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 rollout 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 objective

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 objective

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.

[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 13/07/2021.

For the German SafeVac 2.0 platform,[4,5] the study commenced on 27/12/2020, 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 15/02/2021. 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.

[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

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.

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.

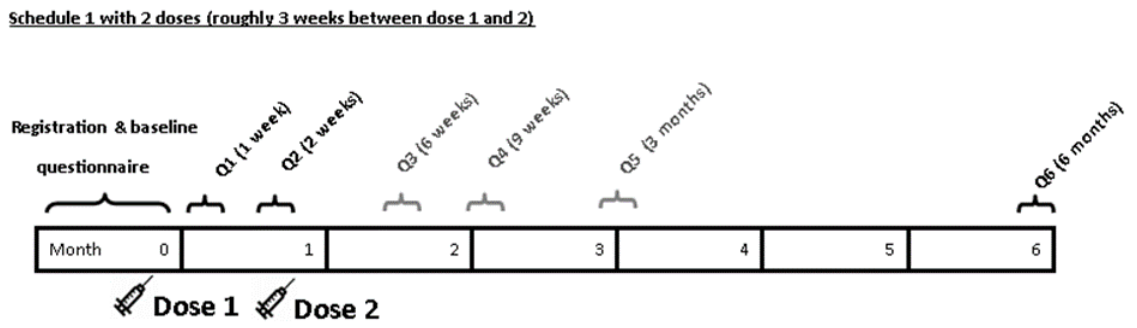

Figure ES1. Questionnaires' schedule at first vaccination cycle.

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.

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).

1.6.2 Secondary Aim

A subset of the general population receiving a first and/or second dose, comprising of 29,844 participants and excluding data from Germany, was analysed using a linear mixed-effects models. For this general population, with increasing age, there is a lower contribution to the occurrence of any ADRs, any solicited ADRs, or fever. The male sex as a predictor has a lower contribution than the female sex. These co-variated have a similar contribution for both doses one and two. A prior SARS-CoV-2 infection as a predictor, gives an OR <0.5 for any ADR and any solicited ADR for dose 1 and for dose 2 an OR of approximately 1.6. For fever, prior COVID-19 infection is a positive predictor for both dose 1 and 2 although the OR is higher for dose 2 (OR 2.4 vs 1.7).

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.

2 List of abbreviations

ACCESS	vACCine covid-19 monitoring readinESS
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease 2019
CVM	Covid-Vaccine-Monitor
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ECVM	Early-Covid-Vaccine-Monitor
GPP	Good Pharmacoepidemiology Practice
GTIN	Global Trade Item Number
LIM	Lareb Intensive Monitoring
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
PV	Pharmacovigilance
RO	Research Online
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

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4 Milestones

Start of project	6 Apr 2021
D1 Study plan	6 May 2021
D2 Study protocol(s)	7 Jun 2021
Study start	7 July 2021
D3 Monthly interim statistical report 1 and update of data on the dashboard	30 Sep 2021
D3 Monthly interim statistical report 2 and update of data on the dashboard	27 Oct 2021
D3 Monthly interim statistical report 3 and update of data on the dashboard	26 Nov 2021
D3 Monthly interim statistical report 4-5 and update of data on the dashboard	31 Jan 2021
D3 Monthly interim statistical report 6 and update of data on the dashboard	28 Feb 2022
D4.1 Interim study report + D3 monthly interim statistical report 7 & SAP	8 Apr 2022
D3 Monthly interim statistical report 8 + 9 + 10 and update of data on the dashboard	30 Jun 2022

D3 Monthly interim statistical report 11 + 12 + 13 + 14 and update of data on the dashboard	31 Oct 2022
D3 Monthly interim statistical report 15 + 16 and update of data on the dashboard	24 Jan 2023
D5.4 Archiving & storage plan	31 Jan 2023
D3 Monthly interim statistical report 17 + 18 + 19 and update of data on the dashboard	28 Apr 2023
D4.2 Final study report	8 May 2023
D5 Manuscript	8 May 2023

5 Rationale and background

Background

The European Medicine Agency's (EMA) mission is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. COVID-19 vaccines in the European Union (EU) were evaluated by EMA via the centralised procedure, based on a rolling review. At the date of this report, seven vaccines (from Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, Novavax, Valneva, Sanofi-GSK) have been granted conditional marketing authorisation and large-scale vaccination campaigns are being rolled out across the EU.

During the 2009 pandemic, major lessons learned were a need for improved collaboration within Europe, and a common approach for the collection of safety data and data-sharing[6]. This contribution could improve signal detection and timely evaluation of safety signals in a forthcoming pandemic. The large scale of the 2009 worldwide H1N1 pandemic vaccination programme prompted several countries to improve and expand their vaccination safety monitoring procedures. Indeed, various intensive monitoring studies were performed in different countries. The results of two intensive monitoring studies on the 2009 pandemic influenza vaccination in Europe were published. (Harmark et al. 2012) Upon the experience with the H1N1 vaccination programmes, the intensive monitoring system was developed further to monitor seasonal influenza vaccination in the Netherlands (cf. Lareb Intensive Monitoring (LIM) system) and has been used since. Such experiences paved the way to design an intensive and prospective monitoring system for COVID-19 vaccination at the European level.

To complement spontaneous reporting systems for signal detection (routine pharmacovigilance) and other initial safety monitoring activities such as pharmaco-epidemiological studies conducted or planned by different stakeholders, EMA procured an early safety monitoring study, the Early Covid Vaccine Monitor (ECVM), which was conducted by the EU PE&PV research network and VAC4EU in six EU Member States (Germany, Croatia, the Netherlands, Belgium, Italy, France) and the UK. The Covid Vaccine Monitor (CVM) study enlarged the ECVM study in five additional EU Member States (Spain, Portugal, Slovakia, Romania and Ireland) and Switzerland to further inform the benefit-risk profile of all COVID-19 vaccines in the EU as immunisation campaigns were expanding, targeting larger population groups.

Rationale

Pivotal licensure clinical trials collect key information on Adverse Events of Special Interest (AESIs) and Adverse Drug Reactions (ADRs) and often include selected persons. During the rollout of vaccines,

[6] www.ema.europa.eu/en/documents/report/pandemic-report-lessons-learned-outcome-european-medicines-agencys-activities-during-2009-h1n1-flu_en.pdf

larger and more diverse populations are vaccinated. Certain groups, such as those at higher risk of developing adverse reactions and/or AESIs had not been included in the pivotal COVID-19 vaccine clinical trials. Therefore, available risk management plans from authorised vaccines were initially lacking information on the safety of COVID-19 vaccines in special populations who had not been vaccinated in the first phases.

Adverse events following immunization (AEFI) can comprise 5 different types[7]:

- Vaccine product-related reaction
- Vaccine quality defect-related reaction
- Immunisation error-related reaction
- Immunisation anxiety-related reaction
- Coincidental event.

Licensure of a vaccine that is rolled out to a large population in a short time requires not only regular spontaneous reporting but also cohort event monitoring to obtain more in-depth information on the safety of the vaccines. In addition to existing spontaneous reporting systems, a large-scale cohort event monitoring system on general and special populations (i.e., pregnant and lactating women, children and adolescents, immunocompromised, people with a history of allergy, and people with prior SARS-CoV-2 infection) allows for the monitoring of marketed COVID-19 vaccines in a larger size and categories that have not been included (or have been included only marginally) in pivotal clinical trials in the EU.

6 Research question and objectives

The CVM-Cohort Event Monitoring (CEM) project aims to collect data on suspected ADRs following COVID-19 vaccines in the general and in specific target populations in 13 EU Member States (Belgium, Croatia, France, Germany, Ireland, Italy the Netherlands, Portugal, Romania, Slovakia, Spain, Switzerland and the UK) to further inform the benefit-risk profile of all COVID-19 vaccines in the EU.

Primary objectives

1. To collect data on patient-reported adverse reactions following COVID-19 vaccines and describe the frequency.
2. To compare incidence rates across the participating countries in the general and special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with a history of allergy, and people with prior SARS-CoV-2 infection) in near-real-time.

Secondary objective

To identify and generate incidence rates and potential predictors of the most frequently reported adverse reactions related to different COVID-19 vaccines after 1 or 2 dose(s) of the first vaccination cycle.

[7] https://apps.who.int/iris/handle/10665/206144

7 Amendments and updates to the protocols

8th of May 2023	Modification of the Secondary Objective definition. "Secondary objective: To identify and generate incidence rates and potential predictors of the most frequently reported adverse reactions related to different COVID-19 vaccines after 1 or 2 dose(s) of the first vaccination cycle". The secondary objective was originally also enlarged to generate predictors of frequent ADRs related to COVID-19 vaccines after booster doses and special cohorts. The creation of a CDM was needed to do this analysis. The first cohort we could perform these analyses was the largest cohort of general population after first/second COVID-19 vaccines' dose. These results are presented here. Unfortunately, the CDM was not ready yet For the booster doses and special cohorts for this final report.

8 Research methods

8.1 Study design

A prospective cohort event monitoring (CEM) study in the general and in special populations

- pregnant and lactating women
- children and adolescents
- immunocompromised
- people with a history of allergy
- people with prior SARS-CoV-2 infection

8.2 Participating sites

Organizations from thirteen European countries participated in this study. These organizations are either National Competent Authorities (NCA) or working in close cooperation with the NCA. See Table 1 for the countries and organizations.

Table 1: Contributing organizations and start of inclusions.

Country	*Organization*	*Inclusions Start date*
Financed through governments		
Germany	Paul-Ehrlich-Institute (PEI), Bereich Pharmacovigilanz	20-12-2020
The Netherlands	Pharmacovigilance Centre Lareb	01-02-2021
Croatia	Agency for Medicinal Products and Medical Devices of Croatia (HALMED)	15-02-2021
(co-) Financed through ECVM (ROC19)		
Italy	University of Verona	09-06-2021

France	University of Bordeaux	14-06-2021
United Kingdom	Drug Safety Research Unit (DSRU)	23-06-2021
Belgium	Federal Agency for Medicines and Health Products (FAMHP)	13-07-2021
Financed through CVM (ROC20)		
Portugal	Portuguese consortium of pharmacovigilance centers	05-02-2022
Switzerland	Institute of primary Health Care (BIHAM), University of Bern - COVIPREG	19-01-2022
Spain	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)	13-12-2021
Slovakia	Faculty of Medicine, Pavol Jozef Safarik University in Kosice	11-01-2022
Ireland	Rotunda Hospital Dublin	20-12-2021
Romania	Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca	01-12-2021

The Luxembourg Institute of Health (LIH) was also motivated to contribute, however in August 2021 they decided to withdraw from the project before any participant was recruited. This decision was made by LIH because of operational difficulties, country specific data protection aspects, and the progress of the vaccination campaign in Luxembourg related to how many subjects could still be recruited at that time. All participating organizations arranged medical ethical approval and made sure that the data collection applications used in this study were according to the research and privacy legislations applicable in their own country. These approvals did take some time for some participating organizations which was one of the causes that some countries could only start recruiting in June or July. The Paul Ehrlich Institute started early, they aligned their protocol as much as possible with the information for the ECVM project available at that time. However later updates in the ECVM protocol could not be implemented any more by PEI. A second set of organizations joined for the CVM-CEM later in 2021, when first vaccinations for adults were mostly finished. These organizations participated in special populations and booster doses.

8.3 Study Population

Inclusion criteria

Participants to be included had to have been vaccinated in one of the participating countries in the period between February 2021 and August 2022 for first dose. Germany extended the inclusion period for first time vaccinees until 30 September 2022. The recruitment period lasted until the end of November 2022 for vaccinees who entered upon a booster dose.

The vaccine recipient was included if the following conditions were fulfilled:

- Be registered for the study prior to (the first) vaccination or no longer than 48 hours from the first dose of COVID-19 vaccination or booster dose
- Be able to understand the language of the survey (translated into the local official languages);
- Be able to register and participate by e-mail;
- Provide informed consent (translated into the local official languages and adapted according to the Country-specific laws). For children, informed consent was required from the parents or legal representatives. Informed consent had to be given if the person wishing to participate in the project was under 16 or 18 years of age, depending on the Country-specific law.

Target groups were classified as general and special populations. People in the special target subgroups were classified based on the following characteristics:

- Pregnant/lactating women included pregnant or breastfeeding women who were vaccinated at any point of pregnancy or in the breastfeeding period;
- Children were aged between 5-11 years old and adolescents were aged between 12-17 years old. Parents or legal representatives were required to enter data on behalf of their children, as needed, based on national legislation;
- Immunocompromised subjects were defined as individuals with self-reported compromised immune systems due to diseases such as HIV/AIDS, transplants, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, psoriasis, psoriatic arthritis) and leukaemia/lymphoma; and/or subjects who were taking drugs affecting their immune system (e.g., myelosuppressive chemotherapy, glucocorticoids, anti-rheumatics drugs, monoclonal antibodies interfering with the immune system);
- Subjects with a self-reported history of allergy, including hay fever, dust mite allergy, allergy to animals, food allergy, allergy to insect bites, allergy to medication or vaccine, etc.
- Subjects with prior SARS-CoV-2 infection were people who had a self-reported suspected/diagnosed SARS-CoV-2 infection (confirmed by a test) at any time prior to vaccination.

8.4 Data collection schedule and tools

8.4.1 Data collection tools

Participants were invited to sign up for the study mostly at vaccination sites but also through (social-) media campaigns. Four different (web-based) applications were used for data collection.

- HALMED used a web-based application called OPeN (Online Platform for Electronic reporting of adverse drug reactions) to collect data in Croatia. The OPeN system includes the educational module (OPeKOM) that serves as a platform for ongoing education of healthcare professionals. OPeN was adapted to provide access to all study participants, not only healthcare professionals, and to include questionnaires.
- Paul-Ehrlich-Institute used the app SafeVac 2.0. This smartphone application was designed specifically to record tolerability of the COVID-19 vaccines in Germany and is developed by the Paul-Ehrlich-Insitute.
- LAREB, FAHMP, University Verona, DSRU and University Bordeaux used the Lareb Intensive Monitoring (LIM) web app. This tool was developed by Lareb for cohort event monitoring prior to the project and was extended to include other countries. Each organization had a country specific website and questionnaires were in the local language(s). Participants created a personal account in which they received the questionnaires. E-mails were sent by the LIM web app when a questionnaire was available to be completed. Ethical approvals and translations of the questionnaires to the local language took time, as well as testing the application in each country using the LIM app. These were reasons that some countries could only start recruiting subjects in June or July.
- In order to boost inclusions for special populations and add the monitoring of the booster vaccines, a new system was created based on the Research Online electronic data collection tooling, managed by UMC Utrecht. Each organization had a country specific website and questionnaires were in the local language(s). This tool was used for inclusions of special populations (upon first or booster dose) or for the general populations entering the study upon booster dose.

- COVIPREG and ORCHESTRA networks were used to recruit pregnant women and immunocompromised patients at booster vaccination, respectively. ORCHESTRA was supporting the recruitment of the fragile population through the dissemination of the CVM information material on an Italian regional and national level. In particular, the ORCHESTRA network has contributed to enrolling immunocompromised vaccinees who received a booster vaccination. COVIPREG network was used for the recruitment of pregnant women. Specifically, the network of Swiss obstetricians and gynecologists already familiar with the COVI-PREG registry asked for information on COVID-19 vaccines in pregnant women, collected by paper questionnaires between 1 March 2021 and 27 December 2021, and was involved in promoting the CVM study. As soon as the CVM study website was operational, the network of Swiss obstetricians and gynecologists was invited to switch to online questionnaires, which are much more user-friendly and efficient for accurate data collection than paper questionnaires.

8.4.2 Data collection schedule

The data collection was harmonized as far as possible and predefined before vaccination schedules were known, but had differences based on the tools available and countries.

Data collection for vaccinees entering upon first dose

Questionnaires[8] were scheduled to capture both short-term and long-term reactions. It was expected that most ADRs would occur within 72 hours after vaccination and the most well-known ADRs recovered within five days after vaccination. Therefore, the first questionnaires were sent in the first and second week after vaccination as shown in Figure 1. To get also the most accurate information on ADRs after the second dose, questionnaires were sent around the expected date of vaccination dose 2. Pregnant women received an additional follow-up questionnaire 1.5 months after the expected delivery date in order to collect newborn-related outcomes.

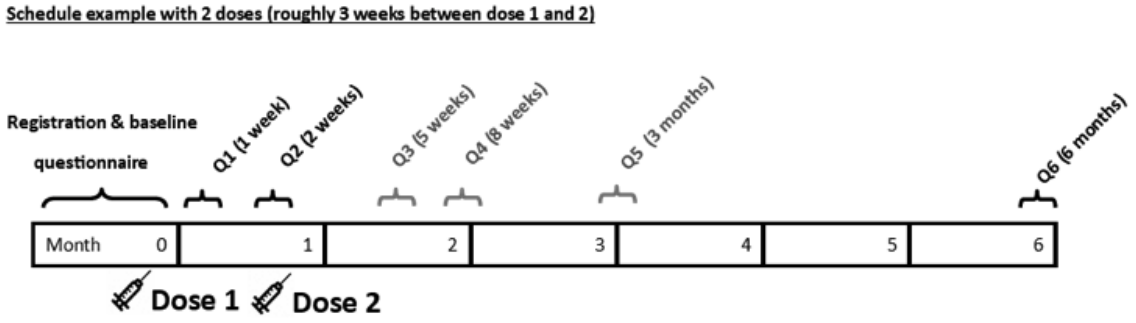

Figure 1: Example questionnaire schedule

As illustrated in Figure 2, the scheduling of the questionnaires was similar but not identical across countries participating in the first vaccinees data collection. The black bar indicates the timeline and the questionnaire scheduling as defined in the protocol.

[8] EUPAS39798 Study Protocol and EUPAS42504 Study Protocol

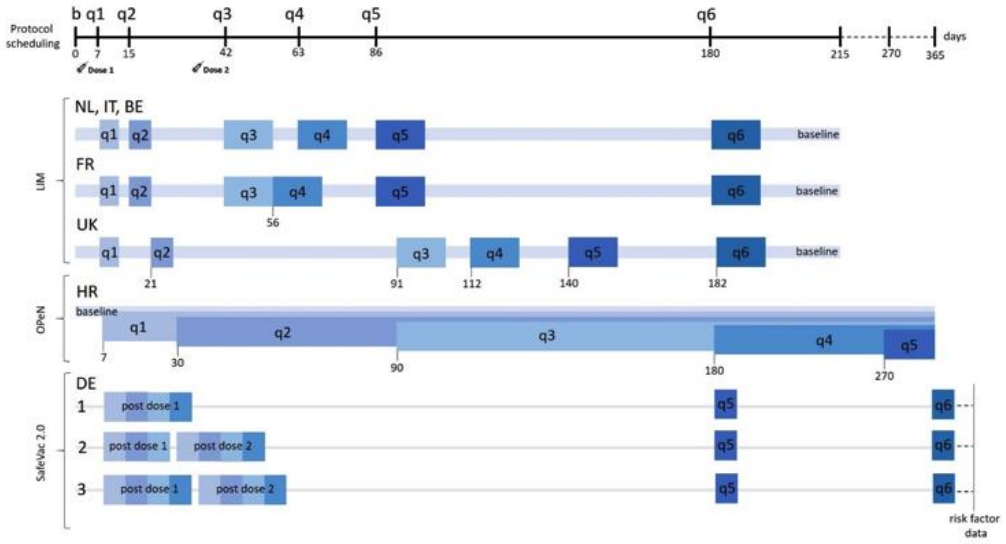

Figure 2: Questionnaire Scheduling schemes for the participating countries over time (days). The upper timeline in black shows the scheduling as it is described in the protocol.

The Netherlands, Italy and Belgium all adhered to the scheduling scheme as described in the initial (E)CVM protocol (Figure 2).[9] The date of the first dose defined the start of the schedule for each participant. The intervals between questionnaires were fixed and similar for all participants per country. France had a minor adjustment in comparison to the standard scheduling scheme of the Netherlands, Italy and Belgium.

For France, the fourth questionnaire was sent after 56 days instead of the standard 63 days after first dose as changes in protocol could not be approved in time for the study start.

The United Kingdom's scheduling scheme differs most compared to the other LIM countries. This is due to their vaccination strategy being focused on vaccinating as many individuals as possible with a first dose before commencing with the administration of a second shot. As a consequence, the decision was made to increase the interval between questionnaire 2 and 3.

Croatia's participants were able to continuously report ADRs within the Croatian application. Instead of sending questionnaires at scheduled intervals, participants were sent reminders at specific moments, enquiring whether they have experienced a new ADR. Throughout the study additional questions were added for participants to answer. For example, questions related to the second dose were made available in the app on day 30. Email reminders are automatically sent after 7, 30, 90, 180 and 270 days.

In contrast to the countries using the LIM app, Germany's scheduling was determined based on the exact vaccination dates of both doses. This approach resulted in three variations of the scheduling scheme (indicated in Figure 2 by the numbering to the left of each timeline). Questionnaires were sent out after 1, 6, 24 or 72 hours and 7, 14, 21 and 28 -days after either dose (indicated in Figure 2 by 'post dose 1' and 'post dose 2'). The day 28 questionnaire is only sent when there is no overlap with the succeeding questionnaire, which occurs with a three-week interval between shots. After the

[9] EUPAS39798 Study Protocol

aforementioned series of questionnaires were completed, each participant also received two questionnaires 182 and 365 days after the date of their first dose administration, in order to collect data on long term follow-up. Additionally, data on the risk factors of individuals were gathered in the final questionnaire of the study, therefore this data was no available in real-time but only at the end of the study.

Data collection for booster dose

Differently from participants receiving a first dose of vaccine, participants receiving a booster vaccination received 5 follow-up questionnaires instead of 6 due to a shorter follow-up time of 3 months.

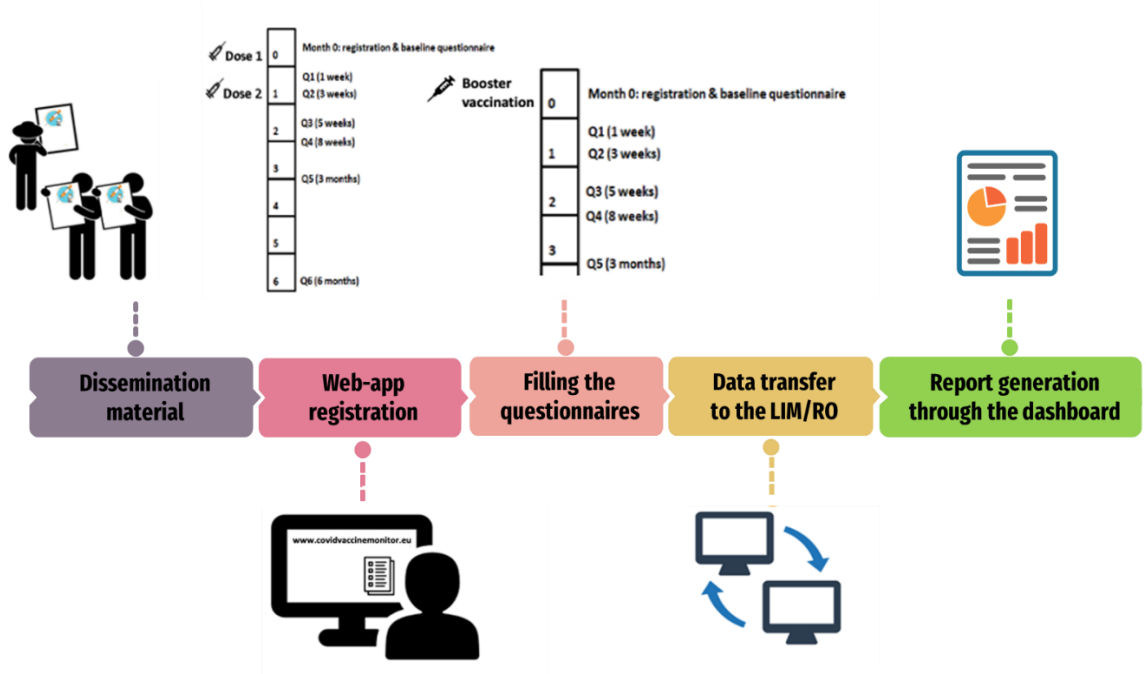

Figure 3. Key steps of the study and timing of sending of the questionnaires

Monitoring and coding of data

To collect complete data, some of the fields in the questionnaires were made compulsory. Questionnaires were validated by dedicated and pharmacovigilance (PV)-trained persons who corrected and coded information provided by the vaccinees, when necessary. The dedicated personnel could also contact the vaccinees in case of inconsistency of the collected information or lack of important information, provided that the participant had given consent to be contacted. Invalid/incomplete questionnaires, for example missing baseline questionnaires or incomplete date of birth, were excluded from the analyses.

8.5 Variables

Data were collected on vaccine exposure, demographic and clinical characteristics, safety outcomes, and ADRs (solicited and non-solicited). For pregnant women baseline variables for pregnancy (e.g.,

gestation, parity, previous pregnancy complications, ongoing pregnancy due date, etc.) and outcomes of the pregnancy and the new-born (i.e., pregnancy complications, end of pregnancy week, delivery mode, pregnancy outcomes, and neonatal outcomes) were collected. In addition, for the booster vaccination: data on the previous cycle of vaccination, including the vaccine brands, and the related adverse drug reactions.

8.5.1 Exposure data

- Vaccine brand & batch number (if available) obtained via the vaccine recipient (e.g., number on vaccination certificate, or uploading a photo)
- Vaccine dose number
- Vaccination date

Information on the second dose of vaccine was asked in questionnaire number 3 (Q3). In case the participant selected that they have not yet received the vaccine in Q3, second dose-related questions were asked in the next questionnaires (Q4, Q5, and Q6). Therefore, information regarding the second dose as well as the information about the interval between the first and the second dose could be collected in Q3-Q6.[10]

8.5.2 Vaccinee demographics and clinical characteristics

- Age
- Height and weight (to calculate body mass index - BMI)
- Contact details of next of kin (if privacy regulations allowed this)
- Geographical area
- Maternal morbidity & obstetric history (see below)
- Previous SARS-CoV2 infection and COVID-19 disease (closed questions, incl. date and severity)
- History of anaphylaxis or anaphylactoid reactions & allergies
- Presence of conditions/treatments that alter immune response
- Additional information to determine country-specific target population for vaccination: health care worker, (informal) caregiver, resident of a nursing home, …
- Current co-medication and previous, other vaccinations (within previous 2 weeks).
- Immuniser (e.g., GP, occupational health service, municipal health authority)
- Vaccination site (e.g., right/left arm/leg)
- Antipyretics intake around time of vaccination
- Prior vaccination with COVID-19 (once booster vaccinations are started)

The following additional information was collected for pregnant women only:

- Gravidity
- Parity:
    - Number of previous C-Section if parity ≥ 1
    - Number of previous vaginal delivery if parity ≥ 1
    - Number of previous early miscarriages (<14 weeks) if gestity > 1

[10] EUPAS39798 Study Protocol and EUPAS42504 Study Protocol

    - Number of previous late miscarriages (≥ 14 weeks) if gestity >1
    - Number of previous terminations of pregnancy if gestity > 1
    - Number of previous stillbirths if gestity >1
- Maternal medication
- Previous pregnancy complications (preterm birth, caesarean section)
- Ongoing pregnancy due date*

*Pregnancy due date could be calculated by the pregnant woman, who is generally aware of her last menstrual period.

This information was used for descriptive data analyses and cohorts' participants' definitions.

8.5.3 ADR data

Solicited adverse reactions

Pre-defined multiple-choice questions (solicited):

- Injection site reaction (redness, warmth, pain, itch, hematoma, swelling, induration, ELS (extensive limb swelling). If 2 or more of the following adverse reactions are mentioned (redness, warmth, pain, swelling), it is asked whether the redness and/or swelling go past the elbow or shoulder.
- Fever/feverishness
- Shivering/chills
- Headache
- Nausea
- Myalgia/muscle pain
- Arthralgia/joint pain
- Malaise
- Fatigue

These solicited adverse reactions were known to occur frequently, as they are linked to reactogenicity of the immune system after receiving a vaccine. The reactions listed as solicited adverse reactions were the same across all participating countries (with the exception of Germany who started data collection in December 2020 and additionally had added dizziness and diarrhea later on) and they could be automatically MedDRA-coded. This improved the data quality and facilitated timely data analysis.

Unsolicited adverse reactions

In addition, it was asked in each questionnaire whether any other suspected adverse reactions occurred (open question/unsolicited). The later questionnaires were meant to monitor suspected adverse reactions with a longer lag time and to assess the course of previously reported adverse reactions (i.e., outcome, duration of symptoms).

Assessors in the different participating countries coded all unsolicited reported adverse reactions into MedDRA lower-level terms (in English) and determined whether they were serious based on the

criteria of the Council for International Organizations of Medical Sciences (CIOMS).[11] Seriousness was reported by the participant, solicited reactions were reviewed to assess the seriousness criteria based on the information reported by the participant in the questionnaire or, when applicable, after follow-up.

Reported adverse reactions which were considered serious based on the above-mentioned CIOMS criteria and other adverse reactions that needed medical clarification were assessed in agreement with national PV legislation in each participating country.

Pregnancy and neonatal outcomes

After the end of pregnancy, a dedicated questionnaire was sent to the woman to collect key information on pregnancy and neonatal outcomes.

- Pregnancy complications
- Occurrence of gestational diabetes, high blood pressure (hypertension), blood clots (thrombosis), preeclampsia, intrauterine growth restriction, abnormal fetal doppler, threatened preterm labour, placenta praevia, preterm premature rupture of membranes, placental abruption, other)
- End of pregnancy weeks (since Last Menstrual Period)
- Delivery mode (vaginal birth, C-section)
- Pregnancy outcomes (livebirth, late miscarriage ≥ 14 weeks, early miscarriage <14 weeks, Termination of pregnancy, stillbirth, other)
- Neonatal outcomes (sex, weight, height, length, physical examination abnormality, death, ICU admission, feeding method at discharge, and whether the baby had COVID-19 infection).

AESI

To be able to monitor reporting of AESI, which were also investigated in the ECVM & CVM -EHR study, ADRs listed below were classified as AESI (Table 2). Corresponding MedDRa codes can be found in Annex 1.

Table 2. List of AESI

Event
Multisystem inflammatory syndrome
Acute respiratory distress syndrome
Acute cardiovascular injury
Microangiopathy
Coronary Artery Disease (CAD)
Arrhythmia
Myocarditis
Pericarditis
Coagulation disorders, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease
Venous Thromboembolism (DVT & PE & Splanchnic)
Cerebral Venous Sinus Thrombosis

[11] CIOMS Working Group VIII. Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII. Geneva2010. Report No.: 9290360828.

Event
Arterial thrombosis
TTS (VTE, arterial thrombosis, or CVST with thrombocytopenia in 10 days)
Hemorrhagic stroke
DIC
Generalised convulsion
Guillain Barré Syndrome (GBS)
Diabetes (type 1 and unspecified type)
Acute kidney injury
Acute liver injury
Anosmia, ageusia
Chilblain-like lesions
Single organ cutaneous vasculitis
Erythema multiforme
Anaphylaxis
Death (any cause) (postvaccination control window)
Sudden death (by codes) (postvaccination control window)
Meningoencephalitis
Acute disseminated encephalomyelitis (ADEM)
Narcolepsy
Thrombocytopenia
Transverse myelitis
Bells' palsy
Haemophagocytic lymphohistiocytosis[4]
Kawasaki's disease
Pancreatitis
Rhabdomyolysis
SCARs
Sensorineural hearing loss
Thyroiditis

Assessment and classification of ADRs

Because data were gathered from the participants through self-reporting methods, it was not possible to perform causality assessments and to determine if all adverse events following Immunisation were caused by the vaccine. Therefore, all adverse reactions should be considered as suspected adverse reactions following Immunisation with COVID-19 vaccines.

All serious adverse reactions were defined as such first by the participants themselves and then evaluated, and possibly confirmed, by qualified assessor (considering all information including possible uploads of documents by participants or comments on these events) based on CIOMS seriousness criteria. When consent has been given by a participant, follow-up was requested by e-mail for verification and upgrading of the clinical documentation grade. Otherwise, serious ADR assessment was carried out by the Regional Center of Pharmacovigilance or local Pharmacovigilance Responsible Person, in agreement with national pharmacovigilance practice and legislation. There were thus two variables regarding the seriousness of an ADR: the seriousness which was reported by the participant and the seriousness as assessed by the trained assessors. In Germany, seriousness was only obtained from self-reports.[12] Seriousness used in all tables in this report section and dashboards was based on the assessed seriousness.

[12] Early Covid-19 Vaccine Monitor: Final Report for Early Cohort Event Monitoring of Safety of COVID-19 Vaccines | Zenodo

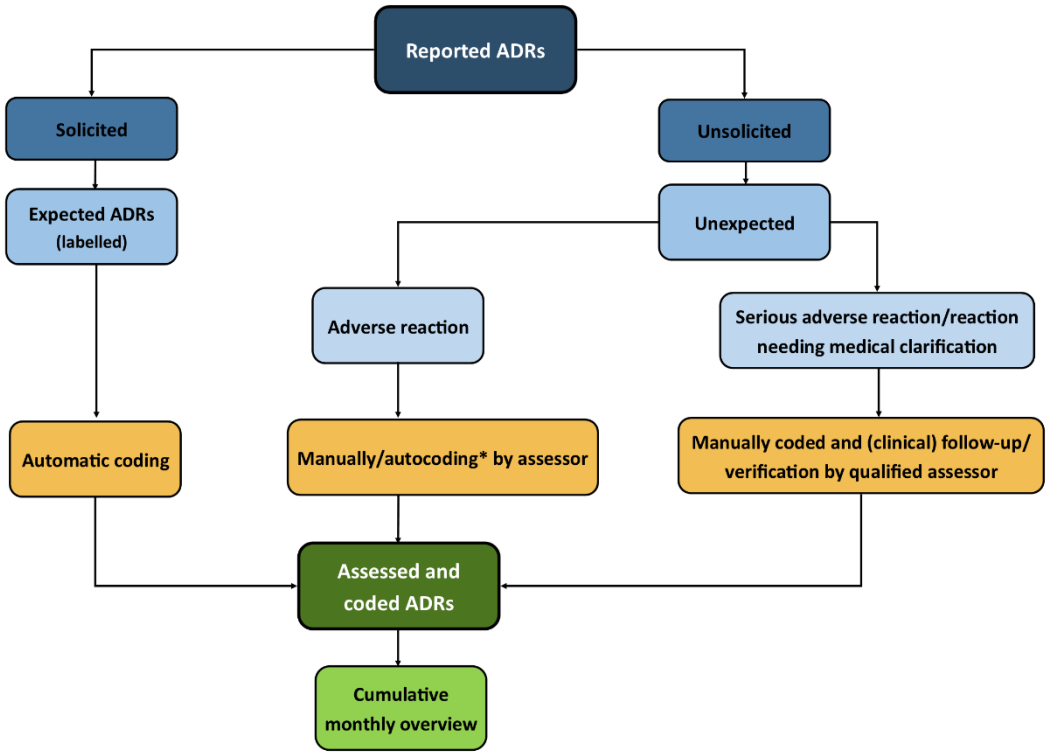

Figure 4. Reported ADRs coding system based on the Early-Covid-Vaccine-Monitor study protocol

8.5.4 Submission of individual case reports to EudraVigilance

The LIM/RO questionnaires were pseudonymised and transformed into ICSR (Individual Case Safety Report) reports in an R3 format (or older version such as R2B, if needed). The ICSR data could only be accessed and downloaded by the country of reference (the country that owns the data). For each partner working with a National Competent Authority (NCA) (e.g., regional PV centre), these reports were sent to the national reporting system and ultimately to the EudraVigilance system (GVP module VI). These reports needed to be checked for duplicates when reported to EudraVigilance (EV). The process of sending ICSR reports, and duplicate checks was the responsibility of each country, based on national PV regulations.

The Netherlands

ICSR were generated per participant, additional information (burden, TTR etc) and new ADRs were added in existing reports as follow-up. A total of 20 691 reports were sent to EV through the CEM study. These reports receive a specific code in order to trace back its origin from CEM and not from spontaneous reporting system.

Belgium

ICSR were created per participant, additional information and ADRs were added to existing reports as follow-up. A total of 25 reports were sent through the CEM study. Three of these reports were nullified

afterwards as 1st questionnaire was completed after 2nd dose (exclusion criteria CEM study). Reports in EV through CEM are referenced/coded and can be traced back.

France

Did not forward reports to EV.

UK

The UK was not required to send reports to EV.

Croatia

ICSR were created per participant and per dose. Additional information or ADRs on the same dose were added as follow-up to the initial case. A total of 1027 ADRs were reported. These reports cannot be traced back to the CEM study in EV.

Italy

ICSR were created per participant new ADRs were added in existing reports as follow-up. These reports receive a specific code in order to trace back its origin from CEM and not from spontaneous reporting system.

