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Vaccine monitoring Collaboration for Europe

Covid-19 medicinal product studies by VAC4EU

Prof. dr. Miriam Sturkenboom

Head of department Datascience & Biostatistics, University Medical Center Utrecht
VAC4EU president

Declaration of interest

- President and co-founder of the Vaccine Monitoring collaboration for Europe (non-remunerated)
- Head of department conducting
 - funded EMA studies (ACCESS, CONSIGN, ECVM, COVE, CVM)
 - EMA required PASS studies for COVID-19 vaccines for Pfizer, J&J and AstraZeneca
 - All according to ENCePP code of conduct



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Vaccine monitoring Collaboration for Europe

Readiness & collaboration has proven to be key to generation of timely and robust RWE for benefit risk monitoring of COVID-19 vaccines in Europe

































Vaccine

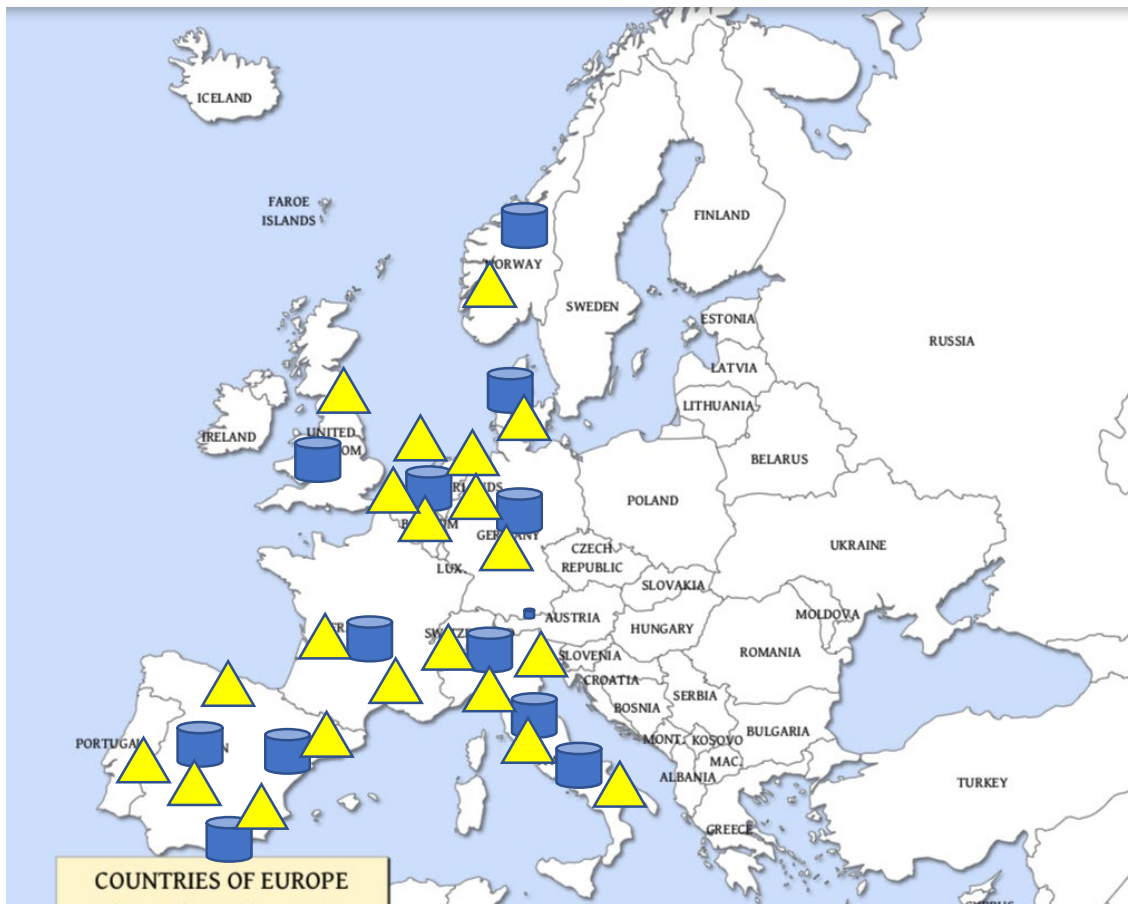
Volume 38, Supplement 2, 22 December 2020, Pages B1-B7




Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines

Miriam Sturkenboom ^{a, b, c}  , Priya Bahri ^d  , Antonella Chiucchiuini ^e  , Tyra Grove Krause ^f  , Susan Hahné ^g  , Alena Khromava ^h  , Maarit Kokki ⁱ  , Piotr Kramarz ⁱ  , Xavier Kurz ^d  , Heidi J. Larson ^j  , Simon de Lusignan ^{k, l}  , Patrick Mahy ^m  , Laurence Torcel-Pagnon ⁿ  , Lina Titievsky ^o  , Vincent Bauchau ^p  , on behalf of the ADVANCE consortium ¹

READINESS: Expertise & Data access in EU

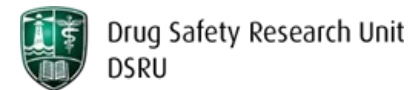


 25 members (expertise and/or data access)

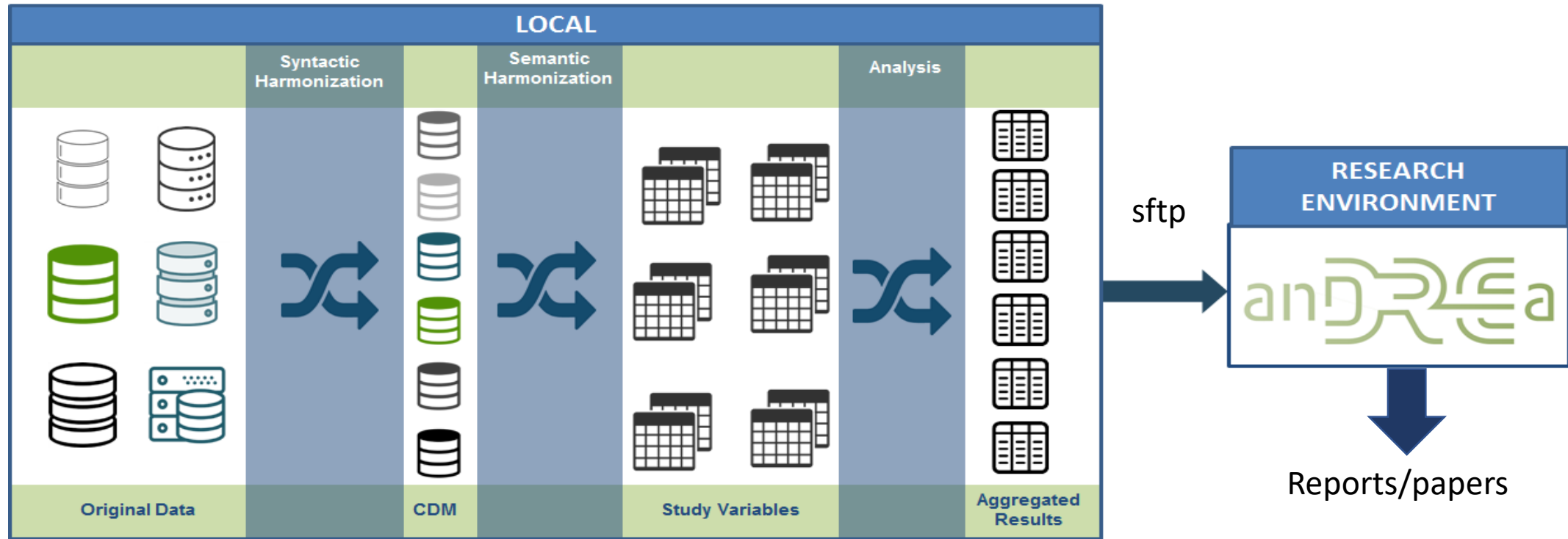
 Access to large national/regional health data from different provenance (Registries/medical record/hospitalizations/insurance) >130 M

