Covid-Vaccine-Monitor

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Final Study Report for Cohort Event Monitoring (WP1, WP2, WP5)

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Cohort Event Monitoring of safety of COVID-19 vaccines in general and in special populations in 13 countries

1 Executive Summary /Abstract

1.1 Title

Cohort Event Monitoring of safety of COVID-19 vaccines in general and in special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection).

1.2 Keywords

COVID-19; vaccines; safety; CEM (Cohort Event Monitoring);

1.3 Rationale and background

Cohort event monitoring is an active safety surveillance tool that can be used during the roll out of vaccines to collect pre-specified (solicited) and unspecified adverse reactions. The US-CDC implemented V-Safe[1] to monitor COVID-19 vaccines, and the EMA-funded vACcine COVID-19 monitoring readinESS ACCESS project[2] created template protocols for cohort event monitoring which were made publicly available in February 2021. In Europe the ACCESS protocols were implemented in the Early Covid Vaccine Monitor (ECVM) study which included first vaccinated persons, this study was continued and complemented by the COVID-19 Vaccine Monitor cohort event monitoring study (CVM),[3] which focused on special populations and booster vaccinations, and included additional countries.

1.4 Research question and objectives

1.4.1 Primary aim

To generate, estimate, describe and compare incidence rates of patient-reported Adverse Drug Reactions (ADRs) of the different COVID-19 vaccines across the participating countries in the general and special populations (pregnant and lactating women, children, and adolescents, immunocompromised, people with history of allergy, and people with prior SARS-CoV-2 infection).

1.4.2 Secondary aim

To identify and generate incidence rates and potential predictors of the most frequently reported ADRs related to different COVID-19 vaccines after the first/second dose(s) of the first vaccination cycle as well as booster doses within the general population and within special cohorts of vaccinees in real-time.

[1] V-safe After Vaccination Health Checker: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/v-safe/index.html

[2] vACcine COVID-19 monitoring readinESS ACCESS project: https://www.encepp.eu/encepp/viewResource.htm?id=39362

[3] Study protocol for Cohort Event Monitoring of safety of COVID-19 vaccines in special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection)

1.5 Methods

1.5.1 Study design

Prospective cohort study that includes newly vaccinees with COVID-19 vaccines first doses and/or boosted individuals that consented to participate and be followed-up up to 6 months after inclusion in the study. Individuals have been recruited for the study by the participant countries and sites that have agreed and applied to the ECVM and CVM study protocols. Croatia and Germany used their own protocol and national data collection tools, characterized by a slightly different study designs, independent recruitment dates and schemes from the ECVM/CVM study, and followed patients for one year.[4] Croat and German aggregated data have been then requested and harmonized to the CVM design for analyses.

Pregnant women and those who entered upon booster vaccination based on the CVM protocol had different follow-up periods. Pregnant women were followed up until 1.5 months after the pregnancy ended. Persons who entered upon booster vaccination were followed up to 3 months from the booster vaccination date. 13 countries were included and allowed for pooling of data.

1.5.2 Data collection and data sources

The data used in this study originated from patient-reported outcomes through electronic questionnaires sent at different time points.

First vaccinees using ECVM protocol (general population)

Croatia, Germany, Netherlands, Belgium, France, UK and Italy participated in the ECVM study (EUPAS39798)[5], where recruitment commenced. Recruitment and follow-up of first vaccinees were continued as part of the CVM study, using either their own system (Croatia and Germany) or the Lareb (Netherland pharmacovigilance centre) Intensive Monitoring (LIM) app[4,5]. The Netherlands commenced on 01/02/2021 while Italy, France and the UK initiated their recruit on 9 June, 14 June and 23 June 2021 respectively. Recruitment in Belgium commenced on 13 July 2021.

For the German SafeVac 2.0 platform,[4,5] the study commenced on 27 December 2020, and questionnaires were sent after the receipt of each dose at 0-6-24 hours, 3-7 days, 2-3-4 weeks, and 6-12 months. A questionnaire on concomitant medications and risk factors was sent to participants following the completion of the initial questionnaire or when a participant leaves the study before completion (12 months).

