# Covid-Vaccine-Monitor

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## Interim Study Report for Cohort Event Monitoring (WP1 & WP2)

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# 1. WP1-2-5: Cohort Event Monitoring of safety of COVID-19 vaccines in general and in special populations

## 1.1 Abstract


**Title**

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

**Keywords**

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

**Rationale and background**

Intensive monitoring of adverse reactions following immunization (AEFI) with COVID19 vaccines or cohort event monitoring has been performed on (sub)national levels. However, the exact data collection and analysis methods, study populations, and vaccines monitored varied. For the already marketed and upcoming COVID-19 vaccines, a pan-European cohort monitoring system is an important addition to existing spontaneous reporting systems for signal detection. This enables the collection of general and fragile populations' patient-reported safety data in near real-time and generates incidence rates of vaccine-related adverse reactions in those cohorts.

**Research question and objectives**

*Primary aim*

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

*Secondary aim*

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

**Study design**

Prospective cohort study in general and special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection). In different countries, on the national level, data are prospectively collected, directly from a cohort of vaccine recipients. The common core data from different countries are pooled, stratified by special cohort and analysed at the European level. The study is set up as a cohort monitoring for a duration of up until 6 months from the first dose vaccination date (except for pregnant women who are followed up until 1.5 month after the pregnancy end).

**Setting**

Participants to be included should be vaccinated in one of the participating countries in the period ranging from December 2020 (in Countries already starting prospective monitoring in ECVM) until August 2022.

This interim report includes LIM and RO data updated until the 9th of February 2022, and Croat OPeN data until the 15th of February 2022. German SafeVac 2.0 datasets are included in batches, with Moderna data updated until May 2021, AstraZeneca until September 2021, and the new BioNTech/Pfizer data until March 2022.

**Subjects and study size**

General and special population vaccinees (pregnant and lactating women, children, adolescents, immunocompromised, people with a history of allergy, and people with prior SARS-CoV-2 infection) who were recruited at multiple vaccination centers within 48 hours from either the first or booster COVID-19 vaccine dose administration. The aim was the inclusion of up to 60,000 vaccine recipients belonging to both general and special cohorts from 12 European countries which would exceed the numbers of vaccinated in clinical trials.

**Variables**

Vaccine brand and batch number, adverse drug reactions (ADRs), age, sex, height and weight, geographical area, medical history including information on comorbidities and concomitant diseases, and concomitant medications.

**Results**

The populations that adhere to this observational study are described in this report by the number of patients included in the cohort for each participating country, gender distribution, age categories, and vaccine brands.

*First vaccination cycle data in general population*

For both general and special populations, dedicated cumulative structured overviews of numbers and incidences of all adverse reactions are provided. Reported adverse events are stratified in solicited, unsolicited, serious adverse events, adverse events of special interest, vaccine brand, country, gender, and age groups when all these informative details can be extrapolated from the data. For the first vaccination cycle, in this report we included 30,108 participants in Belgium, Croatia, France, Italy, the Netherlands, and the United Kingdom, and 520,076 general population participants from Germany. Across the sites 0.2-0.3% % reported at least one serious adverse reaction after receiving the first and/or the second dose. The majority of all reports of an AESI were from females, across all vaccine brands.

*Special populations first vaccination cycle*

Overall, 7,057 special population vaccinees from the LIM app who reported at least one ADR following the first vaccination dose, 17 (0.2%) reported at least one serious ADR. Overall, of 3,793 vaccinees who reported at least one ADR following the second vaccination dose, 9 (0.2%) reported at least one serious ADR. Overall, out of the total of vaccinees who reported at least one ADR following the first (N= 7,057) and second (N= 3,793) vaccination dose, 25 (0.4%) and 15 (0.4%) vaccinees reported at least one AESI following the first and second vaccination dose, respectively.

The most reported solicited local adverse reaction among all the COVID-19 vaccine brands, special cohorts, and between 1st and 2nd dose is injection site pain. This is in line with the general population observations (and with previously published works). Among the solicited systemic adverse reactions, fatigue, headache, malaise, and myalgia, were the most frequently reported events, which is consistent with total populations.

Serious adverse reactions and AESI were uncommon among each of the special cohorts, although sample size and power to detect differs. This is also in line with the general populations' pivotal clinical trials and this study's results in general populations.

Caution should be taken in interpreting the data as analysis considering participants' baseline characteristics and the adverse reaction they reported has not yet been conducted.

On the basis of the Research Online app that was used in Italy, Romania, Slovakia, Spain and Switzerland, 377 first dose vaccinees with one of the special conditions were included mostly children and persons with prior Sars-Cov-2 infection. The rate of serious reactions could not yet be validly estimated.

Pregnant women: 8 cases of spontaneous abortion events were observed among both general and special population data, but only 1 case is recorded as pregnant women at baseline at the date of vaccination. No other AESI were yet observed.

Children/adolescents: Serious ADRs following COVID-19 vaccination are uncommon. No AESI were observed.

Immunocompromised, people with history of allergy, people with prior COVID-19: Serious ADRs and AESI after COVID-19 vaccinations are uncommon. Among the observed AESI, COVID-19 infection, hypersensitivity, and arrhythmia, have been the most frequently reported.

*Booster dose*

A total of 11.100 subjects who received a booster dose were included in this study, all use the RO application for enrolment. Most of the persons were not part of a special population (8493), 419 pregnant or lactating women were included. BioNTech/Pfizer and Moderna are the most commonly administered COVID-19 vaccines in our observational study, in line with EMA recommendations for the booster vaccination campaign. Children/adolescents reported the lowest rate of ADRs among the other cohorts involved in this booster vaccination study. Lactating women reported the highest numbers of ADRs among the other cohorts involved in this booster vaccination study Informative details about the type of the reported ADRs are not yet reported for these booster dose data.

**Conclusion**

This interim report summarizes the safety evidence of covid-19 vaccines in more than 550,000 persons from both the general and special populations that were included after first dose, and booster doses combining data coming from a total of eleven countries and four different data sources. The main limitations for combining these datasets coming from different systems are discussed in the report. Despite the encountered limitations, self-reported information about the safety of the COVID-19 vaccines is described.

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## 1.2. List of abbreviations

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

## 1.3. Investigators

| | |
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## 1.4. Milestones

| | |
|---|---|
| Start of project | 6 Apr 2021 |
| D1 Study plan | 6 May 2021 |
| D2 Study protocol(s) | 7 Jun 2021 |
| Study start | 7 July 2021 |
| D3 Monthly interim statistical report 1 on dashboard | 30 Sep 2021 |
| D3 Monthly interim statistical report 2 on dashboard | 27 Oct 2021 |
| D3 Monthly interim statistical report 3 on dashboard | 26 Nov 2021 |
| D3 Monthly interim statistical report 4-5 on dashboard | 31 Jan 2021 |
| D3 Monthly interim statistical report 6 on dashboard | 28 Feb 2022 |
| D4.1 Interim study report + D3 monthly interim statistical report 7 &SAP | 8 Apr 2022 |
| D3 Monthly interim statistical report 8 + 9 + 10 on dashboard | 30 Jun 2022 |
| D3 Monthly interim statistical report 11 + 12 on dashboard | 16 Sep 2022 |
| D3 Monthly interim statistical report 13 + 14 on dashboard | 31 Oct 2022 |
| D3 Monthly interim statistical report 15 + 16 on dashboard | 16 Jan 2023 |
| D5.4 Archiving & storage plan | 31 Jan 2023 |
| D3 Monthly interim statistical report 17 + 18 on dashboard | 28 Feb 2023 |
| D3 Monthly interim statistical report 19 on dashboard | 28 Apr 2023 |
| D4.2 Final study report | 8 May 2023 |
| D5 Manuscript | 8 May 2023 |

## 1.5. Rationale and background

**Background**

As reported in the Early-Covid-Vaccine-Monitor (ECVM) protocol (EUPAS39798), the European Medicine Agency's (EMA) mission is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. COVID-19 vaccines in the European Union (EU) are evaluated by EMA via the centralised procedure, based on a rolling review. Five vaccines (from Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, Novavax) have been granted conditional marketing authorisation and large-scale vaccination campaigns are being rolled out across the EU.

During the 2009 pandemic, major lessons learned were a need for improved collaboration within Europe, and a common approach for the collection of safety data and data-sharing[1]. This contribution can improve signal detection and timely evaluation of safety signals in a forthcoming pandemic. The large scale of the 2009 worldwide H1N1 pandemic vaccination programme prompted several countries to improve and expand their vaccination safety monitoring procedures. Indeed, various intensive monitoring studies were performed in different countries. The results of two intensive monitoring studies on the 2009 pandemic influenza vaccination in Europe were published. (Harmark et al. 2012) Upon the experience with the H1N1 vaccination programmes, the intensive monitoring system was developed further to monitor seasonal influenza vaccination in the Netherlands (cf. Lareb Intensive Monitoring (LIM) system) and has been used since. Such experiences pave the way to design an intensive monitoring system for COVID-19 vaccination at the European level.

In order to complement spontaneous reporting systems for signal detection (routine pharmacovigilance) and other initial safety monitoring activities such as pharmaco-epidemiological studies conducted or planned by different stakeholders, the Agency procured an early safety monitoring study through its framework contracts (ECVM) which is conducted by the EU PE&PV research network and VAC4EU in seven EU Member States (Germany, Croatia, the Netherlands, Belgium, Luxembourg, Italy, France) and the UK. The CVM project enlarged the ECVM study in four additional EU Member States (Spain, Portugal, Slovakia, and Romania) and Switzerland to further inform the benefit-risk profile of all COVID-19 vaccines in the EU as immunisation campaigns are expanding, targeting larger population groups.

**Rationale**

Pivotal licensure clinical trials collect key information on Adverse Events of Special Interest (AESIs) and Adverse Events Following Immunization (AEFIs) and often include selected persons. During the rollout of vaccines, larger and more diverse populations are vaccinated. Certain groups, such those at higher risk of developing AESIs and/or AEFIs have not been initially included in the pivotal COVID-19 vaccines clinical trials. Therefore, available risk management plans from currently authorized vaccines were lacking information on the safety and effectiveness of COVID-19 vaccines in special populations who have not been vaccinated in the first phases. At the current stage of the vaccination campaigns, new information is available.

AEFIs can comprise 5 different types[2]:

- Vaccine product-related reaction.

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

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

- Vaccine quality defect-related reaction.
- Immunization error-related reaction.
- Immunization anxiety-related reaction.
- Coincidental event.

Licensure of a vaccine that is rolled out to a large population in a short time requires not only regular spontaneous reporting but also cohort event monitoring to obtain more in-depth information on the safety of the vaccines. In addition to existing spontaneous reporting systems, a large-scale cohort event monitoring system on general and special populations (i.e., pregnant and lactating women, children and adolescents, immunocompromised, people with a history of allergy, and people with prior SARS-CoV-2 infection) allows for the monitoring of marketed COVID-19 vaccines in a larger size and categories that have not been included in pivotal clinical trials in the EU. This approach is complementary to spontaneous reporting systems as well as observational studies using healthcare databases in several ways. In particular, it is better suited to capture the more frequent adverse reactions, including those that are not medically attended, and can generate more comprehensive safety data.

## 1.6. Research question and objectives

The CVM project aims to collect data on adverse drug reactions in general and specific target populations for COVID-19 vaccines in 10 EU Member States (Germany, Croatia, the Netherlands, Belgium, Italy, France, Spain, Portugal, Slovakia, and Romania), Switzerland, and the UK to further inform the benefit-risk profile of all COVID-19 vaccines in the EU. Immunisation campaigns have been expanded from general population to larger fragile groups.

**Primary objective**

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

**Secondary objective**

To identify and generate incidence rates and potential predictors of the most frequently reported adverse reactions related to different COVID-19 vaccines after 1/2 dose(s) of the first vaccination cycle as well as booster doses within the general population and special cohorts of vaccinees.

## 1.7. Research methods

### 1.7.1. Study design

Prospective cohort study in the general and special populations (i.e., pregnant and lactating women, children, and adolescents, immunocompromised, people with history of allergy, and people with prior SARS-CoV-2 infection). On the national level, data are prospectively collected in near real-time,

directly from a cohort of vaccine recipients in different countries. Once participants have been invited to participate, via e-mail or flyers, they register themselves and create a study account on a website that is specifically designed for this study for each country. Generally, two data collection tools are used. These are Lareb Intensive Monitoring (LIM) web app, managed by Lareb, and Research Online (RO) web app managed by Julius Centre at UMC Utrecht. Once participants have been invited to participate, via e-mail or flyers, they register themselves and create a study account on a website that is specifically designed for this study for each country in the local language(s). Participants can download the LIM web app and/or the RO web app to their mobile device, access their questionnaires online and receive reminders to fill in questionnaires. People can only register when they meet the local age criteria for inclusion and when they receive their first dose or booster dose within 48 hours. Depending on whether participants received their first or their booster dose, and if they are identified as part of the special target groups or the general population, they will be able to register to either the LIM web app and/or the RO web app.

- Vaccine recipients registering following the first dose of vaccine and not identified as part of the special target group will only be able to register through the LIM web app as part of the ECVM/CVM WP2 project.
- Vaccine recipients registering following the first dose of vaccine and belonging to the special target groups can register to either the LIM web app or the RO web app.
- COVIPREG and ORCHESTRA networks are used to recruit pregnant women and immunocompromised patients at booster vaccination, respectively. The real quantification of COVIPREG and ORCHESTRA contribution in terms of recruited vaccinees is under the identification process on the RO system. ORCHESTRA is supporting the recruitment of the fragile population through the dissemination of the CVM information material on an Italian regional and national level. In particular, the ORCHESTRA network has contributed to enrolling immunocompromised vaccinees who received a booster vaccination. COVIPREG network was used for the recruitment of pregnant women. Specifically, the network of Swiss obstetricians and gyneacologists already familiar with the COVI-PREG registry asked for information on Covid-19 vaccines in pregnant women, collected by paper questionnaires between 1 March 2021 and 27 December 2021, and was involved in promoting the CVM study. As soon as the CVM study website was operational, the network of Swiss obstetricians and gynaecologists was invited to switch to online questionnaires, which are much more user-friendly and efficient for accurate data collection than paper questionnaires.
- Those who received the booster vaccination can only register through the RO web app.

Vaccinees are asked to fill in questionnaires at baseline, and 1 and 3 weeks after the first dose (and possibly after the second dose, at the weeks 5 and 8 from the first dose), and 3 and 6 months after the first dose vaccination in the scenario that the time period between vaccine doses is three weeks. Pregnant women should only register through the RO web app, since specific pregnancy-related questionnaires were built in this web app for the CVM WP1 project. Indeed, pregnant women receive an additional specific “End of Pregnancy” questionnaire within 1.5 months from the estimated delivery to collect information on outcomes related to pregnancy and new-borns. Differently from participants receiving a first dose of vaccine, participants receiving a booster vaccination will receive 5 follow-up questionnaires instead of 6, for a total follow-up time of 3 months.

German and Croatian participants participate in this study through their national data collection tools, the German SafeVac 2.0 and the Croat OPeN, respectively. Datasets coming from these countries are periodically shared with Lareb, who integrate them with the LIM web app aggregated data.

The common core data from different countries is pooled, stratified by special cohorts, and analysed at the European level.

### 1.7.2. Setting

**Inclusion criteria**

Participants to be included should be vaccinated in one of the participating countries in the period ranging from February 2021 (in Countries already starting prospective monitoring in ECVM) until August 2022.

The vaccine recipient or their proxy should:

- register for the study prior to (the first) vaccination or no longer than 48 hours from first dose of COVID-19 vaccination or booster dose be able to understand the language of the survey (translated into the local official languages)
- be able to register and participate by e-mail;
- provide informed consent (translated into the local official languages and adapted according to the Country-specific laws). Regarding children informed consent of the parents or the legal representative will be sought. The informed consent must be given if the person wishing to participate in the project is under 16 or 18 years of age, depending on the Country-specific law.

**Study population**

Target groups are general and special populations. Special populations group includes pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection vaccinated against SARS-COV-2 infection. People in the special target subgroups will have the following characteristics:

- Pregnant/lactating women include pregnant women at any point of pregnancy at the moment of vaccination, which will depend on national vaccination campaign, and during the breastfeeding period
- Children are persons 0-17 years of age. Parents or legal representatives are expected to enter the data on behalf of their children, as needed, based on national legislation.
- Immunocompromised subjects comprise individuals with immune system compromised due to diseases such as HIV/AIDS, transplants, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, psoriasis, psoriatic arthritis), leukaemia/lymphoma; and/or subjects currently taking drugs affecting their immune system (e.g., myelosuppressive chemotherapy, glucocorticoids, anti-rheumatics drugs, monoclonal antibodies interfering with immune system)
- Subjects with history of allergy, including hay fever, dust mite allergy, allergy to animals, food allergy, allergy to insect bites, allergy to medication or vaccine, etc.
- Subjects with prior SARS-CoV-2 infection are people who had a suspected/diagnosed SARS-CoV-2 infection (whether confirmed or not-confirmed by a test) any time prior to the first dose vaccination.

### 1.7.3. Variables

Vaccine brand and batch number, adverse drug reactions (ADRs), age, sex, height and weight, geographical area, medical history including information on comorbidities and concomitant diseases (e.g., diseases or drugs affecting the immune system, history of allergy and SARS-CoV-2 prior infection, etc.) and concomitant medications. Having received another vaccine (e.g., anti-influenza vaccine) within two weeks prior to the COVID-19 vaccination is also recorded. For pregnant women baseline variables for pregnancy (e.g., gestation, parity, previous pregnancy complications, ongoing pregnancy due date, etc.) and outcomes of the pregnancy and the new-born (i.e., pregnancy complications, end of pregnancy week, delivery mode, pregnancy outcomes, and neonatal outcomes) are collected. In addition, for the booster vaccination: data on the previous cycle of vaccination, including the vaccine brands, and the related adverse drug reactions.

**Exposure data**

- Vaccine brand & batch number (if available) obtained via the vaccine recipient (e.g., number on vaccination certificate, or uploading photo)
- Vaccine dose number
- Vaccination date
- Vaccine switch from first to second dose are collected: data on the second dose, including the name of the vaccine received and the day it was received, are asked in questionnaire number 3. In case the participant selected they have not yet received the vaccine in Q3, second dose-related questions will be asked in the next questionnaires (Q4, Q5, and Q6). Therefore, information regarding any vaccine switch from first to second dose as well as the information about the interval between the two doses can be collected in Q3-Q6.

**Vaccinee demographics and clinical characteristics**

The following information are collected upon enrolment.