Country	Type of health data sources	# persons
NL	Record linkage	6 Million
NO	Record linkage	5 million
DK	Record linkage	5.5 million
IT (4)	Medical records (GP/FP Regional record linkage	12 million
ES (4)	Record linkage & medical records	30 million
UK	Medical records & HES	16 million
DE	Insurance	16 million
FR	SNDS (Claims)	60 million

- 25 members from 9 European Countries
 - 18 Data Access Providers (DAPs) and 15 Data Sources for secondary use
 - Overall population covered with accessible data for analysis: ~152 million patients
 - infrastructure for primary data collection (cohort event monitoring)



Individual level original data stay local, unless consented

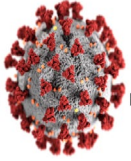


Utilizing the generic RWD-RWE pipeline developed in the IMI-ADVANCE and IMI-ConcePTION projects

- **Participating in 5 studies funded by the European Medicines Agency**
 - **ACCESS:** template protocols, AESI list, background rates for covid-19 vaccine AESI (finalized & presented at PRAC)
 - **Early covid vaccine monitor study:** cohort event monitoring & EHR based near real time monitoring (finalized & presented at PRAC)
 - **Covid-19 vaccine monitor study** cohort event monitoring special populations, safety evaluation & methods (ongoing, results presented at PRAC (myocarditis) & PDCO (pediatric severity))
 - **COVE:** covid-19 vaccine effectiveness of homologous and heterologous primary and booster schemes (submitted)
 - **CONSIGN:** medicines use and effects in covid-19 affected pregnancies (finalized)
- **EMA requested post-authorization safety studies for covid-19 vaccines**
 - Pfizer: 2 interim reports submitted to PRAC
 - AstraZeneca: 1 interim report submitted to PRAC
 - Janssen: 1 interim report submitted to PRAC
 - Moderna: 2 interim report submitted to PRAC
 - Sanofi: protocol phase
- **GVDN genomics and associations studies**
- **ALL PROTOCOLS PUBLICLY AVAILABLE ON EU PAS**

ACCESS

vACCine covid-19



monitoring readinESS

Background rates of AESI widely used by EMA to address signals (O/E analysis)

- List of AESI based defined (August 2020)
- Background rates generated and publicly released
- Data used for O/E analyses by EMA and by vaccine manufacturers for observed/expected analyses



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



August 25, 2021

Report Open Access

Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines

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; Pallejà, M; Aragón, M; Perez-Gutthann, S; Arana, A; Giaquinto, C; Barbieri, E; Stona, L; Huerta, C; Pallejà, M; Aragón, M; García Poza, P; de Burgos, A; Martínez-González, M; Souverein, P; Gardarsdottir, H; Siiskonen, SJ; Weibel, D; Mahy, P; Klungel, O;  Sturkenboom, MCJM

Rationale and background:

5,376

views

1,906

downloads

[See more details...](#)

Indexed in

OpenAIRE

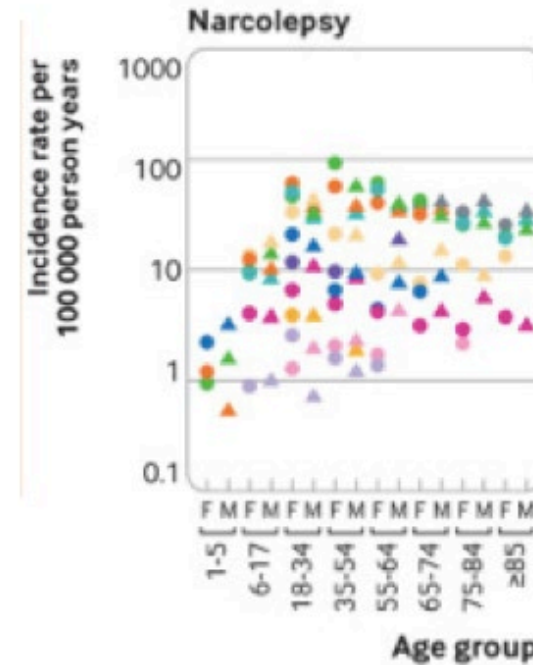
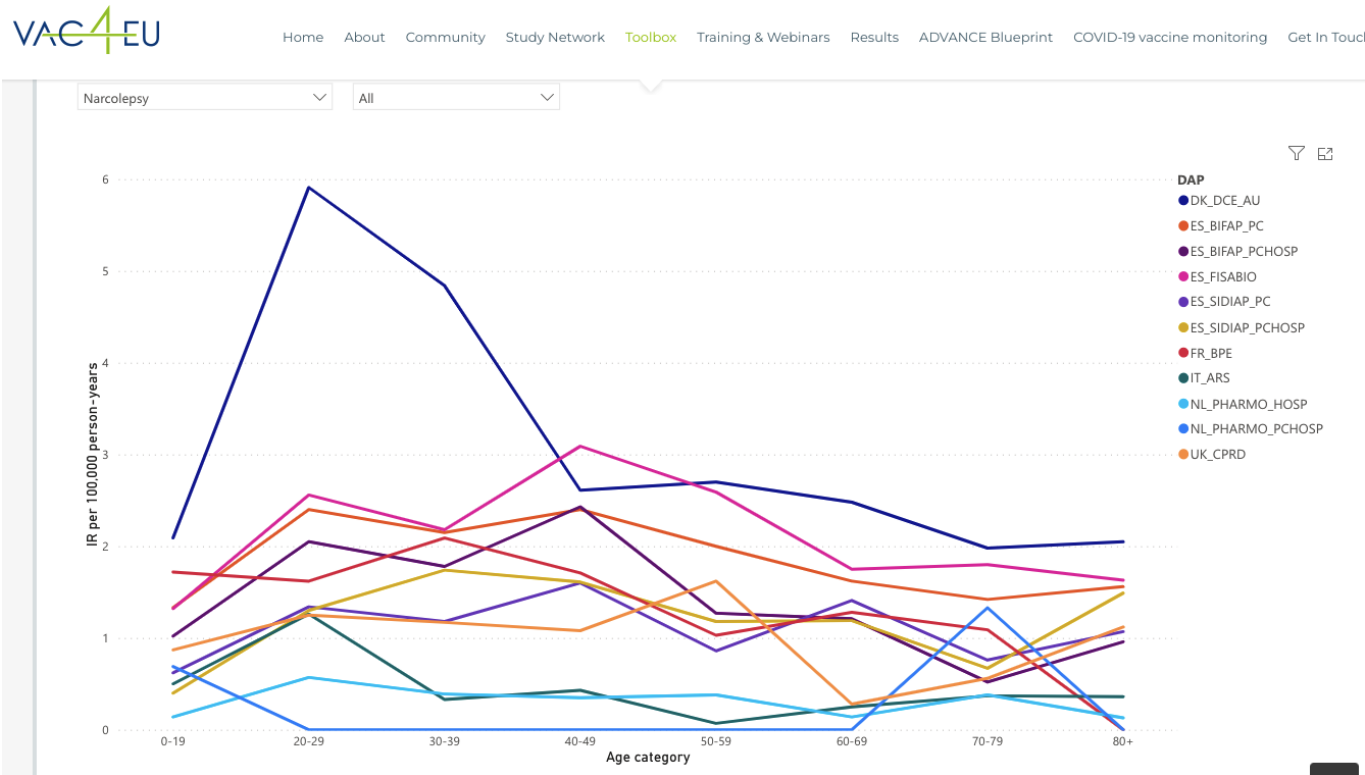
Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study