Agency for Medicinal Products and Medical Devices of Croatia (HALMED) used the web-based application OPeN (Online Platform for Electronic reporting of adverse drug reactions) to collect data in Croatia.[4,5] Data collection commenced on 15 February 2021. Questionnaires were sent after receipt of the first does at day 0, 7, 30, and month 3, 6, 9. Croatia's participants were able to continuously report and update ADRs within the Croatian application and participants received reminders at specific moments (day 21, 91, 112, 140, 182), enquiring whether they have experienced a new ADR. Throughout the study additional questions were added for participants to answer. Questions related to the second dose were made available in the app on day 30 after the first vaccination.

[4] Raethke, Monika, Ruijs, Loes, Schmitz, Jasper, Perez-Gutthan, Susana, Droz, Cécile, Siiskonen, Satu Johanna, Klungel, Olaf, & Sturkenboom, Miriam. (2022). Early Covid-19 Vaccine Monitor: Final Report for Early Cohort Event Monitoring of Safety of COVID-19 Vaccines. Zenodo. https://doi.org/10.5281/zenodo.7128737

[5] EUPAS39798

The LIM app was already developed and implemented by Lareb for cohort event monitoring in the Netherlands, and it was adapted for implementation in other countries as part of the ECVM study. Each organization had a country specific website and questionnaires were in the local language(s). In order to pool data, reactions were coded in MedDRA. For both LIM and SafeVac 2.0 the solicited ADRs could be automatically MedDRA-coded, the unsolicited events were manually assessed and the seriousness was classified by qualified personnel (pharmacovigilance trained personnel study investigators from each participating institution) based on CIOMS seriousness criteria. Some countries, such as the Netherlands and Italy, were required to report ADRs to EudraVigilance as per national regulations. To allow for country specific reporting, unique and study specific WorldWide Case ID (WWCI) were created. The cohort data was translated into a single report and questionnaire data was shared with the European Medicines Agency (EMA) in regular reports.

The figures below show the questionnaires' schedule for participants receiving the first COVID-19 dose using the LIM and RO apps.

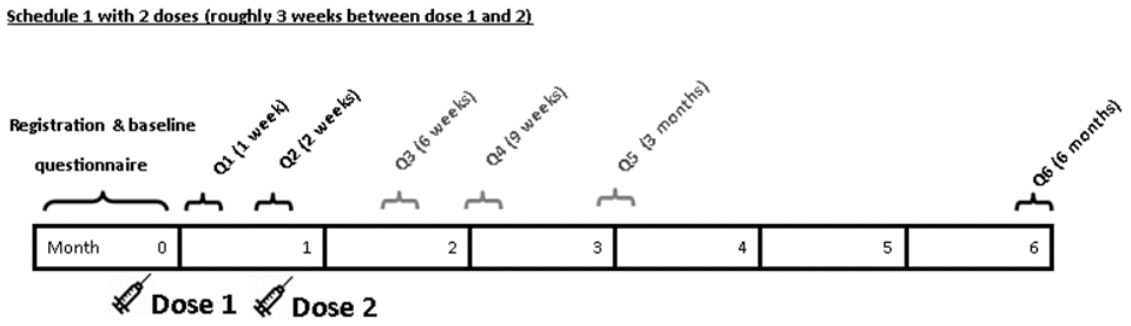

Figure ES1. Questionnaires' schedule at first vaccination cycle.

Special populations & inclusion upon booster vaccination using the CVM protocol

For the CVM cohort event monitoring, which started on the 06/04/2021 as an extension of ECVM, the protocol was adapted to include special populations (first dose) or booster doses in order to include additional countries and vaccinees. LAREB could not support additional changes in the web app content or additional participating countries. Therefore, the Research Online platform, hosted by the University Medical Center Utrecht, was developed. Table ES1 shows which tool was utilized by which country. The content of the ECVM baseline questionnaire developed for the general population was adapted and enlarged to each special cohort with specific questions for the characterisation of the vaccinees. Specifically, extra baseline questions for immunocompromised, people with prior SARS-CoV-2 infection, people with a history of allergy, pregnant and lactating women, and vaccinees who received a booster dose, were developed. Overall, information on vaccinees demographics, comorbidities, concomitant drug use, and vaccine exposure were collected in the baseline questionnaire (see section "variables" for more information). Follow-up questionnaires collected information on solicited ADRs (closed-ended questions), both local and systemic, unsolicited ADRs (open-ended questions) as well as serious ADRs. As for serious ADRs, clinical follow-up was performed with the consent of the participants by qualified pharmacovigilance personnel.

