Timely real world evidence to monitor COVID-19 vaccine
Academic/investigator EU perspective

Prof. dr. Miriam Sturkenboom

Head of department Datascience & Biostatistics, UMC Utrecht
VAC4EU president
Partner in EU PE&PV network led by University Utrecht

Utrecht University

UMC Utrecht

VAC4EU
VAccine monitoring Collaboration for Europe

Readiness & collaboration is key to generation of timely and robust RWE for benefit risk monitoring of COVID-19 vaccines

EUROPE: READY DUE TO LESSONS LEARNED IN H1N1 PANDEMIC AND THE IMI FUNDED ADVANCE PROJECT FROM 2013-2019

ELSEVIER

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]

IMI-ADVANCE (**A**ccelerated **D**evelopment of **VA**ccine be**N**efit-risk **C**ollaboration in **E**urope)

- **Governance readiness**: code of conduct and governance for collaborative vaccine studies.
- **Methods readiness**
- **Data source readiness**
- **Study readiness**

https://vac4eu.org/

ADVANCE 2019: TESTED SYSTEM & GOVERNANCE PLUS ORGANIZATION

Contents lists available at ScienceDirect

Vaccine

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

Review

Guidance for the governance of public-private collaborations in vaccine post-marketing settings in Europe

Laurence Torcel-Pagnon [a,*], Vincent Bauchau [b], Patrick Mahy [c], Myint Tin Tin Htar [d], Marianne van der Sande [e,f,g], Cédric Mahé [a], Tyra Grove Krause [h], Anne Charrat [a], François Simondon [i,j], Xavier Kurz [k], on behalf of the ADVANCE Consortium ☆

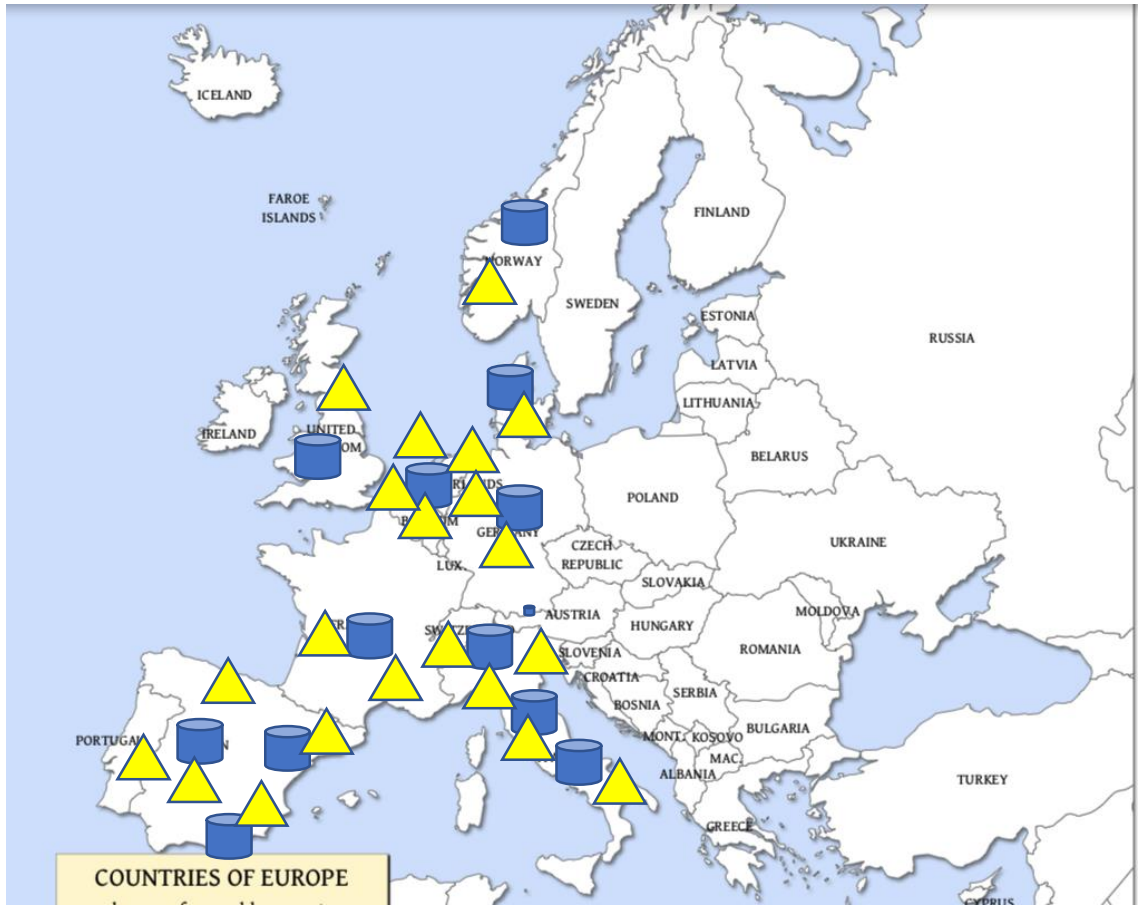
VAC4EU

VAccine monitoring Collaboration for Europe

- Non-for profit International association established January 2020
- Member based organization, set up by membership fees
- Shared tools, infrastructures & processes
- Access to data across multiple organizations
- Rotation of roles/responsibilities

VAC4EU
VAccine monitoring Collaboration for Europe

READINESS: Expertise & Data access in EU



△ 24 members (expertise and/or data access)

