Covid-Vaccine-Monitor: a Cohort Event Monitoring Safety Study of COVID-19 Vaccines in 13 European Countries

Fabio Riefolo[1], Monika Raethke[2], Nicoletta Luxi[3], Loes Ruijs[2], Alexia Giovanazzi[3], Jasper Schmitz[2], Dirk Mentzer[4], Nicolas H. Thurin[5], Nikica Mirosevic Skvrce[6], Megan Liddiard[7], Sandor Schmikli[8], Olaf H. Klungel[9], Gianluca Trifirò[3], Miriam Sturkenboom[8], Covid Vaccine Monitoring project EU PE&PV network and VAC4EU[8,9].

[1]Teamit Institute, Partnerships, Barcelona Health Hub, Barcelona 08025, Spain. [2]Netherlands Pharmacovigilance Centre Lareb, Bijwerkingencentrum, 's Hertogenbosch, The Netherlands. [3]University of Verona, Diagnostics and Public Health, Verona, Italy. [4]Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Safety of Drugs and Medical Devices, Langen, Germany. [5]Université de Bordeaux, Bordeaux PharmacoEpi, INSERM CIC-P 1401, Bordeaux, France. [6]HALMED, Agency for Medicinal Products and Medical Devices of Croatia, Zagreb, Croatia. [7]University of Portsmouth, Drug Safety Research Unit, Portsmouth, United Kingdom. [8]University Medical Centre Utrecht, Data science & Biostatistics, Utrecht, Netherlands. [9]Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Pharmacoepidemiology & Clinical Pharmacology, Utrecht, Netherlands.

Background

Since the WHO declared the COVID-19 global pandemic in March 2020, vaccines to prevent severe SARS-CoV-2 infection have been developed at unprecedented speed. Several vaccines have been conditionally authorized by regulators in December 2020 already. The large-scale vaccination campaigns have undeniably raised the importance of post-authorization evaluations not only through spontaneous reporting but also by cohort event monitoring to obtain more in-depth vaccine safety information, rapidly after launch.

Objectives

To monitor COVID-19 vaccine safety and estimate frequency of solicited and non-solicited, non-serious and serios reactions.

Methods

Study design:

Prospective cohort event monitoring (CEM) study as part of the Covid-Vaccine-Monitor (CVM) project. The CEM collects baseline data and adverse reactions (ADRs) of authorized EU COVID-19 vaccines. Results data from February 2021 to May 2022.

Population:

General and special populations (pregnant and lactating women, children, and adolescents, immunocompromised, allergic, and prior COVID-19 infection people) from 13 countries (Germany, Croatia, Netherlands, Belgium, Italy, France, Spain, Portugal, Slovakia, Romania, Switzerland, Ireland, and UK).

Data sources:

4 data collection platforms: Lareb-managed Intensive Monitoring (LIM), UMC Utrecht Research Online (RO), German (SafeVac 2.0) and Croat (OpeN) national tools

- *LIM: first vaccination cycle, not identified as part of the special target group.*
- *RO and LIM: first vaccination cycle, belonging to the special target groups.*
- *RO: booster vaccinations.*

Exposure:

Participants meet local age criteria, have a first vaccination cycle or a booster dose within 48 hours, and are followed up for 6 (first vaccination cycle) or 3 (booster) months.

Outcomes:

Data are pooled, stratified by special cohorts, and analyzed.

