Early Covid Vaccine Monitor study WP1

Deliverable 4

Final Report v3.4
May 2022

Cohort Event Monitoring of safety of COVID-19 vaccines
Early-Covid-Vaccine-Monitor

Specific Contract 05 implementing framework contract No EMA/2018/28/PE

EU PE&PV research network

Disclaimer & acknowledgements

The research leading to these results was conducted as part of the activities of the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network (led by Utrecht University) with collaboration from the Pharmacovigilance Centre Lareb in the Netherlands. The project has received support from the European Medicines Agency under the Framework service contract nr EMA/2018/28/PE. This report expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties. The work in this report is based on: EU PAS Register No: EUPAS39798

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Abstract

Background

In December 2020 the first European countries initiated their vaccination campaigns with the new COVID-19 vaccines. A cohort event monitoring study in seven European countries was initiated in order to monitor vaccine safety during the roll-out of these vaccines.

Objectives

The primary aim of the research described in this report is to generate (cumulative) incidence rates of patient-reported ADRs of COVID-19 vaccine brand in near real-time from the pooled European data for the first COVID-19 vaccine campaign in which participants received their first and second dose of the vaccine. This report describes the data available for pooling at the end of October 2021.

Study design

Participants were recruited, primarily at vaccination sites, in seven countries using three different web apps. Participants were required to fill in a baseline and at least one questionnaire related to adverse reactions. All solicited adverse reactions were coded automatically while unsolicited adverse reactions were coded manually. Serious adverse reactions, adverse events of special interest (AESI) and other reactions needing (medical) clarification were assessed by a qualified assessor.

Results

The most commonly reported systemic solicited reaction is fatigue which is closely followed by headache and malaise. The types of reported adverse reactions are comparable to the product information however the crude reporting rates varied. A total of 0.2% (0.114, 0.207) of adverse events were reported as serious after first dose; they were uncommon and comparable between the different vaccines, Rates were higher in Germany due to the inclusions of self reported seriousness. Nevertheless, rates of serious adverse reactions were low: 0.7% (0.678, 0.792). The frequency of reporting of AESI were comparable across vaccine brands: roughly 0.1-0.2% of all participants reported an adverse reaction which was considered an AESI.

Conclusion

The well-known, solicited adverse reactions were reported frequently while reporting of both serious adverse reactions and AESI were low. The initiated Early Covid Vaccine Monitor cohort event monitoring was challenging yet showed that an international collaboration is feasible. As additional (follow-up) data becomes available, further analysis on Covid-19 vaccine safety can be done.

1. Introduction

In December 2020 the first European countries initiated their vaccination campaigns with the new COVID-19 vaccines. Safety of the vaccines is studied during clinical trials prior to licensing. Effectiveness and safety of vaccines in subjects participating in these clinical trials may not always be representative for the general population. Furthermore, the number of people in the clinical trials is relatively small compared to all people who are vaccinated. Therefore, the safety of the vaccines is also monitored during rollout of the vaccines. To signal possible adverse drug reactions (ADRs) during rollout, spontaneous reporting systems were in use. Furthermore, cohort event monitoring was set up to actively monitor and obtain in-depth information of the safety of the vaccines. Cohort event monitoring (CEM) generates incidence rates and disease course which cannot be derived from spontaneous reporting systems. During the 2009 H1N1 pandemic, cohort event monitoring systems were already used as additional monitoring of the H1N1 vaccination campaigns, as described in two publications [1.2]. Currently several CEM studies are being done in other countries. The COVID symptom study app was introduced in the UK for vaccines to register data on their COVID-19 vaccination [3]. V-Safe is an app which allows vaccines to report adverse reactions after receiving a COVID-19 vaccine [4]. Not only do these monitoring studies capture a much wider population than most clinical trials can, they also provide a long-term follow-up period [5].

Each European country is responsible for monitoring safety of their inhabitants. However, when sharing expertise and data, knowledge and evidence grows. Therefore, a pan-European multi-country cohort monitoring study has been set up as part of the Early Covid Vaccine Monitor (ECVM). In different countries, data was prospectively collected on the national level on the national level data was prospectively collected in near real time directly from a cohort of vaccine recipients. The common core data from these countries was pooled and analysed at the European level.

The primary aim of the research described in this report is to generate (cumulative) incidence rates of patient-reported ADRs of COVID-19 vaccine brand in near real-time from the pooled European data for the first COVID-19 vaccine campaign in which participants received their first and second dose of the vaccine. This report describes the data available for pooling at the end of October 2021. This dataset can be considered an interim data freeze as the study is currently still including participants.

2. Methods

Details of the study design are described in the study protocol that is published in the EUPAS register (EUPAS39798).

2.1 Study design

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

Table 1: Contributing organizations.

Country	Organization	Inclusions Start date
Belgium	Federal Agency for Medicines and Health Products (FAMHP)	13-07-2021
Croatia	HALMED	15-02-2021
France	University of Bordeaux	14-06-2021
Germany	Paul-Ehrlich-Institute (PEI)	27-12-2020
Italy	University of Verona	09-06-2021
The Netherlands	Pharmacovigilance Centre Lareb	01-02-2021
United Kingdom	Drug Safety Research Unit (DSRU)	23-06-2021

The Luxembourg Institute of Health (LIH) was also motivated to contribute to the ECVM project, 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 reasons that some countries could only start recruiting in June or July.

For Germany it needs to be noted that the data collection started prior to this study. When PEI designed the study protocol for their research 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.

2.2 Data collection

Participants were invited to sign up for the study primarily at vaccination sites but also through (social-) media campaigns. In order to participate in the study, the vaccine recipients had to provide informed

consent and had to register for the study prior to vaccination or no longer than two days after their first COVID-19 vaccination.

Three 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-Institut used the app SafeVac 2.0. This smartphone application is designed specifically to record tolerability of the COVID-19 vaccines in Germany and is developed by the Paul-Ehrlich-Insitut.
- The other organizations used the Lareb Intensive Monitoring (LIM) web app. This tool was developed by Lareb for cohort event monitoring. Participants could register themselves on a website designed specifically for this study. 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. Each organization had a country specific website and questionnaires were in the local language(s). 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 additional reasons that some countries could start recruiting subjects in June or July.

2.2.1 Questionnaires

After signing up, participants were followed for a six-month period (LIM countries) or up to 1 year (Germany and Croatia). During the follow-up period they received several questionnaires. In these questionnaires the participants were asked to report if they experienced any ADRs. For reporting the ADRs a distinction was made between solicited ADRs and unsolicited ADRs. The solicited ADRs are known to frequently occur after vaccination and were defined as fever injection site reaction (redness, warmth, pain, itch, haematoma, swelling, induration) of left and right arm, fatigue, myalgia, arthralgia, headache, chills and malaise. Participants could select these ADRs from a predefined list. Unsolicited ADRs were all other ADRs that participants experienced and these had to be described by the participants in a text field. For all ADRs, both solicited and unsolicited, questions were asked about when it occurred, for how long, and what the impact was. When ADRs were not recovered at the moment of completing a questionnaire the ADR was followed-up in the next questionnaire until the reaction was recovered or until the last questionnaire of the study. Other data collected was on exposure (vaccine brand, batch, date of vaccination), vaccinee demographics and comorbidities.

2.2.2 Questionnaire scheduling

To get accurate data on the reported ADRs, the questionnaires were scheduled to capture both short-term and long-term reactions. It was expected that most ADRs occurred 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

also get the most accurate information on ADRs after the second dose, questionnaires were sent around the expected date of the second vaccination dose.

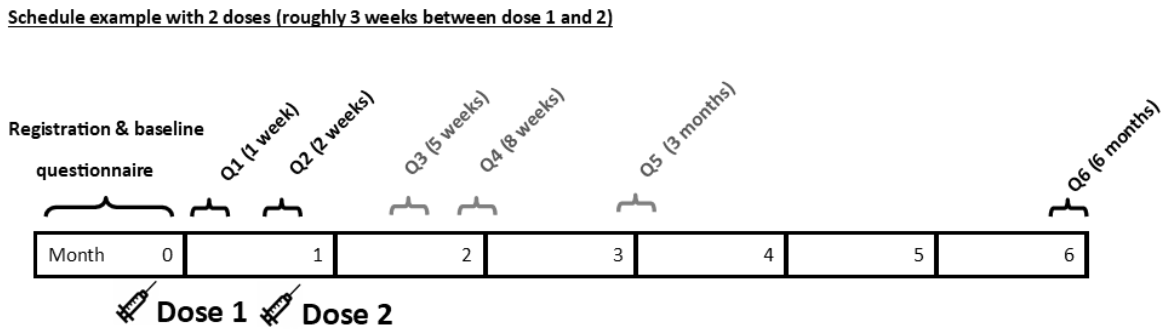

Figure 1: Example questionnaire schedule

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

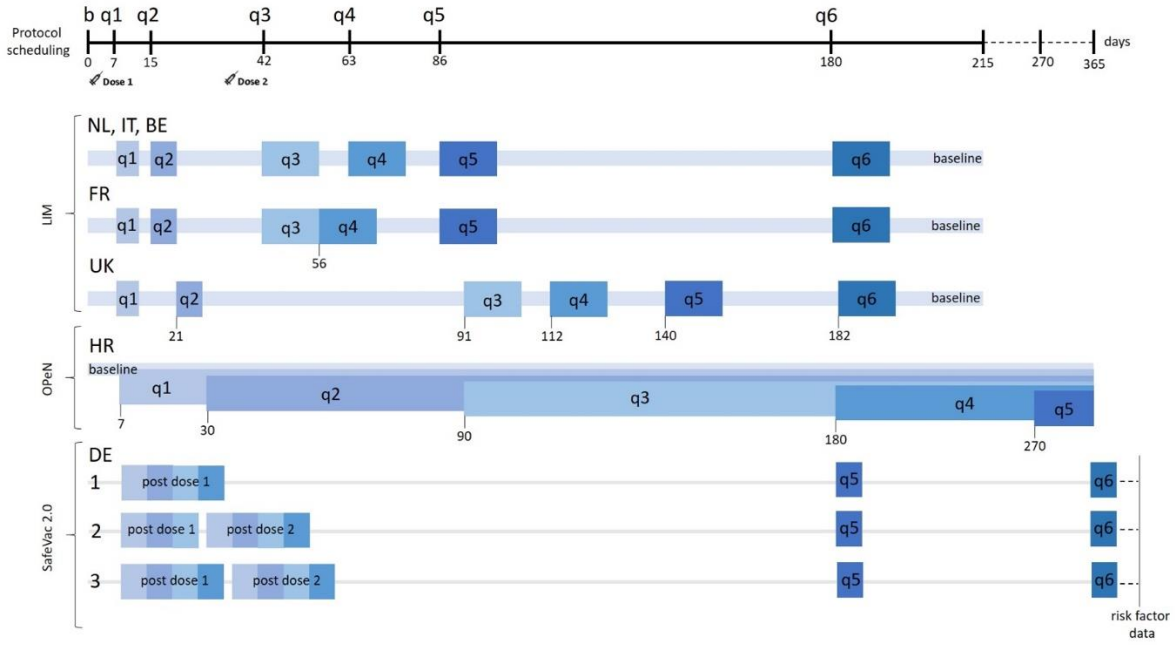

Figure 2: Questionnaire Scheduling schemes for the participating countries over time (days). The upper timeline in black shows the scheduling as it is described in the protocol, the timelines below show the three different data collection tools used (each coloured rectangle represents a questionnaire).

For the countries using the LIM app, due to technical reasons, only one schedule per country based on one reference date could be used and this schedule could not be adjusted after the first inclusions were started for this country. The schedules were created between February and June 2021 and the scheduling of the questionnaires was chosen such that it fitted the vaccination strategies of all vaccine

brands in a country the best. This was done with the knowledge that was available at the time. The Netherlands, Italy and Belgium all adhered to the scheduling scheme as described in the initial protocol (Figure 2). This scheme was determined as having the most optimal intervals regarding the administration of the second doses over all vaccine brands. 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. This timing was based on the previous scheduling scheme that had been determined before the exact intervals between vaccine doses of all brands were known.

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 and update 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 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 at the end of the study. As Germany started their data collection independently from this study, there are some challenges in aligning the data with the other countries' data: Gender has three categories (male, f emale, unknown) rather than the two categories (male, female) and the list of solicited adverse reactions is longer.

2.3 Data processing

In order to be able to pool the data across the different sites on adverse reactions, the ADRs needed to be MedDRA-coded. Where possible this process was aligned and coding agreements were shared at the start of the study. For both LIM and SafeVac 2.0 the solicited ADRs could be automatically MedDRA-coded. All of these ADRs were coded with their corresponding MedDRA Preferred Terms (PT). Except fever and injection site reaction which had more extensive options for coding. This more extensive list of PTs used can be found in Appendix 1. The unsolicited ADRs were manually assessed. Trained assessors in the participating countries coded the reported ADRs into English MedDRA Lower-Level Terms (LLT). In the LIM application, the manual coding of unsolicited ADRs created a library where the reported ADR

text from participants was linked to a MedDRA code chosen by the assessor. From this library MedDRA code suggestions were assigned automatically to future reported unsolicited reactions in the same language and country. This process of auto coding helped improving data quality and minimized time and resources needed for coding, see Figure 3.

The assessors also manually evaluated whether the reported ADR, solicited or unsolicited, met the serious criteria of the Council for International Organizations of Medical Sciences (CIOMS). In case an ADR met these criteria the ADR was considered a Serious ADR. When needed, further (medical) clarification was requested from the participant to do this evaluation.

Each ADR was also evaluated to meet the criteria for Adverse Event of Special Interest (AESI). Adverse events of special interest were defined based on the list of AESI that was established by the ACCESS project for the EMA during the initiation of the study and adjusted during the study to be able to quickly signal rare yet known possible ADRs of the COVID-19 vaccines [3]. The list of AESI and source of AESI used to pool data of ECVM can be found in Appendix 2. This evaluation was done automatically during data analysis.

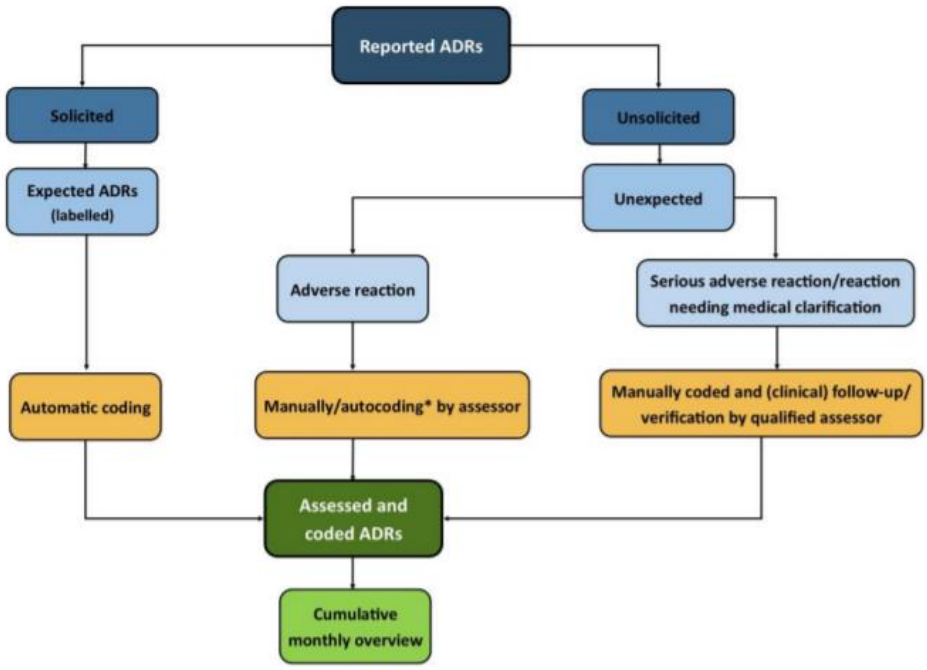

Figure 3: Flow chart of assessment and coding of ADR's

Data from all partners using the LIM application was stored in the Netherlands. Partners only had access to the data from their own country. In order to pool the data on an aggregated level, agreements were made on which data could be shared centrally. For the organizations using the LIM application, scripts were developed so that coded data from each organization was processed the same way. HALMED and the Paul-Ehrlich-Institute shared their coded aggregated data periodically. HALMED shared data from

Croatia on a monthly basis, whereas Paul-Ehrlich-Institute shared data from Germany in two large datasets.

Some countries, such as the Netherlands and Italy, were required to report ADRs to EudraVigilance. 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 added to these reports as follow up. Challenges included compacting the data present in the questionnaires into a standardized form accepted by EudraVigilance, setting up this reporting process per country and automating this process.

2.3 Data analysis

2.3.1 General

To ensure regular near real time insights in the collected data, a Microsoft Power BI dashboard was created by UMC Utrecht (ECVM Work Package 3). This dashboard was available to EMA online through a secure login. Aggregated level data was shared by all participating countries making the following information available: baseline data, risk factor data and information on reported ADRs. This information was stratified on vaccine brand, dose number, country and, where necessary, on gender or age category.

Further data analysis for this final report was done by using SQL, R-studio, and Microsoft Excel. The cumulative incidence rate was calculated for experiencing any ADR by dividing number of persons experiencing at least one ADR with the number of persons who received the vaccine. Additional cumulative incidence rates were calculated for specific solicited ADRs and the most commonly reported non-solicited ADRs. All participants that completed at least the first questionnaire regarding ADRs were included in the dashboard and for analysis in this final report.