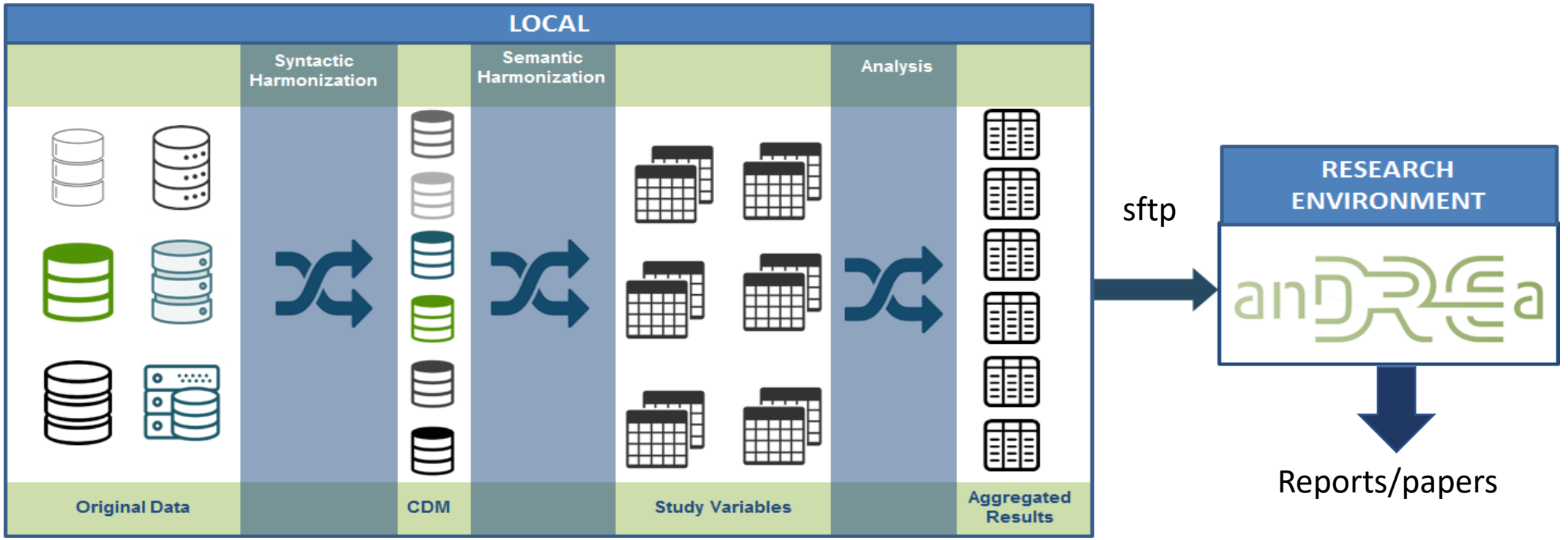
⌭ Access to large national/regional health data from different provenance (Registries/medical record/hospitalizations/insurance) >130 M

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

VAC4EU
VAccine monitoring Collaboration for Europe

READINESS: Generic distributed analytics pipeline

Individual level original data stay local, unless consented

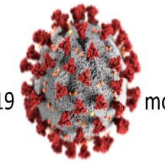


Utilizing the generic RWD-RWE pipeline developed in the last 10 years across EU-ADR, IMI-ADVANCE and IMI-ConcePTION projects

CDM description: https://www.imi-conception.eu/wp-content/uploads/2020/10/ConcePTION-D7.5-Report-on-existing-common-data-models-and-proposals-for-ConcePTION.pdf

EMA tendered independent research to prepare for COVID-19 vaccine monitoring through Framework program (EU PE&PV network and VAC4EU)

ACCESS
vACCine covid-19 monitoring readinESS



List of AESI

Background rates of AESI

Template protocols

May 2020 → January 2021

ACCESS
vACCine covid-19 monitoring readinESS

Public template protocols for different types of data collection (Delivered December 2020)

- **Signal detection** based on cohort event monitoring (EUPAS 38915)
- **Three types of safety protocols for assessment of safety (**EUPAS39361)
  - Rapid assessment of safety signals
  - Safety evaluation of COVID-19 vaccines through electronic health records
  - Safety Protocol for Hospital Case–Based Monitoring
- **Effectiveness studies (**EUPAS39289)
- **Coverage study (EHR/registry based) (**EUPAS39361)