Variables

Vaccine brand and batch number, ADRs, age, sex, height and weight, geographical area, medical history including information on comorbidities and concomitant diseases, and concomitant medications were collected from each vaccinee.

1.5.3 Common Data Model

Since we used multiple primary data collection modalities with very similar protocols for the LIM and RO data collection tools, a common data model (CDM) was created to perform data harmonization and allow for further in-depth analyses that are included in this report and in future CVM publications. By using a common data model, simplified person centric record-based tables can be created which are more accessible for analyses. To create the CDM, basic data frames are created consisting of baseline characteristics of participants, ADRs, ADRs follow-up, medical history, admin data. These data frames are filled with data from different data sources (LIM and RO) and one-by-one the variables are assessed on their definitions and, where necessary, aligned.

LAREB transformed the LIM data to this model and UMC Utrecht transformed the RO output to this format and loaded it in the CDM on the Digital Research Environment (DRE). This allowed for the use of a common analytical script that was created by University Verona and run on the data at LAREB and the DRE. HALMED and Germany provided aggregated data in pre-specified tables. Thanks to the development of the CDM, the following analyses can be performed for the data collected through RO and LIM.

1.5.4 Statistical Analyses

The following analyses have been performed for this report:

- Descriptive analyses: for general population and special cohorts, incidence rates of patient-reported suspected ADRs were calculated using the number of reported ADRs as the numerator and the total number of vaccinees who filled at least 1 FU questionnaire (in each cohort) as the denominator, for special cohorts these were compared with those in the general population 1:1 matched using propensity score methodology.
- Age/brand stratified ADRs frequency tables
- Linear mixed-effects model (LMEM) to examine the occurrence of ADRs after receipt of first or the second vaccine dose and to estimate the contribution of sex, age or a history of prior COVID-19 infection in the general population. The dependent variable was either any ADR, any solicited ADR or fever.
- The time to onset (TTO) and time to recovery (TTR) of reported ADRs (mean and 1st interquartile range and 3rd interquartile range in hours). Participants could report the time to onset (TTO) of an ADR and the time to recovery (TTR) in date format and/or a number of seconds, minutes, hours, days or weeks.
- Heatmaps of the percentage of participants who reported at least one ADR, one solicited ADR and one solicited ADR without injection site reactions, stratified by age group and sex, a medical history of prior COVID-19 infection. Reporting rate is calculated based on n reported in figure and is indicated by gradient colour. Separate heatmaps are also available for booster doses.

1.6 Results

1.6.1 Primary aim

General Overview

The number of included participants who completed the baseline and first follow-up questionnaire are listed in Table ES1.

Table ES1. Overview of the total vaccinees included following the first vaccination cycle and the booster dose, per country, with a focus on vaccinees belonging to at least one special cohort.

Country	General Population* (total)				Special Population**			
	First Cycle		Booster doses		First Cycle		Booster doses	
	Tool	N inclusions	Tool	N inclusions	Tool	N inclusions	Tool	N inclusions
Belgium	LIM	38	-	-	LIM	12	-	-
Croatia***	OPeN	368	OPeN	18	OPeN	68	OPeN	18
France	LIM	1,181	RO	3,843	LIM	592	RO	877
Italy	LIM+RO	891	RO	1,873	LIM+RO	634	RO	630
Netherlands	LIM	27,648	-	-	LIM	5,948	-	-
UK	LIM	228	RO	491	LIM	165	RO	201
Germany***	SV2.0	612,078	-	-	-	-	-	-
Portugal	RO	10	RO	101	RO	10	RO	42
Romania	RO	90	RO	196	RO	86	RO	84
Slovakia	RO	65	RO	9	RO	85	RO	9
Spain	RO	23	RO	197	RO	27	RO	88
Switzerland	RO	12	RO	97	RO	12	RO	93
Ireland	-	-	RO	177	-	-	RO	166
Total		**642,632**		**7,002**		**7,571**		**2,208**

These participants completed the baseline and the first follow-up questionnaire (Q1).