2.3.2 Solicited vs. unsolicited ADRs

In the questionnaires, questions regarding adverse reactions were split into two different types of questions: the predefined list of common adverse reactions that participants could select from and the opportunity to report any other adverse reaction they may have experienced using an open text field. These two types of adverse reactions were defined as solicited and unsolicited. While offering participants the list of solicited adverse reactions allowed for faster processing of data, it may have also prompted participants to report an adverse reaction they would not have reported with an open question.

2.3.3 Systemic vs. local

All adverse reactions following vaccination, both solicited and unsolicited, were divided into systemic and local. Local adverse reactions included reactions at the injection site, such as commonly reported pain or redness. Most other adverse reactions were considered systemic, such as fatigue or fever.

Where applicable, the analyses take this classification into account for easier comparison with other studies that use the same classification.

2.3.4 AESI and serious adverse reactions

Adverse Events of Special Interest (AESI) are possible adverse reactions which are potentially relevant for the four different vaccine brands and require extra monitoring. A list of MedDRA Preferred Terms was used to filter all reported adverse reactions that have been coded. This list can be found in Appendix 2.

All adverse reactions, both solicited and unsolicited, could be marked as serious by a participant by indicating if the reaction led to hospitalisation longer than 24 hours, and/or a life-threatening situation, and/or another serious situation. All adverse reactions were assessed by a trained assessor to check if the reaction met the definition of the CIOMS criteria to be defined as a serious ADR. If required additional information and follow-up could be gathered from the participant when they gave consent to be contacted. Data provided by Germany for this report included only reported seriousness, rather than the assessed seriousness as coded by a trained assessor.

2.3.5 Dose 1 and dose 2 definition

Participants receive questionnaires based on the schedules as described in section 2.2.2. All questionnaires that participants fill in between their dose 1 and dose 2 were considered related to dose 1. All questionnaires completed after dose 2 are considered to be related to dose 2. For a single dose vaccine, all questionnaires are related to dose 1.

3. Results

3.1 Cohort characteristics

3.1.1 Participants included

Participants who have filled in at least one questionnaire on adverse reactions are included both in the dashboard updates and the final report. A total of 117,791 participants returned at least one questionnaire on experienced ADRs, were included and reviewed for ADRs. A total of 89,377 participants received the AstraZeneca vaccine, 14,658 received the BioNtech/Pfizer vaccine, and 11,266 received the Moderna vaccine. Only 2490 of the participants received the single dose Janssen vaccine. Table 2 shows the number of subjects per country per vaccine brand. In table 3 gender and age of the subjects is shown.

Table 2: ECVM cohort by dose and brand of vaccine. Number of subjects (N) per country who gave information about dose 1 and dose 2 vaccinations per vaccine brand. Left column (N) in absolute numbers, right column (%) in % relative to total number of participants per vaccine brand and dose

	AstraZeneca				BioNtech/Pfizer				Moderna				Janssen	
	Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2		Dose 1	
	N		N		N		N		N		N		N	
Belgium	1	0.00%			28	0.19%	6	0.05%	1	0.01%			8	0.32%
Croatia	48	0.05%	6	0.01%	240	1.64%	62	0.53%	25	0.22%	15	0.19%	13	0.52%
France	3	0.00%			947	6.46%	449	3.85%	32	0.28%	10	0.12%	3	0.12%
Germany	80511	90.08%	49957	89.93%					7686	68.22%	5402	66.80%		
Italy	3	0.00%	1	0.00%	472	3.22%	216	1.85%	87	0.77%	48	0.59%	8	0.32%
Netherlands	8811	9.86%	5586	10.06%	12894	87.97%	10937	93.68%	3425	30.40%	2603	32.19%	2458	98.71%
UK	2	0.00%			77	0.53%	10	0.09%	10	0.09%	5	0.06%		
Total	89377		55551		14658		11675		11266		8087		2490	

Table 3: ECVM cohort characteristics. Number of subjects (N) by gender and age per vaccine brand.

	AstraZeneca		BioNtech/Pfizer		Moderna		Janssen		Total
	N		N		N		N		
Female	51100	82.60%	6605	10.70%	2370	3.80%	1777	2.90%	61852
0 - 19 years	800	73.70%	244	22.50%	19	1.80%	22	2.00%	1085
20 - 29 years	9891	87.10%	864	7.60%	346	3.00%	259	2.30%	11360
30 - 39 years	10307	85.10%	1001	8.30%	504	4.20%	301	2.50%	12113
40 - 49 years	10002	84.60%	707	6.00%	688	5.80%	432	3.70%	11829
50 - 59 years	10621	84.10%	534	4.20%	749	5.90%	727	5.80%	12631
60 - 69 years	8209	93.50%	485	5.50%	55	0.60%	34	0.40%	8783
70 - 79 years	1212	41.10%	1728	58.60%	9	0.30%	2	0.10%	2951
80+ years	58	5.30%	1042	94.70%	0	0.00%	0	0.00%	1100
Male	38277	79.30%	8053	16.70%	1210	2.50%	713	1.50%	48253
0 - 19 years	588	77.60%	149	19.70%	12	1.60%	9	1.20%	758
20 - 29 years	6251	91.20%	374	5.50%	120	1.80%	107	1.60%	6852
30 - 39 years	8199	92.60%	405	4.60%	160	1.80%	89	1.00%	8853
40 - 49 years	6138	88.30%	297	4.30%	356	5.10%	157	2.30%	6948
50 - 59 years	6260	85.70%	218	3.00%	493	6.70%	336	4.60%	7307
60 - 69 years	8612	96.40%	257	2.90%	51	0.60%	13	0.10%	8933
70 - 79 years	2154	36.70%	3699	63.00%	18	0.30%	2	0.00%	5873
80+ years	75	2.70%	2654	97.30%	0	0.00%	0	0.00%	2729
Unknown					7686	100.00%		0.00%	7686
0 - 19 years					91	100.00%		0.00%	91
20 - 29 years					1419	100.00%		0.00%	1419
30 - 39 years					2253	100.00%		0.00%	2253
40 - 49 years					1710	100.00%		0.00%	1710
50 - 59 years					1444	100.00%		0.00%	1444
60 - 69 years					476	100.00%		0.00%	476
70 - 79 years					255	100.00%		0.00%	255
80+ years					38	100.00%		0.00%	38
Total	89377	75.90%	14658	12.40%	11266	9.60%	2490	2.10%	117791

Table 3 shows a dataset of gender ‘unknown’ in the Moderna group. The reported gender of this group is available, however not when stratified by age category. This particular subset is data originating from Germany and will be corrected and added to the dataset in the future. Of the 7,686 'unknown’ in Table 2. 2,779 are male participants, 4,893 are female participants and 14 reported their gender as ‘other’. Among those receiving dose 1, a total of 75,313 participants have received a second dose, of which 55,551 (78.8%) received the AstraZeneca vaccine. 11,675 (15.5%) received BioNTech/Pfizer and 8,087 (10.7%) received Moderna. The detailed overview can be found in Appendix 3. As of October 2021, the final update of the EVCM dashboard only 62.1% of participants who received the AstraZeneca vaccine,

79.6% of those who received the BioNtech/Pfizer vaccine and 71.8% who received the Moderna vaccine have reported information after their second dose. A subset of those participants who have not yet reported may be lost to follow-up or they have not yet been prompted to fill in dose 2 related questionnaires. The data collection amongst participants is ongoing, therefore more dose 2 related data will become available at a later stage and reported as part of the CVM study.

3.1.2 Questionnaires completed and time to completion

A total of (148,624) questionnaires have been filled in by participants, all of which have either been coded automatically or assessed on a case-by-case basis and, when applicable, have been coded for analysis. Table 4 summarizes the number of questionnaires by country and vaccine brand. This table only includes data from the LIM countries as these details were not available at the moment of the final report for Germany and Croatia.

Table 4: ECVM questionnaires at different time points by country and vaccine brand

	Baseline	Q1	Q2	Q3	Q4	Q5	Q6	Total
NL	30947	27491	24867	22585	16486	15574	1768	139718
BioNtech/Pfizer	14480	12875	11729	11004	8757	8351	699	67895
AstraZeneca	9805	8814	8084	7159	5641	5882	813	46198
Moderna	3824	3353	2964	2713	1292	800	121	15067
Janssen	2838	2449	2090	1709	796	541	135	10558
FR	1413	1060	910	721	595	377		5076
BioNtech/Pfizer	1365	1021	882	697	578	364		4907
Moderna	41	33	26	22	15	11		148
Janssen	3	3	2	2	2	2		14
AstraZeneca	4	3						7
IT	959	629	515	385	302	234		3024
BioNtech/Pfizer	811	526	437	316	242	184		2516
Moderna	136	92	68	61	54	47		458
Janssen	9	8	8	7	6	3		41
AstraZeneca	3	3	2	1				9
UK	261	183	139	26	18	6		633
BioNtech/Pfizer	237	169	127	18	11	3		565
Moderna	18	10	8	6	5	3		50
AstraZeneca	6	4	4	2	2			18
BE	67	38	32	16	11	9		173
BioNtech/Pfizer	44	28	24	9	5	4		114
Janssen	8	8	7	7	6	5		41
Moderna	8	1						9
AstraZeneca	7	1	1					9
Total	**33647**	**29401**	**26463**	**23733**	**17412**	**16200**	**1768**	**148624**

Table 5 illustrates the variations between the average days it took for participants to complete their questionnaires after their injection date for the Netherlands, France, Italy, the UK and Belgium. Croatia adhered to a different questionnaire scheduling scheme and was thus put in a sperate table (Table 6). Data from Germany was not available at the time of writing of the report.

Table 5: Days to completion of questionnaire (Q) by country (LIM countries)

		mean	standard deviation	minimum	maximim	median	n
Q1	Netherlands	8.83	1.79	7	20	8	27654
	France	9.00	1.81	7	15	8	1111
	Italy	9.26	2.01	7	14	8	705
	UK	8.95	1.93	7	14	8	210
	Belgium	9.16	1.79	7	14	8	38
Q2	Netherlands	16.89	1.70	15	25	16	25532
	France	17.17	1.93	15	23	16	951
	Italy	17.19	1.92	15	22	16	565
	UK	22.85	1.89	21	28	22	175
	Belgium	17.09	1.99	15	22	16	32
Q3	Netherlands	-2.91	19.63	-141	36	8	19183
	France	20.20	7.07	-20	36	22	652
	Italy	14.23	8.53	-20	36	14	362
	UK	33.15	26.40	-20	84	35	34
	Belgium	22.50	9.18	7	36	25	8
Q4	Netherlands	17.79	19.90	-120	68	29	18194
	France	33.70	7.38	-7	54	35	564
	Italy	34.70	8.47	1	57	34	311
	UK	52.96	27.32	2	106	55	27
	Belgium	41.60	13.45	27	59	46	5
Q5	Netherlands	39.86	20.34	-97	80	52	17090
	France	63.54	7.10	23	86	65	464
	Italy	57.37	8.48	23	79	55	253
	UK	92.00	20.21	53	133	89	16
	Belgium	65.80	13.03	52	79	67	5
Q6	Netherlands	136.41	20.02	5	180	147	15012
	France	152.63	8.68	138	170	153	41
	Italy	149.61	5.75	141	169	148	70
	UK	117.67	17.04	95	145	114.5	6
	Belgium						

Table 6: Days to completion of questionnaire for Croatia

	mean	standard deviation	minimum	maximum	median	n
Croatia						
Dose 1	8.29	37.47	0	294	3	345
Dose 2	17.95	22.51	1	73	7	87

Figure 4 shows that the time to completion for questionnaire 1 was quite similar for all countries with participants responding on average 9 days after the first dose of their received vaccine. Completion of questionnaire 2 similarly shows a comparable average time across countries with the exception of the United Kingdom and Croatia. Completion times of questionnaires 3 and 4 show much larger variation after the dose 2 vaccination date. Therefore, follow-up time after questionnaires related to dose 1 are comparable whereas this is not the case for questionnaires following dose 2.

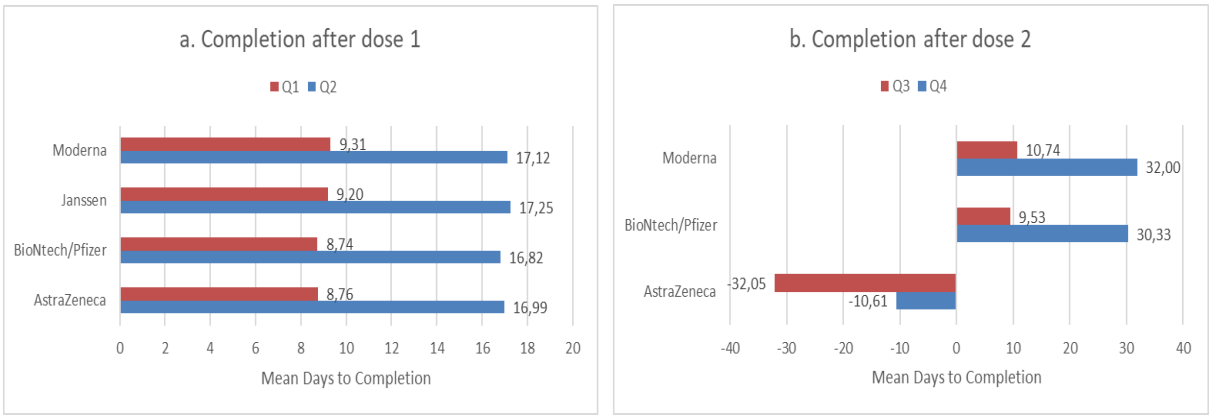

Figure 4: days to completion of questionnaires by vaccine brand

Figure 4 shows the completion time after questionnaire 1 and 2, by vaccine brand across countries. The average days to completion for dose 1 related questionnaires are comparable across all vaccine brands. This is not the case for questionnaires 3 and 4.

3.2 Adverse drug reactions

Participants are able to report adverse reactions in every questionnaire they receive. Figure 5 summarizes the percentage of participants who have reported at least one adverse reaction after their first vaccine dose and before their second dose. Across all vaccine brands, women are more likely to report an adverse reaction when compared to men. This also holds true when stratifying by age group. However the difference between women and men does vary between vaccine brands: the differences are smaller between women and men for participants who received the AstraZeneca vaccine. For both the Moderna and the Janssen recipients, the difference becomes larger for the older age groups. BioNtech/Pfizer shows the lowest reporting rates for at least one adverse reaction.

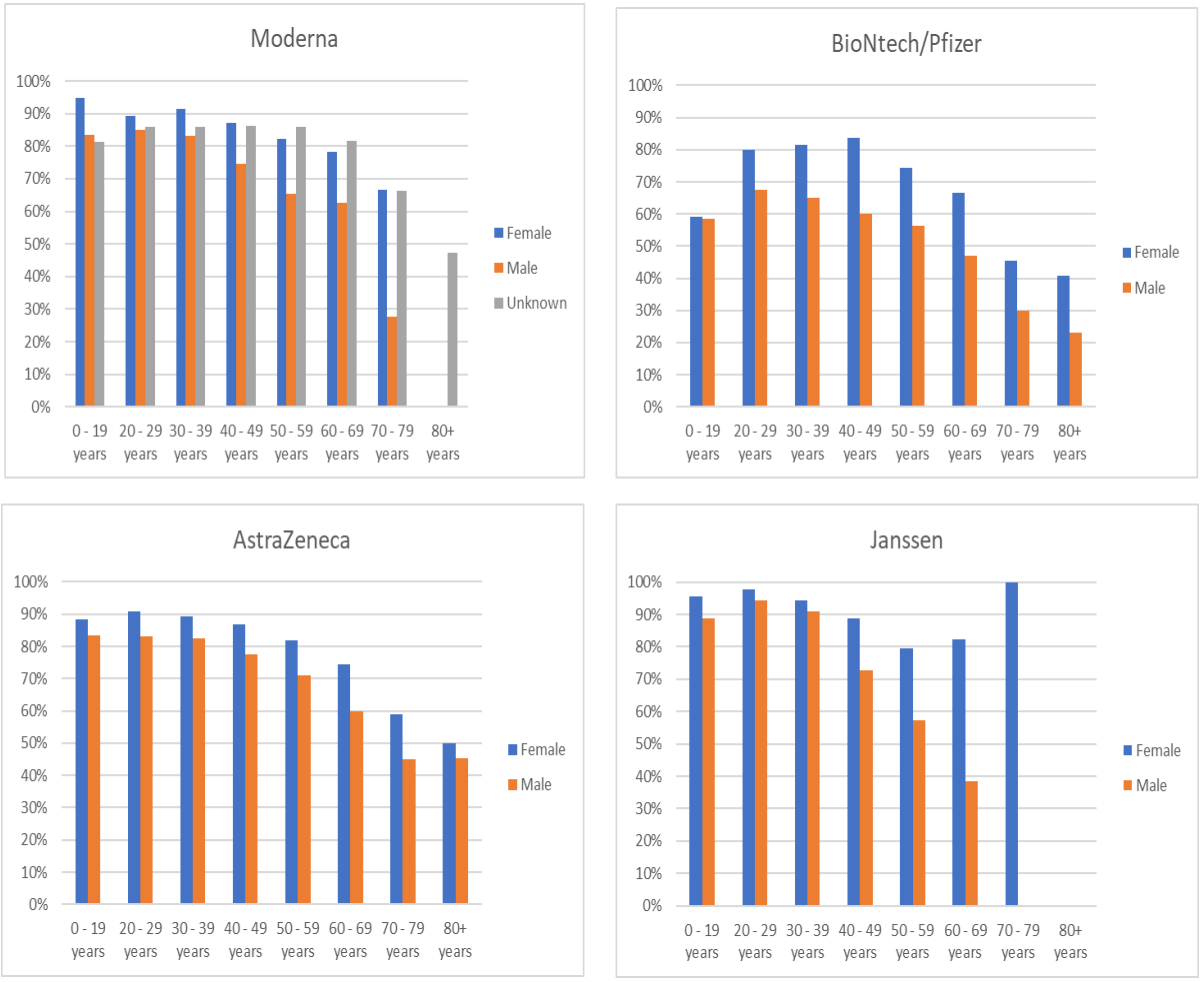

Figure 5: Percentage of participants reporting at least one adverse drug reaction after dose 1 and (when applicable) before dose 2

3.3 Adverse drug reactions solicited

The solicited adverse reactions are a list of predefined reactions that are commonly reported after vaccination which participants can select in every questionnaire. These solicited adverse reactions are coded with a MedDRA term. When fever or injection site reaction is reported by the participant, these are classified according to the definitions as described in the protocol. This is the reason Table 7 shows several different MedDRA terms for fever (body temperature increase, pyrexia, hyperpyrexia) and for different types of injection site reactions. The table also specifies which solicited adverse reactions are classified as systemic and which are classified as local.