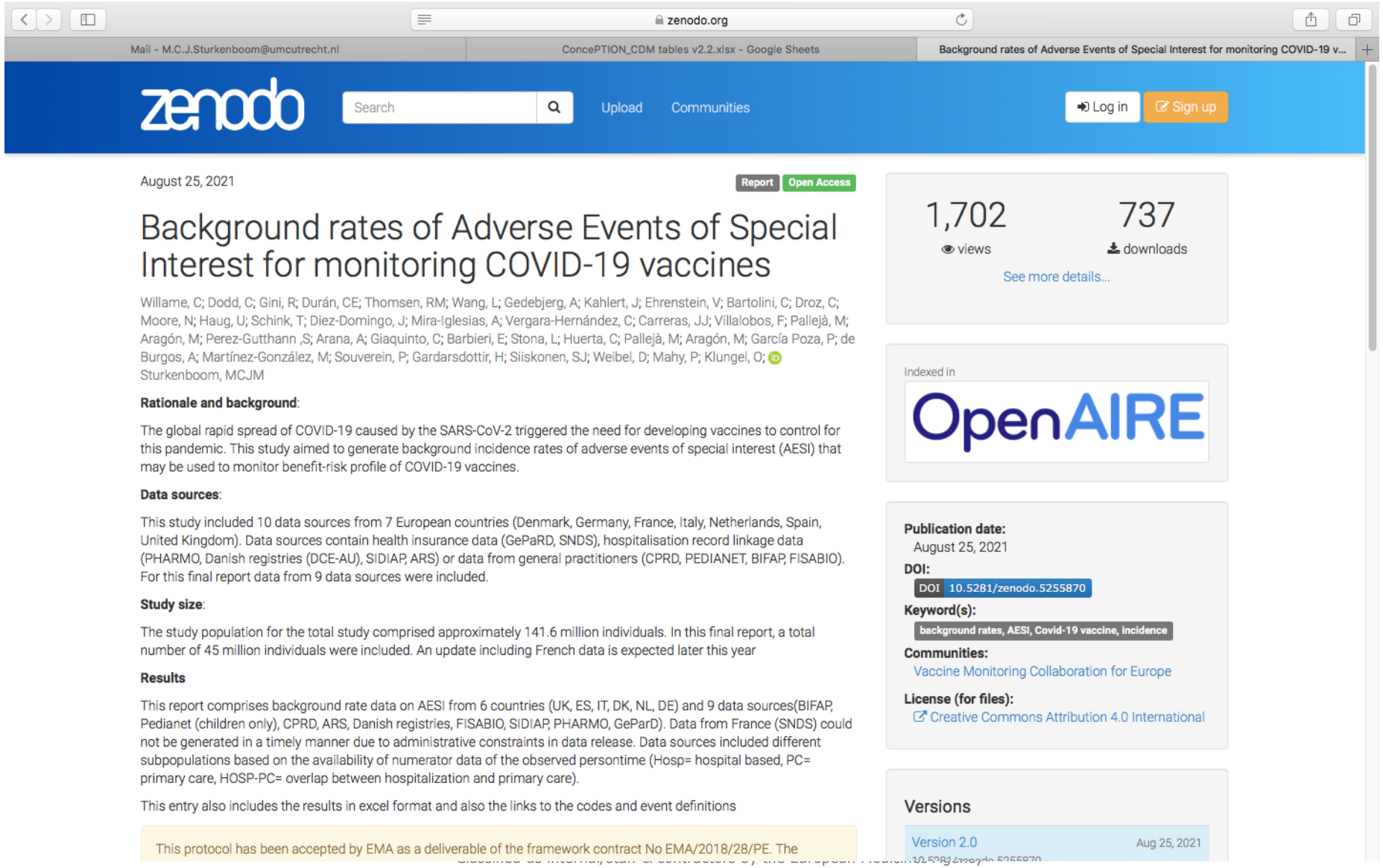
ACCESS
vACCine covid-19 monitoring readinESS

Background rates of AESI

- List of **41** AESI based on SPEAC (August 2020)
- Definition and code lists publicly available (Sept 2020) (see zenodo)
- Protocol registered in EUPAS and publicly available (September 2020)
  - Using common data model and analytics
  - 10 data sources, 7 countries
- Age, gender and time specific background rates generated and publicly available February, April and June
  - Zenodo: https://doi.org/10.5281/zenodo.5255870
- Data used for O/E analyses by EMA and manufacturers
- Ability to rapidly provide data on new events (e.g. TTS)
- Focus on type of outcome data (primary care/hospital)

https://vac4eu.org/covid-19-tool/

Report, definitions and data all available



zenodo.org

Mail - M.C.J.Sturkenboom@umcutrecht.nl | ConcePTION_CDM tables v2.2.xlsx - Google Sheets | Background rates of Adverse Events of Special Interest for monitoring COVID-19 v...

zenodo | Search | Upload | Communities | Log in | Sign up

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:

The global rapid spread of COVID-19 caused by the SARS-CoV-2 triggered the need for developing vaccines to control for this pandemic. This study aimed to generate background incidence rates of adverse events of special interest (AESI) that may be used to monitor benefit-risk profile of COVID-19 vaccines.

Data sources:

This study included 10 data sources from 7 European countries (Denmark, Germany, France, Italy, Netherlands, Spain, United Kingdom). Data sources contain health insurance data (GePaRD, SNDS), hospitalisation record linkage data (PHARMO, Danish registries (DCE-AU), SIDIAP, ARS) or data from general practitioners (CPRD, PEDIANET, BIFAP, FISABIO). For this final report data from 9 data sources were included.

Study size:

The study population for the total study comprised approximately 141.6 million individuals. In this final report, a total number of 45 million individuals were included. An update including French data is expected later this year

Results

This report comprises background rate data on AESI from 6 countries (UK, ES, IT, DK, NL, DE) and 9 data sources(BIFAP, Pedianet (children only), CPRD, ARS, Danish registries, FISABIO, SIDIAP, PHARMO, GeParD). Data from France (SNDS) could not be generated in a timely manner due to administrative constraints in data release. Data sources included different subpopulations based on the availability of numerator data of the observed persontime (Hosp= hospital based, PC= primary care, HOSP-PC= overlap between hospitalization and primary care).

This entry also includes the results in excel format and also the links to the codes and event definitions

This protocol has been accepted by EMA as a deliverable of the framework contract No EMA/2018/28/PE. The

1,702 views | 737 downloads

See more details...