General Population Results

WebApp	Stratification	AstraZeneca		BioNTech/Pfizer		Janssen	Moderna	
Subjects with at least one ADR (%)								
Doses		1st	2nd	1st	2nd	1st	1st	2nd
LIM + OpeN	ADRs, %	100.0		100.0		100.0	100.0	
	Subjects, N	*8873*	*5608*	*15404*	*12369*	*2494*	*3644*	*2722*
SafeVac 2.0	ADRs, %	88.6		74.9		68.7	83.9	
	Subjects, N	*80510*	*49957*	*420622*	*316572*	*27338*	*81220*	*77559*
Local solicited ADRs (%)								
LIM + OpeN	Injection site pain	63.6		38.8		34.2	83.7	
SafeVac 2.0	Injection site pain	53.2		64.6		39.9	61.5	
	Injection site swelling	12.4		14.3		6.7	20.5	
Systemic solicited ADRs (%)								
LIM + OpeN	Fatigue	76.6		31.7		53.5	72.50	
	Headache	78.54		22.0		52.9	57.1	
	Malaise	73.4		20.9		48.9	65.4	
	Myalgia	65.7		28.4		43.4	68.8	
SafeVac 2.0	Fatigue	53.3		46.1		39.1	45.2	
	Headache	52.2		35.8		36.0	37.8	
AESI, *N* (%)								
LIM + OpeN	-	*28* (0.3)	*31* (0.6)	*22* (0.1)	*27* (0.2)	*8* (0.3)	*3* (0.1)	*10* (0.4)
SafeVac 2.0	-	*69* (0.1)		*67* (0.2)		*19* (0.1)	*49* (0.1)	
Serious ADRs, *N* (%)								
LIM + OpeN	-	*21* (0.2)	4 (0.1)	23 (0.2)	16 (0.1)	4 (0.2)	6 (0.2)	4 (0.2)
SafeVac 2.0	-	608 (0.8)		1191 (0.3)		541 (2.0)	1241 (1.5)	

ADRs, % = percentage of the reported adverse reactions (ADRs) out of the total number of participants (*Subjects, N*).
AESI = Adverse Events of Special Interest determined by set list of coded ADRs as per EMA's June 8th, 2021 communication

- 30,462 participants data from Belgium, Croatia, France, Italy, Netherlands, and UK with first vaccination cycle. **Uncommon AESI and serious ADRs**: <1% across all vaccine brands and countries.
- 609,691 participants data from Germany with first vaccination cycle. Serious ADRs are >1%.