C Willame^a, C Dodd^a, CE Durán^a, RJHJ Elbers^b, R Gini^c, C Bartolini^c, O Paoletti^c, L Wang^d, V Ehrenstein^d, J Kahlert^d, U Haug^e, T Schink^f, J Diez-Domingo^g, A Mira-Iglesias^g, JJ Carreras^g, C Vergara-Hernández^g, C Giaquinto^h, E Barbieri^h, L Stonaⁱ, C Huertaⁱ, M Martín-Pérez^k, P García-Poza^k, A de Burgos^k, M Martínez-González^k, V Bryant^k, F Villalobos^l, M Pallejà-Millán^l, M Aragón^m, JJ Carreras^g, P Souvereinⁿ, NH Thurin^o, D Weibel^a, OH Klungelⁿ, MCJM Sturkenboom^{a,*}

VAC4EU

Vaccine monitoring Collaboration for Europe

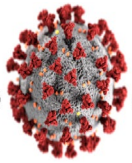
Background rates VAC4EU based approach vs. OHDSI rates (example narcolepsy)



EMA funded independent research to monitor COVID-19 vaccines/medicines

ACCESS

vACCine covid-19



monitoring readinESS

Early



Vaccine- Monitor



C



NSIGN

Covid 19 in pregnancies

CoVE

Covid-19 vaccine effectiveness

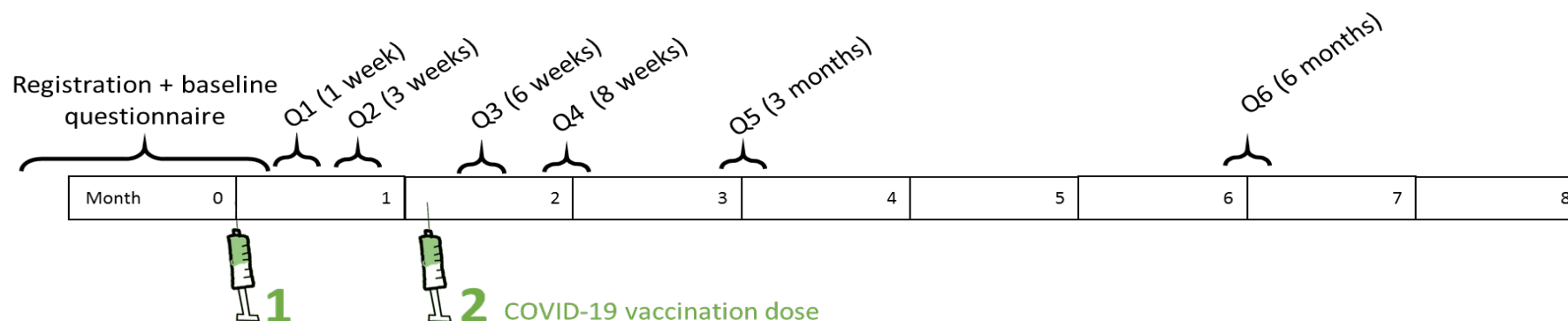
May 2020

January 2021

January 2022

Cohort event monitoring

Covid-19 Vaccine Monitor- Sept 2021-2023



More than 550,000 vaccine recipients included

Countries :

- Romania, Slovakia, Ireland, Switzerland, Spain, Belgium, Netherlands, Germany, Croatia, France Italy, UK

Specific populations targeted

- **Pregnant women**
- Immunocompromised persons
- Former COVID-19
- History of allergies
- Booster doses

<https://vac4eu.org/>

June 9, 2022

Report Open Access

Covid-19 Vaccine Monitor: Interim Study Report for Cohort Event Monitoring of vaccinated persons

Luxi, N; Raethke, M; Ruijs, L; Schmikli, S; Riefolo, F; Trifiro, G; Sturkenboom, MCJM

Hosting institution(s)

Klungel, OH

Project manager(s)

Siiskonen, SJ

Registration authority(s)

Mirošević Skvrce, N; Margan Koletić, Z; Pavičić, M; Kovačić, B; Dujmović Blažo, S; Ljubičić, I; Keller-Stanislawski, B; Mentzer, D

Researcher(s)

Giovanazzi, A; ilmiovaccinoCOVID19 collaborating group; Schmitz, J; Kant, A; Ahmadizar, F; Thurin, N; Dureau-Pournin, C; Guiard, E; Lamarque, S; Bignon, E; Shakir, S; Liddiard, M; Morton, K; Fry, C; Roy, D; Sonderlichová, S; Panchoaud, A; Maisonneuve, E; Farcas, A; Bucsa, C; Batel Marque, F; Ribeiro Vaz, I; Polónia, J; Costa Alves, CM; Villalobos, F; Casajuana, M; Cleary, B; O'Shaughnessy, F

Rationale and background

3,430 1,486

views downloads

See more details...