Indexed in OpenAIRE

Publication date: August 25, 2021

DOI: DOI 10.5281/zenodo.5255870

Keyword(s): background rates, AESI, Covid-19 vaccine, incidence

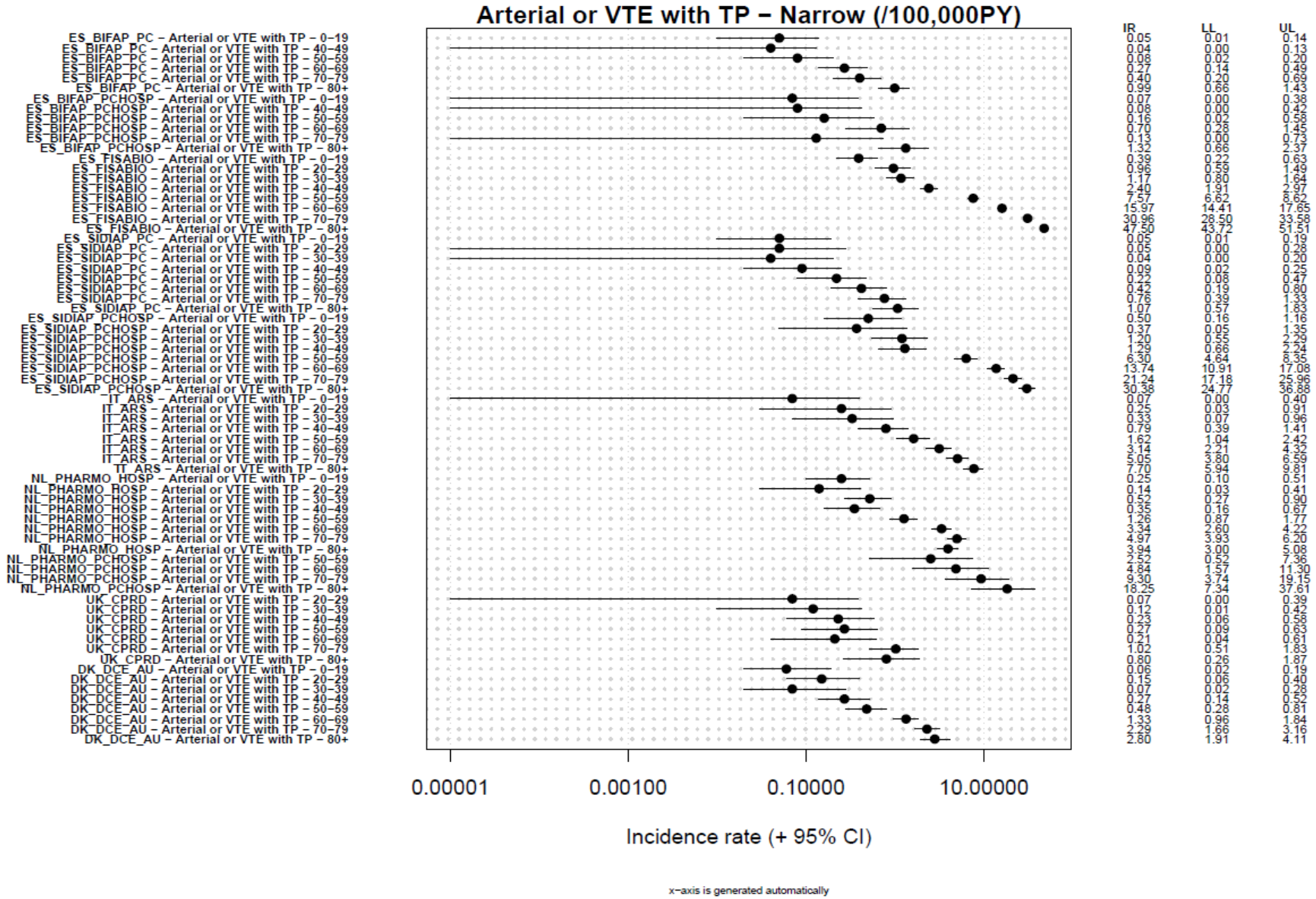
Communities: Vaccine Monitoring Collaboration for Europe

License (for files): Creative Commons Attribution 4.0 International

Versions

Version 2.0 Aug 25, 2021

Example VTE or Arterial thrombosis with thrombocytopenia by age



ACCESS
vACCine covid-19 monitoring readinESS

Willame et al. https://doi.org/10.5281/zenodo.5255870

EMA funded research to monitor COVID-19 vaccines

ACCESS
vACCine covid-19 monitoring readinESS

Coagulopathy study (Oxford)

Cohort event monitoring special populations & Signal testing

Monitoring of AESI and ADRs post-vaccination in cohorts

Background rates of AESI

Template protocols

List of AESI

May 2020 → January 2021

From: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/monitoring-covid-19-medicines-0