The most commonly reported systemic solicited reaction is fatigue which is closely followed by headache and malaise. Fatigue was reported by 53.9% of all participants who received the AstraZeneca vaccine and 50.6% of the participants who received Janssen. Fewer participants reported this adverse reaction after their first dose of BioNtech/Pfizer and Moderna vaccines, a total of 17.2% and 35.2% respectively. Where headache was reported almost as often as fatigue in those receiving AstraZeneca and Janssen, 53.3% and 49.6% respectively. This was lower in the BioNtech/Pfizer (11.9%) and Moderna

(29.8%) group. Participants receiving the AstraZeneca or Janssen vaccine were more likely to report any of the systemic solicited reactions when compared to participants receiving other vaccine brands. Participants who received the BioNtech/Pfizer vaccine were less likely to report any of the systemic solicited adverse reactions when compared to other vaccine brands.

Table 7: Solicited adverse reactions reported after dose 1 and (when applicable) before dose 2 (I.S.=Injection Site)

	AstraZeneca		BioNtech/Pfizer		Janssen		Moderna		Total	
Systemic	**N**		**N**		**N**		**N**		**N**	
Fatigue	48212	53.94%	2519	17.19%	1261	50.64%	3971	35.25%	55963	47.51 %
Headache	47640	53.30%	1745	11.91%	1236	49.64%	3354	29.77%	53975	45.82%
Malaise	32027	35.83%	1480	10.10%	1175	47.19%	2217	19.68%	36899	31.33%
Chills	31795	35.57%	619	4.22%	928	37.27%	1004	8.91%	34346	29.16%
Myalgia	29956	33.52%	2405	16.41%	1047	42.05%	2695	23.92%	36103	30.65%
Pyrexia	28370	31.74%	354	2.42%	762	30.60%	824	7.31%	30310	25.73%
Arthralgia	20175	22.57%	581	3.96%	484	19.44%	1060	9.41%	22300	18.93%
Nausea	13227	14.80%	630	4.30%	490	19.68%	922	8.18%	15269	12.96%
Body temperature increased	904	1.01%	129	0.88%	136	5.46%	125	1.11%	1294	1.10%
Hyperpyrexia	82	0.09%	1	0.01%	11	0.44%		0.00%	94	0.08%
Local										
I.s. pain	47187	52.80%	3538	24.14%	831	33.37%	5755	51.08%	57311	48.66%
I.s. swelling	11585	12.96%	727	4.96%	264	10.60%	2377	21.10%	14953	12.70%
I.s. inflammation	1789	2.00%	749	5.11%	260	10.44%	717	6.36%	3515	2.98%
I.s. warmth	1152	1.29%	451	3.08%	150	6.02%	488	4.33%	2241	1.90%
I.s. erythema	831	0.93%	235	1.60%	96	3.86%	443	3.93%	1605	1.36%
I.s. haematoma	483	0.54%	253	1.73%	113	4.54%	185	1.64%	1034	0.88%
I.s. pruritus	413	0.46%	145	0.99%	42	1.69%	249	2.21%	849	0.72%
I.s.discomfort	215	0.24%	268	1.83%	48	1.93%	115	1.02%	646	0.55%
I.s. induration	97	0.11%	49	0.33%	9	0.36%	96	0.85%	251	0.21%
I.s. bruising	21	0.02%	0	0.00%	0	0.00%	4	0.04%	25	0.02%
I.s. reaction	15	0.02%	14	0.10%	1	0.04%	6	0.05%	36	0.03%
I.s. hypoaesthesia	12	0.01%	4	0.03%	1	0.04%	4	0.04%	21	0.02%
I.s. paraesthesia	8	<0.01%	3	0.02%	2	0.08%	5	0.04%	18	0.02%
I.s. irritation	5	<0.01%	1	<0.01%	0	0.00%	0	0.00%	6	<0.01%
I.s rash	3	<0.01%	1	<0.01%	0	0.00%	5	0.04%	9	0.01%
I.s. cellulitis	2	<0.01%	0	0.00%	0	0.00%	0	0.00%	2	<0.01%
I.s. mass	2	<0.01%	0	0.00%	0	0.00%	0	0.00%	2	<0.01%
I.s. eczema	2	<0.01%	0	0.00%	0	0.00%	0	0.00%	2	<0.01%
I.s. hypersensitivity	2	<0.01%	0	0.00%	0	0.00%	1	<0.01%	3	<0.01%
I.s. haemorrhage	2	<0.01%	0	0.00%	0	0.00%	1	<0.01%	3	<0.01%
I.s. joint pain	1	<0.01%	1	<0.01%	0	0.00%	0	0.00%	2	<0.01%
I.s. urticaria	1	<0.01%	0	0.00%	1	0.04%	3	0.03%	5	<0.01%
I.s. dysaesthesia	1	<0.01%	0	0.00%	0	0.00%	0	0.00%	1	<0.01%
I.s. dryness	1	<0.01%	1	<0.01%	0	0.00%	0	0.00%	2	<0.01%
I.s. joint movement impairment	1	<0.01%	1	<0.01%	0	0.00%	1	<0.01%	3	<0.01%
I.s. discolouration	1	<0.01%	0	0.00%	0	0.00%	1	<0.01%	2	<0.01%
I.s. extravasation	1	<0.01%	0	0.00%	0	0.00%	0	0.00%	1	<0.01%
I.s. oedema	1	<0.01%	0	0.00%	0	0.00%	0	0.00%	1	<0.01%
I.s. papule	1	<0.01%	1	<0.01%	0	0.00%	0	0.00%	2	<0.01%
I.s. infection	0	0.00%	0	0.00%	0	0.00%	1	<0.01%	1	<0.01%
I.s. vesicles	0	0.00%	0	0.00%	0	0.00%	1	<0.01%	1	<0.01%
I.s. abscess	0	0.00%	0	0.00%	0	0.00%	1	<0.01%	1	<0.01%
I.s. exfoliation	0	0.00%	1	<0.01%	0	0.00%	0	0.00%	1	<0.01%

The most commonly reported local reaction across all vaccine brands is coded as 'injection site pain' with participants who received AstraZeneca and Moderna being most frequent to report this reaction. For participants who received Moderna, this was overall the most commonly reported solicited adverse reaction with 51.1%. Participants who received Pfizer/BioNtech reported 'injection site pain' at a higher rate than any of the systemic solicited adverse reactions.

3.4 Adverse drug reactions unsolicited

Participants are able to report adverse reactions other than the predefined list. These reported adverse reactions are coded into MedDRA terms, all of which can be found in Appendix 1. Table 8 shows the top ten reported unsolicited adverse reactions with the top three reported adverse reactions per vaccine brand in bold.

Table 8: Unsolicited adverse reactions reported after dose 1 and (when applicable) before dose 2

	AstraZeneca		BioNtech/Pfizer		Janssen		Moderna		Total	
	N		N		N		N		N	
Dizziness	**17051**	**19.08%**	**158**	**1.08%**	**56**	**2.25%**	**1001**	**8.89%**	**18266**	**15.51%**
Diarrhoea	**3657**	**4.09%**	**120**	**0.82%**	**35**	**1.41%**	**400**	**3.55%**	**4212**	**3.58%**
Lymphadenopathy	376	0.42%	41	0.28%	21	0.84%	**162**	**1.44%**	600	0.51%
Pain in extremity	603	0.67%	**106**	**0.72%**	21	0.84%	119	1.06%	849	0.72%
Nasopharyngitis	546	0.61%	47	0.32%	21	0.84%	107	0.95%	721	0.61%
Oropharyngeal pain	526	0.59%	53	0.36%	19	0.76%	93	0.83%	691	0.59%
Vomiting	**1615**	**1.81%**	21	0.14%	10	0.40%	86	0.76%	**1732**	**1.47%**
Cough	351	0.39%	25	0.17%	12	0.48%	57	0.51%	445	0.38%
Paraesthesia	330	0.37%	61	0.42%	**30**	**1.20%**	53	0.47%	474	0.40%
Pruritus	196	0.22%	34	0.23%	5	0.20%	52	0.46%	287	0.24%

Dizziness is reported most often as an unsolicited adverse reaction across all vaccine brands, with the highest reporting found in those receiving the AstraZeneca vaccine: 19.08% of all participants receiving this vaccine reported dizziness between dose 1 and dose 2. Almost 9% of all Moderna participants also reported dizziness as an unsolicited adverse reaction. Despite this adverse reaction being the most reported unsolicited adverse reaction in the Janssen and BioNtech/Pfizer group, only 2.25% and 1.08% reported experiencing this reaction. Diarrhoea closely follows as second most commonly reported unsolicited reaction, with both AstraZeneca and Moderna showing the highest rates of reporting at 4.09% and 3.55%, respectively. Other than these two adverse reactions, all other adverse reactions vary between vaccines. Appendix 4 includes a list of more than 800 different MedDRA Preferred Terms which represent all reported adverse reactions in their coded form. This list gives an indication for the variation in reported unsolicited adverse reactions.

3.5 Second Dose

Considering the limitations of pooling and comparing first and second dose data, second dose ADR data will be presented independently. Table 9 a-g show all ADRs reported by participants from each country. The data has been stratified by vaccine brand and by country. Additionally the ADRs were grouped in solicited, local (I.s. = injection site) and unsolicited. Percentages were calculated using the total number of participants per group as the denominator and thus represents the percentage of participants within a certain group that experienced the ADR. Tables 9a-g show a subset of ADRs that had a total reported frequency that was above 0.5%.

The most frequently reported solicited ADRs across most countries after dose 2 were fatigue, malaise and myalgia. With other solicited ADRs often being reported frequently. Of the local ADRs, injection site pain, injection site inflammation, and injection site swelling were generally most reported. The most reported unsolicited ADRs varies greatly between countries. Unsolicited reactions were infrequent after the second dose in the Netherlands and France but common in other countries.

Table 9a: Any adverse reactions reported after second dose administration date in the Dutch ECVM participants

Netherlands	**AstraZeneca**		**BioNtech/Pfizer**		**Moderna**		**Total**	
N Vaccinees		5586		10937		2603		19126
Solicited	**N**		**N**		**N**		**N**	
Fatigue	1212	21.70%	1608	14.70%	1284	49.33%	4104	21.46%
Malaise	868	15.54%	1286	11.76%	1372	52.71%	3526	18.44%
Myalgia	754	13.50%	1458	13.33%	1169	44.91%	3381	17.68%
Headache	1046	18.73%	1099	10.05%	1115	42.84%	3260	17.04%
Chills	378	6.77%	521	4.76%	914	35.11%	1813	9.48%
Pyrexia	250	4.48%	339	3.10%	796	30.58%	1385	7.24%
Nausea	280	5.01%	394	3.60%	511	19.63%	1185	6.20%
Arthralgia	261	4.67%	441	4.03%	446	17.13%	1148	6.00%
Body temperature increased	78	1.40%	127	1.16%	184	7.07%	389	2.03%
Local								
I.s. pain	1121	20.07%	1777	16.25%	1122	43.10%	4020	21.02%
I.s. inflammation	321	5.75%	394	3.60%	576	22.13%	1291	6.75%
I.s. swelling	299	5.35%	339	3.10%	497	19.09%	1135	5.93%
I.s. warmth	203	3.63%	273	2.50%	522	20.05%	998	5.22%
I.s. erythema	159	2.85%	205	1.87%	389	14.94%	753	3.94%
I.s. haematoma	133	2.38%	138	1.26%	129	4.96%	400	2.09%
I.s. pruritus	52	0.93%	99	0.91%	133	5.11%	284	1.48%
I.s. discomfort	47	0.84%	102	0.93%	24	0.92%	173	0.90%
Unsolicited								
Dizziness*	50	0.90%	71	0.65%	26	1.00%	147	0.77%
Diarrhoea*	29	0.52%	56	0.51%	22	0.85%	107	0.56%

* Dizziness and diarrhoea were solicited reactions in the German SafeVac app

Table 9b: Any adverse reactions reported after second dose administration date in French ECVM particpants

France	BioNtech/Pfizer		Moderna		Total	
N Vaccinees		449		10		459
Solicited	**N**		**N**		**N**	
Fatigue	130	28.95%	4	40.00%	134	29.19%
Headache	88	19.60%	1	10.00%	89	19.39%
Myalgia	77	17.15%	4	40.00%	81	17.65%
Malaise	55	12.25%	2	20.00%	57	12.42%
Chills	52	11.58%	2	20.00%	54	11.76%
Pyrexia	50	11.14%	1	10.00%	51	11.11%
Nausea	28	6.24%	2	20.00%	30	6.54%
Arthralgia	26	5.79%	2	20.00%	28	6.10%
Body temperature increased	12	2.67%			12	2.61%
Local						
l.s. pain	100	22.27%	5	50.00%	105	22.88%
l.s. swelling	25	5.57%	3	30.00%	28	6.10%
l.s. inflammation	22	4.90%	3	30.00%	25	5.45%
l.s. warmth	15	3.34%	2	20.00%	17	3.70%
l.s. erythema	11	2.45%	3	30.00%	14	3.05%
l.s. pruritus	10	2.23%	1	10.00%	11	2.40%
l.s. haematoma	4	0.89%			4	0.87%
Unsolicited						
Menstrual disorder	4	0.89%		0.00%	4	0.87%
Tinnitus	3	0.67%		0.00%	3	0.65%

Table 9c: Any adverse reactions reported after second dose administration date from Italian ECVM participants

Italy	BioNtech/Pfizer		Moderna		Total	
N Vaccinees		216		48		265
Solicited	**N**		**N**		**N**	
Fatigue	72	33.33%	30	62.50%	102	38.49%
Myalgia	56	25.93%	26	54.17%	82	30.94%
Malaise	47	21.76%	30	62.50%	77	29.06%
Headache	47	21.76%	19	39.58%	66	24.91%
Arthralgia	34	15.74%	21	43.75%	55	20.75%
Body temperature increased	28	12.96%	15	31.25%	43	16.23%
Chills	23	10.65%	19	39.58%	42	15.85%
Pyrexia	7	3.24%	17	35.42%	24	9.06%
Nausea	15	6.94%	7	14.58%	22	8.30%
Local						
l.s. pain	76	3.19%	24	50.00%	100	37.74%
l.s. inflammation	22	10.19%	19	39.58%	41	15.47%
l.s. swelling	20	9.26%	12	25.00%	32	12.08%
l.s. warmth	14	6.48%	13	27.08%	27	10.19%
l.s. erythema	10	4.63%	6	12.50%	16	6.04%
l.s. pruritus	9	4.17%	4	8.33%	13	4.91%
l.s. haematoma	5	2.31%			5	1.89%
l.s. induration	1	0.46%	1	2.08%	2	0.75%
l.s. discomfort						
Unsolicited						
Lymphadenopathy	4	1.85%	1	2.08%	5	1.89%
Abdominal pain	3	1.39%			3	1.13%
Axillary pain	2	0.93%			2	0.75%
Paraesthesia	2	0.93%			2	0.75%
Amenorrhoea	2	0.93%			2	0.75%
Menstruation irregular	1	0.46%	1	2.08%	2	0.75%
Italy	**BioNtech/Pfizer**		**Moderna**		**Total**	
N Vaccinees		216		48		265
Solicited	**N**		**N**		**N**	

Fatigue	72	33.33%	30	62.50%	102	38.49%
Myalgia	56	25.93%	26	54.17%	82	30.94%
Malaise	47	21.76%	30	62.50%	77	29.06%
Headache	47	21.76%	19	39.58%	66	24.91%
Arthralgia	34	15.74%	21	43.75%	55	20.75%
Body temperature increased	28	12.96%	15	31.25%	43	16.23%
Chills	23	10.65%	19	39.58%	42	15.85%
Pyrexia	7	3.24%	17	35.42%	24	9.06%
Nausea	15	6.94%	7	14.58%	22	8.30%
Local						
I.s. pain	76	3.19%	24	50.00%	100	37.74%
I.s. inflammation	22	10.19%	19	39.58%	41	15.47%
I.s. swelling	20	9.26%	12	25.00%	32	12.08%
I.s. warmth	14	6.48%	13	27.08%	27	10.19%
I.s. erythema	10	4.63%	6	12.50%	16	6.04%
I.s. pruritus	9	4.17%	4	8.33%	13	4.91%
I.s. haematoma	5	2.31%			5	1.89%
I.s. induration	1	0.46%	1	2.08%	2	0.75%
I.s. discomfort						
Unsolicited						
Lymphadenopathy	4	1.85%	1	2.08%	5	1.89%
Abdominal pain	3	1.39%			3	1.13%
Axillary pain	2	0.93%			2	0.75%
Paraesthesia	2	0.93%			2	0.75%
Amenorrhoea	2	0.93%			2	0.75%
Menstruation irregular	1	0.46%	1	2.08%	2	0.75%