Indexed in

OpenAIRE

Publication date:

June 9, 2022

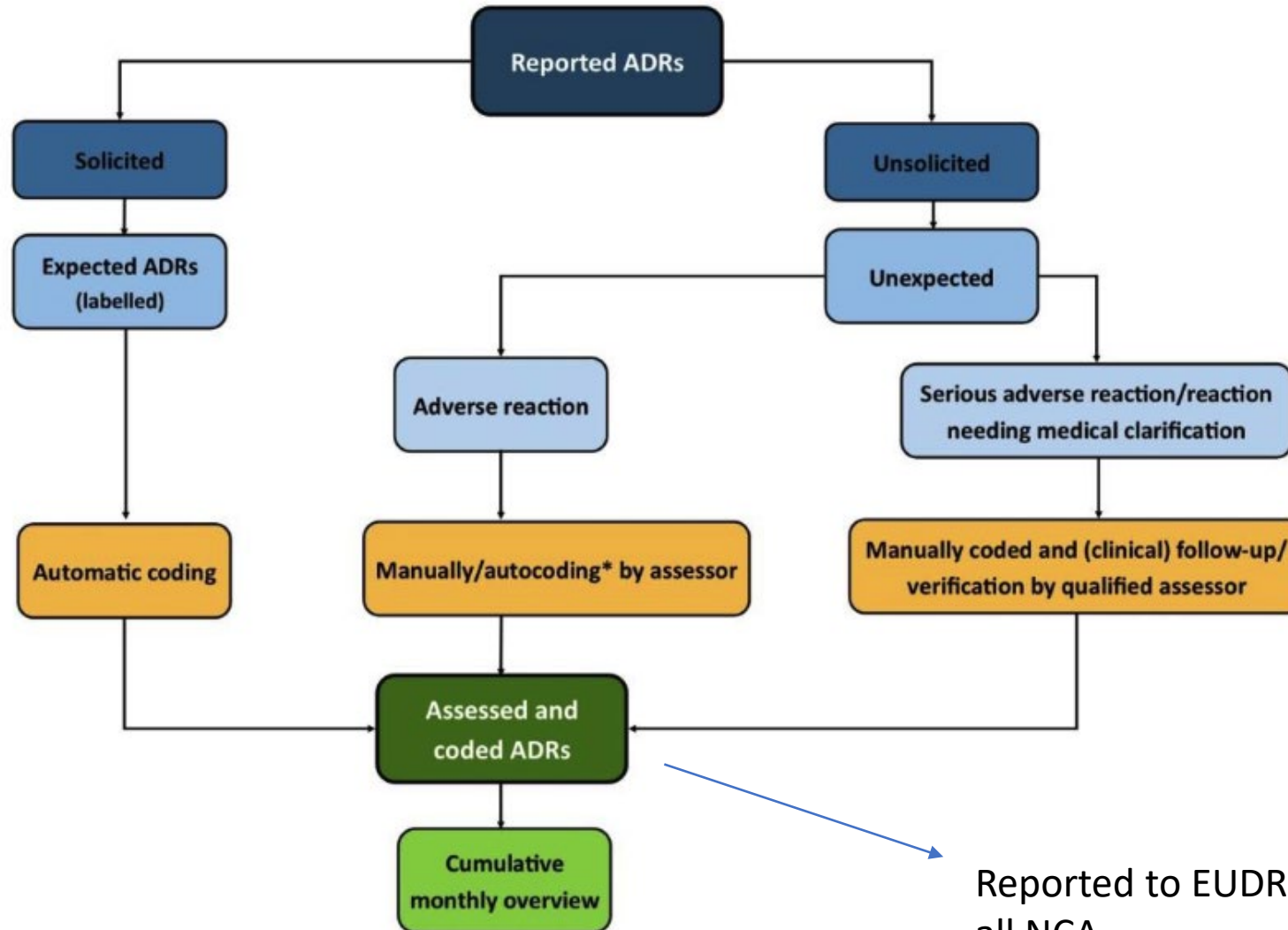
DOI:

DOI: [10.5281/zenodo.6629551](https://doi.org/10.5281/zenodo.6629551)

Keyword(s):

COVID-19 vaccines, safety, cohort event monitoring

Cohort event monitoring: Workflow for reported ADRs



Reported to EUDRAVIGILANCE for all NCA

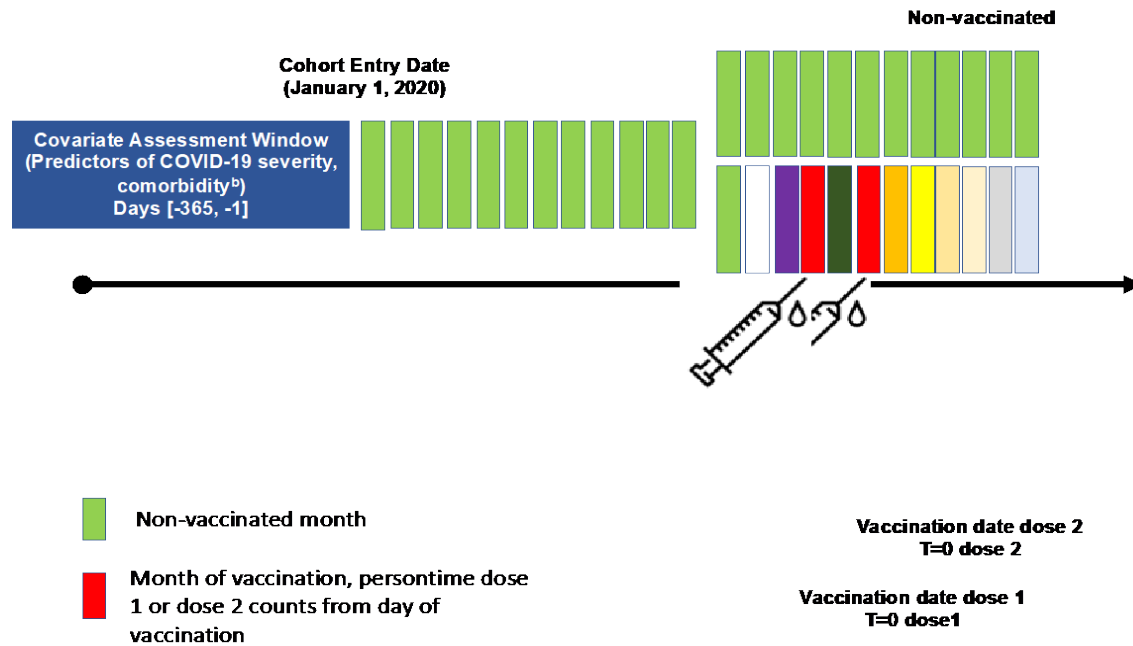
Safety of COVID-19 Vaccines among the Pediatric Population – Comparative Analysis of European Cohort Event Monitoring vs Pivotal Trials

Fariba Ahmadizar*¹, Nicoletta Luxi*², Monika Raethke³, Sandor Schmikli¹, Fabio Riefolo⁴, Putri Widi Saraswati¹, Camelia Bucsa⁵, Alhadi Osman¹, Megan Liddiard⁶, Francisco Batel Maques⁷, Giuliana Petrelli⁸, Simona Sonderlichová⁹, Nicolas H. Thurin¹⁰, Felipe Villalobos¹¹, Gianluca Trifirò^{8**} and Miriam Sturkenboom^{1**} and ilmiovaccinoCOVID19 collaborating group.

