seen after Comirnaty and in ARS after Vaxzevria, upon pooling non-significant elevations remained.

Table 37 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for SOCV

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
none		Background crude incidence rate	4.2 (3.6;5.0)	4.5 (4.0;5.1)	5.9 (4.8;7.1)	5.7 (5.3;6.1)
none		Background age-standardised incidence rate	4.5 (3.8;5.4)	4.6 (4.0;5.2)	5.9 (4.8;7.2)	5.6 (5.2;6.0)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	<5	7	<5	<5
Comirnaty	1	Observed cases	<5	11	0	<5
Comirnaty	1	Age-standardised incidence rate	0.4 (0.0;2.0)	4.6 (2.2;8.5)		3.3 (0.5;11.5)
Comirnaty	1	Age-standardised rate difference	-4.2 (-5.2;-3.1)	0.0 (-2.9;3.0)		-2.3 (-6.7;2.1)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	<5	7	<5	<5
Comirnaty	2	Observed cases	0	12	<5	<5
Comirnaty	2	Age-standardised incidence rate		10.5 (2.2;30.5)	3.2 (0.1;17.8)	3.3 (0.5;10.8)
Comirnaty	2	Age-standardised rate difference		5.9 (-5.9;17.8)	-2.7 (-9.1;3.6)	-2.3 (-6.5;1.9)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	<5	<5	0	7
Vaxzevria	1	Observed cases	5	<5	0	8
Vaxzevria	1	Age-standardised incidence rate	4.2 (1.4;9.9)	6.4 (0.6;24.8)		2.1 (0.8;4.4)
Vaxzevria	1	Age-standardised rate difference	-0.3 (-4.1;3.5)	1.8 (-7.6;11.3)		-3.5 (-5.1;-1.9)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	<5	0	<5
Vaxzevria	2	Observed cases	0	<5	0	<5
Vaxzevria	2	Age-standardised incidence rate		0.8 (0.0;4.5)		0.8 (0.1;2.9)
Vaxzevria	2	Age-standardised rate difference		-3.8 (-5.5;-2.1)		-4.8 (-6.0;-3.6)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	<5	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	<5	0	0
Spikevax	2	Observed cases	0	<5	0	0
Spikevax	2	Age-standardised incidence rate		6.9 (0.8;25.6)		
Spikevax	2	Age-standardised rate difference		2.3 (-7.5;12.1)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	<5	0	.
Janssen	1	Age-standardised incidence rate		7.6 (0.9;27.3)		
Janssen	1	Age-standardised rate difference		3.0 (-7.5;13.5)		
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

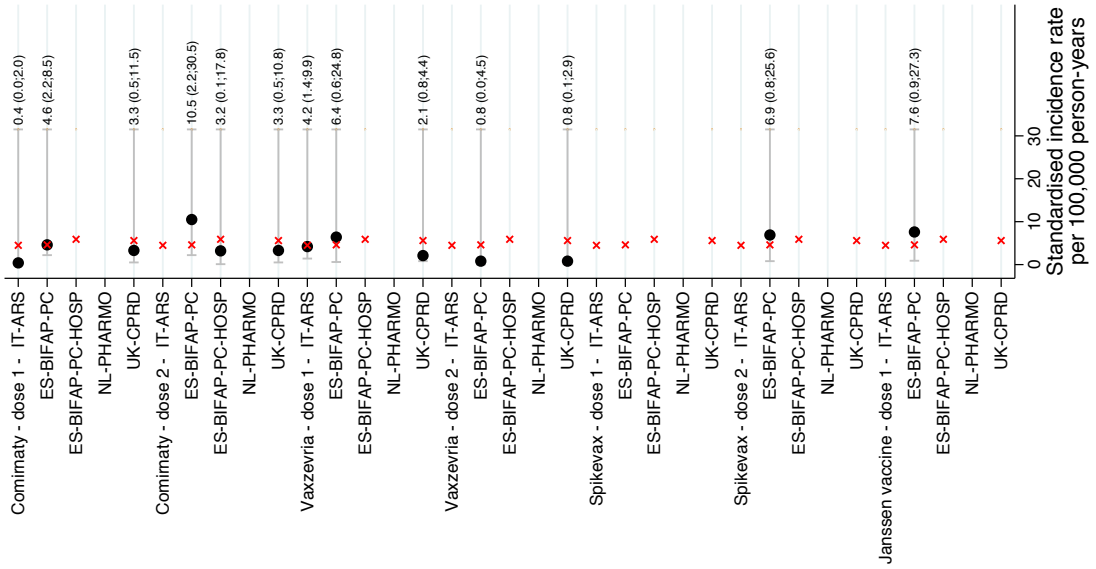
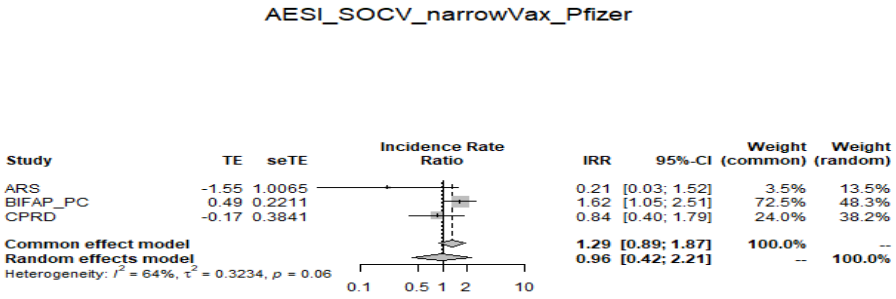


Figure 48 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for SOCV**



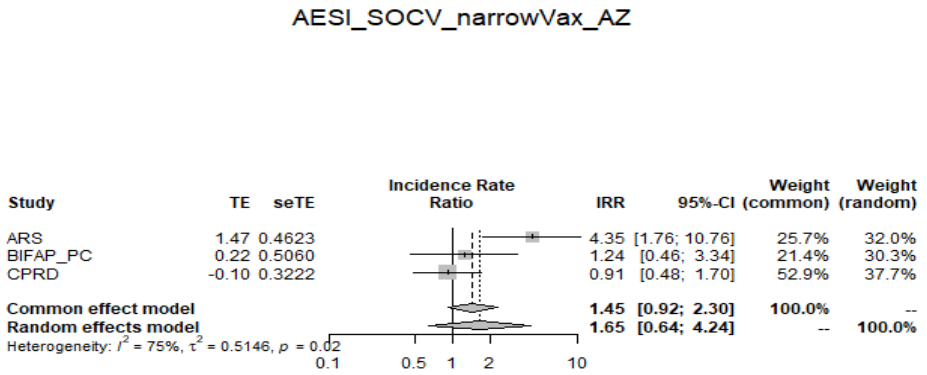


Figure 49 **Partially adjusted incidence rate ratios for narcolepsy between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.21 Stress Cardiomyopathy

Stress cardiomyopathy is a very rare disease and rates are low in BIFAP, which may be related to the codes to identify this disease. We did not observe an association between any of the vaccines and stress cardiomyopathy.

Table 38 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for stress cardiomyopathy

Vaccin	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	7.1 (6.3;8.1)	0.1 (0.1;0.3)	0.9 (0.5;1.4)	1.9 (1.7;2.2)
None		Background age-standardised incidence rate	5.3 (4.6;6.0)	0.1 (0.1;0.2)	0.7 (0.4;1.1)	2.0 (1.8;2.3)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	9	0	0	6
Comirnaty	1	Observed cases	8	0	0	7
Comirnaty	1	Age-standardised incidence rate	3.4 (1.4;7.1)			2.6 (1.0;5.5)
Comirnaty	1	Age-standardised rate difference	-1.8 (-4.5;0.8)			0.5 (-1.5;2.5)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	8	0	0	<5
Comirnaty	2	Observed cases	7	<5	0	6
Comirnaty	2	Age-standardised incidence rate	2.2 (0.9;4.6)	0.9 (0.1;3.6)		1.6 (0.6;3.5)
Comirnaty	2	Age-standardised rate difference	-3.0 (-4.8;-1.2)	0.8 (-0.6;2.2)		-0.5 (-1.8;0.9)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	<5	0	0	8
Vaxzevria	1	Observed cases	<5	<5	0	14
Vaxzevria	1	Age-standardised incidence rate	0.8 (0.0;4.7)	1.3 (0.0;7.2)		3.3 (1.7;5.7)
Vaxzevria	1	Age-standardised rate difference	-4.4 (-6.2;-2.6)	1.2 (-1.4;3.7)		1.2 (-0.6;3.1)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	<5	0	0	<5
Vaxzevria	2	Observed cases	0	0	0	<5
Vaxzevria	2	Age-standardised incidence rate				1.3 (0.1;5.0)
Vaxzevria	2	Age-standardised rate difference				-0.8 (-2.7;1.1)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	<5	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	<5	0	0	0
Spikevax	2	Observed cases	<5	0	0	0
Spikevax	2	Age-standardised incidence rate	6.8 (0.2;38.1)			
Spikevax	2	Age-standardised rate difference	1.6 (-11.8;15.0)			
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	0	0	.
Janssen	1	Age-standardised incidence rate				
Janssen	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

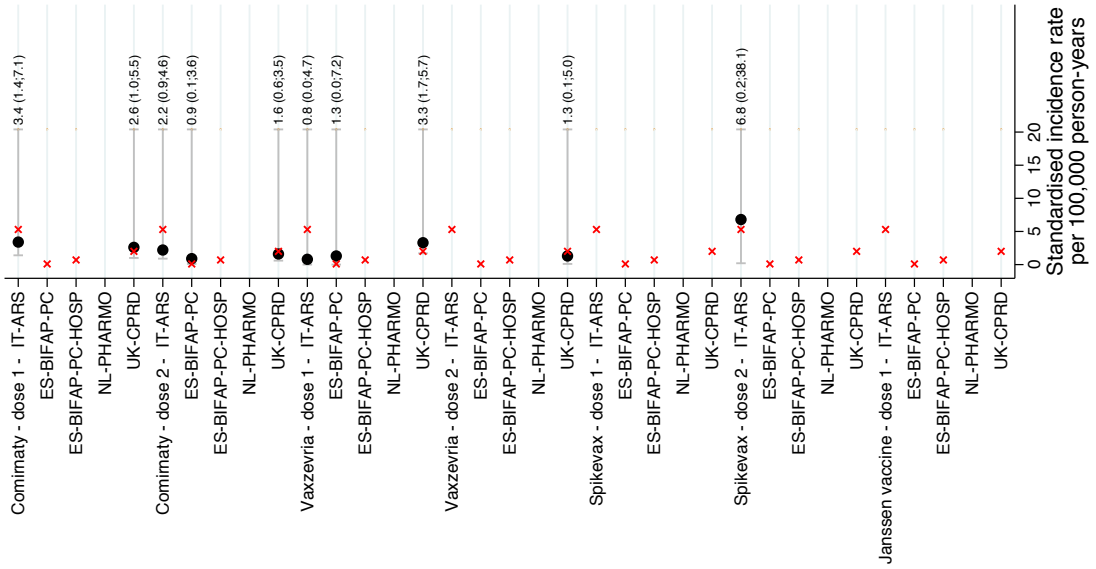
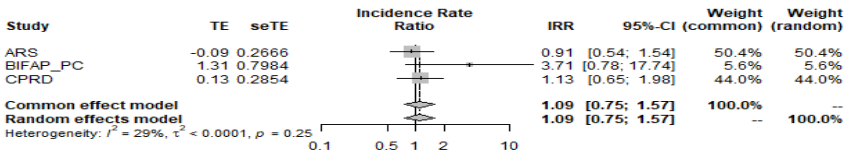
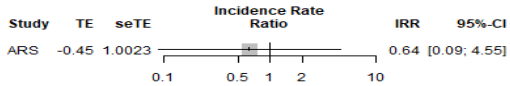


Figure 50 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for stress cardiomyopathy**

AESI_STRCARD_narrowVax_Pfizer



AESI_STRCARD_narrowVax_Moderna



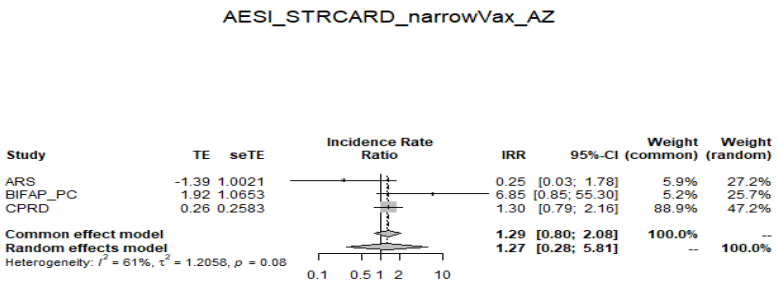


Figure 51 **Partially adjusted incidence rate ratio for stress cardiomyopathy between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.22 Thrombocytopenia

Thrombocytopenia is a very rare event, data in table 38 shows that the rate in PHARMO is too low, and should not be considered in O/E calculations beyond internal comparisons. For transparency and completeness data are included in estimation of IRR, as there were disproporionalities. We observed stastistically significant associations between Moderna and J&J vaccine and thrombocytopenia in the Poisson analysis.

Table 39 **Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for thrombocytopenia**

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	23.8 (22.2;25.5)	34.6 (33.1;36.1)	35.8 (33.1;38.6)	29.8 (28.9;30.8)	3.1 (2.4;3.9)
None		Background age-standardised incidence rate	19.8 (18.4;21.2)	31.5 (30.2;33.0)	30.9 (28.6;33.4)	31.0 (30.0;32.0)	3.1 (2.4;3.9)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	
Comirnaty	1	Expected cases	25	67	7	75	
Comirnaty	1	Observed cases	15	128	<5	92	
Comirnaty	1	Age-standardised incidence rate	16.4 (6.9;32.7)	61.6 (50.6;74.3)	11.4 (1.2;43.2)	52.2 (35.2;74.6)	
Comirnaty	1	Age-standardised rate difference	-3.4 (-15.1;8.3)	**30.0 (18.4;41.7)**	-19.6 (-36.2;-2.9)	**21.2 (2.5;40.0)**	
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	
Comirnaty	2	Expected cases	20	78	8	54	
Comirnaty	2	Observed cases	13	144	<5	67	
Comirnaty	2	Age-standardised incidence rate	10.5 (3.4;24.5)	56.4 (46.3;68.2)	10.4 (2.1;31.1)	42.2 (28.5;60.3)	
Comirnaty	2	Age-standardised rate difference	-9.2 (-18.6;0.1)	**24.9 (14.1;35.6)**	-20.5 (-32.8;-8.2)	11.2 (-3.9;26.4)	
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	
Vaxzevria	1	Expected cases	8	16	<5	109	
Vaxzevria	1	Observed cases	5	48	<5	180	
Vaxzevria	1	Age-standardised incidence rate	14.5 (3.7;38.5)	101.2 (64.1;152.1)	6.3 (0.8;22.6)	61.5 (46.8;79.2)	
Vaxzevria	1	Age-standardised rate difference	-5.3 (-20.2;9.6)	**69.7 (28.2;111.2)**	-24.7 (-33.7;-15.7)	**30.5 (14.8;46.1)**	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	
Vaxzevria	2	Expected cases	<5	11	<5	37	
Vaxzevria	2	Observed cases	0	17	0	48	
Vaxzevria	2	Age-standardised incidence rate		38.0 (14.6;80.6)		58.9 (34.9;93.2)	
Vaxzevria	2	Age-standardised rate difference		6.5 (-22.8;35.8)		**27.9 (0.6;55.3)**	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	
Spikevax	1	Expected cases	<5	11	<5	0	
Spikevax	1	Observed cases	6	19	0	<5	
Spikevax	1	Age-standardised incidence rate	33.0 (11.5;74.0)	52.2 (30.4;83.4)		15.0 (0.4;83.4)	
Spikevax	1	Age-standardised rate difference	13.2 (-14.3;40.7)	20.6 (-4.1;45.4)		-16.0 (-45.4;13.3)	
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	
Spikevax	2	Expected cases	<5	9	<5	0	
Spikevax	2	Observed cases	9	9	<5	0	
Spikevax	2	Age-standardised incidence rate	89.8 (38.2;178.8)	25.4 (11.0;49.9)	11.9 (0.3;66.0)		
Spikevax	2	Age-standardised rate difference	**70.1 (6.8;133.3)**	-6.2 (-23.7;11.4)	-19.1 (-42.4;4.3)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	
Janssen	1	Expected cases	<5	<5	<5	.	
Janssen	1	Observed cases	0	11	0	.	
Janssen	1	Age-standardised incidence rate		63.1 (25.3;130.2)			
Janssen	1	Age-standardised rate difference		31.6 (-15.3;78.4)			
Unknown	1	Observed person-years after vaccination		16			
Unknown	1	Expected cases		0			
Unknown	1	Observed cases		0			
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			
Unknown	2	Expected cases		0			
Unknown	2	Observed cases		0			
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