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

*Additional baseline variables on maternal morbidity & obstetric history*

The following information will be collected for pregnant women:

- Gestity
- Parity:

    - Number of previous C-Section if parity ≥ 1
    - Number of previous vaginal delivery if parity ≥ 1
    - Number of previous early miscarriage (<14 weeks) if gestity > 1
    - Number of previous late miscarriage (≥ 14 weeks) if gestity >1
    - Number of previous terminations of pregnancy if gestity > 1
    - Number of previous stillbirth if gestity >1
- Maternal medication
- Previous pregnancy complications (preterm birth, cesarean section r)
- Ongoing pregnancy due date*

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

**Outcome data**

*Solicited adverse reactions*

Closed dedicated questions (solicited):

- Injection site reaction (redness, warmth, pain, itch, hematoma, swelling, induration, ELS (extensive limb swelling). If 2 or more of the following adverse reactions are mentioned (redness, warmth, pain, swelling), it is asked whether the redness and/or swelling go past the elbow or shoulder.
- Fever/feverishness
- Shivering/chills
- Headache
- Nausea
- Myalgia/muscle pain
- Arthralgia/joint pain
- Malaise
- Fatigue
- These solicited adverse reactions are known to occur frequently. The reactions listed as solicited adverse reactions are the same across all participating countries and they can be automatically MedDRA-coded. This improves the data quality and facilitates timely data analysis.

*Unsolicited adverse reactions*

In addition, it is asked whether any other suspected adverse reactions occurred (open question/unsolicited). The later follow-up periods should serve to monitor suspected adverse reactions with a longer lag time and to assess the course of previously reported adverse reactions (i.e., outcome, duration of symptoms). Assessors in the different participating countries code unsolicited reported adverse reactions into MedDRA lower-level terms (in English), and determine whether they are serious based on the criteria of the Council for International Organizations of Medical Sciences (CIOMS) criteria. Moreover, solicited reactions are reviewed to assess seriousness criteria. Reported adverse reactions which are considered serious based on the above mentioned CIOMS criteria and other adverse reactions that need medical clarification are assessed in agreement with national PV legislation.

### *Pregnancy and neonatal outcomes*

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

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

### *Adverse Drug Reactions*

Suspected short- and medium/long-term adverse drug reactions (ADRs) are reported after each dose of COVID-19 vaccination (as both solicited and unsolicited events) by the participant. Because data are gathered from the participants through self-reporting methods, it is not possible to perform causality assessments and to determine if all adverse events following immunization are caused by the vaccine. Therefore, all adverse reactions should be considered as suspected adverse reactions following immunization with COVID-19 vaccines.

Differently, all serious adverse reactions are assessed by a qualified assessor, considering all information including possible uploads of documents by participants or comments on these events. When consent has been given by a participant, follow-up is requested by e-mail for verification and upgrading of the clinical documentation grade. Otherwise, serious ADR assessment will be carried out by the Regional Center of Pharmacovigilance or local Pharmacovigilance Responsible Person, in agreement with national pharmacovigilance practice and legislation. There are thus two variables regarding the seriousness of an ADR: the seriousness which is reported by the participant and the seriousness as assessed by the trained assessors. Seriousness used in all tables in this report section and dashboards is based on the assessed seriousness. Outcomes of pregnancy and new-born are also explored in pregnant women.

Most of the suspected ADRs that are collected will be expected reactogenicity-type reactions and already labelled as solicited adverse reactions.

***Table 1**. List of AESI as per EMA's June 8th, 2021 communication*

| Event |
|---|
| **Multisystem inflammatory syndrome** |
| **Acute respiratory distress syndrome** |
| **Acute cardiovascular injury** |
| *Microangiopathy* |
| *Coronary Artery Disease (CAD)* |
| *Arrhythmia* |
| *Myocarditis* |
| *Pericarditis* |
| **Coagulation disorders**<br>including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease |
| *Venous Thromboembolism (DVT & PE & Splanchnic)* |
| *Cerebral Venous Sinus Thrombosis* |
| *Arterial thrombosis* |
| *TTS (VTE, arterial thrombosis, or CVST with thrombocytopenia in 10 days)* |
| *Hemorrhagic stroke* |
| *DIC* |
| **Generalised convulsion** |
| **Guillain Barré Syndrome (GBS)** |
| **Diabetes (type 1 and unspecified type)** |
| **Acute kidney injury** |
| **Acute liver injury** |
| **Anosmia, ageusia** |
| **Chilblain-like lesions** |
| **Single organ cutaneous vasculitis** |
| **Erythema multiforme** |
| **Anaphylaxis** |
| **Death (any cause) (postvaccination control window)** |
| **Sudden death (by codes) (postvaccination control window)** |
| **Meningoencephalitis** |
| **Acute disseminated encephalomyelitis (ADEM)** |
| **Narcolepsy** |
| **Thrombocytopenia** |
| **Transverse myelitis** |
| **Bells' palsy** |
| **Haemophagocytic lymphohistiocytosis[4]** |
| **Kawasaki's disease** |
| **Pancreatitis** |
| **Rhabdomyolysis** |
| **SCARs** |
| **Sensorineural hearing loss** |
| **Thyroiditis** |

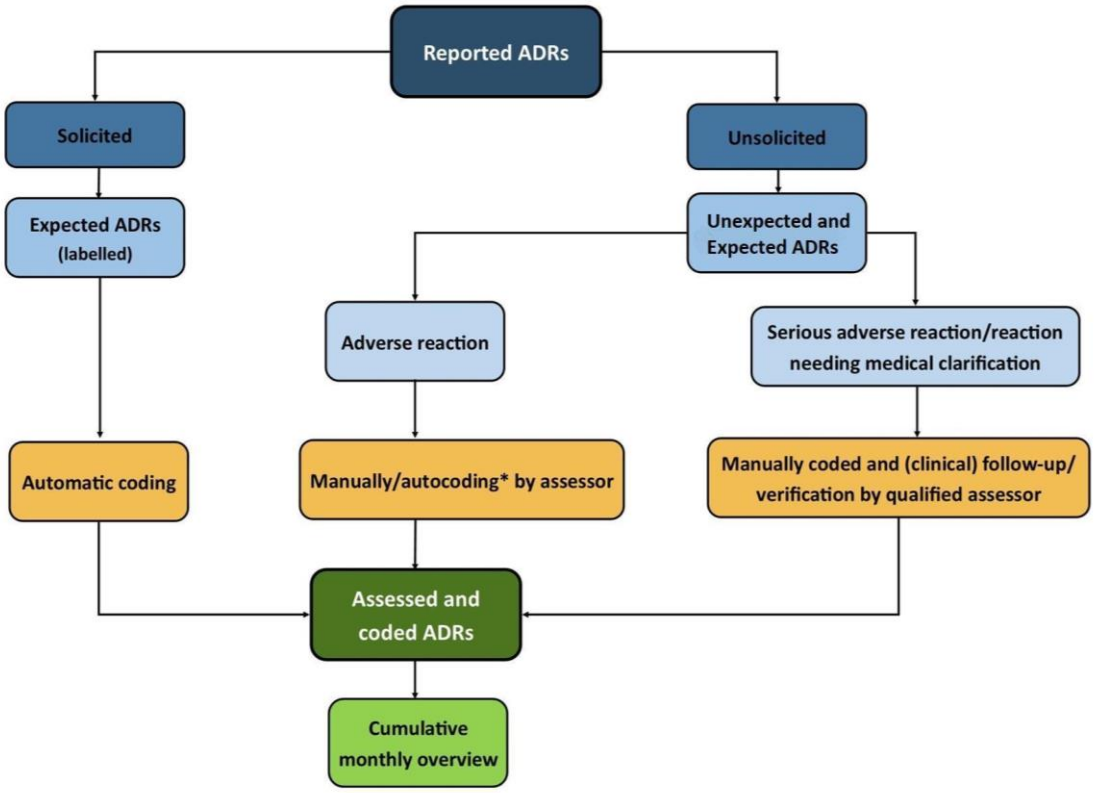



***Figure 1**. Reported ADRs coding system based on the [Early-Covid-Vaccine-Monitor study protocol]*

### 1.7.4. Data sources and measurement

Data collected nationally is stored in centralized databases (at Lareb for LIM app or at UMC Utrecht for Research Online app). Partners have access to the database of the automatically received questionnaires of participants in their own country. Both the admin section and the LIM/RO analysis database of each country contain identifying information but can only be viewed and accessed by the country's partners.

Data on vaccination (both doses or booster doses where relevant), outcomes, and other variables are directly reported by the vaccine recipient. To collect complete data reporting, some of the fields in the questionnaires were made compulsory. Questionnaires have been validated by dedicated and pharmacoviglance (PV)-trained persons who will correct and code all the information provided by the vaccinees. The dedicated personnel can also contact the vaccinees in case of inconsistency of the collected information or lack of important information, provided that the participant has given the consent to be contacted. Invalid/Incomplete questionnaires are excluded from the analyses.

Then, the LIM/RO questionnaires are pseudonymised and transformed into ICSR (Individual Case Safety Report) reports in an R3 format (or older version such as R2B, if needed), as described in Figure 2. The ICSR data can only be accessed and downloaded by the country of reference (the country that owns the data). For each partner working with a National Competent Authority (NCA) (e.g., regional PV centre), these reports are sent to the national reporting system and ultimately to

the EudraVigilance system (GVP module VI). These reports need to be checked for duplicates when reported to EudraVigilance. The process of sending ICSR reports, and duplicate checks is the responsibility of each country, based on national PV regulation.

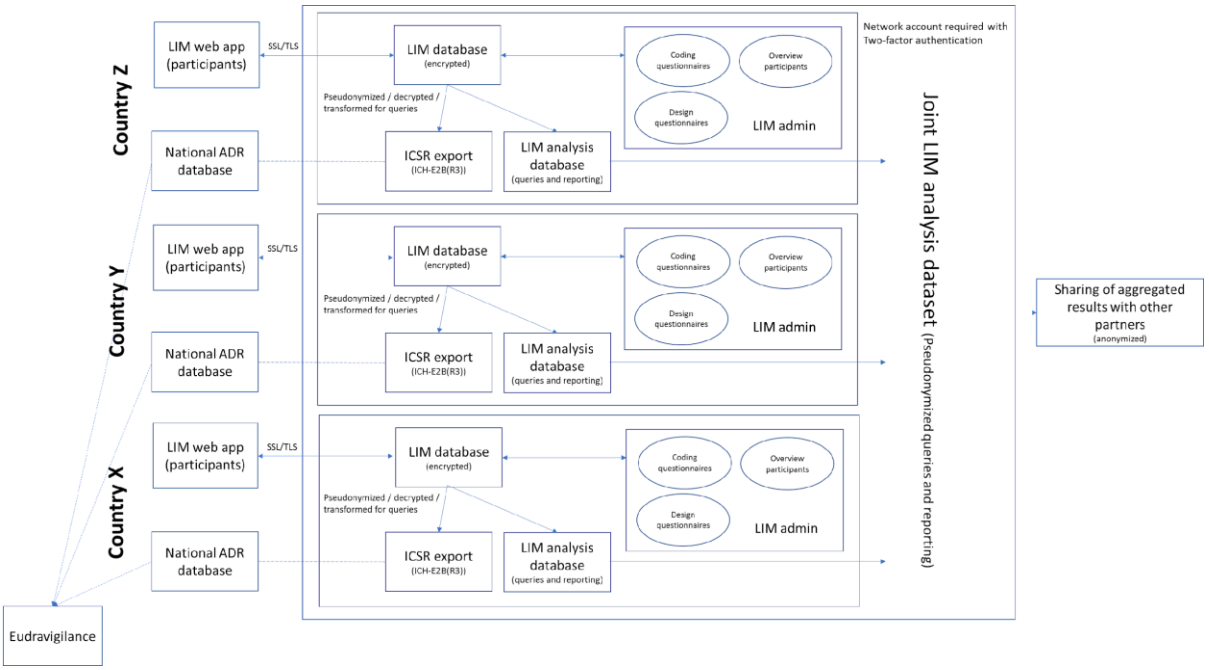



***Figure 2.*** *Data management of the LIM web app (the same applies to ResearchOnline web app) based on the Early-Covid-Vaccine-Monitor study protocol*

Record-based data in the LIM/RO database will be pooled to be shared with all partners at the end of data collection. These data will be harmonized across countries using the LIM/RO web apps, Germany using the SafeVac 2.0 app, and Croatia OPeN application for the collection of the core data at the same follow-up period. The data are currently pooled on an aggregated level, when comparable. Scripts are centrally developed and distributed for local deployment of data analysis. The aggregated results produced by these scripts are considered for pooled analysis using a dedicated dashboard. To perform stratified analyses on this data, countries not using the LIM/RO web apps use the same strata of interest definitions (e.g., age groups). The figure below (Figure 3) shows the key steps of the study project and the timing of the questionnaires in different scenarios (registration following the first dose of the first vaccination cycle or following the receipt of a booster dose).

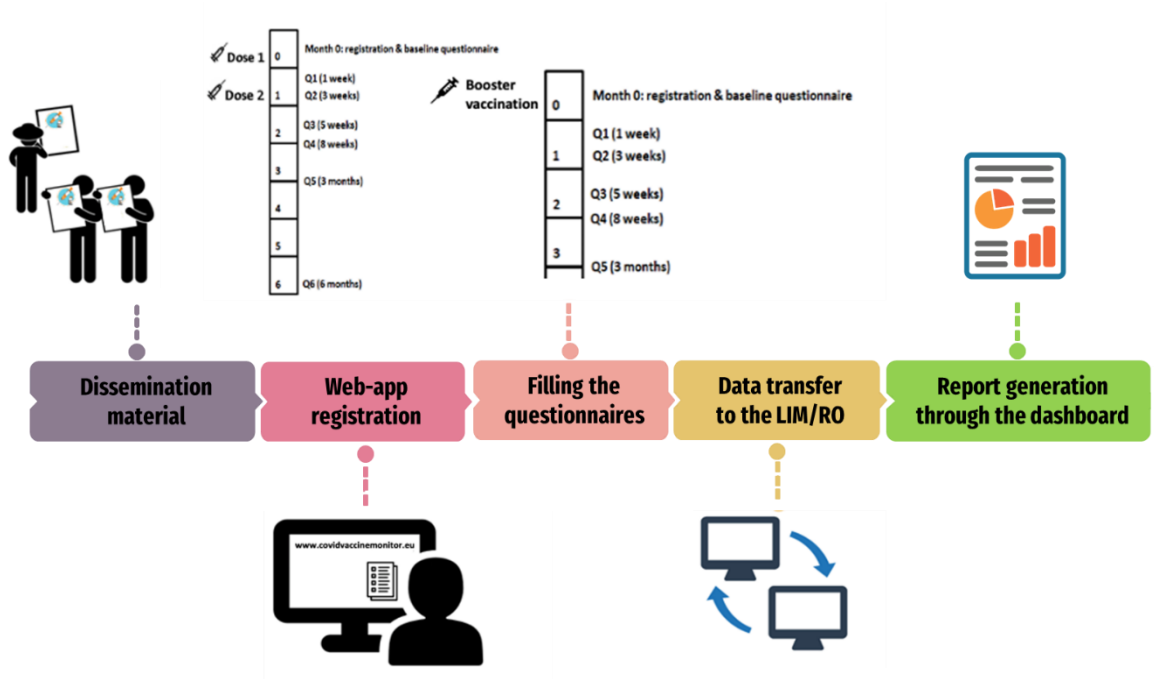



***Figure 3**. Key steps of the study projects and timing of the sending of the questionnaires*

### 1.7.5. Study size

**General target group (LIM)**

Each participating country originally aimed to include at least 2,000 vaccinees, with overall inclusions aiming to up to 39,000 vaccine recipients from 8 European countries

**Special Target groups (LIM and RO)**

Considering that the vaccination campaign status is strongly advanced at the current stage, each participating country originally stated to aim to include at least 1,000 vaccinees in total, independently from the special cohorts. The overall objective would be to include up to 60,000 vaccine recipients belonging to the special cohorts from the participating countries, with a maximum (based on the initial study's predicted calculation of inclusions) of up to 30,000 pregnant women, up to 10,000 children, up to 20,000 immunocompromised, up to 10,000 persons with a history of SARS-CoV-2 infection, and up to 5,000 with a history of allergies.

Study size of recruitment is dependind and will depend on underlying national population, national vaccination rate and phase of vaccination campaign at the moment the study started (e.g., immunocompromised patients have been already vaccinated all over Europe). Some countries have contacts with target groups organization or healthcare professional networks providing care to special cohorts, which helps the recruitment of specific categories of vaccines.

### 1.7.6. Data transformation

Record based data from all four systems is transformed into a common data model (CDM) for aggregated data. These aggregated datasets are divided into sub-sets of the following data: Risk factors, any ADR, any solicited ADR, any AESI, any serious ADR, list of ADR (solicited and unsolicited),

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

- Minors (children/adolescents): all participants <18years old
- Pregnant: as reported in medical history
- Immunosuppressed: as reported in medical history
- Allergy: as reported in medical history
- Prior COVID-19 infection: participants reporting a COVID-19 infection (both confirmed and not confirmed by a test)

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

### 1.7.7. Statistical methods

All data is provided to EMA monthly through an interactive POWERBI dashboard. Data provided are based on the cohort defined as all participants having filled the baseline questionnaire, having already received the vaccine and providing at least one questionnaire on possible adverse reactions.

**Main analyses**

A description of the population at inclusion is made by participating partners, comprising of the number of patients included in the cohort, distribution of gender, age categories, vaccine brands, and country.

For the general population and each special cohort, a dedicated cumulative structured overview of numbers and incidence of all adverse reactions per vaccine is provided, overall, and also stratified by vaccine brand, country, gender, and age group.

A specific Cohort Event Monitoring (WP1-2) statistical analysis plan (SAP) for the comparisons will be developed with WP3-4 (methods group). The ECDC overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA (ECDC, Technical Report, 29 March 2021) will be used to identify different implementation strategies in the different countries.

A comparison of incidence rates of AE between vaccine brands is controlled for these subgroup characteristics in case these are also associated with the AE of interest. We used standard epidemiological methods to obtain adjusted estimates (e.g., matching, standardization, weighting).

### 1.7.8. Quality control

The study is conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008 – available at:

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

## 1.8. Results: Monitoring of the general population receiving a first (and possibly second) dose of any COVID-19 vaccine

### 1.8.1. LIM and Croatian data sources

Among Belgium, Croatia, France, Italy, the Netherlands and the United Kingdom, a total of 30,119 participants were included in the dataset that was created with a data lock on the 9th of February 2022 for the LIM countries and 15th of February 2022 for Croatia. Included participants provided information on vaccine brand, gender, age and have completed at least one questionnaire on the presence or absence of adverse reactions. All countries have provided data on risk factors except for Germany, which will be provided at a later stage. Table 2 shows the number of included participants per country in the report from last months (November 2021, January 2022) and this month (data lock referred to February 2022).