Germany

Due to the large numbers of reports, priority was given to all serious ADRs, which were reported through ICSR.

Spain

All auto-reported ADRs during the recruitment period were reported to the NCA - Agencia Española de Medicamentos y Procedimientos Sanitarios - AEMPS - following their own procedures.[13]

8.6 Data harmonization

Due to limitations experienced using aggregated data, a common data model was developed after data collection was completed. By using a common data model, simplified record-based tables can be created which are more accessible for analyses.
To create the common data model, basic data frames with the following variables were created consisting of:

[13] https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/instrucciones-notificar-promotor-EPA-no-TAC2.pdf

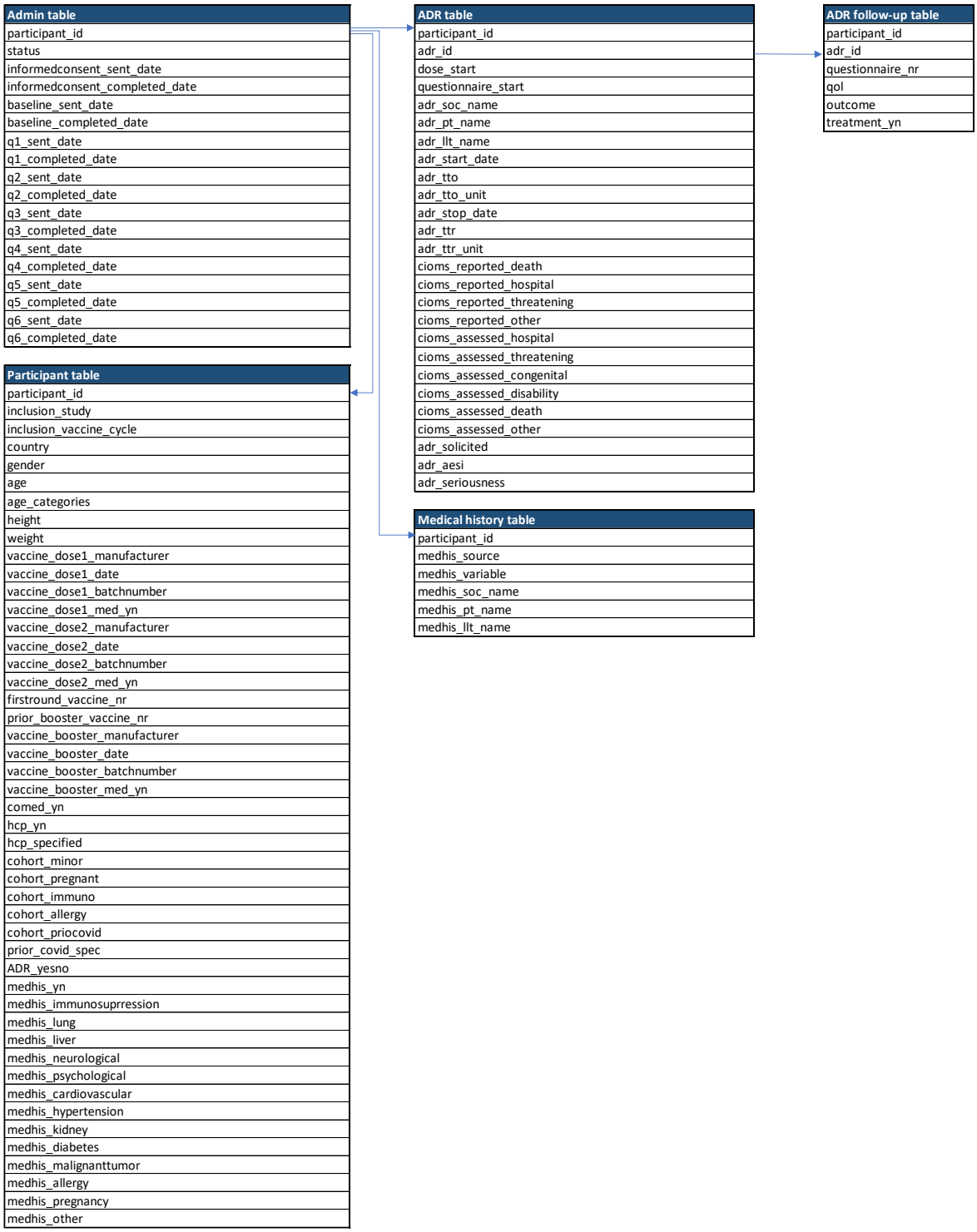

Figure 5. Common Data Model: data harmonization scheme of record-based data.

Record-based data from LIM and RO were transformed into standardized tables for aggregated data from all four data collection tools. These aggregated datasets were divided into tables with the following data: Risk factors, any ADR, any solicited ADR, any AESI, any serious ADR, list of ADR (solicited and unsolicited), list of AESI and list of serious.

Comorbidity data

risk_factors
Manufacturer
SOCName
PTName
N PT
Country
Date
Special_group
Cohortdata

(Solicited) Adverse Reactions by gender

any_AR_by_gender
Manufacturer
Country
Gender
Date
Vaccin No.
N Adverse Reactions
N*
Special_group
Cohortdata

(Solicited) Adverse Reactions by age category

any_AR_by_age_category
Manufacturer
Gender
Vaccin No.
Age category
N Adverse Reactions
N*
Country
Date
Special_group
Cohort_data

Serious Adverse reactions/Adverse Events of

any_SAR
Manufacturer
Gender
N*
N SAR
Vaccin No.
Country
Date
Special_group
Cohortdata

any_SoAR_by_gender
Manufacturer
Country
Gender
Date
Vaccin No.
N Adverse Reactions
N*
Special_group
Cohortdata

any_SoAR_by_age_category
Manufacturer
Gender
Age category
N Adverse Reactions
N*
Vaccin No.
Country
Date
Special_group
Cohort_data

any_AESI
Manufacturer
Gender
N*
N AESI
Vaccin No.
Country
Date
Special_group
Cohortdata

Figure 6. Common Data Model: data harmonization of risk factors, any ADR, any solicited ADR, any AESI, any serious ADR, list of ADR (solicited and unsolicited), list of AESI and list of serious.

Lists of (Serious) Adverse Reactions/AESI

AR_(PT)_per_seperate_soc
Manufacturer
Country
SOCName
PTName
Date
Vaccin No.
N Adverse Reactions
Special_group
Cohortdata

reported_SAR
Manufacturer
Vaccin No.
PTName
N SAR
Country
Date
Special_group
Cohortdata

reported_AESI
Manufacturer
Vaccin No.
PTName
N AESI
Country
Date
Special_group
Cohortdata

Figure 7. Common Data Model: data harmonization of serious adverse reactions and/or AESI.

Aggregated datasets from SafeVac 2.0 and OPeN were sent to Lareb for quality checks. They were combined with the aggregated LIM datasets and shared with the University Medical Center Utrecht (UMCU) via a secured mailing system. With the introduction of the RO application, UMCU was responsible for combining the datasets from received from Lareb with the RO dataset. UMCU was responsible for uploading the aggregated data into the dashboard and reporting any issues back to Lareb.

These data frames are filled with data from different data sources and one-by-one the variables were assessed on their definitions in the different data sources and, where necessary, aligned. Only LIM and RO were available in CDM format for the analyses of the report.

The datasets concerning 'any' are subject based. These should therefore be interpreted as the number of subjects experiencing at least one (solicited) ADR, at least one AESI or at least one serious ADR. The datasets concerning lists are presented on PT level. All datasets are stratified by gender, age group, vaccine brand and dose number for this report. Additional stratification was done for special cohorts, based on the following definitions:

- Minors (children/adolescents): all participants <18 years old
- Pregnant: as reported in medical history
- Immunosuppressed: as reported in medical history
- Allergy: as reported in medical history
- Prior COVID-19 infection: participants reporting a COVID-19 infection (confirmed by a test).

Vaccine brand and gender are reported by the participant in the questionnaires. Age is defined as the age at registration and calculated as the difference between date of birth and date of registration. The dose number is an indication of when the adverse reaction was reported: adverse reactions reported between the dose 1 and dose 2 dates are attributed to dose 1, and all adverse reactions reported after dose 2 are attributed to dose 2.

8.7 Analysis

To ensure regular near real time insights in the collected data a Microsoft Power BI dashboard was created by UMC Utrecht. This interactive dashboard was available to EMA online through a secure login and contained aggregated data.

8.7.1 Main analyses (Primary Objectives)

Analysis for the first study objective were descriptive in nature and included the number of recruited vaccinees, gender and age distribution, vaccine brands, and country.

Descriptive analysis (Primary Objective 1)

For the general population and each special cohort, a dedicated cumulative structured overview of numbers and frequency of all adverse reactions following the first vaccination cycle and the booster dose per vaccine was calculated, overall, and also stratified by vaccine brand, country, gender, and age group.

ADRs analysis (Primary Objective 2)

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 one follow-up questionnaire (in each cohort, for special populations) as the denominator. For special cohorts, incidence rates of suspected ADRs were compared with those in the general population 1:1 matched, using propensity score methodology.

In addition, for the participants with complete vaccination data, a heatmap of the percentage of participants who reported at least one ADR, one solicited ADR and one solicited ADR without injection site reactions were generated using the ggplot package in R; the data were stratified by age group and sex. The same strata were used to calculate the percentages of participants with a reported body temperature of 38.0 °C or higher. We also stratified for a medical history of prior COVID-19 infection.

With descriptive statistics, we provide an overview of the time to onset (TTO) and time to recovery (TTR) of reported reactions (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. We stratified for sex and age.

8.7.2 Secondary analysis (Secondary Objective)

We used a linear mixed-effects model (LMEM) to examine the occurrence of ADRs after receipt of the 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 LMEM fits a random intercept and random slopes for each unit of measurement for the different predictors which vary across the different measurement units. The random intercept/slopes suggest particular variance-covariance structures across different measurements within a unit.

Fixed-effect covariates included sex, age (as a continuous variable), and prior COVID-19 infection confirmed with a PCR test. We included 'country' as a random effects variable because of the variance in terms of vaccination rates and study enrollment both temporally and geographically.

8.8 Quality control

The study is conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008 – available at: https://www.pharmacoepi.org/resources/policies/guidelines-08027/) and according to the ENCePP code of conduct (European Medicines Agency 2018). All partners have experience in conducting pharmaco-epidemiological research and researchers trained in pharmacoepidemiology do the research. Workshops were organised for all project partners to harmonise MedDRA coding of ADRs as well as data analysis. Each country translated the English version of the frontend of the LIM/Research Online web app to the local language(s). Even though very similar questionnaires have previously been validated and used in the LIM/Research Online web app, questionnaires have been piloted before implementation to assess user functionality and user-friendliness (in different languages).

9 Results: Monitoring of the general (total) population recruited at first dose

9.1 Descriptive data for vaccinees recruited at first vaccination (Primary Objective 1)

A total of 642,290 participants were included at first vaccination in the general population, 99.6% of the recruited persons were recruited by countries who had protocols and infrastructures in place when mass vaccination rolled out in January/February 2021. Other countries started only in June/July 2021, as they needed to obtain approvals and systems needed to be implemented.

These are the participants who completed at least the baseline and the first follow-up questionnaire (Q1) (Table 3). Registrations for new participants were closed from August 2021 in the Netherlands, from March 2022 onwards in Belgium and from September 2022 onwards for France, Italy and the United Kingdom. Germany continued to include new participants until 18 September 2022.

Table 3. Number of recruited participants with at least one follow-up questionnaire and relevant dates

General population recruited at first dose					
Country & Organisation	**Number of inclusions**	**Data collection tool**	**Recruitment start date**	**Recruitment end date**	**Final data lock**
Germany - PEI	612.078 (95.3%)	SafeVac 2.0	27-12-2020	1-9-2022	30-11-2022
The Netherlands - Lareb	27647 (4.3%)	LIM	1-2-2021	1-8-2021	11-4-2023
Croatia - Halmed	368 (0.06%)	OPeN	15-2-2021	1-9-2022	1-9-2022
France – Bordeaux PharmacoEpi	1181 (0.2%)	LIM	14-6-2021	1-9-2022	11-4-2023
Italy – University of Verona	751 (0.1%)	LIM	9-6-2021	1-9-2022	11-4-2023
United Kingdom – DSRU	228 (0.04%)	LIM	23-6-2021	1-9-2022	11-4-2023
Belgium - FAMHP Federal Agency for Medicines and Health Products	38 (0.001%)	LIM	13-7-2021	1-3-2022	11-4-2023
Total	**642291**				

*Inclusion target ECVM

Table 4 shows the distribution of the first dose vaccine brands among the participants who were recruited upon first vaccination.

Table 4. Number of participants who submitted questionnaires following dose 1 and dose 2 stratified by vaccine brand upon first dose.

Vaccine brand	**Dose 1 (Number of participants, %)**	**Dose 2 (Number of participants, %)**
AstraZeneca	89509 (13.9)	55682 (11.9)
BioNtech/Pfizer	437939 (68.2)	330001 (70.8)
Janssen	29891 (4.7)	-
Moderna	84907 (13.2)	80307 (17.2)
Novavax	2 (0.0)	2 (0.0)
Unknown	42 (0.0)	18 (0.0)
Total	**642290**	**466010**

Due to loss to follow-up (not responding to subsequent questionnaires) the number of participants who received dose 1 is higher than those who received dose 2, only. The population represented by dose 2 is only a subset of the population represented in dose 1 data. Of the 642,290 participants included, only 43 participants did not report the vaccine they received and were not included in data stratified by vaccine brand.

The age distribution of all participants can be found in Table 5. The age distribution of participants included for dose 1 stratification is comparable to the age distribution of dose 2. Most participants were between 20 and 59 years of age.

Table 5. Vaccinees, as % of total vaccinees, by age category.

General population recruited at first vaccination		
Age category	**Dose 1 (n, %)**	**Dose 2 (n, %)**
0 - 19 years	20720 (3.2)	11935 (2.6)
20 - 29 years	134722 (21.0)	91747 (19.7)
30 - 39 years	152037 (23.7)	105702 (22.7)
40 - 49 years	121793 (19.0)	88581 (19.0)
50 - 59 years	115759 (18.0)	84774 (18.2)
60 - 69 years	62534 (9.7)	55807 (12.0)
70 - 79 years	25726 (4.0)	20962 (4.5)
80+ years	8999 (1.4)	6502 (1.4)
Total	**642290**	**466010**

Gender stratification per vaccine brand is reported in table 6. The majority of participants are female with the exception of Janssen, where males are more frequent.

Table 6. General population recruited at first dose by gender

	AstraZeneca		BioNTech/ Pfizer		Moderna		Novavax		Janssen	Unknown	
N subjects (%)	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 1**	**Dose 2**
Female	51133 (57.1)	29803 (53.5)	224301 (51.2)	171365 (51.9)	44421 (52.3)	42315 (52.7)	1 (50.0)	1 (50.0)	10576 (35.4)	21 (50.0)	8 (44.4)
Male	38316 (42.8)	25840 (46.4)	212798 (48.6)	158119 (47.9)	40328 (47.5)	37858 (47.1)	1 (50.0)	1 (50.0)	19236 (64.4)	21 (50.0)	10 (55.6)
Other	60 (0.1)	39 (0.1)	840 (0.2)	517 (0.2)	158 (0.2)	134 (0.2)	0 (0.0)	0 (0.0)	79 (0.3)	0 (0.0)	0 (0.0)
Total	89509	55682	437939	330001	84907	80307	2	2	29891	42	18

Table 7. General population recruited at first dose by age category

	AstraZeneca		BioNTech/ Pfizer		Moderna		Novavax		Janssen	Unknown	
N subjects (%)	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 1**	**Dose 2**
0–19 years	1385 (1.5)	410 (0.7)	16567 (3.8)	10199 (3.1)	1815 (2.1)	1322 (1.6)			947 (3.2)	6 (14.3)	4 (22.2)
20-29 years	16154 (18.0)	6197 (11.1)	91519 (20.9)	68779 (20.8)	19583 (23.1)	16770 (20.9)			7461 (25.0)	5 (11.9)	1 (5.6)
30-39 years	18536 (20.7)	8413 (15.1)	101344 (23.1)	75797 (23.0)	24187 (28.5)	21489 (26.8)			7966 (26.7)	4 (9.5)	3 (16.7)
40-49 years	16153 (18.0)	8716 (15.7)	81674 (18.6)	62852 (19.0)	17945 (21.1)	17009 (21.2)			6011 (20.1)	10 (23.8)	4 (22.2)
50-59 years	16908 (18.9)	10478 (18.8)	77763 (17.8)	59642 (18.1)	15228 (17.9)	14652 (18.2)	1 (50.0	1 (50.0)	5857 (19.6)	2 (4.8)	1 (5.6)
60-69 years	16862 (18.8)	17327 (31.1)	39673 (9.1)	31231 (9.5)	4504 (5.3)	7246 (9.0)	1 (50.0	1 (50.0)	1488 (5.0)	6 (14.3)	2 (11.1)
70-79 years	3380 (3.8)	4011 (7.2)	20781 (4.7)	15234 (4.6)	1441 (1.7)	1714 (2.1)			120 (0.4)	4 (9.5)	3 16.7)
80+ years	131 (0.1)	130 (0.2)	8618 (2.0)	6267 (1.9)	204 (0.2)	105 (0.1)			41 (0.1)	5 (11.9)	
Total	89509	55682	437939	330001	84907	80307	2	2	29891	42	18

Table 8 shows the most frequently reported co-morbidities per vaccine brand for the current dataset, excluding Germany. Immune system, vascular and respiratory disorders are in the top three of most vaccine brands, although in different order.

Table 8. Top three baseline co-morbidity as reported by participants recruited at first vaccination per vaccine brand

AstraZeneca (n, %)	BioNTechPfizer (n, %)	Janssen (n, %)	Moderna (n, %)	Novavax (n, %)
Immune system disorders (2776, 31.3)	Vascular disorders (3863, 25.5)	Immune system disorders (831, 33.3)	Immune system disorders (1502, 41.3)	Immune system disorders (1, 50.0)
Vascular disorders (987, 11.1)	Immune system disorders (3836, 25.3)	Vascular disorders (164, 6.6)	Respiratory, thoracic and mediastinal disorders (408, 11.2)	Cardiac disorders (1, 50.0)
Respiratory, thoracic and mediastinal disorders (862, 9.7)	Cardiac disorders (2676, 17.6)	Psychiatric disorders (134, 5.4)	Vascular disorders (261, 7.2)	

* excluding Germany; AstraZeneca N = 8870, BioNTech/Pfizer N = 15169; Janssen N = 2492; Moderna N = 3637; Novavax N = 2.

9.2 Adverse reactions in persons recruited at first vaccination (Primary Objective 2)

The most commonly reported solicited local adverse reaction, across all vaccine brands, was injection site pain (I.s pain in Table 9). The solicited systemic adverse reactions varied somewhat across vaccine brands, but these are crude data and may be confounded by age. The solicited local and systemic adverse reactions are summarised in Table 9. The most frequently reported systemic solicited reaction was fatigue and headache for local reactions injection site pain and swelling.

9.2.1 Solicited reactions in total population

Table 9. Local and systemic solicited adverse reactions by vaccine brand reported after dose 1 in the total population

	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna
Local solicited adverse reaction (MedDRA PT) (n (%))				
I.s. erythema	932 (1.0)	1771 (0.4)	122 (0.4)	1750 (2.1)
I.s. haematoma	490 (0.5)	395 (0.1)	117 (0.4)	223 (0.3)
I.s. induration	119 (0.1)	223 (0.1)	15 (0.1)	175 (0.2)
I.s. inflammation	1861 (2.1)	839 (0.2)	290 (1.0)	808 (1.0)
I.s. pain	45994 (51.4)	255062 (58.2)	11807 (39.5)	58663 (69.1)
I.s. pruritus	477 (0.5)	1394 (0.3)	68 (0.2)	1038 (1.2)
I.s. reaction	25 (0.0)	174 (0.0)	4 (0.0)	101 (0.1)
I.s. swelling	11433 (12.8)	60658 (13.9)	2115 (7.1)	21519 (25.3)
I.s. warmth	1184 (1.3)	991 (0.2)	167 (0.6)	818 (1.0)
Systemic solicited adverse reactions (MedDRA PT) (n (%))				
Arthralgia	20163 (22.5)	48029 (11.0)	3774 (12.6)	13501 (15.9)
Body temperature increased	1063 (1.2)	2305 (0.5)	270 (0.9)	788 (0.9)
Chills	31703 (35.4)	44147 (10.1)	5371 (18.0)	17146 (20.2)
Diarrhoea*	3624 (4.0)	19875 (4.5)	906 (3.0)	4195 (4.9)

	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna
Dizziness*	17050 (19.0)	60249 (13.8)	3725 (12.5)	14480 (17.1)
Fatigue	47332 (52.9)	186957 (42.7)	12084 (40.4)	44035 (51.9)
Headache	46750 (52.2)	148346 (33.9)	11187 (37.4)	37448 (44.1)
Hyperpyrexia	82 (0.1)	1 (0.0)	13 (0.0)	2 (0.0)
Malaise	31831 (35.6)	86995 (19.9)	6667 (22.3)	24030 (28.3)
Myalgia	29792 (33.3)	90414 (20.6)	6249 (20.9)	24523 (28.9)
Nausea	13311 (14.9)	34790 (7.9)	2454 (8.2)	10147 (12.0)
Pyrexia	28259 (31.6)	42692 (9.7)	5397 (18.1)	18253 (21.5)
Total subjects	**89509**	**437939**	**29891**	**84907**

"I.s." is used as an abbreviation for Injection site.
* Solicited in SafeVac 2.0 app

9.2.2 Serious ADRs in total population

Of the 642,290 participants who had received a first dose of a COVID-19 vaccine, 3,142 (0.49%, 95%CI: 0.47-0.51%)) reported at least one serious adverse reaction after receiving the first dose. Table 10 summarises the rates by vaccine brand and dose. As Germany was only able to provide the seriousness as reported by the participant, rather than the seriousness as coded by the (medical) assessors, this is likely an overreporting of the adverse reactions reported as serious and we therefore stratify.

Table 10. Number of participants reporting at least one serious adverse reaction after the first or second dose.

Serious adverse reactions (n (% with serious ADR)) in total population recruited with first vaccination					
	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Novavax
Dose 1	621 (0.69)	1678 (0.38)	553 (1.78)	290 (0.34)	0 (0.0)
LIM & Croatia	21 (0.24)	22 (0.15)	4 (0.16)	6 (0.16)	
Germany	600 (0.74)	1656 (0.39)	549 (2.00)	284 (0.35)	
Dose 2	97 (0.17)	1301 (0.39)		299 (0.37)	0 (0.0)
LIM & Croatia	4 (0.07)	17 (0.13)		5 (0.18)	
Germany	93 (0.19)	1284 (0.40)		294 (0.38)	

Dose1 LIM&Croatia: AstraZeneca N=8870, BioNTech/Pfizer N=15169, Janssen N=2492, Moderna N=3637, Novavax N=2
Dose1 Germany: AstraZeneca N=80639, BioNTech/Pfizer N=422770, Janssen N=27399, Moderna N=81270
Dose2 LIM&Croatia: AstraZeneca N=5560, BioNTech/Pfizer N=12233, Moderna N=2717, Novavax N=2
Dose2 Germany: AstraZeneca N=50076, BioNTech/Pfizer N=317768, Moderna N=77590

Table 11 indicates the type of reported serious ADRs following the first or second dose by COVID-19 vaccine. The German data was omitted in table 9 because seriousness was self-reported and not assessed as by assessors as in other countries.

Table 11 List of reported serious Adverse Reactions following the first or second dose by COVID-19 vaccine for LIM countries and Croatia.

COVID-19 vaccine manufacturer	Reported Serious ADR	Dose 1	Dose 2
AstraZeneca (Dose1 N= 8870; D2 N=5606)	Abdominal discomfort	1	
	Abortion missed	1	
	Abortion spontaneous		1
	Acute myocardial infarction	1	1

COVID-19 vaccine manufacturer	Reported Serious ADR	Dose 1	Dose 2
	Angina pectoris	1	
	Arrhythmia	1	
	Asthma	1	
	Atrial fibrillation	1	
	Breast cancer		1
	Cerebral infarction	1	
	Diarrhoea	1	
	Dyspnoea	3	
	Epilepsy	1	
	Gastric ulcer	1	
	Headache	1	
	Hyperpyrexia	1	
	Malaise	2	
	Muscle spasms	1	
	Myalgia	1	
	Myocardial infarction		1
	Nausea	1	
	Other medically important conditions	1	
	Pulmonary embolism	2	
	Pulmonary pain	1	
	Pyrexia	2	
	Rash pruritic	1	
	Respiratory arrest	1	
	Retinal detachment	1	
	Vitreous floaters	1	
BioNTech/Pfizer (Dose1 N=15 169; Dose 2 N=12233)	Abortion spontaneous	2	
	Atrioventricular block complete	1	
	Blood loss anaemia		1
	Cerebrovascular accident	1	
	Chills	1	
	Colitis	1	
	Condition aggravated	1	1
	Depression	1	
	Diarrhoea	1	
	Dysentery	1	
	Dyspnoea	2	1
	Epistaxis	1	
	Eye haemorrhage		1
	Fall		1
	Fatigue	2	
	Haematochezia		1
	Headache	2	
	Herpes zoster		1
	Hyperpyrexia	1	1
	Hypersensitivity	2	
	Hypertension		1
	Hypothermia		1
	Internal haemorrhage		1
	Lacunar infarction		1
	Malaise		1
	Muscle spasms	1	
	Myocardial infarction	2	1
	Nausea	2	

COVID-19 vaccine manufacturer	Reported Serious ADR	Dose 1	Dose 2
	Other medically important condition	2	1
	Oxygen saturation decreased		1
	Paraesthesia	1	
	Pneumonia	1	
	Pruritus	1	
	Pulmonary embolism		1
	Pyrexia	1	1
	Rash	1	
	Respiratory distress	1	
	Swelling face	1	
	Syncope		1
	Tachycardia		1
	Tenosynovitis		1
	Tinnitus		1
	Transient global amnesia	1	
	Transient ischaemic attack	2	1
	Urticaria	1	
	Vomiting	1	
Janssen (Dose1 N=2492)	Abortion spontaneous	1	
	Anaphylactic reaction	1	
	Chills	1	
	Dyspnoea	1	
	Hypoaesthesia	1	
	Limb discomfort	1	
	Malaise	1	
	Other medically important condition	2	
	Pallor	1	
	Palpitations	1	
	Paraesthesia oral	1	
	Restlessness	1	
	Tremor	1	
Moderna (Dose1 N=3637)	Abortion spontaneous	1	2
	Appendicitis	1	
	Arthritis		1
	Body temperature increased		1
	Cerebral infarction	1	
	Dizziness	1	
	Gait disturbance	1	
	Hyperpyrexia	1	
	Hypotension	1	
	Loss of consciousness	1	
	Malaise	1	
	Pulmonary embolism		1
	Vision blurred	1	

9.2.3 AESIs in total population

Of the 642,290 participants who had received a first dose of any COVID-19 vaccine, 2001 (0.31%, 95%CI 0.30-0.33%) subjects reported experiencing at least one AESI between their first and second dose of the vaccine. Table 12 shows the number of participants reporting at least one AESI following the first or second dose by vaccine brand.

Table 12. Number of participants reporting at least one AESI after their first or second dose of the vaccine.

AESI (n (% with AESI))					
Vaccine dose	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Novavax
Dose 1	148 (0.17)	1678 (0.38)	30 (0.10)	145 (0.17)	0 (0.0)
LIM & Croatia	29 (0.33)	22 (0.14)	8 (0.32)	3 (0.08)	
Germany	119 (0.15)	1656 (0.39)	22 (0.08)	142 (0.17)	
Dose 2	53 (0.10)	1311 (0.40)		158 (0.20)	0 (0.0)
LIM & Croatia	32 (0.58)	27 (0.22)		10 (0.37)	
Germany	21 (0.04)	1284 (0.40)		148 (0.19)	

Dose1 LIM&Croatia: AstraZeneca N=8870, BioNTech/Pfizer N=15169, Janssen N=2492, Moderna N=3637, Novavax N=2
Dose1 Germany: AstraZeneca N=80639, BioNTech/Pfizer N=422770, Janssen N=27399, Moderna N=81270
Dose2 LIM&Croatia: AstraZeneca N=5560, BioNTech/Pfizer N=12233, Moderna N=2717, Novavax N=2
Dose2 Germany: AstraZeneca N=50076, BioNTech/Pfizer N=317768, Moderna N=77590

Table 13 lists all reported AESIs following the first and second dose. Only subjects from the Netherlands and France reported these AESIs. German data is not included in this table. Several cases of thromboembolic events were reported following AstraZeneca vaccine, and myocarditis/pericarditis following Pfizer vaccine.

Table 13. List of reported AESI's following the first or second dose by COVID-19 vaccine for LIM countries and Croatia.

COVID-19 vaccine manufacturer	**Reported AESI**	**Dose 1**	**Dose 2**
AstraZeneca (Dose1 N=8870; Dose2 N=5606)	Acute myocardial infarction	1	1
	Arrhythmia	5	4
	COVID-19	6	23
	Epilepsy	2	1
	Facial paralysis	1	
	Facial paresis	1	
	Hypersensitivity	8	2
	Hypersomnia		1
	Myocardial infarction		1
	Product administration error		1
	Pulmonary embolism	2	
	Respiratory arrest	1	
	Thrombosis	1	
	Vasculitis	1	
BioNTech/Pfizer (Dose1 N=15169; Dose2 N=12233)	Anaphylactoid reaction	1	
	Arrhythmia	2	9
	Atrioventricular block complete	1	
	Cerebrovascular accident	1	
	COVID-19	6	6
	Deep vein thrombosis		2
	Epilepsy		1
	Hypersensitivity	6	5
	Myocardial infarction	2	1
	Myocarditis	1	
	Pericarditis	1	1
	Petit mal epilepsy	1	
	Pulmonary embolism		1
	Respiratory distress	1	

COVID-19 vaccine manufacturer	Reported AESI	Dose 1	Dose 2
	Seizure		1
Janssen (Dose1 N=2492)	Anaphylactic reaction	1	
	COVID-19	5	
	Generalised tonic-clonic seizure	1	
	Product administration error	1	
Moderna (Dose1 N=3637; Dose2 N=2717)	Arrhythmia		3
	COVID-19		1
	Deep vein thrombosis		1
	Epilepsy	1	1
	Facial paralysis		1
	Hypersensitivity	1	1
	Hypersomnia	1	1
	Platelet count decreased		1
	Pulmonary embolism		1

9.3 Heatmaps of ADRs in total population recruited at first vaccination (excluding Germany and Croatia)

For advanced analyses, Germany and Croatia were excluded because they delivered aggregated data only. This is a subset of the total population in all LIM App using countries and comprises 29,844 subjects who were included at first vaccination.

Figure 8 shows a heatmap of the percentages of participants who reported any suspected adverse reaction for the 1st and 2nd doses across vaccine brands and age groups and stratified by sex. This shows that reactions were more frequent after first than second dose of AstraZeneca, across all strata and after second dose for Moderna. Older people report less ADRs, across all vaccines and females report more frequently than men.

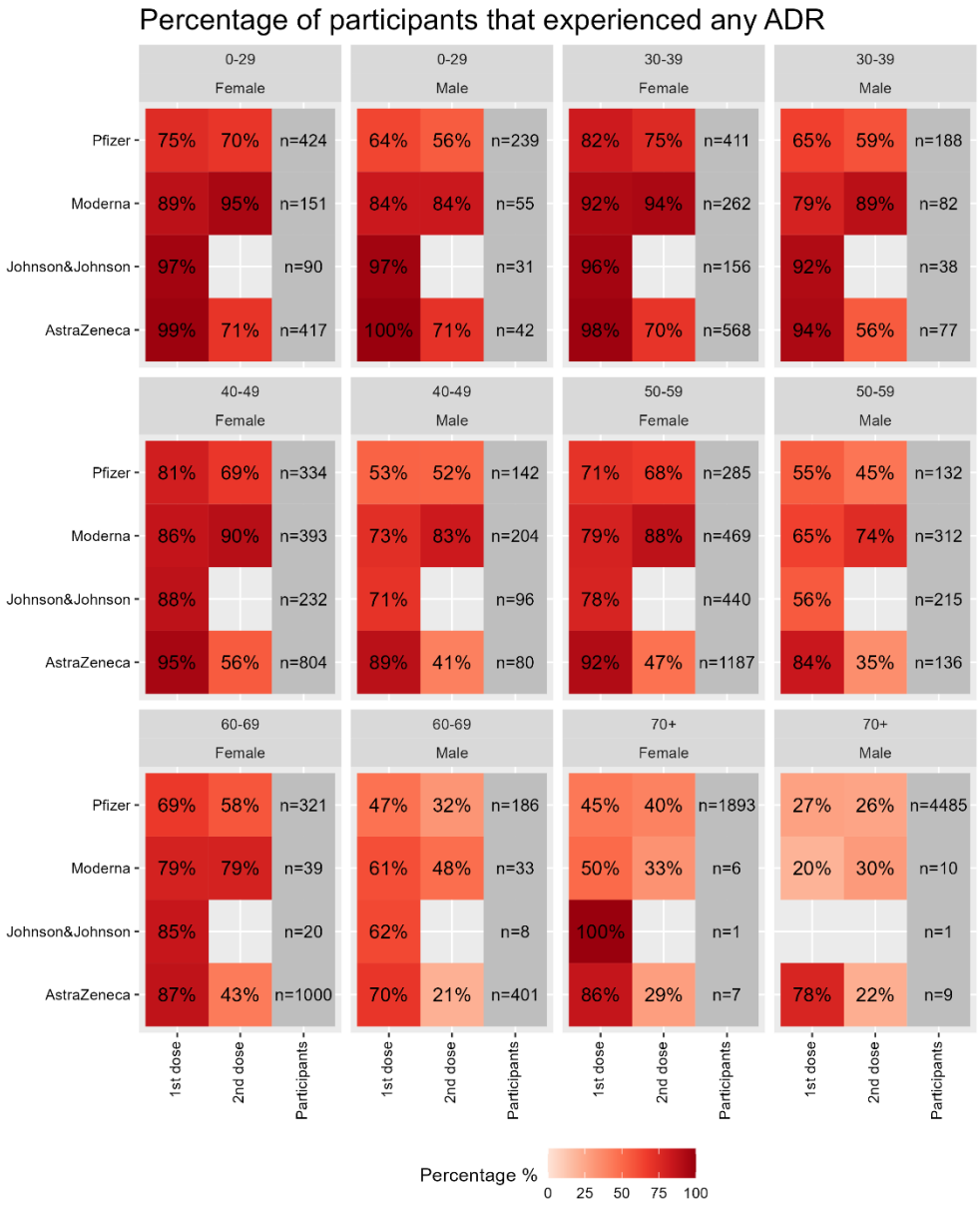

Figure 8. Heatmap for any ADR in total population recruited at first vaccination excluding Germany and Croatia

Figure 9 focuses on the solicited ADR as described above. A similar pattern is observed by excluding the unsolicited the unsolicited adverse reactions: older participants report less adverse reactions than younger age groups. Participants report more adverse reactions after the first dose across all vaccine brands except Moderna, where most participants report more reactions after the second dose. This pattern is not as outspoken in the age categories above 60 years.