EMA funded independent research to monitor COVID-19 vaccines

1. **Monitoring event rates post-vaccination**

   Cohort event monitoring: EUPAS42504, EUPAS39798

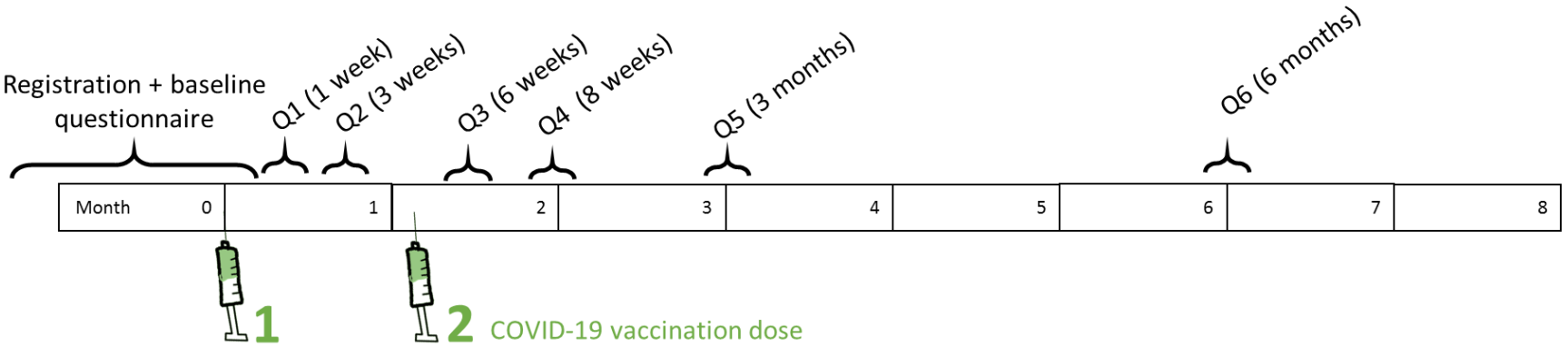
   Cohort study using EHR data sources: EUPAS40404 & EUPAS40414

2. **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

From: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/monitoring-covid-19-medicines-0

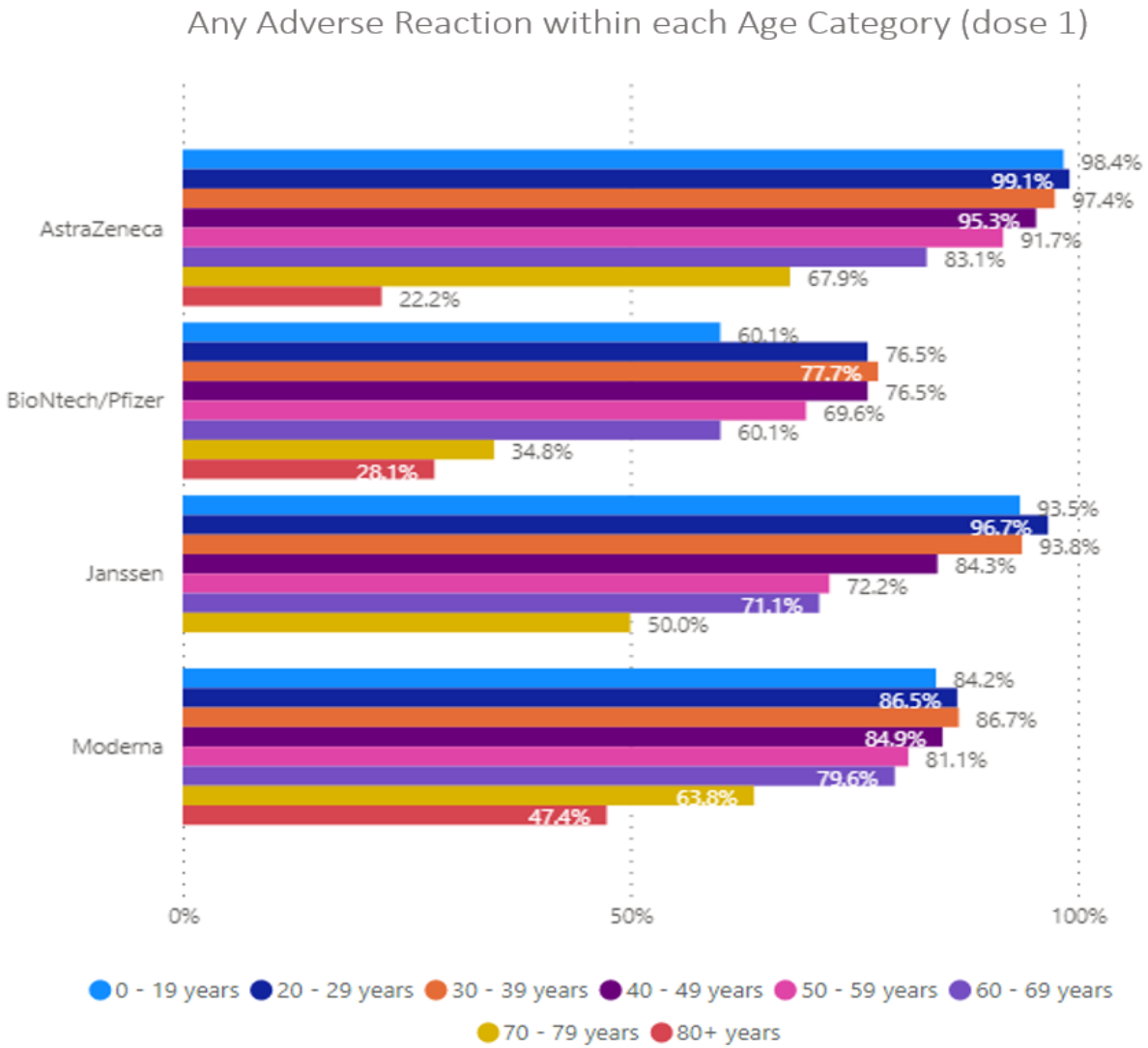
Cohort event monitoring-1 ending Nov. 2021
Early Covid-19 Vaccine Monitor: general population



- Inclusion of patients within 2 days after vaccination, follow for 6 months
- Solicited reactogenicity events and serious unsolicited events by vaccine
- Reported monthly to the EMA on interactive dashboard
- Countries: Netherlands, Germany, Belgium, Croatia, Italy, France