Table 9d: Any adverse reactions reported after second dose administration date from the UK ECVM participants

United Kingdom	**BioNtech/Pfizer**		**Moderna**		**Total**	
N Vaccinees		**10**		**5**		**15**
Solicited	**N**		**N**		**N**	
Fatigue	3	30.00%	3	60.00%	6	40.00%
Malaise	3	30.00%	3	60.00%	6	40.00%
Myalgia	2	20.00%	3	60.00%	5	33.33%
Arthralgia	2	20.00%	2	40.00%	4	26.67%
Body temperature increased	1	10.00%	2	40.00%	3	20.00%
Headache	1	10.00%	1	20.00%	2	13.33%
Chills	1	10.00%	1	20.00%	2	13.33%
Nausea	1	10.00%			1	6.67%
Pyrexia			1	20.00%	1	6.67%
Local						
I.s. pain	3	30.00%	2	40.00%	5	33.33%
I.s. erythema	1	10.00%	1	20.00%	2	13.33%
I.s. swelling	2	20.00%			2	13.33%
I.s. warmth	1	10.00%	1	20.00%	2	13.33%
I.s. haematoma			1	20.00%	1	6.67%
I.s. pruritus			1	20.00%	1	6.67%
Unsolicited						
Pain			1	20.00%	1	6.67%
Insomnia			1	20.00%	1	6.67%

Table 9e: Any adverse reactions reported after second dose administration date from Belgian ECVM participants

Belgium	BioNtech/Pfizer		Total	
N Vaccinees		6		6
Solicited	**N**		**N**	
Myalgia	3	50.00%	3	50.00%
Headache	2	33.33%	2	33.33%
Malaise	2	33.33%	2	33.33%
Arthralgia	1	16.67%	1	16.67%
Body temperature increased	1	16.67%	1	16.67%
Chills	1	16.67%	1	16.67%
Fatigue	1	16.67%	1	16.67%
Nausea	1	16.67%	1	16.67%
Local				
I.s. pain	2	33.33%	2	33.33%
I.s. erythema	1	16.67%	1	16.67%
I.s. induration	1	16.67%	1	16.67%
I.s. inflammation	1	16.67%	1	16.67%
I.s. warmth	1	16.67%	1	16.67%
Unsolicited				
Contusion	1	16.67%	1	16.67%

Table 9f: Any adverse reactions reported after second dose administration date from German ECVM participants

Germany	AstraZeneca		Moderna		Total	
N Vaccinees		49957		5402		55359
Solicited	**N**		**N**		**N**	
Fatigue	18365	36.76%	3636	67.31%	22001	39.74%
Headache	15082	30.19%	3276	60.64%	18358	33.16%
Malaise	7468	14.95%	2302	42.61%	9770	17.65%
Myalgia	7195	14.40%	2422	44.84%	9617	17.37%
Pyrexia	4773	9.55%	1745	32.30%	6518	11.77%
Chills	4464	8.94%	1802	33.36%	6266	11.32%
Arthralgia	4731	9.47%	1379	25.53%	6110	11.04%
Nausea	2534	5.07%	949	17.57%	3483	6.29%
Local						
I.s. pain	19792	39.62%	4712	87.23%	24504	44.26%
I.s. swelling	4306	8.62%	2038	37.73%	6344	11.46%
Unsolicited						
Dizziness*	4959	9.93%	1251	23.16%	6210	11.22%
Diarrhoea*	1613	3.23%	329	6.09%	1942	3.51%
Vomiting	313	0.63%	97	1.80%	410	0.74%
Lymphadenopathy	141	0.28%	266	4.92%	407	0.74%
Nasopharyngitis	224	0.45%	87	1.61%	311	0.56%
Oropharyngeal pain	196	0.39%	89	1.65%	285	0.51%

* Dizziness and diarrhoea were solicited reactions in the German SafeVac app

Table 9g: Any adverse reactions reported after second dose administration date from Croatian ECVM participants

Croatia	AstraZeneca		BioNtech/Pfizer		Moderna		Total	
N Vaccinees	7		57		19		83	
Solicited	**N**		**N**		**N**		**N**	
Pyrexia			18	31.58%	3	15.79%	21	25.30%
Headache			12	21.05%			12	14.46%
Fatigue			11	19.30%			11	13.25%
Chills			6	10.53%	1	5.26%	7	8.43%
Myalgia			5	8.77%			5	6.02%
Malaise			2	3.51%			2	2.41%
Arthralgia				0.00%	1	5.26%	1	1.20%
Local				0.00%				
I.s. pain	2	28.57%	30	52.63%	4	21.05%	36	43.37%
I.s. erythema			3	5.26%	1	5.26%	4	4.82%
I.s. discomfort			1	1.75%	1	5.26%	2	2.41%
I.s. pruritus			1	1.75%	1	5.26%	2	2.41%
I.s. movement impairment			1	1.75%			1	1.20%
I.s. swelling			1	1.75%			1	1.20%
Unsolicited								
Pain in extremity			4	7.02%			4	4.82%
Tinnitus			3	5.26%			3	3.61%
Dyspnoea			2	3.51%			2	2.41%
Oropharyngeal discomfort			2	3.51%			2	2.41%
Intermenstrual bleeding			2	3.51%			2	2.41%
Ear congestion			1	1.75%			1	1.20%
Pruritus			1	1.75%			1	1.20%
Pain			1	1.75%			1	1.20%
Hypersensitivity			1	1.75%			1	1.20%
Sleep disorder			1	1.75%			1	1.20%
Hypotension			1	1.75%			1	1.20%
Back pain			1	1.75%			1	1.20%
Dysphagia			1	1.75%			1	1.20%
Discomfort			1	1.75%			1	1.20%
Rash			1	1.75%			1	1.20%
Lymphadenopathy			1	1.75%			1	1.20%
Axillary pain			1	1.75%			1	1.20%
Dizziness*			1	1.75%			1	1.20%
Epistaxis			1	1.75%			1	1.20%
Eye pain			1	1.75%			1	1.20%
Dry eye			1	1.75%			1	1.20%
Lymph node pain			1	1.75%			1	1.20%
Muscular weakness			1	1.75%			1	1.20%

3.6 AESI

Of the 88,377 participants who received AstraZeneca, 95 reported an adverse reaction which is flagged as an AESI. This 0.1% (0.086,0.129) of the total participants receiving this vaccine included in the study. BioNtech/Pfizer and Moderna had the same AESI reporting rate as AstraZeneca. Janssen on the other hand had a somewhat higher rate at 0.2% (0.065, 0.469), however based on only 2490 participants.

Table 10: Participants reporting at least one AESI between dose 1 and dose 2

	N AESI	Number of participants	% (CI) with AESI
AstraZeneca	95	89377	0.1% (0.086, 0.129)
BioNtech/Pfizer	20	14658	0.1% (0.083, 0.210)
Janssen	5	2490	0.2% (0.065, 0.469)
Moderna	7	11266	0.1% (0.025, 0.128)
Total	**127**	**117791**	**0.1% (0.089, 0.128)**

Participants can report more than one AESI, which is why the total number of participants reporting at least one AESI in Table 10 is smaller than the total number of AESI in Table 11.

Table 11: AESI reported per vaccine brand between dose 1 and dose 2

	AstraZeneca		BioNtech/Pfizer		Janssen		Moderna		Total	
	N		N		N		N		N	
Acute myocardial infarction	1	0.001%							**1**	0.001%
Anaphylactic reaction	3	0.003%			1	0.040%			**4**	0.003%
Arrhythmia	9	0.010%	2	0.014%					**11**	0.009%
Atrioventricular block complete			1	0.007%					**1**	0.001%
Cerebral venous sinus thrombosis	1	0.001%							**1**	0.001%
Cerebrovascular accident			1	0.007%					**1**	0.001%
COVID-19	7	0.008%	6	0.041%	3	0.120%			**16**	0.014%
Death	1	0.001%							**1**	0.001%
Deep vein thrombosis	1	0.001%							**1**	0.001%
Epilepsy	2	0.002%					1	0.009%	**3**	0.003%
Facial paralysis	1	0.001%							**1**	0.001%
Facial paresis	1	0.001%							**1**	0.001%
Hypersensitivity	7	0.008%	5	0.034%			1	0.009%	**13**	0.011%
Hypersomnia							1	0.009%	**1**	0.001%
Myocardial infarction			2	0.014%					**2**	0.002%
Myocarditis			1	0.007%					**1**	0.001%
Pericarditis			1	0.007%					**1**	0.001%
Petit mal epilepsy			1	0.007%					**1**	0.001%
Portal vein thrombosis	1	0.001%							**1**	0.001%
Product administration error					1	0.040%			**1**	0.001%
Pulmonary embolism	2	0.002%							**2**	0.002%
Respiratory arrest	1	0.001%							**1**	0.001%
Respiratory distress	40	0.045%	1	0.007%			3	0.027%	**44**	0.037%
Seizure	2	0.002%							**2**	0.002%
Sudden hearing loss	8	0.009%					1	0.009%	**9**	0.008%
Thrombosis	7	0.008%							**7**	0.006%
Vasculitis	2	0.002%							**2**	0.002%
Total	**97**	**0.109%**	**21**	**0.143%**	**5**	**0.201%**	**7**	**0.062%**	**130**	**0.110%**

The most commonly reported AESI is respiratory distress which was observed 44 times in the AstraZeneca group, three times in the Moderna group and only once in the BioNtech/Pfizer participants. Death has been reported once in the questionnaires as an ADR, as seen in table 11. It is good to know that in most cases where death is an outcome of an ADR, it is reported by a participant's next of kin directly to the organisations collecting the data, rather than via the questionnaires. So there is a differentiation between ADR and outcome.

3.7 Serious adverse reactions

Participants report adverse reactions through a solicited or unsolicited manner, all of these reported reactions can be flagged as serious by a participant by indicating that the reaction led to hospitalisation longer than 24 hours, and/or a life-threatening situation, and/or an other serious situation. To ensure that the reactions are indeed serious, it has been agreed upon to perform additional assessment of the patient reported seriousness by a trained assessor. The assessment of the assessor was used as the definition of the ADR to be serious.

Table 12: Number of ECVM cohort members reporting at least one serious adverse reaction between dose 1 and dose 2 for LIM countries and Croatia

LIM + Croatia	N serious ADR	Number of participants	% (CI) with serious ADR
AstraZeneca	20	8866	0.2% (0.137, 0.348)
BioNtech/Pfizer	16	14658	0.1% (0.062, 0.177)
Janssen	4	2490	0.2% (0.043, 0.411)
Moderna	6	3580	0.2% (0.061, 0.365)
Total	**46**	**29594**	**0.2% (0.114, 0.207)**

For Croatia and LIM countries, table 12 shows that rate of persons with a serious reaction was uncommon for all vaccines . A full list of all adverse reactions that have been classified as serious by the assessor can be found in Appendix 5.

Germany did not include additional assessment of partient reported seriousness in their process. Therefore it is not an assessment by the assessor for the seriousness but the self-reported of the seriousness.

Table 13: Number of ECVM cohort members reporting at least one serious adverse reaction (as reported by patients) between dose 1 and dose 2 for Germany

Germany	N serious ADR	Number of participants	% with serious ADR
AstraZeneca	608	80511	0.8% (0.696, 0.818)
Moderna	39	7686	0.5% (0.361, 0.694)
Total	**647**	**88197**	**0.7% (0.678, 0.792)**

In Germany the self-reported rate of serious ADR was uncommon, but higher than the rates of assessor assessed ADRs in other countries.

Appendix 6 shows that the majority of serious reactions reported in Germany are solicited adverse reactions. A comparison of the self-reported seriousness and assessed seriousness was not conducted on the German data. This comparison was performed for the LIM countries as described below.

Results of the comparison are provided in table 14. Only in 0.12% of all reported ADRs (91 ADRs) the subject and assessor disagreed about the seriousness.

Table 14: Comparison of serious assessment by subject and assessor for Q1 questionnaires for countries using the LIM app.

	IT	FR	UK	BE	NL
Subject and assessor agree that ADR is not serious	1276	1884	140	99	71649
Subject and assessor agree that ADR is serious	1	12	0	0	48
Subject indicates ADR as serious but assessor not	8	1	0	0	79
Subject indicates ADR as not serious but assessor does	2	1	0	0	0

4.Discussion

Among 117,791 vaccinated subjects that were included across 6 EU countries, adverse reactions were frequently reported, ranging from about 20% after a first dose of BioNtech/Pfizer among females older than 80 years of age to more than 90% after a first dose of Moderna and Janssen among females younger than 19 years and Janssen female vaccinees older than 70 years of age. In general, adverse reactions were reported more often by females than males and more often after a first dose of Moderna than other COVID-19 vaccines. However comparisons cannot be made directly because of channeling of COVID-19 vaccines by age. Also the frequency of vaccine brands does not reflect all vaccinated persons, since certain brands may have been targeted more for inclusion and assessment/release (e.g. Germany). Participants of all vaccine brands report pain and swelling at the injection site reaction as one of their most common sollicted local adverse reactions.

4.1 Use of dose 1 and dose 2 definition

In the ECVM study, patients are included and followed by questionnaires that have a sequence in time, which may not overlap with the dosing regimens which differed between the countries.

In order to aggregate data from different countries despite differing schedules and in order to compare the reported rates between vaccines, a general understanding of the follow-up period after dose 1 and dose 2 is essential.

Second dose information is not available for a portion of participants. There are several possible reasons why no second dose information on ADR has been provided.

- A participant might not have received any questionnaires yet for the second dose.
- The participant might not experience any adverse reactions after their second dose and not feel the need to fill in additional questionnaires.
- The participant might simply lack the willingness to further participate and report ADRs.
- Some individuals might also decide against taking a second dose all together.
- The experienced adverse reactions might be so debilitating that the participant is no longer capable of providing information (e.g. hospitalization, death, etc.).

For those who provide second dose information the mean number of days between dose 1 and questionnaires 1 and 2 and the mean number of days between dose 2 and questionnaires 3, 4, 5 and 6, could be calculated. The time to completion for LIM countries is comparable for questionnaires sent between dose 1 and dose 2 of all vaccine brands, but becomes increasingly more variable in later questionnaires.

The mean time it takes to complete questionnaires 3 and 4, in relation to the administration of the second dose, is negative for participants that have received AstraZeneca, this means that the questionnaires are being filled in before the second dose has been administered. This implies that the majority of data of questionnaires 3 and 4 for AstraZeneca contain ADRs related to the first dose, and that second dose information will be in questionnaire 5 and 6, which is understandable as in most countries the recommended distance was more than 70 days. Additionally, the current definition of second dose ADRs is based on the completion date of the questionnaire in relation to the second dose, which can vary. Any further analysis on this period and the period following dose 2 should be based on

a more accurate definition of dose 1 and 2 and should be followed up in the Covid Vaccine Monitor project.

Additionally, the aggregated datasets cannot be used to compare the two-dose vaccines to the one-dose Janssen vaccine as the current definition of dose 1 related data is all adverse reactions that are reported after dose 1 yet before dose 2, as the Janssen vaccine has only one dose all adverse reactions reported are classified as dose 1 related. This effectively creates a longer follow-up period than for the other vaccine brands, making it impossible to compare the reported rates. Better censoring will be needed.

4.2 Solicited adverse drugs reactions

The solicited adverse drug reaction list is based on the most commonly reported adverse reactions after vaccination. It is therefore not surprising that all of these adverse reactions are found in the product information of the vaccine brands, as summarized in table 15. For all vaccine brands, pain and swelling at the injection site reaction was reported as one of their most common adverse reactions. Variations of this local adverse reaction have been reported both in the product information and in the ECVM study. These variations are challenging to analyse as they are dependent on how a participant reported these and how these are coded, which leads to varying rates of reporting. Combining specific codes or reanalysing these local solicited adverse reactions in particular will give a better understanding in these adverse reactions. Furthermore, participants in Germany are able to select from a longer list of solicited adverse reactions than in the LIM countries. This has no impact on tables and figures related to solicited as the data can be selected based on the solicited ADR as defined in the protocol. When analysing the unsolicited ADRs, however, caution should be taken: reactions which are considered unsolicited according to the protocol but are made available as solicited to the participants may differ between Germany and other countries. Any stratification on solicited vs. unsolicited in the future should take this into account.

Several systemic solicited adverse reactions could be coded slightly differently depending on the exact wording used by a participant and the coding chosen by an assessor: the difference between ‘fatigue’ (tiredness) and ‘malaise’ (general feeling of being unwell) is not always clear. To minimize the impact of the interpretation of the assessor, and to make the assessment less time consuming, auto-coding was introduced in the LIM system during the ECVM study. When an ADR was assessed five times with the same coding chosen by an assessor, this ADR was added to the autocoding library. The next time that ADR was recognized by the system, it was coded again with the same term which would simply have to be confirmed by the assesor.