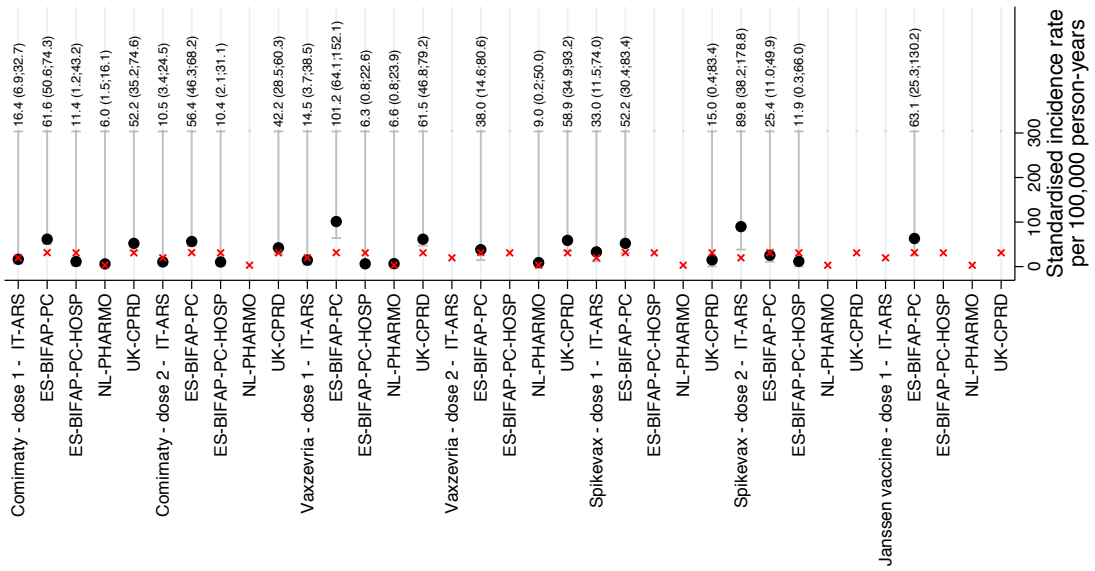
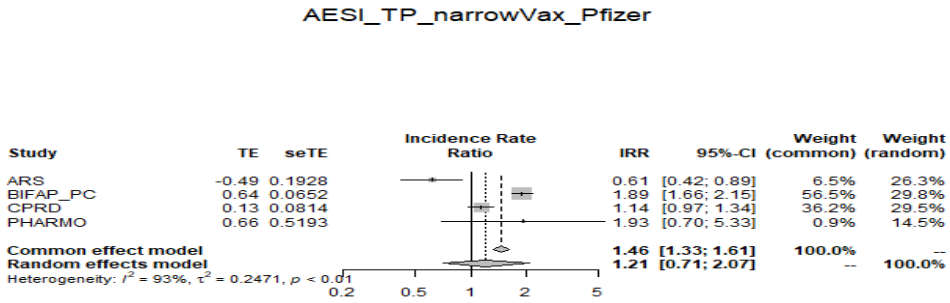
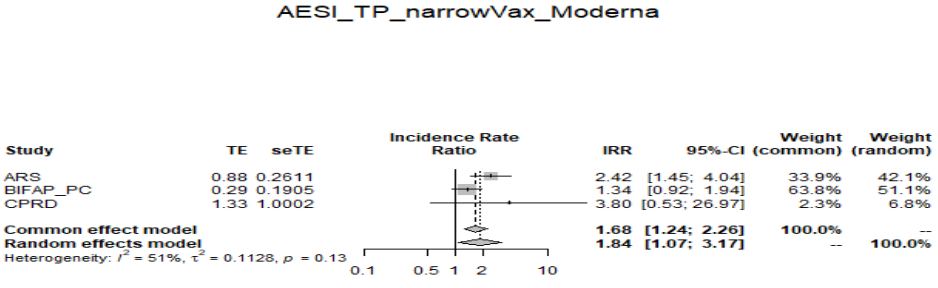


Figure 52 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for thrombocytopenia**





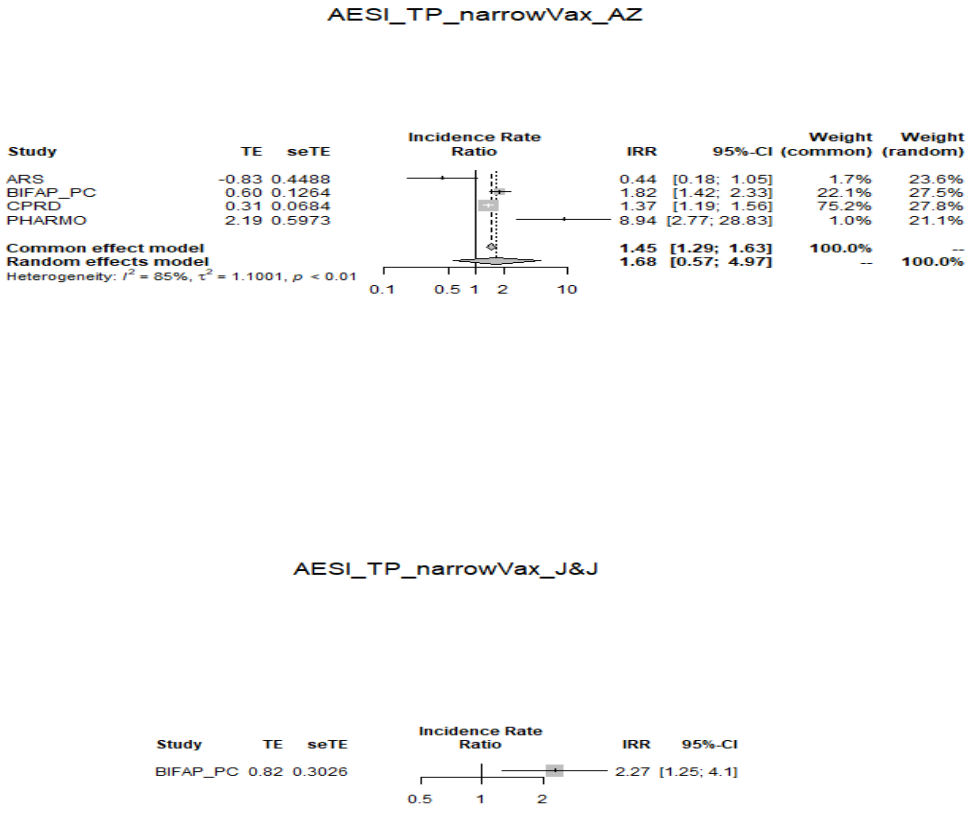


Figure 53 **Partially adjusted incidence rate ratio for thrombocytopenia between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.23 Transverse myelitis

Transverse myelitis is an extremely rare disease, in ICPC there is no code and therefore could not be identified in PHARMO. BIFAP decided their data was not reliable and requested it not to be reported. Transverse myelitis was elevated after Comirnaty in Tuscany, but not in CPRD, and the random effects estimate of the pooled IRR was not significantly elevated.

Table 40 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for transverse myelitis

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	row_PHARMO
None		Background crude incidence rate	0.9 (0.6;1.3)			1.3 (1.1;1.5)	
None		Background age-standardised incidence rate	0.8 (0.6;1.2)			1.3 (1.1;1.5)	
Comirnaty	1	Observed person-years after vaccination	76,904	.	.	135,464	.
Comirnaty	1	Expected cases	<5	.	.	<5	.
Comirnaty	1	Observed cases	<5	.	.	<5	.
Comirnaty	1	Age-standardised incidence rate	6.7 (1.3;20.2)			2.0 (0.4;6.0)	
Comirnaty	1	Age-standardised rate difference	5.9 (-2.0;13.7)			0.7 (-1.6;3.0)	
Comirnaty	2	Observed person-years after vaccination	43,593	.	.	85,610	.
Comirnaty	2	Expected cases	0	.	.	<5	.
Comirnaty	2	Observed cases	<5	.	.	<5	.
Comirnaty	2	Age-standardised incidence rate	1.4 (0.1;6.0)				
Comirnaty	2	Age-standardised rate difference	0.6 (-1.7;2.9)				
Vaxzevria	1	Observed person-years after vaccination	25,477	.	.	268,652	.
Vaxzevria	1	Expected cases	0	.	.	5	.
Vaxzevria	1	Observed cases	0	.	.	5	.
Vaxzevria	1	Age-standardised incidence rate				1.6 (0.5;4.1)	
Vaxzevria	1	Age-standardised rate difference				0.4 (-1.2;1.9)	
Vaxzevria	2	Observed person-years after vaccination	8,367	.	.	59,921	.
Vaxzevria	2	Expected cases	0	.	.	1	.
Vaxzevria	2	Observed cases	0	.	.	0	.
Vaxzevria	2	Age-standardised incidence rate					
Vaxzevria	2	Age-standardised rate difference					
Spikevax	1	Observed person-years after vaccination	12,228	.	.	1,168	.
Spikevax	1	Expected cases	0	.	.	0	.
Spikevax	1	Observed cases	0	.	.	0	.
Spikevax	1	Age-standardised incidence rate					
Spikevax	1	Age-standardised rate difference					
Spikevax	2	Observed person-years after vaccination	6,481	.	.	30	.
Spikevax	2	Expected cases	0	.	.	0	.
Spikevax	2	Observed cases	0	.	.	0	.
Spikevax	2	Age-standardised incidence rate					
Spikevax	2	Age-standardised rate difference					
Janssen	1	Observed person-years after vaccination	4,072	.	.	.	.
Janssen	1	Expected cases	0	.	.	.	.
Janssen	1	Observed cases	0	.	.	.	.
Janssen	1	Age-standardised incidence rate					
Janssen	1	Age-standardised rate difference					

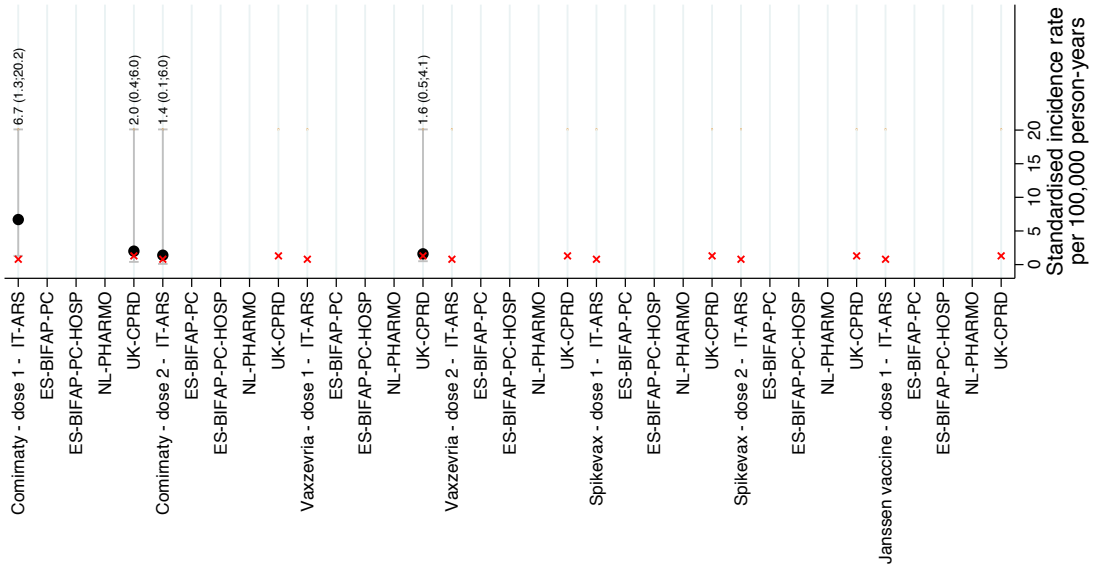
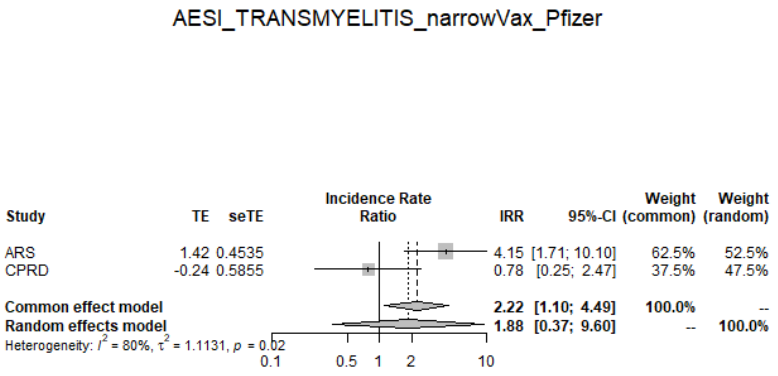


Figure 54 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for transverse myelitis**



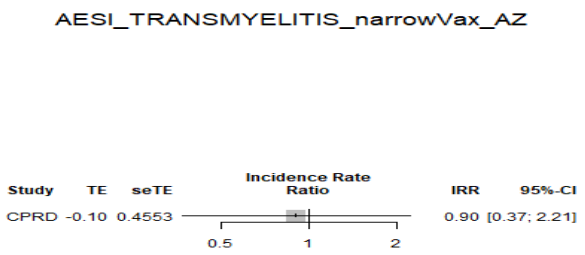


Figure 55 **Partially adjusted incidence rate ratio for transverse myelitis between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.24 Coagulation disorders

3.4.24.1 Hemorrhagic stroke

Hemarrhagic stroke (subarachnoid not included) is a very rare event and associated with covid-19 disease. Level of recording differs between hospitalizations and primary care, rates are lower in only primary care, often because of unclarity about type of stroke. Covid-19 vaccines reduced the risk of hemorrhagic stroke, but not significantly so.

Table 41 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for hemorrhagic stroke

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	67.0 (64.3;69.8)	16.3 (15.3;17.4)	30.6 (28.1;33.2)	24.9 (24.0;25.8)	8.2 (7.0;9.5)
None		Background age-standardised incidence rate	48.3 (46.3;50.3)	13.7 (12.8;14.6)	22.5 (20.7;24.5)	26.2 (25.3;27.1)	7.9 (6.8;9.1)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	86	34	5	81	5
Comirnaty	1	Observed cases	74	44	8	61	7
Comirnaty	1	Age-standardised incidence rate	42.9 (32.3;55.9)	17.1 (12.1;23.4)	37.8 (15.9;75.8)	17.2 (12.8;22.5)	9.6 (3.7;20.3)
Comirnaty	1	Age-standardised rate difference	-5.3 (-16.9;6.2)	3.4 (-2.1;8.9)	15.3 (-11.7;42.2)	**-9.0 (-13.8;-4.3)**	1.7 (-5.8;9.2)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	85	42	6	63	<5
Comirnaty	2	Observed cases	75	50	6	41	<5
Comirnaty	2	Age-standardised incidence rate	55.2 (36.8;79.7)	16.6 (11.2;23.8)	23.0 (8.2;50.9)	14.6 (9.6;21.3)	3.7 (0.4;13.4)
Comirnaty	2	Age-standardised rate difference	7.0 (-13.5;27.5)	2.9 (-3.2;9.0)	0.4 (-18.5;19.4)	**-11.6 (-17.3;-6.0)**	-4.2 (-9.4;1.1)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	23	7	<5	89	<5
Vaxzevria	1	Observed cases	13	11	<5	97	0
Vaxzevria	1	Age-standardised incidence rate	18.0 (7.6;36.0)	14.0 (4.3;33.7)	24.3 (4.1;77.5)	30.5 (24.2;37.9)	
Vaxzevria	1	Age-standardised rate difference	**-30.2 (-43.1;-17.3)**	0.3 (-12.5;13.1)	1.8 (-28.3;31.8)	4.2 (-2.5;11.0)	
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	5	5	<5	38	0
Vaxzevria	2	Observed cases	0	<5	<5	40	0
Vaxzevria	2	Age-standardised incidence rate		10.7 (0.6;48.6)	18.8 (1.4;79.1)	45.1 (25.9;72.9)	
Vaxzevria	2	Age-standardised rate difference		-2.9 (-21.0;15.1)	-3.7 (-33.5;26.0)	18.9 (-3.0;40.8)	
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	6	5	<5	0	0
Spikevax	1	Observed cases	<5	<5	<5	0	0
Spikevax	1	Age-standardised incidence rate	92.1 (6.4;398.3)	10.7 (2.8;28.0)	14.4 (0.4;80.1)		
Spikevax	1	Age-standardised rate difference	43.9 (-104.9;192.6)	-3.0 (-13.8;7.8)	-8.2 (-36.4;20.1)		
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	<5	<5	<5	0	0
Spikevax	2	Observed cases	<5	<5	<5	0	0
Spikevax	2	Age-standardised incidence rate	6.9 (0.2;38.2)	12.2 (3.2;32.0)	23.8 (2.9;85.8)		
Spikevax	2	Age-standardised rate difference	**-41.4 (-55.0;-27.8)**	-1.5 (-13.8;10.8)	1.2 (-31.8;34.2)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	<5	<5	0	.	0
Janssen	1	Observed cases	0	0	0	.	0
Janssen	1	Age-standardised incidence rate					
Janssen	1	Age-standardised rate difference					
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			<5
Unknown	1	Observed cases		0			<5
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			0
Unknown	2	Observed cases		0			<5
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