Cohort event monitoring-1: ending Nov 2021
Early Covid-19 Vaccine Monitor total of 117,707 patients included

Vaccine brand	Dose 1 (Number of participants, %)	Dose 2 (Number of participants)
AstraZeneca	89356 (75,9%)	55550
BioNtech/Pfizer	14603 (12,4%)	11671
Janssen	2490 (2,1%)	0
Moderna	11258 (9,6%)	8080
Total	117707 (100%)	75301

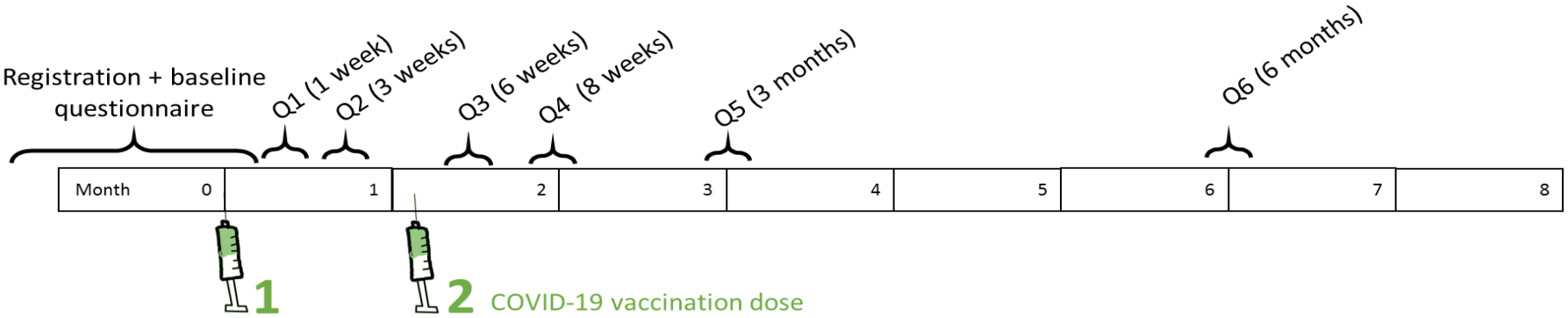


Coordinated by LAREB Center, the Netherlands
(A. Kant, M. Raethke)

Using the Lareb Intensive Monitoring app
Displayed on interactive Dashboard for EMA

Secretariat@vac4eu.org

Cohort event monitoring -2
Covid-19 Vaccine Monitor- Sept 2021-2023



Countries:

- Romenia, Slovakia, Ireland, Switzerland, Spain, France, UK, Italy, Portugal, Netherlands, Belgium

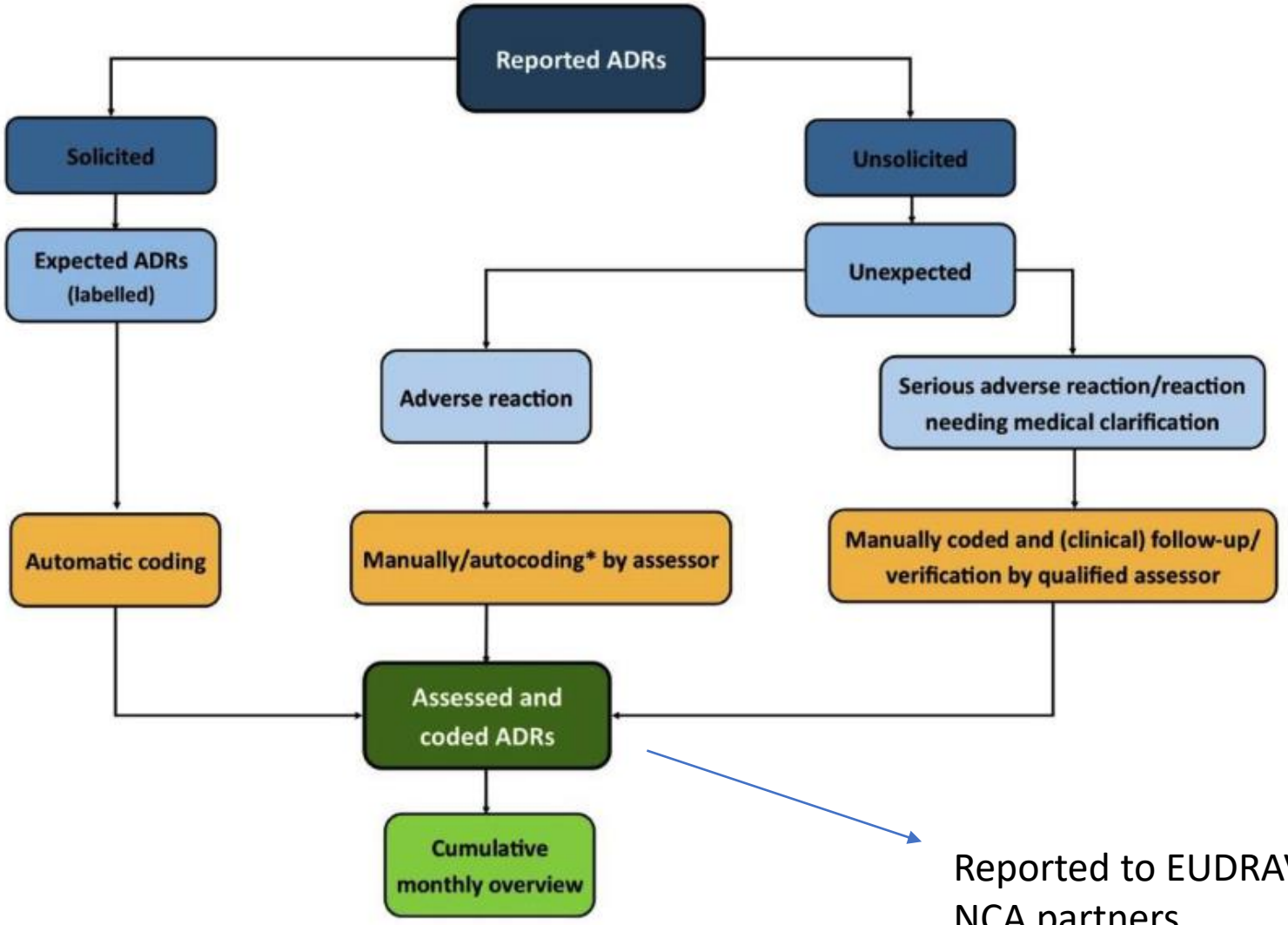
Booster of first vaccination (general population or sub populations)