*The general population includes all vaccinees, including those belonging to the special cohorts.

** Focus on special populations. For the first vaccination cycle, please note that participants may be counted more than once since a single participant may belong to more than one cohort. As for the booster dose, however, a single vaccinee was counted only once.

Incidence rates of patient-reported adverse reactions

The number and rates of ADRs can be found in Table ES2, more details can be found in the report itself.

Table ES2. Local and systemic solicited ADRs with any COVID-19 vaccine, by first vaccination cycle and booster dose.

	General population		Special cohorts																	
			People with Prior SARS-CoV-2 infection			Children/Adolescent (5-17 y.o.)			People with a history of allergy			Immunocompromised			Pregnant women			Lactating women		
Dose of vaccine	**First vaccination cycle N = 642.247**	**Booster N = 6,984**	**1st N= 2,594**	**2nd N = 910**	**Booster N = 827**	**1st N= 732**	**2nd N = 422**	**Booster N = 135**	**1st N= 3,477**	**2nd N = 2,243**	**Booster N = 825**	**1st N = 567**	**2nd N = 416**	**Booster N = 207**	**1st N = 175**	**2nd N = 131**	**Booster N = 358**	**1st N = 26**	**2nd N = 20**	**Booster N = 124**
Vaccinees with ≥1 ADR (solicited and unsolicited), n (%)	495381 (77.1)	4,501 (64.4)	2,333 (89.9)	831 (91.3)	562 (68.0)	404 (55.2)	257 (60.9)	67 (49.6)	3,008 (86.5)	1,952 (87.0)	626 (75.9)	465 (82.0)	336 (80.6)	128 (61.8)	142 (81.1)	113 (86.3)	205 (57.3)	21 (80.8)	15 (75.0)	97 (78.2)
Local solicited ADRs, n (%)																				
Injection site erythema	4575 (0.7)	356 (5.1)	180 (6.9)	46 (5.1)	44 (5.3)	20 (2.7)	7 (1.7)	6 (4.4)	241 (6.9)	137 (6.1)	62 (7.5)	44 (7.8)	22 (5.3)	12 (5.8)	6 (3.4)	6 (4.6)	16 (4.5)	0 (0)	2 (10)	8 (6.5)
Injection site haematoma	1225 (0.2)	149 (2.1)	98 (3.8)	30 (3.3)	21 (2.5)	7 (1)	1 (0.2)	1 (0.7)	151 (4.3)	70 (3.1)	24 (2.9)	21 (3.7)	15 (3.6)	6 (2.9)	7 (4)	4 (3.1)	9 (2.5)	1 (3.8)	2 (10)	6 (4.8)
Injection site induration	532 (0.1)	29 (0.4)	12 (0.5)	1 (0.1)	4 (0.5)	2 (0.3)	0 (0)	0 (0)	40 (1.2)	7 (0.3)	5 (0.6)	1 (0.2)	3 (0.7)	1 (0.5)	1 (0.6)	0 (0)	1 (0.3)	1 (3.8)	1 (5)	1 (0.8)
Injection site inflammation	3798 (0.6)	904 (12.9)	437 (16.8)	98 (10.8)	124 (15.0)	37 (5.1)	20 (4.7)	12 (8.9)	594 (17.1)	266 (11.9)	156 (18.9)	93 (16.4)	37 (8.9)	26 (12.6)	15 (8.6)	14 (10.7)	48 (13.4)	1 (3.8)	2 (10)	21 (16.9)