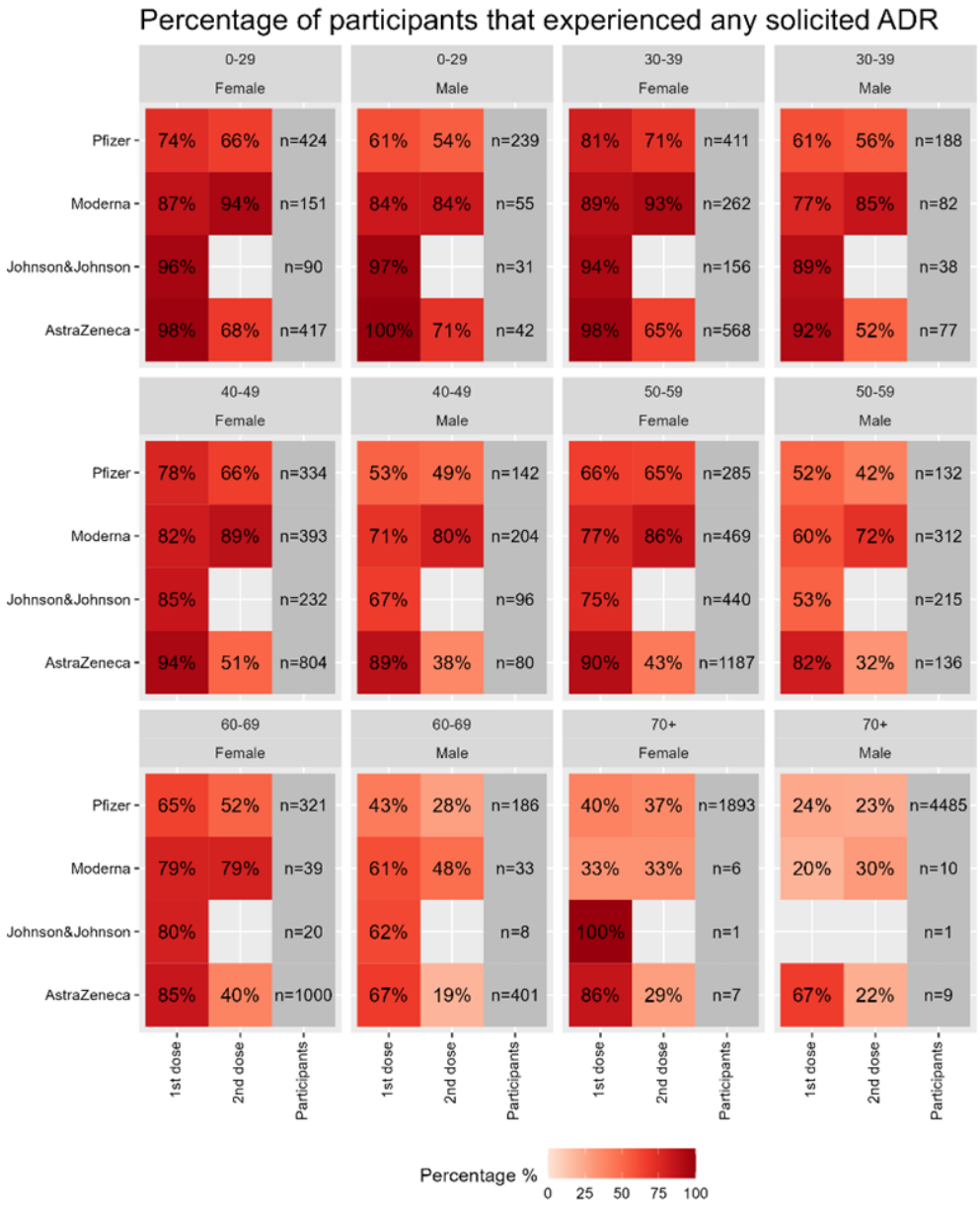

Figure 9. Heatmap for any solicited ADR in total population recruited at first vaccination excluding Germany and Croatia

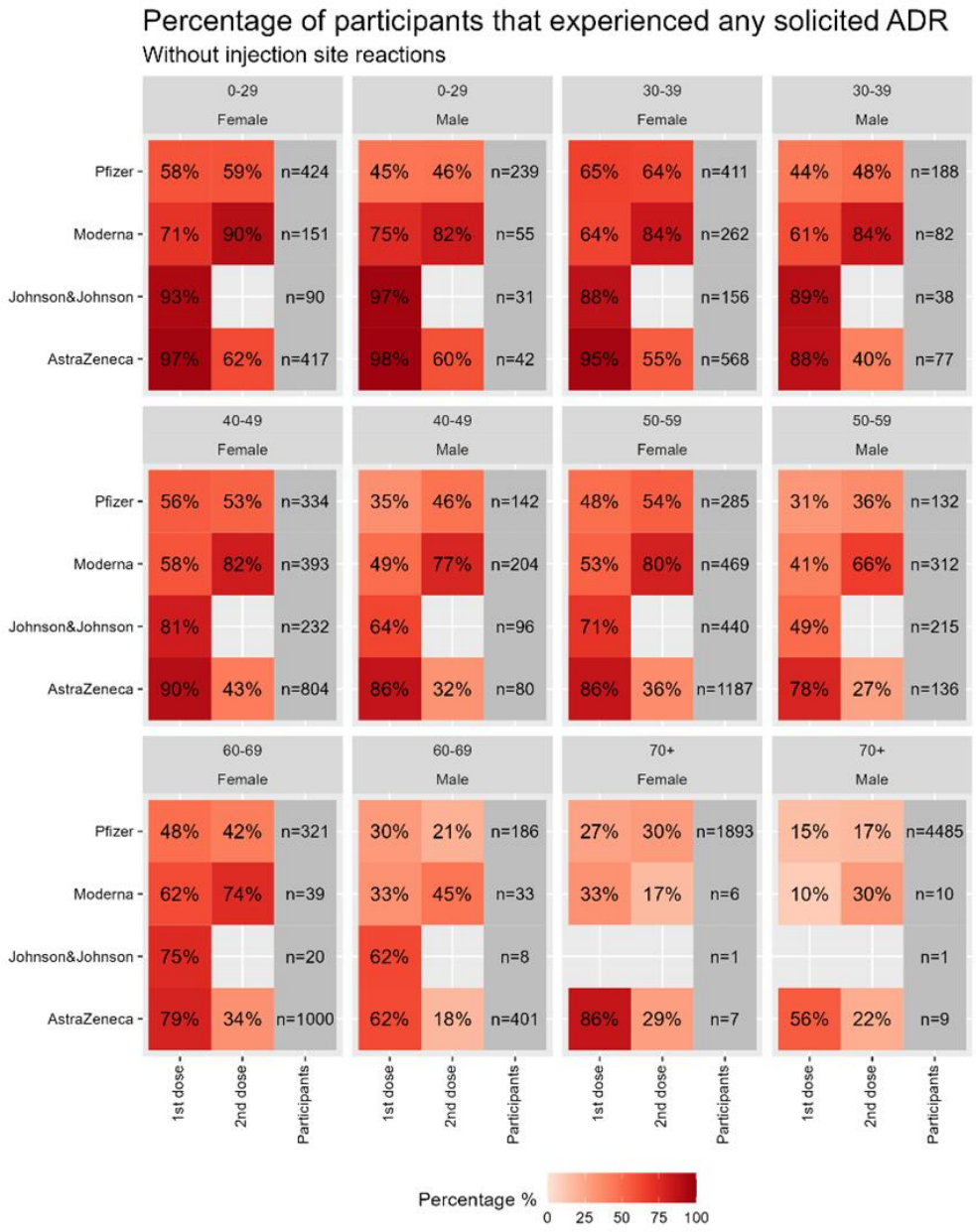

Figure 10. heatmap for any ADR in total population recruited at first vaccination without injection site reactions and excluding Germany and Croatia

Figure 10 shows a similar heatmap focusing on persons who reported any solicited adverse reaction, but for this heatmap injection site reactions were not included. Again we see a high percentage of solicited reactions following dose 1 of the AstraZeneca as compared to dose 2. For Pfizer vaccine there is not much difference between dose 1 and 2, whereas for Moderna, frequency is highest for dose 2.

Figure 11 shows a similar heatmap specifically for a body temperature increase above 38 ˚C. For AstraZeneca, reported fever rates are higher after dose 1 than 2, both in males and females, and mostly in younger persons.

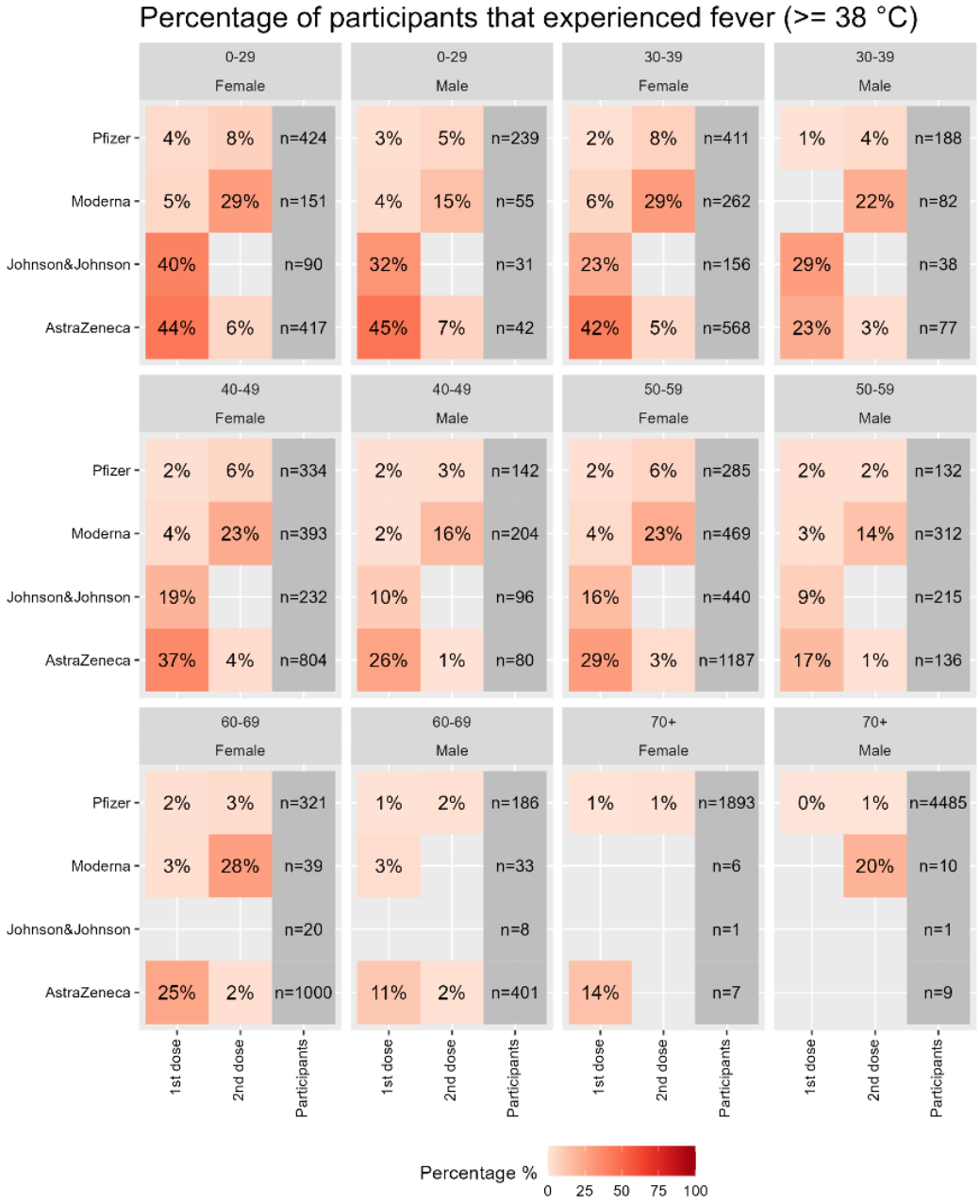

Figure 11. Heatmap of fever for total population recruited at first vaccination excluding Germany and Croatia

Figure 12 shows the percentage of participants who reported at least one adverse reaction stratified by COVID-19 history prior to vaccination. Participants who had COVID-19 (confirmed with a positive test) experienced at least one adverse reaction more often after the first and second dose, compared to participants who did not have a prior COVID-19 infection, with the exception of participants who received the Janssen vaccine. This pattern was observed in both men and women and for all vaccine

brands. For the Pfizer, Moderna and AstraZeneca vaccines, this was also the case after the second dose.

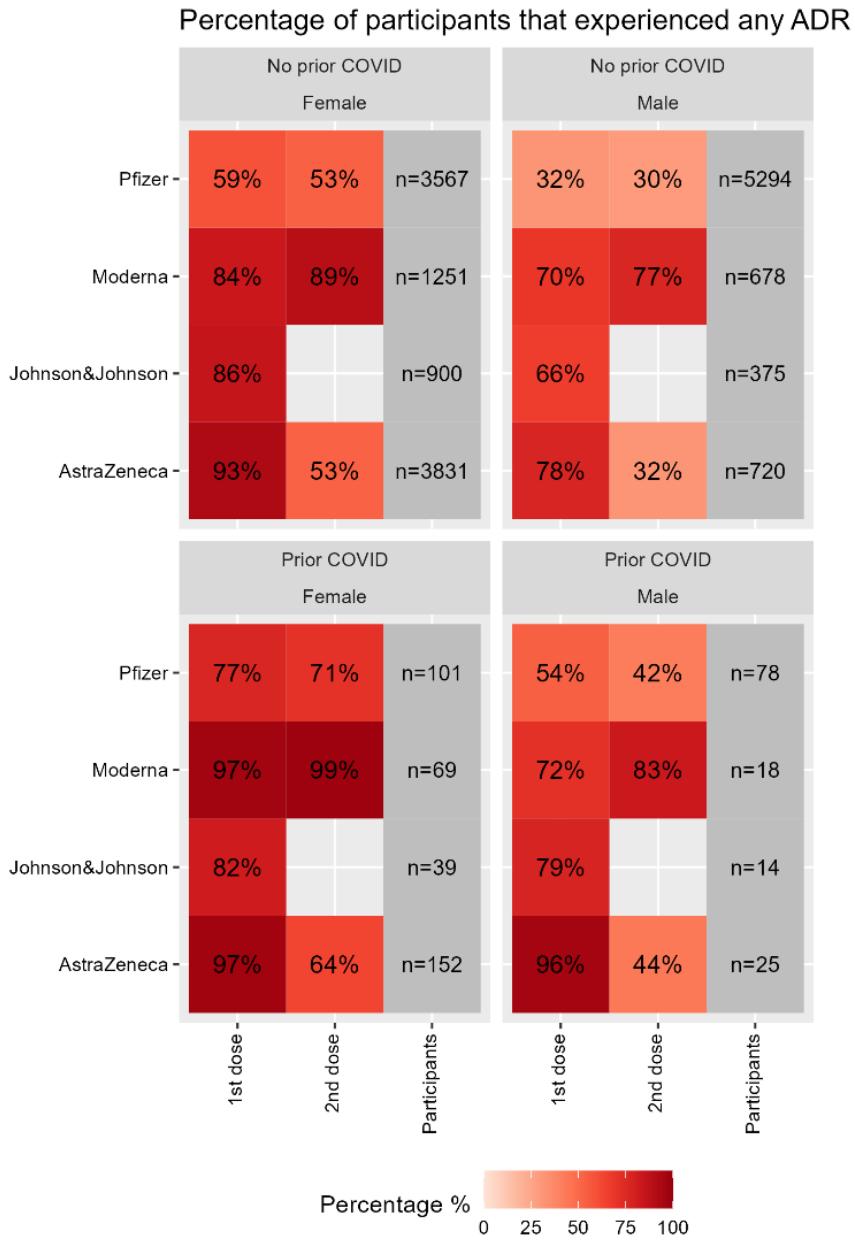

Figure 12. Heatmap of any suspected ADR for total population recruited at first vaccination with or without history of COVID-19 excluding Germany and Croatia

9.3.1 TTO Tables

We compared the Time to Onset (TTO) and Time to recover (TTR) of 'any ADR', local reactions and the solicited adverse reactions between males and females (median TTO or TTR and 1st and 3rd interquartile range in hours). Descriptive data stratified for sex and dose are given in tables 14a and 14b.

TTO was generally within 1 day for solicited ADRs, except for injection site reactions which occurred within the hour. The TTR was generally within 3 days, although there are some exceptions such as the recovery for injection site reactions for the first dose of the Janssen vaccine and the second dose of the Moderna vaccine. Overall, little difference existed between the TTO of the adverse reactions reported by males and females. For both sexes, shorter TTOs were observed for local reactions (often occurring within 24 hours) compared to systemic reactions such as pyrexia, nausea and chills where the median latency times frequently exceeded a day.

Table 14a. TTO and TTR for reported ADRs stratified for brand and sex after dose 1 (unit is hours)

		1st dose			
		Time to onset		Time to recovery	
ADR group	Vaccine brand	Female	Male	Female	Male
Any ADR	All vaccines	24 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
	AstraZeneca	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	Johnson&Johnson	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	Moderna	24 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
	Pfizer	24 (0-48)	24 (0-48)	48 (24-96)	48 (24-72)
Arthralgia	All vaccines	24 (0-24)	24 (8.5-24)	48 (24-72)	48 (24-72)
	AstraZeneca	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-72)
	Johnson&Johnson	24 (0-24)	24 (0-24)	48 (24-48)	48 (24-72)
	Moderna	24 (2-24)	24 (0-24)	48 (24-72)	48 (24-78)
	Pfizer	24 (6-48)	24 (24-72)	72 (48-144)	48 (24-90)
Chills	All vaccines	0 (0-24)	24 (0-24)	24 (24-48)	24 (12-24)
	AstraZeneca	0 (0-24)	12 (0-24)	24 (24-24)	24 (24-24)
	Johnson&Johnson	0 (0-24)	0 (0-24)	24 (6.25-24)	24 (3-24)
	Moderna	24 (0-24)	24 (19.5-24)	24 (24-48)	24 (24-24)
	Pfizer	24 (0-24)	24 (0-48)	24 (24-48)	24 (5.5-48)
Fatigue	All vaccines	24 (0-24)	24 (12-24)	72 (40-144)	48 (24-96)
	AstraZeneca	24 (0-24)	24 (0-24)	72 (48-144)	48 (24-96)
	Johnson&Johnson	24 (0-24)	24 (5-24)	48 (24-120)	48 (24-72)
	Moderna	24 (0-24)	24 (7.25-24)	48 (24-96)	48 (24-72)
	Pfizer	24 (0-48)	24 (24-48)	72 (24-120)	48 (24-96)
Headache	All vaccines	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	AstraZeneca	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	Johnson&Johnson	24 (0-24)	24 (0-24)	30 (24-48)	24 (24-48)
	Moderna	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	Pfizer	24 (0-24)	24 (1.5-48)	48 (24-96)	24 (24-72)
Injection site reactions	All vaccines	0 (0-0)	0 (0-24)	120 (48-240)	48 (48-96)
	AstraZeneca	0 (0-0)	0 (0-6)	120 (72-330)	24 (24-36)
	Johnson&Johnson	0 (0-732)	0 (0-13)	120 (72-120)	96 (48-144)
	Moderna	0 (0-0)	24 (24-24)	120 (60-240)	72 (72-72)
	Pfizer	0 (0-0)	1 (0-24)	72 (24-240)	48 (48-96)
Malaise	All vaccines	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-72)
	AstraZeneca	24 (0-24)	24 (0-24)	48 (24-72)	42 (24-63)
	Johnson&Johnson	8 (0-24)	19.5 (0-24)	48 (24-72)	24 (24-48)
	Moderna	24 (0-24)	24 (7-24)	48 (24-72)	24 (24-48)
	Pfizer	24 (0-48)	24 (4-48)	48 (24-96)	48 (24-72)
Myalgia	All vaccines	24 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
	AstraZeneca	24 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
	Johnson&Johnson	24 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
	Moderna	5 (0-24)	24 (0-24)	48 (48-72)	72 (48-72)
	Pfizer	2 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
Nausea	All vaccines	24 (0-24)	24 (0-24)	24 (24-48)	24 (12-48)
	AstraZeneca	24 (0-24)	24 (0-24)	24 (24-48)	24 (24-24)
	Johnson&Johnson	24 (0-24)	13 (0-24)	24 (24-48)	24 (0.5-24)
	Moderna	24 (0-24)	24 (0-24)	48 (24-48)	24 (24-48)
	Pfizer	24 (0-48)	24 (0-48)	48 (24-72)	24 (12-72)
Pyrexia	All vaccines	12 (0-24)	24 (0-24)	24 (24-48)	24 (24-48)
	AstraZeneca	12 (0-24)	24 (0-24)	24 (24-48)	24 (24-48)
	Johnson&Johnson	0 (0-24)	8 (0-24)	24 (24-48)	24 (24-24)
	Moderna	24 (0-24)	24 (24-24)	24 (24-48)	24 (24-36)
	Pfizer	24 (2.25-24)	24 (24-48)	36 (24-72)	24 (24-48)

Table 14b. TTO and TTR for reported ADRs stratified for brand and sex after dose 2 (unit is hours)

		2nd dose			
		Time to onset		Time to recovery	
ADR group	Vaccine brand	Female	Male	Female	Male
Any ADR	All vaccines	24 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
	AstraZeneca	12 (0-24)	24 (0-24)	48 (24-72)	24 (24-66)
	Johnson&Johnson				
	Moderna	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	Pfizer	24 (0-24)	24 (0-48)	48 (24-72)	48 (24-72)
Arthralgia	All vaccines	24 (0-24)	24 (9-24)	48 (24-72)	48 (24-72)
	AstraZeneca	0 (0-24)	12 (1.5-24)	48 (24-72)	24 (24-48)
	Johnson&Johnson				
	Moderna	24 (0-24)	24 (6-24)	48 (24-72)	24 (24-48)
	Pfizer	24 (3.75-24)	24 (24-60)	48 (24-96)	48 (24-120)
Chills	All vaccines	8 (0-24)	24 (0-24)	24 (24-24)	24 (24-48)
	AstraZeneca	0 (0-24)	12 (0-24)	24 (24-24)	24 (4-48)
	Johnson&Johnson				
	Moderna	9 (0-24)	24 (0-24)	24 (24-24)	24 (24-24)
	Pfizer	24 (0-24)	24 (11-24)	24 (24-48)	24 (24-48)
Fatigue	All vaccines	24 (0-24)	24 (12-24)	48 (24-96)	48 (24-96)
	AstraZeneca	24 (0-24)	24 (0-24)	48 (24-96)	36 (24-72)
	Johnson&Johnson				
	Moderna	24 (0-24)	24 (6-24)	48 (24-96)	48 (24-72)
	Pfizer	24 (0-24)	24 (24-48)	48 (24-120)	48 (24-96)
Headache	All vaccines	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	AstraZeneca	1 (0-24)	24 (0-24)	24 (24-48)	24 (24-48)
	Johnson&Johnson				
	Moderna	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	Pfizer	24 (0-24)	24 (2.25-24)	48 (24-72)	24 (24-48)
Injection site reactions	All vaccines	0 (0-24)	0 (0-0)	132 (48-144)	24 (24-48)
	AstraZeneca	0 (0-24)	12 (6-18)	120 (48-264)	840 (432-1248)
	Johnson&Johnson				
	Moderna	0 (0-0)	24 (24-24)	144 (48-144)	96 (96-96)
	Pfizer	24 (0-48)	0 (0-0)	72 (24-186)	24 (24-48)
Malaise	All vaccines	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	AstraZeneca	2 (0-24)	18 (0-24)	48 (24-72)	24 (24-48)
	Johnson&Johnson				
	Moderna	24 (0-24)	24 (0-24)	48 (24-72)	24 (24-48)
	Pfizer	24 (0-24)	24 (3.75-24)	48 (24-72)	48 (24-72)
Myalgia	All vaccines	10 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
	AstraZeneca	2 (0-24)	8 (0-24)	48 (24-72)	48 (24-72)
	Johnson&Johnson				
	Moderna	12 (0-24)	24 (0-24)	48 (24-72)	48 (24-48)
	Pfizer	10 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)
Nausea	All vaccines	24 (0-24)	24 (5-24)	24 (24-48)	24 (18-48)
	AstraZeneca	8.5 (0-24)	24 (16-48)	24 (24-48)	24 (24-72)
	Johnson&Johnson				
	Moderna	24 (0-24)	24 (3.25-24)	24 (24-48)	24 (24-48)
	Pfizer	24 (0.25-24)	24 (9-48)	24 (24-48)	24 (0-48)
Pyrexia	All vaccines	24 (0-24)	24 (0-24)	24 (24-48)	24 (24-48)
	AstraZeneca	0 (0-24)	0 (0-24)	24 (24-48)	24 (24-24)
	Johnson&Johnson				
	Moderna	24 (0-24)	24 (0-24)	24 (24-48)	24 (24-48)
	Pfizer	24 (0-24)	24 (12.25-24)	24 (24-48)	24 (24-48)

Tables 15a and 15b are similar, only stratified for age in three categories instead of sex.

***Table 15a**. TTO and TTR for reported ADRs after dose 1 stratified for brand and age (unit is hours)*

		1st dose					
		Time to onset			Time to recovery		
ADR group	Vaccine brand	0-17	18-64	65+	0-17	18-64	65+
Any ADR	All vaccines	6 (0-24)	24 (0-24)	24 (0-48)	48 (24-72)	48 (24-72)	48 (24-96)
	AstraZeneca		24 (0-24)	24 (0-24)		48 (24-72)	48 (24-72)
	Johnson&Johnson		24 (0-24)	888 (564-1032)		36 (24-72)	432 (330-588)
	Moderna	24 (24-24)	24 (0-24)	24 (24-24)	48 (24-90)	48 (24-72)	48 (24-72)
	Pfizer	6 (0-24)	24 (0-24)	24 (0-48)	48 (24-72)	48 (24-96)	48 (24-96)
Arthralgia	All vaccines	36 (30-42)	24 (0-24)	24 (24-72)	48 (48-48)	48 (24-72)	72 (48-168)
	AstraZeneca		24 (0-24)	24 (24-24)		48 (24-72)	48 (24-126)
	Johnson&Johnson		24 (0-24)			48 (24-72)	
	Moderna		24 (0-24)	24 (24-24)		48 (24-72)	48 (30-138)
	Pfizer	36 (30-42)	24 (3.25-24)	24 (24-96)	48 (48-48)	48 (24-90)	72 (48-168)
Chills	All vaccines	6 (0-12)	0 (0-24)	24 (0-24)	24 (12-24)	24 (24-24)	24 (24-48)
	AstraZeneca		0 (0-24)	24 (0-24)		24 (24-24)	24 (24-48)
	Johnson&Johnson		0 (0-24)			24 (5-24)	
	Moderna		24 (0-24)	0 (0-12)		24 (24-48)	24 (24-36)
	Pfizer	6 (0-12)	24 (0-24)	24 (3-48)	24 (12-24)	24 (24-48)	24 (24-48)
Fatigue	All vaccines	3 (0-15)	24 (0-24)	24 (24-48)	24 (24-54)	72 (24-120)	48 (24-120)
	AstraZeneca		24 (0-24)	24 (24-24)		72 (48-144)	48 (24-120)
	Johnson&Johnson		24 (0-24)	744 (744-744)		48 (24-120)	1056 (1056-1056)
	Moderna		24 (0-24)	24 (24-24)		48 (24-96)	48 (24-60)
	Pfizer	3 (0-15)	24 (0-24)	24 (24-48)	24 (24-54)	48 (24-120)	48 (24-120)
Headache	All vaccines	7 (0-24)	24 (0-24)	24 (0-48)	15 (8-48)	48 (24-72)	48 (24-72)
	AstraZeneca		24 (0-24)	24 (0-24)		48 (24-72)	48 (24-48)
	Johnson&Johnson		24 (0-24)	1032 (1032-1032)		24 (24-48)	432 (432-432)
	Moderna	24 (24-24)	24 (0-24)	24 (24-78)	24 (24-24)	24 (24-48)	60 (42-150)
	Pfizer	6.5 (0-24)	24 (0-24)	24 (0-66)	13.5 (7.5-48)	48 (24-72)	48 (24-72)
Injection site reactions	All vaccines		0 (0-0)	0 (0-24)		120 (48-240)	48 (24-72)
	AstraZeneca		0 (0-0)	24 (24-24)		108 (66-318)	48 (36-60)
	Johnson&Johnson		0 (0-13)			108 (48-126)	
	Moderna		0 (0-0)			120 (66-240)	
	Pfizer		0 (0-0)	0 (0-24)		240 (48-324)	48 (24-84)
Malaise	All vaccines	6 (0-14)	24 (0-24)	24 (7-48)	48 (48-72)	48 (24-72)	48 (24-72)
	AstraZeneca		24 (0-24)	24 (0-24)		48 (24-72)	48 (24-72)
	Johnson&Johnson		10 (0-24)	528 (276-780)		48 (24-72)	228 (126-330)
	Moderna		24 (0-24)	24 (24-24)		48 (24-72)	24 (24-48)
	Pfizer	6 (0-14)	24 (0-24)	24 (24-72)	48 (48-72)	48 (24-96)	48 (24-96)
Myalgia	All vaccines	3 (0-24)	24 (0-24)	24 (0-24)	48 (48-72)	48 (24-72)	48 (24-72)
	AstraZeneca		24 (0-24)	24 (0-24)		48 (24-72)	48 (24-96)
	Johnson&Johnson		24 (0-24)			48 (24-72)	
	Moderna	12 (6-18)	12 (0-24)	24 (24-24)	84 (78-90)	48 (48-72)	72 (48-96)
	Pfizer	3 (0-20.5)	0.5 (0-24)	24 (0-24)	48 (48-72)	48 (24-72)	48 (24-72)
Nausea	All vaccines	12 (0-72)	24 (0-24)	24 (24-48)	48 (21-60)	24 (24-48)	24 (24-72)
	AstraZeneca		24 (0-24)	24 (24-24)		24 (24-48)	24 (24-48)
	Johnson&Johnson		24 (0-24)			24 (12-48)	
	Moderna		24 (0-24)	36 (30-42)		48 (24-48)	48 (48-48)
	Pfizer	12 (0-72)	24 (0-24)	24 (24-96)	48 (21-60)	48 (12-72)	48 (24-72)
Pyrexia	All vaccines	11 (0-24)	12 (0-24)	24 (11-24)	24 (24-42)	24 (24-48)	24 (24-48)
	AstraZeneca		12 (0-24)	24 (0-24)		24 (24-48)	24 (24-48)
	Johnson&Johnson		2 (0-24)			24 (24-48)	
	Moderna		24 (0-24)	24 (24-24)		24 (24-48)	24 (24-24)
	Pfizer	11 (0-24)	24 (0-24)	24 (24-78)	24 (24-42)	36 (24-48)	24 (24-72)

***Table 15b**. TTO and TTR for reported ADRs after dose 2 stratified for brand and age (unit is hours)*

		2nd dose					
		Time to onset			Time to recovery		
ADR group	Vaccine brand	0-17	18-64	65+	0-17	18-64	65+
Any ADR	All vaccines	0 (0-24)	24 (0-24)	24 (0-48)	24 (24-72)	48 (24-72)	48 (24-96)
	AstraZeneca		12 (0-24)	24 (0-24)		48 (24-72)	48 (24-96)
	Johnson&Johnson						
	Moderna	24 (24-24)	24 (0-24)	24 (0-24)	24 (24-48)	48 (24-48)	48 (24-78)
	Pfizer	0 (0-15.25)	24 (0-24)	24 (0-48)	30 (24-72)	48 (24-72)	48 (24-96)
Arthralgia	All vaccines	3 (0-9.5)	24 (0-24)	24 (24-48)	48 (48-156)	48 (24-72)	48 (24-120)
	AstraZeneca		7 (0-24)	6 (0-24)		48 (24-72)	48 (30-48)
	Johnson&Johnson						
	Moderna		24 (0-24)	24 (24-24)		48 (24-48)	48 (48-48)
	Pfizer	3 (0-9.5)	24 (7.5-24)	24 (24-48)	48 (48-156)	48 (24-72)	72 (24-120)
Chills	All vaccines	6 (0-24)	10 (0-24)	24 (0-24)	24 (12-24)	24 (24-24)	24 (24-48)
	AstraZeneca		0 (0-24)	24 (24-24)		24 (24-24)	24 (24-24)
	Johnson&Johnson						
	Moderna		16 (0-24)	24 (6-24)		24 (24-24)	24 (24-42)
	Pfizer	6 (0-24)	24 (0-24)	24 (0-24)	24 (12-24)	24 (24-48)	24 (24-48)
Fatigue	All vaccines	0 (0-4)	24 (0-24)	24 (24-48)	48 (24-72)	48 (24-96)	72 (24-126)
	AstraZeneca		24 (0-24)	24 (24-24)		48 (24-96)	72 (48-132)
	Johnson&Johnson						
	Moderna	24 (24-24)	24 (0-24)	24 (0-24)	48 (48-48)	48 (24-96)	60 (48-90)
	Pfizer	0 (0-4)	24 (0-24)	24 (24-48)	48 (24-72)	48 (24-96)	72 (24-144)
Headache	All vaccines	0 (0-2)	24 (0-24)	24 (0-24)	24 (24-48)	24 (24-48)	48 (24-72)
	AstraZeneca		3 (0-24)	24 (0-24)		24 (24-48)	24 (24-60)
	Johnson&Johnson						
	Moderna		24 (0-24)	0 (0-24)		48 (24-48)	48 (24-72)
	Pfizer	0 (0-2)	24 (0-24)	24 (0-24)	24 (24-48)	36 (24-48)	48 (24-72)
Injection site reactions	All vaccines		0 (0-12)	0 (0-30)		144 (48-144)	48 (24-144)
	AstraZeneca		0 (0-24)			120 (48-960)	
	Johnson&Johnson						
	Moderna		0 (0-0)			144 (48-144)	
	Pfizer		0 (0-6)	0 (0-30)		96 (42-150)	48 (24-144)
Malaise	All vaccines	1 (0-11.25)	24 (0-24)	24 (0-24)	48 (24-48)	48 (24-72)	48 (24-72)
	AstraZeneca		3 (0-24)	24 (0-24)		48 (24-72)	36 (24-96)
	Johnson&Johnson						
	Moderna		24 (0-24)	24 (0-24)		48 (24-72)	48 (24-84)
	Pfizer	1 (0-11.25)	24 (0-24)	24 (0-24)	48 (24-48)	48 (24-72)	48 (24-72)
Myalgia	All vaccines	0 (0-4)	10 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)	48 (24-72)
	AstraZeneca		2 (0-24)	24 (0-24)		48 (24-72)	48 (48-150)
	Johnson&Johnson						
	Moderna		24 (0-24)	24 (0-24)		48 (24-72)	84 (30-120)
	Pfizer	0 (0-4)	6 (0-24)	24 (0-24)	48 (24-72)	48 (24-72)	48 (24-72)
Nausea	All vaccines	18.5 (3.25-24)	24 (0-24)	24 (0-48)	17 (5.5-24)	24 (24-48)	24 (0-48)
	AstraZeneca		11 (0-24)	24 (12-36)		24 (24-48)	24 (24-24)
	Johnson&Johnson						
	Moderna		24 (0-24)	24 (24-24)		24 (24-48)	24 (18-24)
	Pfizer	18.5 (3.25-24)	24 (3.5-24)	24 (0-48)	17 (5.5-24)	24 (24-48)	24 (0-72)
Pyrexia	All vaccines	6 (0-24)	24 (0-24)	24 (24-48)	24 (19.75-48)	24 (24-48)	24 (24-48)
	AstraZeneca		0 (0-24)	24 (24-60)		24 (24-48)	24 (24-42)
	Johnson&Johnson						
	Moderna	24 (24-24)	24 (0-24)	0 (0-12)	24 (24-24)	24 (24-48)	48 (48-48)
	Pfizer	6 (0-19.5)	24 (0-24)	24 (24-48)	24 (15.5-48)	24 (24-48)	24 (24-48)

9.4 Linear mixed effects models (Secondary Objective – excluding Croatia and Germany)

A subset of the general population receiving a first and/or second dose, comprising of 29844 participants and excluding data from Germany and Croatia, was analysed using a linear mixed-effects models. For this general population, with increasing age, there is a lower contribution to the occurrence of any ADRs, any solicited ADRs, or fever. The male sex as a predictor has a lower contribution than the female sex. These co-variated have a similar contribution for both doses one and two. A prior SARS-CoV-2 infection as a predictor, gives an odds ratios (OR) <0.5 for any ADR and any solicited ADR for dose 1 and for dose 2 an OR of approximately 1.6. For fever, prior COVID-19 infection is a positive predictor for both dose 1 and 2 although the OR is higher for dose 2 (OR 2.4 vs 1.7).

Table 16: The estimated fixed effects of co-variates are presented as odds ratios (ORs) with 95% confidence intervals for experiencing at least one ADR, at least one solicited ADR or experiencing fever.