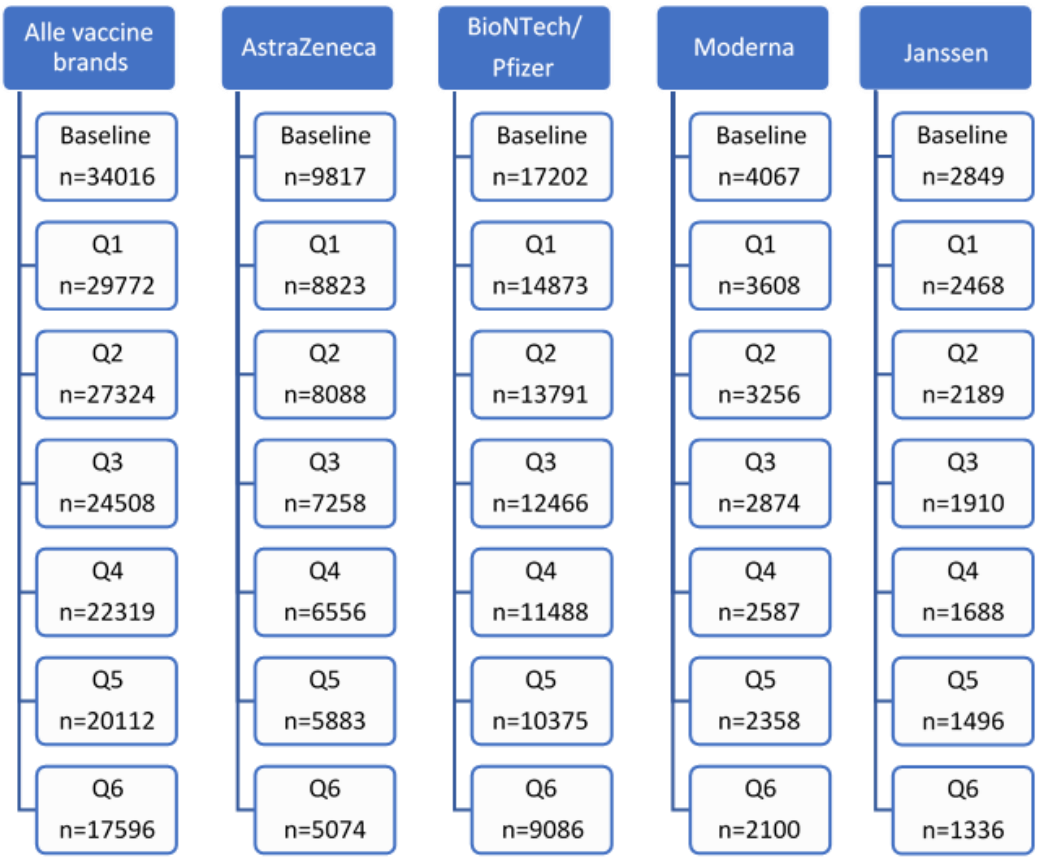



***Figure 4**. Grouped list representing the number of general population participants who filled in each questionnaire.*

Italy, France, and the UK have increased their inclusions compared to the previous month. Croatia, and Belgium have no new inclusions. Inclusions for Belgium have stopped after the ECVM project, but follow-ups will still be included in the CVM project. Croatia have not provided new data since the previous report. The first and second dose vaccination strategies of most countries are close to completion and the focus is now shifted to the booster/third dose, thus, the registration of new inclusions is slowing down.

***Table 2**. Goals for minimum number of inclusions and actual number of participants in April 2022 report (data lock referred to 9th of February 2022) compared to the number of participants in the previous reports.*

| General population | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Country** | **ECVM inclusions target** | **CVM inclusions target** | **November 2021 report** | **January 2022 report** | **April 2022 report** | **Tool** | **Recruitment start date** |
| Belgium | 1000 | - | 38 | 38 | 38 | LIM | 13/07/2021 |
| Croatia | 1000 | 2000 | 326 | 326 | 326 | OPeN | 15/02/2021 |
| France | 2000 | 4000 | 1052 | 1098 | 1166 | LIM | 14/06/2021 |
| Italy | 2000 | 4000 | 615 | 714 | 744 | LIM | 09/06/21 |
| Netherlands | 5000 | 12000 | 27590 | 27589 | 27626 | LIM | 01/02/2021 |
| United Kingdom | 1000 | 2000 | 161 | 207 | 219 | LIM | 23/06/2021 |
| **Total** | **12000** | **24000** | **29782** | **29972** | **30119** | | |

These 30.119 participants received vaccines from AstraZeneca, BioNtech/Pfizer, Janssen, or Moderna. Table 3 shows the distribution of the vaccine brands among the participants.

***Table 3.** Number of participants who received dose 1 and dose 2.*

| | **November 2021 report** | | **January 2022 report** | | **April 2022 report** | |
|---|---|---|---|---|---|---|
| **Vaccine brand** | **Dose 1** Number of participants (%) | **Dose 2** Number of participants (%) | **Dose 1** Number of participants (%) | **Dose 2** Number of participants (%) | **Dose 1** Number of participants (%) | **Dose 2** Number of participants (%) |
| AstraZeneca | 8871 (29.8) | 5601 (27.8) | 8871 (29.5) | 5603 (27.6) | 8875 (29.4) | 5610 (27.5) |
| BioNtech/Pfizer | 14835 (49.8) | 11830 (58.8) | 15011 (50.1) | 11989 (59.1) | 15117 (50.2) | 12109 (59.3) |
| Janssen | 2490 (8.4) | | 2490 (8.3) | | 2493 (12.0) | |
| Moderna | 3585 (12.0) | 2692 (13.4) | 3600 (12.0) | 2697 (13.3) | 3623 (8.3) | 2702 (13.2) |
| **Total** | **29781** | **20123** | **29972** | **20289** | **30108** | **20421** |

All data in this report is stratified by dose 1 and dose 2 information. The number of participants who have received dose 1 will always be higher than the number of participants who have received dose 2 (see Table 3). This can be due to participants becoming lost to follow-up before they respond to questionnaires related to dose 2, or the data lock point may take place before participants are asked to respond to questionnaires related to dose 2. Therefore, it should be kept in mind that the population represented by data in dose 2 is a subset of the population represented in dose 1 data.

Table 4 shows the age distribution of all participants in the study. For both doses, participants within the 70 – 79 age category was the most represented, with 18.3% of the first dose inclusions and 24.3% for the second dose inclusions belonging to that group. The reverse applies to the 0 – 19 age category,

with only 2.4% for the first dose inclusions and 1.5% for the second dose inclusions belonging to the youngest age group.

***Table 4.*** *Vaccinees, as % of total vaccinees, by age category.*

| General population | | |
|---|---|---|
| **Age category** | **Dose 1**<br>Number of participants (%) | **Dose 2**<br>Number of participants (%) |
| 0 - 19 years | 722 (2.4) | 316 (1.5) |
| 20 - 29 years | 3330 (11.1) | 1611 (7.9) |
| 30 - 39 years | 3928 (13.0) | 2190 (10.7) |
| 40 - 49 years | 4514 (15.0) | 2584 (12.7) |
| 50 - 59 years | 5402 (17.9) | 3143 (15.4) |
| 60 - 69 years | 2995 (9.9) | 2312 (11.3) |
| 70 - 79 years | 5510 (18.3) | 4967 (24.3) |
| 80+ years | 3707 (12.3) | 3298 (16.2) |
| **Total** | **30108** | **20421** |

When stratifying the data per country in the dashboard a clear variation in age distribution can be observed. For example, when looking at data from the Netherlands, a substantial drop in the age category of 60-69 years can be seen. In contrast, Italy, France, and the UK have an overall younger cohort with the majority of participants being in the 0 – 49 years of age. The UK even has 42.6% of its cohort within the age category 0-19. The variation in age distribution can be partly explained by the start date of inclusions per country. As most countries generally had similar vaccination strategies that were based on age, starting inclusions at different moments in time resulted in certain age demographics being overly represented. As the Netherlands started data collection early in their vaccination strategy, the age distribution is expected to be normal, however, a sudden drop is observed in the age category 60-69 years old. This can possibly be explained by this demographic being vaccinated at GP offices, where people were unlikely to come across dissemination material for the study. Age stratification per vaccine brand is illustrated in Figures 5 and 6.

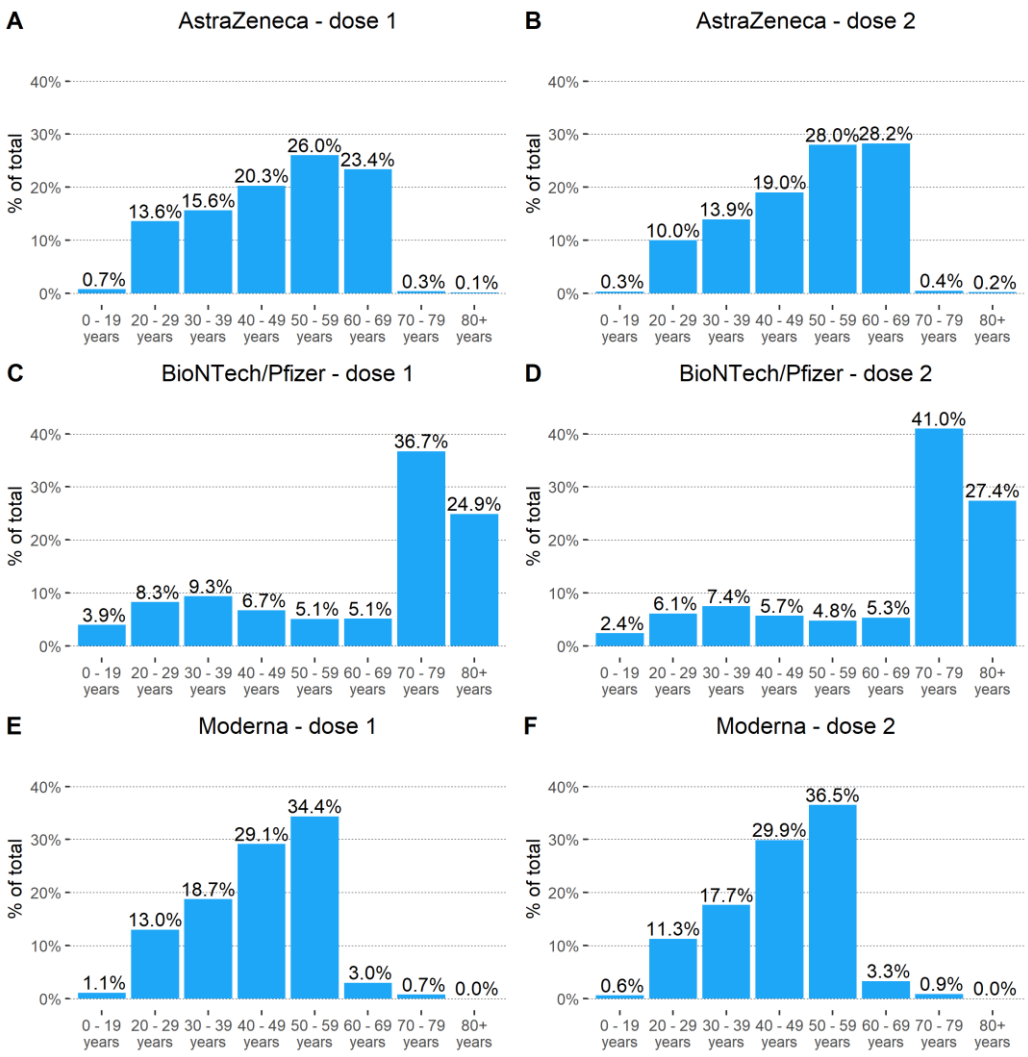



***Figure 5.*** *Vaccinees, as % of total vaccinees, by age category per 2-dose vaccine brand. Left: dose 1, right: dose 2*

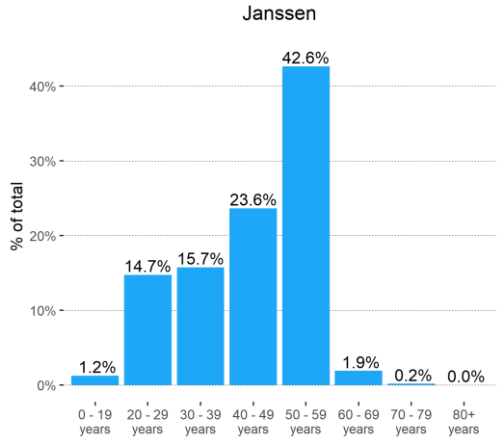



***Figure 6.*** *Vaccinees, as % of total vaccinees, by age category per 1-dose vaccine brand (Janssen).*

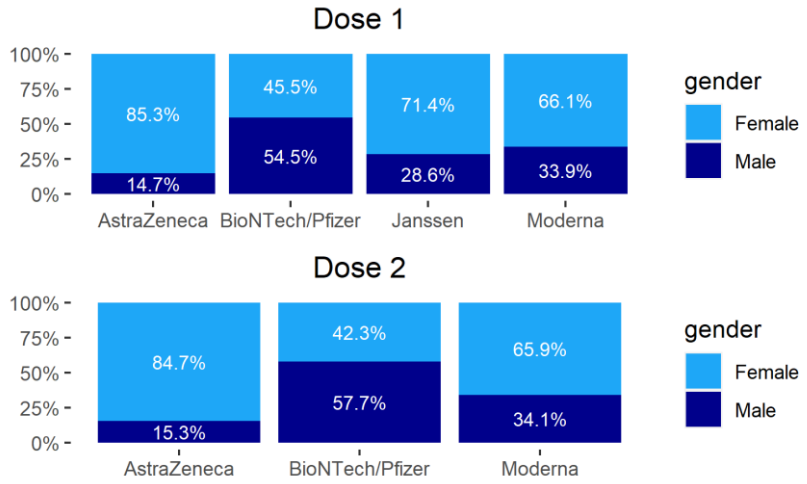



***Figure 7.*** *Vaccinees by gender, divided by dose.*

Gender stratification per vaccine brand is reported in Figure 7. The majority of participants are female with the exception of the BioNtech/Pfizer group. The higher female participation could be explained by the inclusion strategy of the Netherlands, which started their vaccination campaign with medical personnel. As a sizeable portion of the larger dataset consists of Dutch data, it might have influenced the aggregated distribution of male/female participation.

***Table 5.*** *Top three baseline risk factors as reported by participants per vaccine brand for April 2022 (referred to 9th of February 2022 data lock).*

| **April 2022 report** | | | |
|---|---|---|---|
| **AstraZeneca**<br>Number of participants (%) | **BioNtech/Pfizer**<br>Number of participants (%) | **Janssen**<br>Number of participants (%) | **Moderna**<br>Number of participants (%) |
| Vascular disorders<br>992 (21.6) | Vascular disorders<br>3864 (28.5) | Vascular disorders<br>164 (20.3) | Respiratory disorders<br>408 (20.9) |
| Respiratory disorders<br>867 (18.9) | Cardiac disorders<br>2666 (19.7) | Psychiatric disorders<br>134 (16.6) | Vascular disorders<br>260 (13.3) |
| Psychiatric disorders<br>460 (10.0) | Respiratory disorders<br>1500 (11.1) | Respiratory disorders<br>122 (15.1) | Psychiatric disorders<br>207 (10.6) |

Table 5 shows the top three reported baseline risk factors per vaccine brand for the current dataset. Vascular, psychiatric, and respiratory disorders are in the top three of all vaccine brands, that being in different orders.

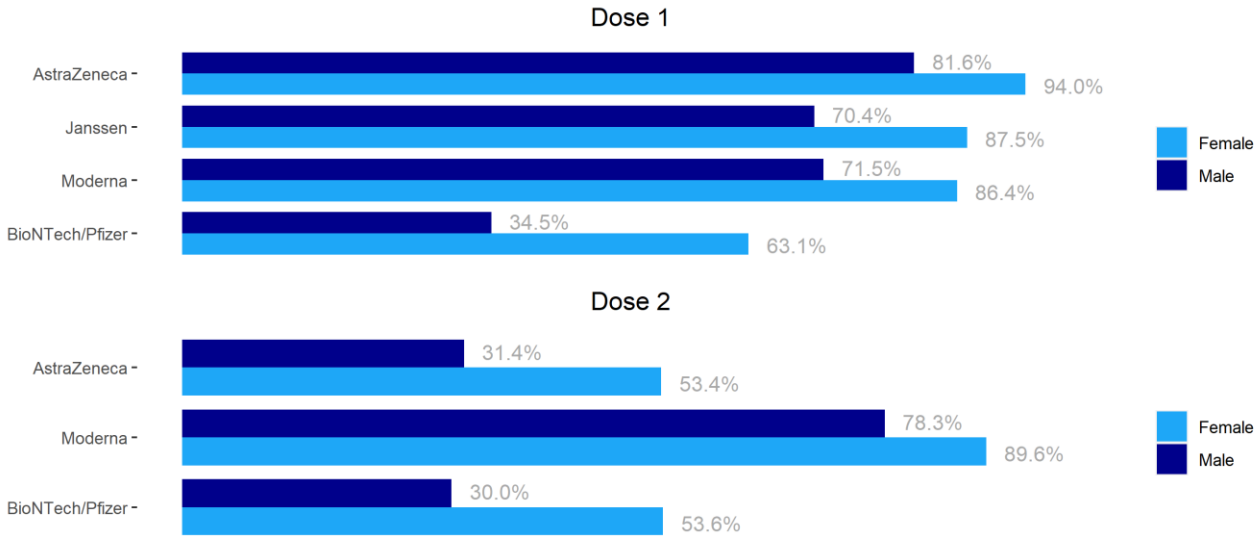



***Figure 8.*** *Any adverse reaction per gender for dose 1 and dose 2*

Figures 8 shows that female participants continue to have a higher rate of reporting any adverse reaction across all vaccine brands. Whether female participants are more likely to report an adverse reaction or whether they indeed experience more adverse reactions than male participants cannot be concluded from this data. Data might be affected by report bias, non-random dropout, and incomplete data.

In figure 9, the reporting of at least one ADR after the administration of dose 1 is stratified across age. The lowest reporting of ADRs can be observed in participants aged from 70 to 80+, this applies to each vaccine brand except BioNtech/Pfizer. Age group 0-19 years does show a slightly lower reporting of adverse reactions compared to the next oldest age group (20-29). This is the case across all vaccine brands, but is most pronounced in BioNtech/Pfizer (53.8%). For AstraZeneca, ADR reporting is high in participants aged 0-59, while reporting decreases in older age groups. Similar distributions apply for Janssen, Moderna and BioNtech/Pfizer, besides the previously mentioned expectations.