Injection site pain	371,526 (57.8)	2,685 (38.4)	1,006 (38.8)	272 (29.9)	345 (41.7)	219 (29.9)	78 (18.5)	41 (30.4)	1,509 (43.4)	648 (28.9)	410 (49.7)	233 (41.1)	106 (25.5)	83 (40.1)	76 (43.4)	44 (33.6)	139 (38.8)	13 (50)	6 (30)	70 (56.5)
Injection site pruritus	2977 (0.5)	222 (3.2)	77 (3)	18 (2)	24 (2.9)	7 (1)	3 (0.7)	1 (0.7)	127 (3.7)	56 (2.5)	41 (5)	20 (3.5)	12 (2.9)	8 (3.9)	4 (2.3)	4 (3.1)	10 (2.8)	-	0 (0)	8 (6.5)
Injection site reaction	304 (0.1)	19 (0.3)	3 (0.1)	0 (0)	1 (0.1)	-	0 (0)	0 (0)	3 (0.1)	3 (0.1)	2 (0.2)	3 (0.5)	0 (0)	1 (0.5)	3 (1.7)	0 (0)	0 (0)	1 (3.8)	0 (0)	0 (0)
Injection site swelling	95,725 (14.9)	951 (13.6)	373 (14.4)	77 (8.5)	111 (13.4)	37 (5.1)	17 (4)	10 (7.4)	511 (14.7)	207 (9.2)	166 (20.1)	85 (15)	38 (9.1)	22 (10.6)	18 (10.3)	12 (9.2)	36 (10.1)	2 (7.7)	1 (5)	23 (18.5)
Injection site warmth	3,160 (0.5)	381 (5.5)	275 (10.6)	63 (6.9)	68 (8.2)	14 (1.9)	14 (3.3)	5 (3.7)	374 (10.8)	201 (9)	71 (8.6)	66 (11.6)	28 (6.7)	12 (5.8)	9 (5.1)	9 (6.9)	27 (7.5)	2 (7.7)	0 (0)	11 (8.9)
Systemic solicited AEFIs, n (%)																				
Arthralgia	85,467 (13.3)	903 (12.9)	456 (17.6)	88 (9.7)	120 (14.5)	22 (3)	22 (5.2)	9 (6.7)	596 (17.1)	236 (10.5)	142 (17.2)	86 (15.2)	38 (9.1)	38 (18.4)	4 (2.3)	7 (5.3)	39 (10.9)	4 (15.4)	1 (5)	24 (19.4)
Chills	98,367 (15.3)	1,332 (19.1)	830 (32)	144 (15.8)	199 (24.1)	28 (3.8)	24 (5.7)	8 (5.9)	927 (26.7)	296 (13.2)	200 (24.2)	127 (22.4)	40 (9.6)	33 (15.9)	6 (3.4)	17 (13)	39 (10.9)	3 (11.5)	2 (10)	31 (25)
Fatigue	290,408 (45.2)	2,433 (34.8)	1,036 (39.9)	250 (27.5)	320 (38.7)	111 (15.2)	83 (19.7)	37 (27.4)	1,502 (43.2)	720 (32.1)	392 (47.5)	216 (38.1)	105 (25.2)	68 (32.9)	51 (29.1)	41 (31.3)	105 (29.3)	9 (34.6)	1 (5)	44 (35.5)
Headache	243,731 (37.9)	1,826 (26.1)	1,019 (39.3)	222 (24.4)	231 (27.9)	84 (11.5)	74 (17.5)	33 (24.4)	1,315 (37.8)	588 (26.2)	293 (35.5)	178 (31.4)	86 (20.7)	45 (21.7)	26 (14.9)	27 (20.6)	84 (23.5)	8 (30.8)	2 (10)	45 (36.3)
Malaise	149,523 (23.3)	1,630 (23.3)	1,014 (39.1)	257 (28.2)	220 (26.6)	62 (8.5)	51 (12.1)	19 (14.1)	1,302 (37.4)	621 (27.7)	257 (31.2)	180 (31.7)	91 (21.9)	51 (24.6)	16 (9.1)	29 (22.1)	73 (20.4)	5 (19.2)	3 (15)	36 (29)
Myalgia	150,978 (23.5)	1,821 (26.1)	1,020 (39.3)	205 (22.5)	226 (27.3)	90 (12.3)	54 (12.8)	19 (14.1)	1,373 (39.5)	596 (26.6)	276 (33.5)	193 (34)	85 (20.4)	49 (23.7)	33 (18.9)	38 (29)	65 (18.2)	4 (15.4)	1 (5)	43 (34.7)