General population			
Outcome	**Predictor**	**OR**	**95% CI**
Any ADR			
Dose1	Age	0,96	0,96; 0,96
	Male	0,44	0,41; 0,48
	Prior SARS-CoV-2 infection	0,45	0,39; 0,52
Dose2	Age	0,97	0,97; 0,97
	Male	0,49	0,45; 0,53
	Prior SARS-CoV-2 infection	1,58	1,38; 1,81
Any sollicited ADR			
Dose1	Age	0,96	0,96; 0,96
	Male	0,45	0,42; 0,49
	Prior SARS-CoV-2 infection	0,49	0,43; 0,57
Dose 2	Age	0,97	0,97; 0,97
	Male	0,5	0,46; 0,53
	Prior SARS-CoV-2 infection	1,61	1,40; 1,85
Fever			
Dose1	Age	0,97	0,97; 0,98
	Male	0,5	0,43; 0,58
	Prior SARS-CoV-2 infection	1,71	1,46; 2,02
Dose 2	Age	0,97	0,97 0,98
	Male	0,52	0,44; 0,62
	Prior SARS-CoV-2 infection	2,43	2,00; 3,00

10 Results: Monitoring of the special target groups receiving a first (and possibly second) dose of any COVID-19 vaccine

10.1 Participants

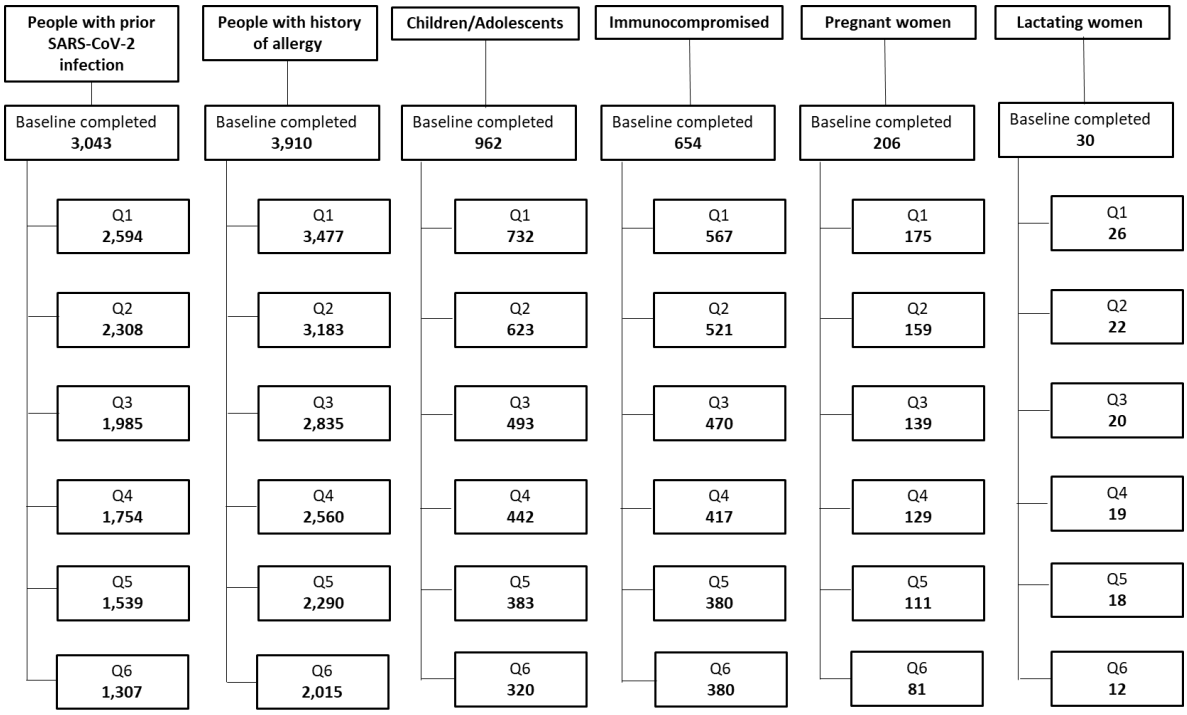

Figure 13. *Flow-chart including the number of questionnaires completed, by special cohorts.*

Data from special cohorts collected in Belgium, France, Italy, the Netherlands, the United Kingdom, Romania, Slovakia, Spain, Portugal, and Switzerland were retrieved from the LIM and RO combined dataset using a CDM (latest dataset update April 17, 2023). Croatia did not use the CDM and therefore the data were analyzed in a separate dedicated section. Table 17 summarises the total number of participants belonging to the special cohorts of interest. Please note that a single participant may belong to more special target groups, and therefore, the table should be read across the columns. In addition, even if some countries are not intentionally enrolling participants belonging to some cohorts, it may still happen that a participant belonging to a targeted group for that country has characteristics that are specific for other groups too.

Table 17. *Number of participants belonging to the special target groups who filled in the baseline questionnaire and, at least, the first follow-up questionnaire by country.*

	Special target group						
	Prior SARS-CoV-2 infection	**Children/ Adolescents (5-17 y.o.)**	**People with history of allergy**	**Immuno-compromised**	**Pregnant women**	**Lactating women**	**Start date**
Belgium	4 (0.2)	-	7 (0.2)	1 (0.2)	-	-	
France	157 (6.1)	187 (25.5)	192 (5.5)	12 (2.1)	44 (25.1)	-	14/06/2021
Italy	123 (4.7)	251 (34.3)	186 (5.3)	20 (3.5)	37 (21.1)	17 (65.4)	09/06/2021
The Netherland	2,242 (86.4)	46 (6.3)	3,045 (87.6)	527 (92.9)	88 (50.3)	-	01/02/2021
Portugal	4 (0.2)	4 (0.5)	-	-	-	2 (7.7)	05/02/2022
UK	38 (1.5)	92 (12.6)	26 (0.7)	6 (1.1)	3 (1.7)	-	23/06/2021
Romania	10 (0.4)	68 (9.3)	6 (0.2)	1 (0.2)	-	1 (3.8)	01/12/2021
Slovakia	8 (0.3)	65 (8.9)	12 (0.3)	-	-	-	11/01/2022
Spain	6 (0.2)	19 (2.6)	2 (0.1)	-	-	-	13/12/2021
Switzerland	2 (0.1)	-	1 (0.0)	-	3 (1.7)	6 (23.1)	19/01/2022
Total	**2,594 (100)**	**732 (100)**	**3,477 (100)**	**567 (100)**	**175 (100)**	**26 (100)**	

Legend: *a single participant may belong to different special cohorts.* ***Abbreviations****: NA= not applicable; y.o.= years old.*

The number of vaccinees recruited reflects the status of the vaccination campaign in the participating countries, where most eligible people had already received at least the first dose of vaccine at the time of the study start. In all countries except Switzerland, which recruited pregnant and lactating women only, the largest number of vaccinees belong to the special cohorts of people with a history of allergy and with prior SARS-CoV-2 infection.

10.2 Descriptive data (Primary Objective 1)

Table 18 shows the distribution of included vaccinees with the female/male ratio by special cohort, COVID-19 vaccine manufacturer and country.

BioNTech/Pfizer vaccine was the most frequently received across all special cohorts, with the exception of people with a previous SARS-CoV-2 infection who mostly received the AstraZeneca vaccine. BioNTech/Pfizer and Moderna are the only two vaccines recommended in children and adolescents, as well as in pregnant and lactating women; however, BioNTech/Pfizer vaccine was the most widely received vaccine in these special cohorts. In the Netherlands, pregnant women also received the AstraZeneca and Janssen vaccines.

Overall, most of participants were females, with the highest female/male (F/M) ratio observed in the group of people with prior SARS-CoV-2 infection (3.0), followed by the group of people with a history of allergy (2.8). The F/M ratio for the Dutch participants seems to be generally higher than the one observed for the other countries, always bearing in mind that most of the vaccinees were recruited in the Netherlands. The lowest F/M ratio has been observed in the children/adolescents' group (1.1) when information from all countries is pooled together. Overall, the median age ranged from 33.0 to 45.0 y.o. across different cohorts, excluded the children/adolescents cohort (5-17 y.o.) that was 10.0 y.o.

Table 18. Number of participants belonging to the special target groups by COVID-19 vaccine manufacturer and country.

		Special target group					
		People with Prior SARS-CoV-2 infection	**Children/ Adolescents (5-17 y.o.)**	**People with history of allergy**	**Immuno-compromised**	**Pregnant women**	**Lactating women**
Belgium							
AstraZeneca	n (%)	-	-	1 (14.3)	-	-	-
	F/M ratio	-	-	0.0	-	-	-
	median age (y.o.)	-	-	67.0	-	-	-
Janssen	n (%)	1 (25.0)	-	1 (14.3)	-	-	-
	F/M ratio	0.0	-	-	-	-	-
	median age (y.o.)	45.0	-	42.0	-	-	-
BioNTech/Pfizer	n (%)	3 (75.0)	-	5 (71.4)	1 (100)	-	-
	F/M ratio	2.0	-	1.5	-	-	-
	median age (y.o.)	24.0	-	30.0	27.0	-	-
All vaccines	**n (%)**	**4 (100)**	**-**	**7 (100)**	**1 (100)**	**-**	**-**
	F/M ratio	**1.0**	**-**	**1.3**	**-**	**-**	**-**
	median age (y.o.)	**26.5**	**-**	**36.0**	**27.0**	**-**	**-**
France							
BioNTech/ Pfizer	n (%)	151 (96.2)	185 (98.9)	177 (93.2)	12 (100)	42 (95.5)	-
	F/M ratio	2.2	1.2	2.2	11	-	-
	median age (y.o.)	35.0	14.0	34.0	44.0	32.5	-
Janssen	n (%)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	-
	F/M ratio	0.0	-	-	-	-	-
	median age (y.o.)	64	-	-	-	-	-
Moderna	n (%)	4 (2.5)	2 (1.1)	13 (6.8)	0 (0)	2 (4.5)	-
	F/M ratio	3.0	1.0	3.3	-	-	-
	median age (y.o.)	39.5	15.5	39	-	28.5	-
All vaccines	**n (%)**	**157 (100)**	**187 (100)**	**192 (100)**	**12 (100)**	**44 (100)**	**-**
	F/M ratio	**2.2**	**1.2**	**2.2**	**11.0**	**-**	**-**
	median age (y.o.)	**37.0**	**14.0**	**35.0**	**44.0**	**31.5**	**-**
Italy							
AstraZeneca	n (%)	0 (0.0)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)
	F/M ratio	-	-	-	-	-	-
	median age (y.o.)	-	-	64.0	-	-	-
BioNTech/ Pfizer	n (%)	96 (78.0)	238 (94.8)	157 (84.4)	17 (85.0)	34 (91.9)	14 (82.4)
	F/M ratio	1.2	1.0	1.8	3.3	-	-
	median age (y.o.)	31.5	11.0	30.0	33.0	35.0	37.0
Janssen	n (%)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	F/M ratio	0	-	-	-	-	-
	median age (y.o.)	-	-	-	-	-	-
Moderna	n (%)	24 (19.5)	13 (5.2)	26 (14.0)	2 (10.0)	3 (8.1)	2 (11.8)

		Special target group					
		People with Prior SARS-CoV-2 infection	**Children/ Adolescents (5-17 y.o.)**	**People with history of allergy**	**Immuno-compromised**	**Pregnant women**	**Lactating women**
	F/M ratio	1.5	0.6	2.3	-	-	-
	median age (y.o.)	35.0	13.0	36.0	24.5	38.0	36.5
Novavax	n (%)	1 (0.8)	0 (0)	1 (0.5)	1 (5.0)	0 (0)	1 (5.9)
	F/M ratio	-	-	-	-	-	-
	median age (y.o.)	56.0	-	38.0	58.0	-	38.0
All vaccines	**n (%)**	**123 (100)**	**251 (100)**	**186 (100)**	**20 (100)**	**37 (100)**	**17 (100)**
	F/M ratio	**1.3**	**1**	**1.9**	**4**	**-**	**-**
	median age (y.o.)	**34.0**	**11.0**	**32.0**	**32.5**	**35.0**	**37.0**
The Netherlands							
AstraZeneca	n (%)	963 (43.0)	3 (6.5)	1,086 (35.7)	165 (31.3)	2 (2.3)	-
	F/M ratio	7.2	0.5	8.5	6.3	-	-
	median age (y.o.)	43.0	17.0	44.0	51.0	-	-
BioNTech/ Pfizer	n (%)	600 (26.9)	43 (93.5)	1,113 (36.6)	241 (45.7)	38 (43.2)	-
	F/M ratio	1.6	2.6	1.6	1.1	-	-
	median age (y.o.)	51.0	16.0	50.0	74.0	32.5	-
Janssen	n (%)	268 (12.0)	0 (0)	343 (11.3)	21 (4.0)	2 (2.3)	-
	F/M ratio	3.9	-	2.9	25.0	-	-
	median age (y.o.)	45.0	-	41.0	47.0	31.5	-
Moderna	n (%)	406 (18.1)	0 (0)	496 (16.3)	98 (18.6)	48 (54.5)	-
	F/M ratio	2.7	-	2.6	2.6	-	-
	median age (y.o.)	44.0	-	43.0	50.0	33.0	-
All vaccines	**n (%)**	**2,242 (100)**	**46 (100)**	**3,045 (100)**	**527 (100)**	**88 (100)**	**-**
	F/M ratio	**3.4**	**2.3**	**3.0**	**2.1**	**-**	**-**
	median age (y.o.)	**49.0**	**16.0**	**51.0**	**56.0**	**33.0**	**-**
United Kingdom							
AstraZeneca	n (%)	-	-	1 (3.8)	-	-	-
	F/M ratio	-	-	-	-	-	-
	median age (y.o.)	-	-	37.0	-	-	-
BioNTech/ Pfizer	n (%)	32 (84.2)	86 (93.5)	23 (88.5)	6 (100)	3 (100)	-
	F/M ratio	1	1	1.1	0.8	-	-
	median age (y.o.)	15.0	14.0	17.0	62.0	36.0	-
Moderna	n (%)	4 (10.5)	0 (0)	2 (7.7)	0 (0)	0 (0)	-
	F/M ratio	3	-	-	-	-	-
	median age (y.o.)	28.0	-	30.5	-	-	-
All vaccines	**n (%)**	**38 (100)**	**92 (100)**	**26 (100)**	**6 (100)**	**3 (100)**	**-**
	F/M ratio	**1.0**	**1.0**	**1.4**	**0.8**	**-**	**-**
	median age (y.o.)	**15.0**	**14.0**	**22.5**	**62.0**	**36.0**	**-**
Portugal							
BioNTech/ Pfizer	n (%)	3 (75.0)	4 (100)	-	-	-	2 (100)
	F/M ratio	0	1.0	-	-	-	-

		Special target group					
		People with Prior SARS-CoV-2 infection	Children/ Adolescents (5-17 y.o.)	People with history of allergy	Immuno-compromised	Pregnant women	Lactating women
	median age (y.o.)	24.0	7.0	-	-	-	28.5
Moderna	n (%)	1 (25.0)	0 (0)	-	-	-	0 (0)
	F/M ratio	0	-	-	-	-	-
	median age (y.o.)	61.0	-	-	-	-	-
All vaccines	**n (%)**	**4 (100)**	**4 (100)**	**-**	**-**	**-**	**2 (100)**
	F/M ratio	**0.0**	**1.0**	**-**	**-**	**-**	**-**
	median age (y.o.)	**28.0**	**7.0**	**-**	**-**	**-**	**28.5**
Romania							
BioNTech/ Pfizer	n (%)	9 (90.0)	68 (100)	5 (83.3)	1 (100)	-	1 (100)
	F/M ratio	0.9	0.8	1.5	0.0	-	-
	median age (y.o.)	11.0	9.0	11.0	8.0	-	30.0
Janssen	n (%)	1 (10.0)	-	1 (16.7)	-	-	-
	F/M ratio	1.0	-	1.0	-	-	-
	median age (y.o.)	25.0	-	25.0	-	-	
All vaccines	**n (%)**	**10 (100)**	**68 (100)**	**6 (100)**	**1 (100)**	**-**	**1 (100)**
	F/M ratio	**1.0**	**0.8**	**2.0**	**0.0**	**-**	**-**
	median age (y.o.)	**14.5**	**9.0**	**18.0**	**8.0**		**30.0**
Slovakia							
BioNTech/ Pfizer	n (%)	8 (100)	65 (100)	12 (100)	-	-	-
	F/M ratio	1.7	1.0	1.4	-	-	-
	median age (y.o.)	8.5	8.0	7.5	-	-	-
All vaccines	**n (%)**	**8 (100)**	**65 (100)**	**12 (100)**	**-**	**-**	**-**
	F/M ratio	**1.7**	**1.0**	**1.4**	**-**	**-**	**-**
	median age (y.o.)	**8.5**	**8.0**	**7.5**	**-**	**-**	**-**
Spain							
BioNTech/ Pfizer	n (%)	4 (66.7)	17 (89.5)	1 (50.0)	-	-	-
	F/M ratio	1.0	1.4	0.0	-	-	-
	median age (y.o.)	9.0	10.0	12.0	-	-	-
Moderna	n (%)	0 (0)	0 (0)	1 (50.0)	-	-	-
	F/M ratio	-	-	-	-	-	-
	median age (y.o.)	-	-	37.0	-	-	-
All vaccines	**n (%)**	**6 (100)**	**19 (100)**	**2 (100)**	**-**	**-**	**-**
	F/M ratio	**1.0**	**1.4**	**1.0**	**-**	**-**	**-**
	median age (y.o.)	**8.0**	**8.0**	**24.5**	**-**	**-**	**-**
Switzerland							
BioNTech/ Pfizer	n (%)	1 (50.0)	-	1 (100)	-	3 (100)	4 (66.7)
	F/M ratio	-	-	-	-	-	-
	median age (y.o.)	32.0	-	38.0	-	30.0	34.5
Moderna	n (%)	1 (50.0)	-	0 (0)	-	0 (0)	2 (33.3)
	F/M ratio	-	-	-	-	-	-

		Special target group					
		People with Prior SARS-CoV-2 infection	Children/ Adolescents (5-17 y.o.)	People with history of allergy	Immuno-compromised	Pregnant women	Lactating women
	median age (y.o.)	33.0	-	-	-	-	31.5
All vaccines	**n (%)**	**2 (100)**	**-**	**1 (100)**	**-**	**3 (100)**	**6 (100)**
	F/M ratio	**-**	**-**	**-**	**-**	**-**	**-**
	median age (y.o.)	**32.5**	**-**	**38.0**	**-**	**30.0**	**33.0**
All countries							
AstraZeneca	n (%)	963 (37.1)	3 (0.4)	1,089 (31.3)	165 (29.1)	2 (1.1)	0 (0)
	F/M ratio	7.2	0.5	8.5	6.3	-	-
	median age (y.o.)	43.0	17.0	44.0	51	-	-
BioNTech/ Pfizer	n (%)	907 (35.0)	706 (96.4)	1,494 (43.0)	278 (49.0)	120 (68.6)	21 (80.8)
	F/M ratio	1.6	1.1	1.7	1.2	-	-
	median age (y.o.)	42.0	11.0	42.0	73.0	33.0	35.0
Janssen	n (%)	272 (10.5)	0 (0)	345 (9.9)	21 (3.72	2 (1.1)	0 (0)
	F/M ratio	3.8	-	2.9	25.0	-	-
	median age (y.o.)	45.0	-	41.0	47.0	31.5	-
Moderna	n (%)	440 (17.0)	15 (2.0)	538 (15.5)	100 (17.6)	53 (30.3)	4 (15.4)
	F/M ratio	2.6	0.7	2.6	2.6	-	-
	median age (y.o.)	44.0	14.0	42.0	50.0	33.0	34.5
Novavax	n (%)	1 (0.0)	0 (0.0)	1 (0.0)	1 (0.2)	0 (0)	1 (3.8)
	F/M ratio	-	-	-	-	-	1
	median age (y.o.)	56.0	-	38.0	58.0	-	38.0
All vaccines	**n (%)**	**2,594 (100)**	**732 (100)**	**3,477 (100)**	**567 (100)**	**175 (100)**	**26 (100)**
	F/M ratio	**3.0**	**1.1**	**2.8**	**2.3**	**-**	**-**
	median age (y.o.)	**45.0**	**10.0**	**47.0**	**55.0**	**33.0**	**35.0**

*****Including also vaccines with unknown brand.

Legend: *i)* percentages are calculated based on the total number of all vaccines administered to participants belonging to a specific special target group, by country. *ii)* A F/M ratio > 1 indicates that the number of female participants is higher than the number of male participants. **Abbreviations:** F=female; M=male; NA=not applicable; n=number; y.o.=years old.

The demographic characteristics of the vaccinees who filled in the baseline questionnaire and, at least, the first follow-up questionnaire, are shown in Table 19.

Most of the participants belonging to the groups of people with prior SARS-CoV-2 infection and people with a history of allergy were aged between 30 and 59 years. The largest percentage of pregnant (69.1%) and lactating women (92.3%) were between 30 and 39 years old.

The children/adolescents' cohort, including vaccinees aged between 5 and 17 years, was identified based on the age indicated by the parent/legal representative filling in the baseline questionnaire on their behalf. In addition, children in the age category 0-4 years (N=4) were also included, even though they were enrolled before the approval of vaccination in children aged between 6 months and 4 years. It is therefore likely that these subjects reported an incorrect date of birth when completing the baseline questionnaire. Since these children may belong to different cohorts, they were included in the denominators.

Medical history is reported as MedDRA Preferred Term (PT). The PT list originates from the coding of the disorders and situations at the Lowest Level Term (LLT) in agreement with Lareb's "Work Instruction FlexLIM" (Version date 9-6-2021) document.

For people with prior SARS-CoV-2 infection, people with a history of allergy and immunocompromised, hypertension and lung disorder were the most frequently reported MedDRA PTs. Participants in the children/adolescents' cohort and the pregnant women often reported having conditions related to lung disorders.

Tables 20, 21, 22, 23, 24 and 25 show for each special cohort the demographic and clinical characteristics of the participants by vaccine manufacturer. To compare baseline characteristics, each vaccinee belonging to a special cohort was matched, when possible (Tables 20, 22, 23, 24 and 25), with a vaccinee belonging to the general population based on sex, age at study registration, and dose of vaccination (ratio 1:1).

Table 19. Demographic and clinical characteristics of participants belonging to the special target group following the receipt of the first dose of any vaccine

	Special target group					
	People with prior SARS-CoV-2 infection	**Children/ Adolescents (5-17 y.o.)**	**People with a history of allergy**	**Immuno-compromised**	**Pregnant women**	**Lactating women**
N of participants (%)	**2,594 (100)**	**732 (100)**	**3,477 (100)**	**567 (100)**	**175 (100)**	**26 (100)**
Age group (y.o.)						
00-04	-	4 (0.5)	1 (0.03)	-	-	-
05-11	44 (1.7)	307 (41.9)	34 (1.0)	2 (0.4)	-	-
12-17	54 (2.1)	421 (57.5)	65 (1.9)	4 (0.7)	-	-
18 – 24	233 (9.0)	-	224 (6.4)	17 (3.0)	-	1 (3.8)
25 – 29	211 (8.1)	-	268 (7.7)	22 (3.9)	43 (24.6)	-
30 – 39	419 (16.2)	-	606 (17.4)	72 (12.7)	121 (69.1)	24 (92.3)
40 – 49	525 (20.2)	-	647 (18.6)	91 (16.0)	10 (5.7)	1 (3.8)
50 – 59	657 (25.3)	-	762 (21.9)	117 (20.6)	1 (0.6)	-
60 – 69	256 (9.9)	-	332 (9.5)	74 (13.1)	-	-
70 – 79	131 (5.1)	-	358 (10.3)	111 (19.6)	-	-
>80	64 (2.5)	-	177 (5.1)	57 (10.1)	-	-
Sex, n (%)						
Female	1,943 (74.9)	380 (51.9)	2,565 (73.8)	386 (68.1)	175 (100)	26 (100)
Male	651 (25.1)	352 (48.1)	912 (26.2)	181 (31.9)	-	-
Medical history (MedDRA PT), n (%)						
Cardiovascular disorder	119 (4.6)	1 (0.1)	219 (6.3)	67 (11.8)	2 (1.1)	-
Diabetes mellitus	63 (2.4)	1 (0.1)	103 (3.0)	39 (6.9)	5 (2.9)	-
Hypertension	247 (9.5)	-	443 (12.7)	95 (16.8)	1 (0.6)	-
Immunosuppression	42 (1.6)	1 (0.1)	100 (2.9)	567 (100)	2 (1.1)	-
Liver disorder	5 (0.2)	1 (0.1)	16 (0.5)	14 (2.5)	-	-
Lung disorder	208 (8.0)	86 (11.7)	693 (19.9)	97 (17.1)	8 (4.5)	2 (7.7)
Mental disorder	26 (1.0)	9 (1.2)	47 (1.4)	33 (5.8)	-	-
Neoplasm malignant	18 (0.7)	-	33 (0.9)	34 (6.0)	-	-
Nervous system disorder	85 (3.3)	9 (1.2)	261 (7.5)	32 (5.6)	6 (3.4)	-
Renal disorder	19 (0.7)	3 (0.4)	41 (1.2)	23 (4.1)	-	-

Note: a single participant may belong to different cohorts and reports more than one medical history. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

People with prior SARS-CoV-2 infection

Table 20. Demographic and clinical characteristics of people with prior SARS-CoV-2 infection by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**General population**
N of participants (%)	**963 (100)**	**907 (100)**	**272 (100)**	**440 (100)**	**1 (100)**	**2,594 (100) ***	**2,594 (100)**
Sex, n (%)							
Female	846 (87.9)	558 (61.5)	214 (78.7)	317 (71.9)	1 (100)	1,943 (74.9)	1943 (74.9)
Male	117 (12.1)	349 (38.5)	58 (21.3)	123 (27.9)	-	651 (25.1)	651 (25.1)
Medical history (MedDRA PT), n (%)							
Cardiovascular disorder	31 (3.2)	72 (7.9)	4 (1.5)	11 (2.5)	1 (100)	119 (4.6)	106 (4.1)
Diabetes mellitus	24 (2.5)	30 (3.3)	1 (0.4)	7 (1.6)	0 (0)	63 (2.4)	70 (2.7)
Hypertension	93 (9.7)	110 (12.1)	19 (7)	25 (5.7)	0 (0)	247 (9.5)	235 (9.1)
Immunosuppression	19 (2)	13 (1.4)	4 (1.5)	6 (1.4)	0 (0)	42 (1.6)	62 (2.4)
Liver disorder	1 (0.1)	3 (0.3)	0 (0)	1 (0.2)	0 (0)	5 (0.2)	8 (0.3)
Lung disorder	77 (8)	76 (8.4)	11 (4)	43 (9.8)	1 (100)	208 (8)	180 (6.9)
Mental disorder	29 (3)	26 (2.9)	11 (4)	18 (4.1)	0 (0)	85 (3.3)	123 (4.7)
Neoplasm malignant	4 (0.4)	9 (1)	3 (1.1)	2 (0.5)	-	18 (0.7)	25 (1)
Nervous system disorder	9 (0.9)	8 (0.9)	5 (1.8)	4 (0.9)	0 (0)	26 (1)	26 (1)
Renal disorder	6 (0.6)	11 (1.2)	0 (0)	2 (0.5)	0 (0)	19 (0.7)	20 (0.8)

*****Including 11 vaccinees who reported an unknown vaccine brand. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Children/Adolescents (5-17 years)

Table 21. Demographics and clinical characteristics of children/adolescents by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer			
	AstraZeneca	**BioNTech/Pfizer**	**Moderna**	**All vaccines**
N of participants (%)	**3 (100)**	**706 (100)**	**15 (100)**	**732 (100) ***
Sex, n (%)				
Female	1 (33.3)	371 (52.5)	6 (40.0)	380 (51.9)
Male	2 (66.7)	335 (47.5)	9 (60.0)	352 (48.1)
Medical history (MedDRA PT), n (%)				
Cardiovascular disorder	-	1 (0.1)	-	1 (0.1)
Diabetes mellitus	-	1 (0.1)	-	1 (0.1)
Hypertension	-	0 (0)	-	0 (0)
Immunosuppression	-	6 (0.8)	-	6 (0.8)
Liver disorder	-	1 (0.1)	-	1 (0.1)
Lung disorder	-	37 (5.2)	1 (6.7)	38 (5.2)
Mental disorder	-	9 (1.3)	-	9 (1.2)
Neoplasm malignant	-	0 (0)	-	0 (0)
Nervous system disorder	-	9 (1.3)	-	9 (1.2)
Renal disorder	-	3 (0.4)	-	3 (0.4)

*****Including 8 vaccinees who reported an unknown vaccine brand. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

People with a history of allergy

Table 22. Demographics and clinical characteristics of people with a history of allergy by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**General population**
N of participants (%)	**1,089 (100)**	**1,494 (100)**	**345 (100)**	**538 (100)**	**1 (100)**	**3,477 (100) ***	**3,477 (100)**
Sex, n (%)							
Female	973 (89.3)	937 (62.7)	257 (74.5)	388 (72.1)	1 (100)	2,565 (73.8)	2,563 (73.7)
Male	116 (10.7)	557 (37.3)	88 (25.5)	150 (27.9)	-	912 (26.2)	914 (26.3)
Medical history (MedDRA PT), n (%)							
Cardiovascular disorder	40 (3.7)	160 (10.7)	3 (0.9)	14 (2.6)	-	219 (6.3)	171 (4.9)
Diabetes mellitus	33 (3)	62 (4.1)	1 (0.3)	7 (1.3)	-	103 (3)	99 (2.8)
Hypertension	119 (10.9)	272 (18.2)	24 (7)	28 (5.2)	-	443 (12.7)	362 (10.4)
Immunosuppression	31 (2.8)	51 (3.4)	4 (1.2)	13 (2.4)	-	100 (2.9)	50 (1.4)
Liver disorder	3 (0.3)	10 (0.7)	0 (0)	3 (0.6)	-	16 (0.5)	10 (0.3)
Lung disorder	244 (22.4)	288 (19.3)	30 (8.7)	129 (24)	-	693 (19.9)	193 (5.6)
Mental disorder	86 (7.9)	102 (6.8)	22 (6.4)	49 (9.1)	-	261 (7.5)	121 (3.5)
Neoplasm malignant	7 (0.6)	21 (1.4)	4 (1.2)	1 (0.2)	-	33 (0.9)	33 (0.9)
Nervous system disorder	9 (0.8)	29 (1.9)	6 (1.7)	3 (0.6)	-	47 (1.4)	43 (1.2)
Renal disorder	8 (0.7)	31 (2.1)	0 (0)	2 (0.4)	-	41 (1.2)	23 (0.7)

*****Including 10 vaccinees who reported an unknown vaccine brand. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Immunocompromised

Table 23. Demographics and clinical characteristics of immunocompromised people by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**General population**
N of participants (%)	**165 (100)**	**278 (100)**	**21 (1003**	**100 (100)**	**1 (100)**	**567 (100)***	**567 (100)**
Sex, n (%)							
Female	141 (85.5)	152 (54.7)	20 (95.2)	71 (71)	1 (100)	386 (68.1)	386 (68.1)
Male	24 (14.5)	126 (45.3)	1 (4.8)	29 (29)	-	181 (31.9)	181 (31.9)
Medical history (MedDRA PT), n (%)							
Cardiovascular disorder	10 (6.1)	51 (18.3)		4 (4)	1 (100)	67 (11.8)	60 (10.6)
Diabetes mellitus	9 (5.5)	25 (9)		5 (5)		39 (6.9)	19 (3.4)
Hypertension	23 (13.9)	65 (23.4)	-	5 (5)		95 (16.8)	98 (17.3)
Immunosuppression	165 (100)	278 (100)	-	100 (100)	1 (100)	567 (100)	0 (0)
Liver disorder	5 (3)	9 (3.2)		0 (0)		14 (2.5)	2 (0.4)
Lung disorder	26 (15.8)	50 (18)	-	17 (17)	-	97 (17.1)	46 (8.1)

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**General population**
Mental disorder	5 (3)	18 (6.5)	-	5 (5)	-	32 (5.6)	18 (3.2)
Neoplasm malignant	6 (3.6)	21 (7.6)	-	7 (7)	-	34 (6)	9 (1.6)
Nervous system disorder	8 (4.8)	19 (6.8)	-	6 (6)	-	33 (5.8)	7 (1.2)
Renal disorder	3 (1.8)	16 (5.8)	-	4 (4)	-	23 (4.1)	7 (1.2)

*****Including 2 vaccinees who reported an unknown vaccine brand. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Pregnant women

Table 24. Demographics and clinical characteristics of pregnant women by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer					
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**All vaccines**	**General population**
N of participants (%)	-	**120 (100)**	**2 (100)**	**53 (100)**	**175 (100)**	**175 (100)**
Medical history (MedDRA PT), n (%)						
Cardiovascular disorder	-	2 (1.7)	-	-	2 (1.1)	2 (1.1)
Diabetes mellitus	-	4 (3.3)	-	1 (1.9)	5 (2.9)	0 (0)
Hypertension	-	-	-	1 (1.9)	1 (0.6)	1 (0.6)
Immunosuppression	-	1 (0.8)	-	1 (1.9)	2 (1.1)	3 (1.7)
Liver disorder	-	-	-	-	0 (0)	0 (0)
Lung disorder	-	4 (3.3)	-	4 (7.5)	8 (4.6)	14 (8)
Mental disorder	-	4 (3.3)	1 (50.0)	1 (1.9)	6 (3.4)	13 (7.4)
Neoplasm malignant	-	-	-	-	0 (0)	0 (0)
Nervous system disorder	-	-	-	-	0 (0)	2 (1.1)
Renal disorder	-	-		-	0 (0)	2 (1.1)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Lactating women

Table 25. Demographics and clinical characteristics of lactating women by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer				
	BioNTech/ Pfizer	**Moderna**	**Novavax**	**All vaccines**	**General population**
N of participants (%)	**21 (100)**	**4 (100)**	**1 (100)**	**26 (100)**	**26 (100)**
Medical history (MedDRA PT), n (%)					
Cardiovascular disorder	-	-	-	-	-
Diabetes mellitus	-	-	-	-	-
Hypertension	-	-	-	-	-
Immunosuppression	-	-	-	-	-
Liver disorder	-	-	-	-	-
Lung disorder	1 (0.0)	1 (25.0)	-	2 (7.7)	1 (3.8)
Mental disorder	-	-	-	-	-
Neoplasm malignant	-	-	-	-	-
Nervous system disorder	-	-	-	-	-
Renal disorder	-	-	-	-	-

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

10.3 Outcome data: special population adverse reaction data (Primary Objective 2)

Table 26 provides an overview of the frequency of all reported adverse reactions (solicited and unsolicited), with their percentages calculated based on the number of participants receiving a specific vaccine. The frequency of the reported ADRs is depicted by special target group, vaccine manufacturer, following the first or the second dose of vaccine. Please note that participants can report more than one ADR, but Table 26 only shows the number of participants having reported at least one ADR. In all special target groups, more than half participants reported having experienced at least one ADR. This can be observed following a first or second dose of vaccine when all information on vaccine manufacturers is pooled together.

Table 26. Overview of the number of vaccinee-reported solicited and non-solicited ADRs over the total number of vaccinees by special target group, following the first and the second dose of any vaccine.

	Special target group					
	People with prior SARS-CoV-2 infection Any ADR/Any vaccinees (%)	**Children and Adolescents (5-17 y.o.)** Any ADR/Any vaccinees (%)	**People with history of allergy** Any ADR/Any vaccinees (%)	**Immuno-compromised** Any ADR/Any vaccinees (%)	**Pregnant Women** Any ADR/Any vaccinees (%)	**Lactating women** Any ADR/Any vaccinees (%)
First dose						
AstraZeneca	938/963 (97.4)	3 /3 (100)	1,044 /1,089 (95.9)	156/175 (89.1)	-	-
BioNTech/ Pfizer	717/907 (79.1)	385/706 (54.5)	1,141/1,494 (76.4)	194/278 (69.8)	94/120 (78.3)	17/21 (81.0)
Janssen	251/272 (92.3)	-	309/345 (89.6)	19/21 (90.5)	2/2 (100)	-
Moderna	418/440 (95.0)	10/15 (66.7)	506/538 (94.1)	94/100 (94.0)	46/53 (86.8)	4/4 (100)
Novavax	1/1 (100)	-	0/1 (0.0)	1/1 (100)	-	0/1 (0.0)
All vaccines*	**2,333/2,594 (89.9)**	**404/732 (55.2)**	**3,008/3,477 (86.5)**	**465/567 (82.0)**	**142/175 (81.1)**	**21/26 (80.8)**
Second dose						
AstraZeneca	366/372 (98.4)	0/1 (0.0)	655/685 (95.6)	91/95 (95.8)	-	-
BioNTech/ Pfizer	300/369 (81.3)	247/407 (60.7)	905/1,146 (79.0)	165/236 (69.9)	75/90 (83.3)	11/14 (78.6)
Moderna	164/168 (97.6)	7/9 (77.8)	388/403 (96.3)	78/83 (94.0)	38/41 (92.7)	4/4 (100)
Novavax	-	-	0/1 (0.0)	1/1 (100)	-	0/1 (0.0)
All vaccines*	**831/910 (91.3)**	**257/422 (60.9)**	**1,952/2,243 (87.0)**	**336/416 (80.8)**	**113/131 (86.3)**	**15/20 (75.0)**

***Including also vaccines with unknown brand. **Note:** percentages are calculated based on the number of vaccinee-reported solicited and non-solicited adverse reactions over the number of vaccinees receiving a specific vaccine, by special target group. The table includes data pooled across countries. **Abbreviations:** ADR=adverse reaction; y.o.=years old.

The next two Tables 27 and 26 show the frequency of reported solicited ADRs following the first and the second dose, respectively, using the PT and classified as either local solicited ADR or systematic solicited ADR. Percentages have been calculated based on the total number of vaccinees who received a first or a second dose of vaccine, by special cohort.

Following the receipt of both the first and the second dose, injection site pain was the most frequently reported ADR among the local solicited ADRs in all special target groups, whereas fatigue, headache, malaise and myalgia were the systemic solicited ADRs most frequently reported.

Overall, slightly lower percentages of ADRs were reported following the second dose as compared to the first dose.