	5-11 years		12-17 years				Total	
	Comirnaty		Comirnaty		Spikevax		First dose	Second dose
	First dose	Second dose	First dose	Second dose	First dose	Second dose		
Vaccinees included in the analysis who received the first and the second doses of the COVID-19 vaccine	250 (100)	123 (100)	395 (100)	226 (100)	13 (100)	8 (100)	658 (100)	357 (100)
At least one ADR, n (%)	72 (28.8)	21 (17.1)	214 (54.2)	118 (52.2)	7 (53.8)	3 (37.5)	293 (44.5)	142 (39.8)
At least one serious ADR, n (%)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)
At least one unsolicited ADR	10 (4.0)	3 (2.4)	40 (10.1)	20 (8.8)	4 (30.8)	-	54 (8.2)	23 (6.4)

EHR cohort monitoring of 31 AESI after vaccines

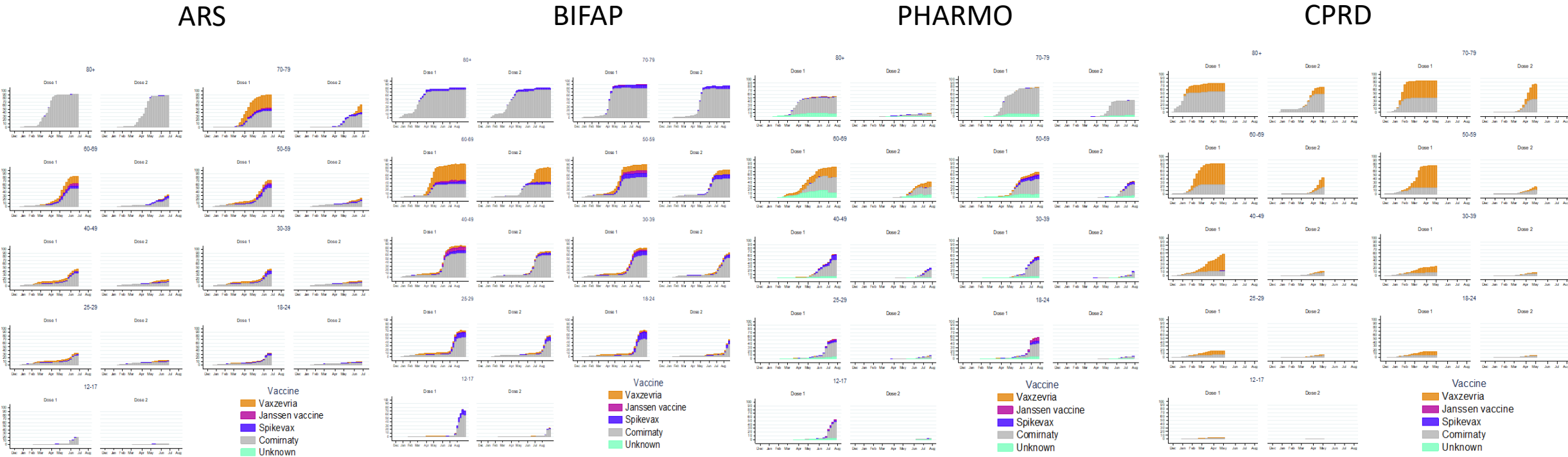
EUPAS40404



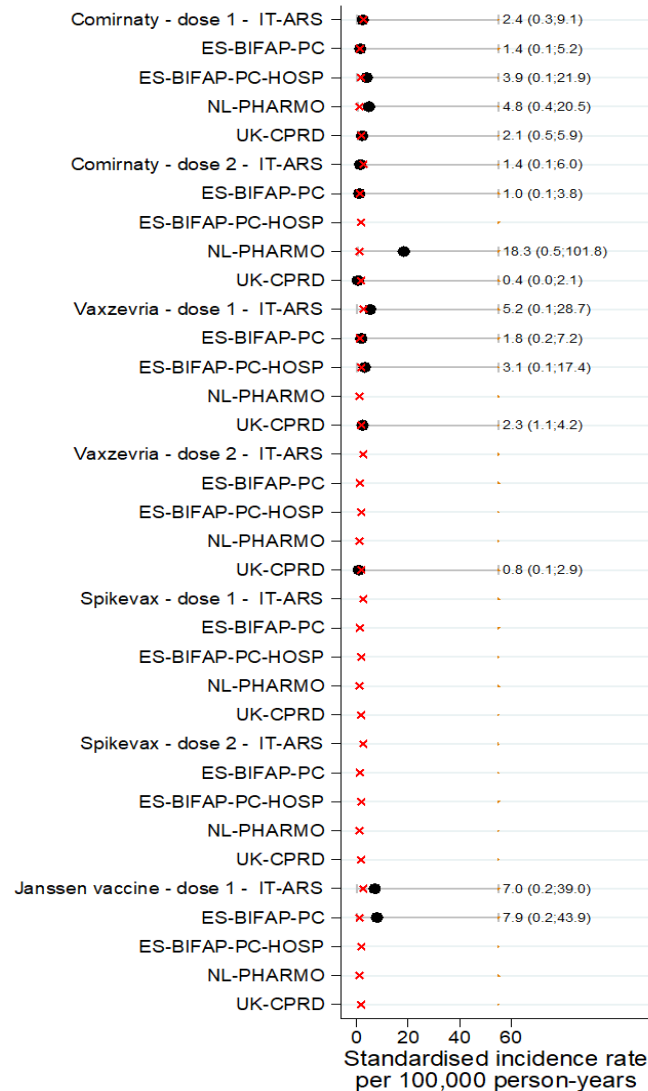
Four data sources selected on short lag times, allowing for near real time monitoring : 25 million
Using ConcePTION CDM and pipeline & VAC4EU tools

Sturkenboom, MCJM, Messina, D, Paoletti, O, de Burgos, A, Garcia, P, Huerta Álvarez Consuelo, Llorente, A, Klungel, O, Martin, M, Martinez, M, Martin, I, Overbeek, J, Souverein, P, Swart, K, & Gini, R. (2022). Cohort monitoring of Adverse Events of Special Interest and COVID-19 diagnoses prior to and after COVID-19 vaccination (1.0). Zenodo. <https://doi.org/10.5281/zenodo.6762311>