Specific sub populations targeted

- Pregnant women
- Immunocompromised persons
- Former COVID-19
- History of allergies
- Children

Coordinated by University Verona (G. Trifiro)
Data collection through UMCU Research online

Cohort event monitoring: Workflow for reported ADRs



Reported to EUDRAVIGILANCE by NCA partners

From Raethke et al. July Report ECVM)

EMA funded independent research to monitor COVID-19 vaccines

1. **Monitoring event rates post-vaccination**

   Cohort event monitoring: EUPAS42504, EUPAS39798

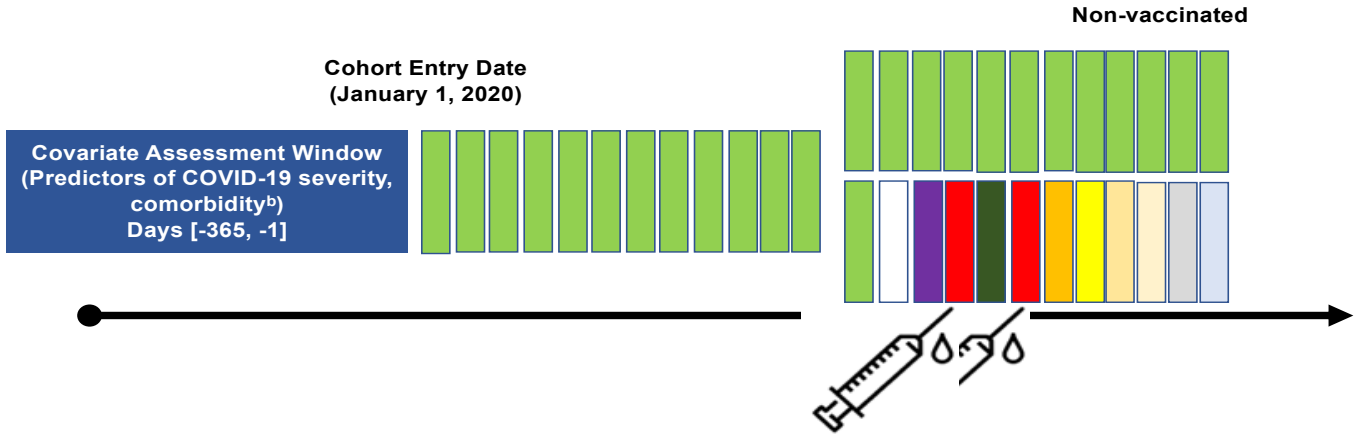
   Cohort studies using EHR datasources

   EUPAS40404 & EUPAS40414

2. **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

EHR cohort monitoring of AESI after vaccines EUPAS40404



Status:

- Rates periodically updated and submitted to EMA in past year
- Interactive Dashboard with detailed data available to PRAC April, July, October
- November 2021 final report

Data sources selected on short lag times:

- BIFAP-ES: 15 million
- Tuscany- IT: 4.5 million
- PHARMO-NL: 3 million
- CPRD-UK: 18 million

Using ConcePTION CDM and pipeline

Dose		ARS, Italy		BIFAP, Spain		PHARMO, NL		CPRD, UK		Total
AstraZeneca dose 1		332872	17.6%	537122	13.4%	68655	8.2%	3671672	66.8%	4,610,321
AstraZeneca dose 2		187052	56.2%	397186	73.9%	28779	41.9%	1172745	31.9%	1,785,762
Other vaccine dose 2		7150	2.1%	7298	1.4%			3113	0.1%	
Amongst persons with AstraZeneca dose 2 distance	Min	20		14		70		14		
	P25	84		71		76		70		
	P50	84		82		77		77		
	P75	84		84		84		78		
	Max	126		193		155		127		
Janssen dose 1	N	58513	3.1%	201543	5%	22455	2.7%			282,511
Janssen dose 2	N	0	0%	0	0%	0	0%			0
Other vaccine dose 2	N	0	0%	63	0%	15	0.1%			
Moderna dose 1	N	184013	9.7%	447401	11.2%	67689	8.1%	27023	0.5%	726,126
Moderna dose 2	N	100673	54.7%	363226	81.2%	25638	37.9%	<5	0%	489,537
Other vaccine dose 2	N	125	0.1%	590	0.1%			9	0%	
Amongst persons with Moderna dose 2 distance	Min	16		14		21		28		
	P25	28		28		35		28		
	P50	28		28		35		28		
	P75	28		28		35		44		
	Max	124		224		160		91		
Pfizer dose 1	N	1320326	69.6%	2808700	70.3%	568119	67.6%	1801355	32.8%	6,498,500
Pfizer dose 2	N	653580	49.5%	2372395	84.5%	232351	40.9%	1332285	74%	4,590,611
Other vaccine dose 2	N	138	0%	1179	0%			6226	0.3%	
Amongst persons with Pfizer dose 2 distance	Min	14		14		21		14		
	P25	21		21		35		70		
	P50	21		21		35		76		
	P75	21		21		36		78		
	Max	174		244		169		147		