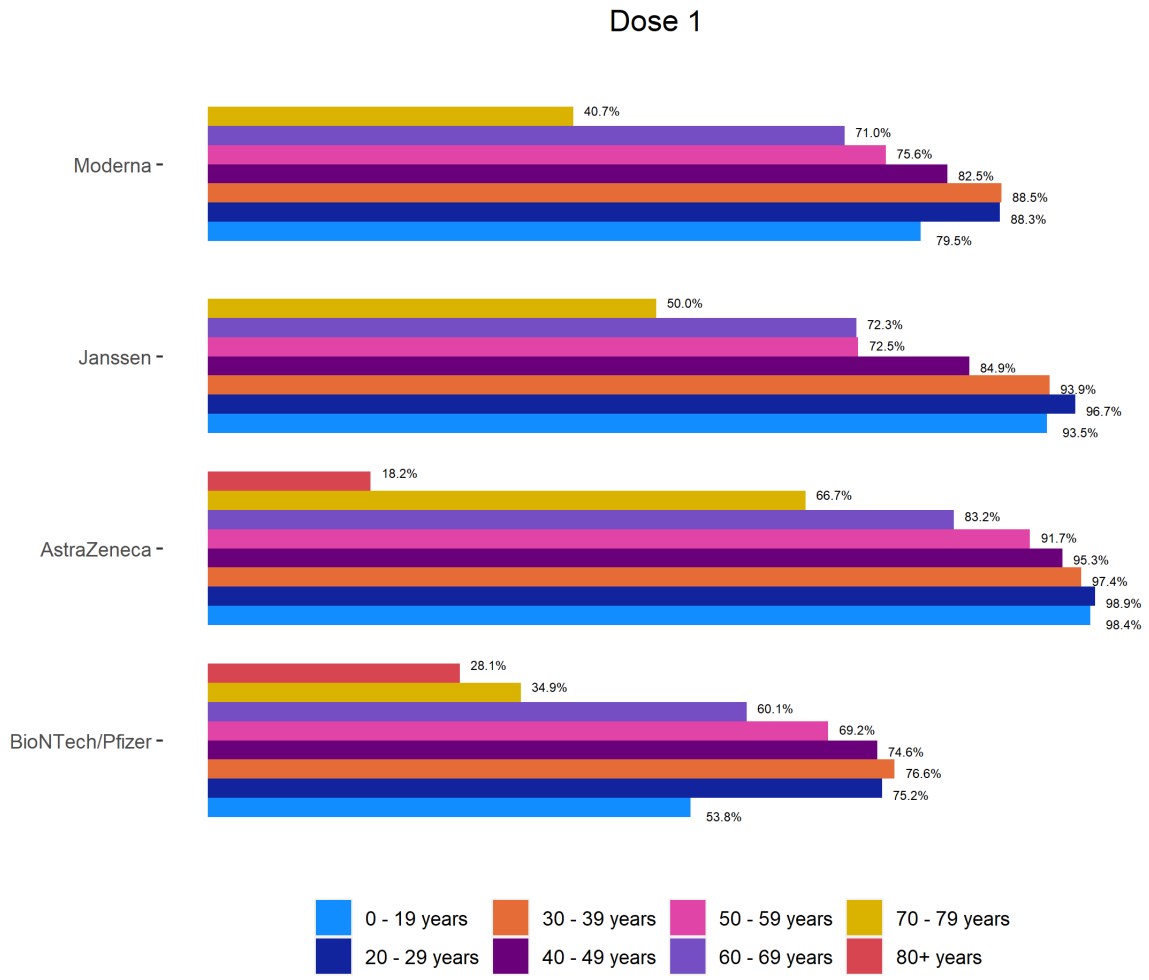



***Figure 9.*** *Any adverse reaction by age group after dose 1 of the different vaccines*

In figure 10, the reporting of at least one ADR after the administration of dose 2 is stratified across age. Participants of all vaccine brands that were within the age group 20-29 were most likely to report an ADR. Additionally, across all vaccine brands, we can observe that the older a participant is, the less likely they are to report an ADR. However, the latter statement does not apply to 0–19-year-olds, as ADR reporting is lower here when compared to the next age group (20-29).

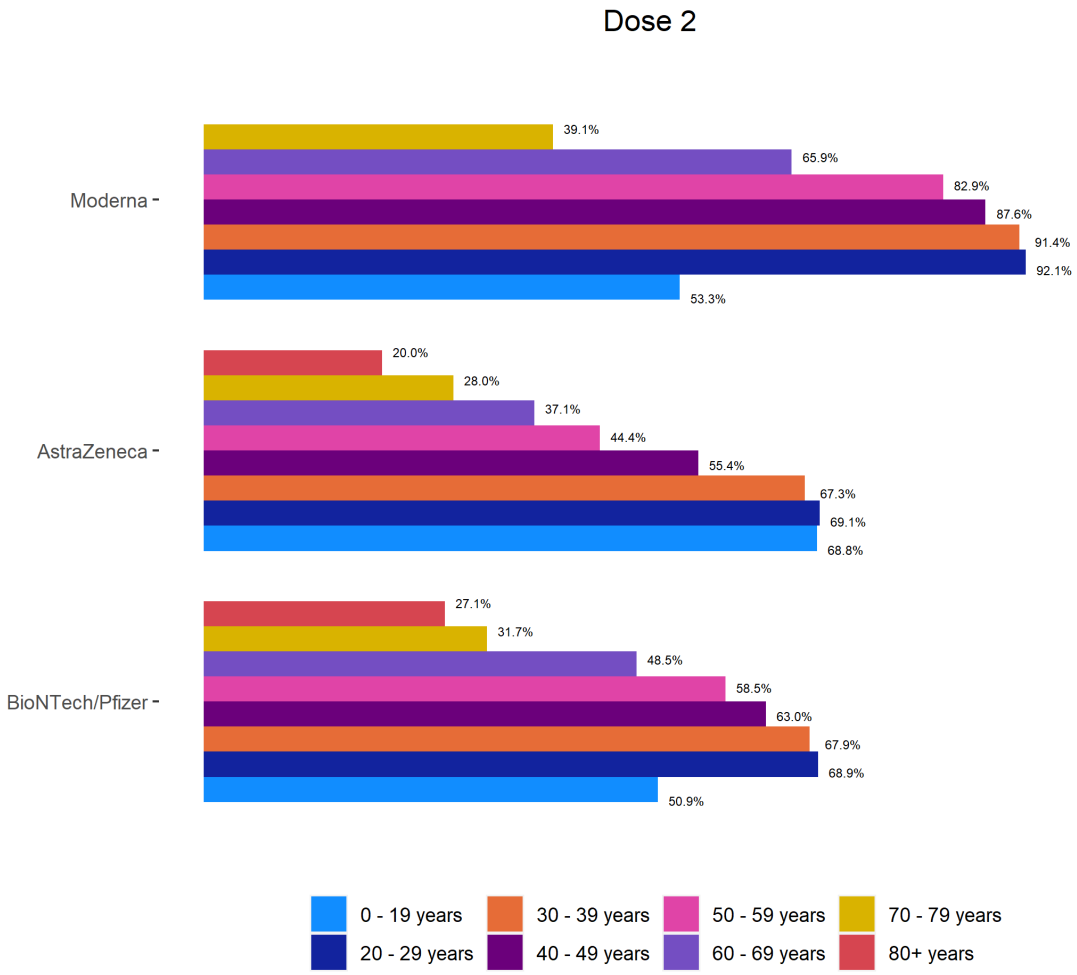



***Figure 10.*** *Any adverse reaction by age group after dose 2 of the different vaccines.*

In figures 9 and 10 all vaccine brands generally show lower reporting of any adverse reactions in older participants compared to younger participants. These gradual age-related differences are observed when considering all adverse reactions and when specifically looking at the solicited adverse reactions after the first dose. Stratifying the 0-19 age group into smaller age categories would give insight into the lower reporting of any ADR of this age group in comparison to the next age group. However, the numbers might currently be too low to allow for this.

The most commonly reported solicited local adverse reaction, across all vaccine brands, was injection site pain. The solicited systemic adverse reactions varied somewhat across vaccine brands. The solicited local and systemic adverse reactions are summarized in table 6.

***Table 6.*** *Local and systemic solicited adverse reactions by vaccine brand reported after dose 1.*

| **Subjects with at least one adverse reaction** | **Moderna (N=3623)** | **AstraZeneca (N=8875)** | **BioNTech/Pfizer (N=15118)** | **Janssen (N=2493)** |
|---|---|---|---|---|
| Number of participants (%) | 2946 (81.3) | 8180 (92.2) | 7183 (47.5) | 2059 (82.6) |
| **Local solicited adverse reaction (MedDRA PT)** Number of participants (%) | | | | |
| I.s. erythema | 372 (10.3) | 765 (8.6) | 254 (1.7) | 98 (3.9) |
| I.s. haematoma | 188 (5.2) | 484 (5.5) | 262 (1.7) | 113 (4.5) |
| I.s. induration | 99 (2.7) | 93 (1.05) | 54 (0.4) | 9 (0.4) |
| I.s. inflammation | 748 (20.6) | 1805 (20.3) | 786 (5.2) | 264 (10.6) |
| I.s. pain | 1840 (50.8) | 4500 (50.7) | 3752 (24.8) | 853 (34.2) |
| I.s. pruritus | 202 (5.6) | 360 (4.06) | 156 (1.0) | 43 (1.7) |
| I.s. reaction | 2 (0.06) | 7 (0.08) | 15 (0.1) | 1 (0.04) |
| I.s. swelling | 641 (17.7) | 1596 (18.0) | 769 (5.1) | 268 (10.8) |
| I.s. warmth | 500 (13.8) | 1155 (13.0) | 489 (3.2) | 154 (6.2) |
| **Systemic solicited adverse reactions (MedDRA PT)** Number of participants (%) | | | | |
| Arthralgia | 310 (8.6) | 2620 (29.5) | 625 (4.1) | 502 (20.1) |
| Chills | 447 (12.3) | 5011 (56.5) | 670 (4.4) | 937 (37.6) |
| Fatigue | 1210 (33.4) | 5498 (61.9) | 2690 (17.8) | 1318 (52.9) |
| Headache | 879 (24.3) | 5870 (66.1) | 1890 (12.5) | 1295 (51.9) |
| Malaise | 900 (24.8) | 5594 (63.0) | 1601 (10.6) | 1211 (48.6) |
| Myalgia | 1245 (34.4) | 5033 (56.7) | 2551 (16.9) | 1068 (42.8) |
| Nausea | 402 (11.1) | 2409 (27.1) | 683 (4.5) | 505 (20.2) |
| Body temperature increased | 110 (3.0) | 540 (6.1) | 141 (0.9) | 138 (5.5) |
| Pyrexia | 302 (8.3) | 3746 (42.2) | 372 (2.5) | 764 (30.6) |
| Hyperpyrexia | 1 (0.03) | 83 (0.9) | 1 (0.01) | 12 (0.5) |
| Dizziness | 54 (1.5) | 273 (3.1) | 162 (1.1) | 62 (2.5) |
| Diarrhoea | 47 (1.3) | 115 (1.3) | 124 (0.8) | 36 (1.4) |

Although most participants experience an adverse reaction, the vast majority of these are not flagged as serious or AESI. Of the 30108 participants who had received a first dose of a COVID-19 vaccine, 48 (0.2%) reported at least one serious adverse reaction after receiving the first dose. This rate varied only slightly per vaccine brand with 6 (0.2%) and 23 (0.3%) of participants receiving Moderna and AstraZeneca respectively reported experiencing at least one serious adverse reaction, while this rate was slightly lower for BioNTech/Pfizer at 20 (0.1%) and for Janssen 2 (0.1%) subjects reporting at least one serious reaction. Stratifying by age group and gender, as is shown in table 7, leads to very small groups, however focusing on age group stratification on all vaccine brands shows the majority of serious adverse reactions being reported by the age group 60 - 69years old: 10 (20.8%) of the 48 reports were in this age group. Most of these serious adverse reactions in this group were reported by subjects who had received AstraZeneca: 8 of the 10 reported serious adverse reactions in this age category. Stratifying the 48 reported serious adverse reactions by gender show that 12 (25.0%) were reported by men while 36 (75.0%) were reported by women. The majority of these 36 reports by women were subjects who had received the AstraZeneca vaccine.

Table 8 indicates the type of reported serious ADRs following the first or second dose by COVID-19 vaccine for both LIM countries and Croatia.

***Table 7.*** *Any serious adverse reaction per dose 1 and dose 2 per age and gender.*

| | **COVID-19 vaccine manufacturer** | | | | |
|---|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer** | **Janssen** | **Moderna** | **Total vaccines** |
| **Dose 1** Number of participants (%) | | | | | |
| **Subjects with at least one serious adverse reaction** Number of participants | **23** | **20** | **2** | **6** | **48** |
| 0 - 19 years | 1 (5.0) | 1 (5.0) | 0 | 0 | 2 (4.2) |
| 20 - 29 years | 1 (5.0) | 1 (5.0) | 0 | 2 (33.3) | 4 (8.3) |
| 30 - 39 years | 3 (15.0) | 3 (15.0) | 2 (100.0) | 0 | 8 (16.7) |
| 40 - 49 years | 2 (10.0) | 5 (25.0) | 0 | 2 (33.3) | 9 (18.8) |
| 50 - 59 years | 5 (25.0) | 0 | 0 | 0 | 5 (10.4) |
| 60 - 69 years | 8 (40.0) | 0 | 0 | 2 (33.3) | 10 (20.8) |
| 70 - 79 years | 0 | 6 (30.0) | 0 | 0 | 6 (12.5) |
| 80+ years | 0 | 4 (20.0) | | | 4 (8.3) |
| Male | 3 (15.0) | 6 | 0 | 3 (50.0) | 12 (25.0) |
| Female | 17 (85.0) | 14 | 2 | 3 (50.0) | 36 (75.0) |
| **Dose 2** Number of participants (%) | | | | | |
| **Subjects with at least one serious adverse reaction** Number of participants | **4** | **14** | | **4** | **22** |
| 0 - 19 years | 0 | 1 (7.1) | | 0 | 1 (4.5) |
| 20 - 29 years | 0 | 0 | | 0 | 0 |
| 30 - 39 years | 1 (25.0) | 1 (7.1) | | 2 (50.0) | 4 (18.2) |
| 40 - 49 years | 0 | 0 | | 1 (25.0) | 1 (4.5) |
| 50 - 59 years | 2 (50.0) | 1 (7.1) | | 1 (25.0) | 4 (18.2) |
| 60 - 69 years | 1 (25.0) | 3 (21.4) | | 0 | 4 (18.2) |
| 70 - 79 years | 0 | 4 (28.6) | | 0 | 4 (18.2) |
| 80+ years | 0 | 4 (28.6) | | | 4 (18.2) |
| Male | 0 | 7 (50.0) | | 0 | 7 (31.8) |
| Female | 4 | 7 (50.0) | | 4 (100.0) | 15 (68.2) |

***Table 8.*** *List of reported serious Adverse Reactions following the first or second dose by COVID-19 vaccine for LIM countries and Croatia.*

| COVID-19 vaccine manufacturer | Reported serious adverse reactions | Dose 1 | Dose 2 |
|---|---|---|---|
| AstraZeneca | Abdominal discomfort | 1 | |
| | Abortion missed | 1 | |
| | Abortion spontaneous | | 1 |
| | Acute myocardial infarction | 1 | 1 |
| | Angina pectoris | 1 | |
| | Arrhythmia | 1 | |
| | Asthma | 1 | |
| | Atrial fibrillation | 1 | |
| | Breast cancer | | 1 |
| | Cerebral infarction | 1 | |
| | Diarrhoea | 1 | |
| | Dyspnoea | 3 | |
| | Epilepsy | 1 | |
| | Gastric ulcer | 1 | |
| | Headache | 1 | |
| | Hyperpyrexia | 1 | |
| | Malaise | 2 | |
| | Muscle spasms | 1 | |
| | Myalgia | 1 | |
| | Myocardial infarction | | 1 |
| | Nausea | 1 | |
| | Other medically important condition | 1 | |
| | Pulmonary embolism | 2 | |
| | Pulmonary pain | 1 | |
| | Pyrexia | 2 | |
| | Rash pruritic | 1 | |
| | Respiratory arrest | 1 | |
| | Retinal detachment | 1 | |
| | Vitreous floaters | 1 | |
| BioNTech/Pfizer | Abortion spontaneous | 2 | |
| | Atrioventricular block complete | 1 | |
| | Blood loss anaemia | | 1 |
| | Cerebrovascular accident | 1 | |
| | Chills | 1 | |
| | Colitis | 1 | |
| | Diarrhoea | 1 | |
| | Dysentery | 1 | |
| | Dyspnoea | 2 | 1 |
| | Epistaxis | 1 | |
| | Eye haemorrhage | | 1 |
| | Fall | | 1 |
| | Fatigue | 2 | |
| | Haematochezia | | 1 |
| | Headache | 2 | |
| | Herpes zoster | | 1 |
| | Hyperpyrexia | 1 | 1 |
| | Hypersensitivity | 2 | |
| | Hypertension | | 1 |
| | Injection site pain | 1 | |
| | Internal haemorrhage | | 1 |
| | Lacunar infarction | | 1 |
| | Malaise | | 1 |
| | Muscle spasms | 1 | |
| | Myocardial infarction | 2 | 1 |
| | Nausea | 2 | |
| | Other medically important condition | 2 | 1 |

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

Of the 30,108 participants who had received a first dose of any COVID-19 vaccine, 61 (0.2%) subjects reported experiencing at least one AESI between their first and second dose of the vaccine. The majority of these AESI were reported by the age group 50 – 59 years with 15 (24.6%) participants reporting an AESI, followed by the age group 30 – 39 years with 11 (18.0%) participants. The participants in the age group 50 – 59 years, who reported an AESI, most received the AstraZeneca vaccine followed by the Janssen vaccine: 6 of the 15 reports. The younger participants in the 30 – 39 years old age group, 5 of the 11 reports of an AESI received the BioNTech/Pfizer vaccine. Table 10 shows the type of reported AESI's following the first or second dose by COVID-19 vaccine for LIM countries and Croatia.