Table 15: Adverse reactions per vaccine brand as reported in product information [4,5,6,7]

	BioNtech/Pfizer	AstraZeneca	Moderna	Janssen
Very common (>1 in 10)	Pain and swelling at the injection site Tiredness Headache Muscle and joint Pain Chills Fever Diarrhoea	Pain and bruising at the injection site Tiredness Headache Muscle pain Chills Fever Tenderness General feeling of being unwell Joint pain Nausea	Pain and swelling at the injection site Tiredness Headache Muscle and joint Pain Chills Fever Nausea Swollen or tender lymph nodes under the arm Vomiting	Pain at the injection site Tiredness Headache Muscle pain Nausea
Common (<1 in 10)	Redness at the injection site Nausea Vomiting	Swelling and redness at the injection site Vomiting Thrombocytopenia (low levels of blood platelets) Diarrhoea Pain in legs or arms Flu-like illness and asthenia	Redness at the injection site Diarrhoea Hives and rash at the injection site (sometimes occurring more than a week after injection) Rash	Redness and swelling at the injection site Coughing Joint pain Chills Fever
Uncommon (<1 in 100)	Itching at the injection site Pain in the arm where the vaccine was injected Enlarged lymph nodes Difficulty sleeping Feeling unwell Decreased appetite Lethargy Hyperhidrosis Night sweats Asthenia Allergic reactions (such as rash. itching. itchy rash. rapid swelling under the skin)	Lymphadenopathy Decreased appetite Lethargy Sweating Itching. rash. uticaris Dizziness Sleepiness Abdominal pain Muscle spasms	Itching at the injection site Dizziness	Sweating Dizziness Pain in legs or arms Weakness and generally feeling unwell Tremor Paraesthesia Muscle weakness Diarrhoea Throat pain Rash Sneezing Backache
Rare (<1 in 1000)	Weakness in muscles on one side of face (acute peripheral facial paralysis or palsy)	Weakness in muscles on one side of face (acute peripheral facial paralysis or palsy)	Weakness in muscles on one side of face (acute peripheral facial paralysis or palsy) Swelling of the face (which may affect people who had facial cosmetic injections in the past) Hypoesthesia (reduced sensation to touch. pain and temperature)	Venous thromboembolism Lymphadenopathy Hypoesthesia Tinnitus Itchy rash Vomiting Hypersensitivity (allergy)

More than 1 in 10 participants receiving the BioNtech/Pfizer vaccine in this study reported fatigue, headache, malaise and injection site pain. These four adverse reactions were reported as common (<1 in 10) on the vaccine's product information. Chills and fever however, were considered very common (>1 in 10) in the clinical trials whereas the reporting of these adverse reactions in our study were lower: 4.22% for chills and 2.42% for pyrexia (fever). An explanation for these differences in reporting may be found in the differences in the population included in the BioNtech/Pfizer group. Taking into account the age group and gender stratification reveals that 43.3% of all participants in this study who received BioNtech/Pfizer are above the age of 70 years old and male. It is plausible that these participants report

less common, unsolicited adverse reactions which lead to a lower rate in the more common solicited adverse reactions, and the reactogenicity may be lower due to a changing immune system. However, when looking at figure 6 which shows which percentage of participants report at least one adverse reaction, BioNtech/Pfizer vaccine reported adverse reactions less frequently across all age groups when compared to other vaccines and an especially in participants age 70 years and older. Direct comparisons cannot be made due to selection bias and confounding. What we can conclude is that the solicited adverse reactions are generally less commonly reported than the expected numbers based on the trial results.

Frequencies of adverse reactions reported by AstraZeneca vaccinees in our study are similar to frequencies mentioned in the product information (very common) with the exception of tenderness. This is not directly reported by participants of our ECVM study, however other injection site reaction codes may have been used instead, for example injection site discomfort. A separate analysis of the reported local adverse reaction would give insight into any possible variation despite aligning of coding and automatic coding.

The solicited and unsolicited adverse reactions are reported more often by participants receiving Moderna or AstraZeneca. Whereas the participants receiving BioNtech/Pfizer are dominated by an older male cohort, both the Moderna and AstraZeneca cohort show a more equal age/gender distribution. The AstraZeneca cohort only has slightly more women (51.1%) being included than men (48.9%) and age groups showing a generally normal distribution. For Moderna recipients the gender was unfortunately unknown in a large number of subjects when stratified by age. Due to the large differences between the populations represented in each vaccine brand, it is difficult to compare the reported adverse reactions without stratifying these additionally on age and gender. Figure 6 implies that upon stratification on age and gender, participants receiving BioNtech/Pfizer in this study reported much less adverse reactions than the other 2-dose vaccine brands.

4.3 Adverse events of special interest

The frequency of reporting of AESI seems to be comparable across vaccine brands: roughly 0.1-0.2% of all participants reported an adverse reaction which was considered an AESI. Time to AESI was not considered here and may vary.

4.4 Serious adverse events

Crude serious adverse events after first dose were uncommon and comparable between the different vaccines, rates were higher in Germany but still uncommon, since this included self reported seriousness. In the LIM countries of all ADRs only 0.12% differed between assessor and patient.

4.5 Study limitations

The fast and somewhat unpredictable developments around national vaccination strategies was one of the biggest challenges faced in this study. Countries had to develop vaccination strategies based on assumptions of which vaccines would be available at which point in time and for which population. The (fragile) elderly and healthcare providers are amongst the first to get vaccinated in most countries, the groups following them often varied by country. Starting data collection as soon as the first vaccinations

were being given was an essential but also an impossible task. Protocol development, inviting of (new) partners to participate, varying METC guidelines, translating and testing of questionnaires and data collecting tools and training in the use of the data collection system and assessment tools all cost time. New data collection tools take a considerable amount of time to develop, therefore using existing systems is the reasonable choice. However, the processes mentioned above should be taken into account for future studies.

Using existing systems does have its drawbacks as technical aspects may differ and adjusting these may not be possible. Where SafeVac 2.0 in Germany could schedule questionnaires based on different vaccines brands and/or two vaccination dates, the LIM and Croation systems allowed schedules to be based on only one date. Basing analyses on questionnaires time-stamps was not possible and specific, record based data is necessary in order by-pass scheduling issues. This specific data, for example startdate of an ADR, was not available in the agreed upon aggregated dataset for ECVM. Adjusting the aggregated dataset to include these should be considered for the continuation of this project.

Agreeing to an aggregated dataset made pooling of data possible despite minor differences in data collection. The drawback of using aggregated datasets from three systems is that any changes in this dataset, whether it was an adjustment of existing data or tables or adding new information, was a tedious process. It was necessary to do checks to ensure that data was indeed comparable and changes could often only be implemented weeks later. Defining a clear and suitable dataset structure early on in the process and stream lining the process of adjusting or adding data will be beneficial to a more efficient updating of reports and other data visualisations, such as the dashboard.

Because of the large amounts of registrations for the studies in a short period of time, countries that started data collection early in their vaccination strategies had to deal with large amounts of data that needed coding or assessment. The Netherlands was able to code and assess data with a slight lag time. Germany however had to make the decision to code and assess data in a by-need manner: the most important and serious adverse reactions were assessed with priority and data was coded on a batch-by-batch basis. Due to this data on two vaccine brands are available while data on the other vaccine brands is pending. Other countries did not have such a peak in registrations due to the late start of their studies. The drawback of this is that only a specific population was captured in the datasets. While the German dataset does differ in certain aspects, we argue that as long as the pooled data is stratified by gender, age, manufacturer and aggregated based on predefined terms, the incompatibility of the data and the resulting impact on the interpretation should remain minimal. Nevertheless, to what extent variations in data collection or vaccination strategy impact the comparability of data between countries is a question that remains important and should be taken into consideration in future, more complex analysis.

Limitations such as definition of solicited and unsolicited, differences in questionnaire scheduling can be overcome in future with additional data and analyses. Furthermore dose 2 related ADRs, long term ADRs and additional analyses on gender, age and comorbidities need to be explored. All ECVM participating countries, with the exception of Belgium, will also continue with the inclusion of new participants in CVM. With the conclusion of the ECVM project, the CVM project will continue following the participants included during ECVM.

Large differences in inclusions per country might also initially be observed as a limitation. However, even though varying inclusions per country could be problematic, stratifying data by age, gender and manufacturer eliminates some of the concerns. The same can be said for the differences in data cut-off points between countries.

Reporting bais is a concern and can lead to reporting of particular ADRs during specific points in time. Varying media and regulatory attention could influence reporting frequency. For example, in April 2021 EMA confirmed a possible link between AstraZeneca and the rare combination of blood clots combined with low platelet count [8] which lead to a (temporary) halt in vaccinating specific sub-populations with this vaccine. During this period it is likely that participants became aware of this risk and may have been more inclined to report ADRs related to trombotic events. Additionally vaccination of particular age groups was temporarly halted and restarted at different time points leading to possible lower inclusions for certain vaccine groups and age groups. Analysing this data in a chronological fashion would give more insite into the possible impact of media and regulatory attention. The impact of these variations fall outside the scope of the available aggregated data used in this report.

5.Conclusion

The Early Covid Vaccine Monitor cohort event monitoring was set up during a challenging pandemic time in which decisions had to be made rapidly and a protocol was written when there were many unknowns: about the vaccines that would be used, whether they would be available in all countries, what would the exact intervals be between doses etc. Despite these challenges, prospective data collection systems were set up rapidly in several different European countries with the opportunity to monitor the early phase of the COVID-19 vaccine roll-outs, some of the national funded data collections could be used for the ECVM study (NL, DE, CR). The monthly updates of the data provided the initial monitoring information about these roll-outs, in addition and communication to the spontaneous reporting systems that exist. The calculation of cumulative incidence rates (after first dose) gives additional insight needed to understand differences between the vaccine brands introduced and the frequency of adverse events as found in the randomised controlled clinical trials. A main limitation of the current analyses is that only aggregated data was available. The next phase of the project, the Covid Vaccine Monitor, will allow for further analysis of individual subject-based data and a better understanding of the reported ADRs.

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Appendix 1

All MedDRA PTterms coded as 'solicited ADR'

Arthralgia
Body temperature increased
Chills
Extensive swelling of vaccinated limb
Fatigue
Headache
Hyperpyrexia
Injection site abscess
Injection site bruising
Injection site cellulitis
Injection site discolouration
Injection site discomfort
Injection site dryness
Injection site dysaesthesia
Injection site eczema
Injection site erythema
Injection site exfoliation
Injection site extravasation
Injection site haematoma
Injection site haemorrhage
Injection site hypersensitivity
Injection site hypoaesthesia
Injection site induration
Injection site infection
Injection site inflammation
Injection site irritation
Injection site joint movement impairment
Injection site joint pain
Injection site lymphadenopathy
Injection site mass
Injection site movement impairment
Injection site oedema
Injection site pain
Injection site papule
Injection site paraesthesia
Injection site pruritus
Injection site rash
Injection site reaction
Injection site swelling
Injection site urticaria
Injection site vesicles
Injection site warmth
Malaise
Myalgia
Nausea
Pyrexia
Vaccination site abscess
Vaccination site bruising
Vaccination site discolouration
Vaccination site discomfort
Vaccination site dryness
Vaccination site dysaesthesia
Vaccination site erythema
Vaccination site haematoma
Vaccination site hyperaesthesia
Vaccination site hypersensitivity
Vaccination site induration
Vaccination site inflammation
Vaccination site irritation
Vaccination site joint discomfort
Vaccination site joint erythema
Vaccination site joint movement impairment
Vaccination site joint pain
Vaccination site joint swelling
Vaccination site joint warmth
Vaccination site lymphadenopathy
Vaccination site mass
Vaccination site movement impairment
Vaccination site oedema
Vaccination site pain
Vaccination site paraesthesia
Vaccination site pruritus
Vaccination site pustule
Vaccination site rash
Vaccination site reaction
Vaccination site swelling
Vaccination site thrombosis
Vaccination site urticaria
Vaccination site warmth

Appendix 2

Predefined list of AESI (Adverse Events of Special Interest)

AESI – MedDRA Preferred Term	
Acquired amegakaryocytic thrombocytopenia	Immune-mediated cholangitis
Acquired haemophilia	Immune-mediated cholestasis
Acute aseptic arthritis	Immune-mediated encephalitis
Acute cardiac event	Immune-mediated hepatic disorder
Acute coronary syndrome	Immune-mediated hepatitis
Acute disseminated encephalomyelitis	Immune-mediated myocarditis
Acute encephalitis with refractory. repetitive partial seizures	Immune-mediated nephritis
Acute generalised exanthematous pustulosis	Immune-mediated neuropathy
Acute haemorrhagic leukoencephalitis	Immune-mediated pancreatitis
Acute hepatic failure	Immune-mediated pancreatitis
Acute interstitial pneumonitis	Immune-mediated renal disorder
Acute kidney injury	Immune-mediated thyroiditis
Acute left ventricular failure	Intestinal infarction
Acute motor axonal neuropathy	Ischaemic pancreatitis
Acute motor-sensory axonal neuropathy	Ischaemic stroke
Acute myocardial infarction	Jugular vein embolism
Acute pulmonary oedema	Kawasaki's disease
Acute respiratory distress syndrome	Kounis syndrome
Acute respiratory failure	Lacunar stroke
Acute right ventricular failure	Latent autoimmune diabetes in adults
Amegakaryocytic thrombocytopenia	Left ventricular failure
Anaphylactic reaction	Leukoencephalomyelitis
Anaphylactic shock	Limbic encephalitis
Anaphylactoid reaction	Meningism
Anaphylactoid shock	Meningitis
Arachnoiditis	Meningitis aseptic
Arrhythmia	Meningitis eosinophilic
Aseptic cavernous sinus thrombosis	Meningitis noninfective

Asymptomatic COVID-19	Mesenteric artery embolism
Atonic seizures	Mesenteric vein thrombosis
Atrioventricular block	Miller Fisher syndrome
Atrioventricular block complete	Multisystem inflammatory syndrome in children
Atrioventricular block second degree	Muscle necrosis
Atypical haemolytic uraemic syndrome	Myelitis
Autoimmune haemolytic anaemia	Myelitis transverse
Autoimmune hepatitis	Myocardial infarction
Autoimmune myocarditis	Myocarditis
Autoimmune nephritis	Myopathy toxic
Autoimmune neuropathy	Narcolepsy
Autoimmune pancreatitis	Necrotising myositis
Autoimmune pancreatitis	Noninfectious myelitis
Autoimmune pericarditis	Noninfective encephalitis
Autoimmune thyroiditis	Noninfective encephalomyelitis
Axillary vein thrombosis	Oculofacial paralysis
Basal ganglia stroke	Oedematous pancreatitis
Basedow's disease	Optic neuritis
Bell's palsy	Pachymeningitis
Bickerstaff's encephalitis	Pancreatic abscess
Brain natriuretic peptide increased	Pancreatic haemorrhage
Brain stem embolism	Pancreatitis acute
Brain stem haemorrhage	Pancreatitis necrotising
Brain stem stroke	Pancreatitis relapsing
Brugada syndrome	Pericardial disease
Cardiac arrest	Pericardial effusion
Cardiac failure	Pericardial rub
Cardiac failure acute	Pericarditis
Cardiac fibrillation	Pericarditis adhesive
Cardiac tamponade	Pericarditis constrictive
Cardiogenic shock	Peripheral nerve injury

Cardiomyopathy acute	Petit mal epilepsy
Cardiopulmonary failure	Platelet count abnormal
Cardiotoxicity	Platelet count decreased
Cataplexy	Platelet disorders
Cavernous sinus thrombosis	Pleuropericarditis
Cerebellar embolism	Portal vein thrombosis
Cerebellar haemorrhage	Pulmonary embolism
Cerebellar stroke	Pulmonary thrombosis
Cerebral artery embolism	Pulmonary venous thrombosis
Cerebral haemorrhage	Pulseless electrical activity
Cerebral thrombosis	Respiratory arrest
Cerebral venous sinus thrombosis	Respiratory distress
Cerebral venous thrombosis	Rhabdomyolysis
Cerebrovascular accident	Right ventricular failure
Clonic convulsion	Seizure
Cor pulmonale acute	Severe fever with thrombocytopenia syndrome
Coronary artery embolism	Silent myocardial infarction
COVID-19	Silent thyroiditis
COVID-19 pneumonia	Sleep attacks
Cutaneous vasculitis	Spinal stroke
Cytokine release syndrome	Splanchnic thrombosis
Cytokine storm	Splenic artery thrombosis
Death	Splenic infarction
Deep vein thrombosis	Splenic thrombosis
Demyelinating polyneuropathy	Splenic vein thrombosis
Demyelination	Status epilepticus
Disseminated intravascular coagulation	Stevens-Johnson syndrome
Drug reaction with eosinophilia and systemic symptoms	Stress cardiomyopathy
Drug-induced liver injury	Subacute inflammatory demyelinating polyneuropathy
Embolic stroke	Subarachnoid haemorrhage

Embolism	Subclavian artery embolism
Embolism venous	Subdural haemorrhage
Encephalitis	Sudden cardiac death
Encephalitis allergic	Sudden death
Encephalitis autoimmune	Sudden hearing loss
Encephalitis brain stem	Superior sagittal sinus thrombosis
Encephalitis post immunisation	Tachycardia induced cardiomyopathy
Encephalomyelitis	Thalamus haemorrhage
Eosinophilic myocarditis	Thrombocytopenia
Epilepsy	Thrombocytopenic purpura
Erythema multiforme	Thrombosis
Facial paralysis	Thrombosis mesenteric vessel
Facial paresis	Thrombotic stroke
Febrile convulsion	Thrombotic thrombocytopenic purpura
Femoral artery embolism	Thyroiditis acute
Fulminant type 1 diabetes mellitus	Thyrotoxic myopathy
Generalised tonic-clonic seizure	Tonic convulsion
Giant cell myocarditis	Torsade de pointes
Glomerulonephritis acute	Toxic epidermal necrolysis
Guillain-Barre syndrome	Transverse sinus thrombosis
Haemolytic uraemic syndrome	Trifascicular block
Haemophagocytic lymphohistiocytosis	Truncus coeliacus thrombosis
Haemorrhage intracranial	Tubulointerstitial nephritis
Haemorrhagic cerebral infarction	Vaccination failure
Haemorrhagic infarction	Vaccine associated enhanced disease
Haemorrhagic necrotic pancreatitis	Vaccine associated enhanced respiratory disease
Haemorrhagic stroke	Vaccine breakthrough infection
Haemorrhagic transformation stroke	Vaccine derived SARS-CoV-2 infection
Henoch-Schonlein purpura	Vasculitic rash
Henoch-Schonlein purpura nephritis	Vasculitis
Heparin-induced thrombocytopenia	Vasculitis necrotising