Tables 29, 30, 31, 32, 33 and 34 show the frequency of reported local and systemic solicited ADRs (MedDRA PT) by COVID-19 vaccine manufacturers for each special target group. To compare frequency of ADRs, each vaccinee belonging to a special cohort was matched, when possible (Tables 29, 31, 32, 33 and 34), with a vaccinee belonging to the general population based on sex, age at study registration, and dose of vaccination (ratio 1:1).

Table 27. Frequency of reported local and systemic solicited ADRs following the first dose of any vaccine, by a special target group

	Special target group					
	People with prior SARS-CoV-2 infection N= 2,594 (100)	**Children/ Adolescents (5-17 y.o.) N= 732 (100)**	**People with history of allergy N= 3,477 (100)**	**Immuno-compromised N= 567 (100)**	**Pregnant women N= 175 (100)**	**Lactating women N= 26 (100)**
Subjects with at least one solicited ADR, n (%)	1,719 (66.3)	322 (44.0)	2,643 (76.0)	402 (70.9)	120 (68.6)	18 (69.2)
Local solicited adverse reaction (MedDRA PT), n (%)						
Injection site erythema	180 (6.9)	20 (2.7)	241 (9.3)	44 (7.8)	6 (3.4)	0 (0)
Injection site haematoma	98 (3.8)	7 (1)	151 (5.8)	21 (3.7)	7 (4)	1 (3.8)
Injection site induration	12 (0.5)	2 (0.3)	40 (1.5)	1 (0.2)	1 (0.6)	1 (3.8)
Injection site inflammation	437 (16.8)	37 (5.1)	594 (22.9)	93 (16.4)	15 (8.6)	1 (3.8)
Injection site pain	1,006 (38.8)	219 (29.9)	1,509 (58.2)	233 (41.1)	76 (43.4)	13 (50)
Injection site pruritus	77 (3)	7 (1)	127 (4.9)	20 (3.5)	4 (2.3)	-
Injection site reaction	3 (0.1)	-	3 (0.1)	3 (0.5)	3 (1.7)	1 (3.8)
Injection site swelling	373 (14.4)	37 (5.1)	511 (19.7)	85 (15)	18 (10.3)	2 (7.7)
Injection site warmth	275 (10.6)	14 (1.9)	374 (14.4)	66 (11.6)	9 (5.1)	2 (7.7)
Systemic solicited adverse reactions (PT), n (%)						
Arthralgia	456 (17.6)	22 (3)	596 (23)	86 (15.2)	4 (2.3)	4 (15.4)
Chills	830 (32)	28 (3.8)	927 (35.7)	127 (22.4)	6 (3.4)	3 (11.5)
Fatigue	1,036 (39.9)	111 (15.2)	1,502 (57.9)	216 (38.1)	51 (29.1)	9 (34.6)
Headache	1,019 (39.3)	84 (11.5)	1,315 (50.7)	178 (31.4)	26 (14.9)	8 (30.8)
Malaise	1,014 (39.1)	62 (8.5)	1,302 (50.2)	180 (31.7)	16 (9.1)	5 (19.2)
Myalgia	1,020 (39.3)	90 (12.3)	1,373 (52.9)	193 (34)	33 (18.9)	4 (15.4)
Nausea	434 (16.7)	41 (5.6)	613 (23.6)	89 (15.7)	11 (6.3)	2 (7.7)
Body temperature increased	100 (3.9)	15 (2)	121 (4.7)	20 (3.5)	2 (1.1)	-
Pyrexia	685 (26.4)	34 (4.6)	702 (27.1)	82 (14.5)	2 (1.1)	-
Hyperpyrexia	15 (0.6)	-	13 (0.5)	4 (0.7)	-	-

Legend: percentages are calculated based on the total number of vaccinees who received a first dose of vaccine, by special cohort. The table includes data pooled for countries and COVID-19 vaccine brands. Vaccinees who filled in the baseline questionnaire and at least one follow-up questionnaire were considered. **Abbreviations:** ADR=adverse reaction; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; y.o.=years old.

Table 28. Frequency of reported local and systemic solicited ADRs following the second dose of any vaccine, by a special target group

	Special target group					
	People with prior SARS-CoV-2 infection N= 910	**Children/ Adolescents (5-17 y.o.) N= 422**	**People with history of allergy N= 2,243**	**Immuno-compromised N= 416**	**Pregnant women N= 131**	**Lactating women N= 20**
Subjects with at least one solicited ADR, n (%)	522 (57.4)	146 (34.6)	1,369 (61.0)	211 (50.7)	79 (60.3)	9 (45.0)
Local solicited adverse reaction (MedDRA PT), n (%)						
Injection site erythema	46 (5.1)	7 (1.7)	137 (6.1)	22 (5.3)	6 (4.6)	2 (10)
Injection site haematoma	30 (3.3)	1 (0.2)	70 (3.1)	15 (3.6)	4 (3.1)	2 (10)
Injection site induration	1 (0.1)	0 (0)	7 (0.3)	3 (0.7)	0 (0)	1 (5)
Injection site inflammation	98 (10.8)	20 (4.7)	266 (11.9)	37 (8.9)	14 (10.7)	2 (10)
Injection site pain	272 (29.9)	78 (18.5)	648 (28.9)	106 (25.5)	44 (33.6)	6 (30)
Injection site pruritus	18 (2)	3 (0.7)	56 (2.5)	12 (2.9)	4 (3.1)	0 (0)
Injection site reaction	0 (0)	0 (0)	3 (0.1)	0 (0)	0 (0)	0 (0)
Injection site swelling	77 (8.5)	17 (4)	207 (9.2)	38 (9.1)	12 (9.2)	1 (5)
Injection site warmth	63 (6.9)	14 (3.3)	201 (9)	28 (6.7)	9 (6.9)	0 (0)
Systemic solicited adverse reactions (MedDRA PT), n (%)						
Arthralgia	88 (9.7)	22 (5.2)	236 (10.5)	38 (9.1)	7 (5.3)	1 (5)
Chills	144 (15.8)	24 (5.7)	296 (13.2)	40 (9.6)	17 (13)	2 (10)
Fatigue	250 (27.5)	83 (19.7)	720 (32.1)	105 (25.2)	41 (31.3)	1 (5)
Headache	222 (24.4)	74 (17.5)	588 (26.2)	86 (20.7)	27 (20.6)	2 (10)
Malaise	257 (28.2)	51 (12.1)	621 (27.7)	91 (21.9)	29 (22.1)	3 (15)
Myalgia	205 (22.5)	54 (12.8)	596 (26.6)	85 (20.4)	38 (29)	1 (5)
Nausea	92 (10.1)	27 (6.4)	252 (11.2)	43 (10.3)	7 (5.3)	1 (5)
Body temperature increased	27 (3)	17 (4)	79 (3.5)	12 (2.9)	7 (5.3)	1 (5)
Pyrexia	123 (13.5)	33 (7.8)	262 (11.7)	40 (9.6)	9 (6.9)	0 (0)
Hyperpyrexia	1 (0.1)	1 (0.2)	4 (0.2)	0 (0)	0 (0)	0 (0)

Legend: percentages are calculated based on the total number of vaccinees who received a second dose of vaccine, by special cohort. The table includes data pooled for countries and COVID-19 vaccine brands. Vaccinees who filled in the baseline questionnaire and at least one follow-up questionnaire after dose 2 were considered. **Abbreviations:** ADR = adverse reaction; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; y.o.=years old.

People with prior SARS-CoV-2 infection

Injection site pain was the most frequently reported local ADR following both the first and the second dose of any vaccine. Overall, fatigue, headache, malaise and myalgia were the most frequently reported systemic ADRs following the first dose of any vaccines. However, a lower rate of systemic ADRs was observed with BioNTech/Pfizer as compared to the other vaccines. In general, higher rates of all systemic solicited ADRs were observed for AstraZeneca as compared to the other vaccines.

On the contrary, following the second dose, a lower rate of systemic ADRs was observed with AstraZeneca, and a higher rate was observed with BioNTech/Pfizer and Moderna vaccines as compared to the first dose.

Table 29. Frequency of reported local and systemic solicited ADRs in the group of people with prior SARS-CoV-2 infection by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
First dose							
Number of vaccinees	**963 (100)**	**907 (100)**	**272 (100)**	**440 (100)**	**1 (100)**	**2594 (100) ***	**2594 (100)**
Subjects with at least one solicited ADR, n (%)	763 (79.2)	437 (48.2)	246 (90.4)	266 (60.5)	1 (100)	1719 (66.3)	1984 (76.5)
Local solicited adverse reaction (MedDRA PT), n (%)							
Injection site erythema	96 (10)	25 (2.8)	18 (6.6)	41 (9.3)	-	180 (6.9)	144 (15.8)
Injection site haematoma	46 (4.8)	19 (2.1)	21 (7.7)	12 (2.7)	-	98 (3.8)	115 (12.6)
Injection site induration	4 (0.4)	4 (0.4)	2 (0.7)	2 (0.5)	-	12 (0.5)	33 (3.6)
Injection site inflammation	218 (22.6)	82 (9)	55 (20.2)	80 (18.2)	-	437 (16.8)	381 (41.9)
Injection site pain	453 (47)	263 (29)	121 (44.5)	165 (37.5)	-	1006 (38.8)	1100 (120.9)
Injection site pruritus	44 (4.6)	9 (1)	7 (2.6)	17 (3.9)	-	77 (3)	67 (7.4)
Injection site reaction	1 (0.1)	2 (0.2)	0 (0)	0 (0)	-	3 (0.1)	1 (0.1)
Injection site swelling	184 (19.1)	62 (6.8)	48 (17.6)	78 (17.7)	-	373 (14.4)	321 (35.3)
Injection site warmth	141 (14.6)	55 (6.1)	25 (9.2)	53 (12)	-	275 (10.6)	223 (24.5)
Systemic solicited adverse reactions (MedDRA PT), n (%)							
Arthralgia	260 (27)	61 (6.7)	72 (26.5)	61 (13.9)	-	456 (17.6)	429 (47.1)
Chills	496 (51.5)	112 (12.3)	116 (42.6)	104 (23.6)	-	830 (32)	748 (82.2)
Fatigue	498 (51.7)	211 (23.3)	165 (60.7)	159 (36.1)	1 (100)	1036 (39.9)	1103 (121.2)
Headache	536 (55.7)	184 (20.3)	166 (61)	128 (29.1)	1 (100)	1019 (39.3)	1041 (114.4)
Malaise	535 (55.6)	165 (18.2)	154 (56.6)	158 (35.9)	1 (100)	1014 (39.1)	930 (102.2)
Myalgia	485 (50.4)	219 (24.1)	153 (56.3)	160 (36.4)	-	1020 (39.3)	1019 (112)
Nausea	232 (24.1)	66 (7.3)	63 (23.2)	70 (15.9)	-	434 (16.7)	430 (47.3)
Body temperature increased	46 (4.8)	21 (2.3)	12 (4.4)	19 (4.3)	-	100 (3.9)	94 (10.3)
Pyrexia	12 (1.2)	0 (0)	2 (0.7)	1 (0.2)	-	685 (26.4)	555 (61)
Hyperpyrexia	404 (42)	73 (8)	109 (40.1)	97 (22)	-	15 (0.6)	15 (1.6)
Second dose							
Number of vaccinees	372 (100)	367 (100)	-	168 (100)	-	**910 (100)****	**910 (100)**
Subjects with at least one solicited ADR, n (%)	183 (49.2)	200 (54.5)	-	138 (82.1)	-	522 (57.4)	486 (53.4)
Local solicited adverse reactions (MedDRA PT), n (%)							
Injection site erythema	13 (3.5)	11 (3)	-	22 (13.1)	-	46 (5.1)	42 (4.6)

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
Injection site haematoma	16 (4.3)	8 (2.2)	-	6 (3.6)	-	30 (3.3)	23 (2.5)
Injection site induration	0 (0)	1 (0.3)	-	0 (0)	-	1 (0.1)	1 (0.1)
Injection site inflammation	33 (8.9)	22 (6)	-	43 (25.6)	-	98 (10.8)	86 (9.5)
Injection site pain	99 (26.6)	96 (26)	-	76 (45.2)	-	272 (29.9)	235 (25.8)
Injection site pruritus	6 (1.6)	8 (2.2)	-	4 (2.4)	-	18 (2)	10 (1.1)
Injection site reaction	0 (0)	0 (0)	-	0 (0)	-	0 (0)	0 (0)
Injection site swelling	23 (6.2)	21 (5.7)	-	33 (19.6)	-	77 (8.5)	68 (7.5)
Injection site warmth	20 (5.4)	16 (4.3)	-	27 (16.1)	-	63 (6.9)	69 (7.6)
Systemic solicited adverse reactions (MedDRA PT), n (%)							
Arthralgia	20 (5.4)	33 (8.9)	-	35 (20.8)	-	88 (9.7)	62 (6.8)
Chills	33 (8.9)	53 (14.4)	-	58 (34.5)	-	144 (15.8)	109 (12)
Fatigue	78 (21)	91 (24.7)	-	81 (48.2)	-	250 (27.5)	255 (28)
Headache	80 (21.5)	79 (21.4)	-	63 (37.5)	-	222 (24.4)	209 (23)
Malaise	63 (16.9)	103 (27.9)	-	91 (54.2)	-	257 (28.2)	217 (23.8)
Myalgia	59 (15.9)	72 (19.5)	-	73 (43.5)	-	205 (22.5)	185 (20.3)
Nausea	21 (5.6)	32 (8.7)	-	39 (23.2)	-	92 (10.1)	70 (7.7)
Body temperature increased	7 (1.9)	11 (3)	-	9 (5.4)	-	27 (3)	25 (2.7)
Pyrexia	0 (0)	1 (0.3)	-	-	-	123 (13.5)	89 (9.8)
Hyperpyrexia	22 (5.9)	45 (12.2)	-	56 (33.3)	-	1 (0.1)	1 (0.1)

*****Including 11 vaccinees who reported an unknown vaccine brand. ******Including 3 vaccinees who reported an unknown vaccine brand. **Legend:** percentages are calculated based on the total number of vaccinees who received a first or a second dose of vaccine, by COVID-19 vaccine manufacturer. The table includes data pooled across countries. **Abbreviations:** ADR=adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.=years old.

Children/Adolescents (5-17 years old)

Children and adolescents mostly received BioNTech/Pfizer. Injection site pain was the most frequently reported local ADR following both the first and the second dose, while fatigue, headache, malaise and myalgia were the most frequently reported systemic ADRs.

Table 30. Frequency of reported local and systemic solicited ADRs in the group of children/adolescents by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine

	COVID-19 vaccine manufacturer			
	AstraZeneca	**BioNTech/Pfizer**	**Moderna**	**All vaccines**
First dose				
Number of vaccinees	**3 (100)**	**706 (100)**	**15 (100)**	**732 (100)** *
Subjects with at least one solicited ADR, n (%)	2 (66.7)	309 (43.8)	7 (46.7)	322 (44.0)
Local solicited adverse reaction (MedDRA PT), n (%)				
Injection site erythema	-	18 (2.5)	2 (13.3)	20 (2.7)
Injection site haematoma	-	7 (1)	-	7 (1)

	COVID-19 vaccine manufacturer			
	AstraZeneca	**BioNTech/Pfizer**	**Moderna**	**All vaccines**
Injection site induration	-	1 (0.1)	1 (6.7)	2 (0.3)
Injection site inflammation	1 (33.3)	33 (4.7)	2 (13.3)	37 (5.1)
Injection site pain	1 (33.3)	208 (29.5)	6 (40)	219 (29.9)
Injection site pruritus	-	7 (1)	-	7 (1)
Injection site reaction	-	-	-	-
Injection site swelling	1 (33.3)	35 (5)	1 (6.7)	37 (5.1)
Injection site warmth	-	12 (1.7)	2 (13.3)	14 (1.9)
Systemic solicited adverse reactions (MedDRA PT), n (%)				
Arthralgia	-	21 (3)	1 (6.7)	22 (3)
Chills	1 (33.3)	26 (3.7)	1 (6.7)	28 (3.8)
Fatigue	1 (33.3)	108 (15.3)	1 (6.7)	111 (15.2)
Headache	1 (33.3)	79 (11.2)	3 (20)	84 (11.5)
Malaise	1 (33.3)	58 (8.2)	3 (20)	62 (8.5)
Myalgia	-	84 (11.9)	4 (26.7)	90 (12.3)
Nausea	1 (33.3)	37 (5.2)	1 (6.7)	41 (5.6)
Body temperature increased	0 (0)	11 (1.6)	2 (13.3)	15 (2)
Pyrexia	2 (66.7)	30 (4.2)	1 (6.7)	34 (4.6)
Hyperpyrexia	-	-	-	-
Second dose				
Number of vaccinees	**1 (100)**	**407 (100)**	**9 (100)**	**422 (100)** **
Subjects with at least one solicited ADR, n (%)	-	140 (34.4)	3 (33.3)	146 (34.6)
Local solicited adverse reaction (MedDRA PT), n (%)				
Injection site erythema	-	6 (1.5)	1 (11.1)	7 (1.7)
Injection site haematoma	-	1 (0.2)	-	1 (0.2)
Injection site induration	-	-	-	-
Injection site inflammation	-	18 (4.4)	2 (22.2)	20 (4.7)
Injection site pain	-	74 (18.2)	2 (22.2)	78 (18.5)
Injection site pruritus	-	2 (0.5)	1 (11.1)	3 (0.7)
Injection site reaction	-	-	-	-
Injection site swelling	-	15 (3.7)	2 (22.2)	17 (4)
Injection site warmth	-	12 (2.9)	2 (22.2)	14 (3.3)
Systemic solicited adverse reactions (MedDRA PT), n (%)				
Arthralgia	-	22 (5.4)	-	22 (5.2)
Chills	-	24 (5.9)	-	24 (5.7)
Fatigue	-	82 (20.1)	1 (11.1)	83 (19.7)
Headache	-	73 (17.9)	1 (11.1)	74 (17.5)
Malaise	-	48 (11.8)	1 (11.1)	51 (12.1)
Myalgia	-	52 (12.8)	0 (0)	54 (12.8)
Nausea	-	26 (6.4)	0 (0)	27 (6.4)
Body temperature increased	-	15 (3.7)	2 (22.2)	17 (4)
Pyrexia	-	31 (7.6)	2 (22.2)	33 (7.8)
Hyperpyrexia	-	1 (0.2)	-	1 (0.2)

*****Including 8 vaccinees who reported an unknown vaccine brand. ******Including 5 vaccinees who reported an unknown vaccine brand. **Legend:** percentages are calculated based on the total number of vaccinees who received a first or a second dose of vaccine, by COVID-19 vaccine manufacturer. The table include data pooled across countries. **Abbreviations:** ADR=adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.=years old.

People with a history of allergy

Injection site pain was the most frequently reported local ADR following both the first and the second dose of any vaccine. Overall, fatigue, headache, malaise and myalgia were the most frequently reported systemic ADRs following both the first and the second dose of any vaccines. However, a lower rate of systemic ADRs was observed with BioNTech/Pfizer and Moderna as compared to AstraZeneca and Janssen. In general, higher rates of all systemic solicited ADRs were observed for AstraZeneca as compared to the other vaccines. On the contrary, following the second dose, a lower rate of systemic ADRs was observed with AstraZeneca, as compared to the other vaccines and first dose, and a higher rate was observed with Moderna vaccines as compared to the first dose. Although Janssen requires a single dose, ADRs have been reported following a second dose of Janssen, possibly due to medical error or misreporting.

Table 31. Frequency of reported local and systemic solicited ADRs in the group of people with a history of allergy by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
First dose							
Number of vaccinees	**1,089 (100)**	**1,494 (100)**	**345 (100)**	**538 (100)**	**1 (100)**	**3,477 (100) ***	**3,477 (100)**
Subjects with at least one solicited ADR, n (%)	996 (91.5)	911 (61)	300 (87)	428 (79.6)	-	2,643 (76.0)	2,451 (70.5)
Local solicited adverse reaction (MedDRA PT), n (%)							
Injection site erythema	121 (11.1)	50 (3.3)	15 (4.3)	54 (10)	-	241 (6.9)	214 (6.2)
Injection site haematoma	67 (6.2)	37 (2.5)	13 (3.8)	34 (6.3)	-	151 (4.3)	144 (4.1)
Injection site induration	14 (1.3)	13 (0.9)	3 (0.9)	10 (1.9)	-	40 (1.2)	36 (1)
Injection site inflammation	281 (25.8)	140 (9.4)	53 (15.4)	117 (21.7)	-	594 (17.1)	495 (14.2)
Injection site pain	569 (52.2)	518 (34.7)	142 (41.2)	275 (51.1)	-	1509 (43.4)	1354 (38.9)
Injection site pruritus	58 (5.3)	24 (1.6)	8 (2.3)	36 (6.7)	-	127 (3.7)	100 (2.9)
Injection site reaction	1 (0.1)	2 (0.1)	-	-	-	3 (0.1)	2 (0.1)
Injection site swelling	226 (20.8)	135 (9)	50 (14.5)	98 (18.2)	-	511 (14.7)	429 (12.3)
Injection site warmth	181 (16.6)	90 (6)	21 (6.1)	81 (15.1)	-	374 (10.8)	306 (8.8)
Systemic solicited adverse reactions (MedDRA PT), n (%)							
Arthralgia	363 (33.3)	109 (7.3)	71 (20.6)	49 (9.1)	-	596 (17.1)	491 (14.1)
Chills	621 (57)	99 (6.6)	132 (38.3)	70 (13)	-	927 (26.7)	938 (27)
Fatigue	687 (63.1)	414 (27.7)	192 (55.7)	205 (38.1)	-	1502 (43.2)	1346 (38.7)
Headache	709 (65.1)	272 (18.2)	191 (55.4)	139 (25.8)	-	1315 (37.8)	1258 (36.2)
Malaise	705 (64.7)	279 (18.7)	180 (52.2)	133 (24.7)	-	1302 (37.4)	1193 (34.3)
Myalgia	645 (59.2)	381 (25.5)	141 (40.9)	199 (37)	-	1373 (39.5)	1284 (36.9)
Nausea	322 (29.6)	142 (9.5)	78 (22.6)	68 (12.6)	-	613 (17.6)	507 (14.6)
Body temperature increased	65 (6)	21 (1.4)	19 (5.5)	15 (2.8)	-	121 (3.5)	113 (3.2)
Pyrexia	12 (1.1)	-	1 (0.3)	-	-	702 (20.2)	694 (20)

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
Hyperpyrexia	492 (45.2)	62 (4.1)	109 (31.6)	37 (6.9)	-	13 (0.4)	10 (0.3)
Second dose							
Number of vaccinees	**685 (100)**	**1,146 (100)**	**3 (100)**	**405 (100)**	**1 (100)**	**2,243 (100) ****	**2,243 (100)**
Subjects with at least one solicited ADR, n (%)	371 (54.2)	642 (56)	1 (33.3)	354 (87.4)	-	1,369 (61)	1,161 (51.8)
Local solicited adverse reaction (MedDRA PT), n (%)							
Injection site erythema	27 (3.9)	45 (3.9)	-	65 (16)	-	137 (6.1)	112 (3.2)
Injection site haematoma	18 (2.6)	27 (2.4)	-	25 (6.2)	-	70 (3.1)	50 (1.4)
Injection site induration	1 (0.1)	3 (0.3)	-	3 (0.7)	-	7 (0.3)	6 (0.2)
Injection site inflammation	63 (9.2)	96 (8.4)	-	107 (26.4)	-	266 (11.9)	207 (6)
Injection site pain	157 (22.9)	318 (27.7)	1 (33.3)	172 (42.5)	-	648 (28.9)	541 (15.6)
Injection site pruritus	8 (1.2)	25 (2.2)	-	23 (5.7)	-	56 (2.5)	45 (1.3)
Injection site reaction	-	3 (0.3)	-	-	-	3 (0.1)	1 (0)
Injection site swelling	45 (6.6)	86 (7.5)	-	76 (18.8)	-	207 (9.2)	166 (4.8)
Injection site warmth	38 (5.5)	71 (6.2)	-	92 (22.7)	-	201 (9)	134 (3.9)
Systemic solicited adverse reactions (MedDRA PT), n (%)							
Arthralgia	38 (5.5)	116 (10.1)	-	82 (20.2)	-	236 (10.5)	170 (4.9)
Chills	48 (7)	106 (9.2)	-	142 (35.1)	-	296 (13.2)	258 (7.4)
Fatigue	176 (25.7)	322 (28.1)	-	222 (54.8)	-	720 (32.1)	601 (17.3)
Headache	144 (21.0)	248 (21.6)	-	196 (48.4)	-	588 (26.2)	474 (13.6)
Malaise	125 (18.2)	267 (23.3)	-	229 (56.5)	-	621 (27.7)	465 (13.4)
Myalgia	119 (17.4)	277 (24.2)	-	199 (49.1)	-	596 (26.6)	490 (14.1)
Nausea	50 (7.3)	97 (8.5)	-	104 (25.7)	-	252 (11.2)	158 (4.5)
Body temperature increased	9 (1.3)	33 (2.9)	-	37 (9.1)	-	79 (3.5)	52 (1.5)
Pyrexia	-	-	-	4 (1)	-	262 (11.7)	205 (5.9)
Hyperpyrexia	41 (6)	85 (7.4)	-	136 (33.6)	-	4 (0.2)	-

*****Including 10 vaccinees who reported an unknown vaccine brand. ******Including 3 vaccinees who reported an unknown vaccine brand. **Legend:** percentages are calculated based on the total number of vaccinees who received a first or a second dose of vaccine, by COVID-19 vaccine manufacturer. The table include data pooled across countries. **Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.=years old.

Immunocompromised

Injection site pain was the most frequently reported local ADR following both the first and the second dose of any vaccine, whereas fatigue, headache, malaise and myalgia were the most frequently reported systemic ADRs. However, a lower rate of systemic ADRs was observed with BioNTech/Pfizer and Moderna as compared to AstraZeneca and Janssen. In general, higher rates of all systemic solicited ADRs were observed for AstraZeneca as compared to the other vaccines. On the contrary, following the second dose, a lower rate of systemic ADRs was observed with AstraZeneca, as compared to the first dose, and a higher rate was observed with Moderna vaccines as compared to the first dose.

Table 32. Frequency of reported local and systemic solicited ADRs in the immunocompromised by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
First dose							
Number of vaccinees	**165 (100)**	**278 (100)**	**21 (100)**	**100 (100)**	**1 (100)**	**567 (100) ***	**567 (100)**
Subjects with at least one solicited ADR, n (%)	146 (88.5)	157 (56.5)	17 (81)	81 (81)	0 (0.0)	402 (70.9)	365 (64.4)
Local solicited adverse reaction (MedDRA PT), n (%)							
Injection site erythema	21 (12.7)	14 (5)	1 (4.8)	8 (8)	-	44 (7.8)	33 (5.8)
Injection site haematoma	8 (4.8)	8 (2.9)	-	5 (5)	-	21 (3.7)	26 (4.6)
Injection site induration	-	1 (0.4)	-	-	-	1 (0.2)	4 (0.7)
Injection site inflammation	48 (29.1)	27 (9.7)	1 (4.8)	17 (17)	-	93 (16.4)	76 (13.4)
Injection site pain	86 (52.1)	89 (32)	10 (47.6)	48 (48)	-	233 (41.1)	215 (37.9)
Injection site pruritus	12 (7.3)	3 (1.1)	-	5 (5)	-	20 (3.5)	12 (2.1)
Injection site reaction	2 (1.2)	1 (0.4)	-	-	-	3 (0.5)	1 (0.2)
Injection site swelling	41 (24.8)	24 (8.6)	-	20 (20)	-	85 (15)	63 (11.1)
Injection site warmth	34 (20.6)	20 (7.2)	-	12 (12)	-	66 (11.6)	48 (8.5)
Systemic solicited adverse reactions (MedDRA PT), n (%)							
Arthralgia	44 (26.7)	24 (8.6)	6 (28.6)	12 (12)	-	86 (15.2)	60 (10.6)
Chills	81 (49.1)	22 (7.9)	9 (42.9)	14 (14)	-	127 (22.4)	116 (20.5)
Fatigue	91 (55.2)	73 (26.3)	14 (66.7)	38 (38)	-	216 (38.1)	186 (32.8)
Headache	94 (57)	40 (14.4)	12 (57.1)	32 (32)	-	178 (31.4)	166 (29.3)
Malaise	89 (53.9)	47 (16.9)	13 (61.9)	30 (30)	-	180 (31.7)	160 (28.2)
Myalgia	84 (50.9)	62 (22.3)	10 (47.6)	36 (36)	-	193 (34)	145 (25.6)
Nausea	45 (27.3)	25 (9)	5 (23.8)	14 (14)	-	89 (15.7)	66 (11.6)
Body temperature increased	7 (4.2)	7 (2.5)	1 (4.8)	4 (4)	-	20 (3.5)	20 (3.5)
Pyrexia	4 (2.4)	-	-	-	-	82 (14.5)	92 (16.2)
Hyperpyrexia	57 (34.5)	11 (4)	5 (23.8)	9 (9)	-	4 (0.7)	-
Second dose							
Number of vaccinees	**95 (100)**	**236 (100)**	**-**	**83 (100)**	**1 (100)**	**416 (100) ****	**416 (100)**
Subjects with at least one solicited ADR, n (%)	43 (45.3)	103 (43.6)	-	64 (77.1)	1 (100)	211 (50.7)	200 (48.1)
Local solicited adverse reaction (MedDRA PT), n (%)							
Injection site erythema	4 (4.2)	11 (4.7)	-	7 (8.4)	-	22 (5.3)	13 (3.1)
Injection site haematoma	2 (2.1)	7 (3)	-	6 (7.2)	-	15 (3.6)	9 (2.2)
Injection site induration	-	3 (1.3)	-	-	-	3 (0.7)	-
Injection site inflammation	6 (6.3)	15 (6.4)	-	16 (19.3)	-	37 (8.9)	29 (7)
Injection site pain	18 (18.9)	49 (20.8)	-	38 (45.8)	1 (100)	106 (25.5)	101 (24.3)
Injection site pruritus	1 (1.1)	4 (1.7)	-	6 (7.2)	1 (100)	12 (2.9)	8 (1.9)
Injection site reaction	-	-	-	-	-	-	-
Injection site swelling	6 (6.3)	16 (6.8)	-	16 (19.3)	-	38 (9.1)	19 (4.6)
Injection site warmth	5 (5.3)	14 (5.9)	-	9 (10.8)	-	28 (6.7)	18 (4.3)
Systemic solicited adverse reactions (MedDRA PT), n (%)							
Arthralgia	4 (4.2)	16 (6.8)	-	18 (21.7)	-	38 (9.1)	24 (5.8)
Chills	5 (5.3)	13 (5.5)	-	22 (26.5)	-	40 (9.6)	49 (11.8)

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
Fatigue	22 (23.2)	39 (16.5)	-	44 (53)	-	105 (25.2)	90 (21.6)
Headache	22 (23.2)	34 (14.4)	-	29 (34.9)	1 (100)	86 (20.7)	77 (18.5)
Malaise	17 (17.9)	32 (13.6)	-	42 (50.6)	-	91 (21.9)	72 (17.3)
Myalgia	12 (12.6)	40 (16.9)	-	33 (39.8)	-	85 (20.4)	81 (19.5)
Nausea	4 (4.2)	20 (8.5)	-	18 (21.7)	1 (100)	43 (10.3)	27 (6.5)
Body temperature increased	1 (1.1)	6 (2.5)	-	5 (6)	-	12 (2.9)	8 (1.9)
Pyrexia	-	-	-	-	-	40 (9.6)	39 (9.4)
Hyperpyrexia	3 (3.2)	10 (4.2)	-	27 (32.5)	-	-	-

*****Including 2 vaccinees who reported an unknown vaccine brand. ******Including 1 vaccinee who reported an unknown vaccine brand. **Legend:** percentages are calculated based on the total number of vaccinees who received a first or a second dose of vaccine, by COVID-19 vaccine manufacturer. The table includes data pooled across countries. **Abbreviations:** ADR=adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.=years old.

Pregnant women

Pregnant women mostly received BioNTech/Pfizer and Moderna. Injection site pain was the most frequently reported local ADR following the first and the second dose with both BioNTech/Pfizer and Moderna. Fatigue, headache and myalgia were the most frequently reported systemic ADRs following the first dose. The same was observed following the second dose of both vaccines with lower rate for BioNTech/Pfizer compared to the first dose and a higher rate for Moderna compared with the first dose.

Table 33. Frequency of reported local and systemic solicited ADRs in the pregnant women group by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine

	COVID-19 vaccine manufacturer					
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**All vaccines**	**Matched general population**
First dose						
Number of vaccinees	-	**120 (100)**	**2 (100)**	**53 (100)**	**175 (100)**	**175 (100)**
Subjects with at least one solicited ADR, n (%)	-	79 (65.8)	2 (100)	39 (73.6)	120 (68.6)	133 (76.0)
Local solicited adverse reaction (MedDRA PT), n (%)						
Injection site erythema	-	4 (3.3)	-	2 (3.8)	6 (3.4)	6 (3.4)
Injection site haematoma	-	2 (1.7)	1 (50)	4 (7.5)	7 (4)	10 (5.7)
Injection site induration	-	-	-	1 (1.9)	1 (0.6)	5 (2.9)
Injection site inflammation	-	9 (7.5)	-	6 (11.3)	15 (8.6)	24 (13.7)
Injection site pain	-	49 (40.8)	-	27 (50.9)	76 (43.4)	87 (49.7)
Injection site pruritus	-	1 (0.8)	-	3 (5.7)	4 (2.3)	5 (2.9)
Injection site reaction	-	3 (2.5)	-	-	3 (1.7)	-
Injection site swelling	-	10 (8.3)	1 (50)	7 (13.2)	18 (10.3)	24 (13.7)
Injection site warmth	-	6 (5)	-	3 (5.7)	9 (5.1)	15 (8.6)
Systemic solicited adverse reactions (MedDRA PT), n (%)						
Arthralgia	-	2 (1.7)	1 (50)	1 (1.9)	4 (2.3)	29 (16.6)
Chills	-	3 (2.5)	1 (50)	2 (3.8)	6 (3.4)	46 (26.3)
Fatigue	-	38 (31.7)	2 (100)	11 (20.8)	51 (29.1)	87 (49.7)
Headache	-	19 (15.8)	1 (50)	6 (11.3)	26 (14.9)	75 (42.9)

	COVID-19 vaccine manufacturer					
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**All vaccines**	**Matched general population**
Malaise	-	13 (10.8)	1 (50)	2 (3.8)	16 (9.1)	62 (35.4)
Myalgia	-	19 (15.8)	1 (50)	13 (24.5)	33 (18.9)	66 (37.7)
Nausea	-	8 (6.7)	-	3 (5.7)	11 (6.3)	25 (14.3)
Body temperature increased	-	1 (0.8)	-	1 (1.9)	2 (1.1)	4 (2.3)
Pyrexia	-	-	-	-	2 (1.1)	32 (18.3)
Hyperpyrexia	-	1 (0.8)	1 (50)	-	-	1 (0.6)
Second dose						
Number of vaccinees	-	**90 (100)**	**-**	**41 (100)**	**131 (100)**	**131 (100)**
Subjects with at least one solicited ADR, n (%)	-	43 (47.8)	-	36 (87.8)	79 (60.3)	83 (63.4)
Local solicited adverse reaction, n (%)						
Injection site erythema	-	1 (1.1)	-	5 (12.2)	6 (4.6)	11 (8.4)
Injection site haematoma	-	1 (1.1)	-	3 (7.3)	4 (3.1)	5 (3.8)
Injection site induration	-	-	-	-	-	2 (1.5)
Injection site inflammation	-	7 (7.8)	-	7 (17.1)	14 (10.7)	21 (16)
Injection site pain	-	23 (25.6)	-	21 (51.2)	44 (33.6)	50 (38.2)
Injection site pruritus	-	4 (4.4)	-	-	4 (3.1)	5 (3.8)
Injection site reaction	-	-	-	-	-	-
Injection site swelling	-	5 (5.6)	-	7 (17.1)	12 (9.2)	16 (12.2)
Injection site warmth	-	4 (4.4)	-	5 (12.2)	9 (6.9)	12 (9.2)
Systemic solicited adverse reactions, n (%)						
Arthralgia	-	3 (3.3)	-	4 (9.8)	7 (5.3)	17 (13)
Chills	-	6 (6.7)	-	11 (26.8)	17 (13)	25 (19.1)
Fatigue	-	25 (27.8)	-	16 (39)	41 (31.3)	51 (38.9)
Headache	-	20 (22.2)	-	7 (17.1)	27 (20.6)	35 (26.7)
Malaise	-	12 (13.3)	-	17 (41.5)	29 (22.1)	36 (27.5)
Myalgia	-	18 (20)	-	20 (48.8)	38 (29)	41 (31.3)
Nausea	-	3 (3.3)	-	4 (9.8)	7 (5.3)	16 (12.2)
Body temperature increased	-	3 (3.3)	-	4 (9.8)	7 (5.3)	8 (6.1)
Pyrexia	-	-	-	-	9 (6.9)	20 (15.3)
Hyperpyrexia	-	4 (4.4)	-	5 (12.2)	0 (0)	1 (0.8)

Legend: percentages are calculated based on the total number of vaccinees who received a first or a second dose of vaccine, by COVID-19 vaccine manufacturer. The table includes data pooled across countries. **Abbreviations:** ADR=adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.=years old.