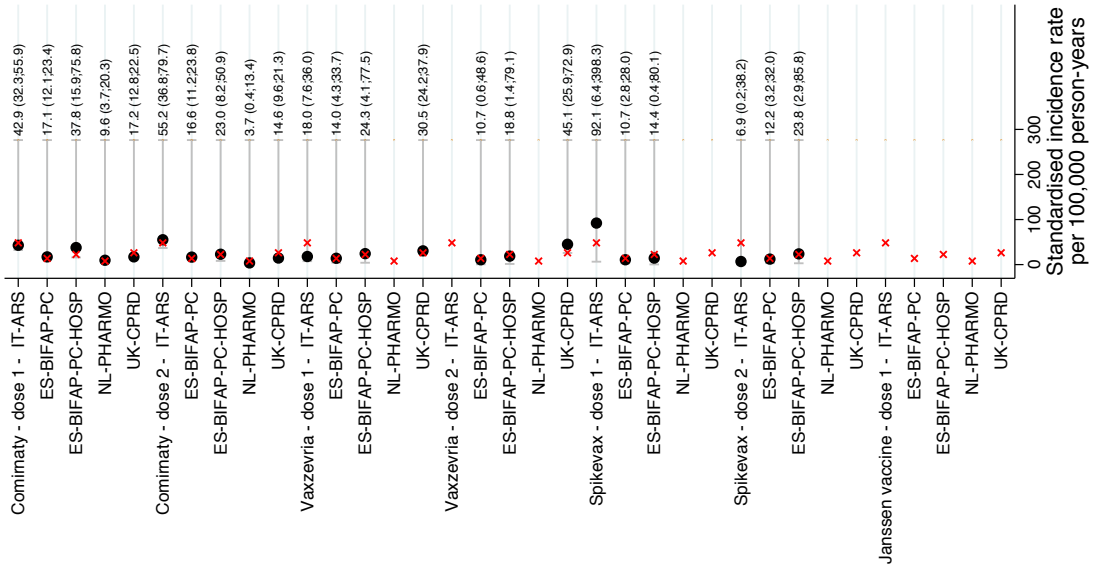
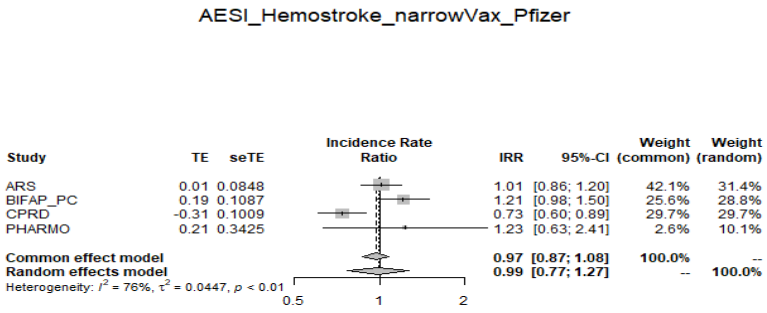


Figure 56 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for hemorrhagic stroke**



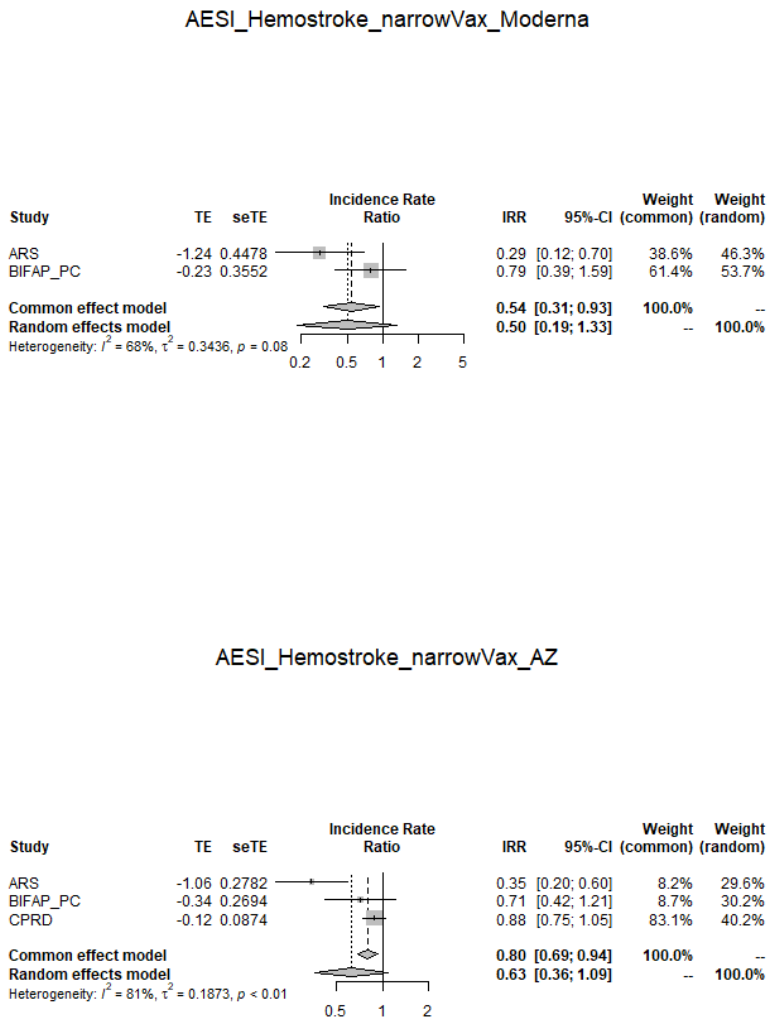


Figure 57 **Incidence rate ratio for hemorrhagic stroke between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.24.2 Ischemic stroke

Ischemic stroke is an uncommon event, in all data sources except PHARMO where it was lower. PHARMO rates should not be used for other sources to benchmark but weres used for within data source comparisons. Standardized rate differences indicate excess rates for some vaccines, but after adjustment for age, gender, prior covid and risk factors for severe covid-19, this did not remain.

Table 42 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for ischemic stroke

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	196.2 (191.5;200.9)	120.4 (117.6;123.2)	178.1 (172.2;184.2)	120.8 (119.0;122.7)	40.2 (37.6;43.0)
None		Background age-standardised incidence rate	139.4 (136.0;142.8)	99.2 (96.8;101.6)	129.5 (125.1;134.1)	129.1 (127.1;131.1)	38.3 (35.8;40.9)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	258	260	29	409	24
Comirnaty	1	Observed cases	267	332	37	431	21
Comirnaty	1	Age-standardised incidence rate	163.2 (142.0;186.6)	128.8 (114.3;144.6)	186.9 (129.1;261.7)	143.9 (129.2;159.7)	39.5 (24.0;61.2)
Comirnaty	1	Age-standardised rate difference	**23.8 (1.6;46.0)**	**29.6 (14.5;44.8)**	57.3 (-6.0;120.7)	14.8 (-0.4;30.0)	1.2 (-16.5;18.8)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	258	324	35	313	11
Comirnaty	2	Observed cases	243	384	42	263	13
Comirnaty	2	Age-standardised incidence rate	173.1 (139.5;212.4)	115.9 (103.5;129.3)	167.8 (119.1;229.9)	109.9 (93.6;128.2)	45.2 (19.8;88.2)
Comirnaty	2	Age-standardised rate difference	33.7 (-1.8;69.3)	**16.7 (3.8;29.6)**	38.3 (-14.9;91.5)	-19.2 (-36.2;-2.1)	6.9 (-24.0;37.8)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	66	46	10	476	<5
Vaxzevria	1	Observed cases	60	52	11	505	<5
Vaxzevria	1	Age-standardised incidence rate	86.1 (61.2;117.8)	41.8 (28.6;59.2)	49.5 (21.1;98.3)	144.5 (130.9;159.1)	3.3 (0.1;18.5)
Vaxzevria	1	Age-standardised rate difference	-53.3 (-80.6;-26.0)	-57.3 (-72.1;-42.5)	-80.0 (-115.1;-45.0)	15.4 (1.4;29.4)	-35.0 (-42.0;-28.0)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	14	32	8	200	<5
Vaxzevria	2	Observed cases	9	21	5	167	<5
Vaxzevria	2	Age-standardised incidence rate	**61.0 (23.4;129.5)**	**39.9 (18.5;75.0)**	**52.3 (14.4;133.0)**	**124.6 (100.5;152.7)**	**18.0 (2.2;64.9)**
Vaxzevria	2	Age-standardised rate difference	-78.4 (-125.7;-31.1)	-59.3 (-85.1;-33.5)	-77.2 (-128.3;-26.2)	-4.5 (-29.9;20.9)	-20.3 (-45.4;4.7)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	17	35	10	<5	<5
Spikevax	1	Observed cases	26	33	11	0	0
Spikevax	1	Age-standardised incidence rate	440.7 (184.9;884.2)	98.0 (66.6;139.1)	155.7 (72.7;291.4)		
Spikevax	1	Age-standardised rate difference	301.3 (-12.7;615.2)	-1.2 (-35.7;33.4)	26.2 (-73.3;125.6)		
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	13	33	9	0	0
Spikevax	2	Observed cases	16	35	10	0	0
Spikevax	2	Age-standardised incidence rate	124.7 (70.3;204.4)	106.3 (73.2;149.3)	125.7 (59.9;232.1)		
Spikevax	2	Age-standardised rate difference	-14.7 (-77.2;47.7)	7.2 (-29.2;43.5)	-3.8 (-82.4;74.8)		
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	8	10	<5	.	0
Janssen	1	Observed cases	6	14	<5	.	0
Janssen	1	Age-standardised incidence rate	61.8 (21.3;139.5)	414.8 (74.9;1283.7)	125.8 (30.8;339.4)		
Janssen	1	Age-standardised rate difference	-77.6 (-129.6;-25.6)	315.6 (-181.7;812.9)	-3.7 (-134.6;127.1)		
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			5
Unknown	1	Observed cases		0			6
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			1
Unknown	2	Observed cases		0			1
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

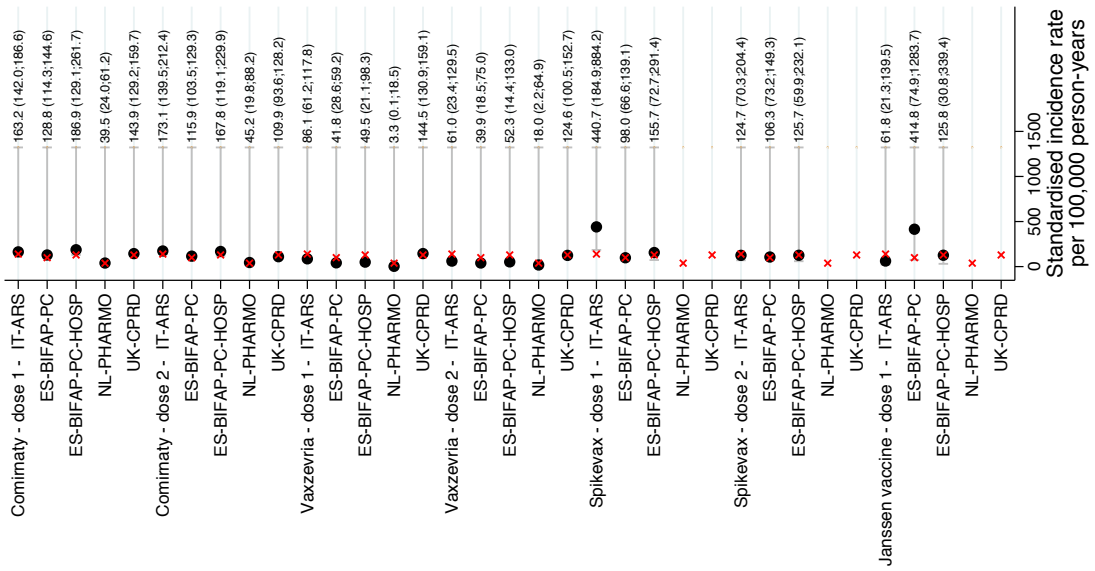
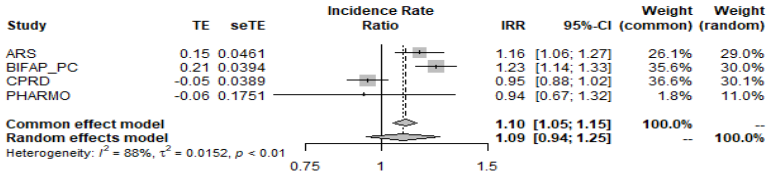
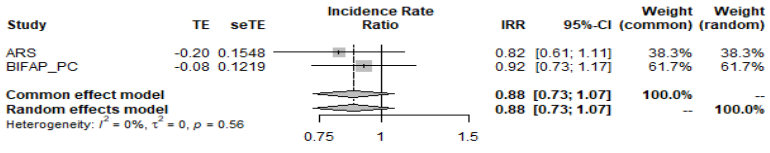


Figure 58 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for ischemic stroke**

AESI_Ischstroke_narrowVax_Pfizer



AESI_Ischstroke_narrowVax_Moderna



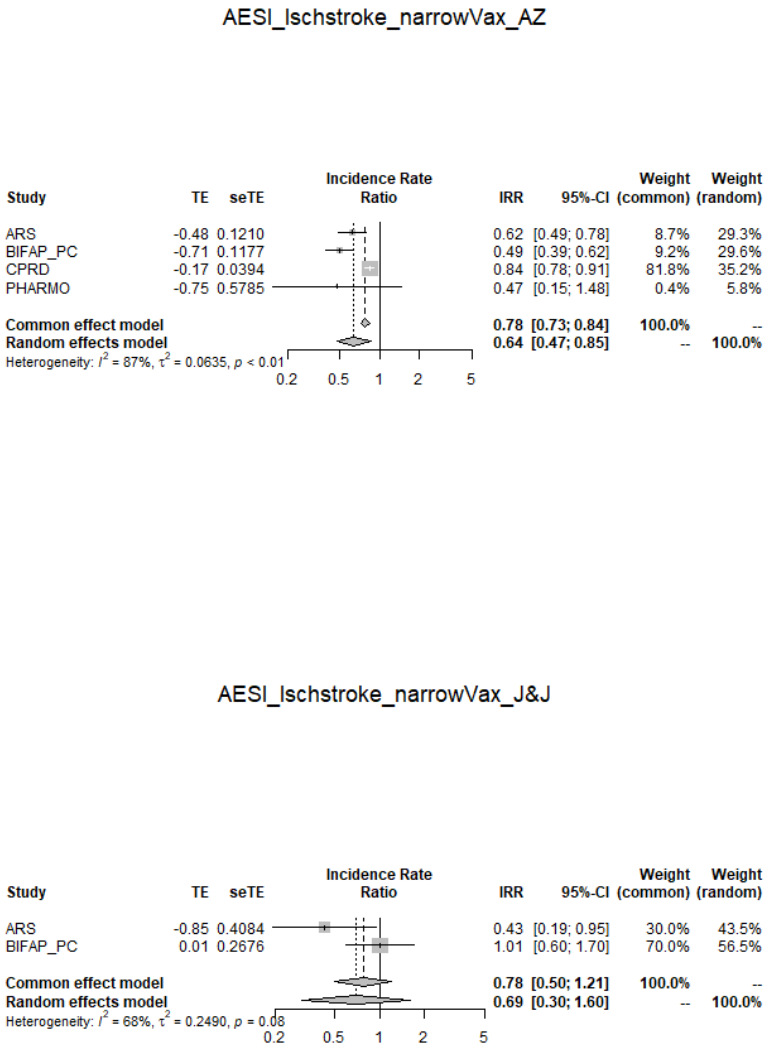


Figure 59 **Incidence rate ratio for ischemic stroke between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.24.3 Coronary artery disease (CAD)

Coronary artery disease comprises all acute ischemic heart disease and is an uncommon event, none of the covid-19 vaccines was associated with an increase in risk of CAD

Table 43 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for coronary artery disease