Hepatic artery embolism	Vena cava embolism
Hepatic vascular thrombosis	Vena cava thrombosis
Hepatic vein embolism	Venous thrombosis
Hepatic vein thrombosis	Ventricular arrhythmia
Hepatitis acute	Ventricular asystole
Hepatitis fulminant	Ventricular failure
Hypersensitivity	Ventricular fibrillation
Hypersensitivity myocarditis	Ventricular tachyarrhythmia
Hypersensitivity vasculitis	Vertebrobasilar stroke
Hypersomnia	VIIth nerve injury
Immune thrombocytopenia	Visceral venous thrombosis

Appendix 3

ECVM participants who have received the 2nd dose and have provided at least one questionnaire on ADR

	AstraZeneca (N)	AstraZeneca (%)	BioNtech/Pfizer (N)	BioNtech/Pfizer (%)	Moderna (N)	Moderna (%)	Total (N)
Female	29740	81.8%	4843	13.3%	1770	4.9%	36353
0 - 19 years	226	68.9%	98	29.9%	4	1.2%	328
20 - 29 years	3801	84.5%	475	10.6%	223	5.0%	4499
30 - 39 years	4637	83.1%	587	10.5%	354	6.3%	5578
40 - 49 years	5168	84.0%	446	7.3%	536	8.7%	6150
50 - 59 years	6345	86.7%	381	5.2%	596	8.1%	7322
60 - 69 years	8209	94.8%	399	4.6%	49	0.6%	8657
70 - 79 years	1311	45.6%	1559	54.2%	8	0.3%	2878
80+ years	43	4.6%	898	95.4%	0	0.0%	941
Male	25811	76.9%	6832	20.4%	915	2.7%	33558
0 - 19 years	183	71.2%	68	26.5%	6	2.3%	257
20 - 29 years	2381	89.2%	210	7.9%	78	2.9%	2669
30 - 39 years	3761	91.1%	252	6.1%	117	2.8%	4130
40 - 49 years	3533	88.6%	182	4.6%	273	6.8%	3988
50 - 59 years	4103	88.2%	162	3.5%	387	8.3%	4652
60 - 69 years	9078	97.3%	217	2.3%	39	0.4%	9334
70 - 79 years	2683	44.3%	3352	55.4%	15	0.2%	6050
80+ years	89	3.6%	2389	96.4%	0	0.0%	2478
Unknown					5402	100.0%	5402
0 - 19 years					76	100.0%	76
20 - 29 years					1226	100.0%	1226
30 - 39 years					1471	100.0%	1471
40 - 49 years					1190	100.0%	1190
50 - 59 years					1035	100.0%	1035
60 - 69 years					267	100.0%	267
70 - 79 years					85	100.0%	85
80+ years					52	100.0%	52
Total	55551	73.8%	11675	15.5%	8087	10.7%	75313

Appendix 4

Complete list of reported possible ADRs, coded as MedDRA Preferred Term, after dose 1 in alphabetical order

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Abdominal discomfort	66	18	8	10	102
Abdominal distension	15	<5	<5	<5	20
Abdominal lymphadenopathy	<5				<20
Abdominal pain	217	36	15	26	294
Abdominal pain lower	45	<5		<5	52
Abdominal pain upper	135	5	7	13	160
Abnormal dreams	5	8	<5	<5	<20
Abnormal faeces	6	<5			<20
Abnormal sensation in eye	<5	<5			<20
Abnormal weight gain	<5				<20
Abortion missed	<5				<20
Abortion spontaneous	<5	<5	<5	<5	<20
Acne	7	<5	<5	<5	<20
Acute lung injury	<5				<20
Acute myocardial infarction	<5				<20
Acute sinusitis				<5	<20
Adenoidal disorder				<5	<20
Adjustment disorder with depressed mood	<5				<20
Administration site pain	<5				<20
Administration site warmth	<5			<5	<20
Adnexa uteri pain		<5			<20
Adverse event		<5			<20
Adverse reaction	<5				<20
Affect lability	<5		<5		<20
Affective disorder	<5				<20
Ageusia	39	8	<5		51
Aggression	<5				<20
Agitation	<5				<20
Alanine aminotransferase increased	<5				<20
Allergic bronchitis	<5				<20
Allergic cough	<5				<20
Allergic respiratory disease	<5				<20
Allergy to arthropod bite				<5	<20
Allergy to arthropod sting		<5			<20
Alopecia	7	<5	<5	<5	<20
Altered state of consciousness	<5				<20
Amenorrhoea	10	<5	6	<5	21
Amnesia		<5	<5	<5	<20
Anaemia	<5				<20
Anal haemorrhage	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Analgesic intervention supportive therapy	<5				<20
Anaphylactic reaction	<5		<5		<20
Anaphylactic shock	<5				<20
Anger			<5		<20
Angina pectoris	19			<5	20
Angioedema		<5			<20
Ankylosing spondylitis				<5	<20
Anosmia	<5	<5	<5	<5	<20
Anxiety	20	<5	<5	<5	27
Anxiety disorder			<5		<20
Apathy	6				<20
Aphasia	9	<5			<20
Aphonia	<5	<5	<5	<5	<20
Aphthous ulcer	19	<5	<5	<5	25
Apnoea test abnormal		<5			<20
Appendicitis	<5			<5	<20
Appetite disorder				<5	<20
Application site coldness	<5				<20
Application site erythema	<5				<20
Application site haematoma	<5				<20
Application site haemorrhage	<5				<20
Application site hypoaesthesia	<5				<20
Application site induration	<5			<5	<20
Application site paraesthesia	<5				<20
Application site warmth				<5	<20
Arrhythmia	36	<5		6	44
Arthralgia	20175	581	484	1060	22300
Arthritis	<5		<5	<5	<20
Arthropod bite		<5			<20
Arthropod sting	<5				<20
Asphyxia			<5		<20
Asthenia	116	9	5	<5	134
Asthenopia	<5	<5		<5	<20
Asthma	14	<5	<5	<5	21
Atrial fibrillation	7	<5		<5	<20
Atrioventricular block complete		<5			<20
Auditory disorder	8	<5		<5	<20
Axillary pain	30	6	<5	34	71
Back pain	429	18	19	30	496
Bacterial vaginosis	<5				<20
Balance disorder	7	9	<5	<5	<20
Benign breast neoplasm	<5				<20
Biliary colic		<5			<20
Bleeding time prolonged	<5	<5			<20
Blepharitis	<5	<5			<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Blepharospasm	8	<5	<5	<5	<20
Blindness	<5				<20
Blister	<5				<20
Blood alkaline phosphatase increased	<5				<20
Blood blister	<5				<20
Blood count abnormal	<5				<20
Blood glucose decreased	<5				<20
Blood glucose fluctuation	<5			<5	<20
Blood glucose increased	7	<5		<5	<20
Blood pressure abnormal	31			<5	32
Blood pressure decreased	10	<5		<5	<20
Blood pressure diastolic decreased	<5				<20
Blood pressure fluctuation	5	<5			<20
Blood pressure increased	83	8	5	10	106
Blood pressure measurement	<5				<20
Blood pressure systolic increased	<5				<20
Blood test abnormal	<5				<20
Blood urine present	<5	<5			<20
Body temperature abnormal	<5				<20
Body temperature decreased	12	<5	<5		<20
Body temperature fluctuation	5	<5	<5	<5	<20
Body temperature increased	904	129	136	125	1294
Bone pain	18	<5	<5	<5	21
Bowel movement irregularity	<5	<5			<20
Bradycardia	<5				<20
Bradykinesia			<5		<20
Bradyphrenia	<5			<5	<20
Breast discomfort	<5		<5		<20
Breast enlargement		<5			<20
Breast inflammation	<5		<5		<20
Breast mass			<5		<20
Breast pain	35	<5	<5	<5	40
Breast swelling	<5	<5			<20
Breast tenderness		<5	<5		<20
Bronchial irritation	<5				<20
Bronchial secretion retention	<5				<20
Bronchitis	<5	<5		<5	<20
Burning sensation	20	5		<5	27
Burning sensation mucosal	<5				<20
Burnout syndrome	<5				<20
Bursa disorder	<5				<20
Bursitis	<5	<5		<5	<20
Candida infection	<5	<5			<20
Capillary disorder		<5			<20
Cardiac discomfort	5	<5			<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Cardiac flutter	<5				<20
Cardiovascular disorder	17			5	22
Cardiovascular insufficiency	5				<20
Carpal tunnel syndrome	<5				<20
Cellulitis	<5				<20
Cerebellar infarction	<5				<20
Cerebral infarction	<5			<5	<20
Cerebral venous sinus thrombosis	<5				<20
Cerebral venous thrombosis	<5				<20
Cerebrovascular accident		<5			<20
Cheilitis		<5			<20
Chest discomfort	128	13	6	11	158
Chest pain	103	23	11	10	147
Chillblains	<5		<5		<20
Chills	31795	619	928	1004	34346
Choking sensation				<5	<20
Chromaturia	<5	<5			<20
Chronic obstructive pulmonary disease	<5	<5			<20
Chronic pigmented purpura	<5				<20
Circadian rhythm sleep disorder	<5				<20
Circulatory collapse	23			<5	27
Cluster headache	<5	<5		<5	<20
Cold sweat	12	<5		<5	<20
Cold urticaria				<5	<20
Colitis	<5	<5			<20
Colitis ulcerative	<5				<20
Coma	<5				<20
Condition aggravated	13	12	<5	<5	32
Confusional state	16	5	<5	<5	29
Conjunctival haemorrhage	<5	<5			<20
Conjunctivitis	5	<5		5	<20
Conjunctivitis allergic	<5				<20
Constipation	25	5	<5	<5	35
Contusion	14	<5	<5	7	23
Coordination abnormal	6				<20
Corneal disorder		<5			<20
Coronavirus infection				<5	<20
Coronavirus test positive	5			<5	<20
Cough	351	25	12	57	445
COVID-19	7	6	<5		<20
Crohn's disease	<5			<5	<20
Crying	<5	<5	<5	<5	<20
CSF test abnormal	<5				<20
Cubital tunnel syndrome	<5				<20
Cyanosis		<5			<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Cyst			<5		<20
Cystitis	8	<5	<5		<20
Cystitis noninfective	18			5	23
Daydreaming				<5	<20
Deafness transitory	<5				<20
Deafness unilateral	<5	<5			<20
Death	<5				<20
Decreased appetite	249	8	7	10	274
Decreased immune responsiveness	<5				<20
Deep vein thrombosis	<5			<5	<20
Dehydration	<5	<5			<20
Dental discomfort	<5				<20
Depressed level of consciousness		<5			<20
Depressed mood	14	5		<5	23
Depression	5				<20
Dermatitis		<5			<20
Dermatitis acneiform				<5	<20
Dermatitis allergic	7				<20
Dermatitis bullous	<5	<5			<20
Dermatitis contact		<5			<20
Diabetes mellitus inadequate control	<5				<20
Diaphragmalgia		<5			<20
Diaphragmatic spasm	<5				<20
Diarrhoea	3657	120	35	400	4212
Diarrhoea haemorrhagic	<5				<20
Diplopia	<5	<5			<20
Discomfort	7	<5	<5	<5	<20
Disorientation	<5	<5	<5		<20
Dissociation	<5				<20
Disturbance in attention	133	20	<5	<5	161
Diverticulitis	<5	<5			<20
Dizziness	17051	158	56	1001	18266
Dizziness exertional	<5		<5	<5	<20
Dizziness postural	<5				<20
Dry eye	10	<5	<5	<5	<20
Dry mouth	73	5	<5	9	91
Dry skin	11		<5	<5	<20
Dry throat	10	<5	<5	5	20
Dysaesthesia	13				<20
Dysentery		<5			<20
Dysgeusia	86	14	7	16	123
Dyskinesia	<5				<20
Dysmenorrhoea	<5	6	<5		<20
Dyspepsia	38	<5		6	45
Dysphagia	23	<5	<5	<5	27