Special Population and Booster Doses Results

Special cohort		COVID-19		Children *5-11 y.*		Adolescents *12-17 y.*		Allergy		Immuno-compromised		Pregnant		Lactating	
Subjects with at least one ADR (%)															
Doses		1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Subjects, N		***2568***	***849***	***259***	***164***	***411***	***236***	***3454***	***2141***	***589***	***413***	***174***	***132***	***18***	***13***
All vaccines	**ADRs, %**	**88.0**	**45.5**	**29.3**	**13.4**	**54.5**	**51.7**	**81.3**	**52.4**	**75.0**	**45.3**	**72.4**	**59.1**	**72.2**	**23.1**
AstraZeneca	ADRs, %	97.4	14.1	-	-	100	-	95.8	12.3	95.9	7.8	100	0.0	-	-
	Subjects, N	*964*	*327*	-		*3*	-	*1091*	*594*	*175*	*90*	*2*	*2*	-	
BioNTech/ Pfizer	ADRs, %	74.1	57.6	29.3	13.4	54.2	52.2	66.4	60.3	59.6	47.7	69.0	47.1	80.0	27.3
	Subjects, N	*900*	*356*	*259*	*164*	*395*	*228*	*1484*	*1145*	*282*	*237*	*116*	*87*	*12*	*11*
Janssen	ADRs, %	93.0		-		-		90.1		84.6		100		-	
	Subjects, N	*270*		-		-		*345*		*26*		*2*		-	
Moderna	ADRs, %	93.1	81.3	-		53.8	37.5	87.2	89.3	82.9	77.9	77.8	86.0	50.0	0.0
	Subjects, N	*434*	*166*	-		*13*	*8*	*533*	*402*	*105*	*86*	*54*	*43*	*2*	*2*
Local solicited ADRs (%)															
Injection site pain		56.3	21.8	29.3 (1st)		18.8 (2nd)		49.5	24.1	46.0	22.8	46.0	34.1	66.7	15.4
Systemic solicited ADRs (%)															
Fatigue		57.2	22.3	16.4		20.0		51.3	28.2	46.3	21.5	32.8	32.6	44.4	7.7
Headache		55.4	19.2	12.8		17.5		44.9	22.1	38.9	15.3	16.1	21.2	33.3	7.7
Malaise		54.1	23.8	9.9		12.5		0.4	25.2	38.0	19.1	11.5	22.7	22.2	7.7
Myalgia		54.3	18.0	13.6		12.3		45.2	23.8	38.5	17.9	22.4	30.3	11.1	-
AESI, N (%)															
-		*4* (0.2)	-	-		-		*20* (0.6)	*9* (0.3)	*1* (0.2)	*3* (0.5)	-	-	-	-
Serious ADRs, N (%)															
-		*9* (0.4)	*1* (0.0)	*2* (0.8)		*1* (0.2)		*16* (0.5)	*7* (0.2)	*4* (0.7)	*3* (0.5)	*2* (1.1)	-	-	-
Booster Doses															
Subjects with at least one ADR (%)															
Subjects, N		**604**		**37**		**56**		**592**		**139**		**174**		**77**	
All vaccines	**ADRs, %**	**46.8**		**4.3**		**42.9**		**68.1**		**49.6**		**28.7**		**71.4**	
AstraZeneca	ADRs, %	66.7		-		-		33.3		0.0		-		-	
	Subjects, N	*3*		-		-		*3*		*1*		-		-	
BioNTech/ Pfizer	ADRs, %	55.6		24.3		42.9		63.8		48.9		24.1		60.0	
	Subjects, N	*331*		*37*		*56*		*312*		*92*		*133*		*40*	
Moderna	ADRs, %	65.6		-		0.0		73.3		52.2		43.9		83.8	
	Subjects, N	*270*		-		*1*		*277*		*46*		*41*		*37*	
Local solicited ADRs (%)															
Injection site pain		24.5		19.4		36.0		20.9		32.2		46.8			
Systemic solicited ADRs (%)															
Fatigue		29.1		23.7		45.1		25.2		30.5		37.7			
Headache		21.9		21.5		32.1		12.2		25.3		33.8			
Malaise		18.7		10.8		26.4		15.8		17.8		27.3			
Myalgia		19.9		12.9		29.7		20.1		19.0		35.1			
AESI, N (%)															
-		*1* (0.2)		*1* (1.1)		*1* (0.2)		-		-		-			
Serious ADRs, N (%)															
-		*1* (0.2)		*1* (1.1)		*1* (0.2)		-		-		-			

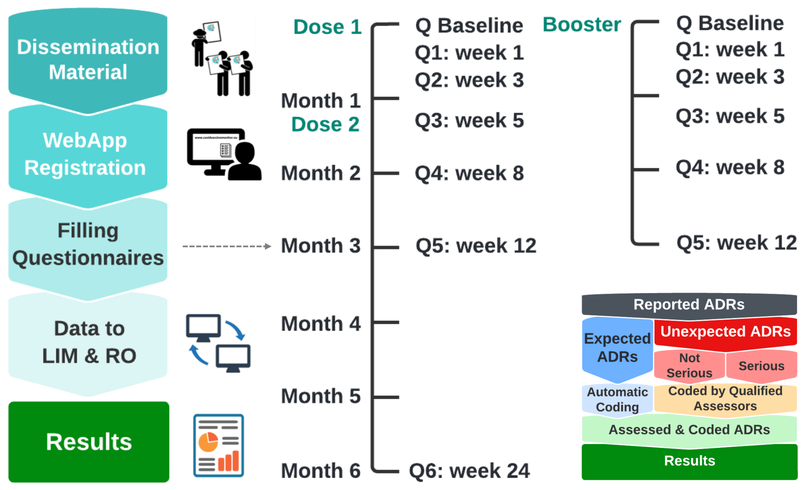
ADRs, % = percentage of the reported adverse reactions (ADRs) out of the total number of participants (*Subjects, N*).
AESI = Adverse Events of Special Interest determined by set list of coded ADRs as per EMA's June 8th, 2021 communication.