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	229.7 (224.7;234.9)	80.0 (77.7;82.3)	124.5 (119.6;129.6)	139.0 (137.1;141.1)	145.4 (140.4;150.6)
None		Background age-standardised incidence rate	172.9 (169.0;176.8)	70.2 (68.1;72.3)	98.4 (94.4;102.5)	147.7 (145.6;149.9)	136.6 (131.9;141.5)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	279	157	23	418	83
Comirnaty	1	Observed cases	254	154	23	410	73
Comirnaty	1	Age-standardised incidence rate	163.8 (142.4;187.4)	70.6 (59.0;83.7)	109.3 (67.3;167.6)	156.6 (140.3;174.3)	125.4 (96.8;159.9)
Comirnaty	1	Age-standardised rate difference	-9.1 (-31.6;13.3)	0.4 (-11.8;12.6)	10.8 (-36.4;58.1)	8.9 (-8.1;25.8)	-11.2 (-42.1;19.7)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	241	189	28	300	38
Comirnaty	2	Observed cases	196	187	29	255	35
Comirnaty	2	Age-standardised incidence rate	182.0 (145.3;225.2)	69.6 (59.3;81.3)	105.7 (69.1;154.8)	127.8 (109.3;148.5)	125.8 (76.4;195.2)
Comirnaty	2	Age-standardised rate difference	9.1 (-29.9;48.1)	-0.6 (-11.5;10.4)	7.3 (-33.4;48.0)	-20.0 (-39.3;-0.6)	-10.8 (-66.7;45.1)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	94	51	11	607	14
Vaxzevria	1	Observed cases	63	50	15	572	15
Vaxzevria	1	Age-standardised incidence rate	83.4 (61.7;110.2)	33.6 (24.0;45.7)	161.1 (25.5;525.9)	146.3 (133.5;160.0)	372.0 (90.2;1008.8)
Vaxzevria	1	Age-standardised rate difference	-89.5 (-113.2;-65.9)	-36.6 (-47.2;-26.0)	62.6 (-140.8;266.1)	-1.5 (-14.7;11.8)	235.4 (-153.5;624.3)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	20	36	9	213	5
Vaxzevria	2	Observed cases	9	24	7	153	8
Vaxzevria	2	Age-standardised incidence rate	73.4 (30.2;149.2)	27.7 (16.7;43.2)	61.0 (20.4;139.9)	126.0 (100.3;156.3)	149.0 (28.5;450.2)
Vaxzevria	2	Age-standardised rate difference	-99.5 (-153.0;-46.0)	-42.5 (-55.0;-29.9)	-37.4 (-89.9;15.0)	-21.8 (-49.0;5.5)	12.4 (-162.1;186.9)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	27	26	7	<5	5
Spikevax	1	Observed cases	33	25	6	0	8
Spikevax	1	Age-standardised incidence rate	251.6 (114.1;480.2)	74.2 (46.9;111.6)	105.4 (31.8;255.7)		103.9 (41.0;216.5)
Spikevax	1	Age-standardised rate difference	78.7 (-87.2;244.6)	4.0 (-26.6;34.6)	7.0 (-90.0;104.0)		-32.7 (-111.1;45.6)
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	19	24	7	0	2
Spikevax	2	Observed cases	34	33	8	0	5
Spikevax	2	Age-standardised incidence rate	298.6 (202.9;423.7)	96.3 (65.1;137.2)	89.2 (37.8;177.9)		641.5 (42.0;2821.4)
Spikevax	2	Age-standardised rate difference	**125.7 (20.5;230.8)**	26.1 (-8.3;60.4)	-9.2 (-72.2;53.9)		504.9 (-545.0;1554.9)
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	14	12	<5	.	<5
Janssen	1	Observed cases	8	15	<5	.	0
Janssen	1	Age-standardised incidence rate	75.9 (31.0;154.9)	126.5 (59.7;235.0)	16.0 (0.4;89.1)		
Janssen	1	Age-standardised rate difference	-97.0 (-152.6;-41.4)	56.3 (-23.5;136.0)	-82.4 (-114.0;-50.8)		
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			20
Unknown	1	Observed cases		0			24
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			5
Unknown	2	Observed cases		0			8
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

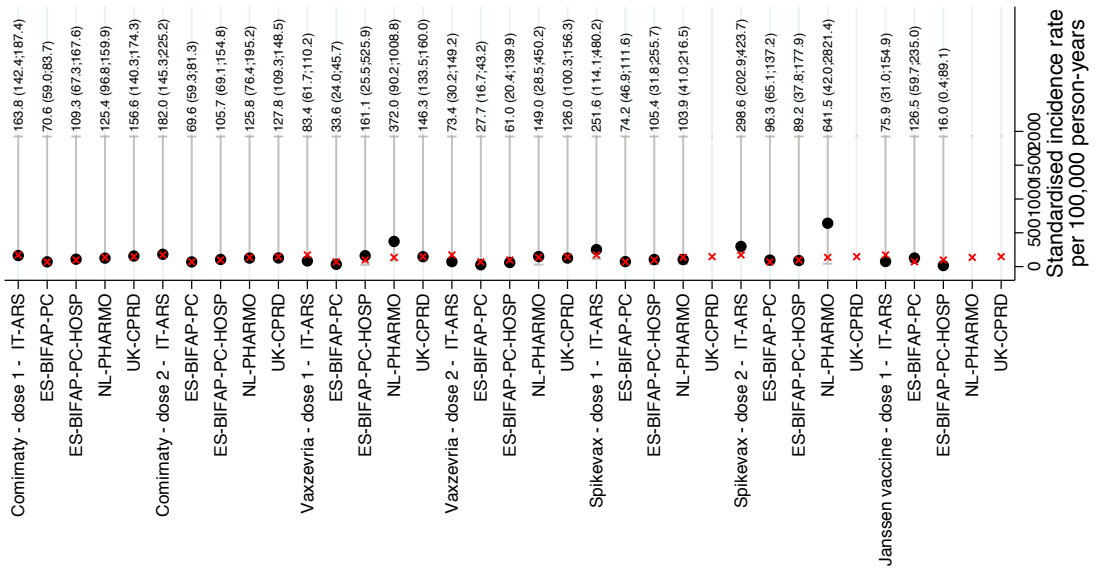
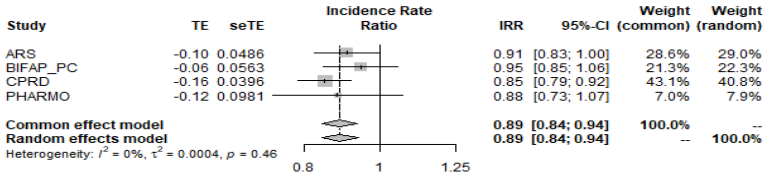
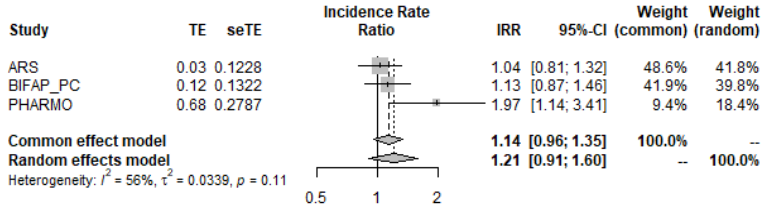


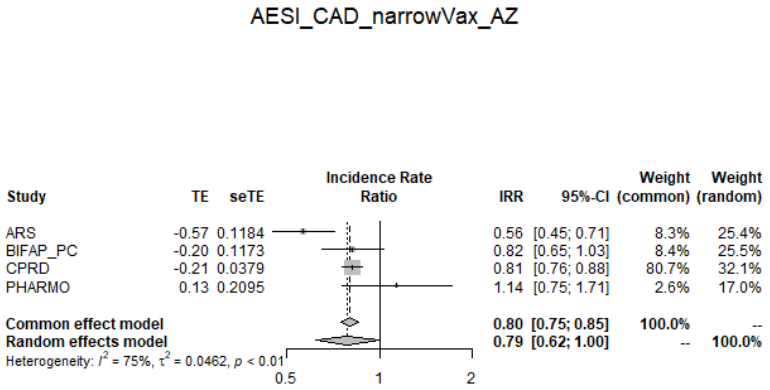
Figure 60 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for coronary artery disease**

AESI_CAD_narrowVax_Pfizer



AESI_CAD_narrowVax_Moderna





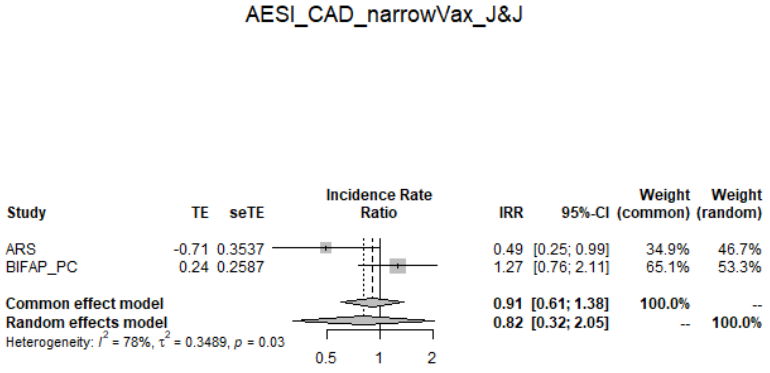


Figure 61 **Incidence rate ratio for coronary artery disease between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and**

3.4. 24.4 Venous thromboembolism (VTE)

VTE is an uncommon disease, and age standardized rate differences were elevated for some vaccines (Comirnaty dose 1 and 2, Spikevax and Vaxzevria), after partial adjustment for the covariates we could adjust for (age, gender, prior covid-19, any risk factor for severe covid) significant associations remained for Comirnaty and Moderna.

Table 44 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for venous thromboembolism

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD	PHARMO
None		Background crude incidence rate	160.1 (155.9;164.4)	133.8 (130.9;136.9)	188.8 (182.6;195.0)	123.2 (121.3;125.1)	161.1 (155.8;166.6)
None		Background age-standardised incidence rate	122.8 (119.5;126.1)	117.1 (114.5;119.8)	151.2 (146.2;156.3)	128.6 (126.7;130.6)	154.9 (149.8;160.2)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464	37,990
Comirnaty	1	Expected cases	190	272	35	325	87
Comirnaty	1	Observed cases	203	344	29	354	99
Comirnaty	1	Age-standardised incidence rate	148.7 (126.6;173.5)	151.0 (134.2;169.4)	143.5 (93.7;210.3)	158.1 (139.4;178.5)	186.7 (148.5;231.8)
Comirnaty	1	Age-standardised rate difference	**25.9 (2.7;49.1)**	**33.9 (16.4;51.4)**	-7.7 (-63.1;47.8)	**29.4 (10.1;48.7)**	31.8 (-9.0;72.6)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610	13,856
Comirnaty	2	Expected cases	167	326	42	231	38
Comirnaty	2	Observed cases	171	413	29	243	31
Comirnaty	2	Age-standardised incidence rate	245.1 (113.7;461.0)	158.0 (138.5;179.4)	118.5 (78.0;172.7)	136.4 (114.4;161.5)	144.9 (85.6;229.8)
Comirnaty	2	Age-standardised rate difference	122.3 (-35.4;280.1)	**40.9 (20.6;61.1)**	-32.6 (-77.8;12.5)	7.8 (-15.3;30.9)	-10.0 (-77.6;57.7)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652	5,172
Vaxzevria	1	Expected cases	60	67	14	497	13
Vaxzevria	1	Observed cases	49	80	13	587	20
Vaxzevria	1	Age-standardised incidence rate	84.9 (50.2;134.4)	93.7 (63.6;133.2)	154.6 (22.0;526.7)	171.9 (156.3;188.6)	1189.8 (496.8;2394.5)
Vaxzevria	1	Age-standardised rate difference	-37.9 (-77.4;1.6)	-23.4 (-56.6;9.8)	3.5 (-199.8;206.7)	**43.2 (27.2;59.3)**	1034.9 (183.5;1886.3)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921	1,779
Vaxzevria	2	Expected cases	14	46	11	163	5
Vaxzevria	2	Observed cases	8	48	5	172	4
Vaxzevria	2	Age-standardised incidence rate	57.9 (22.8;120.7)	74.0 (44.1;116.4)	31.8 (7.7;86.0)	178.8 (142.0;222.4)	36.1 (9.8;92.5)
Vaxzevria	2	Age-standardised rate difference	-64.9 (-108.7;-21.1)	-43.2 (-77.1;-9.2)	-119.4 (-152.9;-85.9)	**50.2 (11.1;89.3)**	-118.8 (-154.6;-83.0)
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168	4,208
Spikevax	1	Expected cases	18	42	10	1	6
Spikevax	1	Observed cases	41	70	6	0	8
Spikevax	1	Age-standardised incidence rate	428.7 (204.0;792.6)	206.1 (159.2;262.6)	126.0 (39.7;299.0)		399.0 (99.6;1067.1)
Spikevax	1	Age-standardised rate difference	**306.0 (37.9;574.1)**	**89.0 (38.9;139.0)**	-25.1 (-138.0;87.7)		244.0 (-166.7;654.8)
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30	1,397
Spikevax	2	Expected cases	12	38	10	0	2
Spikevax	2	Observed cases	34	59	11	0	1
Spikevax	2	Age-standardised incidence rate	314.5 (203.1;465.1)	196.5 (148.2;255.5)	195.7 (89.9;370.4)		21.9 (0.6;122.3)
Spikevax	2	Age-standardised rate difference	**191.8 (67.9;315.7)**	**79.4 (27.6;131.1)**	44.5 (-82.8;171.8)		-133.0 (-176.3;-89.7)
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.	1,282
Janssen	1	Expected cases	8	17	4	.	1
Janssen	1	Observed cases	4	23	6	.	1
Janssen	1	Age-standardised incidence rate	36.6 (9.5;95.9)	90.5 (55.0;140.5)	170.5 (55.6;396.9)		199.1 (5.0;1109.4)
Janssen	1	Age-standardised rate difference	-86.2 (-123.2;-49.2)	-26.6 (-66.8;13.6)	19.3 (-129.7;168.4)		44.2 (-346.1;434.5)
Unknown	1	Observed person-years after vaccination		16			8,282
Unknown	1	Expected cases		0			20
Unknown	1	Observed cases		0			32
Unknown	1	Age-standardised incidence rate					
Unknown	1	Age-standardised rate difference					
Unknown	2	Observed person-years after vaccination		9			2,044
Unknown	2	Expected cases		0			5
Unknown	2	Observed cases		0			3
Unknown	2	Age-standardised incidence rate					
Unknown	2	Age-standardised rate difference					

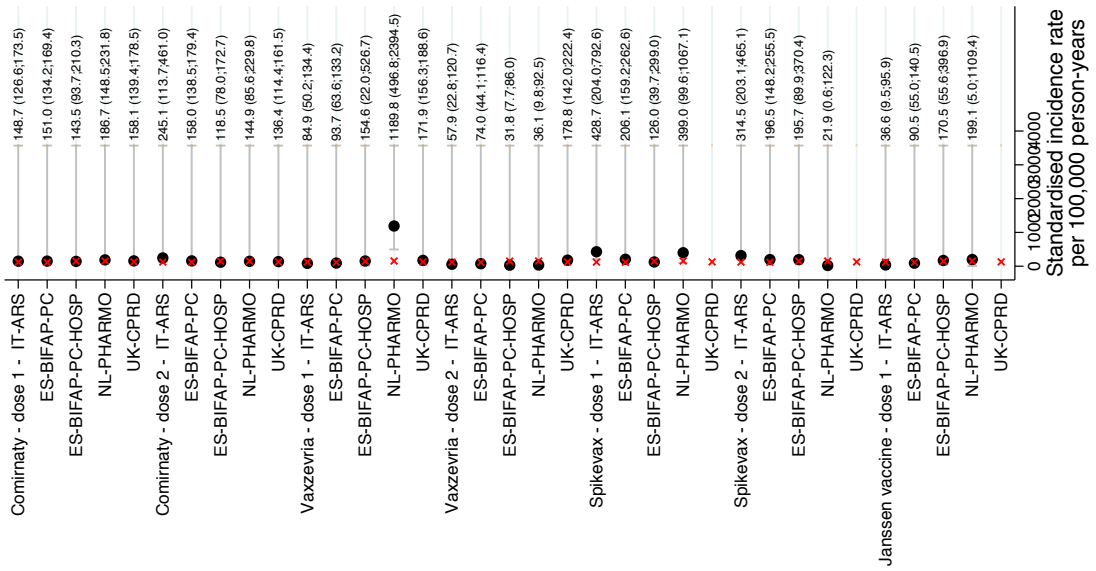
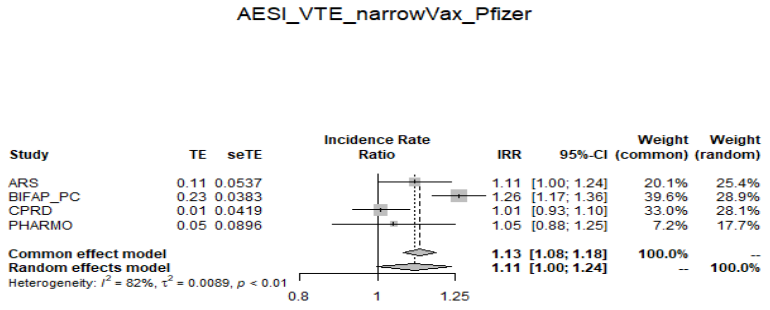
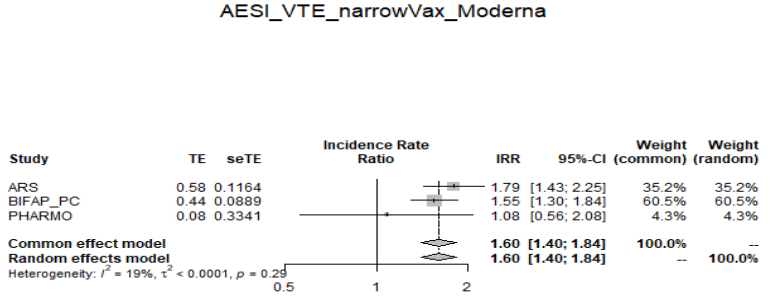