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Dysphonia	22	5	<5	6	34
Dyspnoea	349	58	27	37	471
Dyspnoea at rest		<5			<20
Dyspnoea exertional	17	<5	<5	<5	25
Dysuria	8	<5		<5	<20
Ear congestion	<5				<20
Ear discomfort	40	<5		8	51
Ear haemorrhage	<5				<20
Ear infection	<5	<5	<5	<5	<20
Ear pain	139	9	<5	12	162
Ear pruritus			<5	<5	<20
Ear swelling	<5				<20
Ecchymosis	<5	<5			<20
Echopraxia	<5				<20
Eczema	7	5	<5	<5	<20
Electrocardiogram abnormal	<5				<20
Emergency care	<5				<20
Emotional disorder	<5	<5			<20
Encephalopathy	<5				<20
Endocarditis	<5				<20
Energy increased				<5	<20
Enteritis	<5				<20
Eosinophil count increased			<5		<20
Epigastric discomfort	<5				<20
Epilepsy	<5			<5	<20
Epileptic aura	<5				<20
Epistaxis	89	18	5	13	125
Eructation	<5				<20
Erysipelas	5			<5	<20
Erythema	40	16	<5	19	77
Erythema of eyelid	<5				<20
Excessive eye blinking		<5			<20
Executive dysfunction	<5				<20
Exercise tolerance decreased	12	<5	<5	<5	<20
Exercise tolerance increased	<5				<20
Exertional headache	<5			<5	<20
Exfoliative rash	<5				<20
Exposure via breast milk	<5	<5			<20
Extensive swelling of vaccinated limb	91	32	12	41	176
External ear inflammation	<5				<20
External ear pain		<5			<20
Extrasystoles	8				<20
Eye complication associated with device		<5		<20	
Eye discharge	<5				<20
Eye haemorrhage	8	<5			<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Eye infection	<5	<5			<20
Eye inflammation	<5	<5		<5	<20
Eye irritation	25	<5	<5		29
Eye pain	141	5	<5	6	156
Eye paraesthesia		<5			<20
Eye pruritus	9	<5	<5		<20
Eye swelling	9	<5	<5	<5	<20
Eyelid infection	<5		<5		<20
Eyelid irritation	<5				<20
Eyelid oedema	<5				<20
Eyelid rash		<5			<20
Eyelids pruritus			<5		<20
Face oedema	<5				<20
Facial discomfort	<5	<5			<20
Facial neuralgia	<5				<20
Facial pain	<5	<5	<5	<5	<20
Facial paralysis	<5				<20
Facial paresis	6				<20
Faeces soft	<5			<5	<20
Fall	<5	<5		<5	<20
Fatigue	48212	2519	1261	3971	55963
Fear	<5	<5	<5		<20
Feeling abnormal	34	14	10	10	68
Feeling cold	310	6	<5	21	341
Feeling drunk	<5	<5	<5	<5	<20
Feeling hot	66	14	<5	13	97
Feeling jittery	<5	<5		<5	<20
Feeling of body temperature change	16		<5	<5	21
Femoral pulse increased	<5				<20
Fibrin D dimer increased	<5				<20
Fibromyalgia	<5				<20
Flank pain	12	<5			<20
Flatulence	23	<5		<5	29
Fluid retention	<5	<5	<5		<20
Flushing	72	<5		7	81
Food aversion	<5				<20
Food craving	8			<5	<20
Food intolerance	<5				<20
Foreign body sensation in eyes	<5			<5	<20
Formication	<5				<20
Frequent bowel movements	<5	<5	<5	<5	<20
Fungal infection	<5		<5		<20
Fungal pharyngitis		<5			<20
Fungal skin infection	<5				<20
Furuncle		<5	<5		<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Gait disturbance	6	<5	<5	<5	<20
Gamma-glutamyltransferase increased	<5				<20
Gastric disorder	<5				<20
Gastric pH decreased	<5				<20
Gastric ulcer	<5				<20
Gastritis	<5			<5	<20
Gastroenteritis	<5				<20
Gastroenteritis viral		<5			<20
Gastrointestinal disorder	<5	<5		<5	<20
Gastrointestinal inflammation	<5				<20
Gastrointestinal pain	34	<5		<5	39
Gastrointestinal stoma complication		<5			<20
Gastrooesophageal reflux disease	6				<20
General physical health deterioration	8	<5	<5	<5	<20
Generalised oedema	<5				<20
Genital herpes	<5				<20
Genital pain	<5				<20
Genital rash	<5	<5			<20
Giant cell arteritis	<5	<5			<20
Gingival bleeding	<5	<5		<5	<20
Gingival discomfort	<5	<5		<5	<20
Gingival oedema				<5	<20
Gingival pain	5		<5	<5	<20
Gingivitis	<5				<20
Glaucoma		<5			<20
Glossitis		<5			<20
Glossodynia	<5	<5	<5		<20
Goitre	<5	<5	<5		<20
Gout	5	<5			<20
Granuloma		<5			<20
Groin pain	10	<5		<5	<20
Habit cough	<5				<20
Haemangioma	<5				<20
Haematochezia	<5				<20
Haematoma	39	9	5	<5	57
Haematuria	<5			<5	<20
Haemoglobin increased				<5	<20
Haemorrhage	<5				<20
Haemorrhage in pregnancy	<5				<20
Haemorrhagic erosive gastritis	<5				<20
Haemorrhoidal haemorrhage	<5				<20
Haemorrhoids	<5	<5			<20
Hallucination	6		<5		<20
Hallucination, auditory				<5	<20
Hallucination, visual	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Hand dermatitis				<5	<20
Hangover			<5	<5	<20
Head discomfort	51	6	6	<5	66
Headache	47640	1745	1236	3354	53975
Heart rate		<5			<20
Heart rate abnormal	<5				<20
Heart rate decreased	<5	<5	<5		<20
Heart rate increased	158	14	8	11	191
Heart rate irregular	5	5	<5	<5	<20
Heart rate variability increased	<5				<20
Heavy menstrual bleeding	15	13	12	<5	44
Hemianaesthesia	<5				<20
Hepatic enzyme abnormal				<5	<20
Hepatic pain				<5	<20
Herpes ophthalmic	<5				<20
Herpes simplex	<5	<5			<20
Herpes virus infection	30			6	36
Herpes zoster	25	<5	<5	10	40
Hiccups	<5	<5			<20
High-pitched crying	<5				<20
Hordeolum	5				<20
Hormone level abnormal	<5				<20
Hospitalisation	6				<20
Hot flush	144	17	9	14	184
Hunger	<5	<5	<5	<5	<20
Hyperacusis	9	<5		<5	<20
Hyperaesthesia	82		<5	<5	88
Hyperaesthesia teeth	<5	<5			<20
Hypercoagulation	<5				<20
Hyperhidrosis	430	25	7	31	493
Hyperpyrexia	82	<5	11		94
Hyperresponsive to stimuli	<5	<5			<20
Hypersensitivity	47	5		6	58
Hypersomnia	<5			<5	<20
Hypertension	50	5		<5	59
Hypertensive crisis	<5				<20
Hypertonia	<5				<20
Hypertrichosis			<5		<20
Hyperventilation	<5	<5	<5	<5	<20
Hypoacusis	<5				<20
Hypoaesthesia	134	24	5	23	186
Hypoaesthesia oral	21	<5	<5	<5	24
Hypogeusia	8	<5	<5	<5	<20
Hypoglycaemia	5			<5	<20
Hypokinesia	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Hypomenorrhoea	<5				<20
Hypopnoea	<5		<5		<20
Hyporesponsive to stimuli	<5				<20
Hyposmia	<5			<5	<20
Hypotension	23	<5	<5	<5	35
Hypothermia	<5		<5		<20
Hypotonia	30	<5			31
Hypoventilation	9				<20
Illness	<5				<20
Illusion	<5				<20
Immune system disorder	<5				<20
Immune thrombocytopenia	<5				<20
Impaired healing	<5				<20
Impaired work ability	<5				<20
Implant site pruritus	<5				<20
Incontinence	<5				<20
Increased appetite	<5	<5	<5	<5	<20
Increased insulin requirement	<5			<5	<20
Increased tendency to bruise	<5		<5		<20
Increased upper airway secretion	<5	<5			<20
Increased viscosity of upper respiratory secretion	<5	<5		<5	<20
Infection	<5				<20
Infectious mononucleosis	<5				<20
Inflammation	<5				<20
Inflammatory marker increased	<5				<20
Influenza	<5	<5			<20
Influenza like illness	201	13	<5	22	240
Infusion related reaction	9				<20
Infusion site haematoma	<5				<20
Initial insomnia	8	<5	<5	<5	<20
Injected limb mobility decreased	30	22	<5	19	73
Injection site abscess				<5	<20
Injection site bruising	21			<5	25
Injection site cellulitis	<5				<20
Injection site discolouration	<5			<5	<20
Injection site discomfort	215	268	48	115	646
Injection site dryness	<5	<5			<20
Injection site dysaesthesia	<5				<20
Injection site eczema	<5				<20
Injection site erythema	831	235	96	443	1605
Injection site exfoliation		<5			<20
Injection site extravasation	<5				<20
Injection site haematoma	483	253	113	185	1034
Injection site haemorrhage	<5			<5	<20
Injection site hypersensitivity	<5			<5	<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Injection site hypoaesthesia	12	<5	<5	<5	21
Injection site induration	97	49	9	96	251
Injection site infection				<5	<20
Injection site inflammation	1789	749	260	717	3515
Injection site irritation	5	<5			<20
Injection site joint movement impairment	<5	<5		<5	<20
Injection site joint pain	<5	<5			<20
Injection site mass	<5				<20
Injection site movement impairment	<5				<20
Injection site oedema	<5				<20
Injection site pain	47187	3538	831	5755	57311
Injection site papule	<5	<5			<20
Injection site paraesthesia	8	<5	<5	5	<20
Injection site pruritus	413	145	42	249	849
Injection site rash	<5	<5		5	<20
Injection site reaction	15	14	<5	6	36
Injection site swelling	11585	727	264	2377	14953
Injection site urticaria	<5		<5	<5	<20
Injection site vesicles				<5	<20
Injection site warmth	1152	451	150	488	2241
Inner ear disorder				<5	<20
Insomnia	175	8	<5	17	202
Intensive care	<5				<20
Intermenstrual bleeding	5	15	6	<5	28
International normalised ratio decreased	<5	<5			<20
International normalised ratio increased	<5			<20	
Intracranial hypotension	<5				<20
Intracranial pressure increased	<5				<20
Iron deficiency			<5		<20
Iron deficiency anaemia	<5				<20
Irregular breathing				<5	<20
Irritability	<5	<5		<5	<20
Jaw disorder			<5		<20
Joint dislocation	<5				<20
Joint effusion		<5			<20
Joint noise	<5	<5			<20
Joint range of motion decreased				<5	<20
Joint stiffness	<5				<20
Joint swelling	5	<5		<5	<20
Labile blood pressure		<5		<5	<20
Labour pain				<5	<20
Lacrimation increased	9	<5	<5	<5	<20
Lactation disorder	<5	<5			<20
Laryngeal discomfort	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Laryngeal inflammation	<5				<20
Laryngeal oedema	<5				<20
Laryngitis	<5			<5	<20
Larynx irritation	21			<5	22
Lethargy			<5		<20
Libido increased			<5		<20
Lichen planus				<5	<20
Lichen sclerosus				<5	<20
Limb discomfort	202	31	25	33	291
Limb injury		<5			<20
Lip blister	<5				<20
Lip dry	<5	<5			<20
Lip oedema	<5	<5			<20
Lip swelling	13	<5			<20
Listless	5	6	<5	<5	<20
Livedo reticularis	<5				<20
Liver function test increased	<5				<20
Local reaction	15	<5		6	22
Localised infection	<5				<20
Localised oedema	<5				<20
Loss of consciousness	7	<5		<5	<20
Loss of libido	<5				<20
Loss of personal independence in daily activities	<5				<20
Lumbar puncture	<5				<20
Lung disorder			<5		<20
Lymph node pain	26	<5		19	46
Lymphadenitis	10	<5		<5	<20
Lymphadenopathy	376	41	21	162	600
Lymphangitis				<5	<20
Lymphoedema				<5	<20
Magnetic resonance imaging brain abnormal	<5				<20
Malaise	32027	1480	1175	2217	36899
Mastication disorder	<5				<20
Mastitis				<5	<20
Maternal exposure during breast feeding	<5	<5			<20
Medical device discomfort		<5			<20
Medical device site hypersensitivity	<5				<20
Medical device site pain		<5			<20
Memory impairment	15	<5	<5	<5	22
Meningism	<5			<5	<20
Meniscus injury	<5				<20
Menopausal symptoms	<5				<20
Menopause delayed	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Menorrhagia	<5				<20
Menstrual cycle management	<5			<5	<20
Menstrual disorder	8	24	<5	8	44
Menstruation delayed	<5	8	6	<5	21
Menstruation irregular	7	6	8	8	29
Mental disorder		<5			<20
Mental fatigue	<5				<20
Mental impairment	<5	<5			<20
Meralgia paraesthetica	<5				<20
Metrorrhagia	11			<5	<20
Microcytosis	<5				<20
Micturition disorder		<5			<20
Micturition urgency	17				<20
Middle insomnia	14			<5	<20
Migraine	87	7	<5	20	116
Migraine with aura	8	<5	<5	<5	<20
Mobility decreased	<5	<5			<20
Monoplegia	<5			<5	<20
Mood altered	<5			<5	<20
Mood swings	<5		<5	<5	<20
Mouth injury				<5	<20
Mouth swelling	<5		<5		<20
Mouth ulceration	<5				<20
Movement disorder	5			<5	<20
Mucosal dryness	<5				<20
Mucous stools	<5			<5	<20
Multiple sclerosis relapse	<5				<20
Muscle contractions involuntary	<5		<5		<20
Muscle discomfort	5		<5	<5	<20
Muscle spasms	71	16	5	9	101
Muscle spasticity			<5		<20
Muscle strain	<5				<20
Muscle swelling			<5		<20
Muscle tightness	39			6	45
Muscle twitching	19	9	<5	<5	32
Muscular weakness	34	16	6	8	64
Musculoskeletal chest pain	9	<5			<20
Musculoskeletal discomfort	17			8	25
Musculoskeletal pain	<5	<5	<5	<5	<20
Musculoskeletal stiffness	43	15	<5	6	68
Myalgia	29956	2405	1047	2695	36103
Myasthenia gravis	<5				<20
Mydriasis		<5			<20
Myocardial infarction	<5	<5			<20
Myocarditis		<5			<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Myofascial pain syndrome	<5				<20
Myosclerosis	<5				<20
Myositis	<5			<5	<20
Nasal congestion	56	<5	<5	<5	63
Nasal discomfort	<5	<5		<5	<20
Nasal dryness	<5			<5	<20
Nasal herpes	<5				<20
Nasal inflammation	<5				<20
Nasal mucosal disorder	<5				<20
Nasal vestibulitis	<5			<5	<20
Nasopharyngitis	546	47	21	107	721
Nausea	13227	630	490	922	15269
Neck pain	180	17	<5	23	222
Nephrolithiasis	<5				<20
Nervousness	<5				<20
Neuralgia	35	<5		<5	40
Neurodermatitis	8			<5	<20
Neurological symptom	<5				<20
Neuropathy peripheral	7	<5	<5	<5	<20
Night sweats	116	5	9	11	141
Nightmare	9	<5		<5	<20
Nipple inflammation		<5			<20
No adverse event	<5				<20
Nocturia	<5				<20
Nodule	<5				<20
Noninfective gingivitis	11			<5	<20
Nuchal rigidity	7	<5			<20
NULL	8	1290	18	99	1415
Ocular discomfort	57	<5	<5	<5	68
Ocular hyperaemia	5				<20
Ocular hypertension	<5				<20
Odynophagia	9	<5			<20
Oedema	<5				<20
Oedema blister				<5	<20
Oedema mucosal	<5			<5	<20
Oedema peripheral	9	<5	<5	6	<20
Oesophageal pain	<5				<20
Oligomenorrhoea		<5	<5		<20
Onychoclasis		<5			<20
Onychomycosis	<5				<20
Ophthalmic migraine	6			<5	<20
Oral blood blister	<5				<20
Oral candidiasis		<5			<20
Oral discomfort	<5	<5			<20
Oral disorder	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Oral dysaesthesia	<5				<20
Oral fungal infection			<5		<20
Oral herpes	84	12	<5	16	113
Oral mucosal blistering	<5	<5	<5		<20
Oral mucosal discolouration		<5			<20
Oral mucosal erythema		<5			<20
Oral pain	<5		<5		<20
Oropharyngeal blistering	5				<20
Oropharyngeal discomfort	12	5	<5	<5	21
Oropharyngeal pain	526	53	19	93	691
Oropharyngeal swelling	<5	<5	<5		<20
Orthopnoea	<5				<20
Osteitis			<5		<20
Osteoarthritis		<5			<20
Osteomyelitis	<5				<20
Otitis media	<5		<5		<20
Oxygen saturation decreased	<5		<5	<5	<20
Oxygen saturation increased		<5			<20
Pain	65	15	6	19	105
Pain in arm	<5				<20
Pain in extremity	603	106	21	119	849
Pain in jaw	26	<5	<5	<5	34
Pain of skin	45	<5	8	<5	57
Painful respiration	15		<5		<20
Palatal disorder	<5				<20
Palatal swelling	<5				<20
Palate injury	<5				<20
Pallor	<5		<5		<20
Palpitations	337	43	17	41	438
Pancreatitis	<5				<20
Pancreatitis necrotising	<5				<20
Panic attack	8	<5	<5		<20
Panic reaction	<5		<5		<20
Papule		<5	<5	<5	<20
Paraesthesia	330	61	30	53	474
Paraesthesia oral	35	8	5	8	56
Paranasal sinus discomfort	11			5	<20
Paranasal sinus inflammation		<5		<5	<20
Paranoia		<5			<20
Parosmia	18	5	<5	5	30
Pelvic pain		<5			<20
Performance status decreased	<5				<20
Pericarditis		<5			<20
Peri-implantitis	<5				<20
Perioral dermatitis	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Periorbital swelling	<5	<5			<20
Peripheral circulatory failure	<5				<20
Peripheral coldness	66	<5	<5		70
Peripheral swelling	33	7	<5	<5	45
Peripheral vascular disorder	92			<5	95
Petechiae	21	<5	<5	<5	27
Petit mal epilepsy		<5			<20
Pharyngeal disorder	<5				<20
Pharyngeal erythema		<5			<20
Pharyngeal hypoaesthesia	<5				<20
Pharyngeal inflammation	<5				<20
Pharyngeal oedema				<5	<20
Pharyngeal paraesthesia	<5				<20
Pharyngeal swelling	<5	<5		<5	<20
Pharyngitis	<5			<5	<20
Phlebitis	<5			<5	<20
Photophobia	34	<5	<5	<5	42
Photopsia	<5	<5			<20
Photosensitivity reaction	33	<5	<5	<5	36
Piloerection	<5				<20
Pityriasis rosea	<5				<20
Platelet count decreased	<5				<20
Pleural effusion		<5			<20
Pleuritic pain	<5				<20
Pneumonia	<5	<5			<20
Pneumonitis	<5				<20
Pollakiuria	13	<5	<5	<5	<20
Polydipsia	<5				<20
Polymenorrhoea	<5	5	6	<5	<20
Polyuria	7			<5	<20
Poor peripheral circulation	<5				<20
Poor quality sleep	26	<5	<5	<5	36
Portal vein thrombosis	<5				<20
Postmenopausal haemorrhage	<5	<5	<5		<20
Posture abnormal		<5			<20
Pre-existing condition improved		<5			<20
Pregnancy				<5	<20
Premenstrual pain	<5				<20
Premenstrual syndrome	<5				<20
Presyncope	24	21	<5	8	55
Product administration error			<5		<20
Productive cough	11	<5	<5		<20
Proteinuria	<5	<5			<20
Pruritus	196	34	5	52	287
Pseudohallucination	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Psoriasis	<5	<5	<5		<20
Psychomotor hyperactivity	<5			<5	<20
Pulmonary embolism	<5				<20
Pulmonary function test decreased	<5		<5		<20
Pulmonary pain	17	<5	<5		21
Pulpitis dental	<5			<5	<20
Pulse abnormal	<5				<20
Pupillary disorder			<5		<20
Pustule	<5				<20
Pyelonephritis	<5			<5	<20
Pyrexia	28370	354	762	824	30310
Rash	230	23	8	35	296
Rash erythematous	8	5	<5	<5	<20
Rash macular	6	<5		<5	<20
Rash maculo-papular	<5				<20
Rash morbilliform		<5			<20
Rash papular	6	<5	<5	<5	<20
Rash pruritic	43	15	<5	9	68
Rash pustular	<5				<20
Rash vesicular	<5				<20
Raynaud's phenomenon	<5				<20
Red blood cell sedimentation rate increased	<5				<20
Renal disorder	<5			<5	<20
Renal impairment	<5				<20
Renal pain	59			<5	62
Respiration abnormal	5				<20
Respiratory arrest	<5				<20
Respiratory distress	42	<5		5	48
Respiratory tract haemorrhage	<5				<20
Respiratory tract infection	<5			<5	<20
Respiratory tract irritation	<5		<5		<20
Respiratory tract oedema				<5	<20
Restless legs syndrome	14	<5	<5	<5	20
Restlessness	82	6	<5	<5	93
Retching	<5		<5		<20
Retinal detachment	<5				<20
Retinal migraine		<5			<20
Rheumatoid arthritis	<5				<20
Rhinitis	31	7		6	44
Rhinitis allergic	5			<5	<20
Rhinorrhoea	51	27	<5	<5	84
Rotator cuff syndrome		<5			<20
Salivary hypersecretion	13			<5	<20
SARS-CoV-1 test positive			<5		<20
SARS-CoV-2 test negative	<5				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
SARS-CoV-2 test positive	40	7	7	<5	55
Scar pain			<5		<20
Sciatica	<5				<20
Screaming	<5				<20
Seasonal allergy	20	<5	<5	5	29
Sebaceous glands overactivity			<5		<20
Secretion discharge	<5		<5		<20
Sedation	<5				<20
Seizure	<5				<20
Sensation of foreign body	5				<20
Sense of oppression	<5				<20
Sensitive skin	20		<5		24
Sensory disturbance	9				<20
Sensory level abnormal	11			<5	<20
Sensory overload	<5				<20
Sinus congestion	<5			<5	<20
Sinus pain	<5		<5		<20
Sinus tachycardia	<5				<20
Sinusitis	16	<5	<5	6	26
Skin burning sensation	18			<5	22
Skin discolouration	6	<5			<20
Skin discomfort	<5	<5		<5	<20
Skin exfoliation	<5			<5	<20
Skin fissures	<5				<20
Skin haemorrhage	<5				<20
Skin infection	<5				<20
Skin irritation	<5	<5		<5	<20
Skin odour abnormal		<5		<5	<20
Skin papilloma	<5				<20
Skin reaction	<5				<20
Skin sensitisation				<5	<20
Skin tightness	<5				<20
Skin warm	<5				<20
Skin wound		<5			<20
Sleep disorder	119	5	<5	11	136
Sleep terror		<5			<20
Slow response to stimuli	<5	<5	<5		<20
Sluggishness			<5		<20
Sneezing	12	9	<5	<5	27
Somatic symptom disorder	<5				<20
Somnolence	57	27	<5	<5	90
Speech disorder	<5		<5		<20
Spider vein	<5				<20
Spinal cord disorder	<5				<20
Spinal pain	14				<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Spontaneous haematoma	<5				<20
Stomatitis	<5				<20
Stress	<5		<5		<20
Subcutaneous abscess				<5	<20
Subcutaneous haematoma			<5		<20
Sudden hearing loss	8			<5	<20
Suicidal ideation	<5				<20
Sunburn	<5				<20
Suppressed lactation	<5				<20
Suspected COVID-19	<5	<5		<5	<20
Swelling	6	<5	<5	<5	<20
Swelling face	21	<5		9	33
Swelling of eyelid	9	<5		<5	<20
Swollen tongue	16	7	<5	<5	27
Syncope	46	13	8	5	72
Synovial cyst				<5	<20
Tachycardia	154	<5	<5	6	163
Taste disorder	45	10	<5	6	64
Teething				<5	<20
Temporomandibular joint syndrome	<5				<20
Tenderness	13			<5	<20
Tendon discomfort	<5				<20
Tendonitis	<5	<5			<20
Tension	<5				<20
Tension headache	<5	<5		<5	<20
Testicular pain	<5		<5		<20
Therapeutic response unexpected	5	<5	<5	<5	<20
Thirst	101	<5	8	<5	111
Throat irritation	18	<5		<5	25
Throat tightness	5	<5		<5	<20
Thrombocytopenia	<5				<20
Thrombophlebitis	<5				<20
Thrombosis	5				<20
Thyroid disorder	<5				<20
Thyroid pain	<5				<20
Tinea pedis	<5				<20
Tinnitus	109	20	13	15	157
Tongue blistering	<5	<5			<20
Tongue coated	<5			<5	<20
Tongue discolouration			<5		<20
Tongue discomfort	<5	<5			<20
Tongue dry		<5			<20
Tongue geographic		<5			<20
Tongue injury	<5				<20
Tongue pruritus				<5	<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Tongue rough	<5				<20
Tonsillar hypertrophy	<5	<5	<5		<20
Tonsillar inflammation	<5				<20
Tonsillitis	<5				<20
Tooth disorder	<5				<20
Tooth fracture	<5				<20
Tooth infection	<5				<20
Toothache	43	7	<5	<5	52
Torticollis	<5				<20
Tracheal pain			<5		<20
Transient global amnesia	<5	<5			<20
Transient ischaemic attack	<5	<5			<20
Tremor	23	<5	<5	<5	32
Trigeminal neuralgia	6				<20
Trigger finger		<5			<20
Trismus	<5				<20
Type 1 diabetes mellitus	<5				<20
Upper limb fracture	<5				<20
Upper respiratory tract infection	<5				<20
Upper respiratory tract irritation		<5			<20
Urinary hesitation	<5				<20
Urinary incontinence	<5				<20
Urinary tract discomfort		<5			<20
Urinary tract infection	6	<5	<5		<20
Urine analysis abnormal	<5				<20
Urine odour abnormal	<5	<5		<5	<20
Urine output decreased	<5				<20
Urticaria	50	10	<5	7	69
Uterine pain		<5			<20
Vaccination site abscess	<5				<20
Vaccination site bruising		5	<5	<5	<20
Vaccination site discolouration	<5				<20
Vaccination site discomfort	<5	<5	<5	<5	<20
Vaccination site dryness	<5				<20
Vaccination site dysaesthesia				<5	<20
Vaccination site erythema	21	8	<5	33	62
Vaccination site haematoma	23	<5	<5	<5	25
Vaccination site hyperaesthesia	<5				<20
Vaccination site induration	15			5	20
Vaccination site inflammation	<5			<5	<20
Vaccination site irritation	<5				<20
Vaccination site joint discomfort		<5			<20
Vaccination site joint erythema		<5	<5		<20
Vaccination site joint movement impairment	<5				<20
Vaccination site joint pain		5	<5		<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Vaccination site joint swelling				<5	<20
Vaccination site joint warmth	<5			<5	<20
Vaccination site lymphadenopathy	<5	<5	<5		<20
Vaccination site mass				<5	<20
Vaccination site movement impairment	9	14	<5	12	35
Vaccination site oedema	6	12	<5	5	23
Vaccination site pain	179	126	<5	40	348
Vaccination site paraesthesia	5			<5	<20
Vaccination site pruritus	39	<5	<5	40	82
Vaccination site pustule	<5				<20
Vaccination site rash	<5			13	<20
Vaccination site reaction	8			5	<20
Vaccination site swelling	22	<5		7	30
Vaccination site thrombosis	<5				<20
Vaccination site urticaria				<5	<20
Vaccination site warmth	18	6	<5	12	36
Vaginal discharge	<5	<5			<20
Vaginal haemorrhage	8	<5	<5	<5	<20
Varicose vein	<5	<5			<20
Vascular pain	<5	<5			<20
Vascular resistance systemic decreased	<5				<20
Vasculitis	<5				<20
Vasodilatation	<5	<5			<20
Vein disorder		<5			<20
Venous thrombosis	<5				<20
Vertigo	6	11	<5	5	23
Vertigo positional	<5				<20
Viral rash	<5				<20
Viral upper respiratory tract infection				<5	<20
Vision blurred	41	17	<5	<5	65
Visual acuity reduced	<5				<20
Visual field defect	<5	<5			<20
Visual impairment	70	7	<5	<5	80
Vitamin B12 deficiency			<5		<20
Vitreous floaters	<5				<20
Vitreous haemorrhage				<5	<20
Vocal cord dysfunction	<5				<20
Vomiting	1615	21	10	86	1732
Vulvovaginal candidiasis	<5	<5			<20
Vulvovaginal discomfort	<5				<20
Vulvovaginal mycotic infection	<5	<5			<20
Vulvovaginal pruritus				<5	<20
Weight abnormal			<5		<20
Weight bearing difficulty	5		<5		<20
Weight decreased		<5			<20