***Table 9.*** *Any AESI per dose 1 and dose 2 per age and gender*

| | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer** | **Janssen** | **Moderna** | **Total vaccines** |
| **Dose 1** Number of participants (%) | | | | | |
| **Subjects with at least one AESI** Number of participants | **28** | **22** | **8** | **3** | **61** |
| 0 - 19 years | 1 (3.6) | 0 | 0 | 0 | 1 (1.6) |
| 20 - 29 years | 5 (17.9) | 2 (9.1) | 0 | 1 (33.3) | 8 (13.1) |
| 30 - 39 years | 3 (10.7) | 5 (22.7) | 2 (25.0) | 1 (33.3) | 11 (18.0) |
| 40 - 49 years | 5 (17.9) | 2 (9.1) | 1 (12.5) | 0 | 8 (13.1) |
| 50 - 59 years | 6 (21.4) | 3 (13.6) | 5 (62.5) | 1 (33.3) | 15 (24.6) |
| 60 - 69 years | 8 (28.6) | 1 (4.5) | 0 | 0 | 9 (14.8) |
| 70 - 79 years | 0 | 6 (27.3) | 0 | 0 | 6 (9.8) |
| 80+ years | 0 | 3 (13.6) | 0 | 0 | 3 (4.9) |
| Male | 4 (14.3) | 6 (27.3) | 0 | 3 (100.0) | 13 (21.3) |
| Female | 24 (85.7) | 16 (72.7) | 8 (100.0) | 0 | 48 (78.7) |
| **Dose 2** Number of participants (%) | | | | | |
| **Subjects with at least one AESI** Number of participants | **31** | **27** | **NA** | **10** | **68** |
| 0 - 19 years | 0 | 1 (3.7) | | 0 | 1 (1.5) |
| 20 - 29 years | 4 (12.9) | 0 | | 3 (30.0) | 7 (10.3) |
| 30 - 39 years | 5 (16.1) | 3 (11.1) | | 0 | 8 (11.8) |
| 40 - 49 years | 4 (12.9) | 3 (11.1) | | 2 (20.) | 9 (13.2) |
| 50 - 59 years | 12 (38.7) | 0 | | 5 (50.0) | 17 (25.0) |
| 60 - 69 years | 6 (19.4) | 1 (3.7) | | 0 | 7 (10.3) |
| 70 - 79 years | 0 | 13 (48.1) | | 0 | 13 (19.1) |
| 80+ years | 0 | 6 (22.2) | | 0 | 6 (8.8) |
| Male | 1 (3.2) | 15 (56.6) | | 3 (30.0) | 19 (27.9) |
| Female | 30 (96.8) | 12 (44.4) | | 7 (70.0) | 49 (72.1) |

***Table 10.*** *List of reported AESI's following the first or second dose by COVID-19 vaccine for LIM countries and Croatia.*

| COVID-19 vaccine manufacturer | Reported AESI | 1st dose | 2nd dose |
|---|---|---|---|
| AstraZeneca | Acute myocardial infarction | 1 | 1 |
| | Arrhythmia | 5 | 4 |
| | COVID-19 | 6 | 22 |
| | Epilepsy | 2 | 1 |
| | Facial paralysis | 1 | |
| | Facial paresis | 1 | |
| | Hypersensitivity | 7 | 2 |
| | Hypersomnia | | 1 |
| | Myocardial infarction | | 1 |
| | Product administration error | | 1 |
| | Pulmonary embolism | 2 | |
| | Respiratory arrest | 1 | |
| | Thrombosis | 1 | |
| | Vasculitis | 1 | |
| BioNTech/Pfizer | Anaphylactoid reaction | 1 | |
| | Arrhythmia | 2 | 9 |
| | Atrioventricular block complete | 1 | |
| | Cerebrovascular accident | 1 | |
| | COVID-19 | 6 | 6 |
| | Deep vein thrombosis | | 2 |
| | Epilepsy | | 1 |
| | Hypersensitivity | 6 | 5 |
| | Myocardial infarction | 2 | 1 |
| | Myocarditis | 1 | |
| | Pericarditis | 1 | 1 |
| | Petit mal epilepsy | 1 | |
| | Pulmonary embolism | | 1 |
| | Respiratory distress | 1 | |
| | Seizure | | 1 |
| Janssen | Anaphylactic reaction | 1 | |
| | COVID-19 | 5 | |
| | Generalised tonic-clonic seizure | 1 | |
| | Product administration error | 1 | |
| Moderna | Arrhythmia | | 3 |
| | COVID-19 | | 1 |
| | Deep vein thrombosis | | 1 |
| | Epilepsy | 1 | 1 |
| | Facial paralysis | | 1 |
| | Hypersensitivity | 1 | 1 |
| | Hypersomnia | 1 | 1 |
| | Platelet count decreased | | 1 |

## 1.8.2. Germany general population

The German partners were able to provide a batch of Moderna data in May 2021, a batch of AstraZeneca data in September 2021, and a new batch containing BioNTech/Pfizer data in March 2022. As the last data lock and dashboard update took place in February 2022, the most recent BioNTech/Pfizer dataset could not be included in the dashboard. Due to this and some concerns related to comparability of the current datasets from Germany with other countries, the German data is presented separately in this report.

***Table 11.*** *Expected and total inclusions until March 2022 in Germany*

| Country | Partner | Expected inclusions ECVM | Expected inclusions CVM | Total inclusions ECVM and CVM | Tool | Recruitment start date |
|---|---|---|---|---|---|---|
| Germany | Paul Ehrlich Institute (PEI) | 5000 | 15000 | 520,076 | SafeVac 2.0 | 27/12/2020 |

Germany exceeded the expectation of 5,000 inclusions for ECVM and the 15,000 inclusions for CVM by including a total of 520,076 inclusions. Of the 520,076 inclusions, 80,510 (15.5%) received the AstraZeneca vaccine, 420,622 (80.9%) received the BioNTech/Pfizer vaccine and 18944 (3.6%) received the Moderna vaccine. Table 10 indicates that of the 520,076 inclusions, 373754 (71.9%) have also provided information on the second dose.

***Table 12.*** *Number of participants who received dose 1 and dose 2 in Germany*

| Vaccine brand | Dose 1<br>Number of participants (%) | Dose 2<br>Number of participants (%) |
|---|---|---|
| AstraZeneca | 80510 (15.5) | 49957 (13.4) |
| BioNtech/Pfizer | 420622 (80.9) | 316572 (84.7) |
| Moderna | 18944 (3.6) | 7225 (1.9) |
| **Total** | **520076** | **373754** |

Stratifying all inclusions from Germany by age category shows that the 20 – 29 years and 30 -39 years categories participated most at 21.1% and 23.4% respectively. The distribution of the inclusions in the different age categories is similar for both dose 1 and dose 2 data.

***Table 13.*** *Vaccinees, as % of total vaccinees, by age category in Germany*

| Age category | Dose 1<br>Number of participants (%) | Dose 2<br>Number of participants (%) |
|---|---|---|
| 0 - 19 years | 17667 (3.4) | 10364 (2.8) |
| 20 - 29 years | 109653 (21.1) | 75150 (20.1) |
| 30 - 39 years | 121791 (23.4) | 84157 (22.5) |
| 40 - 49 years | 98350 (18.9) | 71137 (19.0) |
| 50 - 59 years | 94382 (18.1) | 69179 (18.5) |
| 60 - 69 years | 54231 (10.4) | 46387 (12.4) |
| 70 - 79 years | 18914 (3.6) | 14288 (3.8) |
| 80+ years | 5088 (1.0) | 3092 (0.8) |
| **Total** | **520076** | **373754** |

While table 13 is indicative of a general young population being included in the monitoring study, further stratification of the age categories into vaccine brands shows varying distributions (Figure 11). While the participants receiving the first dose of AstraZeneca are spread almost equally across all age categories, the majority of participants receiving the first dose of BioNTech/Pfizer or Moderna are much younger.

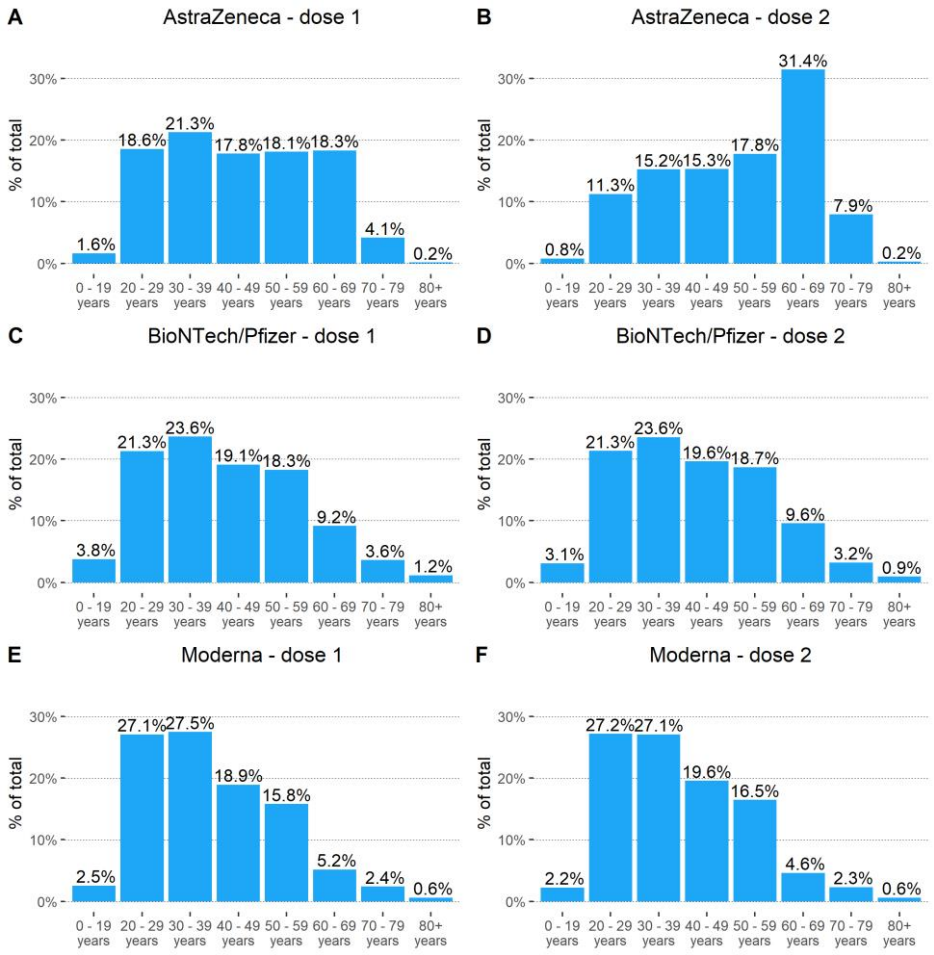



***Figure 11.*** *Vaccinees, as % of total vaccinees, by age category per 2-dose vaccine brand. Left: dose 1, right: dose 2, in germany*

Stratifying the data by vaccine brand and gender is summarized in Figure 12. Both dose 1 and dose 2 for AstraZeneca and BioNTech/Pfizer is equally distributed across the gender's 'male' and 'female'. Participants receiving the Moderna vaccine are almost equally distributed in the dose 1 data, however there is a slight shift in the dose 2 data: 61.1% of all participants receiving the Moderna vaccine who have provided dose 2 information are female.

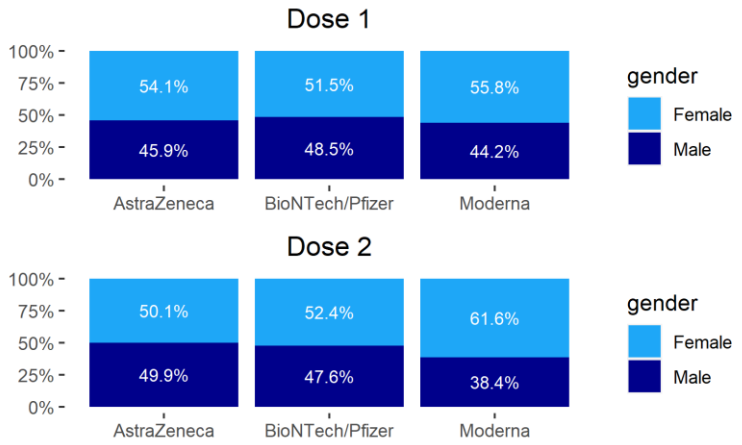



***Figure 12.*** *Vaccinees by gender, divided by dose in Germany*

Figures 13 and 14 show participants reporting at least one adverse reaction after dose 1 and dose 2 respectively. Participants receiving AstraZeneca and BioNTech/Pfizer are more likely to report at least one adverse reaction, with the highest reporting rate in the age category 20 – 29 years: 80.2% of all participants receiving BioNTech/Pfizer reported at least one adverse reaction in this age category and 86.9% of participants receiving Moderna reported at least one adverse reaction. The older the participant, the less likely they are to report an adverse reaction. The lowest reporting rates are found in the 70 – 79 years and 80 years and older age category: 51.6% and 42.2%, respectively, for participants receiving BioNTech/Pfizer and 49.9% and 49.2%, respectively, for those who received AstraZeneca. Participants receiving the Moderna vaccine were much less likely to report an adverse reaction with the 50 – 59 years age category having the highest report rate: 41.5% of this group reported at least one adverse reaction.

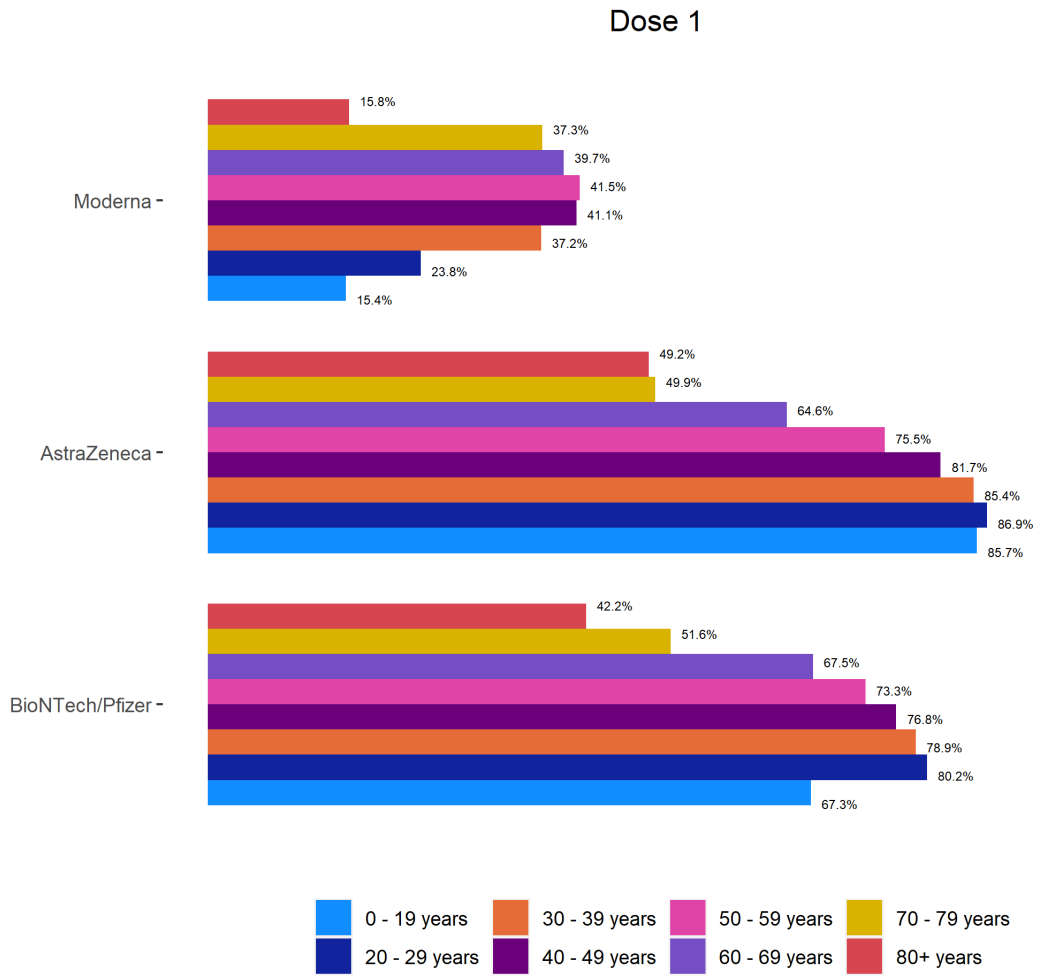



***Figure 13.*** *Participants reporting at least one adverse reaction after dose 1 per vaccine brand and age category in Germany*

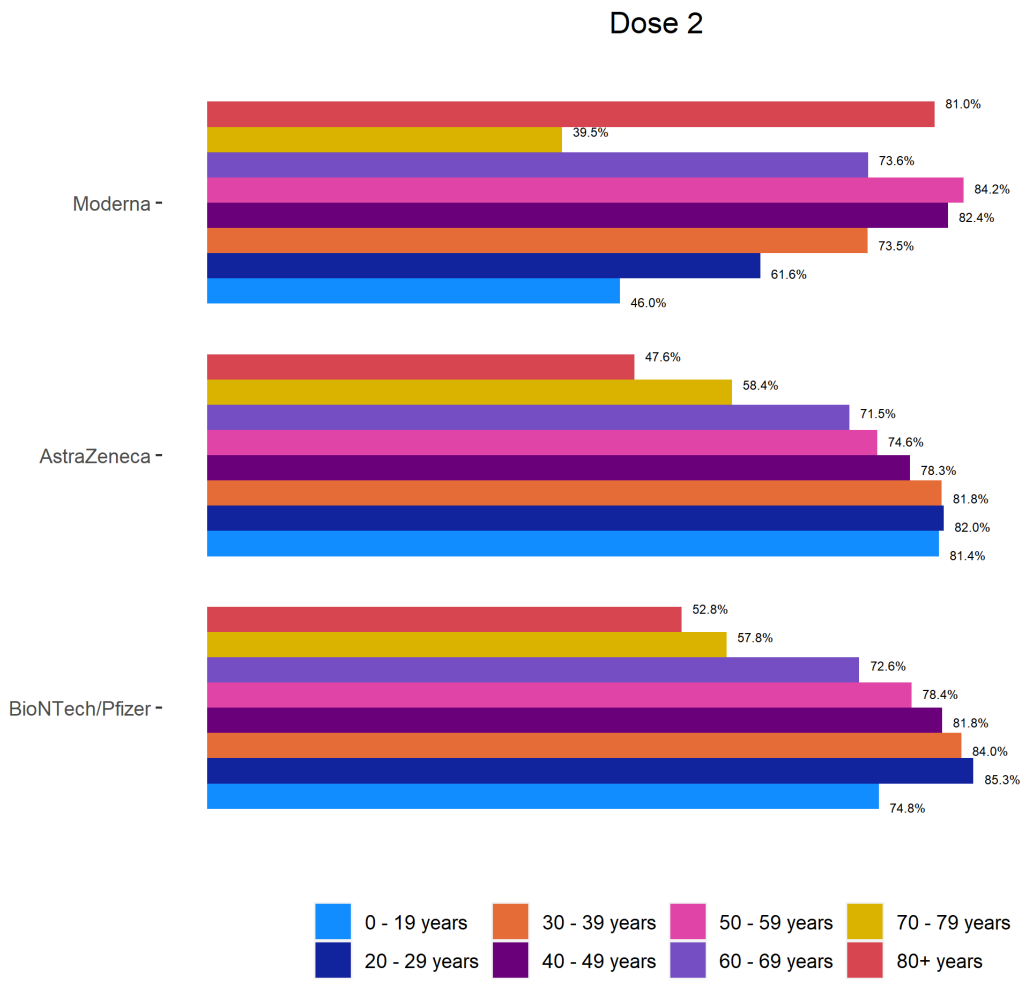



***Figure 14.*** *Participants reporting at least one adverse reaction after dose 2 per vaccine brand and age category in Germany*

Figure 14 shows a very similar reporting rate of ADRs for both BioNTech/Pfizer and AstraZeneca after the second dose: younger participants are more likely to report at least one adverse reaction. When comparing the reporting rate between dose 1 and dose 2, reporting of at least one adverse reaction is equal or slightly higher after dose 2, across all age categories for BioNTech/Pfizer and AstraZeneca. Participants receiving Moderna, however, are much more likely to report an adverse reaction after dose 2 when compared to dose 1. While 41.5% of 50 – 59-year-old report an adverse reaction after dose 1, 84.2% report at least one adverse reaction after dose 2.