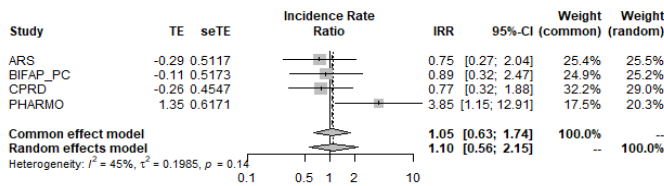
Results: uptake of vaccination by age, dose



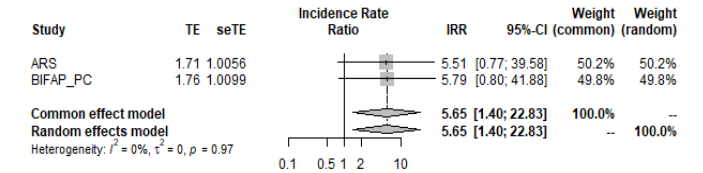
Results: Incidence rates of GBS



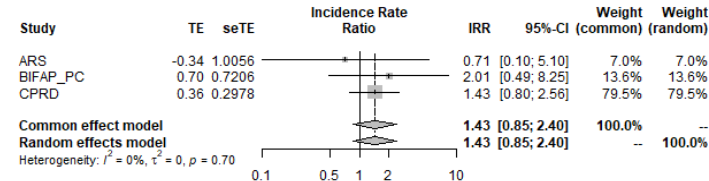
AESI_GBS_narrowVax_Pfizer



AESI_GBS_narrowVax_J&J

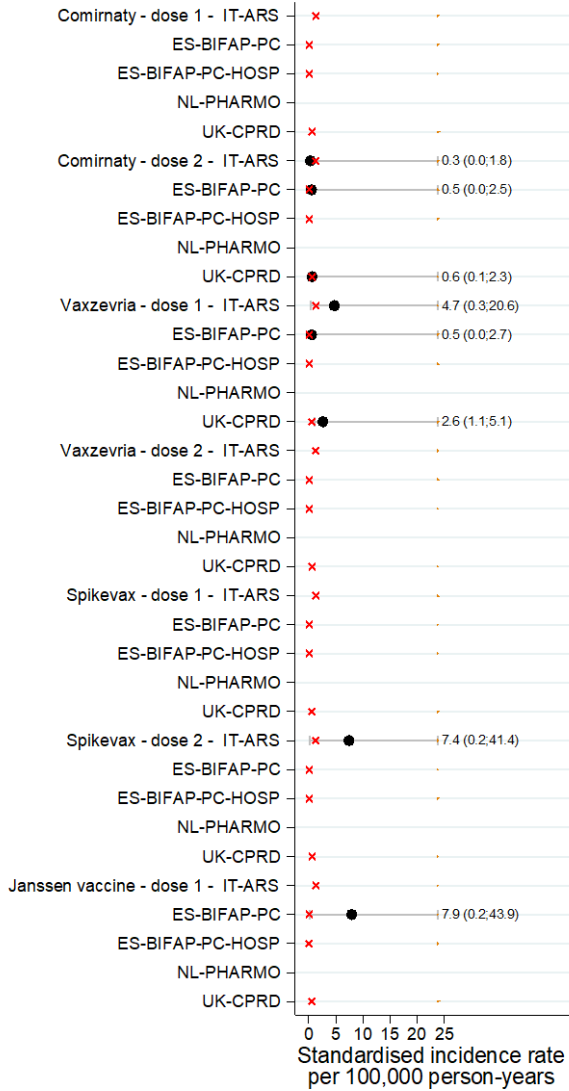
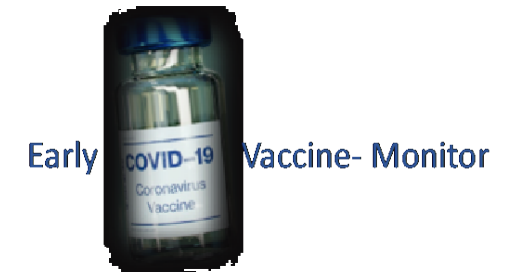


AESI_GBS_narrowVax_AZ

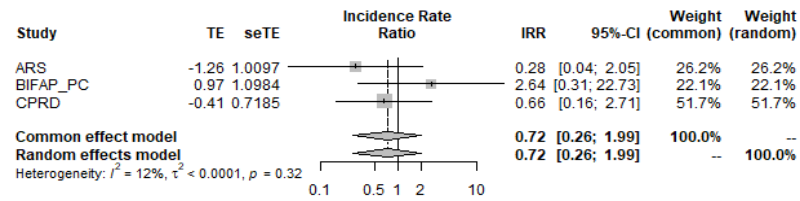


Zenodo. <https://doi.org/10.5281/zenodo.6762311>

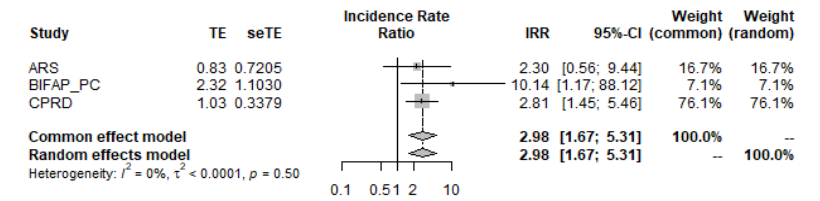
Results: Incidence rates of TTS



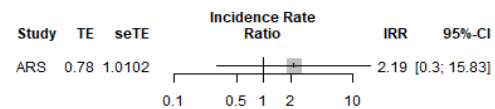
AESI_ArterialVTETPVax_Pfizer



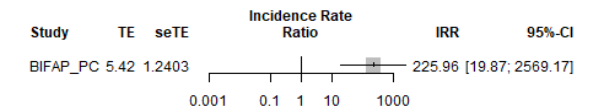
AESI_ArterialVTETPVax_AZ



AESI_ArterialVTETPVax_Moderna



AESI_ArterialTPVax_J&J



Zenodo. <https://doi.org/10.5281/zenodo.6762311>

EMA funded independent research to monitor COVID-19 vaccines

Testing signals

Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources (EUPAS42467) Covid-19 Vaccine Monitor-EHR