Lactating women

Lactating women mostly received BioNTech/Pfizer. Injection site pain was the most frequently reported local ADR following the first and the second dose. Fatigue, headache and myalgia were the most frequently reported systemic ADRs following the first dose. The same was observed following the second dose but with a lower rate compared to the first dose.

Table 34. Frequency of reported local and systemic solicited ADRs in the lactating women group by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine.

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
First dose							
Number of vaccinees	-	**21 (100)**	**-**	**4 (100)**	**1 (100)**	**26 (100)**	**26 (100)**
Subjects with at least one solicited ADR, n (%)	-	15 (71.4)	-	3 (75)	0 (0.0)	18 (69.2)	13 (50)
Local solicited adverse reaction (MedDRA PT), n (%)							
Injection site erythema	-	-	-	-	-	0 (0)	2 (7.7)
Injection site haematoma	-	1 (4.8)	-	-	-	1 (3.8)	-
Injection site induration	-	1 (4.8)	-	-	-	1 (3.8)	-
Injection site inflammation	-	-	-	1 (25)	-	1 (3.8)	1 (3.8)
Injection site pain	-	11 (52.4)	-	2 (50)	-	13 (50)	10 (38.5)
Injection site pruritus	-	-	-	0 (0)	-	0 (0)	1 (3.8)
Injection site reaction	-	1 (4.8)	-	0 (0)	-	1 (3.8)	1 (3.8)
Injection site swelling	-	2 (9.5)	-	0 (0)	-	2 (7.7)	5 (19.2)
Injection site warmth	-	1 (4.8)	-	1 (25)	-	2 (7.7)	2 (7.7)
Systemic solicited adverse reactions (MedDRA PT), n (%)							
Arthralgia	-	2 (9.5)	-	2 (50)	-	4 (20)	1 (3.8)
Chills	-	1 (4.8)	-	2 (50)	-	3 (15)	1 (3.8)
Fatigue	-	6 (28.6)		3 (75)	-	9 (45)	5 (19.2)
Headache	-	6 (28.6)	-	2 (50)	-	8 (40)	2 (7.7)
Malaise	-	3 (14.3)	-	2 (50)	-	5 (25)	3 (11.5)
Myalgia	-	3 (14.3)	-	1 (25)	-	4 (20)	2 (7.7)
Nausea	-	1 (4.8)	-	1 (25)	-	2 (10)	0 (0)
Body temperature increased	-	-	-	-	-	-	1 (3.8)
Pyrexia	-	-	-	-	-	-	1 (3.8)
Hyperpyrexia	-	-	-	-	-	-	-
Second dose							
Number of vaccinees	-	**14 (100)**	**-**	**4 (100)**	**1 (100)**	**20 (100)***	**20 (100)**
Subjects with at least one solicited ADR, n (%)	-	7 (50)	-	2 (50)	0 (0.0)	9 (45)	10 (50)
Local solicited adverse reaction, n (%)							10
Injection site erythema	-	2 (14.3)	-	0 (0)	-	2 (10)	1 (5)
Injection site haematoma	-	1 (7.1)	-	1 (25)	-	2 (10)	-
Injection site induration	-	-	-	1 (25)	-	1 (5)	-
Injection site inflammation	-	1 (7.1)	-	1 (25)	-	2 (10)	-
Injection site pain	-	5 (35.7)	-	1 (25)	-	6 (30)	5 (25)
Injection site pruritus	-	-	-	-	-	0 (0)	2 (10)
Injection site reaction	-	-	-	-	-	0 (0)	0 (0)
Injection site swelling	-	1 (7.1)	-	-	-	1 (5)	1 (5)
Injection site warmth	-	-	-	-	-	0 (0)	1 (5)
Systemic solicited adverse reactions, n (%)							
Arthralgia	-	1 (7.1)	-	-	-	1 (5)	2 (10)
Chills	-	1 (7.1)	-	1 (25)	-	2 (10)	3 (15)
Fatigue	-	1 (7.1)	-	0 (0)	-	1 (5)	5 (25)

	COVID-19 vaccine manufacturer						
	AstraZeneca	**BioNTech/ Pfizer**	**Janssen**	**Moderna**	**Novavax**	**All vaccines**	**Matched general population**
Headache	-	1 (7.1)	-	1 (25)	-	2 (10)	5 (25)
Malaise	-	2 (14.3)	-	1 (25)	-	3 (15)	3 (15)
Myalgia	-	-	-	1 (25)	-	1 (5)	4 (20)
Nausea	-	-	-	1 (25)	-	1 (5)	-
Body temperature increased	-	1 (7.1)	-	-	-	1 (5)	2 (10)
Pyrexia	-	-	-	-	-	-	1 (5)
Hyperpyrexia	-	-	-	-	-	-	-

*****Including 1 vaccinee who reported an unknown vaccine brand. **Legend:** percentages are calculated based on the total number of vaccinees who received a first or a second dose of vaccine, by COVID-19 vaccine manufacturer. The table includes data pooled across countries. **Abbreviations:** ADR=adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.=years old.

10.4 Main results: special population serious adverse reaction data

10.4.1 Vaccinee-reported serious adverse reactions following the first and the second dose

Overall, 6 (0.2%) vaccinees in the cohort of allergy (N= 3,477), 4 (0.2%) vaccinees with prior SARS-CoV-2 infection (N= 2,594), 3 (0.5%) immunocompromised vaccinees (N= 567), 2 (0.3%) vaccinees in the children/adolescents' cohort (N= 732) and 1 (0.6%) pregnant woman (N= 175) reported at least one serious ADR following the first dose of any COVID-19 vaccine. Tables 35 shows the list of reported serious ADRs following the first dose, by country, special cohort and COVID-19 vaccine manufacturer.

Table 35. List of reported serious ADRs following the first dose in special cohorts by COVID-19 vaccine and country.

	COVID-19 vaccine manufacturer	**Reported serious adverse reactions**	**N. of reported serious ADRs**
The Netherlands			
People with prior SARS-CoV-2 infection	AstraZeneca	Dyspnoea	1
	AstraZeneca	Epistaxis	1
		Eye inflammation	1
		Hyperresponsive to stimuli	1
		Injection site haematoma	1
		Musculoskeletal pain	1
		Oral herpes	1
		Pain in extremity	1
		Palpitations	1
		Pruritus	1
		Rash	1
		Retinal detachment	1
		Vertigo	1
		Vitreous floaters	1
		Vomiting	1
	BioNTech/Pfizer	Dyspnoea	1
	BioNTech/Pfizer	Eye haemorrhage	1
	BioNTech/Pfizer	Hypersensitivity	1
	BioNTech/Pfizer	Pruritus	1

	COVID-19 vaccine manufacturer	Reported serious adverse reactions	N. of reported serious ADRs
	BioNTech/Pfizer	Rash	1
	Janssen	Abdominal discomfort	1
		COVID-19	1
		Chest discomfort	1
		Cyst	1
		Dysphonia	1
		Limb discomfort	1
		Panic reaction	1
	Janssen	Tinnitus	1
		Tracheal pain	1
	Moderna	Dizziness	1
		Lymphadenopathy	1
		Therapeutic response unexpected	1
People with a history of allergy	AstraZeneca	Anxiety	1
	AstraZeneca	Asthenia	2
	AstraZeneca	Chronic pigmented purpura	1
		Dizziness	1
		Dry skin	1
		Erythema	1
		Exercise tolerance decreased	1
		Headache	1
		Hypersensitivity	2
		Muscular weakness	1
		Neck pain	1
		Oropharyngeal pain	1
		Pain in extremity	3
		Pain of skin	1
		Photophobia	1
		Pruritus	1
		Pulmonary pain	1
		Rash	2
		Rash pruritic	1
		Restless legs syndrome	1
		Swelling face	1
		Tendonitis	1
		Vertigo	1
	BioNTech/Pfizer	Ageusia	1
		Cough	1
	Janssen	Diarrhoea	1
	Janssen	Dizziness	2
	Janssen	Dysmenorrhoea	1
	Janssen	Erythema	1
	Moderna	Gingival bleeding	1
	Moderna	Goitre	1
	Moderna	Hyperhidrosis	1
	Moderna	Hyperresponsive to stimuli	1
		Influenza	1
		Myocardial infarction	1
		Oedema peripheral	1

	COVID-19 vaccine manufacturer	Reported serious adverse reactions	N. of reported serious ADRs
		Paraesthesia	2
		Paraesthesia oral	1
		Photophobia	1
		Pruritus	1
		Rash	2
		Swelling	1
		Vision blurred	1
	Janssen	Abdominal discomfort	1
		Abdominal pain	1
		Abortion spontaneous	1
		Anaphylactic reaction	1
		Chills	1
		Discomfort	1
		Eye pain	1
		Fatigue	1
		Generalised tonic-clonic seizure	1
	Janssen	Heavy menstrual bleeding	1
		Malaise	1
		Muscle spasms	1
		Nasopharyngitis	1
		Oligomenorrhoea	1
		Palpitations	1
		Paraesthesia	2
		Respiratory tract irritation	1
		Sinusitis	1
	Moderna	Amenorrhoea	1
		Constipation	1
		Cough	1
		Diarrhoea	1
		Dizziness	2
		Dysgeusia	1
		Flushing	1
		Gait disturbance	1
		Hypotension	1
		Injection site discomfort	3
		Injection site rash	1
		Inner ear disorder	1
		Loss of consciousness	1
		Ophthalmic migraine	1
		Oropharyngeal pain	1
		Pruritus	1
		Rash	1
		Throat tightness	1
		Vision blurred	1
		Vomiting	1
Pregnant women	BioNTech/Pfizer	Abortion spontaneous	1
	Moderna	Injection site pain	1
Immunocompromised	AstraZeneca	Asthma	1
	AstraZeneca	Dyspnoea	1
		Medical device site hypersensitivity	1
		Pruritus	1

	COVID-19 vaccine manufacturer	Reported serious adverse reactions	N. of reported serious ADRs
		Swollen tongue	1
		Taste disorder	1
	BioNTech/Pfizer	Abortion spontaneous	1
		Asthma	1
		Palpitations	1
		Paraesthesia	1
		Rash	1
	Moderna	Cough	1
		Ophthalmic migraine	1
		Throat tightness	1
Italy			
People with prior SARS-CoV-2 infection	Moderna	Hyperpyrexia	1
People with history of allergy	BioNTech/Pfizer	Dysentery	1
Immunocompromised people	Moderna	Malaise	1
Children and Adolescent	Moderna	Arthralgia	1
	Moderna	Headache	1
	Moderna	Myalgia	1
	Moderna	Paraesthesia	1
	Moderna	Pyrexia	1
France			
Children and adolescents	BioNTech/Pfizer	Paraesthesia	1
	BioNTech/Pfizer	Swelling face	1

Note: a single participant can belong to different cohorts and more than one serious adverse reaction can be reported by a single participant.

Overall, 10 (0.4%) vaccinees in the cohort of allergy (N=2,243), 2 (0.2%) vaccinees with prior SARS-CoV-2 infection (N=910), 2 (0.5%) immunocompromised vaccinees (N=416), 1 (0.2%) vaccinee in the children/adolescents' cohort (N=422) and 1 (0.8%) pregnant woman (N=131) reported at least one serious ADR following the second dose of any COVID-19 vaccine. Table 36 shows the list of reported serious ADRs following the second dose, by country, special cohort and COVID-19 vaccine manufacturer.

Table 36. List of reported serious adverse reactions following the second dose in special target group by COVID-19 vaccine manufacturer and country.

	COVID-19 vaccine manufacturer	Reported serious adverse reactions	N. of reported serious ADRs
Belgium			
	BioNTech/Pfizer	Hypothermia	1
The Netherlands			
People with prior SARS-CoV-2 infection	AstraZeneca	Dizziness	1
	BioNTech/Pfizer	Dizziness	1
People with history of allergy	AstraZeneca	Axillary pain	1
	BioNTech/Pfizer	COVID-19	1
	BioNTech/Pfizer	Depressed mood	1
	Moderna	Dizziness	1
		Hypersensitivity	1
		Hypomenorrhoea	1
		Injection site discomfort	1

	COVID-19 vaccine manufacturer	Reported serious adverse reactions	N. of reported serious ADRs
		Nasopharyngitis	1
		Ocular hyperaemia	1
	BioNTech/Pfizer	Abdominal distension	1
		Asthenia	1
		Body temperature increased	1
		Chest discomfort	1
		Diarrhoea	1
		Dizziness	2
		Gastrointestinal pain	1
		Hypersensitivity	1
		Hypertension	1
		Influenza like illness	1
		Injection site discomfort	1
		Lacunar infarction	1
		Malaise	1
		Nasopharyngitis	2
		Ocular discomfort	1
		Paraesthesia oral	1
		Polyuria	1
		Postmenopausal haemorrhage	1
		Pyrexia	1
		Swelling	1
		Syncope	1
		Therapeutic response unexpected	1
	Moderna	Arthritis	1
		Body temperature increased	1
		Cardiac discomfort	1
		Injected limb mobility decreased	1
		Nasopharyngitis	1
Immunocompromised	BioNTech/Pfizer	Chest discomfort	1
	BioNTech/Pfizer	Hot flush	1
	Moderna	Hypertension	1
		Injection site paraesthesia	1
		Malaise	1
		Pruritus	1
	Moderna	Arthritis	1
Pregnant women	BioNTech/Pfizer	Rhinorrhoea	1
		Sneezing	1
	Moderna	Foetal growth restriction	1
Italy			
People with history of allergy	BioNTech/Pfizer	Haematochezia	1
	BioNTech/Pfizer	Herpes zoster	1
Children/adolescents	BioNTech/Pfizer	Haematochezia	1
France			
People with history of allergy	BioNTech/Pfizer	Syncope	1

Note: a single participant can belong to different cohorts and more than one serious adverse reaction can be reported by a single participant.

10.5 Vaccinee-reported adverse events of special interest following the first and second dose

11 Results: Monitoring of the special target groups and general population receiving a booster dose of any COVID-19 vaccine

Overall, 15 (0.4%) vaccinees in the cohort of allergy (N= 3,477), 2 (0.1%) vaccinees with prior SARS-CoV-2 infection (N= 2,594) and 1 (0.2%) immunocompromised vaccinee (N= 567) reported at least one AESI following the first dose of any COVID-19 vaccine. As for the second dose, 5 (0.2%) vaccinees in the cohort of allergy (N= 2,243) and 1 (0.2%) immunocompromised vaccinee (N= 416) reported at least one AESI following the second dose of any COVID-19 vaccine. Tables 37 and 38 show the list of the reported AESIs following the first and second doses, respectively.

Table 37. List of reported adverse events of special interest following the first dose in special target group by COVID-19 vaccine manufacturer and country.

	COVID-19 vaccine manufacturer	Reported AESI	N. of AESI
The Netherlands			
People with prior SARS-CoV-2 infection	BioNTech/Pfizer	Hypersensitivity	1
	Moderna	Hypersomnia	1
People with history of allergy	AstraZeneca	Facial paralysis	1
		Hypersensitivity	5
	BioNTech/Pfizer	Hypersensitivity	4
		Myocardial infarction	1
	Janssen	Anaphylactic reaction	1
		Generalised tonic-clonic seizure	1
	Moderna	Hypersensitivity	1
Immunocompromised	AstraZeneca	Epilepsy	1
France			
People with history of allergy	BioNTech/Pfizer	Pericarditis	1

Note: a single participant can belong to different cohorts and more than one serious adverse reaction can be reported by a single participant.

Table 38. List of reported adverse events of special interest following the second dose in special target group by COVID-19 vaccine manufacturer and country.

	COVID-19 vaccine manufacturer	Reported AESI	N. of AESI
The Netherlands			
People with history of allergy	AstraZeneca	Hypersensitivity	1
	BioNTech/Pfizer	Hypersensitivity	2
	Moderna	Pancreatitis acute	1
Immunocompromised people	Moderna	Platelet count decreased	1

Note: a single participant can belong to different cohorts and more than one serious adverse reaction can be reported by a single participant.

12 Results: Monitoring of the special target groups and general population receiving a booster dose of any COVID-19 vaccine

12.1 Participants

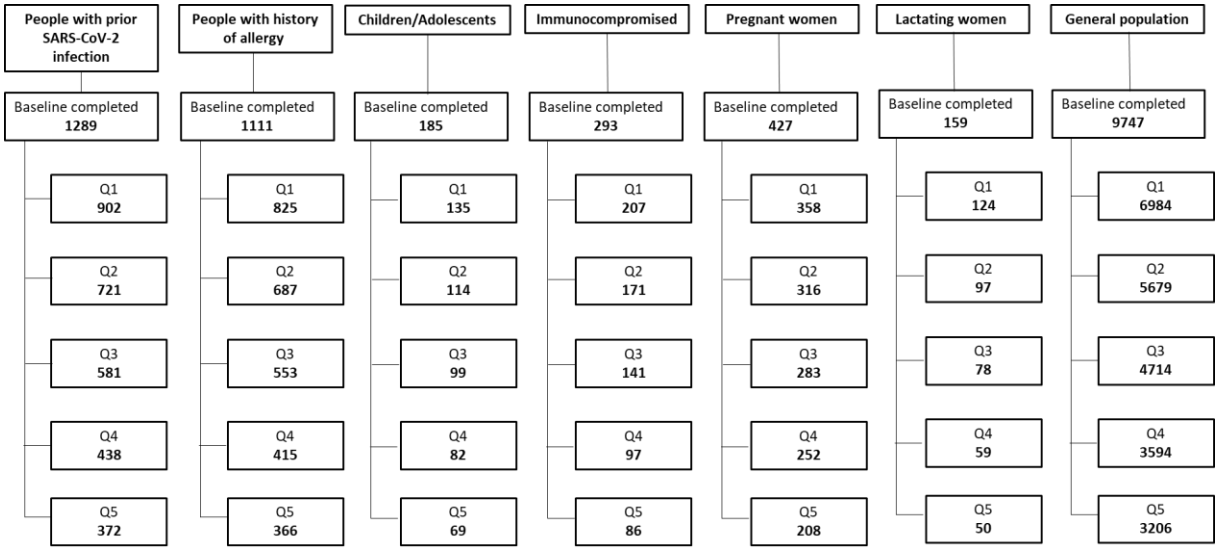

***Figure** 14. Flow-chart including the number of questionnaires completed, by special cohorts and the general population (that includes special cohorts).*

Data from general and special populations collected in France, Italy, Ireland, Portugal, Romania, Slovakia, Spain, Switzerland and the United Kingdom were retrieved from the RO dataset using a CDM (latest update April 17, 2023). Overall, 6,984 vaccinees from the general population, including special cohorts, who received a booster dose of COVID-19 vaccine and completed the baseline questionnaire and, at least, the Q1 were included. Table 39 summarises the total number of participants included by country, from both the general population and each special cohort. Please note that a single participant may belong to more special target groups, and therefore, the table should be read across the columns. In addition, even if some countries are not intentionally enrolling participants belonging to some cohorts, it may still happen that a participant belonging to a targeted group for that country has characteristics that are specific for other groups too.

Table 39. Overview of the total vaccinees included following the booster dose, per country, with a focus on vaccinees belonging to at least one special cohort.

	Special cohorts*						General population**	Start date
	People with prior SARS-CoV-2 infection	Children/ Adolescents	People with a history of allergy	Immuno-compromised	Pregnant women	Lactating women		
France	351 (38.2)	29 (21.5)	463 (56.1)	65 (31.4)	37 (10.3)	25 (20.2)	3,843 (55.0)	14/06/2021
Ireland	13 (1.6)	NA	11 (1.3)	2 (1.0)	163 (45.5)	7 (5.6)	177 (2.5)	09/06/2021
Italy	213 (25.8)	75 (55.6)	235 (28.5)	89 (43.0)	59 (16.5)	47 (37.9)	1,873 (26.8)	01/02/2021
Portugal	13 (1.6)	NA	15 (1.8)	6 (2.9)	10 (2.8)	3 (2.4)	101 (1.4)	05/02/2022
Romania	59 (7.1)	7 (5.2)	19 (2.3)	3 (1.4)	3 (0.8)	4 (3.2)	196 (2.8)	23/06/2021
Slovakia	NA	7 (5.2)	2 (0.2)	NA	NA	1 (0.8)	9 (0.1)	01/12/2021
Spain	50 (6.0)	10 (7.4)	31 (3.8)	6 (2.9)	3 (0.8)	4 (3.2)	197 (2.8)	11/01/2022
Switzerland	30 (3.6)	NA	11 (1.3)	NA	81 (22.6)	18 (14.5)	97 (1.4)	13/12/2021
The UK	133 (16.1)	7 (5.2)	38 (4.6)	36 (17.4)	2 (0.6)	15 (12.1)	491 (7.0)	19/01/2022
Total	**827 (100)**	**135 (100)**	**825 (100)**	**207 (100)**	**358 (100)**	**124 (100)**	**6,984 (100)**	

Note: These participants completed the baseline questionnaire and the first follow-up questionnaire (Q1). *****Focus on special cohorts. Please note that a single participant may belong to different special cohorts. ******The general population includes also vaccinees belonging to a special cohort. **Abbreviations**: NA= not applicable; y.o.= years old.

The children/adolescents' cohort, including vaccinees aged between 5 and 17 years, was identified based on the age indicated by the parent/legal representative filling in the baseline questionnaire on their behalf. In addition, children in the age category 0-4 years (N=6) were also included, even though they were enrolled before the approval of vaccination in children aged between 6 months and 4 years. It is therefore likely that these subjects reported an incorrect date of birth when completing the baseline questionnaire. Since these children may belong to different cohorts, they were included in the denominators. Considering the recruitment start date, the highest number of subjects was registered in France and Italy. Specifically, France and Italy mostly recruited vaccinees with prior SARS-CoV-2 infection and with a history of allergy. A major contribution of the group of pregnant women came from Ireland. For the children/adolescents cohort, most subjects were registered in Italy. However, the late start of the vaccination campaign for the first dose in children (5-11 years old) in all countries should be considered.

12.2 Descriptive data (Primary Objective 1)

Table 40 shows the distribution of registered vaccinees with the female/male ratio by special cohort, COVID-19 vaccine manufacturer and country. As expected, participants were almost exclusively vaccinated with the BioNTech/Pfizer and the Moderna vaccines, the first vaccines to be approved by the EMA for the booster vaccination. Most of the participants in each cohort received the BioNTech/Pfizer vaccine. Overall, most of the participants in all special cohorts were female. When stratifying by vaccine manufacturer and country, some variability is observed. When information from all countries and all vaccine manufacturers are pooled together, the highest F/M ratio was found in the group of people with a history of allergy, while the lowest was in the group of children/adolescents. Please note that Ireland and Switzerland should recruit only female subjects. No information on the median age was included in the dashboard.

Table 40. Number of participants and female/male (F/M) ratio by county and COVID-19 vaccine manufacturer.

		Special cohorts						
		Prior SARS-CoV-2 infection	**Children/ Adolescents**	**People with history of allergy**	**Immuno-compromised**	**Pregnant women**	**Lactating women**	**General population**
France								
AstraZeneca	n vaccinees (%)	NA	NA	NA	NA	NA	NA	5 (0.1)
	F/M ratio	NA	NA	NA	NA	NA	NA	0.3
	median age (y.o.)	NA	NA	NA	NA	NA	NA	59.0
BioNTech/ Pfizer	n vaccinees (%)	141 (44.6)	27 (93.1)	204 (44.1)	33 (50.8)	20 (54.1)	6 (24.0)	1,638 (42.6)
	F/M ratio	2.1	1.3	2.1	0.9	-	-	1.7
	median age (y.o.)	39.0	14.0	46.5	50.0	32.5	30.0	46
Janssen	n vaccinees (%)	NA	NA	NA	NA	NA	NA	1 (0.0)
	F/M ratio	NA	NA	NA	NA	NA	NA	-
	median age (y.o.)	NA	NA	NA	NA	NA	NA	57.0
Moderna	n vaccinees (%)	175 (55.4)	2 (6.9)	258 (55.7)	32 (49.2)	17 (45.9)	19 (76.0)	2,198 (57.2)
	F/M ratio	1.5	-	2.5	1.1	-	-	1.3
	median age (y.o.)	46.0	NA	47.0	57.0	35.0	34.0	46.0
All vaccines	**n vaccinees (%)**	**316 (100)**	**29 (100)**	**463 (100)**	**65 (100)**	**37 (100)**	**25 (100)**	**3,843 (100)**
	F/M ratio	**1.6**	**1.4**	**2.3**	**1.0**	**-**	**-**	**1.5**
	median age (y.o.)	**44.0**	**14.0**	**47.0**	**54.0**	**33.0**	**34.0**	**48.0**
Ireland								
AstraZeneca	n vaccinees (%)	NA	NA	NA	NA	NA	NA	1 (0.6)
	F/M ratio	NA	NA	NA	NA	NA	NA	1.5
	median age (y.o.)	NA	NA	NA	NA	NA	NA	25.0
BioNTech/ Pfizer	n vaccinees (%)	10 (76.9)	NA	8 (72.7)	1 (50.0)	130 (79.8)	5 (71.4)	138 (78.0)
	F/M ratio	-	-	-	-	-	-	137.0
	median age (y.o.)	36.0	-	34.5	32.0	35.0	32.0	35.0
Moderna	n vaccinees (%)	3 (23.1)	NA	3 (27.3)	1 (50.0)	33 (20.2)	2 (28.6)	38 (21.5)
	F/M ratio	-	NA	-	-	-	-	-
	median age (y.o.)	37.0	NA	35.0	37.0	36.0	40.5	36.0
All vaccines	**n vaccinees (%)**	**13 (100)**	**NA**	**11 (100)**	**2 (100)**	**163 (100)**	**7 (100)**	**177 (100)**
	F/M ratio	**-**	-	**-**	**-**	**-**	**-**	**176.0**
	median age (y.o.)	**36.5**	**-**	**35.0**	**34.5**	**36.0**	**35.0**	**35.0**
Italy								
AstraZeneca	n vaccinees (%)	1 (0.5)	NA	1 (0.4)	-	-	-	12 (0.6)
	F/M ratio	0.0	NA	0.0	-	-	-	1.4
	median age (y.o.)	68.0	NA	42.0	-	-	-	49.0
BioNTech/ Pfizer	n vaccinees (%)	159 (74.6)	75 (100)	144 (61.3)	61 (68.5)	49 (83.1)	29 (61.7)	1,175 (62.7)
	F/M ratio	1.6	1.0	3.5	2.8	-	-	1.8
	median age (y.o.)	46.0	11.0	42.5	47.0	36.0	34.0	43.0
Janssen	n vaccinees (%)	NA	NA	NA	NA	NA	NA	2 (0.1)
	F/M ratio	NA	NA	NA	NA	NA	NA	-

		Special cohorts						
		Prior SARS-CoV-2 infection	Children/ Adolescents	People with history of allergy	Immuno-compromised	Pregnant women	Lactating women	General population
	median age (y.o.)	NA	NA	NA	NA	NA	NA	73.5
Moderna	n vaccinees (%)	53 (24.9)	NA	88 (37.4)	28 (31.5)	10 (16.9)	17 (36.2)	678 (36.2)
	F/M ratio	1.7	NA	3.0	1.5	-	-	1.3
	median age (y.o.)	39.5	NA	45.5	49.5	34.5	37.0	44.0
Novavax	n vaccinees (%)	-	-	1 (0.4)	-	-	1 (2.1)	4 (0.2)
	F/M ratio	-	-	-	-	-	-	1.0
	median age (y.o.)	-	-	38.0	-	-	-	38.0
All vaccines	**n vaccinees (%)**	**213 (100)**	**75 (100)**	**235 (100)**	**89 (100)**	**59 (100)**	**47 (100)**	**1,873 (100)**
	F/M ratio	**1.6**	**1.0**	3.3	**2.3**	**-**	**-**	**1.6**
	median age (y.o.)	**44.0**	**11.0**	**44.0**	**48.0**	**36.0**	**36.0**	**44.0**
Romania								
BioNTech/ Pfizer	n vaccinees (%)	41 (69.5)	7 (100)	16 (84.2)	2 (66.7)	3 (100)	3 (75.0)	134 (68.4)
	F/M ratio	2.2	2.5	1.0	1.0	-	-	1.4
	median age (y.o.)	33.0	14.0	30.5	37.0	30.0	29 .0	32.0
Moderna	n vaccinees (%)	18 (30.5)	-	3 (15.8)	1 (33.3)	-	1 (25.0)	60 (30.6)
	F/M ratio	1.3	-	2.0	-	-	-	1.2
	median age (y.o.)	35.5	-	34.0	51.0	-	37.0	32.5
Janssen	n vaccinees (%)	NA	NA	NA	NA	NA	NA	2 (1.0)
	F/M ratio	NA	NA	NA	NA	NA	NA	0.0
	median age (y.o.)	NA	NA	NA	NA	NA	NA	43.5
All vaccines	**n vaccinees (%)**	**59 (100)**	**7 (100)**	**19 (100)**	**3 (100)**	**3 (100)**	**4(100)**	**196 (100)**
	F/M ratio	**1.8**	**2.5**	**1.1**	**2.0**	**-**	**-**	**1.3**
	median age (y.o.)	**33.0**	**14.0**	**32.0**	**39.0**	**30.0**	**30.0**	**32.0**
Slovakia								
BioNTech/ Pfizer	n vaccinees (%)	NA	7 (100)	1 (50.0)	NA	NA	NA	8 (88.9)
	F/M ratio	NA	2.5	0.0	NA	NA	NA	1.7
	median age (y.o.)	NA	15.0	32.0	NA	NA	NA	15.5
Moderna	n vaccinees (%)	NA	NA	1 (150.0)	NA	NA	1 (100)	1 (11.1)
	F/M ratio	NA	NA	-	NA	NA	-	-
	median age (y.o.)	NA	NA	28.0	NA	NA	28.0	28.0
All vaccines	**n vaccinees (%)**	**NA**	**7 (100)**	**2 (100)**	**NA**	**NA**	**1 (100)**	**9 (100)**
	F/M ratio	**NA**	**2.5**	**1.0**	**NA**	**NA**	**-**	**2.0**
	median age (y.o.)	**NA**	**15.0**	**30.0**	**NA**	**NA**	**28.0**	**16.0**
Spain								
AstraZeneca	n vaccinees (%)	NA	NA	NA	NA	NA	NA	1 (0.5)
	F/M ratio	NA	NA	NA	NA	NA	NA	0.0
	median age (y.o.)	NA	NA	NA	NA	NA	NA	36.0
BioNTech/ Pfizer	n vaccinees (%)	30 (60.0)	8 (80.0)	12 (38.7)	2 (33.3)	1 (33.3)	NA	72 (36.5)
	F/M ratio	2.3	1.0	2.0	1.0	-	-	1.6

		Special cohorts						
		Prior SARS-CoV-2 infection	Children/ Adolescents	People with history of allergy	Immuno-compromised	Pregnant women	Lactating women	General population
Moderna	median age (y.o.)	41.0	16.0	40.0	50.0	38.0	NA	39.5
	n vaccinees (%)	18 (36.0)	-	19 (61.3)	4 (66.7)	2 (66.7)	4 (100)	121 (61.4)
	F/M ratio	1.3	-	1.7	3.0	-	-	1.4
	median age (y.o.)	37.0	-	42.0	33.5	31.5	36.0	43.0
All vaccines	**n vaccinees (%)**	**50 (100)**	**10 (100)**	**31 (100)**	**6 (100)**	**3 (100)**	**4 (100)**	**197 (100)**
	F/M ratio	**1.6**	**0.7**	**1.8**	**2.0**	**-**	**-**	**1.4**
	median age (y.o.)	**38.5**	**16.0**	**41.0**	**42.0**	**33.0**	**36.0**	**41.0**
Switzerland								
BioNTech/ Pfizer	n vaccinees (%)	14 (46.7)	NA	6 (54.5)	NA	33 (40.7)	9 (50.0)	42 (43.3)
	F/M ratio	-	-	-	NA	-	-	-
	median age (y.o.)	33.0	NA	35.0	NA	33.0	31.0	33.0
Moderna	n vaccinees (%)	16 (53.3)	NA	5 (45.5)	NA	47 (58.0)	9 (50.0)	54 (55.7)
	F/M ratio	-	-	-	NA	-	-	-
	median age (y.o.)	35.0	NA	34.0	NA	35.0	33.0	34.0
All vaccines	**n vaccinees (%)**	**30 (100)**	**NA**	**11 (100)**	**NA**	**81 (100)**	**18 (100)**	**97 (100)**
	F/M ratio	**-**	**-**	**-**	**NA**	**-**	**-**	**-**
	median age (y.o.)	**35.0**	**NA**	**34**	**NA**	**34.0**	**33.0**	**33.0**
United Kingdom								
AstraZeneca	n vaccinees (%)	2 (1.5)	NA	2 (5.3)	1 (2.8)	NA	NA	9 (1.8)
	F/M ratio	0.0	NA	-	0.0	NA	NA	0.5
	median age (y.o.)	54.0	NA	53.5	64.0	NA	NA	49.0
BioNTech/ Pfizer	n vaccinees (%)	75 (56.4)	6 (85.7)	29 (76.3)	28 (77.8)	2 (100)	11 (73.3)	300 (61.1)
	F/M ratio	2.4	5.0	1.9	1.5	-	-	2.0
	median age (y.o.)	46.0	17.0	48.0	59.0	36.0	30.0	42.0
Moderna	n vaccinees (%)	56 (42.1)	1 (14.3)	7 (18.4)	6 (16.7)	-	3 (20.0)	176 (35.8)
	F/M ratio	2.7	-	6.0	1.0	-	-	2.1
	median age (y.o.)	48.5	16.0	56.0	64.5	-	31.0	47.0
All vaccines	**n vaccinees (%)**	**133 (100)**	**7 (100)**	**38 (100)**	**36 (100)**	**2 (100)**	**15 (100)**	**491 (100)**
	F/M ratio	**2.6**	**6.0**	**2.5**	**1.4**	**-**	**-**	**2.0**
	median age (y.o.)	**48.0**	**17.0**	**49.5**	**60.5**	**36.0**	**31.0**	**43.0**
Portugal								
BioNTech/ Pfizer	n vaccinees (%)	7 (53.8)	-	8 (53.3)	3 (50.0)	6 (60.0)	2 (66.7)	63 (62.4)
	F/M ratio	0.4	-	-	2.0	-	-	4.3
	median age (y.o.)	49.0	-	21.5	37.0	33.0	37.5	27.0
Moderna	n vaccinees (%)	6 (46.2)	-	7 (46.7)	3 (50.0)	4 (40.0)	1 (33.3)	38 (37.6)
	F/M ratio	2.0	-	1.3	2.0	-	-	3.2
	median age (y.o.)	27.0	-	31.0	31.0	31.0	32.0	24.5
All vaccines	**n vaccinees (%)**	**13 (100)**	**-**	**15 (100)**	**6 (100)**	**10 (100)**	**3 (100)**	**101 (100)**
	F/M ratio	**0.9**	**-**	**4.0**	**2.0**	**-**	**-**	**3.8**

		Special cohorts						
		Prior SARS-CoV-2 infection	Children/ Adolescents	People with history of allergy	Immuno-compromised	Pregnant women	Lactating women	General population
	median age (y.o.)	**31.0**	**-**	**25.0**	**34.0**	**31.5**	**35.0**	**25.0**
All countries								
AstraZeneca	n vaccinees (%)	3 (0.4)	NA	3 (0.4)	1 (0.5)	NA	NA	28 (0.4)
	F/M ratio	0.0	NA	2.0	0.0	NA	NA	0.8
	median age (y.o.)	58.0	NA	48.0	64.0	NA	NA	48.5
BioNTech/ Pfizer	n vaccinees (%)	477 (57.7)	130 (96.3)	428 (51.9)	130 (62.8)	244 (68.2)	65 (52.4)	3,570 (51.1)
	F/M ratio	2.0	1.2	2.6	1.8	-	-	1.9
	median age (y.o.)	41.0	13.0	42.5	50.5	35.0	33.0	42.0
Novavax	n vaccinees (%)	NA	NA	1 (0.1)	NA	NA	1 (0.8)	4 (0.1)
	F/M ratio	NA	NA	-	NA	NA	.-	1.0
	median age (y.o.)	NA	NA	38.0	NA	NA	38.0	38.0
Moderna	n vaccinees (%)	345 (41.7)	3 (2.2)	391 (47.4)	75 (36.2)	113 (31.6)	57 (46.0)	3,364 (48.2)
	F/M ratio	1.8	-	2.7	1.4	-	-	1.4
	median age (y.o.)	43.0	3.0	46.0	51.0	35.0	35.0	47.0
Janssen	n vaccinees (%)	NA	NA	NA	NA	NA	NA	5 (0.1)
	F/M ratio	NA	NA	NA	NA	NA	NA	1.5
	median age (y.o.)	NA	NA	NA	NA	NA	NA	57.0
All vaccines *	**n vaccinees (%)**	**827 (100)**	**135 (100)**	**825 (100)**	**207 (100)**	**358 (100)**	**124 (100)**	**6,984 (100)**
	F/M ratio	**1.9**	**1.3**	**2.6**	**1.6**	**-**	**-**	**1.6**
	median age (y.o.)	**42.5**	**13.0**	**44.0**	**51.0**	**35.0**	**34.0**	**45.0**

*****Including vaccines whose brand name is unknown. **Legend**: *i)* percentages are calculated based on the total number of all vaccines administered to participants belonging to a specific special target group, by country. *ii)* A F/M ratio > 1 indicates that the number of female participants is higher than the number of male participants.