Table 14 summarizes the solicited adverse reactions, both local and systemic, after dose 1 of the different vaccine brands. The most commonly reported solicited adverse reaction is injection site pain: 64.6% of all BioNTech/Pfizer participants reported this adverse reaction after dose 1. More than half of participants receiving AstraZeneca also reported this reaction after dose 1, however participants who receiving Moderna were much less likely to report this. Injection site swelling was reported less often across all vaccine brands. Fatigue and headache were the most commonly reported solicited adverse reaction after dose 1 across all vaccine brands: 53.3% and 52.2% respectively for participants who received AstraZeneca, 46.1% and 35.8% respectively for those who received BioNTech/Pfizer. Only 14.8% of participants who received Moderna reported experiencing fatigue, 13.3% of these participants reported headache.

***Table 14.*** *Solicited adverse reactions by vaccine brand after dose 1.*

| Type of adverse reaction | Moderna | AstraZeneca | BioNTech/Pfizer |
|---|---|---|---|
| **Local solicited adverse reaction (MedDRA PT)** Number of participants (%) | | | |
| Injection site pain | 3978 (21.0) | 42793 (53.2) | 271635 (64.6) |
| Injection site swelling | 1754 (9.3) | 10000 (12.4) | 60258 (14.3) |
| **Systemic solicited adverse reactions (MedDRA PT)** Number of participants (%) | | | |
| Arthralgia | 761 (4.0) | 17613(21.9) | 43231 (10.3) |
| Chills | 573 (3.0) | 26835 (33.3) | 42612 (10.1) |
| Fatigue | 2808 (14.8) | 42930 (53.3) | 193782 (46.1) |
| Headache | 2513 (13.3) | 42033 (52.2) | 150385 (35.8) |
| Malaise | 1346 (7.1) | 26557 (33.0) | 81357 (19.3) |
| Myalgia | 1489 (7.9) | 25032 (31.1) | 82493 (19.6) |
| Nausea | 535 (2.8) | 10867 (13.5) | 28525 (6.8) |
| Pyrexia | 526 (2.8) | 24639 (30.6) | 40647 (9.7) |
| Diarrhoea* | 355 (1.9) | 3546 (4.4) | 16975 (4.0) |
| Dizziness* | 948 (5.0) | 16783 (20.8) | 52784 (12.5) |

*Solicited adverse reactions not included in protocol

Data related to serious adverse events and AESI from Germany could only be stratified on gender at the time of writing and not additionally on age group. Additionally, serious adverse events have not been coded by an assessor but are the seriousness as reported by the participant. Therefore, it is currently not possible to compare German data concerning seriousness with data from the other partners in WP1. Of the 520,076 participants from Germany who had received the first dose of a COVID-19 vaccine, 1,838 (0.3%) reported experiencing at least one serious adverse reaction. A total of 1,191 (0.2%) and 39 (0.2%) participants receiving BioNTech/Pfizer and Moderna respectively reported experiencing a serious adverse reaction while 608 (0.7%) receiving AstraZeneca reported a serious reaction, since age and gender may differ these crude rates cannot be directly compared. Most of the reported serious adverse reactions after AstraZeneca and Moderna were described by women: 425 (69.9%) and 28 (71.8%) respectively.

***Table 15.*** *Any serious adverse reaction per dose 1 and dose 2 per age and gender.*

| | COVID-19 vaccine manufacturer | | | |
|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer** | **Moderna** | **Total vaccines** |
| **Dose 1** Number of participants (%) | | | | |
| **Subjects with at least one serious adverse event** Number of participants | **608** | **1191** | **39** | **1838** |
| Male | 183 (30.1) | 530 (44.5) | 11 (28.2) | 724 (39.4) |
| Female | 425 (69.9) | 661 (55.5) | 28 (71.8) | 1114 (60.6) |
| **Dose 2** Number of participants (%) | | | | |
| **Subjects with at least one serious adverse reaction** Number of participants | **138** | **906** | **31** | **1075** |
| Male | 64 (46.4) | 409 (45.1) | 3 (9.7) | 476 (44.3) |
| Female | 74 (53.6) | 497 (54.9) | 28 (90.3) | 599 (55.7) |

A total of 140 (0.03%) of the 520 076 participants receiving the first dose of the vaccines reported an adverse event which was flagged as an AESI. AstraZeneca had a slightly higher reporting rate of AESI with 69 (0.08%) of the participants reporting at least one AESI, while BioNTech/Pfizer and Moderna both had a reporting rate of 0.02%, represented by 67 and 4 participants respectively. The majority of all reports of an AESI were from females, across all vaccine brands. To explain these numbers a more detailed analysis of the risk factors and characteristics of the analysed population is needed.

***Table 16.*** *Any AESI per dose 1 and dose 2 per age and gender.*

| | **COVID-19 vaccine manufacturer** | | | |
|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer** | **Moderna** | **Total vaccines** |
| **Dose 1** Number of participants (%) | | | | |
| **Subjects with at least one AESI** Number of participants | **69** | **67** | **4** | **140** |
| Male | 28 (40.6) | 26 (38.8) | 1 (25.0) | 55 (39.3) |
| Female | 41 (59.4) | 41 (61.2) | 3 (75.0) | 85 (60.7) |
| **Dose 2** Number of participants (%) | | | | |
| **Subjects with at least one AESI** Number of participants | **22** | **51** | **6** | **79** |
| Male | 10 (45.5) | 18 (35.3) | 4 (66.7) | 32 (40.5) |
| Female | 12 (54.5) | 33 (64.7) | 2 (33.3) | 47 (59.5) |

## 1.9. Discussion: Monitoring of the general population receiving a first (and possibly second) dose of any COVID-19 vaccine

### 1.9.1. Key findings

This study provides data on more than 550,000 vaccinated persons across seven countries, 5 used the same LIM system, whereas Germany and Croatia used their own system. The vast majority of persons were included in Germany followed by the Netherlands, since these countries had their systems in place upon initial roll out of the vaccines, whereas other countries were waiting for the protocol approval and technical installations. It shows that people and infrastructure readiness is crucial for the collection of cohort event monitoring data.

Many patients across all vaccines report systemic and local solicited reactions, which has been as well in the clinical trials. In all countries, reporting of serious ADRs as well as AESI was very rare (far below 1%). Reporting was higher in women, and in younger age groups, which makes direct comparisons between vaccines difficult as they have been channelled to varying age groups.

### 1.9.2. Limitations

This study has tried to align methdology across all the LIM using sites which followed the LAREB approach but differences exist in implementation of the scheduling of questionnaires, and with the Croatian and German approach. Besides differences, we ere able to aggregate the data and present it together. Loss to follow-up was substantial in some countries, where people registered but never returned the first questionnaire. It is not clear whether these persons did not have an ADR or just did not mind to respond. Therefore, the rate of reporting is potentially overestimated.

While most partners are able to provide regular updates on all strata, German data could only be provided in batches by vaccine brand due to the heavy workload to assess. Limited access to data and the immense amount of inclusions in Germany are the main drivers for this manner of sharing data. The German partners are working on software and hardware changes in order to have better accessibility to this data in future. The Moderna dataset from Germany was last updated in May. This dataset therefore only includes the population that was initially vaccinated early on in the roll-out of this vaccine brand: Health care providers and older age groups.

In this analysis we provide descriptive results, and no comparison can be conducted, since channelling of vaccine was strong, for the final analysis we may do some adjustments and standardization.

### 1.9.3. Discussion

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

Additionally, stratification on the specified seriousness, for example hospitalisation or permanent disability, may reveal more valuable information on these adverse reactions and will make comparison with other studies easier.

Germany was the first country to initiate data collection on monitoring of the novel COVID-19 vaccines. The existing application SafeVac 2.0, previously used for the monitoring of yearly flu vaccines, was adjusted for the use in the monitoring of the COVID-19 vaccines. The questionnaires used in this monitoring tool are comparable to the protocol used for the LIM web app and the OPeN data collection tool. The SafeVac 2.0 app allows participants to report two additional solicited adverse reactions than those proposed in the ECVM/CVM protocol: diarrhoea and dizziness. An additional example data collection in Germany diverging from the protocol is the question on gender allowing a third answer option “other”. While data on age and gender are collected at registration, data on comorbidities is collected at a later stage of participation rather than collecting this information at the

start of the study as described in the protocol. Due to this, the additional gender option and analysis of the risk factors have not been included in this report.

The above differences are taken into account, when possible, by ensuring that the aggregated data used for regular reports and the dashboard is comparable: definitions of aggregated variables have been agreed upon and data is stratified on vaccine brand, gender and age. However, caution should currently be taken in interpreting the data between strata. Doing any extensive statistical analysis would nevertheless require additional testing of compatibility of the data used for that analysis.

## 1.10. Conclusions: Monitoring of the general population receiving a first (and possibly second) dose of any COVID-19 vaccine

This general population section summarizes the main observations related to the data coming from Belgium, Croatia, France, Italy, the Netherlands, Germany, and the United Kingdom, through three different data sources. The LIM web-app collects data from Belgium, France, Italy, the Netherlands, and the United Kingdom, whereas Croat data are collected by the OPeN application. These datasets are updated until the 9$^{th}$ and 15$^{th}$ of February 2022 respectively. German data are collected using the SafeVac 2.0 application and have different dated updates for each reported COVID-19 vaccine brand. In general, serious adverse reactions and AESI are rare for all the vaccine brands. With respect to solicited reactions, injection site pain shows the most frequently reported local solicited reaction across all vaccine brands.

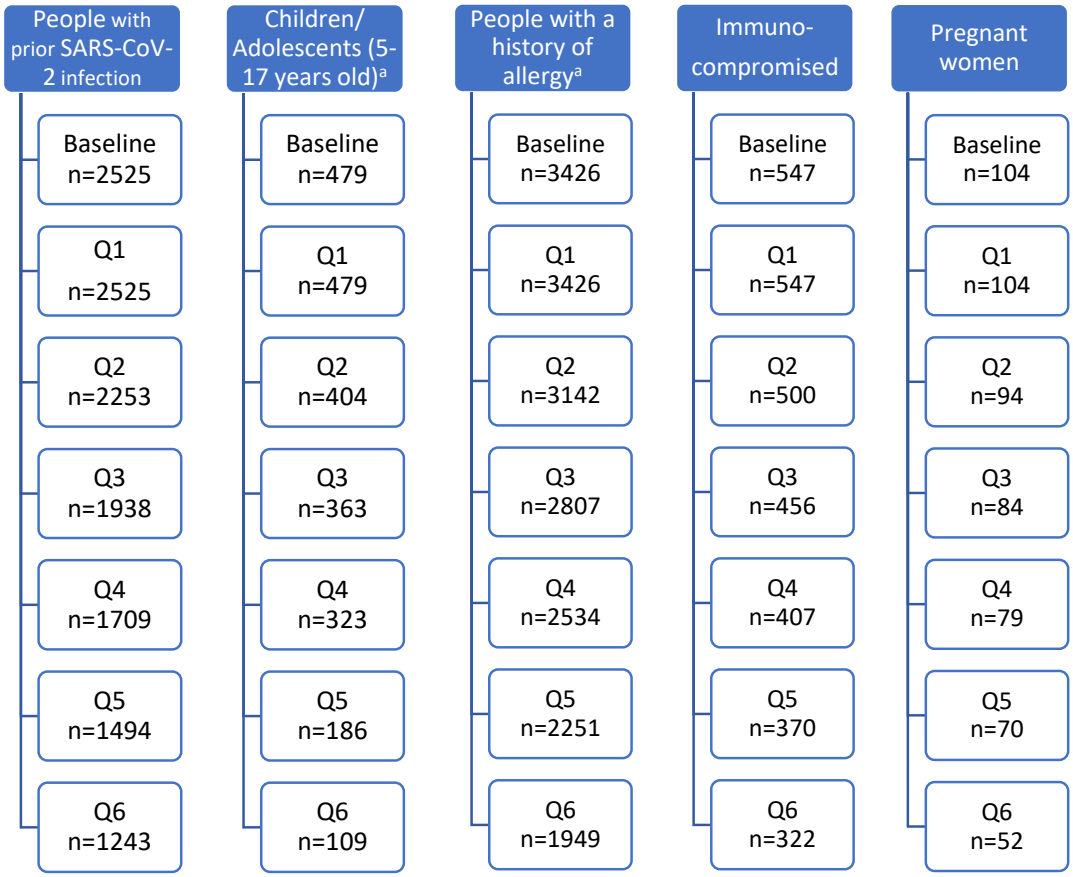
## 1.11. Results: Monitoring of the special target groups receiving a first (and possibly second) dose of any COVID-19 vaccine

### 1.11.1. LIM data source

In this section, we present data from the special populations collected in the ECVM project through the LIM app from four countries: France, Italy, The Netherlands, and the United Kingdom. While the data are also included in the ECVM report as part of the overall population, for this WP1 analysis it is restricted to those special populations. Please note that the children and adolescents' group include participants between 0 and 17 years of age (which differs from the age range considered in the September, October, and November reports). Comprehensive data is provided through the interactive POWERBI dashboard.

Figure 15 shows the number of participants who filled in each questionnaire (baseline and follow-up questionnaires) by special target group. For this report, the children/adolescents' group is either described as children aged 5-11 years and adolescents aged 12-17 years, or as individual group (5-17 years). This is due to difficulties in extrapolating specific information on a subject due to the data being available on the aggregated level only.

Since we identified one subject belonging to this special target group for which no age was recorded, the number of children/adolescents may vary of one unit across the report. Croatia had only one subject belonging to the group of people with prior SARS-CoV-2 infection, so we decided to not include Croatian data in this section, except for the Figure 15.




**Legend: a**. Includes one subject with no recorded age information

***Figure 15.*** *Grouped list representing the number of participants who filled in each questionnaire, by special target group.*

Table 17 summarizes the total number of participants who belong to the special cohorts of interest on the 9th of February 2022, including those participants with missing vaccine manufacturer information. To be aligned with the available data of the WP1 CVM dashboard, the next result sections only consider the subjects providing the vaccine manufacturer information. For this reason, the total number of special target group subjects may differ from the previous reports. Please note that a single participant may belong to more special target groups, and therefore, the table should be read across the columns.

***Table 17.*** *Number of participants belonging to the special target groups who filled in the baseline questionnaire and received the vaccine by country.*

| Country | Special target group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Prior SARS-CoV-2 infection** | **Children 5-11 y.o.[b]** | **Adolescents 12-17 y.o.[b]** | **People with history of allergy** | **Immuno-compro-mised** | **Pregnant women** | **Tool** | **Recruitment Start date** |
| **France** | 154 | 21 | 161 | 191 | NA | NA | LIM | 14/06/2021 |
| **Italy** | 95 | 53 | 109 | 164 | 18 | 13 | LIM | 09/06/21 |
| **Netherlands** | 2243 | 0 | 45 | 3049 | 529 | 91 | LIM | 01/02/2021 |
| **United Kingdom** | 33 | 0 | 89 | 22 | NA | NA | LIM | 23/06/2021 |
| **Total** | **2525[a]** | **74** | **404[a]** | **3426[a]** | **547[a]** | **104** | | |

***Legend****: a. Special target groups with at least one subject with no reported vaccine manufacturer information. b. Subject with no recorded age excluded.* ***Abbreviations****: NA= not applicable, y.o.= years old;*

### 1.11.1.1. Baseline characteristics

Table 18 shows the distribution of registered vaccinees and the female/male ratio by subgroup and COVID-19 vaccine manufacturer for France, Italy, the Netherlands, and the United Kingdom.

For all special groups except for the group of people with prior SARS-CoV-2 infection, the BioNTech/Pfizer vaccine was the most frequently received. Children and adolescents were vaccinated almost exclusively with the BioNTech/Pfizer vaccine across all countries (>93.2%). Please note that children aged between 5 and 11 years are receiving a different dosage of BioNTech/Pfizer than the one currently offered to adults and adolescents aged between 12 and 17 years. Pregnant women were vaccinated almost exclusively with the BioNTech/Pfizer vaccine or the Moderna vaccine both, in Italy and the Netherland. A significant number of participants with a history of allergy (31.9%), those with a prior SARS-CoV-2 infection (38.3%) and the immunocompromised (30.5%) received the AstraZeneca vaccine.

Overall, most of participants were females, with the highest female/male (F/M) ratio observed in the group of people with prior SARS-CoV-2 infection (3.1), followed by the group of people with history of allergy (2.8). The F/M ratio for the Italian, French, and British participants seem to be generally lower than the one observed for the Dutch participants, except for the ratio observed in the Italian immunocompromised group, which is however represented by only 17 participants. The lowest F/M ratio has been observed in the children/adolescents' group (1.2) when information from all countries is pooled together.

In Table 18 the median age is also provided. The median age for the group of people with prior SARS-CoV-2 infection and people with a history of allergy is quite similar, being 47 and 48 years, respectively. Immunocompromised had the highest median age (56 years), while pregnant women had the lowest median age (33), after children and adolescents. 50% of the children/adolescents were below 13 at the time the baseline questionnaire was filled in for them.