Figure 62 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for venous thromboembolism**





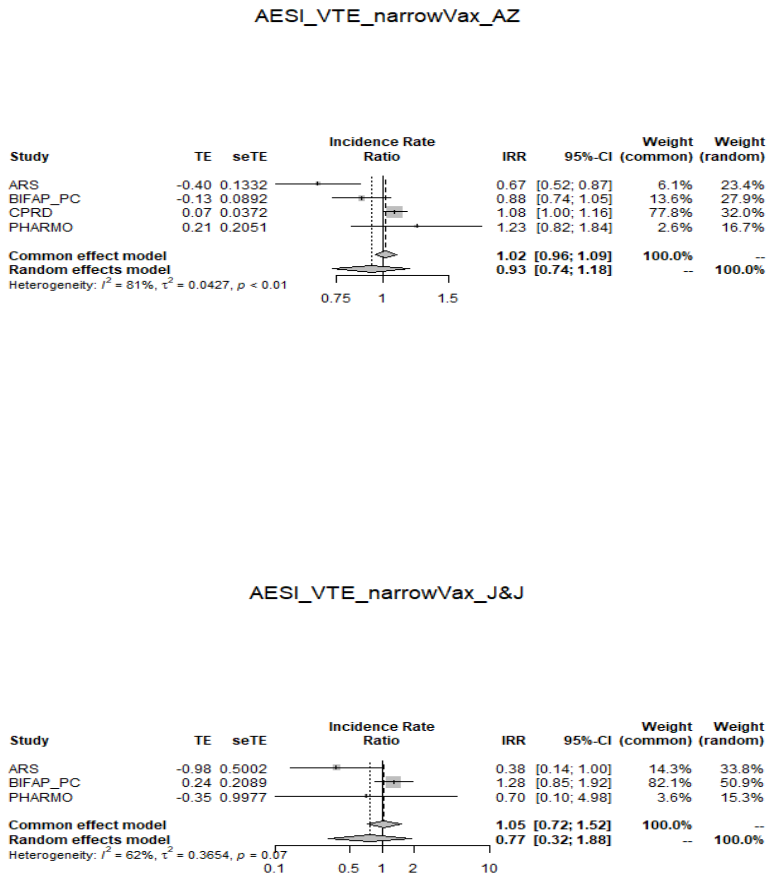


Figure 63 **Incidence rate ratio for venous thromboembolism between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

3.4.24.5 Cerebral venous sinus thrombosis (CVST)

CVST is an extremely rare disease in each of the data sources, and hardly any case was observed following vaccination.

Table 45 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for CVST

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	1.0 (0.7;1.4)	0.2 (0.1;0.4)	0.5 (0.3;1.0)	0.3 (0.2;0.3)
None		Background age-standardised incidence rate	1.0 (0.7;1.3)	0.2 (0.1;0.4)	0.6 (0.3;1.1)	0.2 (0.2;0.3)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	<5	0	0	0
Comirnaty	1	Observed cases	0	0	0	0
Comirnaty	1	Age-standardised incidence rate				
Comirnaty	1	Age-standardised rate difference				
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	0	0	0	0
Comirnaty	2	Observed cases	0	0	0	0
Comirnaty	2	Age-standardised incidence rate				
Comirnaty	2	Age-standardised rate difference				
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	0	0	0	<5
Vaxzevria	1	Observed cases	<5	<5	0	0
Vaxzevria	1	Age-standardised incidence rate	6.0 (0.3;27.8)	0.5 (0.0;2.7)		
Vaxzevria	1	Age-standardised rate difference	5.0 (-5.2;15.3)	0.2 (-0.7;1.2)		
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	0
Vaxzevria	2	Observed cases	0	0	0	0
Vaxzevria	2	Age-standardised incidence rate				
Vaxzevria	2	Age-standardised rate difference				
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	0	0	0	0
Spikevax	2	Age-standardised incidence rate				
Spikevax	2	Age-standardised rate difference				
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	0	0	.
Janssen	1	Age-standardised incidence rate				
Janssen	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

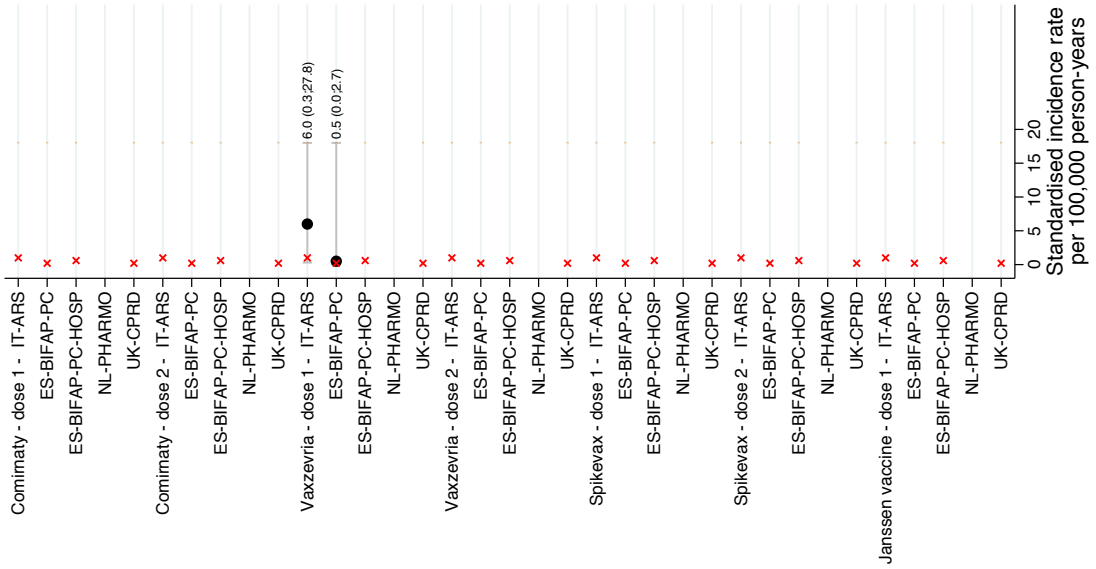


Figure 64 Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for CVST

Due to the small numbers no Poisson analysis was conducted.

3.4.24.6 Thrombotic microangiopathy

Thrombotic microangiopathy is an extremely rare disease in each data source, it was not possible to estimate in PHARMO.

Table 46 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for thrombotic microangiopathy

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	0.3 (0.2;0.6)	0.5 (0.3;0.7)	0.3 (0.1;0.7)	0.5 (0.4;0.7)
None		Background age-standardised incidence rate	0.3 (0.2;0.6)	0.5 (0.3;0.7)	0.3 (0.1;0.8)	0.5 (0.4;0.7)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	0	<5	0	<5
Comirnaty	1	Observed cases	0	0	0	<5
Comirnaty	1	Age-standardised incidence rate				0.5 (0.0;2.6)
Comirnaty	1	Age-standardised rate difference				-0.1 (-1.0;0.8)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	0	<5	0	<5
Comirnaty	2	Observed cases	0	<5	0	0
Comirnaty	2	Age-standardised incidence rate		0.3 (0.0;1.6)		
Comirnaty	2	Age-standardised rate difference		-0.2 (-0.8;0.4)		
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	0	0	0	<5
Vaxzevria	1	Observed cases	0	<5	0	<5
Vaxzevria	1	Age-standardised incidence rate		1.3 (0.0;7.2)		0.4 (0.0;1.5)
Vaxzevria	1	Age-standardised rate difference		0.8 (-1.7;3.3)		-0.1 (-0.7;0.5)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	<5
Vaxzevria	2	Observed cases	0	<5	0	0
Vaxzevria	2	Age-standardised incidence rate		0.8 (0.0;4.5)		
Vaxzevria	2	Age-standardised rate difference		0.3 (-1.3;1.9)		
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	0	0	0	0
Spikevax	2	Age-standardised incidence rate				
Spikevax	2	Age-standardised rate difference				
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	0	0	.
Janssen	1	Age-standardised incidence rate				
Janssen	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

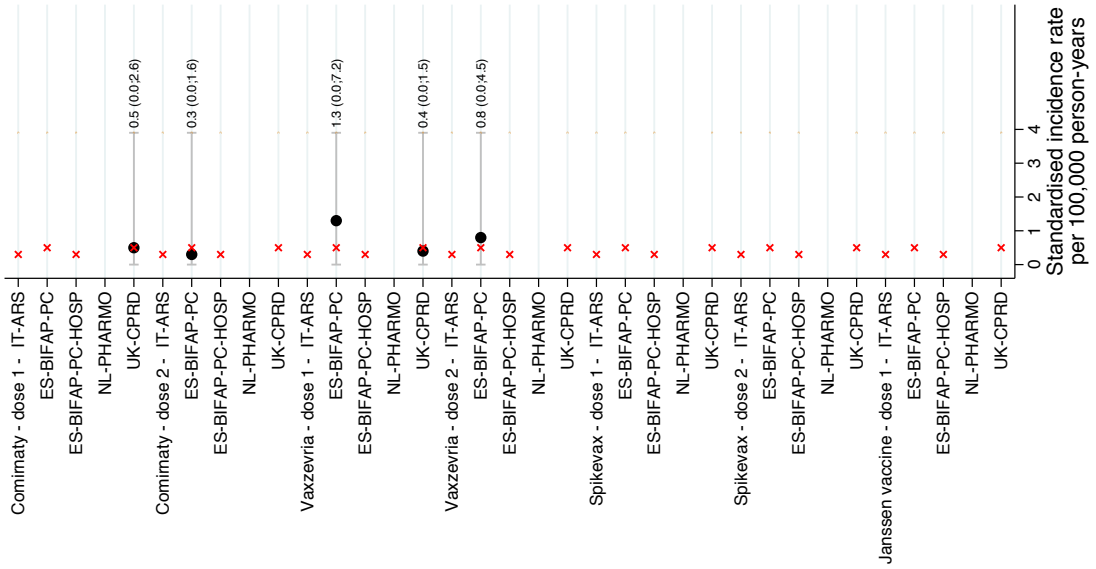


Figure 65 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for thrombotic microangiopathy**

3.4.24.7 Disseminated intravascular coagulation (DIC)

DIC is an extremely rare condition in each of the data sources, and more frequently detected in ARS. PHARMO could not extract this event. Standardized rate differences did not show an excess risk after vaccination. Data were too sparse for Poisson regression.

Table 47 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for DIC

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	1.3 (0.9;1.8)	0.2 (0.1;0.3)	0.0 (0.0;0.2)	0.1 (0.1;0.2)
None		Background age-standardised incidence rate	1.0 (0.7;1.4)	0.2 (0.1;0.3)		0.1 (0.1;0.2)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	<5	0	0	0
Comirnaty	1	Observed cases	0	0	0	0
Comirnaty	1	Age-standardised incidence rate				
Comirnaty	1	Age-standardised rate difference				
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	<5	0	0	0
Comirnaty	2	Observed cases	<5	0	0	0
Comirnaty	2	Age-standardised incidence rate	3.9 (0.2;19.7)			
Comirnaty	2	Age-standardised rate difference	2.9 (-4.2;10.1)			
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	<5	0	0	0
Vaxzevria	1	Observed cases	<5	0	0	0
Vaxzevria	1	Age-standardised incidence rate	0.8 (0.0;4.7)			
Vaxzevria	1	Age-standardised rate difference	-0.2 (-1.8;1.5)			
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	0
Vaxzevria	2	Observed cases	0	0	0	0
Vaxzevria	2	Age-standardised incidence rate				
Vaxzevria	2	Age-standardised rate difference				
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	0	0	0	0
Spikevax	2	Age-standardised incidence rate				
Spikevax	2	Age-standardised rate difference				
Janssen vaccine	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen vaccine	1	Expected cases	0	0	0	.
Janssen vaccine	1	Observed cases	0	0	0	.
Janssen vaccine	1	Age-standardised incidence rate				
Janssen vaccine	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

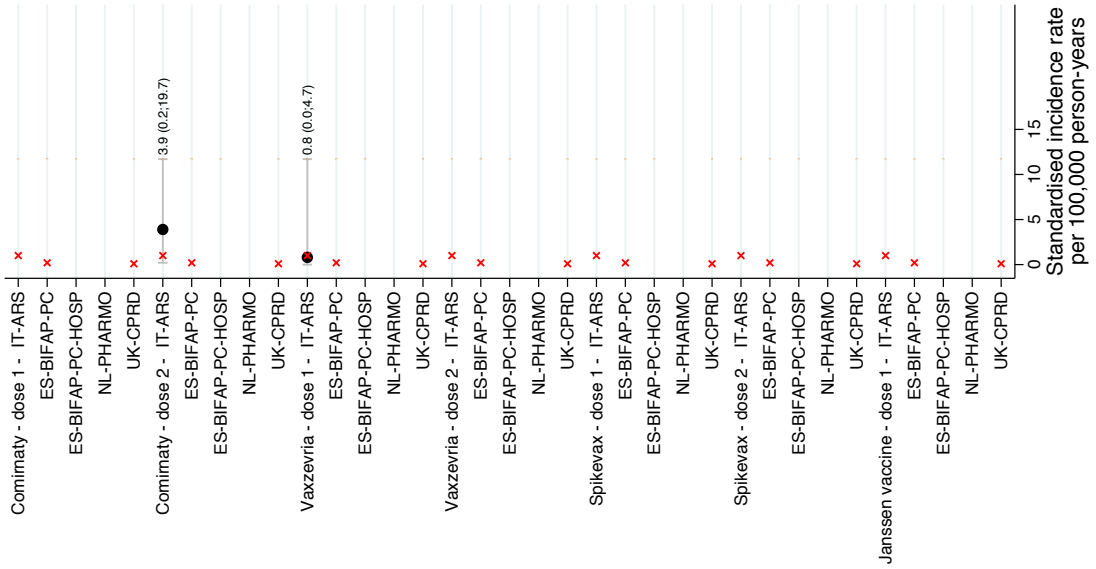


Figure 66 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for DIC**

3.4.24.8 Microangiopathy

Microangiopathy is an extremely rare disease in all data sources (<1/100,000PY), and slightly more frequent in CPRD. The event could not be identified in PHARMO due to lack of specific ICPC codes. Standardized rate differences did not show excess risk post-vaccination. Data were too sparse for an adjusted Poisson regression.