EMA funded independent research to monitor COVID-19 vaccines

1. **Monitoring event rates post-vaccination**

   Cohort event monitoring: EUPAS42504, EUPAS39798

   Cohort studies using EHR datasources: EUPAS40404 & EUPAS40414

2. **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 approved: cohort & SCRI

Data sources:

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

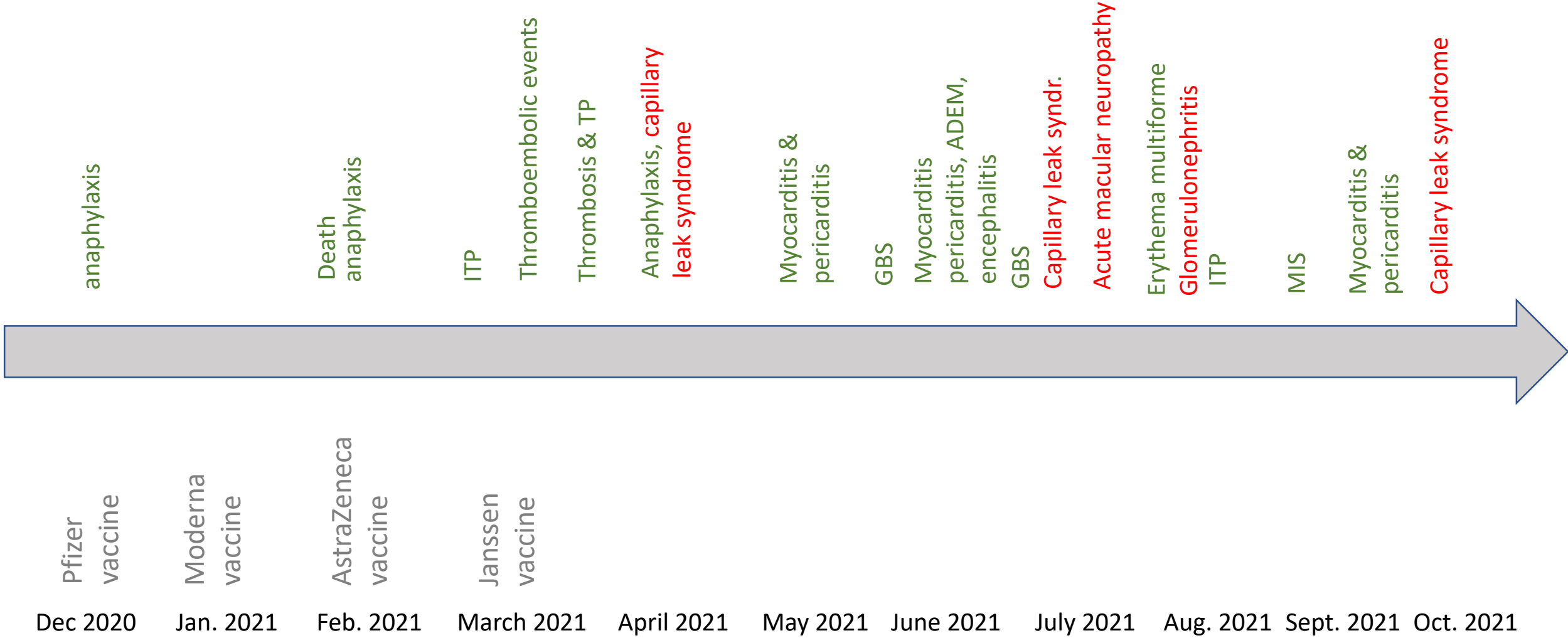
Two signal verification requests: MIS and Myocarditis

- Cohort analysis for rates pre and post vaccination
- SCCS for Myocarditis & pericarditis

Status

- Both requests generated information for EMA within one month
- MIS: signal closed by PRAC (very few cases)
- Myocarditis: excess rates in younger persons with mRNA platform vaccines
  - To be discussed in upcoming PRAC

Serious new events discussed in PRAC for COVID-19 vaccines



Conclusion

- The ACCESS/SPEAC AESI list has been well predictive for serious issues that occurred
- Incidence rates on 41 events were available for O/E analyses through ACCESS from 9 data sources in Europe, including TTS, GBS, myocarditis
- The ECVM study provided
  - incidence rates of all AESI post vaccination from EHR data (n=12,117,458 vaccinated)
  - Sollicited and non-sollicited ADR rates from 117,707 vaccinated persons who were consented and responded in cohort event monitoring
- The CVM study is focusing on
  - Cohort event monitoring of booster doses and special populations in 10 countries
  - Signal testing capacity in 10 data sources in Europe

- There is an infrastructure and readiness of people, data and tools to address heterogeneity in Europe and leverage the vast amount of expertise and data in ENCePP centers through the EU PE &PV network and VAC4EU

Utrecht University

UMC Utrecht

VAC4EU

VAccine monitoring Collaboration for Europe

Thanks to all the incredible contributors of all centers in EU PE/PV and VAC4EU

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/