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

| Country/ COVID-19 vaccine manufacturer | Distribution | Special target group | | | | |
|---|---|---|---|---|---|---|
| | | People with prior SARS-CoV-2 infection | Children and Adolescents (5-17 y.o.) | People with a history of allergy | Immuno-compromised | Pregnant women |
| **France** | | | | | | |
| BioNTech/ Pfizer | n vaccinees (%) | 148 (96.7) | 180 (98.9)[a] | 177 (93.2) | NA | NA |
| | F/M ratio | 2.2 | 1.2 | 2.2 | NA | NA |
| | median age (years) | 35 | 13 | 34 | NA | NA |
| Janssen | n vaccinees (%) | 1 (0.7) | NA | NA | NA | NA |
| | F/M ratio | 0 | NA | NA | NA | NA |
| | median age (years) | 64 | NA | NA | NA | NA |
| Moderna | n vaccinees (%) | 4 (2.6) | 2 (1.1) | 13 (6.8) | NA | NA |
| | F/M ratio | 3 | 1 | 3.3 | NA | NA |
| | median age (years) | 39.5 | 15.5 | 39 | NA | NA |
| **All vaccines** | **n vaccinees (%)** | **153 (100)** | **182 (100)[a]** | **190 (100)** | **NA** | **NA** |
| | **F/M ratio** | **2.2** | **1.2** | **2.3** | **NA** | **NA** |
| **Italy** | | | | | | |
| AstraZeneca | n vaccinees (%) | NA | NA | 1 (0.6) | NA | NA |
| | F/M ratio | NA | NA | - | NA | NA |
| | median age (years) | NA | NA | 64 | NA | NA |
| BioNTech/ Pfizer | n vaccinees (%) | 74 (78.7) | 151 (93.2) | 141 (86.5) | 16 (88.9) | 13 (100) |
| | F/M ratio | 1.6 | 1.2 | 1.8 | 3 | - |
| | median age (years) | 36.5 | 12 | 32 | 33 | 35 |
| Janssen | n vaccinees (%) | 1 (1.1) | NA | NA | NA | NA |
| | F/M ratio | 0 | NA | NA | NA | NA |
| | median age (years) | 45 | NA | NA | NA | NA |
| Moderna | n vaccinees (%) | 19 (20.2) | 11 (6.8) | 21 (12.9) | 2 (11.1) | NA |
| | F/M ratio | 1.1 | 0.6 | 2 | - | NA |
| | median age (years) | 34 | 13 | 34 | 24.5 | NA |
| **All vaccines** | **n vaccinees (%)** | **94 (100)** | **162 (100)** | **163 (100)** | **18 (100)** | **13 (100)** |
| | **F/M ratio** | **1.4** | **1.1** | **1.9** | **3.5** | **-** |
| **The Netherlands** | | | | | | |
| AstraZeneca | n vaccinees (%) | 964 (43.0) | 3 (6.7) | 1090 (35.8) | 166 (31.5) | 2 (2.2) |
| | F/M ratio | 7.2 | 0.5 | 8.5 | 5.9 | - |
| | median age (years) | 48 | 17 | 50 | 51 | 41.5 |
| BioNTech/ Pfizer | n vaccinees (%) | 602 (26.9) | 42 (93.3) | 1113 (36.6) | 241 (45.7) | 38 (41.8) |
| | F/M ratio | 1.6 | 2.5 | 1.6 | 1.1 | - |
| | median age (years) | 52 | 17 | 66 | 75 | 33 |
| Janssen | n vaccinees (%) | 268 (12.0) | NA | 345 (11.3) | 22 (4.2) | 2 (2.2) |
| | F/M ratio | 3.9 | NA | 2.9 | 2.1 | - |
| | median age (years) | 50.5 | NA | 46 | 46.5 | 31.5 |
| Moderna | n vaccinees (%) | 406 (18.1) | NA | 494 (16.3) | 98 (18.6) | 49 (53.8) |
| | F/M ratio | 2.7 | NA | 2.6 | 2.4 | - |
| | median age (years) | 46.5 | NA | 45 | 50 | 33 |
| **All vaccines** | **n vaccinees (%)** | **2240 (100)** | **45 (100)** | **3042 (100)** | **527 (100)** | **91 (100)** |
| | **F/M ratio** | **3.4** | **2.2** | **3** | **2.1** | **-** |
| **United Kingdom** | | | | | | |
| AstraZeneca | n vaccinees (%) | NA | NA | 1 (4.5) | NA | NA |
| | F/M ratio | NA | NA | - | NA | NA |
| | median age (years) | NA | NA | 37 | NA | NA |
| BioNTech/ Pfizer | n vaccinees (%) | 29 (93.5) | 83 (100) | 20 (91.0) | NA | NA |
| | F/M ratio | 0.8 | 1 | 1 | NA | NA |
| | median age (years) | 15 | 13 | 16.5 | NA | NA |
| Moderna | n vaccinees (%) | 2 (6.5) | NA | 1 (4.5) | NA | NA |
| | F/M ratio | - | NA | - | NA | NA |
| | median age (years) | 24.5 | NA | 26 | NA | NA |
| **All vaccines** | **n vaccinees (%)** | **31 (100)** | **83 (100)** | **22 (100)** | **NA** | **NA** |
| | **F/M ratio** | **0.9** | **1** | **1.2** | **NA** | **NA** |

| Country/ COVID-19 vaccine manufacturer | Distribution | Special target group | | | | |
|---|---|---|---|---|---|---|
| | | People with prior SARS-CoV-2 infection | Children and Adolescents (5-17 y.o.) | People with a history of allergy | Immuno-compromised | Pregnant women |
| **All countries** | | | | | | |
| AstraZeneca | n vaccinees (%) | 964 (38.3) | 3 (0.6) | 1092 (31.9) | 166 (30.5) | 2 (1.9) |
| | F/M ratio | 7.2 | 0.5 | 8.5 | 5.9 | - |
| | median age (years) | 48 | 17 | 50 | 51 | 41.5 |
| BioNTech/ Pfizer | n vaccinees (%) | 853 (33.9) | 456 (96.6)[a] | 1451 (42.5) | 257 (47.2) | 51 (49.1) |
| | F/M ratio | 1.7 | 1.2 | 1.7 | 1.1 | - |
| | median age (years) | 44 | 13 | 50 | 74 | 33 |
| Janssen | n vaccinees (%) | 270 (10.7) | NA | 345 (10.1) | 22 (4.0) | 2 (1.9) |
| | F/M ratio | 3.8 | NA | 2.9 | 21 | - |
| | median age (years) | 50.5 | NA | 46 | 46.5 | 31.5 |
| Moderna | n vaccinees (%) | 431 (17.1) | 13 (2.8) | 529 (15.5) | 100 (18.3) | 49 (47.1) |
| | F/M ratio | 2.6 | 0.6 | 2.6 | 2.4 | - |
| | median age (years) | 46 | 13 | 45 | 50 | 33 |
| **All vaccines** | **n vaccinees (%)** | **2518 (100)** | **472 (100)[a]** | **3417 (100)** | **545 (100)** | **104 (100)** |
| | **F/M ratio** | **3.1** | **1.2** | **2.8** | **2.1** | **-** |

**Legend**: percentages are calculated based on the total number of participants belonging to a specific special target group. A F/M ratio > 1 indicates that the number of female participants is higher than the number of male participants. **a.** Subject with no recorded age excluded. **Abbreviations:** F=female, M=male, NA=not applicable, n=number, y.o.=years old.

The demographic characteristics of the participants who filled in the baseline questionnaire and received the first dose of vaccine are depicted in Table 19.

Most of participants belonging to the groups of people with prior SARS-CoV-2 infection, a history of allergy, and immunocompromised were aged between 40 and 59 years. It is worth noting that the immunocompromised group aged between 70 and 79 years represented almost a quarter of the total number of participants. Most of registered children and adolescents (84.1%) were aged between 12 and 17 years. Children and adolescents were also included as participants of other special target groups: 59 (12.5%) children/adolescents had a prior SARS-CoV-2 infection and 70 (14.8%) reported to have had or have at least one allergy. Three quarter of the total number of pregnant women indicated to be aged between 30 and 39 years. Only six indicated to be 40 years old or older at the time they filled in the baseline questionnaire.

Medical history is reported as MedDRA Preferred Term (PT). The PT list originates from the coding of the disorders and situations at Lowest Level Term (LLT) in agreement with the Lareb' "Work Instruction FlexLIM" (Version date 9-6-2021) document. Because more than one LLT may relate to the same PT, and only PTs are now available in our dataset, the percentage of the number of participants having a specific medical history condition over the number of total participants cannot be provided.

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

Tables 20, 21, 22, 23, 24 show the demographics and clinical characteristics of the participants by vaccine manufacturer for each special target group.

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

| Characteristics | Special target group | | | | |
|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection** | **Children/ Adolescents (0-17 y.o.)[a]** | **People with a history of allergy** | **Immuno-compromised** | **Pregnant women** |
| **Number of participants (%)** | **2518 (100.0)** | **473 (100.0)** | **3417 (100.0)** | **545 (100.0)** | **104 (100.0)** |
| **Age group (y.o.)** Number of participants (%) | | | | | |
| 5 – 11 | 9 (0.4) | 74 (15.6) | 9 (0.3) | NA | 0 (0.0) |
| 12 – 17 | 50 (2.0) | 398 (84.1) | 61 (1.8) | 3 (0.5) | 0 (0.0) |
| 18 – 24 | 223 (8.9) | 0 (0.0) | 224 (6.5) | 16 (2.9) | 0 (0.0) |
| 25 – 29 | 206 (8.2) | 0 (0.0) | 263 (7.7) | 21 (3.9) | 20 (19.2) |
| 30 – 39 | 412 (16.4) | 0 (0.0) | 596 (17.4) | 70 (12.8) | 78 (75.0) |
| 40 – 49 | 516 (20.5) | 0 (0.0) | 641 (18.8) | 87 (16.0) | 4 (3.9) |
| 50 – 59 | 653 (25.9) | 0 (0.0) | 759 (22.2) | 111 (20.4) | 2 (1.9) |
| 60 – 69 | 254 (10.1) | 0 (0.0) | 327 (9.6) | 70 (12.8) | 0 (0.0) |
| 70 – 79 | 131 (5.2) | 0 (0.0) | 359 (10.5) | 110 (20.2) | 0 (0.0) |
| >80 | 64 (2.5) | 0 (0.0) | 177 (5.2) | 57 (10.5) | 0 (0.0) |
| No age recorded | 0 (0.0) | 1 (0.2) | 1 (0.0) | 0 (0.0) | 0 (0.0) |
| **Sex** Number of participants (%) | | | | | |
| Female | 1904 (75.6) | 258 (54.5) | 2526 (73.9) | 370 (67.9) | 104 (100.0) |
| Male | 614 (24.4) | 215 (45.5) | 891 (26.1) | 175 (32.1) | NA |
| **Medical history (MedDRA PT)** Number of participants (%) | | | | | |
| Cardiovascular disorder | 134 | 0 | 240 | 69 | 2 |
| Diabetes mellitus | 68 | 2 | 116 | 41 | 1 |
| Hypertension | 282 | 0 | 483 | 100 | 2 |
| Immunosuppression | 52 | 4 | 108 | 600 | 2 |
| Liver disorder | 5 | 1 | 17 | 13 | 0 |
| Lung disorder | 237 | 37 | 776 | 102 | 6 |
| Mental disorder | 107 | 12 | 282 | 32 | 3 |
| Neoplasm malignant | 19 | 0 | 37 | 31 | 0 |
| Nervous system disorder | 31 | 8 | 54 | 37 | 0 |
| Renal disorder | 25 | 1 | 13 | 25 | 0 |

**Legend:** percentages are calculated based on the total number of participants belonging to a specific special target group. **a.** Includes one subject with no recorded age information. **Abbreviations**: MedDRA= Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term

## People with prior SARS-CoV-2 infection

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

| Characteristics | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer** | **Janssen** | **Moderna** | **All vaccines** |
| **Number of participants** | 964 | 853 | 270 | 431 | 2518 |
| **Median age** (years) | 48 | 44 | 50.5 | 46 | 47 |
| **Sex** Number of participants (%) | | | | | |
| Female | 847 (87.9) | 533 (62.5) | 213 (78.9) | 311 (72.2) | 1904 (75.6) |
| Male | 117 (12.1) | 320 (37.5) | 57 (21.1) | 120 (27.8) | 614 (24.4) |
| **Medical history (MedDRA PT)** Number of participants (%) | | | | | |
| Cardiovascular disorder | 33 | 84 | 6 | 11 | 134 |
| Diabetes mellitus | 26 | 34 | 1 | 7 | 68 |
| Hypertension | 107 | 128 | 20 | 27 | 282 |
| Immunosuppression | 24 | 14 | 5 | 9 | 52 |
| Liver disorder | 1 | 3 | 0 | 1 | 5 |
| Lung disorder | 88 | 89 | 12 | 48 | 237 |
| Mental disorder | 40 | 37 | 11 | 19 | 107 |
| Neoplasm malignant | 4 | 10 | 3 | 2 | 19 |
| Nervous system disorder | 9 | 12 | 5 | 5 | 31 |
| Renal disorder | 7 | 12 | 0 | 6 | 25 |

**Legend:** percentages are calculated based on the total number of participants belonging to a specific special target group. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term

## Children/Adolescents (5-17 years)

***Table 21.*** *Demographics and clinical characteristics of children/adolescents (0-17 years) by COVID-19 vaccine manufacturer*

| Characteristics | COVID-19 vaccine manufacturer | | | |
|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer[a]** | **Moderna** | **All vaccines[a]** |
| **Number of participants (%)** | 3 (100) | 457 (100) | 13 (100) | 473 (100) |
| **Median age** (years) | 17 | 13 | 13 | 13 |
| **Sex** Number of participants (%) | | | | |
| Female | 1 (33.3) | 252 (55.1) | 5 (38.5) | 258 (54.5) |
| Male | 2 (66.7) | 205 (44.9) | 8 (61.5) | 215 (45.5) |
| **Medical history (MedDRA PT)** Number of participants (%) | | | | |
| Diabetes mellitus | 0 | 2 | 0 | 2 |
| Immunosuppression | 0 | 4 | 0 | 4 |
| Liver disorder | 0 | 1 | 0 | 1 |
| Lung disorder | 0 | 36 | 1 | 37 |
| Mental disorder | 0 | 12 | 0 | 12 |
| Nervous system disorder | 0 | 8 | 0 | 8 |
| Renal disorder | 0 | 1 | 0 | 1 |

**Legend:** percentages are calculated based on the total number of participants belonging to a specific special target group. **a.** Includes one subject with no recorded age information. **Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term

## People with a history of allergy

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

| Characteristics | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/ Pfizer** | **Janssen** | **Moderna** | **All vaccines** |
| **Number of participants (%)** | 1092 (100) | 1451 (100) | 345 (100) | 529 (100) | 3417 (100) |
| **Median age** (years) | 50 | 50 | 46 | 45 | 48 |
| **Sex** Number of participants (%) | | | | | |
| Female | 977 (89.5) | 912 (62.9) | 256 (74.2) | 381 (72.0) | 2526 (73.9) |
| Male | 115 (10.5) | 539 (37.1) | 89 (25.8) | 148 (28.0) | 891 (26.1) |
| **Medical history (MedDRA PT)** Number of participants (%) | | | | | |
| Cardiovascular disorder | 42 | 179 | 4 | 15 | 240 |
| Diabetes mellitus | 38 | 67 | 2 | 9 | 116 |
| Hypertension | 129 | 300 | 24 | 30 | 483 |
| Immunosuppression | 34 | 52 | 5 | 17 | 108 |
| Liver disorder | 3 | 10 | 0 | 4 | 17 |
| Lung disorder | 277 | 327 | 32 | 140 | 776 |
| Mental disorder | 94 | 113 | 23 | 52 | 282 |
| Neoplasm malignant | 7 | 24 | 4 | 2 | 37 |
| Nervous system disorder | 9 | 34 | 7 | 4 | 54 |
| Renal disorder | 8 | 36 | 0 | 4 | 48 |

**Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term

## Immunocompromised

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

| Characteristics | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/ Pfizer** | **Janssen** | **Moderna** | **All vaccines** |
| **Number of participants (%)** | 166 (100) | 257 (100) | 22 (100) | 100 (100) | 545 (100) |
| **Median age** (years) | 51 | 74 | 46.5 | 50 | 56 |
| **Sex** Number of participants (%) | | | | | |
| Female | 142 (85.5) | 136 (52.9) | 21 (95.5) | 71 (71.0) | 370 (67.9) |
| Male | 24 (14.5) | 121 (47.1) | 1 (4.5) | 29 (29.0) | 175 (32.1) |
| **Medical history (MedDRA PT)** Number of participants (%) | | | | | |
| Cardiovascular disorder | 10 | 54 | 1 | 4 | 69 |
| Diabetes mellitus | 9 | 27 | 0 | 5 | 41 |
| Hypertension | 25 | 66 | 2 | 7 | 100 |
| Immunosuppression | 188 | 272 | 25 | 115 | 600 |
| Liver disorder | 5 | 7 | 0 | 1 | 13 |
| Lung disorder | 29 | 49 | 4 | 20 | 102 |
| Mental disorder | 7 | 16 | 4 | 5 | 32 |
| Neoplasm malignant | 6 | 17 | 0 | 8 | 31 |
| Nervous system disorder | 9 | 21 | 0 | 7 | 37 |
| Renal disorder | 3 | 16 | 0 | 6 | 25 |

**Legend:** percentages are calculated based on the total number of participants belonging to a specific special target group.
**Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term

**Pregnant women**

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

| Characteristics | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/ Pfizer** | **Janssen** | **Moderna** | **All vaccines** |
| **Median age** (years) | 41.5 | 33 | 31.5 | 33 | 33 |
| **Medical history (MedDRA PT)** Number of participants (%) | | | | | |
| Cardiovascular disorder | 0 | 0 | 0 | 2 | 2 |
| Diabetes mellitus | 1 | 0 | 0 | - | 1 |
| Hypertension | 1 | 0 | 0 | 1 | 2 |
| Immunosuppression | 0 | 1 | 0 | 1 | 2 |
| Lung disorder | 1 | 1 | 0 | 4 | 6 |
| Mental disorder | 0 | 1 | 1 | 1 | 3 |

**Legend:** percentages are calculated based on the total number of participants belonging to a specific special target group.
**Abbreviations**: MedDRA=Medical Dictionary for Regulatory Activities, n=number, PT=preferred term

### 1.11.1.2. Vaccinee-reported adverse reactions

Table 25 provides an overview of the frequency of all reported adverse reactions (solicited and unsolicited), with their percentages calculated based on the number of participants receiving a specific vaccine. The frequency of the reported ADRs is depicted by special target group, vaccine manufacturer, following the first or the second dose of vaccine. Please note that participants can report more than one ADR but Table 25 only shows the number of participants having reported at least one ADR.

In all special target groups, more than half participants reported to have experienced at least one ADR, except for the group of children aged 5-11 years old. This can be observed following a first or a second dose of vaccine, when all information on vaccine manufacturers is pooled together.

The ADR reporting rate following the second dose decreased quite significantly in the groups of people with prior SARS-CoV-2 infection, a history of allergy, immunocompromised, and pregnant women, when compared to the ADR reporting rate related to the first dose of vaccine.