	General population		Special cohorts																	
			People with Prior SARS-CoV-2 infection			Children/Adolescent (5-17 y.o.)			People with a history of allergy			Immunocompromised			Pregnant women			Lactating women		
Dose of vaccine	**First vaccination cycle N = 642.247**	**Booster N = 6,984**	**1st N= 2,594**	**2nd N = 910**	**Booster N = 827**	**1st N= 732**	**2nd N = 422**	**Booster N = 135**	**1st N= 3,477**	**2nd N = 2,243**	**Booster N = 825**	**1st N = 567**	**2nd N = 416**	**Booster N = 207**	**1st N = 175**	**2nd N = 131**	**Booster N = 358**	**1st N = 26**	**2nd N = 20**	**Booster N = 124**
Nausea	60702 (9.5)	590 (8.4)	434 (16.7)	92 (10.1)	85 (10.3)	41 (5.6)	27 (6.4)	7 (5.2)	613 (17.6)	252 (11.2)	117 (14.2)	89 (15.7)	43 (10.3)	21 (10.1)	11 (6.3)	7 (5.3)	38 (10.6)	2 (7.7)	1 (5)	12 (9.7)
Body temperature increased	4426 (0.7)	7 (0.1)	100 (3.9)	27 (3)	66 (8.0)	15 (2)	17 (4)	12 (8.9)	121 (3.5)	79 (3.5)	70 (8.5)	20 (3.5)	12 (2.9)	11 (5.3)	2 (1.1)	7 (5.3)	14 (3.9)	-	1 (5)	11 (8.9)
Pyrexia	94,601 (14.7)	838 (12)	685 (26.4)	123 (13.5)	117 (14.1)	34 (4.6)	33 (7.8)	10 (7.4)	702 (20.2)	262 (11.7)	140 (17)	82 (14.5)	40 (9.6)	27 (13)	2 (1.1)	9 (6.9)	18 (5)	-	0 (0)	16 (12.9)
Hyperpyrexia	0 (0)	7 (0.1)	15 (0.6)	1 (0.1)	1 (0.19	-	1 (0.2)	0 (0)	13 (0.4)	4 (0.2)	1 (0.1)	4 (0.7)	0 (0)	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)
Vaccinees with ≥1 AESI n (%)	2,001 (0.3)	18 (0.3)	2 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.7)	15 (0.4)	5 (0.2)	3 (0.4)	1 (0.2)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vaccinees with ≥1 serious AEFI, n (%)	3,142 (0.5)	18 (0.3)	4 (0.2)	2 (0.2)	1 (0.1)	2 (0.3)	1 (0.2)	1 (0.7)	6 (0.2)	10 (0.4)	2 (0.2)	3 (0.5)	2 (0.5)	0 (0)	1 (0.6)	1 (0.8)	3 (0.8)	0 (0)	0 (0)	2 (1.6)

Legend: N is the total number of vaccinees who received a 1st, 2nd and a booster dose, used as the denominator. **Note**: For general population's first dose analysis, only vaccinees recruited via LIM, OPeN and SV2.0 were included (N=642,247, not including 45 unknown vaccine brand). For the special cohort's first vaccination cycle, vaccinees recruited via LIM and RO were included (N= 7,555); for the booster dose, vaccinees recruited via RO were included (N=6,952). For special population's first vaccination cycle and booster, vaccinees from Croatia were excluded from the denominator and analysed only in the general population section.

First vaccination cycle in total population

A total of 642,632 first vaccinated persons have been included across 13 countries through 4 data collection tools for the first vaccination cycle. Germany included the large majority of vaccinees (n=612,078, 95.2%). Croatia collected data from 368 (0 newly vaccinated persons. Through the LIM data collection tool, a total of 29,846 persons (4.6%) have been included from 5 countries. A small portion of first cycle inclusions came from the RO platform (225 vaccinees) as part of the special populations.