Abbreviations: F=female; M=male; NA=not applicable; n=number; y.o.=years old.

Overall demographic and clinical characteristics of the vaccinees who filled in the baseline questionnaire and the Q1 are shown in Table 41.

Most of participants belonging to the general population and the cohorts of people with prior SARS-CoV-2 infection, people with a history of allergy and immunocompromised were aged between 30 and 59 years. Most of registered children and adolescents (65.9%) were aged between 12 and 17 years. The largest percentage of pregnant (81.6 %) and lactating women (72.6 %) indicated to be aged between 30 and 39 years. Overall, lower percentages of clinical conditions were reported by the vaccinees.

Table 41. Overall demographic and clinical characteristics of participants belonging to the special cohorts and general population following the receipt of the booster dose of any vaccine

	Special cohorts						**General population**
	Prior SARS-CoV-2 infection	**Children/ Adolescents (5-17 y.o.)**	**People with a history of allergy**	**Immuno-compromised**	**Pregnant women**	**Lactating women**	
N of participants (%)	**827 (100)**	**135 (100)**	**825(100)**	**207 (100)**	**358 (100)**	**124 (100)**	**6,984 (100)**
Age group (y.o.), n (%)							
00-04	-	6 (4.4)	-	-	-	-	6 (0.1)
05-11	4 (0.5)	44 (34.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	44 (0.6)
12 – 17	16 (1.9)	85 (65.9)	8 (1.0)	2 (1.0)	-	-	85 (1.2)
18 – 24	67 (8.1)	-	55 (6.7)	8 (3.9)	2 (0.6)	3 (2.4)	482 (6.9)
25 – 29	86 (10.4)	-	65 (7.9)	13 (6.3)	26 (3.9)	15 (12.1)	536 (7.7)
30 – 39	183 (22.1)	-	184 (22.3)	25 (12.1)	292 (81.6)	90 (72.6)	1,549 (22.2)
40 – 49	188 (22.7)	-	205 (24.8)	43 (20.8)	38 (10.6)	16 (12.9)	1,568 (22.5)
50 – 59	179 (21.3)	-	177 (21.5)	60 (29)	-	-	1,419 (20.3)
60 – 69	86 (10.4)	-	113 (13.7)	36 (17.4)	-	-	1,003 (14.4)
70 – 79	17 (2.1)	-	16 (1.9)	18 (8.7)	-	-	262 (3.8)
>80	4 (0.5)	-	1 (0.1)	2 (1)	-	-	30 (0.4)
Sex, n (%)							
Female	543 (65.7)	75 (58.1)	596 (72.2)	128 (61.8)	358 (100)	124 (100)	4,341 (62.2)
Male	284 (34.3)	60 (46.5)	229 (27.8)	79 (38.2)	-	-	2,643 (37.8)
Medical history (MedDRA PT), n (%)							
Cardiovascular disorder	23 (2.8)	-	28 (3.4)	8 (3.9)	2 (0.6)	1 (0.8)	184 (2.6)
Diabetes mellitus	16 (1.9)	-	12 (1.5)	17 (8.2)	6 (1.7)	-	154 (2.2)
Hypertension	60 (7.3)	-	83 (10.1)	32 (15.5)	4 (1.1)	4 (3.2)	623 (8.9)
Immunosuppression	19 (2.3)	2 (1.6)	33 (4)	207 (100)	4 (1.1)	3 (2.4)	207 (3.0)
Liver disorder	2 (0.2)	-	6 (0.7)	4 (1.9)	1 (0.3)	-	29 (0.4)
Lung disorder	56 (6.8)	6 (4.7)	159 (19.3)	19 (9.2)	21 (5.9)	6 (4,8)	386 (5.5)
Mental disorder	30 (3.6)	2 (1.6)	43 (5.2)	8 (3.9)	6 (1.7)	4 (3,2)	246 (3.5)
Neoplasm malignant	8 (1.0)	-	7 (0.8)	19 (9.2)	-	-	64 (0.9)
Nervous system disorder	6 (0.7)	1 (0.8)	10 (1.2)	9 (4.3)	2 (0.6)	1 (0.8)	61 (0.9)
Renal disorder	4 (0.5)	-	2 (0.2)	8 (3.9)	1 (0.3)	-	32 (0.5)

Abbreviations: MedDRA= Medical Dictionary for Regulatory Activities; PT=preferred term; y.o.= years old.

Tables 42, 43, 44, 45, 46 and 47 show in depth the demographic and clinical characteristics of vaccinees included in each special cohort, by vaccine manufacturer. To compare baseline characteristics, each vaccinee belonging to a special cohort was matched, when possible (Tables 42, 44, 45, 46 and 47), with a vaccinee belonging to the general population based on sex, age at study registration, and dose of vaccination (ratio 1:1).

People with prior SARS-CoV-2 infection

Table 42. Demographic and clinical characteristics of people with prior SARS-CoV-2 infection by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer				
	AstraZeneca	**BioNTech/Pfizer**	**Moderna**	**All vaccines**	**General population for SARS-CoV-2 (matched cohort)**
N of participants (%)	**3 (100)**	**477 (100)**	**345 (100)**	**827 (100) ***	**827 (100)**
Sex, n (%)					
Female	-	321 (67.3)	243 (70.4)	543 (65.7)	543 (65.7)
Male	3 (100)	156 (32.7)	133 (38.6)	284 (34.3)	284 (34.3)
Medical history (MedDRA PT), n (%)					
Cardiovascular disorder	0 (0.0)	15 (3.1)	8 (2.3)	23 (2.8)	14 (1.7)
Diabetes mellitus	0 (0.0)	7 (1.5)	9 (2.6)	16 (1.9)	19 (2.3)
Hypertension	1 (33.3)	33 (6.9)	26 (7.5)	60 (7.3)	71 (8.6)
Immunosuppression	0 (0.0)	15 (3.1)	4 (1.2)	19 (2.3)	14 (1.7)
Liver disorder	0 (0.0)	1 (0.2)	1 (0.3)	2 (0.2)	4 (0.5)
Lung disorder	0 (0.0)	32 (6.7)	24 (7.0)	56 (6.8)	48 (5.9)
Mental disorder	1 (33.3)	15 (3.1)	14 (4.1)	30 (3.6)	23 (2.8)
Neoplasm malignant	0 (0.0)	6 (1.3)	2 (0.6)	8 (1.0)	5 (0.6)
Nervous system disorder	0 (0.0)	4 (0.8)	2 (0.6)	6 (0.7)	3 (0.4)
Renal disorder	0 (0.0)	3 (0.6)	1 (0.3)	4 (0.5)	7 (0.8)

*****the total number of all vaccines includes 2 vaccines whose brand name is unknown**. Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Children/Adolescents (5-17 years)

Table 43. Demographic and clinical characteristics of children/adolescents by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer			
	AstraZeneca	**BioNTech/Pfizer**	**Moderna**	**All vaccines**
N of participants (%)	-	**130 (100)**	**3 (100)**	**135 (100) ***
Sex, n (%)				
Female	-	72 (55.4)	3 (100)	75 (56.4)
Male	-	58 (44.6)	-	58 (43.6)
Medical history (MedDRA PT), n (%)				
Cardiovascular disorder	-	-	-	-
Diabetes mellitus	-	-	-	
Hypertension	-	-	-	-
Immunosuppression	-	2 (1.5)	-	2 (1,5)
Liver disorder	-	-	-	-
Lung disorder	-	5 (3.8)	1 (33.3)	6 (4.5)
Mental disorder	-	1 (0.8)	1 (33.3)	2 (1.5)
Neoplasm malignant	-	-	-	-
Nervous system disorder	-	1 (0.8)	-	1 (0.8)
Renal disorder	-	-	-	-

*****the total number of all vaccines includes 2 vaccines whose brand name is unknown.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

People with history of allergy

Table 44. Demographic and clinical characteristics of people with history of allergy by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer					
	AstraZeneca	**BioNTech/ Pfizer**	**Moderna**	**Novavax**	**All vaccines**	**General population for people with a history of allergy (matched cohort)**
N of participants (%)	**3 (100)**	**428 (100)**	**391 (100)**	**1 (100)**	**823 (100) ***	**825 (100)**
Sex, n (%)						
Female	2 (66.7)	308 (72)	284 (72.6)	1 (100)	595 (72.3)	596 (72.2)
Male	1 (33.3)	120 (28)	107 (27.4)	-	228 (27.7)	229 (27.8)
Medical history (MedDRA PT), n (%)						
Cardiovascular disorder	-	20 (4.7)	8 (2)	-	28 (3.4)	12 (1.5)
Diabetes mellitus	1 (33.3)	5 (1.2)	6 (1.5)	-	11 (1.3)	17 (2.1)
Hypertension	-	50 (11.7)	33 (8.4)	-	83 (10.1)	58 (7)
Immunosuppression	-	21 (4.9)	12 (3.1)	-	33 (4)	-
Liver disorder	-	1 (0.2)	5 (1.3)	-	6 (0.7)	1 (0.1)
Lung disorder	-	84 (19.6)	75 (19.2)	-	159 (19.3)	28 (3.4)
Mental disorder	-	31 (7.2)	12 (3.1)	-	43 (5.2)	25 (3)
Neoplasm malignant	-	6 (1.4)	1 (0.3)	-	7 (0.9)	6 (0.7)
Nervous system disorder	-	6 (1.4)	4 (1)	-	10 (1.2)	4 (0.5)
Renal disorder	-	2 (0.5)	-	-	2 (0.2)	9 (1.1)

*****the total number of all vaccines includes 2 vaccines whose brand name is unknown. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Immunocompromised

Table 45. Demographic and clinical characteristics of immunocompromised people by COVID-19 vaccine manufacturer.

	COVID-19 vaccine manufacturer				
	AstraZeneca	**BioNTech/ Pfizer**	**Moderna**	**All vaccines**	**General population for immunocompromised people (matched cohort)**
N of participants (%)	**1 (100)**	**130 (100)**	**75 (100)**	**206 (100) ***	**207 (100)**
Sex, n (%)					
Female	-	83 (63.8)	44 (58.7)	127 (61.7)	128 (61.8)
Male	1 (100)	47 (36.2)	31 (41.3)	79 (38.3)	79 (38.2)
Medical history (MedDRA PT), n (%)					
Cardiovascular disorder	-	4 (3.1)	4 (5.3)	8 (3.9)	8 (3.9)
Diabetes mellitus	1 (100)	8 (6.2)	7 (9.3)	16 (7.8)	10 (4.8)
Hypertension	-	21 (16.2)	10 (13.3)	31 (15)	30 (14.5)
Immunosuppression	1 (100)	130 (100)	75 (100)	206 (100)	-
Liver disorder	-	2 (1.5)	2 (2.7)	4 (1.9)	-
Lung disorder	-	9 (6.9)	10 (13.3)	19 (9.2)	14 (6.8)
Mental disorder	-	6 (4.6)	2 (2.7)	8 (3.9)	7 (3.4)
Neoplasm malignant	-	13 (10)	6 (8)	19 (9.2)	1 (0.5)
Nervous system disorder	-	7 (5.4)	2 (2.7)	9 (4.4)	NA
Renal disorder	1 (100)	4 (3.1)	3 (4)	8 (3.9)	2 (1)

*****the total number of all vaccines includes 1 vaccine whose brand name is unknown. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Pregnant women

Table 46. Demographic and clinical characteristics of pregnant women by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer				
	AstraZeneca	**BioNTech/ Pfizer**	**Moderna**	**All vaccines**	**General population for pregnant women (matched cohort)**
N of participants (%)	-	**244 (100)**	**113 (100)**	**358 (100) ***	**358 (100)**
Medical history (MedDRA PT), n (%)					
Cardiovascular disorder	-	1 (0.4)	1 (0.9)	2 (0.6)	6 (1.7)
Diabetes mellitus	-	4 (1.6)	2 (1.8)	6 (1.7)	2 (0.6)
Hypertension	-	2 (0.8)	2 (1.8)	4 (1.1)	6 (1.7)
Immunosuppression	-	2 (0.8)	2 (1.8)	4 (1.1)	(0)
Liver disorder	-	-	1 (0.9)	1 (0.3)	1 (0.3)
Lung disorder	-	12 (4.9)	9 (8.0)	31 (8.7)	21 (5.9)
Mental disorder	-	4 (1.6)	2 (1.8)	6 (1.7)	11 (3.1)
Neoplasm malignant	-	-	-	-	3 (0.8)

Nervous system disorder	-	2 (0.8)	-	2 (0.3)	-
Renal disorder	-	1 (0.4)	-	1 (0.3)	2 (0.6)

*****the total number of all vaccines includes 1 vaccine whose brand name is unknown. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

Lactating women

Table 47. Demographic and clinical characteristics of lactating women by COVID-19 vaccine manufacturer

	COVID-19 vaccine manufacturer				
	BioNTech/ Pfizer	**Moderna**	**Novavax**	**All vaccines**	**General population for lactating women (matched cohort)**
N of participants (%)	**65 (100)**	**57 (100)**	**1 (100)**	**123 (100) ***	**124 (100)**
Cardiovascular disorder	1 (1.5)	-	-	1 (0,8)	1 (0.8)
Diabetes mellitus	-	-		-	-
Hypertension	3 (4.6)	1 (1.8)	-	4 (3,3)	1 (0.8)
Immunosuppression	3 (4.6)	-	-	3 (2,4)	-
Liver disorder	-	-	-	-	-
Lung disorder	2 (3.1)	4 (7.0)	-	6 (4.9)	6 (4.8)
Mental disorder	3 (4.6)	1 (1.8)	-	4 (3.3)	4 (3.2)
Neoplasm malignant	-	-	-	-	-
Nervous system disorder	1 (1.5)	-	-	1 (0.8)	2 (1.6)
Renal disorder	-	-		-	-

*****the total number of all vaccines includes 1 vaccine whose brand name is unknown. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.

12.3 Outcome data: adverse reaction data (Primary Objective 2)

Table 48 provides an overview of the frequency of all reported ADRs (solicited and unsolicited), with their percentages calculated based on the total number of participants receiving the booster dose by special cohort and general population. The lowest rate of reported ADRs was observed in the children cohort (5-11 years), while the highest was observed in the lactating women cohort. Overall, the percentage of vaccinees-reported ADRs following the receipt of Moderna was higher than the one reported following the receipt of BioNTech/Pfizer.

Table 48. Overview of the number of vaccinee-reported solicited and non-solicited ADRs over the total number of vaccinees belonging to a special cohort and having filled in the baseline questionnaire and at least one follow-up questionnaire by COVID-19 vaccine manufacturer.

	Special target group						
	Prior SARS-CoV-2 infection Any ADR/ Any vaccinees (%)	**Children/ Adolescents (5-17 y.o.)** Any ADR/ Any vaccinees (%)	**People with history of allergy** Any ADR/ Any vaccinees (%)	**Immuno-compromised** Any ADR/ Any vaccinees (%)	**Pregnant Women** Any ADR/ Any vaccinees (%)	**Lactating women** Any ADR/ Any vaccinees (%)	**General population** Any ADR/ Any vaccinees (%)
AstraZeneca	2 /3 (66.7)	NA	1/3 (33.3)	0/1 (0.0)	NA	NA	13/28 (46.4)
BioNTech/ Pfizer	303/477 (63.5)	62/130 (47.7)	307 /428 (71.7)	78/130 (60.0)	126/244 (51.6)	47/65 (72.3)	2,181/3,570 (61.1)
Moderna	255/345 (73.9)	3/3 (100)	316/391 (80.8)	49/75 (65.3)	79/113 (69.9)	49/57 (86.0)	2,296/3,364 (68.3)
All vaccines*	**562/827 (68.0)**	**67/135 (49.6)**	**626/825 (75.9)**	**128/207 (61.8)**	**205/358 (57.3)**	**97/124 (78.2)**	**4,501/6,984 (64.4)**

***Including vaccines whose brand name is unknown. **Legend:** percentages are calculated based on the number of vaccinee-reported solicited and non-solicited adverse reactions over the number of vaccinees receiving a specific vaccine, by a special target group. The table includes data pooled across countries. **Abbreviations:** ADR = adverse reaction; NA= not applicable; y.o.= years old.

Table 49 shows the frequency of reported solicited ADRs following the booster dose, using MedDRA PTs and classified as either local or systematic solicited ADRs. Percentages have been calculated based on the total number of vaccinees who received the booster dose of vaccine, by special cohort and general population.

Overall, half of the vaccinees belonging to the special cohorts and the general population reported at least one solicited ADR following the booster dose. As for the first vaccination cycle, injection site pain was the most frequently reported local ADR among all special cohorts and the general population; fatigue, headache, myalgia and malaise were the most frequently reported systemic ADRs. Chills were also frequently reported among lactating women.

Table 49. Frequency of reported local and systemic solicited ADRs following the booster dose of any vaccine, by special target group

	Special target group						
	People with prior SARS-CoV-2 infection N= 827	**Children/ Adolescents (5-17 y.o.) N= 135**	**People with a history of allergy N= 825**	**Immuno-compromised N= 207**	**Pregnant women N= 358**	**Lactating women N= 124**	**General population N =6,984**
Subjects with at least one solicited ADR, n (%)	540 (65.3)	65 (48.1)	614 (74.4)	125 (60.4)	202 (56.4)	94 (75.8)	4,327 (61.9)
Local solicited adverse reaction (MedDRA PT), n (%)							
Injection site erythema	44 (5.3)	6 (4.4)	62 (7.5)	12 (5.8)	16 (4.5)	8 (6.5)	356 (5.1)
Injection site haematoma	21 (2.5)	1 (0.7)	24 (2.9)	6 (2.9)	9 (2.5)	6 (4.8)	149 (2.1)
Injection site induration	4 (0.5)	0 (0)	5 (0.6)	1 (0.5)	1 (0.3)	1 (0.8)	29 (0.4)
Injection site inflammation	124 (15.0)	12 (8.9)	156 (18.9)	26 (12.6)	48 (13.4)	21 (16.9)	904 (12.9)
Injection site pain	345 (41.7)	41 (30.4)	410 (49.7)	83 (40.1)	139 (38.8)	70 (56.5)	2,685 (38.4)
Injection site pruritus	24 (2.9)	1 (0.7)	41 (5)	8 (3.9)	10 (2.8)	8 (6.5)	222 (3.2)
Injection site reaction	1 (0.1)	0 (0)	2 (0.2)	1 (0.5)	0 (0)	0 (0)	19 (0.3)
Injection site swelling	111 (13.4)	10 (7.4)	166 (20.1)	22 (10.6)	36 (10.1)	23 (18.5)	951 (13.6)
Injection site warmth	68 (8.2)	5 (3.7)	71 (8.6)	12 (5.8)	27 (7.5)	11 (8.9)	381 (5.5)
Systemic solicited adverse reactions (PT), n (%)							
Arthralgia	120 (14.5)	9 (6.7)	142 (17.2)	38 (18.4)	39 (10.9)	24 (19.4)	903 (12.9)
Chills	199 (24.1)	8 (5.9)	200 (24.2)	33 (15.9)	39 (10.9)	31 (25)	1,332 (19.1)
Fatigue	320 (38.7)	37 (27.4)	392 (47.5)	68 (32.9)	105 (29.3)	44 (35.5)	2,433 (34.8)
Headache	231 (27.9)	33 (24.4)	293 (35.5)	45 (21.7)	84 (23.5)	45 (36.3)	1,826 (26.1)
Malaise	220 (26.6)	19 (14.1)	257 (31.2)	51 (24.6)	73 (20.4)	36 (29)	1,630 (23.3)
Myalgia	226 (27.3)	19 (14.1)	276 (33.5)	49 (23.7)	65 (18.2)	43 (34.7)	1,821 (26.1)
Nausea	85 (10.3)	7 (5.2)	117 (14.2)	21 (10.1)	38 (10.6)	12 (9.7)	590 (8.4)
Body temperature increased	66 (8.0)	12 (8.9)	70 (8.5)	11 (5.3)	14 (3.9)	11 (8.9)	7 (0.1)
Pyrexia	117 (14.1)	10 (7.4)	140 (17)	27 (13)	18 (5)	16 (12.9)	838 (12)
Hyperpyrexia	1 (0.19	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	7 (0.1)

Legend: percentages are calculated based on the total number of vaccinees who received a booster dose, by special cohort. The table includes data pooled for countries and COVID-19 vaccine brands. **Abbreviations:** ADR=adverse reaction; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; y.o.= years old.

Tables 50, 51, 52, 53, 54 and 55 show, for each special cohort, the frequency of reported local and systemic solicited ADRs, by COVID-19 vaccine manufacturers. To compare frequency of ADRs, each vaccinee belonging to a special cohort was matched, when possible (tables 50, 52, 53, 54 and 55), with a vaccinee belonging to the general population based on sex, age at study registration, and dose of vaccination (ratio 1:1).

People with prior SARS-CoV-2 infection

Table 50. Frequency of reported local and systemic solicited ADRs in the group of people with prior SARS-CoV-2 infection by COVID-19 vaccine manufacturer, following the booster dose of vaccine

	COVID-19 vaccine manufacturer				
	AstraZeneca	**BioNTech/ Pfizer**	**Moderna**	**All vaccines**	**Matched General Population**
Number of vaccinees	**3 (100)**	**477 (100)**	**345 (100)**	**827 (100) ***	**827 (100)**
Subjects with at least one solicited ADR, n (%)	2 (66.7)	289 (60.6)	247 (71.6)	540 (65.3)	505 (61.1)
Local solicited adverse reactions (MedDRA PT), n (%)					
Injection site erythema	-	26 (5.5)	18 (5.2)	44 (5.3)	54 (6.5)
Injection site haematoma	-	10 (2.1)	11 (3.2)	21 (2.5)	20 (2.4)
Injection site induration	-	2 (0.4)	2 (0.6)	4 (0.5)	3 (0.4)
Injection site inflammation	-	69 (14.5)	55 (15.9)	124 (15)	148 (17.9)
Injection site pain	-	187 (39.2)	157 (45.5)	345 (41.7)	340 (41.1)
Injection site pruritus	-	15 (3.1)	9 (2.6)	24 (2.9)	25 (3.0)
Injection site reaction	-	1 (0.2)	-	1 (0.1)	1 (0.1)
Injection site swelling	-	53 (11.1)	58 (16.8)	111 (13.4)	152 (18.4)
Injection site warmth	-	40 (8.4)	27 (7.8)	68 (8.2)	66 (8.0)
Systemic solicited adverse reactions (MedDRA PT), n (%)					
Arthralgia	-	69 (14.5)	51 (14.8)	120 (14.5)	107 (12.9)
Chills	1 (33.3)	103 (21.6)	94 (27.2)	199 (24.1)	148 (17.9)
Fatigue	1 (33.3)	175 (36.7)	142 (41.2)	320 (38.7)	278 (33.6)
Headache	-	108 (22.6)	122 (35.4)	231 (27.9)	229 (27.7)
Malaise	1 (33.3)	115 (24.1)	103 (29.9)	220 (26.6)	200 (24.2)
Myalgia	2 (66.7)	122 (25.6)	101 (29.3)	226 (27.3)	211 (25.5)
Nausea	-	44 (9.2)	41 (11.9)	85 (10.3)	56 (6.8)
Body temperature increased	-	37 (7.8)	28 (8.1)	66 (8.0)	44 (5.3)
Pyrexia	1 (33.3)	55 (11.5)	61 (17.7)	117 (14.1)	98 (11.9)
Hyperpyrexia	-	1 (0.2)	-	1 (0.1)	-

*****the total number of all vaccines includes 2 vaccines whose brand name is unknown. **Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.= years old.

Children/Adolescents (5-17 years old)

Table 51. Frequency of reported local and systemic solicited ADRs in the group of children/adolescents by COVID-19 vaccine manufacturer, following the booster dose of vaccine.

	COVID-19 vaccine manufacturer		
	BioNTech/ Pfizer	**Moderna**	**All vaccines**
Number of vaccinees	**130 (100)**	**3 (100)**	**135 (100) ***
Subjects with at least one solicited ADR, n (%)	60 (46.2)	3 (100)	65 (48.1)
Local solicited adverse reactions (MedDRA PT), n (%)			
Injection site erythema	6 (4.6)	-	6 (4.4)
Injection site haematoma	1 (0.8)	-	1 (0.7)
Injection site induration	0 (0)	-	0 (0)
Injection site inflammation	12 (9.2)	-	12 (8.9)
Injection site pain	38 (29.2)	2 (66.7)	41 (30.4)
Injection site pruritus	1 (0.8)	-	1 (0.7)
Injection site reaction	0 (0)	-	0 (0)
Injection site swelling	10 (7.7)	-	10 (7.4)
Injection site warmth	4 (3.1)	-	5 (3.7)
Systemic solicited adverse reactions (MedDRA PT), n (%)			
Arthralgia	8 (6.2)	1 (33.3)	9 (6.7)
Chills	7 (5.4)	-	8 (5.9)
Fatigue	33 (25.4)	2 (66.7)	37 (27.4)
Headache	31 (23.8)	1 (33.3)	33 (24.4)
Malaise	17 (13.1)	1 (33.3)	19 (14.1)
Myalgia	17 (13.1)	1 (33.3)	19 (14.1)
Nausea	7 (5.4)	-	7 (5.2)
Body temperature increased	11 (8.5)	-	12 (8.9)
Pyrexia	-	-	-
Hyperpyrexia	10 (7.7)	-	10 (7.4)

*****the total number of all vaccines includes 2 vaccines whose brand name is unknown. **Note:** in the children/adolescents' cohort, concerning PTs related to local and systemic solicited ADRs, it was not possible to filter out those vaccinees aged 0-4 years old and who received BioNTech/Pfizer. **Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.= years old.

People with history of allergy

Table 52. Frequency of reported local and systemic solicited ADRs in the group of people with a history of allergy by COVID-19 vaccine manufacturer, following the booster dose of vaccine

	COVID-19 vaccine manufacturer					
	AstraZeneca	**BioNTech/ Pfizer**	**Moderna**	**Novavax**	**All vaccines**	**General population for people with a history of allergy (matched cohort)**
Number of vaccinees	**3 (100)**	**428 (100)**	**391 (100)**	**1 (100)**	**825 (100)***	**825 (100)**
Subjects with at least one solicited ADR, n (%)	1 (33.3)	300 (70.1)	311 (79.5)	1 (100)	614 (74.4)	519 (62.9)
Local solicited adverse reactions (MedDRA PT), n (%)						
Injection site erythema	-	28 (6.5)	33 (8.4)	1 (100)	62 (7.5)	50 (6.1)
Injection site haematoma	-	12 (2.8)	12 (3.1)	-	24 (2.9)	18 (2.2)
Injection site induration	-	2 (0.5)	3 (0.8)	-	5 (0.6)	3 (0.4)
Injection site inflammation	-	74 (17.3)	81 (20.7)	1 (100)	156 (18.9)	132 (16)
Injection site pain	1 (33.3)	195 (45.6)	213 (54.5)	1 (100)	410 (49.7)	344 (41.7)
Injection site pruritus	-	20 (4.7)	21 (5.4)	-	41 (5)	27 (3.3)
Injection site reaction	-	1 (0.2)	1 (0.3)	-	2 (0.2)	-
Injection site swelling	-	80 (18.7)	86 (22)	-	166 (20.1)	128 (15.5)
Injection site warmth	-	36 (8.4)	34 (8.7)	1 (100)	71 (8.6)	59 (7.2)
Systemic solicited adverse reactions (MedDRA PT), n (%)						
Arthralgia	1 (33.3)	74 (17.3)	66 (16.9)	-	142 (17.2)	110 (13.3)
Chills	1 (33.3)	89 (20.8)	110 (28.1)	-	200 (24.2)	165 (20)
Fatigue	1 (33.3)	189 (44.2)	201 (51.4)	1 (100)	392 (47.5)	284 (34.4)
Headache	1 (33.3)	135 (31.5)	156 (39.9)	1 (100)	293 (35.5)	234 (28.4)
Malaise	1 (33.3)	122 (28.5)	134 (34.3)	-	257 (31.2)	188 (22.8)
Myalgia	1 (33.3)	126 (29.4)	147 (37.6)	-	276 (33.5)	209 (25.3)
Nausea	1 (33.3)	57 (13.3)	58 (14.8)	1 (100)	117 (14.2)	50 (6.1)
Body temperature increased	-	32 (7.5)	38 (9.7)	-	70 (8.5)	47 (5.7)
Pyrexia	1 (33.3)	46 (10.7)	93 (23.8)	-	140 (17)	113 (13.7)
Hyperpyrexia	-	1 (0.2)	-	-	1 (0.1)	-

*****the total number of all vaccines includes 2 vaccines whose brand name is unknown. **Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.= years old.

Immunocompromised

Table 53. Frequency of reported local and systemic solicited ADRs in the immunocompromised by COVID-19 vaccine manufacturer, following the booster dose of vaccine.

	COVID-19 vaccine manufacturer				
	AstraZeneca	**BioNTech/ Pfizer**	**Moderna**	**All vaccines**	**General population for immunocompromised people (matched cohort)**
Number of vaccinees	**1 (100)**	**130 (100)**	**75 (100)**	**207 (100)***	**207 (100)**
Subjects with at least one solicited ADR, n (%)	0 (0.0)	76 (58.5)	48 (64)	125 (60.4)	128 (61.8)
Local solicited adverse reactions (MedDRA PT), n (%)					
Injection site erythema	-	6 (4.6)	6 (8)	12 (5.8)	17 (8.2)
Injection site haematoma	-	3 (2.3)	3 (4)	6 (2.9)	8 (3.9)
Injection site induration	-	-	1 (1.3)	1 (0.5)	1 (0.5)
Injection site inflammation	-	9 (6.9)	16 (21.3)	26 (12.6)	32 (15.5)
Injection site pain	-	49 (37.7)	33 (44)	83 (40.1)	86 (41.5)
Injection site pruritus	-	5 (3.8)	2 (2.7)	8 (3.9)	9 (4.3)
Injection site reaction	-	1 (0.8)	-	1 (0.5)	-
Injection site swelling	-	7 (5.4)	14 (18.7)	22 (10.6)	34 (16.4)
Injection site warmth	-	5 (3.8)	6 (8)	12 (5.8)	19 (9.2)
Systemic solicited adverse reactions (MedDRA PT), n (%)					
Arthralgia	-	19 (14.6)	19 (25.3)	38 (18.4)	25 (12.1)
Chills	-	19 (14.6)	14 (18.7)	33 (15.9)	34 (16.4)
Fatigue	-	40 (30.8)	28 (37.3)	68 (32.9)	60 (29)
Headache	-	29 (22.3)	15 (20)	45 (21.7)	57 (27.5)
Malaise	-	28 (21.5)	22 (29.3)	51 (24.6)	51 (24.6)
Myalgia	-	33 (25.4)	16 (21.3)	49 (23.7)	46 (22.2)
Nausea	-	13 (10)	8 (10.7)	21 (10.1)	8 (3.9)
Body temperature increased	-	4 (3.1)	7 (9.3)	11 (5.3)	14 (6.8)
Pyrexia	-	14 (10.8)	12 (16)	27 (13)	19 (9.2)
Hyperpyrexia	-	-	-	-	1 (0.5)

*****the total number of all vaccines includes 1 vaccine whose brand name is unknown. **Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term, y.o.= years old.

Pregnant women

Table 54. Frequency of reported local and systemic solicited ADRs in the pregnant women group by COVID-19 vaccine manufacturer, following the booster dose of vaccine

	COVID-19 vaccine manufacturer			
	BioNTech/ Pfizer	**Moderna**	**All vaccines**	**General population for pregnant women (matched cohort)**
Number of vaccinees	**244 (100)**	**113 (100)**	**358 (100) ***	**358 (100)**
Subjects with at least one solicited ADR, n (%)	124 (50.8)	78 (69)	202 (56.4)	271 (75.7)
Local solicited adverse reactions (MedDRA PT), n (%)				
Injection site erythema	8 (3.3)	8 (7.1)	16 (4.5)	30 (8.4)
Injection site haematoma	5 (2)	4 (3.5)	9 (2.5)	13 (3.6)
Injection site induration	-	1 (0.9)	1 (0.3)	4 (1.1)
Injection site inflammation	23 (9.4)	25 (22.1)	48 (13.4)	86 (24)
Injection site pain	86 (35.2)	53 (46.9)	139 (38.8)	190 (53.1)
Injection site pruritus	5 (2)	5 (4.4)	10 (2.8)	20 (5.6)
Injection site reaction	-	-	-	-
Injection site swelling	22 (9)	14 (12.4)	36 (10.1)	83 (23.2)
Injection site warmth	13 (5.3)	14 (12.4)	27 (7.5)	36 (10.1)
Systemic solicited adverse reactions (MedDRA PT), n (%)				
Arthralgia	21 (8.6)	18 (15.9)	39 (10.9)	25 (7)
Chills	17 (7)	22 (19.5)	39 (10.9)	34 (9.5)
Fatigue	56 (23)	49 (43.4)	105 (29.3)	60 (16.8)
Headache	45 (18.4)	39 (34.5)	84 (23.5)	57 (15.9)
Malaise	35 (14.3)	38 (33.6)	73 (20.4)	51 (14.2)
Myalgia	36 (14.8)	29 (25.7)	65 (18.2)	46 (12.8)
Nausea	24 (9.8)	14 (12.4)	38 (10.6)	8 (2.2)
Body temperature increased	10 (4.1)	4 (3.5)	14 (3.9)	14 (3.9)
Pyrexia	7 (2.9)	11 (9.7)	18 (5)	19 (5.3)
Hyperpyrexia	-	-	-	1 (0.3)

*****The total number of all vaccines includes 7 vaccines whose brand name is unknown. **Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term, y.o.= years old.

Lactating women

Table 55. Frequency of reported local and systemic solicited ADRs in the lactating women group by COVID-19 vaccine manufacturer, following the booster dose of vaccine.

	COVID-19 vaccine manufacturer				
	BioNTech/ Pfizer	**Moderna**	**Novavax**	**All vaccines**	**General population for lactating women (matched cohort)**
Number of vaccinees	**65 (100)**	**57 (100)**	**1 (100)**	**124 (100)***	**124 (100)**
Subjects with at least one solicited ADR, n (%)	47 (72.3)	48 (84.2)	1 (100)	94 (75.8)	90 (72.6)
Local solicited adverse reactions (MedDRA PT), n (%)					
Injection site erythema	3 (4.6)	4 (7)	1 (1.8)	8 (6.5)	12 (9.7)
Injection site haematoma	2 (3.1)	4 (7)	-	6 (4.8)	3 (2.4)
Injection site induration	-	1 (1.8)	-	1 (0.8)	1 (0.8)
Injection site inflammation	11 (16.9)	9 (15.8)	1 (1.8)	21 (16.9)	36 (29)
Injection site pain	33 (50.8)	36 (63.2)	1 (1.8)	70 (56.5)	65 (52.4)
Injection site pruritus	5 (7.7)	3 (5.3)	-	8 (6.5)	3 (2.4)
Injection site reaction	-	-	-	-	-
Injection site swelling	11 (16.9)	12 (21.1)	-	23 (18.5)	27 (21.8)
Injection site warmth	6 (9.2)	4 (7)	1 (1.8)	11 (8.9)	19 (15.3)
Systemic solicited adverse reactions (MedDRA PT), n (%)					
Arthralgia	11 (16.9)	13 (22.8)	-	24 (19.4)	18 (14.5)
Chills	15 (23.1)	16 (28.1)	-	31 (25)	18 (14.5)
Fatigue	21 (32.3)	22 (38.6)	1 (1.8)	44 (35.5)	48 (38.7)
Headache	18 (27.7)	26 (45.6)	1 (1.8)	45 (36.3)	46 (37.1)
Malaise	17 (26.2)	19 (33.3)	-	36 (29)	31 (25)
Myalgia	19 (29.2)	23 (40.4)	1 (1.8)	43 (34.7)	30 (24.2)
Nausea	4 (6.2)	7 (12.3)	1 (1.8)	12 (9.7)	7 (5.6)
Body temperature increased	5 (7.7)	6 (10.5)	-	11 (8.9)	9 (7.3)
Pyrexia	7 (10.8)	9 (15.8)	-	16 (12.9)	8 (6.5)
Hyperpyrexia	-	-	-	-	-

*****the total number of all vaccines includes 1 vaccine whose brand name is unknown. **Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term, y.o.= years old.