Table 48 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for Microangiopathy

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	0.3 (0.2;0.6)	0.2 (0.1;0.4)	0.3 (0.1;0.6)	1.2 (1.0;1.4)
None		Background age-standardised incidence rate	0.3 (0.2;0.6)	0.2 (0.1;0.3)	0.3 (0.1;0.7)	1.2 (1.0;1.4)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	0	0	0	<5
Comirnaty	1	Observed cases	0	0	0	5
Comirnaty	1	Age-standardised incidence rate				2.1 (0.6;4.9)
Comirnaty	1	Age-standardised rate difference				0.9 (-1.0;2.7)
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	0	0	0	<5
Comirnaty	2	Observed cases	0	0	0	<5
Comirnaty	2	Age-standardised incidence rate				0.8 (0.1;2.8)
Comirnaty	2	Age-standardised rate difference				-0.4 (-1.5;0.6)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	0	0	0	5
Vaxzevria	1	Observed cases	0	<5	0	5
Vaxzevria	1	Age-standardised incidence rate		0.5 (0.0;2.7)		1.1 (0.3;2.5)
Vaxzevria	1	Age-standardised rate difference		0.3 (-0.7;1.3)		-0.1 (-1.1;0.8)
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	<5
Vaxzevria	2	Observed cases	0	<5	0	0
Vaxzevria	2	Age-standardised incidence rate		0.8 (0.0;4.5)		
Vaxzevria	2	Age-standardised rate difference		0.6 (-1.0;2.2)		
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	0	0	0	0
Spikevax	2	Age-standardised incidence rate				
Spikevax	2	Age-standardised rate difference				
Janssen vaccine	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen vaccine	1	Expected cases	0	0	0	.
Janssen vaccine	1	Observed cases	0	0	0	.
Janssen vaccine	1	Age-standardised incidence rate				
Janssen vaccine	1	Age-standardised rate difference				
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

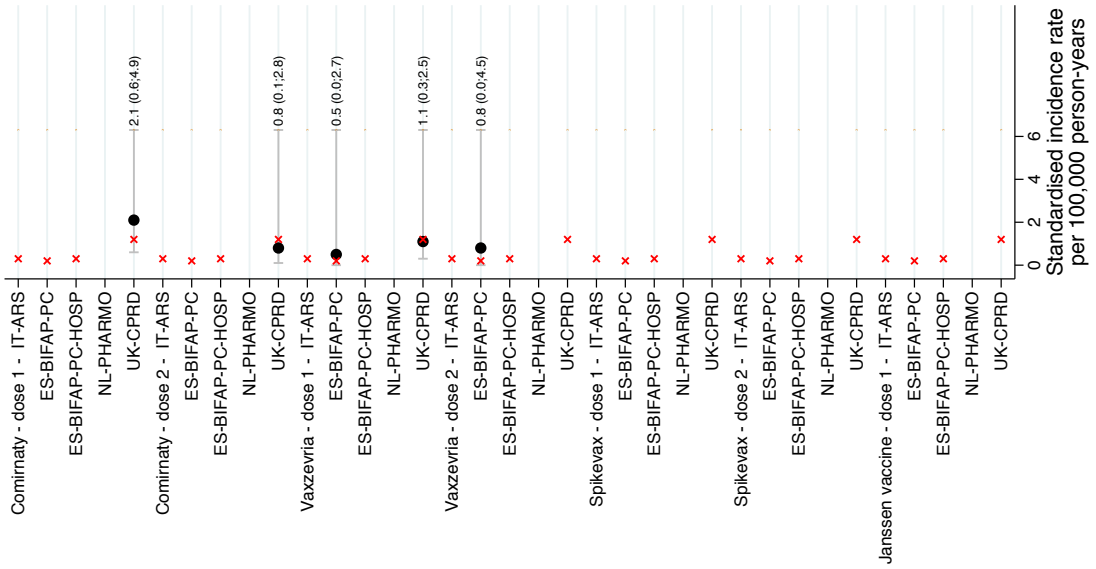


Figure 67 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for Microangiopathy**

3.4.25 TTS (thrombotic thrombocytopenia syndrome): arterial or venous thrombosis with TP within 10 days

TTS which was operationalized as a thrombotic event with thrombocytopenia within 10 days was an extremely rare event, although slightly higher in Tuscany. PHARMO could not identify this event due to lack of appropriate ICPC codes. An excess rate of TTS was found after vaccination with Vaxzevria and with J&J, although the latter was only based on data from BIFAP.

Table 49 Incidence rates (directly standardised to Eurostat population) per 100,000 PY by dose of vaccine. Rate difference with 2020 background rates for TTS

Vaccine	Dose	Estimate	ARS	BIFAP_PC	BIFAP_PC_HOSP	CPRD
None		Background crude incidence rate	1.7 (1.3;2.1)	0.1 (0.0;0.2)	0.1 (0.0;0.4)	0.6 (0.5;0.7)
Noe		Background age-standardised incidence rate	1.3 (1.0;1.7)	0.1 (0.0;0.2)	0.1 (0.0;0.5)	0.6 (0.5;0.8)
Comirnaty	1	Observed person-years after vaccination	76,904	160,809	20,159	135,464
Comirnaty	1	Expected cases	<5	0	0	<5
Comirnaty	1	Observed cases	0	0	0	0
Comirnaty	1	Age-standardised incidence rate				
Comirnaty	1	Age-standardised rate difference				
Comirnaty	2	Observed person-years after vaccination	43,593	164,795	21,808	85,610
Comirnaty	2	Expected cases	<5	0	0	<5
Comirnaty	2	Observed cases	<5	<5	0	<5
Comirnaty	2	Age-standardised incidence rate	0.3 (0.0;1.8)	0.5 (0.0;2.5)		0.6 (0.1;2.3)
Comirnaty	2	Age-standardised rate difference	-1.0 (-1.7;-0.3)	0.4 (-0.5;1.2)		-0.0 (-0.9;0.9)
Vaxzevria	1	Observed person-years after vaccination	25,477	41,122	6,020	268,652
Vaxzevria	1	Expected cases	<5	0	0	<5
Vaxzevria	1	Observed cases	<5	<5	0	10
Vaxzevria	1	Age-standardised incidence rate	4.7 (0.3;20.6)	0.5 (0.0;2.7)		2.6 (1.1;5.1)
Vaxzevria	1	Age-standardised rate difference	3.4 (-4.3;11.0)	0.4 (-0.6;1.4)		**2.0 (0.2;3.8)**
Vaxzevria	2	Observed person-years after vaccination	8,367	28,769	4,525	59,921
Vaxzevria	2	Expected cases	0	0	0	<5
Vaxzevria	2	Observed cases	0	0	0	0
Vaxzevria	2	Age-standardised incidence rate				
Vaxzevria	2	Age-standardised rate difference				
Spikevax	1	Observed person-years after vaccination	12,228	33,140	5,337	1,168
Spikevax	1	Expected cases	0	0	0	0
Spikevax	1	Observed cases	0	0	0	0
Spikevax	1	Age-standardised incidence rate				
Spikevax	1	Age-standardised rate difference				
Spikevax	2	Observed person-years after vaccination	6,481	23,386	4,095	30
Spikevax	2	Expected cases	0	0	0	0
Spikevax	2	Observed cases	<5	0	0	0
Spikevax	2	Age-standardised incidence rate	7.4 (0.2;41.4)			
Spikevax	2	Age-standardised rate difference	6.1 (-8.4;20.7)			
Janssen	1	Observed person-years after vaccination	4,072	14,667	2,404	.
Janssen	1	Expected cases	0	0	0	.
Janssen	1	Observed cases	0	<5	0	.
Janssen	1	Age-standardised incidence rate		7.9 (0.2;43.9)		
Janssen	1	Age-standardised rate difference		7.8 (-7.7;23.2)		
Unknown	1	Observed person-years after vaccination		16		
Unknown	1	Expected cases		0		
Unknown	1	Observed cases		0		
Unknown	1	Age-standardised incidence rate				
Unknown	1	Age-standardised rate difference				
Unknown	2	Observed person-years after vaccination		9		
Unknown	2	Expected cases		0		
Unknown	2	Observed cases		0		
Unknown	2	Age-standardised incidence rate				
Unknown	2	Age-standardised rate difference				

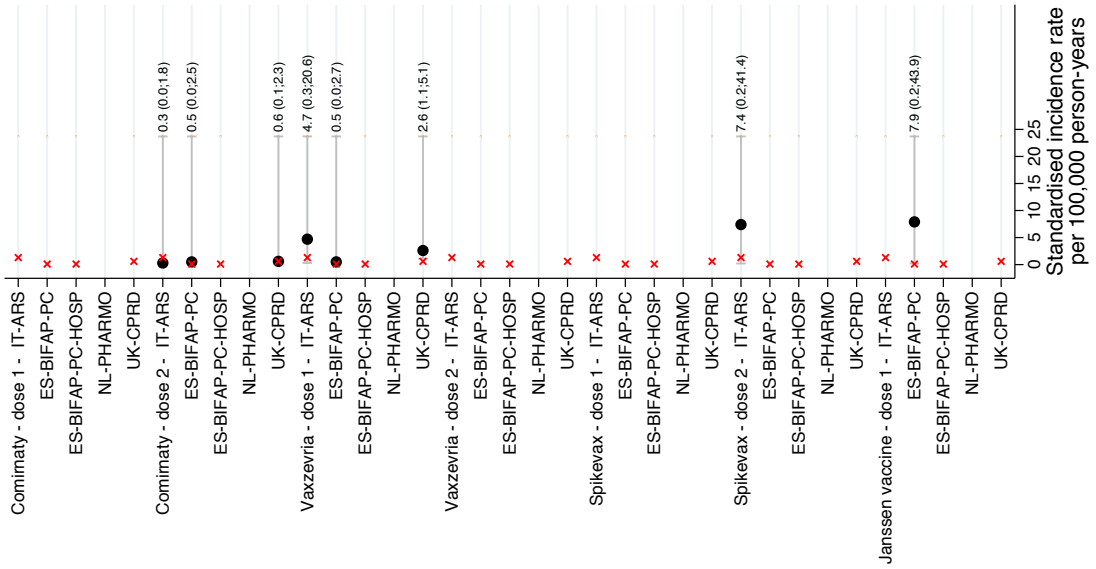
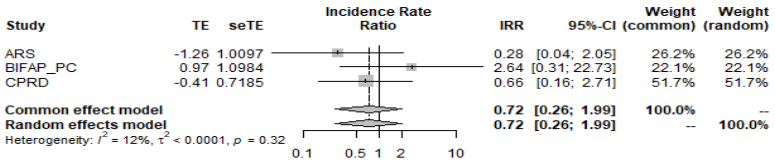
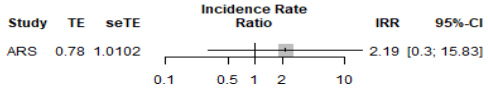


Figure 68 **Standardised incidence rates in background 2020 (red cross) and the standardised incidence rate post dose 1 or 2 (max 28 days) with 95%CI for TTS**

AESI_ArterialVTETPVax_Pfizer



AESI_ArterialVTETPVax_Moderna



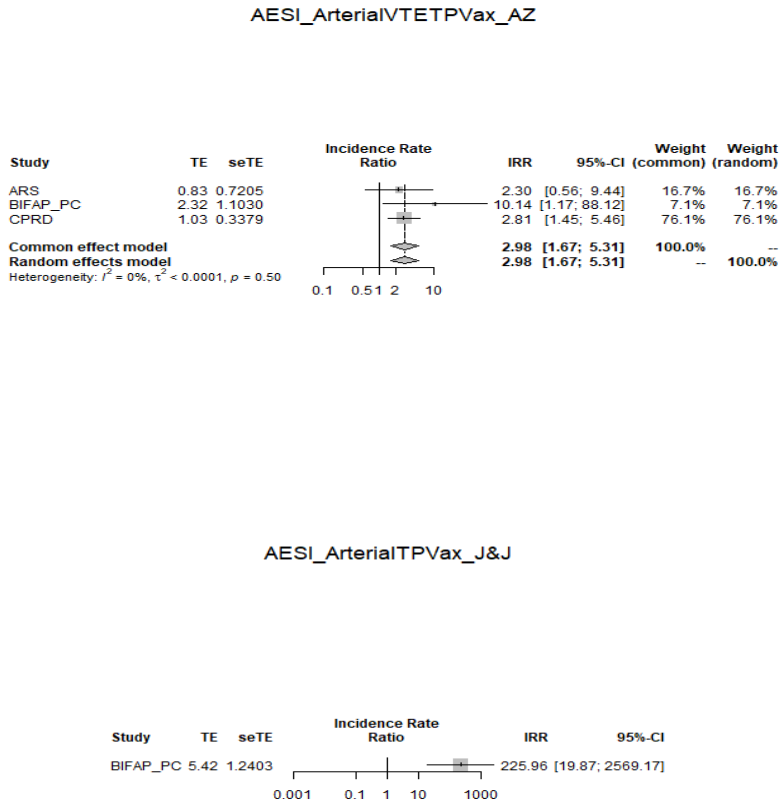


Figure 69 **Partially adjusted incidence rate ratio for TTS between post vaccination dose 1 and 2 (28 days), versus background rates in 2020 with adjustments for age, gender, prior COVID-19 and any risk factor for severe COVID-19**

Table 50 Crude Incidence rate ratios for TTS by dose 1 or 2 of vaccine

	ARS		BIFAP-PC		BIFAP-PC-HOSP		CPRD	
	events	IRR	events	IRR	events	IRR	events	IRR
AZ	<5	3.57 (0.87,14.61)	<5	13.78 (1.66,Inf)	0	0.00 (0.00,Inf)	10	5.10 (2.64,9.84)
J&J	0	0.00 (0.00,Inf)	<5	65.57 (7.89,Inf)	0	0.00 (0.00,Inf)	0	0.00 (0.00,0.00)
Moderna	<5	3.22 (0.45,23.24)	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)	0	0.00 (0.00,Inf)
Pfizer	<5	0.50 (0.07,3.62)	<5	2.96 (0.36,24.56)	0	0.00 (0.00,Inf)	<5	1.52 (0.37,6.17)
Background	56		<5		<5		77	

3.4.26 COVID-19 disease

3.4.26.1 Tuscany

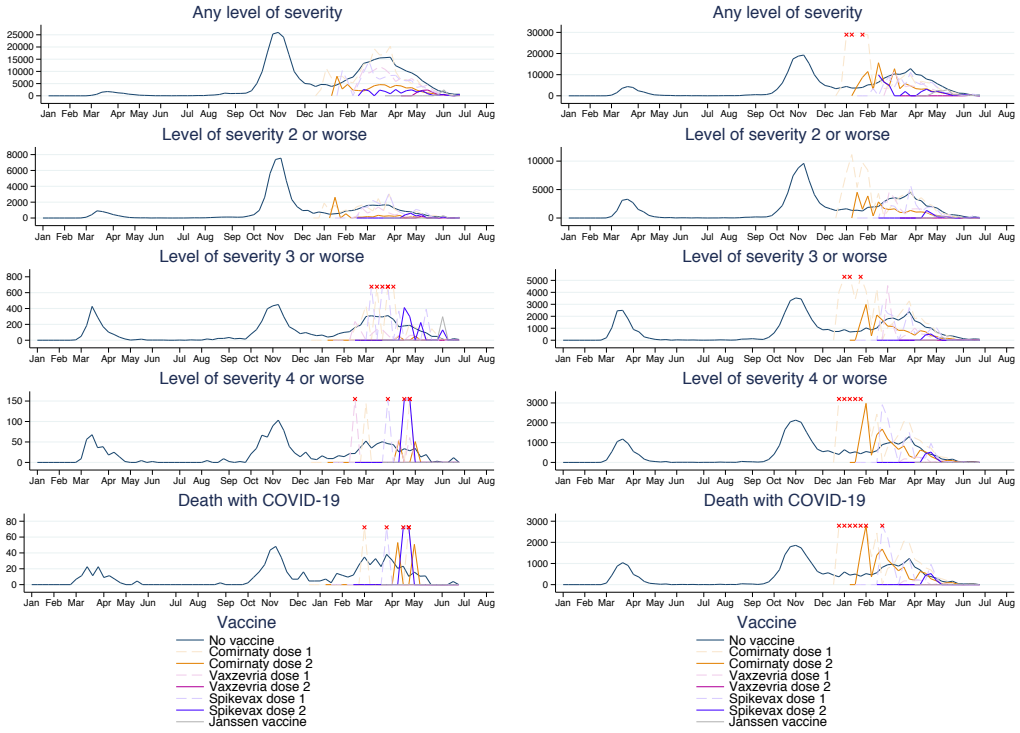
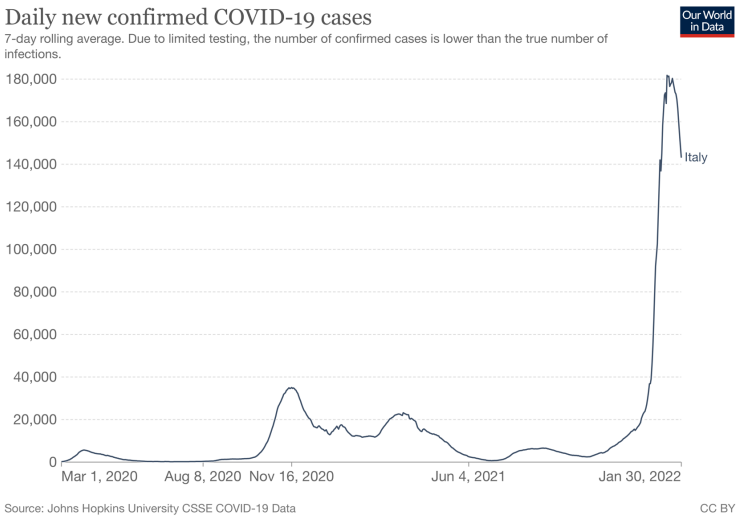


Figure 70 Weekly incidence (per 100,000 PY) of COVID-level severity in young (left) and old (right) persons in Tuscany (note y-axis scales change). X-axis starts at 1/1/2020. Red crosses represent outliers.