Preferred Term	AstraZeneca	BioNtech/Pfizer	Janssen	Moderna	Total
Weight increased	<5		<5		<20
Wound complication		<5	<5		<20
Wound haemorrhage	<5				<20
Yawning	<5			<5	<20

Appendix 5

Complete list of reported Serious ADRs, coded as MedDRA Prefterred Term, after dose 1 in alphabetical order

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Abdominal discomfort	1				1
Abdominal pain	5				5
Abdominal pain upper	1				1
Abnormal faeces	1				1
Abortion missed	1				1
Abortion spontaneous	1	2	1	1	5
Acne	1				1
Acute myocardial infarction	1				1
Ageusia	3				3
Amenorrhoea	1				1
Anal haemorrhage	1				1
Anaphylactic reaction			1		1
Anaphylactic shock	2				2
Angina pectoris	2				2
Anxiety	1				1
Appendicitis	2			1	3
Application site haematoma	1				1
Application site haemorrhage	1				1
Arrhythmia	3				3
Arthralgia	238			7	245
Arthritis	1				1
Asthenia	3				3
Asthma	1				1
Atrial fibrillation	3				3
Atrioventricular block complete		1			1
Auditory disorder	1				1
Axillary pain				2	2
Back pain	17				17
Blood pressure abnormal	2				2
Blood pressure increased	16				16
Body temperature decreased	1				1
Body temperature increased	5				5
Bone pain	1				1
Breast pain	4				4
Burning sensation	2				2
Cardiovascular disorder	3				3
Carpal tunnel syndrome	1				1
Cellulitis	1				1
Cerebellar infarction	1				1
Cerebral infarction	1			1	2

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Cerebral venous sinus thrombosis	1				1
Cerebral venous thrombosis	1				1
Cerebrovascular accident		1			1
Chest discomfort	4			1	5
Chest pain	2				2
Chills	310	1	1	9	321
Circulatory collapse	4				4
Cluster headache	1				1
Colitis	1	1			2
Confusional state	1				1
Constipation	1				1
Contusion	2			1	3
Coordination abnormal	1				1
Coronavirus test positive	1				1
Cough	2			1	3
COVID-19	1				1
CSF test abnormal	1				1
Cystitis	1				1
Death	1				1
Decreased appetite	1				1
Deep vein thrombosis	1			1	2
Dehydration	1				1
Dental discomfort	1				1
Diarrhoea	72	1		5	78
Disturbance in attention	7				7
Dizziness	309			18	327
Dry eye	1				1
Dry mouth	2				2
Dry throat	1				1
Dysaesthesia	2				2
Dysentery		1			1
Dysgeusia	3				3
Dyspnoea	19	2	1		22
Dysuria	2				2
Ear discomfort	1				1
Ear pain	4				4
Electrocardiogram abnormal	1				1
Emergency care	1				1
Enteritis	1				1
Epilepsy	1				1
Epistaxis	1	1			2
Erythema	1				1
Erythema of eyelid	1				1
Eye haemorrhage	1				1
Eye pain	4				4

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Facial pain	1				1
Facial paresis	3				3
Fatigue	438	1		24	463
Fibrin D dimer increased	2				2
Flushing	3				3
Food aversion	1				1
Food craving	1				1
Foreign body sensation in eyes				1	1
Gait disturbance				1	1
Gastric ulcer	1				1
Gastrointestinal pain	2				2
Generalised oedema	1				1
Giant cell arteritis	1				1
Gingival bleeding	1				1
Haematochezia	1				1
Haematoma	1				1
Haematuria	1				1
Haemorrhage in pregnancy	1				1
Haemorrhagic erosive gastritis	1				1
Haemorrhoidal haemorrhage	1				1
Head discomfort	3				3
Headache	486	1		28	515
Heart rate increased	4				4
Herpes ophthalmic	1				1
Herpes zoster				2	2
Hospitalisation	5				5
Hot flush	2				2
Hypercoagulation	1				1
Hyperhidrosis	3				3
Hyperpyrexia	1	1			2
Hypersensitivity	8	1		1	10
Hypertension	8			1	9
Hypertensive crisis	1				1
Hyperventilation	3				3
Hypoacusis	1				1
Hypoaesthesia	10		1		11
Hypoaesthesia oral	3				3
Hypogeusia	1				1
Hypoglycaemia	1				1
Hypotension				1	1
Hypotonia	1				1
Immune thrombocytopenia	1				1
Increased insulin requirement	1				1
Increased upper airway secretion	1				1
Infectious mononucleosis	1				1

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Inflammatory marker increased	1				1
Influenza like illness	6			2	8
Initial insomnia	1				1
Injection site bruising	1				1
Injection site erythema	3				3
Injection site hypersensitivity	1				1
Injection site pain	414			26	440
Injection site swelling	152			15	167
Intracranial hypotension	1				1
Intracranial pressure increased	1				1
Joint swelling	1				1
Labile blood pressure				1	1
Lacrimation increased				1	1
Limb discomfort	3		1		4
Lip swelling	2				2
Loss of consciousness	2			1	3
Lumbar puncture	1				1
Lymph node pain	1				1
Lymphadenitis	1				1
Lymphadenopathy	10			3	13
Magnetic resonance imaging brain abnormal	1				1
Malaise	369		1	23	393
Memory impairment	2				2
Menorrhagia	1				1
Menstrual disorder	1				1
Migraine	3				3
Mobility decreased	2				2
Mouth swelling	1				1
Movement disorder	1				1
Multiple sclerosis relapse	1				1
Muscle spasms	2				2
Muscle tightness	1			1	2
Musculoskeletal discomfort	1				1
Musculoskeletal stiffness				1	1
Myalgia	311			14	325
Myocardial infarction	3	2			5
Myositis	1				1
Nasal congestion	1				1
Nasal vestibulitis	1				1
Nasopharyngitis	2				2
Nausea	236	1		14	251
Neck pain	7			1	8
Neurodermatitis	1				1
Night sweats	2				2
Ocular discomfort	1				1

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Ocular hyperaemia	1				1
Oral herpes	1				1
Oropharyngeal pain	5				5
Oropharyngeal swelling	1				1
Other medically important condition			2		2
Pain	1				1
Pain in extremity	21			2	23
Pain in jaw	1				1
Pain of skin	1				1
Pallor			1		1
Palpitations	14		1	1	16
Pancreatitis	1				1
Panic attack	2				2
Paraesthesia	21	1			22
Paraesthesia oral	3		1		4
Peripheral swelling	3				3
Peripheral vascular disorder	2				2
Petechiae	6				6
Pharyngeal hypoaesthesia	1				1
Phlebitis				1	1
Photophobia	1			1	2
Pityriasis rosea	1				1
Platelet count decreased	1				1
Pneumonia	1	1			2
Portal vein thrombosis	1				1
Productive cough	1				1
Pruritus	3	1		1	5
Pulmonary embolism	2				2
Pulmonary pain	2				2
Pyelonephritis				1	1
Pyrexia	311	1		5	317
Rash	6	1			7
Rash erythematous	1				1
Rash macular	1				1
Rash pruritic	2			1	3
Red blood cell sedimentation rate increased	1				1
Renal pain	1				1
Respiratory arrest	1				1
Respiratory distress	4	1			5
Respiratory tract oedema				1	1
Restlessness	3		1		4
Retching	1				1
Retinal detachment	1				1
Rhinorrhoea	2				2
Sciatica	1				1

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Seizure	1				1
Sensory disturbance	2				2
Sensory level abnormal	1				1
Sleep disorder	2				2
Somnolence	3				3
Swelling face	5	1		2	8
Swelling of eyelid	1				1
Swollen tongue	1				1
Syncope	6				6
Tachycardia	17			1	18
Taste disorder	2				2
Tenderness	1				1
Tension	1				1
Thirst	1				1
Thrombocytopenia	3				3
Thrombophlebitis	1				1
Tinnitus	4				4
Tonsillar inflammation	1				1
Tonsillitis	1				1
Transient global amnesia		1			1
Transient ischaemic attack	1	2			3
Tremor			1		1
Trigeminal neuralgia	1				1
Upper limb fracture	1				1
Urinary hesitation	1				1
Urticaria	5			1	6
Vaccination site discomfort	1				1
Vaccination site erythema	2			1	3
Vaccination site haematoma	1				1
Vaccination site hyperaesthesia	1				1
Vaccination site induration	1				1
Vaccination site pain	6			1	7
Vaccination site pruritus				1	1
Vaccination site rash	1				1
Vaccination site swelling	1				1
Vaccination site thrombosis	1				1
Vaccination site warmth	2				2
Vaginal haemorrhage	1				1
Vision blurred	1			1	2
Visual field defect	2				2
Visual impairment	4				4
Vitreous floaters	1				1
Vomiting	60	1		4	65

Appendix 6

Top twenty most reported serious adverse reactions for dose 1 shown per vaccine brand and country of origin.

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Headache	**486**	**1**		**28**	**515**
DE	485			28	513
FR		1			1
NL	1				1
Fatigue	**438**	**1**		**24**	**463**
DE	438			24	462
FR		1			1
Injection site pain	**414**			**26**	**440**
DE	414			26	440
Malaise	**369**		**1**	**23**	**393**
DE	367			22	389
IT				1	1
NL	2		1		3
Dizziness	**309**			**18**	**327**
DE	309			17	326
NL				1	1
Myalgia	**311**			**14**	**325**
DE	310			14	324
NL	1				1
Chills	**310**	**1**	**1**	**9**	**321**
DE	310			9	319
FR		1			1
NL			1		1
Pyrexia	**311**	**1**		**5**	**317**
DE	309			4	313
FR		1			1
IT				1	1
NL	2				2
Nausea	**236**	**1**		**14**	**251**
DE	235			14	249
FR		1			1
NL	1				1
Arthralgia	**238**			**7**	**245**
DE	238			7	245
Injection site swelling	**152**			**15**	**167**
DE	152			15	167
Diarrhoea	**72**	**1**		**5**	**78**
DE	71			5	76
NL	1	1			2

Preferred Term	AstraZeneca	BioNTech/Pfizer	Janssen	Moderna	Total
Vomiting	**60**	**1**		**4**	**65**
DE	60			4	64
NL		1			1
Pain in extremity	**21**			**2**	**23**
DE	21			2	23
Paraesthesia	**21**	**1**			**22**
DE	21				21
FR		1			1
Dyspnoea	**19**	**2**	**1**		**22**
DE	16				16
NL	3	2	1		6
Tachycardia	**17**			**1**	**18**
DE	17			1	18
Back pain	**17**				**17**
DE	17				17
Blood pressure increased	**16**				**16**
DE	16				16
Palpitations	**14**		**1**	**1**	**16**
DE	14			1	15
NL			1		1
Lymphadenopathy	**10**			**3**	**13**
DE	10			3	13