A total of 3,142 (0.49%, 95%CI: 0.47-0.51%) of the 642,632 vaccinated persons reported at least one serious adverse reaction after receiving the first dose. Due to constraints in resources and time, Germany was only able to provide the reported seriousness and not the assessed seriousness. Both the reported and assessed serious adverse reactions varied considerably across type of reaction, across vaccine brand and dose.

Of the 642,290 participants who had received a first dose of any COVID-19 vaccine, 0.31% (95%CI 0.30-0.33%) subjects reported experiencing at least one AESI between their first and second dose of the vaccine.

Injection site pain (57.8%, n=371,526) was the most commonly reported, solicited ADR, for each vaccine and both doses. Fatigue, headache, malaise, and myalgia were the most frequently reported solicited systemic adverse reactions (≥20%).

Potential predictors of experiencing any adverse reaction, any solicited adverse reaction and fever were analysed using a linear mixed-effects model. For the general population, with increasing age, there is lower contribution to the occurrence of any adverse reaction (OR=0.96, 95% CI[0.96, 0.96]), any solicited adverse reaction (OR=0.96, 95% CI[0.96, 0.96]) or fever (OR=0.97, 95% CI[0.97, 0.98]). Male sex as a predictor has a lower contribution than female sex for any adverse reaction (OR=0.44, 95% CI[0.41, 0.48]), any solicited adverse reaction (OR=0.45, 95% CI[0.42, 0.49]) and fever (OR=0.50, 95% CI[0.43, 0.58]). These co-variates have a similar contribution for both dose one and two. A prior Covid-19 infection as a predictor, gives an OR <0.5 for any adverse reaction (OR=0.44, 95% CI[0.39, 0.52]) and any solicited adverse reaction (OR=0.49, 95% CI[0.43, 0.57]) for dose 1. A prior Covid-19 infection as a predictor, gives an OR >1.5 for any adverse reaction (OR=1.58, 95% CI[1.38, 1.82]) and any solicited adverse reaction (OR=1.61, 95% CI[1.41, 1.85]) for dose 2. For fever, prior Covid-19 infection is a positive predictor for both dose 1 and 2.

First vaccination cycle in special populations

A total of 7,503 vaccinees (excluding vaccinees from Croatia) belonging to a special cohort (children and adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection and pregnant women) were included at first vaccination cycle through either LIM or RO.
Serious ADR rates were 0.2% (95%CI: 0.1-0.4%) in people with prior SARS-CoV-2 infection, 0.2% (95%CI: 0.1-0.4%) in people with history of allergy, 0.5% (95%CI: 0.1-1.5%) in immunocompromised, 0.3% (95%CI: 0.1-1.0%) in children/adolescents and 0.6% (95%CI 0.1-3.2%) in pregnant women.

As for the AESI rates, 0.1% (95%CI: 0.0-0.3%) in people with prior SARS-CoV-2 infection, 0.4% (95%CI: 0.3-0.7%) in people with history of allergy, 0.2% (95%CI: 0.0-1.0%) in immunocompromised were observed. Overall, more than half of the vaccinees in each cohort reported at least one ADR (solicited or unsolicited) following the first dose of any vaccine. The most frequently reported solicited local ADRs among all special cohorts and considering all COVID-19 vaccine brands pooled together, was injection site pain with a percentage of 41% following the first dose and lower percentage following

the second dose (28%). This is in line with the total population (and with previously published works). Among the solicited systemic ADRs, fatigue (first dose= 33%; second dose= 24%), headache (first dose= 28%; second dose= 20%), malaise (first dose= 24%; second dose= 21%), and myalgia (first dose= 27%; second dose= 19%), were the most frequently reported events, which is comparable with the total population. Please note that the denominator is different for each cohort and vaccine dose.

Booster dose in the total population

Overall, 6,984 vaccinees (excluding vaccinees from Croatia) from the total population, including special cohorts (N=2,190, 31.4%) were included upon a COVID-19 vaccination booster dose using the RO platform.