Readiness to rapidly quantify signals



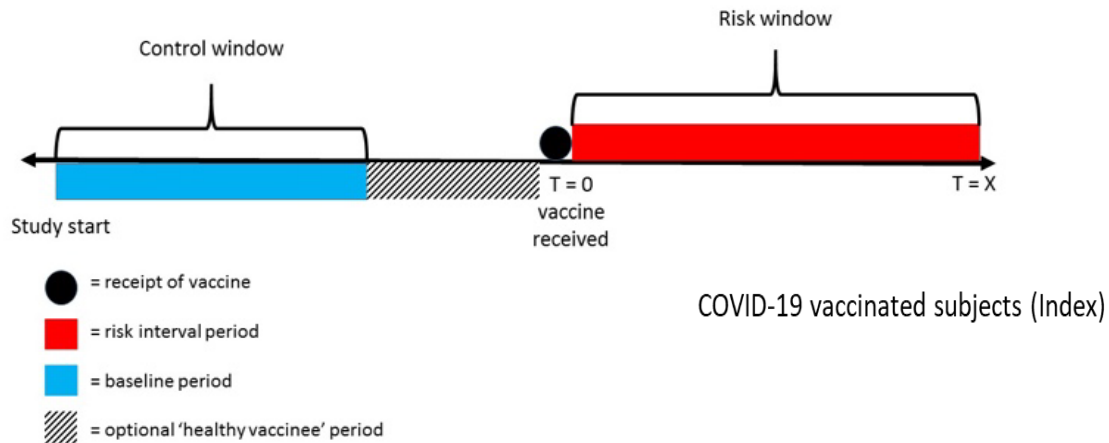
Preparedness

- Extract, transform load relevant data into ConcePTION Common Data Model
- Run quality checks & background rates (vaccination data, AESI identification)
- Protocols pre-approved
- Methods testing

Data sources:

- Italy (3): Tuscany region, Lazio Region, Caserta
- Spain (3):
 - BIFAP, Spanish Medicines Agency
 - SIDIAP data (Catalunya)
 - FISABIO (Valencia)
- NL (1): PHARMO
- UK (1): CPRD
- No (1): Norwegian registers

Signal testing designs & methods work



COVID-19 vaccinated subjects (Index)

Reference cohort

- = Follow-up period
- = Reference date

Assessment window
prior exposure
(eg. covariates, baseline
conditions)



Assessment window
prior reference date
(eg. covariates, baseline
conditions)





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Check for updates

OPEN ACCESS

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to this work and share first authorship

SPECIALTY SECTION

This article was submitted to
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Bots SH, Riera-Arnau J, Belitser SV,
Messina D, Aragón M, Alsina E,
Douglas IJ, Durán CE, García-Poza P,
Gini R, Herings RMC, Huerta C,
Sisay MM, Martín-Pérez M, Martín I,
Overbeek JA, Paoletti O

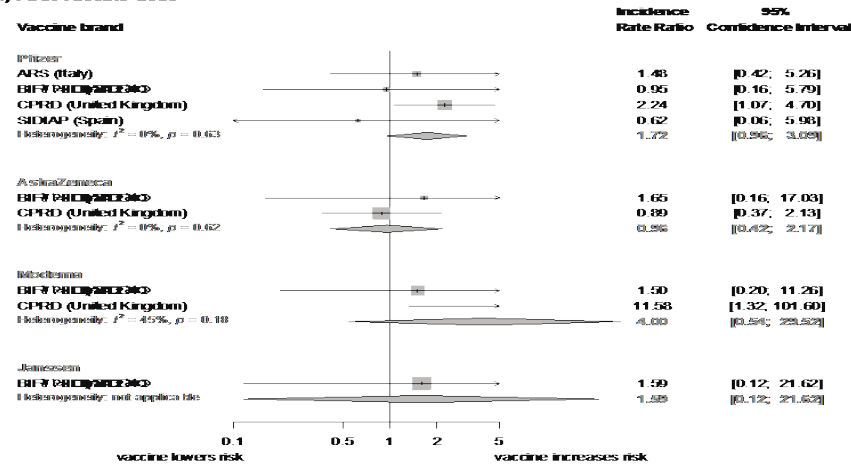
Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries

Sophie H. Bots^{1†}, Judit Riera-Arnau^{2,3†}, Svetlana V. Belitser¹, Davide Messina⁴, Maria Aragón⁵, Ema Alsina^{2,3}, Ian J. Douglas⁶, Carlos E. Durán^{2,3}, Patricia García-Poza⁷, Rosa Gini⁴, Ron M. C. Herings⁸, Consuelo Huerta⁷, Malede Mequanent Sisay^{2,3}, Mar Martín-Pérez⁷, Ivonne Martín^{2,3}, Jetty A. Overbeek⁸, Olga Paoletti⁴, Meritxell Pallejà-Millán⁹, Anna Schultze⁶, Patrick Souverein¹, Karin M. A. Swart⁸, Felipe Villalobos⁵, Olaf H. Klungel¹ and Miriam C. J. M. Sturkenboom^{2,3*}