Figure 70 shows the waves of COVID-19 infection by level of severity, and the rates following vaccination. Rates in those 60 years and older were much higher and differences increased with higher level of severity. With increasing severity, and at the beginning of the vaccination campaign with each vaccine while person time is still being accrued, rates get spiky, however figure 70 shows for any level of severity that eventually rates of covid disease post-vaccination are lower than in non-vaccinated, both in younger and older persons. The figure below shows the number of reported cases and the peak in the winter of 2020 and spring of 2021.



3.4.26.2 BIFAP-PC

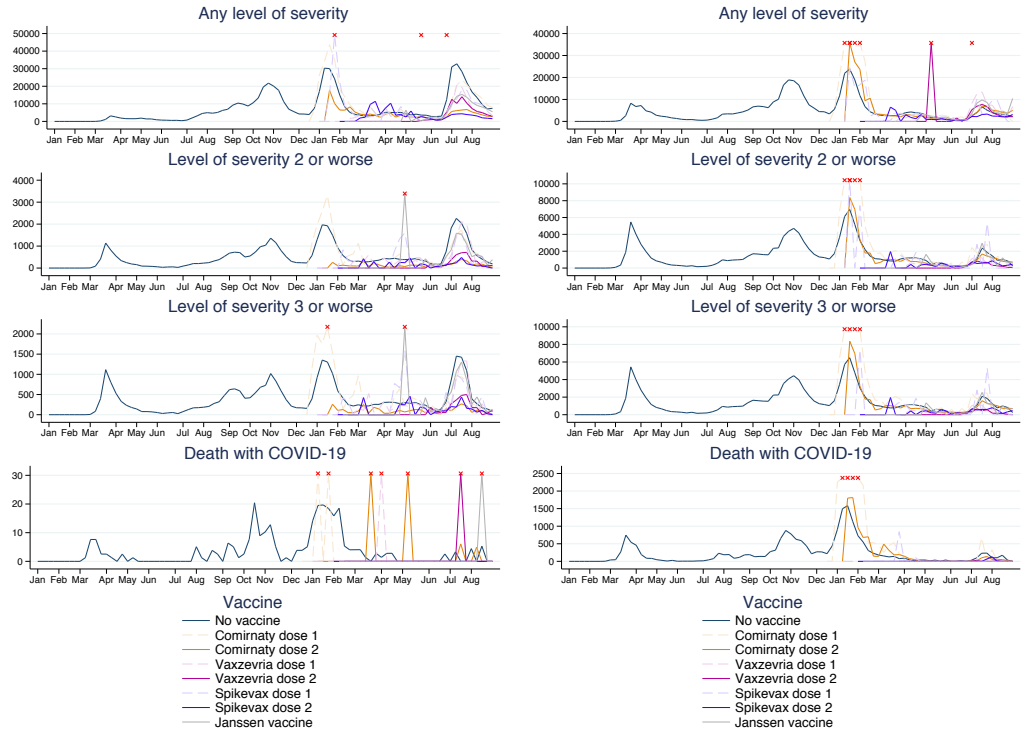
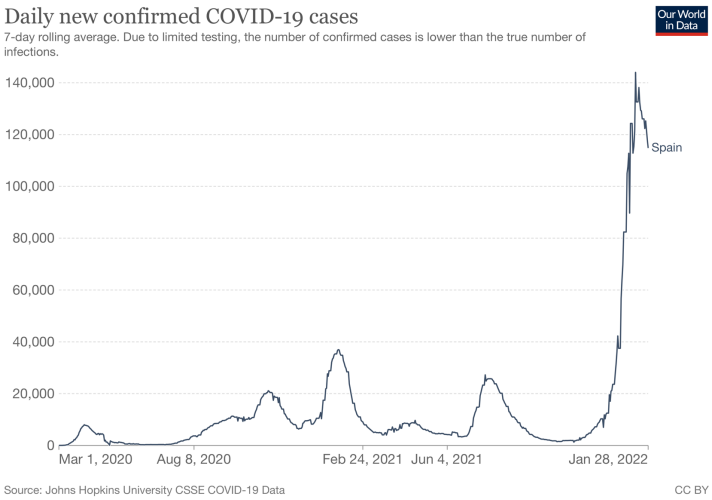


Figure 71 Weekly incidence (per 100,000 PY) of COVID-level severity in young (left) and older (right) persons in BIFAP-PC (note y-axis scales change). X-axis starts at 1/1/2020, Red crosses represent outliers.

Figure 71 shows the waves of COVID-19 infection by level of severity, and the rates following vaccination. Rates in those 60 years and older were much higher and differences in rates increased with higher level of severity, showing that age is a risk factor for severe covid disease. With increasing severity, and at the beginning of the vaccination campaign with each vaccine while person time is still being accrued, rates get spiky, however figure 71 shows that for any level of severity, rates of covid disease post-vaccination are lower than in non-vaccinated, both in younger and older persons. The figure below shows the same pattern of recorded infections as we observe, two peaks in the fall of 2020 and the peak in August 2021 (young people).



3.4.26.3 CPRD

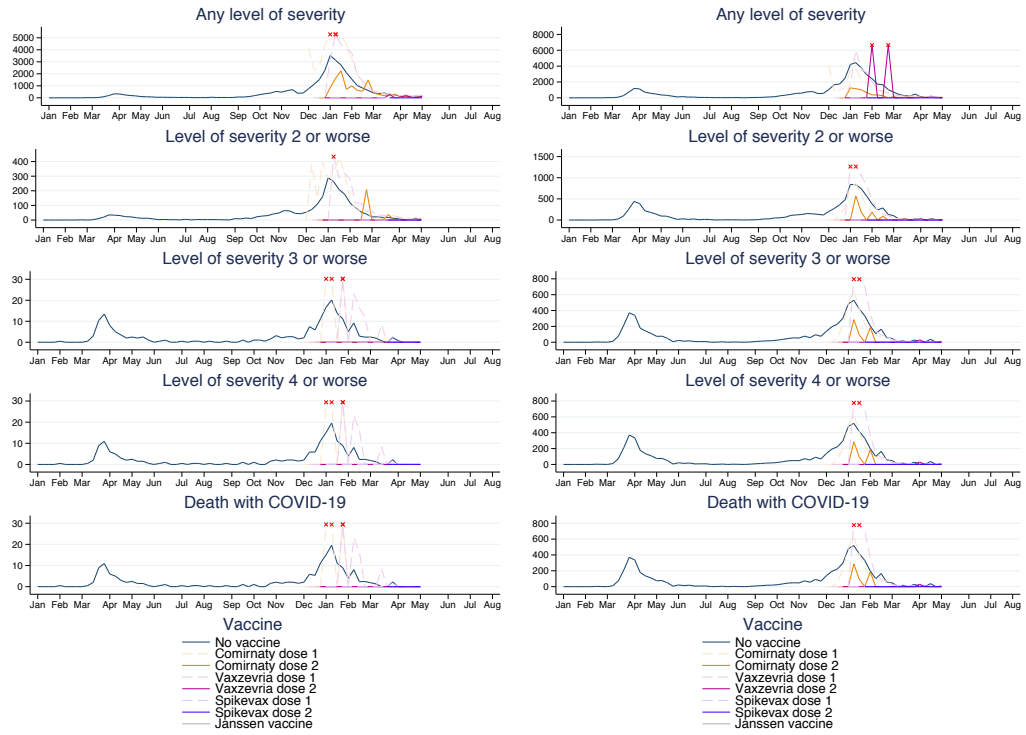
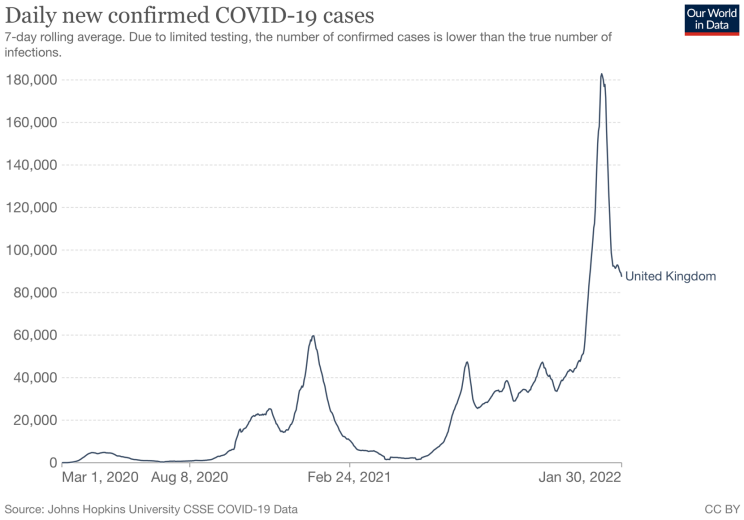


Figure 72 Weekly incidence (per 100,000 PY) of COVID-level severity in young (left) and older (right) persons in CPRD (note y-axis scales change). X-axis starts at 1/1/2020. Red crosses represent outliers.

Figure 72 shows the waves of COVID-19 infection by level of severity recorded in the CPRD, and the rates following vaccination. Rates in those 60 years and older were much higher and differences in rates increased with higher level of severity, showing that age is a risk factor for severe covid disease. With increasing severity, and at the beginning of the vaccination campaign with each vaccine while person time is still being accrued, rates get spiky, however figure 72 shows that for any level of severity, rates of covid disease post-vaccination were initially higher (pointing at channeling at those at higher risk) but became lower than in non-vaccinated,

both in younger and older persons. Data from our world in data is shown in the figure below and shows the peak around December 2020, February 2021and the reduction thereafter.



3.4.26.4 PHARMO

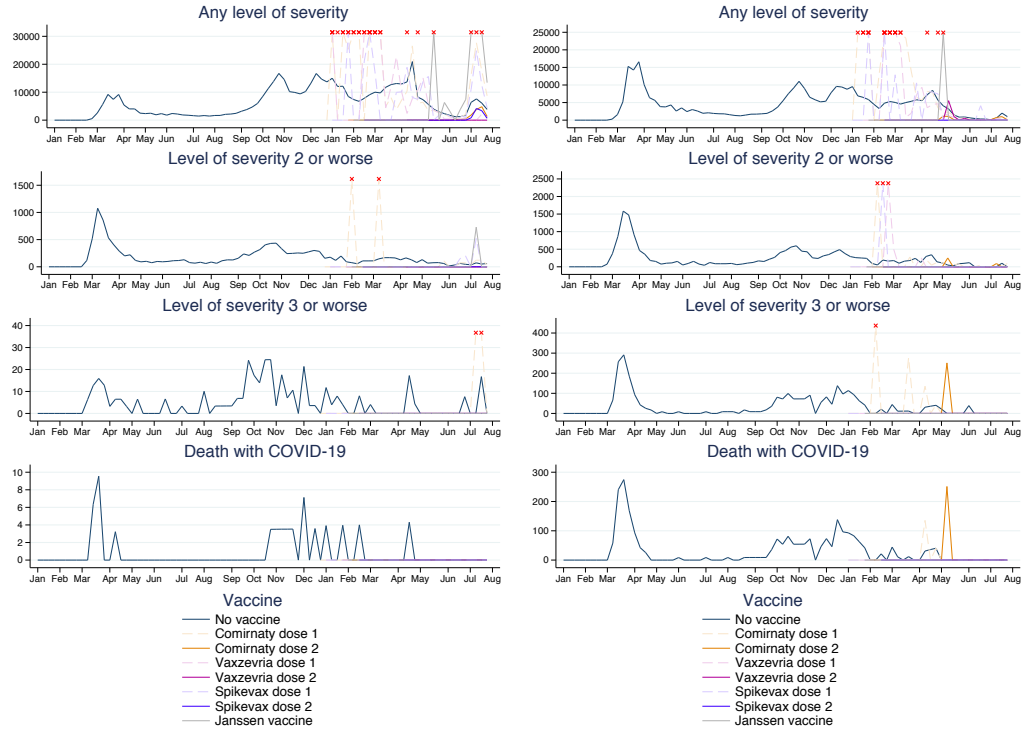
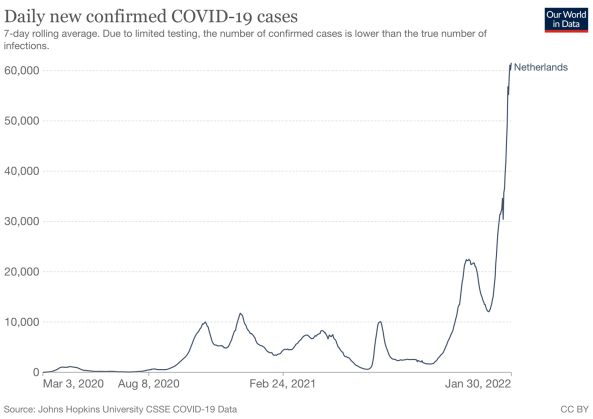


Figure 73 Weekly incidence (per 100,000 PY) of COVID-level severity in young (left) and older (right) persons in PHARMO (note y-axis scales change). X-axis starts at 1/1/2020. Red crosses represent outliers.

Figure 73 shows the waves of COVID-19 infection by level of severity recorded in the PHARMO database, and the rates following vaccination. Rates in those 60 years and older were much higher and differences in rates increased with higher level of severity, showing that age is a risk factor for severe covid disease. With increasing severity, and at the beginning of the vaccination campaign with each vaccine while person time is still being accrued, rates get spiky. Data from our world in data is shown in the figure below and shows the peak around October 2020, January 2021and the reduction thereafter. The rates observed in PHARMO are slightly different.



4. Discussion

4.1 Major findings

This study aimed to monitor the safety of the four different COVID-19 vaccines that were authorized through the European Medicines Agency and MHRA in 2020-2021. These include two mRNA platform vaccines (Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 or Comirnaty and Moderna mRNA-1273 COVID-19 vaccine or Spikevax) and two that use an adenovirus vector (AstraZeneca COVID-19 vaccine / Vaxzevria and COVID-19 vaccine Janssen Ad26. COV2-S [recombinant]).

To monitor the safety of these vaccines we used four different health care data sources comprising more than 25 million people, among them 12.1 million persons had received at least one COVID-19 vaccination and were monitored for 31 pre-specified AESI. There was no a-priori hypothesis, and the study was not set up for causal inference, just for monitoring purposes.

The majority of COVID-19 vaccine recipients received either Comirnaty or Vaxzevria, the share of Spikevax (6%) and Janssen (2%) was very low in those data sources. Vaccination patterns differed substantially between the UK and EU countries. UK used mostly Vaxzevria, whereas other countries used mostly Comirnaty. Comirnaty recipients were consistently older, reflecting the early availability of this vaccine and the roll out strategies that selectively first targeted the eldest and most fragile people in the population. What we observe is consistent with the vaccination strategies described by the European Center for Disease Control and prevention. From the start, vaccinations have been rolled out in phases through various priority groups. Countries initially prioritised elderly people, residents and personnel of long-term care facilities, healthcare workers, social care personnel, and people with certain comorbidities[16]. All EU/EEA countries then opened vaccination to the general population, with all offering vaccination to those aged 12 years and over. The alerts about safety concerns have had different impact in the various European countries.

- In Italy, Vaxzevria and Janssen vaccine are restricted to those 60 years and older, following the signals about (thrombotic)thromboembolic events with the adenovirus platform vaccines.

- In Spain Comirnaty and Spikevax are recommended for elderly (≥70), pregnant women and individuals with high-risk conditions, and other age groups are according to availability. Vaxzevria should only be used in 60-69 years and older, Second dose vaccination for individuals who had received the first dose of AZ vaccine under 60 years was resumed after deciding to offer the possibility of being vaccinated with a second dose of Pfizerand Janssen COVID-19 vaccine primarily for those > 40 years of age.

- In the Netherlands Comirnaty and Spikevax can be used in all people, Vaxzevria was used in those above 60, but not anymore, Janssen vaccine was initially used only for 18 years and older and in difficult to reach populations. Spikevax had a similar user profile as Comirnaty but had very limited use. Janssen vaccine was used by very few people and mostly in young people.

- In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) advised for both Pfizer/BioNTech and Oxford/AstraZeneca that the vaccine should first be given to residents in a care home for older adults and their carers, then to those over 80 years old as well as frontline health and social care workers, then to the rest of the population in order of age and clinical risk factors. The JCVI also decided that the impact of the second dose is likely to be modest and most of the initial protection from clinical disease is after the first dose of vaccine, they decided that prioritising the first doses of vaccine for as many people as possible on the priority list would protect the greatest number of at-risk people in the shortest possible time this meant that second doses of both vaccines were to be administered towards the end of the recommended

[16] European Centre for Disease Prevention and Control. Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA. 11 November 2021. Stockholm: ECDC; 2021.

vaccine dosing schedule of 12 weeks[17]. Our data reflect the initial roll out strategy with long distances between dose 1 and 2 for both Vaxzevria as well as Comirnaty.