- 7,473 special cohorts' participants with first vaccination cycle. **Uncommon AESI**: 0.2-0.6% and 0.3-0.5% following the 1st and 2nd dose, respectively. **Uncommon serious ADRs**: 0-4-1.1% and 0.2-0.5% following the 1st and 2nd dose, respectively.
- Most reported ADRs among vaccines: injection site pain (locally), and fatigue, headache, malaise, and myalgia (systemically).
- 1,679 special cohorts' participants receiving a booster dose. Among different cohorts, **children and dolescents reported the lowest number of ADRs, while lactating women reported the highest**.

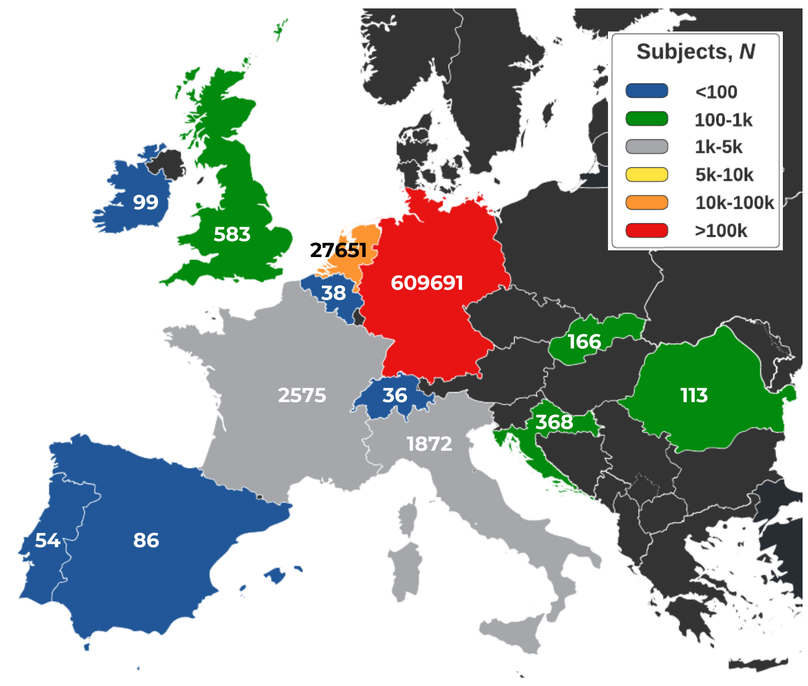
Variables

- Vaccine brand and batch number
- Adverse drug reactions (ADRs)
- Age and Sex
- Height and Weight
- Geographical area
- Medical history

Study Design



Countries Inclusions



Conclusions

We collected and analyzed COVID-19 vaccines safety evidence in more than 640,000 general and special population persons after first cycle and booster doses from 13 countries. Data confirm common ADR rates that are already listed in the summary of product characteristics, and that serious reactions are uncommon. Additional follow-up is ongoing.

Conflicts of interest

This study is funded by the European Medicines Agency. The authors and their departments conduct research for government, public, and private organizations, including pharmaceutical companies, according to the ENCePP code of conduct.

References EU PAS Register Number: EUPAS42504; EU PAS Register Number: EUPAS39798; Luxi, N, Raethke, M, Ruijs, L, Schmikli, S, Riefolo, F, Trifiro, G, & Sturkenboom, MCJM. (2022). Covid-19 Vaccine Monitor: Interim Study Report for Cohort Event Monitoring of vaccinated persons (1.0). Zenodo. https://doi.org/10.5281/zenodo.6629551