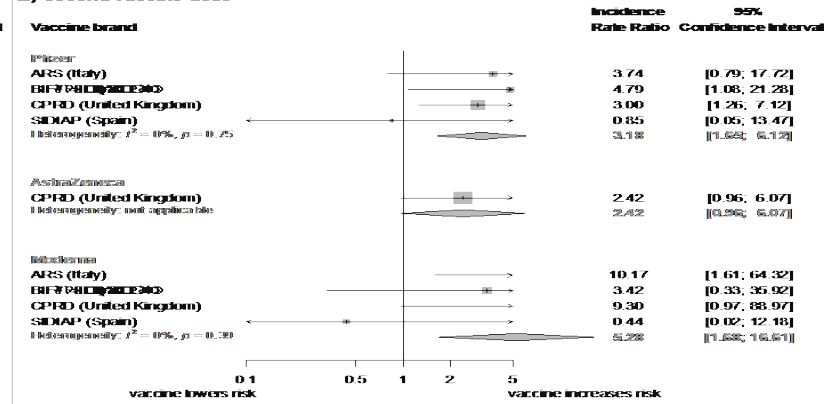


MYOCARDITIS

A) First vaccine dose

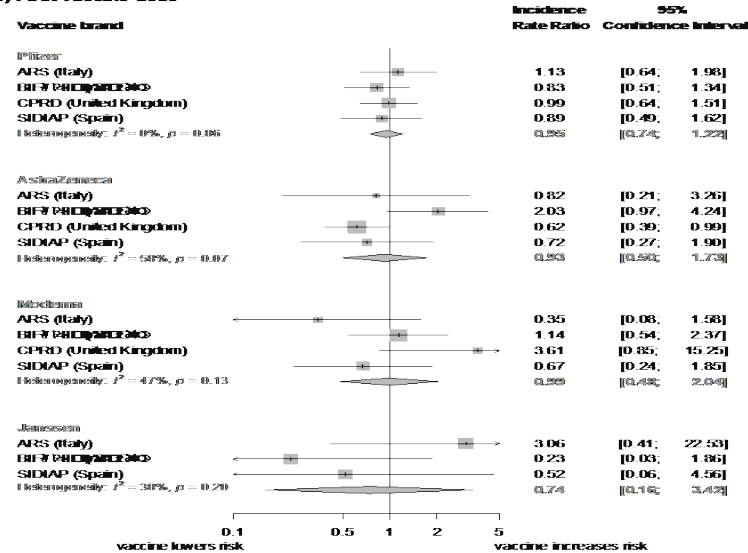


B) Second vaccine dose

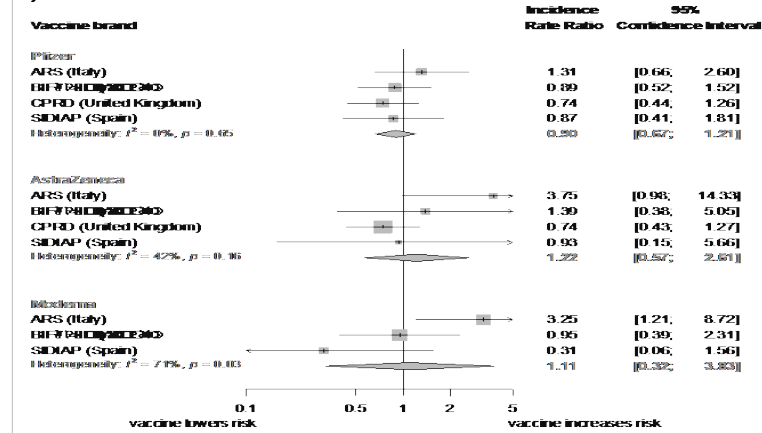


PERICARDITIS

C) First vaccine dose



D) Second vaccine dose





Incidence and severity of COVID-19 in children

Level 1. Diagnosis of COVID-19 disease or positive test without hospitalization.

Level 2. Hospitalization related to COVID-19 disease.

Level 3. ICU admission related to COVID-19 disease.

Level 4. Death after COVID-19 disease.



Results: 1st vaccination

- **ARS:**

- 79% Pfizer, 21% Moderna.
- History of COVID-19: 7-8%

- **Caserta:**

- 98.6% Pfizer.
- History of COVID-19: 7-10%

- **Pedianet:**

- Unknown brand, 3262 subjects.
- History of COVID-19: 8.5%

- **BIFAP:**

- 88.6% Pfizer, 11.2% Moderna.
- History of COVID-19: 5-9%

- **VID:**

- 90.6% Pfizer, 9.3% Moderna.
- History of COVID-19: ~10%

- **SIDIAP:**

- 91% Pfizer, 7.1% Moderna.
- History of COVID-19: 8 - 11%

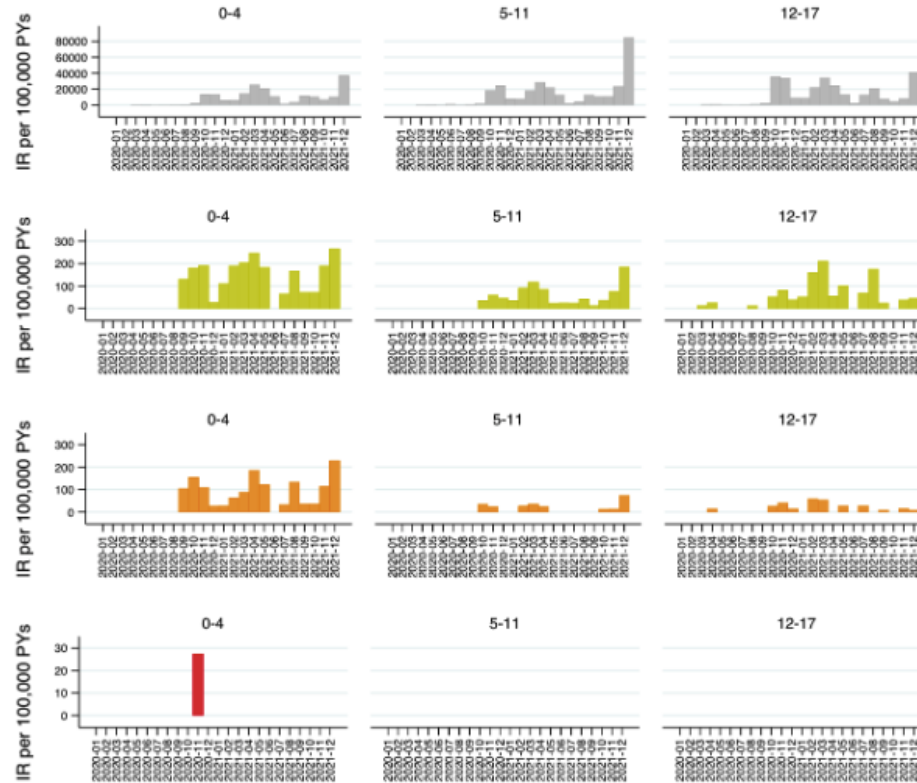


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Results: COVID-19 incidence and severity - ARS



- Severity of covid
- Any covid severity
 - Covid hospitalised or worse
 - Covid in ICU or dead
 - Death after covid



Conclusions of study

- Vaccination rates were high for 12-17 years of age, but lower in younger ages.
- Rate of non-severe COVID-19 disease (disease not requiring hospitalization) was high in children non-vaccinated, especially for the delta and omicron variant.
- Hospitalizations, ICU admission and death following COVID-19 disease were very rare in each of the age category, prior and after vaccination.

Reflections

H1N1 and COVID-19 showed that readiness is crucial to address pandemic vaccine safety concerns

- Data, protocols, infrastructures, code lists and persons need to be ready
- Cohort event monitoring is useful to re-assure, mostly for solicited reactions
- EHR data crucial for monitoring and evaluation of AESI
- VAC4EU has created a community working according to certain procedures and share tools, code lists with an open science spirit



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Vaccine monitoring Collaboration for Europe

Thanks to all the partners

University Medical Center Utrecht, Utrecht, The Netherlands (UMCU), Universiteit Utrecht (UU), Utrecht, Aarhus University, RIVM, Lazio region, Pedianet, Agenzia Regionale di Sanita' Toscana (ARS), LAREB, RTI Health Solutions (RTI-HS), Spain & US, PHARMO Institute, University of Verona, Paul Ehrlich Institut (PEI), Bereich Pharmacovigilanz, Université de Bordeaux, Bordeaux PharmacoEpi (BPE), France, University of Oslo (UiO), Norway, Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Luxembourg Institute of Health (LIH), Spanish Agency on Medicines and Medical Devices (AEMPS) -BIFAP database, London School of Hygiene and Tropical Medicine (LSHTM), Team-it Research SL (TEAMIT), University of Bern, Switzerland, Drug Safety Research Unit (DSRU), UK, CLPP Vaccines Network, Portugal, SLOVACRIN Pavol Jozef Šafárik University in Košice, Faculty of Medicine, Slovakia , Masaryk University, Faculty of Medicine, Brno, Czech Republic

Keep updated about results

<https://vac4eu.org/>

<https://zenodo.org/communities/vac4eu/>