4.2 Vaccination coverage & vaccination data

Our vaccination coverage data were consistent with reported national/regional data for vaccine uptake in Italy (41%) in week 26, and for BIFAP (66% in week 34)[18], except in one region, which missed vaccines that were given to frail elderly. In ARS, information on vaccinations was retrieved from the regional registry, including all vaccination facilities. In Spain Vaccines are being administered in many different settings. Some of them are in primary care, but this is mainly restricted to the elderly. Most people have been vaccinated in hospitals or massive vaccination centers. Vaccines data come from an indepent registry, with the information provided by the participants regions, that is linked to the primary care medical records in BIFAP
In PHARMO coverage (31.4%) was lower than published national data (53% in 18 years an older) and for many vaccines the brand was unknown. In the Netherlands, data on covid-19 vaccination arrives from the regional public health systems and other vaccination outlets (hospitals for immunocompromised, health care workers), which use different systems, and therefore recording in primary care records lags behind. Recording was also lower in the CPRD, for the same reason as PHARMO, the medical records of GPs receive information from the national immunization systems with a delay. Data from public health England showed uptake of first dose of 60%, and we estimated 39%.[19]

4.3 Incidence rates & rates post-vaccination

Background incidence rates in 2020 were consistent with those observed during the ACCESS project, but lower than 2017-2019 for some cardiac injury events, that are frequent and influenced by COVID-19[20].

Event rates for the majority of AESI were very rare (<10/100,000 PY) and for those we had limited power to detect elevations of incidence rates post-vaccination. Even when monitoring 12.1 million exposed persons, the risk period is very short: 56 days maximum for 2-dose regimens, and 28 days for a one dose regimen. For adequate monitoring of such events more data sources should be included.
For several events we observed that incidence rates post-vaccination exceeded those that would be expected based on background rates.

ADEM
ADEM has been discussed as signal to Vaxzevria[21], in our study we noted a significant association with Comirnaty in ARS, and non-significant elevations in other datasources (BIFAP-PC-HOSP), cases have been reported in the literature[22]. We did not observe any cases in the risk intervals post-Vaxzevria. Upon pooling of adjusted incidence rate ratios the association did not remain elevated

Guillain Barre Syndrome

[17] https://www.gov.uk/government/publications/uk-covid-19-vaccines-delivery-plan/uk-covid-19-vaccines-delivery-plan
[18]https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab
[19] https://coronavirus.data.gov.uk/details/vaccinations
[20] Willame, C, Dodd, C, Gini, R, Durán, CE, Thomsen, RM, Wang, L, Gedebjerg, A, Kahlert, J, Ehrenstein, V, Bartolini, C, Droz, C, Moore, N, Haug, U, Schink, T, Diez-Domingo, J, Mira-Iglesias, A, Vergara-Hernández, C, Carreras, JJ, Villalobos, F, … Sturkenboom, MCJM. (2021). Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo. https://doi.org/10.5281/zenodo.5255870

[21] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-18-june-2021_en.pdf
[22] Vogrig, A., Janes, F., Gigli, G. L., Curcio, F., Negro, I. D., D'Agostini, S., Fabris, M., & Valente, M. (2021). Acute disseminated encephalomyelitis after SARS-CoV-2 vaccination. Clinical neurology and neurosurgery, 208, 106839. https://doi.org/10.1016/j.clineuro.2021.106839

Several case reports of GBS following Comirnaty have been reported[23], but causality has not been proven yet and according to the MHRA, the number of reports have not reached the number of expected[24], we observed a relevant association with Janssen vaccine.

Narcolepsy
Narcolepsy was associated with Vaxzevria in BIFAP, based on few cases. Besides concerns that narcolepsy may be associated after COVID-19 vaccines in the narcolepsy society, no literature points to cases or associations, and the short risk interval after vaccination would not match normal onset of delay times[25]. Upon pooling of adjusted incidence rate ratios the association did not remain elevated

Thrombocytopenia
We found an association between Thrombocytopenia and Janssen vaccine, Vaxzevria and Spikevax. Thrombocytopenia or low platelets after Vaxzevria and Janssen vaccine have been assessed, and this has been included in the summary of product characteristics[26]. Cases of ITP have been discussed, but a clear causal relationship could not yet be assessed[27]. In our study we observed an increase rate of thrombocytopenia following Janssen vaccine and Spikevax.

Coagulation disorders
Several coagulation disorders were associated with vaccine in our study. Hypercoagulability is a consequence of COVID-19 disease as well, probably due to a high grade systemic inflammatory response. Our study is consistent with the signal that was brought forward in March 2021 through several cases series and discussions in the PRAC[28], which led to restrictions in use of Vaxzevria in many countries. Similar concerns appeared for Janssen COVID-19 vaccine, which already had an imbalance in thromboembolic events in the clinical trials[29]. After adjustment for factors associated with early roll out and pooling TTS and Vaxzevria and Janssen vaccine remained associated with TTS.

Single organ cutaneous vasculitis, erythema multiforme
We observed an association between Janssen COVID-19 vaccine and SOCV, just recently some cases have been reported following Vaxzevria[30] and after Comirnaty[31]. Cutaneous vasculitis may be a result of COVID-19 disease[32]. The same holds for erythema multiforme which have been observed following COVID-19 disease, and were associated with Spikevax in our study. In the October 2021 meeting PRAC decided that based on the case reports and the fact that there is a plausible mechanism for how the vaccine may cause EM, the product information should be updated to include erythema multiforme as a side effect of Spikevax and Comirnaty[33] [34]

Comparison with published studies
Our data are compatible with the findings from the US based Vaccine Safety Datalink which monitored 23 AESI across almost 12 million mRNA COVID-19 vaccine doses (57% Pfizer-BioNTech, 43% Moderna) administered to 6.2 million individuals aged 12 years or older. No outcomes met the prespecified signaling criteria for statistical

[23] Waheed S, Bayas A, Hindi F et al (2021) Neurological complications of COVID-19: Guillain–Barre syndrome following Pfizer COVID-19 vaccine. Cureus 13:2–5. https://doi.org/10.7759/cureus.13426
[24] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1037340/Greenbook-chapter-14a-30Nov21.pdf
[25] Mignot E, Black S. Narcolepsy risk and COVID-19. J Clin Sleep Med. 2020;16(10):1831–1833.
[26] https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-27-30-september-2021
[27] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-spikevax-previously-covid-19-vaccine-moderna-14-july-2021_en.pdf
[28] https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-3-6-may-2021
[29] https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-27-30-september-2021
[30] Cavalli G, Colafrancesco S, De Luca G, Rizzo N, Priori R, Conti F, Dagna L. Cutaneous vasculitis following COVID-19 vaccination. Lancet Rheumatol. 2021 Nov;3(11):e743-e744. doi: 10.1016/S2665-9913(21)00309-X. Epub 2021 Sep 30. PMID: 34611627; PMCID: PMC8483649.
[31] Cohen, S. R., Prussick, L., Kahn, J. S., Gao, D. X., Radfar, A., & Rosmarin, D. (2021). Leukocytoclastic vasculitis flare following the COVID-19 vaccine. International journal of dermatology, 60(8), 1032–1033. https://doi.org/10.1111/ijd.15623
[32] Abdelrahman O, Shadan A, Al Dabal L, Keloth T, R: Leukocytoclastic Vasculitis as a Cutaneous Manifestation of COVID-19 Infection with a Positive Skin Antigen Test. Dubai Med J 2021;4:156-160. doi: 10.1159/000514069
[33] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-6-october-2021_en.pdf
[34] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-spikevax-previously-covid-19-vaccine-moderna-6-october-2021_en.pdf

significance. Rate ratios (RRs) were largest for thrombotic thrombocytopenic purpura (2.60), cerebral venous sinus thrombosis (1.55), and transverse myelitis (1.45), but these measures of association had wide 95% CIs and nonsignificant P values. The highest estimates of excess cases per million doses were 7.5 (95% CI, −0.1 to 14.0) for venous thromboembolism, 1.2 (95% CI, −6.9 to 8.3) for acute myocardial infarction, and 1.2 (95% CI, −2.1 to 3.3) for myocarditis/pericarditis[35].

Limitations

Our study monitored four vaccines across a wide range of pre-specified AESI across 25 million persons, however this study has several limitations. First of all, the study was designed for monitoring of AESI occurrence and not for causal inference. Since comparisons need to be made for monitoring, we compared the period after each dose, and more in detail the 28-day period post-vaccination, to the background rate in 2020 rather than using a parallel comparator. Since the lockdown has lowered health care seeking behavior, the 2020 rate may be lower than other years, which we observed for cardiac injury conditions in the ACCESS study. This is why we use an IRR of 2 or more as threshold.

While we adjusted for main risk factors (age, sex, COVID-19 disease and conditions that are a risk factor for serious COVID-19 disease, all of which were related to the vaccination chance) we cannot exclude residual confounding. Co-variates were selected based on the chance of exposure and not for specific outcomes and this means that residual confounding cannot be ruled out. Moreover, case counts were limited and too few for accurate adjustment. Our attempt to adjust was to limit as much as possible confounding, acknowledging it could not all be eliminated.

Although comparisons are done within data source, where event recording may stay relatively stable, temporal effects due to awareness (e.g., TTS, myocarditis) and therefore differential misclassification cannot be excluded.

There are also limitations due to specifics in the data sources that we use and the data that they capture:

- ARS data comprises emergency care visits and hospitalizations, which explains why the rates of anaphylaxis were higher than in other data sources. It also explains the lower rates of conditions that are not typically seen in this setting such as chilblains and anosmia/ageusia. COVID-19 vaccination data were obtained from regional registers and reflected the coverage observed in the population. Pattern of use of corticosteroids in Italy is known to be very different from other countries, namely, occasional use in persons with asthma is often observed. This has increased the category of immunosuppressant users.

- In BIFAP-PC there could be some misclassification of certain events i.e., more severe cases, since these cases will be better recorded in the hospital setting. However, since BIFAP data in a subset of regions has been linked to hospital diagnoses, we were able to use this PC_HOSP subpopulation to more precisely ascertain AESI cases. Results for both BIFAP subpopulations (PC and PC_HOSP) are generally consistent with those of other DAPS with similar characteristics. Although the study variables have been created in a harmonized manner, there may exist some residual discrepancies in the list of codes among the different coding systems used by the DAPs participating in this study, which may have affected some AESI IRs and lead to some differences with IRs from other data sources. This may be the case of meningoencephalitis, which shows an age pattern slightly different to the rest of DAPs in the oldest age groups in 2020, Thrombotic microangiopathy, for which greater post-vaccination IRs have been found in BIFAP and this was not consistent with those of other databases or CAD, where IRs in 2020 are lower than databases with similar characteristics In addition to this, the lower IRs observed for CAD in BIFAP might also be explained by the fact that lower IRs of ischemic heart disease in Spain compared to those in other European countries has also been seen. The second report on cardiovascular disease (CVD) statistics for the member countries of the European Society of Cardiology (ESC) reported a lower incidence of ischemic heart disease in 2017 in Spain than in Italy, the Netherlands, and the UK[36]. Vaccine records come from the National Vaccine Registry; nonetheless, due to the intense workload of the healthcare workers responsible for administering the vaccines and registering vaccine and patient

[35] Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. *JAMA*. 2021;326(14):1390–1399. doi:10.1001/jama.2021.15072

[36] Atlas Writing Group, ESC Atlas of Cardiology is a compendium of cardiovascular statistics compiled by the European Heart Agency, a department of the European Society of Cardiology., Developed in collaboration with the national societies of the European Society of Cardiology member countries, Timmis, A., Townsend, N., Gale, C. P., ... & Vardas, P. (2020). European Society of Cardiology: cardiovascular disease statistics 2019 (executive summary). *European Heart Journal-Quality of Care and Clinical Outcomes*, *6*(1), 7-9.

data, in this massive COVID-19 vaccination campaign, some residual recording errors cannot be ruled out, e.g. duplicated doses, wrong or missing brand vaccine.

- For PHARMO, vaccination status and date of vaccination was obtained from the EMR of the GP and was incomplete. The GP Database contains vaccinations administered by GPs and by the public health service, as GPs receive an automated notification when a patient has been vaccinated via the public health service (provided that individuals have given their consent). Vaccines administered at hospitals were missed. In addition, only ICPC coded events were considered in this study. For some events, ICPC codes do not exist. Events that were diagnosed in secondary care were only captured if recorded by the GP. Another limitation is that within the PHARMO data death is under-recorded or delayed. As a result, persontime, especially person time in older persons may be overestimated, which leads to an underestimation of the rates. The event rates in this group will be underestimated accordingly.

- In CPRD Aurum, only data from primary care were used in this study. Hospital data was not available for the relevant time window. Like in PHARMO, events diagnosed in secondary care were only captured when recorded in the GP practice, which means that some outcomes could have been underdiagnosed. Data from CPRD Aurum ran until the beginning of May 2021, which means that the number of vaccinations among younger individuals was still relatively low with the vaccination strategy in the UK compared to other DAPs. Vaccinations delivered in a mass vaccination centres are all being fed through to the GP electronically, which should improve capture of vaccination status, but some misclassification cannot be excluded.

Some of the relative risks that were disproportional after adjusting for key factors associated with vaccination were observed, but are often based on a small number of events; that is the case of Microangiopathy and Thrombotic microangiopathy with Vaxzevria or SOCV and TTS (Diagnosed or possible CAD or IS, concurrent with TP) with Janssen vaccine in BIFAP_PC. Thus, caution must be taken when interpreting these results, if a hypothesis testing would be needed this would require larger populations.
This could be obtained by including longer time periods, as well as a wider range of data sources. Longer time period would include larger population, and namely larger strata of the non-at-risk population, thus allowing to address channeling. A wider range of data sources would allow tailoring the analysis of each AESI to the data sources best equipped to study it, or to discuss in a more complete manner the strengths and limitations of each data source.

4.2 Discussions related to the dashboard and monitoring of events

The design of the dashboard was based on the dashboard for near real time monitoring of pertussis vaccines, developed during the ADVANCE project. However, that dashboard was populated with real world data based on a vaccine that was part of routine immunization since decades. On the contrary, COVID-19 vaccines were delivered for the first time, and the roll out of the vaccination campaign was highly channelled to persons at higher risk for severe covid-19 and age.
Most AESIs were very rare which made graphical representation of weekly rates post-vaccination very unstable. Crude accumulation of person time after vaccination increased readability. Presentation of crude rates post-vaccination did not deal with the strong confounding, especially for those AESI which are associated with age or with risk factors for severe COVID, such as death or cardiovascular events. The comparator was the general population, stratification for a single factor that was possible in the dashboard (age, or risk factor) was insufficient to eliminate confounding.

The dashboard was not utilized as expected by EMA or PRAC, and paper-based, commented data were preferred. Although the dashboard was a success in ADVANCE, we need to conclude this was not a useful way for EMA or PRAC to monitor a new vaccine, and rather, repeated analyses that can deal with confounding should be conducted, with interpretation included in a report.

Graphical representation of weekly rates proved however useful to comment some events which are less associated with risk factors for severe COVID, and is included in some cases in this report, as it is useful to reveal time patterns of risk elevation after vaccination.

4.3 Conclusion

This study has provided many lessons

10) It showed that we could monitor a large number of AESI and COVID-19 across 4 data sources in four countries based on the ConcePTION common data model, and common analytics pipeline, and that semantic harmonization was possible across the different disease terminologies
11) Monitoring could start very early in the vaccination campaign, and repeated updates were possible
12) The same population and data source was used both to compute background rates, and to retrieve observed events after vaccination. This design avoids a limitation of using, on the one hand, real-world data to assess background rates, and, on the other, spontaneous reporting to assess observed cases: underestimation, if any, is more likely to affect the two periods is a uniform way, thus improving the validity of comparison.
13) Underestimation of an AESI can be discussed, based on the characteristics of the data source in relation with the AESI. For example, ICPC codes do not allow for studying the majority for rare AESI, which affected the ability of PHARMO of monitoring such AESI; or, events that do not require hospitalisation or access to emergency room cannot be studied in the ARS data source.
14) COVID-19 vaccines had very different user patterns across the countries in terms of type, distance between dose 1 and 2 and the populations targeted. We observed strong channelling of the different vaccines that differed across countries
15) AESI incidence rates were mostly very low, especially for neurological, immunological and hematological events. Coagulations disorders and cardiac disorders were more frequent, at the same time such events were those with stronger confounding
16) For several AESI we observed disproportionalities between post-vaccination observed and expected rates. Most of these events had been the topic of regulatory discussions, based on public records such as the haematological events, neurological events and erythema multiforme.
17) In spite of the large numbers of vaccinees, power is limited for the events that are very rare <10/100,000 PY and continuous monitoring and scaling up (across countries and over time) is required.
18) This study was for monitoring purposes and not for testing signals, if this needs to be done, proper pharmacoepidemiological designs (such as matching/restriction) should be applied to deal with confounding.

Annexes

- Annex 1: Code counts
- Annex 2: Code sheets
- Annex 3: Age specific incidence rates of AESI and monitoring graphics by AESI