12.4 Heatmaps of ADRs in total population recruited at booster vaccination

For the booster dose Figure 15 and Figure 16 show the heatmaps for the percentage of participants that experienced any ADR and any solicited ADR across vaccine brands and age groups and stratified by sex. These heatmaps show that reactions were more frequent after the Moderna vaccine across all strata, except for the age group 70+ male of any ADR and for both male and female aged 70+ of any solicited ADR. Note that some strata have high frequencies, up to 100% for any solicited ADRs occur in participants, but the strata size can be very small (n=1).

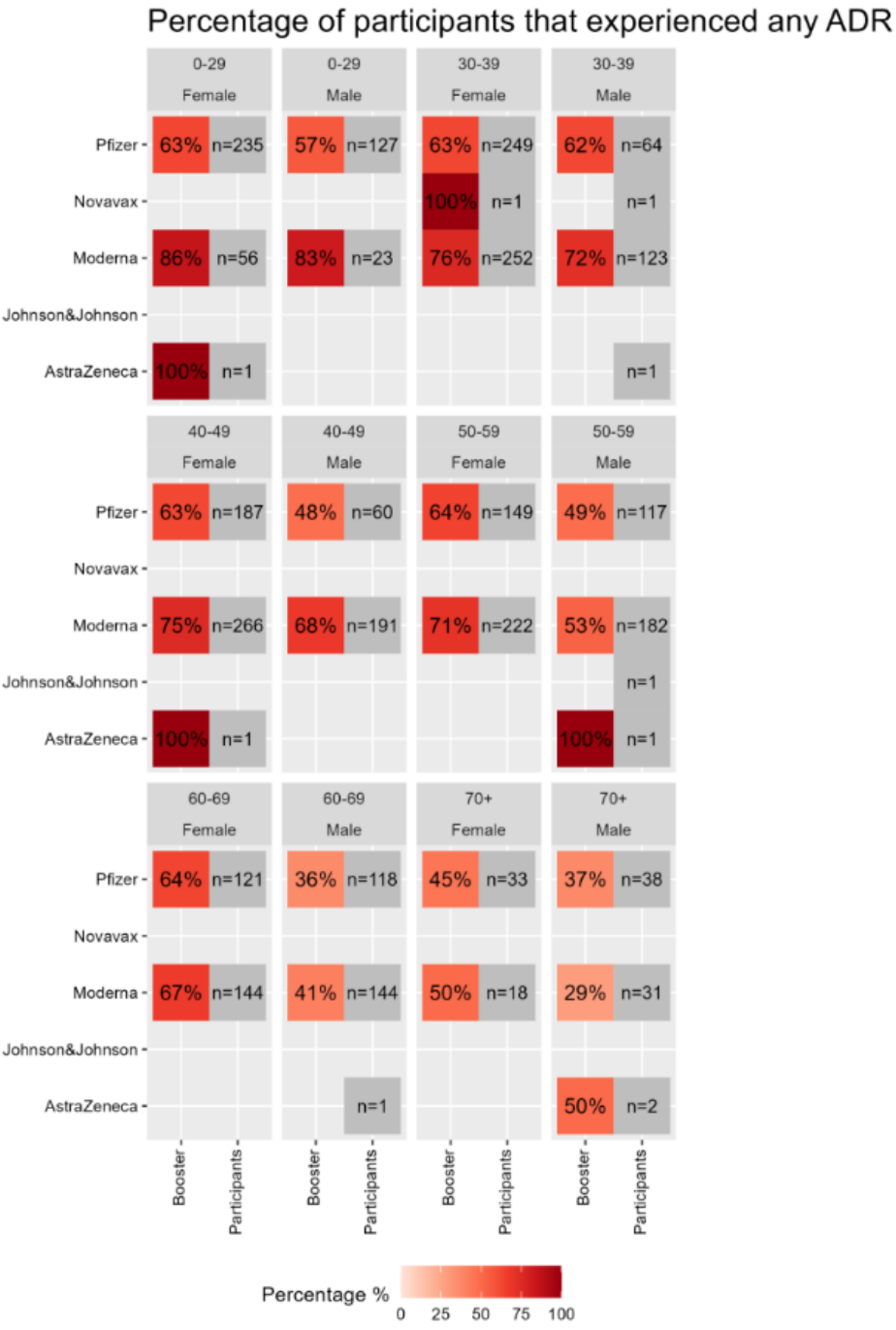

Figure 15. Heatmaps for any ADR in the total population recruited at booster vaccination

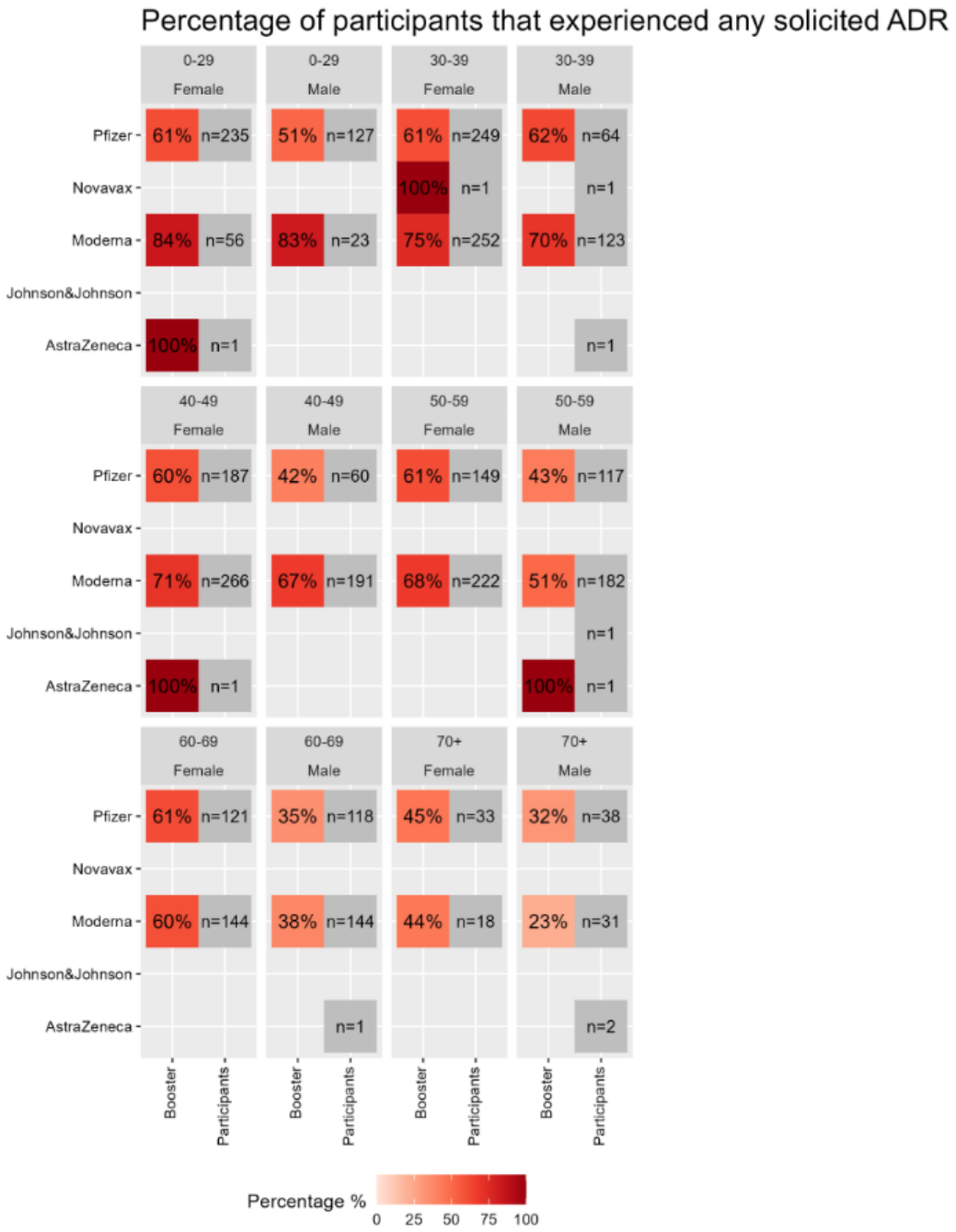

***Figure 16**. Heatmaps for any solicited ADR in the total population recruited at booster vaccination.*

Furthermore, for the booster doses Figure 17 and Figure 18 provide an overview of participants with any solicited ADR without injection site reactions and fever (temperature >38 degrees Celsius). Figure 17 shows that female reported the higher percentage of any solicited ADR (without injection site reactions) across all age groups and vaccine brand. Reported fever rates, showed in Figure 18, are higher for Moderna across all strata, except for female aged 60-69 y.o.

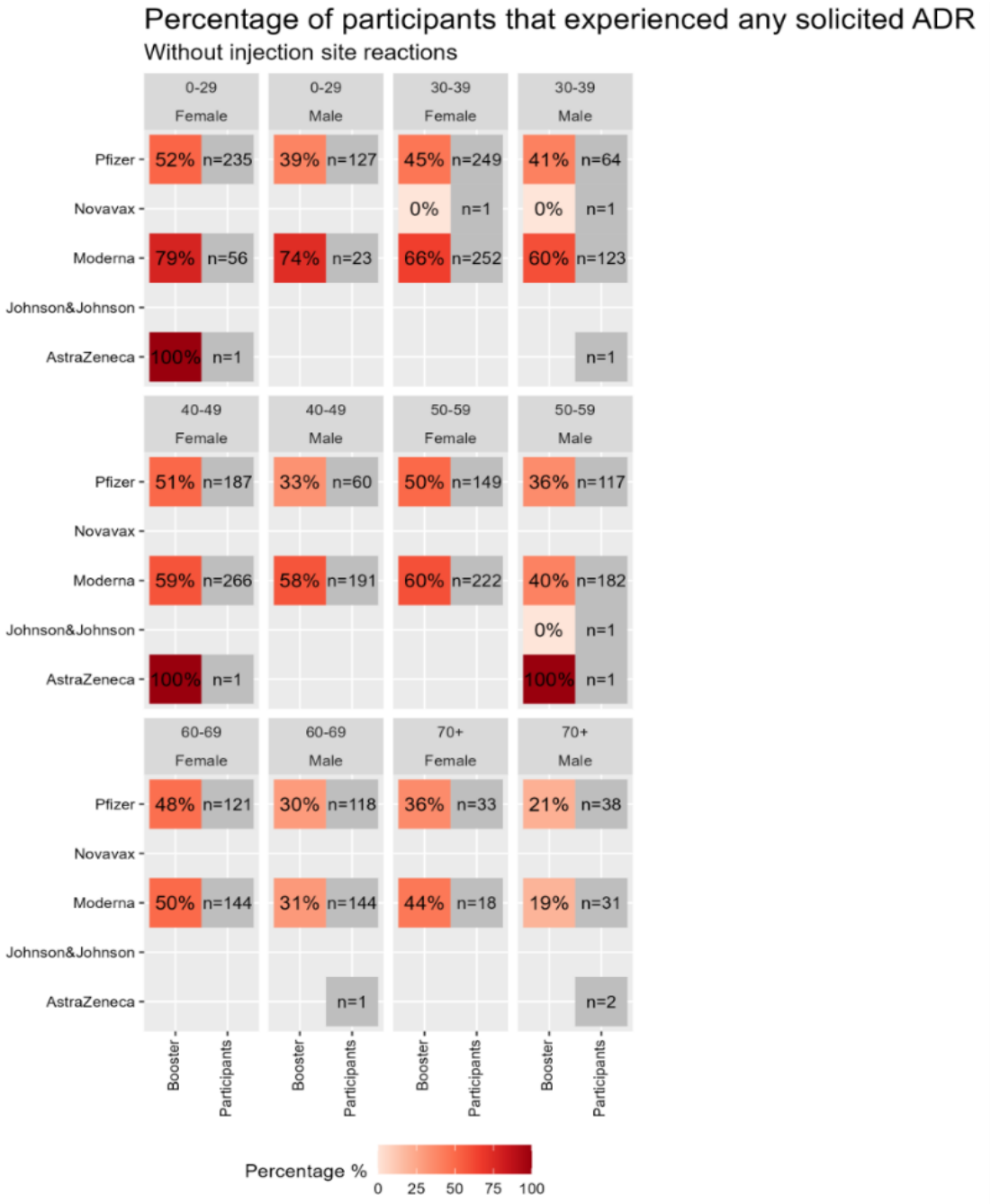

***Figure 17**. Heatmaps for any solicited ADR (without injection site reaction) in the total population recruited at booster vaccination*

Figure 18. Heatmaps of fever for total population recruited at booster vaccination.

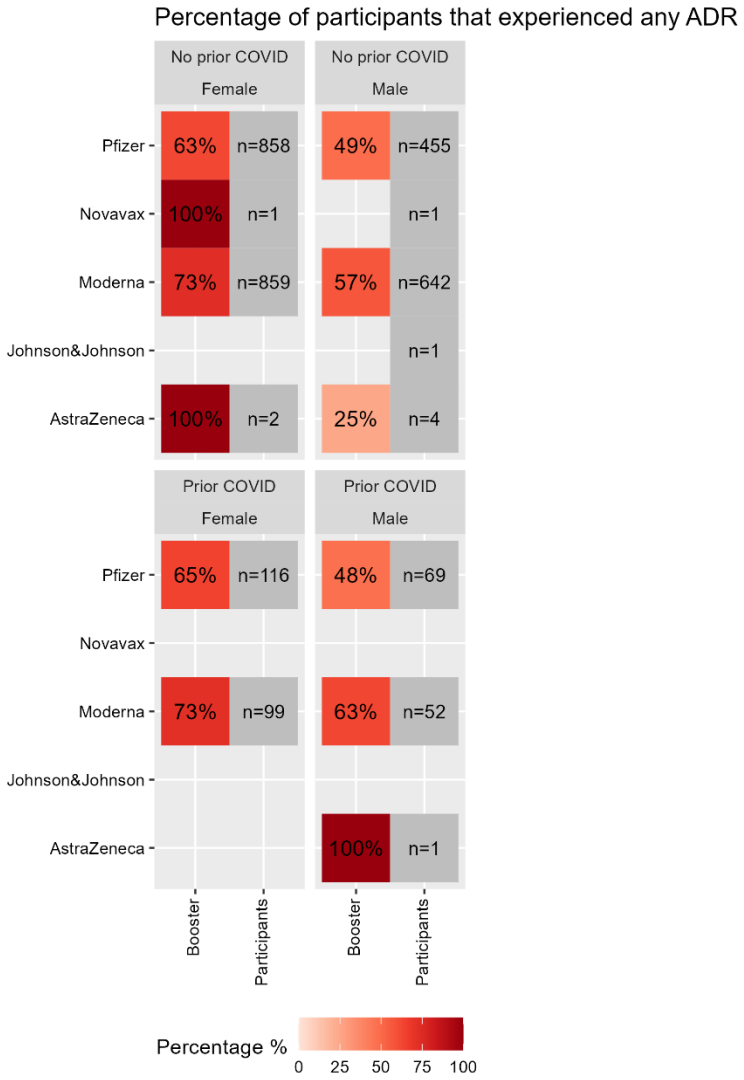

Figure 19. Heatmap of any suspected ADR for total population recruited at booster vaccination with or without history of COVID-19.

In Figure 19 the participants recruited at booster vaccination are split into two groups: one with a prior SARS-COV 2 infection (confirmed with a test) and the rest. Across both groups, females were more likely to report experiencing at least one ADR when compared to males. Participants who reported a prior SARS-COV-2 infection had a slightly higher reporting rate across all strata, except for men who received Pfizer.

12.5 Main results: serious adverse reaction data

Overall, 18 (0.3%) vaccinees from the general population reported at least one serious ADR following a booster dose: 2 (0.2%) vaccinees in the cohort of allergy (N= 825), 1 (0.1%) vaccinee with prior SARS-CoV-2 infection (N= 902), 2 (1.6%) lactating women (N= 124), 1 (0.7%) vaccinee in children/adolescents' cohort (N= 135), 3 (0.8%) pregnant women (N= 358) and 10 (0.2%) vaccinees not belonging to any of the cohorts (N= 4,733). Table 56 shows the list of the reported serious ADRs by COVID-19 vaccine manufacturers following the booster dose.

***Table 56**. List of reported serious ADRs following the booster in special cohorts and the general population by country and COVID-19 vaccine manufacturer.*

	COVID-19 vaccine manufacturer	Reported serious ADRs	N. of reported serious ADRs
Switzerland			
Pregnant women	BioNTech/Pfizer	Congenital anomaly	1
France			
People with a history of allergy	BioNTech/Pfizer	Tachycardia	1
None of the cohorts	BioNTech/Pfizer	Tachycardia	1
Italy			
Pregnant women	BioNTech/Pfizer	Loss of consciousness	1
Lactating women	BioNTech/Pfizer	Pyrexia	2
	Moderna	Pyrexia	1
People with a history of allergy	Moderna	Pyrexia	1
People with prior SARS-CoV-2 infection	BioNTech/Pfizer	Hyperpyrexia	1
Children/Adolescents	BioNTech/Pfizer	Pneumothorax	1
None of the cohorts	BioNTech/Pfizer	Cystitis	1
	BioNTech/Pfizer	Gastritis	1
	Moderna	Arrhythmia	1
	Moderna	Hyperpyrexia	1
	Moderna	Infarction	1
	Moderna	Pyrexia	2
Ireland			
Pregnant women	BioNTech/Pfizer	Haemorrhage in pregnancy	1
Portugal			
None of the cohorts	BioNTech/Pfizer	Headache	1
	BioNTech/Pfizer	Nausea	1
The United Kingdom			
None of the cohorts	BioNTech/Pfizer	Chest pain	1

Note: a single participant can belong to different cohorts and more than one serious adverse reaction can be reported by a single participant. None of the cohorts= subjects not belonging to any of the special cohorts of interest.

12.6 Vaccinee-reported adverse events of special interest following the booster dose

Overall, 18 (0.3%) vaccinee from the general population reported at least one AESI: 3 (0.4%) vaccinees in the cohort of allergy (N= 825), 1 (0.1%) vaccinees with prior SARS-CoV-2 infection (N= 902), 1 (0.7%) vaccinee in children/adolescents' cohort (N= 135) and 14 (0.3%) vaccinees not belonging to any of the cohorts (N= 4,733). Table 57 shows the list of the reported AESIs following the booster dose.

Table 57. List of reported adverse events of special interest following the booster dose in the special target group and the general population by COVID-19 vaccine manufacturer and country.

	COVID-19 vaccine manufacturer	Reported AESIs	N. of reported AESIs
Italy			
Children and adolescents	BioNTech/Pfizer	COVID-19	1
People with a history of allergy	BioNTech/Pfizer	Arrhythmia	1
None of the cohorts*	BioNTech/Pfizer	COVID-19	3
	Moderna	Arrhythmia	1
France			
People with prior SARS-CoV-2 infection	Moderna	Hypersensitivity	1
People with a history of allergy	Moderna	Hypersensitivity	1
	BioNTech/Pfizer	Pericarditis	1
None of the cohorts	BioNTech/Pfizer	Arrhythmia	2
	Moderna	Arrhythmia	3
	BioNTech/Pfizer	Bell's palsy	1
	Moderna	Facial paralysis	2
The United Kingdom			
None of the cohorts	BioNTech/Pfizer	COVID-19	1
	BioNTech/Pfizer	Hypersomnia	1

Note: a single participant can belong to different cohorts and more than one serious adverse reaction can be reported by a single participant. *None of the cohorts= subjects not belonging to any of the special cohorts of interest.

13 Discussion

13.1 Key results

Total population recruited upon first vaccination

A total of 642,290 persons were included who returned at least one follow-up questionnaire. 99.6% of the included persons came from the countries who had set up infrastructure before vaccination campaigns started and could include people from the start of these campaigns. The large majority (95%) was from Germany. Of the 642,290, 72.6% also provided information after dose 2 vaccination. Most participants (81.7%) were between 20 and 59 years of age. Most of the vaccinees were included after first dose of BioNTech Pfizer vaccine (n=437,939, 68%), followed by AstraZeneca (n=89,509, 14%), Moderna (n=84,907, 13%) and Janssen (n=29,891, 5%). Solicited local reactions were very frequent, and injection site pain most frequent after a Moderna vaccination (69.1%), followed by Pfizer (58.2%). Injection site swelling was also most frequent after Moderna vaccination. Systemic solicited reactions varied, most frequent was fatigue after Moderna and Astrazeneca dose 1 (both around 50%) and headache (52%) for Astrazeneca. Fever was highest after Astrazeneca vaccination dose 1 (31.6%). Arthralgia was reported by 22.5% of persons after first dose of AstraZeneca. Comparisons of dose patterns while stratifying by age and gender could be conducted in the 29,844 subjects for which data was available on individual level. In general frequency of any ADRs was higher

after the first dose of all vaccine brands, except for Moderna where participants were more likely to report an ADR after dose 2. Time to onset was within one day for most solicited reactions, except for injection site pain that started within an hour. For systemic reactions median onset time often exceeded a day.

Among the total study population, the overall rate of serious ADRs was 0.49% (95%CI: 0.47-0.51%). Analysing Germany separately showed a slightly higher rate of serious ADRs with 0.50% (95%CI:0.48-0.52). It is likely that this higher rate is due to Germany providing the reported seriousness rather than the assessed seriousness as coded by trained assessors. Despite this potential overreporting, the reporting rate of serious ADRs was <1.0% across all vaccines, except for Janssen which was <2.0%. This is likely due to a longer follow-up period included for those participants receiving the Janssen vaccine and one of the limitations of using aggregated data rather than the later developed common data model for the analysis.

The rate of an AESI after the first dose was 0.31% (95%CI: 0.30-0.33%), several cases of venous or arterial thromboembolism were reported after AstraZeneca first dose (n=4) and 1 after the second dose. Myocarditis and pericarditis were reported after Pfizer (n=2) and 2 cases of thromboembolic event after second dose of Moderna vaccine.

Analysing the predictor factors using a linear mixed-effects models, across a subset of more than 29,000 participants from the first vaccination cycle general population (excluding Germany), it was clear how the age plays a key role in the occurrence of ADRs (any), which are less reported with the increment of the age. Moreover, the male sex as a predictor has a lower contribution than the female sex. Interestingly, prior COVID-19 infection reveals to be a positive predictor for fever following COVID-19 vaccine doses 1 and 2.

Special populations recruited upon first vaccination

Using a common data model for data collected through LIM and RO the special populations could be pooled for 10 countries: Belgium, France, Italy, the Netherlands, the United Kingdom, Romania, Slovakia, Spain, Portugal and Switzerland. Persons recruited and completing at least one follow-up questionnaire for the different populations were: 2,594 for people with prior SARS-Cov-2 infection, 3,477 for people with history of allergy, 732 children/adolescents, 567 immunocompromised, 175 pregnant women and 26 lactating women. The majority of vaccinees were female across all groups. The rates of any ADR (solicited and non-solicited) reported after dose 1 was highest in people with prior SARS-CoV-2 (89.9%), especially after AstraZeneca (97%) or Moderna vaccine (95%), rates after dose 2 were even higher (91%) overall in this group. In children/adolescents any ADR rates were lower than in other populations: 55.2% after dose 1 and 60.9% after dose 2, which was mostly BioNTech/Pfizer vaccine. Rate of any ADR was 86.5% in people with a history of allergy, 82% in people who were immunocompromised, 81% in pregnant women and 81% in lactating women, rates after dose 2 were similar. Serious ADR rates were 0.15% (95%CI: 0.05-0.39%) in people with prior SARS-CoV-2 infection, 0.17% (95%CI: 0.07-0.37%) in people with history of allergy, 0.52% (95%CI: 0.1-1.5%) in immunocompromised, 0.27% (95%CI: 0.07-0.99%) in children/adolescents and 0.57% (95%CI 0.1-3.2%) in pregnant women.

General and special populations recruited at booster dose

A total of 9,747 vaccinees were recruited in 10 countries: France, Italy, Ireland, Portugal, Romania, Slovakia, Spain, Switzerland and the United Kingdom, whereas Germany, who contributed to most to

the recruited vaccinees for the first and second dose, did not participate for booster doses. Of them, 6,984 vaccinees filled the baseline questionnaire and at least one follow-up questionnaire and thus were included in the analyses. The rate of any ADR reported after the booster dose was lower than after first or second dose: 64% overall, with consistently lower rates in each of the special populations compared with dose 1 or 2 of the first vaccination cycle. Booster doses were almost exclusively BioNTech/Pfizer or Moderna. The rate of serious ADRs was 0.26% (95%CI: 0.16-0.41%), similar to the rate of serious ADR observed in the general population after dose 1.

13.2 Strengths and Limitations

This study has tried to align methodology across all the LIM using sites which followed the Lareb approach, but differences exist in the implementation of the scheduling of questionnaires, and with the Croatian and German approaches. Despite these differences, it was possible to aggregate the data and present it together. Some adjustments in data extraction and timely quality control allowed that German data was combined with the other data sources, allowing further analysis. Loss to follow-up was substantial in some countries, where people registered and filled in a baseline but never returned the first questionnaire. It is not clear whether these persons did not have an ADR or were not motivated to continue due to other reasons. Therefore, the rate of reporting is potentially overestimated. The importance of participation, whether adverse reactions are experienced or not, could be emphasized in future studies and campaigns for cohort event monitoring.

In the previous reports, we were unable to present aggregated data from all participating countries due to issues in data sharing. All data in this report have been aligned and can be aggregated with the exception of the data related to the potential seriousness of adverse reactions. The seriousness in the German data was the seriousness reported by participants rather than the seriousness as assessed and coded by trained assessors. The assumption based on quality control done in the LIM datasets is that participants are more likely to report an adverse reaction as serious while it is not coded as serious by an assessor, rather than the opposite. This would suggest a potential over-reporting of serious adverse reactions from Germany. Less than 1% of the adverse reactions are reported as serious, despite this potential overreporting.

In order to assess adverse reactions, in particular AESI or serious adverse reactions, assessors could contact participants for additional information related to their reported reactions. This included possible questions on impact, type of reaction or a diagnosis by a medical professional. It was not tracked how many participants were contacted, which additional information was obtained and how many resources were necessary to collect this information and to discuss cases. In future it would give more insight into the resources necessary for this intensive process and what additional information was gained.

The aggregated datasets provided overviews of the data being collected in real-time, however additional analyses such as formal comparisons between age, sex and vaccine brands were not possible with these datasets. A common data model was developed to further harmonise data and make further analyses possible, however it was only developed at a later stage of the study. Demographic analyses, heatmaps, mixed-effects model were the first analyses conducted using the common data model datasets. Despite all efforts to harmonise questionnaires and data prior to the

start of the study, this was not sufficient and common data models should be considered early on in a study to aid in further data harmonising.

Further practical aspects need to be considered. Specifically, the start date was not the same for all countries and this is reflected in the number of vaccinees enrolled (which also depends on the status of the vaccination campaign at the time of enrolment). Having a tool ready and working is essential for a timely start. We can indeed observe that the Netherlands and Germany have the largest number of vaccinees recruited after the first dose since it is the country that started first. While in other countries, the tool has been translated and adapted to country-specific needs. In addition, not all countries participate in the recruitment of vaccinees in all cohorts. Any last minute changes needed in the questionnaires were often not feasible as changes in questionnaires would lead to changes in the data collection tools, which often need extensive testing which is not possible when a tool is live and in use. Additionally, changes in questionnaires meant a change in the protocol which in some countries need new approval from ethical committees. Despite fast-track options during the COVID-19 pandemic, new approval would not have been in time for a timely start of data collection. This is a difficult factor to take into account in future pandemics as committees were often overloaded, despite rapid assessment of approvals. Having CEM protocols and questionnaires ready for future pandemics are essential in avoiding some of the issues mentioned above, however this is also limited by factors such as knowing what type of vaccine, number of doses and the dose interval early on in a pandemic.

Moreover, we should also consider that we had two tools and we had to switch from LIM to RO while the study was ongoing (starting again with the design, adaptation and translation of the tool itself). Although most countries used only one of the two web-apps, LIM or RO (except Italy which used both), all the new countries participating in the CVM used exclusively RO, and RO was launched (and not at the same time in all countries) when nearly the entire population had already received at least one dose of vaccine (with the exception of children cohort). As for the booster dose, recruitment of vaccinees was only possible through RO. Therefore, countries that used LIM for data collection at the first dose had to switch to RO for data collection at the booster dose. Similarly, it should be also considered that monitoring of pregnant and lactating women (at both the first and the booster dose) with extra specific questions was only possible through RO, and this is reflected in the low number of vaccinated women belonging to these special cohorts as almost all of them had already received a first dose of vaccine at the time the RO was launched.

Concerning the immunocompromised, they were the first subjects to be vaccinated according to the vaccination strategy in all countries, so most of them had already been vaccinated with the first dose at the time of the study start. Regarding, the children and adolescent cohort, it is possible that some subjects belonging to this cohort are not correctly identified if the parents/legal representative who filled in the questionnaire on their behalf have erroneously indicated their own date of birth instead of that of their children.

Of note, to be included in the analyses, vaccinees had to have completed the baseline and at least the Q1. However, having a look at the number of completed questionnaires, loss to follow-up was substantial across different cohorts. In particular, at Q1 we lost about 15-30% participants recruited at baseline, and if we consider long-term follow-ups (at 6 months after the first dose and 3 months after the booster dose) we lost more than half of the vaccinees (up to 70%), with some differences between the different cohorts but still considering the different sample size.

13.3 Interpretation

General population's first vaccination cycle

Injection site pain was the most commonly reported local solicited reaction across all vaccine brands, which is confirmed by the systemic review conducted by McDonald et al 2021. Another reassuring observation is that serious adverse reactions and AESI are rare, both seen in clinical trials (Baden et al. 2020, Polack et al. 2020, Voysey et al. 2021) and confirmed by this real-world data. Despite the fact that the German data on seriousness is based on self-reported data, rather than the seriousness assessed and confirmed by the (medical) assessors, the reporting rates are comparable to those seen in data from other partners which has been confirmed by an assessor. A comparison of the self-reported and assessed seriousness in the ECVM final report showed very few discrepancies between these two data sources in LIM data. This comparison together with the similar reporting rates between Germany and the other partners may suggest that the German self-reported seriousness rates could be similar to seriousness as determined by a trained assessor.

In previous reports, data from Germany was analysed separately from the other data. The pooled data mainly consisted of data from the Netherlands. In this report, all data provided on general populations were pooled. This leads to the majority of the data consisting of data from Germany. For most analyses this should not be a limitation, however, it should be kept in mind that factors such as national vaccination strategy, manner of reporting or changes in vaccination programmes potentially have a larger impact on the data. Whether these differences exist in the datasets should be assessed in more detail.

The above differences are taken into account, when possible, by ensuring that the aggregated data used for regular reports and the dashboard is comparable: definitions of aggregated variables have been agreed upon and data is stratified on vaccine brand, gender and age. However, caution should continue to be taken in interpreting the data between strata. Doing any extensive statistical analysis would nevertheless require additional testing of the compatibility of the data used for that analysis. This will be done using the data of the common data model that has been developed and finalized during the last months of the study.

Special population first vaccination cycle

Solicited ADRs are common whereas serious ADRs and AESIs are uncommon to rare, across each of the special populations. However, a conclusion should be cautious as the sample size in each of the special groups is limited. Pfizer/BioNTech, Moderna and Novavax are the only COVID-19 vaccines authorised in the 12-17 age group and initially only Pfizer/BioNTech was authorised in the 5-11 age group. Only later, an extension of indication for the Moderna vaccine use in children aged between 6 and 11 was recommended by the EMA. However, given the vaccination strategy, Pfizer/BioNTech was the most administered vaccine in the children/adolescents' cohort. Overall, most of the vaccinees included in the study were females among all special cohorts, although the F/M ratio in the children/adolescents' cohort is lower. A possible explanation for the sex gap between participants observed in this study could relate to the propensity of females to report drug ADRs more often than males (Watson et al. De Vries et al). The less pronounced difference in the female/male ratio in the group of children and adolescents may be explained by the fact that these subjects require a legal representative to register and fill out the questionnaires for them. Therefore, the number of

children/adolescents should not reflect the tendency of women to be overrepresented in studies based on spontaneous reporting systems. Age differed widely among the different vaccine recipients participating in this study; older participants represent only a narrower study population. In terms of time, the probability to enrol these subjects in the study was low as the vaccination campaign prioritised the vaccination of fragile people, such as the elderly. Moreover, older people may face difficulties using technologies like smartphones and computers, which are essential tools for filling in the questionnaires. The percentage of reported solicited and non-solicited ADRs was similar across all the special cohorts, with the exception of the children/adolescents' cohort for which the percentages were lower. According to the available information collected through the LIM and RO web-apps on the solicited ADRs in the general population and to already published studies (Mac Donald. et al) injection site pain as a local reaction and headache, fatigue, myalgia, and malaise as systemic reactions were the most frequently ADRs reported following both the first and the second dose among all the special cohorts. The percentage of severe ADRs and AESIs is very low, although the limited sample size in each of the special cohorts should be considered. In the children/adolescents' cohort, most ADRs are solicited, with injection site pain and fatigue being the most frequently reported, as showed in pivotal clinical trials (Frenck et al., Ali et al., Walter et al.). Serious ADRs and AESIs were rare, with no reported cases of myocarditis and pericarditis. Similar findings were observed in the special groups of pregnant and lactating women. Except for children, results from specific clinical pivotal trials about the safety of the EU-marketed COVID-19 vaccines in most of the special populations' cohorts of this observational study are not published, limiting the comparisons between our and other reliable sources of data. On the other hand, this lack of clinical trials in special cohorts confers more emphasis on the COVID-19 vaccines' safety information that can be extrapolated by this study about these populations.

General and special populations booster doses

BioNTech/Pfizer and Moderna were the two vaccines mainly administered for the booster vaccination. Overall, most of the recruited vaccinees were aged between 18 and 59 years. Despite some countries have started to recruit participants at the beginning of the COVID-19 booster campaign, we might have missed the peak of the campaign for the fragile people, such as the elderly and/or the immunocompromised. Moreover, older people may face difficulties using technologies like smartphones and computers, which are essential tools for filling in the questionnaires. Regarding the children/adolescents' cohort, as expected, most were in the 12-17 age group considering that at the time of the start of the booster vaccination campaign vaccination with a first dose was recommended in children aged between 5 and 11 years.

Females represented more than half of the recruited vaccinees in all cohorts with some less pronounced differences in the female/male ratio for the group of children and adolescents. This may be explained by the fact that these vaccinees required a parent/legal representative to register and fill out the questionnaires for them. Therefore, the number of children/adolescents should not reflect the tendency of women to be overrepresented in studies based on spontaneous reporting systems.

14 Conclusion

Self-reported safety data of COVID-19 vaccines from more than 650,000 vaccinees among 13 countries and collected from four different data sources have been included in this report. Most of the vaccinees (>95%) were from Germany and the majority was enrolled for the first and second doses (>97%%).

Collectively the data show that 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 channeled to. Serious adverse reactions and AESI are uncommon for all vaccines, after the first doses and booster, in the general as well as special populations.

Some limitations have been encountered in combining the datasets coming from different data sources, as extensively discussed in this report. While aggregated datasets allowed for the aligning and pooling of data, the aggregated nature allowed for minimal analysis options. A common data model was developed which currently pools LIM and RO data. This final pooling strategy allowed us to develop a specific cohort event monitoring statistical analysis plan, and easily analyse all the data we have in our hands to disseminate related scientific publications.

During this cohort event monitoring, the readiness of data collection infrastructure and ethical approvals timings was crucial. Countries that had prompt governmental support and a functioning data collection tool before vaccines were launched made it in time to include a large number of vaccinated persons since the first vaccination, which had a strong acceleration in Europe during the preparation phase of this study and of the LIM and RO web app data collection platforms. Differently, during the preparedness phase, the prompt switch to collect booster doses by participating countries and web-app developers gave important advantages to monitoring those related events. Despite preparation and rapid response to changes in vaccination strategies, additional harmonization through the development of a common data model was necessary should be considered the readiness phase to ensure easy and rapid analysis of data in the future.. 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. In future additional attention can be paid to encouraging participants to continue participation, whether they experience and adverse reaction or not. This study, as others of the same design, requires noticeable human resources, due to the assessment of all serious reactions. Most regulatory agencies/pharmacovigilance centers that participated also reported adverse drug reactions to EudraVigilance. Many of them, as reported in this report, were solicited reactions. 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.

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