The rate of serious ADRs was 0.1% (95%CI: 0.0-0.7%) in people with prior SARS-CoV-2 infection, 0.7% (95%CI: 0.1-4.1%) in children and adolescents, 0.4% (95%CI: 0.1-1.1%) in people with history of allergy. As for the AESIs reported following the booster dose, the rate was 0.1% (95%CI: 0.0-0.7%) in people with prior SARS-CoV-2 infection, 0.7% (95%CI: 0.1-4.1%) in children and adolescents, 0.2% (95%CI: 0.1-0.9%) in people with history of allergy, 0.8% (95%CI: 0.3-2.4%) in pregnant women, 1.6% (95%CI: 0.4-5.7%) in lactating women.

More than half of the vaccinees in the general population and in each cohort reported at least one ADR (solicited and unsolicited) following the booster dose of any COVID-19 vaccine (except children who reported lower percentages), which showed lower percentages than after the first vaccination cycle. Reporting of any ADR was similar to that for the first doses. Among the special cohorts of interest included upon booster, children and adolescents reported the lowest percentage of ADR, while lactating women reported the highest, always considering the limited sample size (N=135 and N=97, respectively).

1.7 Discussion

This executive summary gives an overall overview of the safety evidence of COVID-19 vaccines in persons from both the general and special populations (excluding Germany and Croatia) that were included after the first vaccination cycle and booster dose combining data coming from a total of 13 countries and four different data collection tools. Self-reported safety data of COVID-19 vaccines from more than 642,632 vaccinees have been reported here.

Collectively, percentages of reported serious ADRs and AESIs remain low (below 0.9%) across the general population and different cohorts, vaccine brands, age, previous medical history. Solicited adverse reactions are common, especially injection site reactions across all populations, with differences between vaccines, which can be related to the populations they were channelled to.

One of the main limitations of our rate estimates is that data came mostly from Germany. While large variations in reported adverse reactions were not observed, the impact of the varying vaccination campaigns may had led to channelling of certain vaccine brands to particular subpopulations in certain time points. This was not analysed in this report. Additionally, due to time constraints, Germany was only able to provide the seriousness as reported by participants rather than the assessed seriousness, which may have led to overreporting.

For this report, the readiness of data collection infrastructures and ethical approvals timings was crucial. Countries that had prompt governmental support before vaccines were launched made it in

time to include a large number of vaccinated persons since the first vaccination. In comparison, booster doses and self-reported events were promptly collected in this study. Cohort event monitoring studies may suffer from selection bias and loss to follow-up, but they have a proper denominator, and allow for stratification and adjustments.

Regarding the loss to follow-up, the study would further benefit from in-depth sensitivity analysis and results to be compared with those from the herein shown primary analyses, thus, investigating the loss to follow-up impacts. Consortium experts are planning to further evaluate this aspect and conducting inverse probability weighting for selective loss to follow-up and the results will be published.

Important human resources, due to the assessment of all serious reactions, was required during this study. Regulatory agencies/pharmacovigilance centers that participated to this study also reported collected adverse drug reactions to EudraVigilance. The majority from this report were solicited reactions. Data was harmonized across all different data collection tools. A Common Data Model to pool LIM and RO data, as detailed in section 1.5.3, was developed to aid in future analyses.

1.8 Conclusions

The reported serious ADRs and AESIs remain low (below 0.9%) across the general population and the different sub-populations. Solicited adverse reactions are very common across with more than half of the general population and special cohorts reporting at least one adverse reaction.

Despite the limitations discussed above, Cohort Even Monitoring studies can allow prompt and almost real-time observations of the safety of medications directly from a patient-centred perspective, which can play a crucial role for regulatory bodies during an emergency setting such as the COVID-19 pandemic. On the other hand, these studies are time-, personnel-, resource-consuming, which may conduct to restrict their applications to urgent situations as results also need important retrospective validations to be entirely taken as reliable.

Further, detailed investigations on how these data were handled by both regulatory bodies and vaccine manufacturers would be beneficial in improving the impact of these cohort event monitoring studies for ongoing decision-making processes and investigators could use these outcomes to further improve these study designs, their fit-to-purpose applications, potentially allowing this important tool to become general practice in regulatory safety evaluations.