Children aged between 5 and 11 years were exclusively vaccinated with the BioNTech/Pfizer vaccine. The majority of adolescents aged between 12 and 17 years were also vaccinated with the BioNTech/Pfizer, although a small number of participants received either Moderna or AstraZeneca. Among 74 children (5-11 years) receiving the first dose of the vaccine, 23 (31.1%) experienced at least one ADR. Among 21 receiving the second dose of the vaccine, 6 (28.6%) experienced at least one ADR. 54.8% of 398 adolescents (12-17 years) reported at least one ADR, either solicited or non-solicited, following the receipt of the first dose. A similar percentage (50.5%) of adolescents reporting ADRs was observed following the receipt of the second dose.

***Table 25**. Overview of the number of vaccinee-reported solicited and non-solicited adverse reactions over the number of vaccinees by special target group, following the first and the second dose of any vaccine*

| COVID-19 vaccine manufacturer | Special target group | | | | | |
|---|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection**<br><br>Any ADR/Any vaccinees (%) | **Children (5-11 y.o.)[a]**<br><br>Any ADR/Any vaccinees (%) | **Adolescents (12-17 y.o.)[a]**<br><br>Any ADR/Any vaccinees (%) | **People with a history of allergy**<br><br>Any ADR/Any vaccinees (%) | **Immuno-compromised**<br><br>Any ADR/Any vaccinees (%) | **Pregnant Women**<br><br>Any ADR/Any vaccinees (%) |
| **Dose 1** | | | | | | |
| AstraZeneca | 938/964 (97.3) | NA | 3/3 (100.0) | 1034/1092 (94.7) | 154/166 (92.8) | 2/2 (100.0) |
| BioNTech/Pfizer | 638/853 (74.8) | 23/74 (31.1) | 208/382 (54.5) | 973/1451 (67.1) | 149/257 (58.0) | 41/51 (80.4) |
| Janssen | 250/270 (92.6) | NA | NA | 310/345 (89.9) | 20/22 (90.9) | 2/2 (100.0) |
| Moderna | 401/431 (93.0) | NA | 7/13 (53.8) | 460/529 (87.0) | 82/100 (82.0) | 40/49 (81.6) |
| **All vaccines** | **2227/2518 (88.4)** | **23/74 (31.1)** | **218/398 (54.8)** | **2777/3417 (81.3)** | **405/545 (74.3)** | **85/104 (81.7)** |
| **Dose 2** | | | | | | |
| AstraZeneca | 186/374 (49.7) | NA | NA | 387/693 (55.8) | 45/96 (46.9) | 1/2 (50.0) |
| BioNTech/Pfizer | 204/332 (61.4) | 6/21 (28.6) | 108/211 (51.2) | 679/1111 (61.1) | 108/222 (48.6) | 19/39 (48.7) |
| Moderna | 139/165 (84.2) | NA | 2/7 (28.6) | 354/397 (89.2) | 67/83 (80.7) | 36/40 (90.0) |
| **All vaccines** | **529/871 (60.7)** | **6/21 (28.6)** | **110/218 (50.5)** | **1420/2201 (64.5)** | **220/401 (54.9)** | **56/81 (69.1)** |

**Legend:** percentages calculated based on the number of vaccinee-reported solicited and non-solicited adverse reactions over the number of vaccinees receiving a specific vaccine by special target group. The table include data pooled across countries. **a.** Subject with no recorded age excluded. This subject has reported at least one adverse reaction. **Abbreviations:** ADR = adverse reaction, NA= not applicable, y.o.= years old

The next two Tables 26 and 27 show the frequency of reported solicited ADRs using the PT and classified as either local solicited ADR or systematic solicited ADR. Table 26 refers to the first dose of vaccine, while Table 27 refers to the second. Percentages have been calculated based on the number of participants having reported at least one ADR following the first or the second dose of the vaccine.

Following the receipt of the first dose, injection site pain was the most frequently reported ADR among the local solicited ADRs in all special target groups, whereas fatigue was the most frequently reported within the list of systematic solicited ADR.

As for the first dose, injection site pain was the most frequently reported ADR among the local solicited ADRs across all special target groups following the receipt of the second dose. Within the list of systematic solicited ADR, fatigue was the most frequently reported across all groups, except for the people with prior SARS-CoV-2 infection, for which malaise was reported at a higher rate.

Tables 28, 29, 30, 31, 32 show the frequency of reported local and systemic solicited ADRs (MedDRA PT) by COVID-19 vaccine manufacturer for each special target group.

***Table 26.*** *Frequency of reported local and systemic solicited ADRs following the first dose of any vaccine, by special target group*

| **Type of ADR** | **Special target group** | | | | |
|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection** | **Children/ Adolescents (5-17 y.o.)** | **People with a history of allergy** | **Immuno-Compromised** | **Pregnant women** |
| **Subjects with at least one ADR** Number of participants | 2227 | 242[a] | 2777 | 405 | 85 |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 238 (10.7) | 11 (4.5) | 258 (9.3) | 45(11.1) | 4 (4.7) |
| Injection site haematoma | 128 (5.7) | 7 (2.9) | 155 (5.6) | 21 (5.2) | 6 (7.1) |
| Injection site induration | 13 (0.6) | 2 (0.8) | 41 (1.5) | 1 (0.2) | 1 (1.2) |
| Injection site inflammation | 574 (25.8) | 27 (11.2) | 597 (21.5) | 91 (22.5) | 11 (12.9) |
| Injection site pain | 1360 (61.1) | 156 (64.5) | 1582 (57.0) | 236 (58.3) | 50 (58.8) |
| Injection site pruritus | 100 (4.5) | 8 (3.3) | 137 (4.9) | 20 (4.9) | 3 (3.5) |
| Injection site reaction | 4 (0.2) | 0 (0.0) | 3 (0.1) | 3 (0.7) | 1 (1.2) |
| Injection site swelling | 515 (23.1) | 31 (12.8) | 533 (19.2) | 87 (21.5) | 13 (15.3) |
| Injection site warmth | 377 (16.9) | 14 (5.8) | 404 (14.5) | 68 (16.8) | 8 (9.4) |
| **Systemic solicited ADR (PT)** Number of participants (%) | | | | | |
| Arthralgia | 599 (26.9) | 21 (8.7) | 644 (23.2) | 90 (22.2) | 5 (5.9) |
| Chills | 1057 (47.5) | 24 (9.9) | 961 (34.6) | 130 (32.1) | 8 (9.4) |
| Fatigue | 1391 (62.5) | 95 (39.3) | 1617 (58.2) | 224 (55.3) | 34 (40.0) |
| Headache | 1345 (60.4) | 73 (30.2) | 1415 (51.0) | 183 (45.2) | 15 (17.6) |
| Malaise | 1315 (59.0) | 53 (21.9) | 1384 (49.8) | 190 (46.9) | 16 (18.8) |
| Myalgia | 1333 (59.9) | 85 (35.1) | 1444 (52.0) | 197 (48.6) | 30 (35.3) |
| Nausea | 576 (25.9) | 34 (14.0) | 656 (23.6) | 95 (23.5) | 8 (9.4) |
| Body temperature increased | 140 (6.3) | 10 (4.1) | 129 (4.6) | 19 (4.7) | 1 (1.2) |
| Pyrexia | 881 (39.6) | 29 (12.0) | 738 (26.6) | 84 (20.7) | 3 (3.5) |
| Hyperpyrexia | 16 (0.7) | 0 (0.0) | 14 (0.5) | 4 (1.0) | 0 (0.0) |

**Legend:** percentages calculated based on the specific PT Term for solicited ADR over the number of vaccinee-reported solicited and non-solicited ADRs, by special target group. The table include data pooled across countries. **a.** Includes one subject reporting at least one adverse reaction with no recorded age information. **Abbreviations:** ADR=adverse reaction; MedDRA=Medical Dictionary for Regulatory Activities; n=number; PT=preferred term; y.o.= years old

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

| Type of ADR | Special target group | | | | |
|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection** | **Children/ Adolescents (0-17 y.o.)** | **People with a history of allergy** | **Immuno-Compromised** | **Pregnant women** |
| **Subjects with at least one ADR** Number of participants (%) | 529 (100) | 116 (100) | 1420 (100 | 220 (100) | 56 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 46 (8.7) | 4 (3.4) | 139 (9.8) | 21 (9.5) | 6 (10.7) |
| Injection site haematoma | 31 (5.9) | 1 (0.9) | 72 (5.1) | 16 (7.3) | 4 (7.1) |
| Injection site induration | 1 (0.2) | 0 (0.0) | 7 (0.5) | 2 (0.9) | 0 (0.0) |
| Injection site inflammation | 85 (16.1) | 16 (13.8) | 238 (16.8) | 34 (15.5) | 14 (25.0) |
| Injection site pain | 268 (50.7) | 59 (50.9) | 651 (45.8) | 105 (47.7) | 32 (57.1) |
| Injection site pruritus | 18 (3.4) | 2 (1.7) | 56 (3.9) | 11 (5.0) | 1 (1.8) |
| Injection site reaction | 0 (0.0) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 76 (14.4) | 13 (11.2) | 211 (14.9) | 37 (16.8) | 10 (17.9) |
| Injection site warmth | 66 (12.5) | 13 (11.2) | 206 (14.5) | 26 (11.8) | 8 (14.3) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 87 (16.4) | 18 (15.5) | 227 (16.0) | 43 (19.5) | 5 (8.9) |
| Chills | 145 (27.4) | 25 (21.6) | 317 (22.3) | 43 (19.5) | 13 (23.2) |
| Fatigue | 243 (45.9) | 66 (56.9) | 723 (50.9) | 113 (51.4) | 27 (48.2) |
| Headache | 223 (42.2) | 58 (50.0) | 585 (41.2) | 86 (39.1) | 15 (26.8) |
| Malaise | 260 (49.1) | 41 (35.3) | 627 (44.2) | 94 (42.7) | 23 (41.1) |
| Myalgia | 202 (38.2) | 39 (33.6) | 596 (42.0) | 86 (39.1) | 29 (51.8) |
| Nausea | 91 (17.2) | 24 (20.7) | 257 (18.1) | 41 (18.6) | 6 (10.7) |
| Body temperature increased | 27 (5.1) | 14 (12.1) | 76 (5.4) | 12 (5.5) | 4 (7.1) |
| Pyrexia | 126 (23.8) | 23 (19.8) | 269 (18.9) | 42 (19.1) | 7 (12.5) |
| Hyperpyrexia | 1 (0.2) | 1 (0.9) | 4 (0.3) | 0 (0.0) | 0 (0.0) |

**Legend:** percentages calculated based on the specific PT Term for solicited ADR over the number of vaccinee-reported solicited and non-solicited ADRs, by special target group. The table include data pooled across countries. **Abbreviations:** ADR = adverse reaction; MedDRA=Medical Dictionary for Regulatory Activities; n=number; PT=preferred term; y.o.= years old

### People with prior SARS-CoV-2 infection

Among the local solicited ADRs and following the receipt of the first and the second dose, injection site pain was the most frequently reported ADR for all vaccine manufacturers. Among the list of systematic solicited ADR and following the receipt of the first dose, headache was the most frequently reported ADR for the AstraZeneca and the Janssen vaccines, while fatigue and malaise were for the BioNTech/Pfizer and the Moderna vaccines, respectively. Following the receipt of the second dose, headache remained the most frequently ADR for the AstraZeneca vaccines. Malaise was reported at higher rate within the group of participants receiving the BioNTech/Pfizer or the Moderna vaccines. Ç

***Table 28**. Frequency of reported local and systemic solicited ADRs in the group of people with SARS-CoV-2 infection by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine*

| Type of ADR | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer** | **Janssen** | **Moderna** | **Total vaccines** |
| **Dose 1** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 938 (100) | 638 (100) | 250 (100) | 401 (100) | 2227 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 118 (12.6) | 36 (5.6) | 19 (7.6) | 65 (16.2) | 238 (10.7) |
| Injection site haematoma | 58 (6.2) | 27 (4.2) | 21 (8.4) | 22 (5.5) | 128 (5.7) |
| Injection site induration | 5 (0.5) | 4 (0.6) | 2 (0.8) | 2 (0.5) | 13 (0.6) |
| Injection site inflammation | 266 (28.4) | 128 (20.1) | 51 (20.4) | 129 (32.2) | 574 (25.8) |
| Injection site pain | 586 (62.5) | 392 (61.4) | 122 (48.8) | 260 (64.8) | 1360 (61.1) |
| Injection site pruritus | 50 (5.3) | 18 (2.8) | 8 (3.2) | 24 (6.0) | 100 (4.5) |
| Injection site reaction | 1 (0.1) | 2 (0.3) | | 1 (0.2) | 4 (0.2) |
| Injection site swelling | 236 (25.2) | 102 (16.0) | 50 (20.0) | 127 (31.7) | 515 (23.1) |
| Injection site warmth | 176 (18.8) | 88 (13.8) | 27 (10.8) | 86 (21.4) | 377 (16.9) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 332 (35.4) | 96 (15.0) | 77 (30.8) | 94 (23.4) | 599 (26.9) |
| Chills | 624 (66.5) | 154 (24.1) | 119 (47.6) | 160 (39.9) | 1057 (47.5) |
| Fatigue | 639 (68.1) | 333 (52.2) | 174 (69.6) | 245 (61.1) | 1391 (62.5) |
| Headache | 692 (73.8) | 271 (42.5) | 175 (70.0) | 207 (51.6) | 1345 (60.4) |
| Malaise | 673 (71.7) | 233 (36.5) | 161 (64.4) | 248 (61.8) | 1315 (59.0) |
| Myalgia | 616 (65.7) | 322 (50.5) | 158 (63.2) | 237 (59.1) | 1333 (59.9) |
| Nausea | 300 (32.0) | 98 (15.4) | 66 (26.4) | 112 (27.9) | 576 (25.9) |
| Body temperature increased | 59 (6.3) | 36 (5.6) | 12 (4.8) | 33 (8.2) | 140 (6.3) |
| Pyrexia | 513 (54.7) | 103 (16.1) | 111 (44.4) | 154 (38.4) | 881 (39.6) |
| Hyperpyrexia | 12 (1.3) | 0 | 3 (1.2) | 1 (0.2) | 16 (0.7) |
| **Dose 2** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 186 (100) | 204 (100) | NA | 139 (100) | 529 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 13 (7.0) | 9 (4.4) | NA | 24 (17.3) | 46 (8.7) |
| Injection site haematoma | 16 (8.6) | 8 (3.9) | NA | 7 (5.0) | 31 (5.9) |
| Injection site induration | 0 (0.0) | 1 (0.5) | NA | 0 (0.0) | 1 (0.2) |
| Injection site inflammation | 30 (16.1) | 18 (8.8) | NA | 37 (26.6) | 85 (16.1) |
| Injection site pain | 97 (52.2) | 93 (45.6) | NA | 78 (56.1) | 268 (50.7) |
| Injection site pruritus | 6 (3.2) | 8 (3.9) | NA | 4 (2.9) | 18 (3.4) |
| Injection site reaction | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 22 (11.8) | 21 (10.3) | NA | 33 (23.7) | 76 (14.4) |
| Injection site warmth | 20 (10.8) | 16 (7.8) | NA | 30 (21.6) | 66 (12.5) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 20 (10.8) | 30 (14.7) | NA | 37 (26.6) | 87 (16.4) |
| Chills | 31 (16.7) | 56 (27.5) | NA | 58 (41.7) | 145 (27.4) |
| Fatigue | 73 (39.2) | 86 (42.2) | NA | 84 (60.4) | 243 (45.9) |
| Headache | 76 (40.9) | 80 (39.2) | NA | 67 (48.2) | 223 (42.2) |
| Malaise | 62 (33.3) | 101 (49.5) | NA | 97 (69.8) | 260 (49.1) |
| Myalgia | 57 (30.6) | 70 (34.3) | NA | 75 (54.0) | 202 (38.2) |
| Nausea | 21 (11.3) | 30 (14.7) | NA | 40 (28.8) | 91 (17.2) |
| Body temperature increased | 7 (3.8) | 11 (5.4) | NA | 9 (6.5) | 27 (5.1) |
| Pyrexia | 20 (10.8) | 47 (23.0) | NA | 59 (42.4) | 126 (23.8) |
| Hyperpyrexia | 0 (0.0) | 1 (0.5) | NA | 0 (0.0) | 1 (0.2) |

**Legend:** percentages calculated based on the specific PT Term for solicited ADR over the number of vaccinee-reported solicited and non-solicited ADRs, by COVID-19 vaccine manufacturer. The table include data pooled across countries.
**Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term, y.o.= years old

**Children/Adolescents (5-17 years old)**

Among the local solicited ADRs and following the receipt of the first and the second dose, injection site pain was the most frequently reported ADR for all vaccine manufacturers. Among the list of systematic solicited ADR and following the receipt of the first dose, fatigue and myalgia were the most frequently reported ADR for participants vaccinated with the BioNTech/Pfizer vaccine and the Moderna vaccines, respectively. Following the receipt of the second dose, fatigue was the most frequently ADR for the participants receiving the BioNTech/Pfizer vaccine.

***Table 29.*** *Frequency of reported local and systemic solicited ADRs in the group of children/adolescents by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine*

| **Type of ADR** | **COVID-19 vaccine manufacturer** | | | |
|---|---|---|---|---|
| | **AstraZeneca** | **BioNTech/Pfizer** | **Moderna** | **Total vaccines** |
| **Dose 1** | | | | |
| **Subjects with at least one ADR** Number of participants | 3 | 232 [a] | 7 | 242 [a] |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | |
| Injection site erythema | 0 (0.0) | 9 (3.9) | 2 (28.6) | 11 (4.6) |
| Injection site haematoma | 0 (0.0) | 7 (3.0) | 0 (0.0) | 7 (2.9) |
| Injection site induration | 0 (0.0) | 1 (0.4) | 1 (14.3) | 2 (0.8) |
| Injection site inflammation | 1 (33.3) | 24 (10.3) | 2 (28.6) | 27 (11.2) |
| Injection site pain | 2 (66.7) | 149 (64.2) | 5 (71.4) | 156 (64.5) |
| Injection site pruritus | 0 (0.0) | 8 (3.4) | 0 (0.0) | 8 (3.3) |
| Injection site reaction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 1 (33.3) | 29 (12.5) | 1 (14.3) | 31 (12.8) |
| Injection site warmth | 0 (0.0) | 12 (5.2) | 2 (28.6) | 14 (5.8) |
| **Systemic solicited adverse reactions (MedDRA PT)** Number of participants (%) | | | | |
| Arthralgia | 1 (33.3) | 20 (8.6) | 0 (0.0) | 21 (8.7) |
| Chills | 2 (66.7) | 22 (9.5) | 0 (0.0) | 24 (9.9) |
| Fatigue | 2 (66.7) | 92 (39.7) | 1 (14.3) | 95 (39.3) |
| Headache | 2 (66.7) | 70 (30.2) | 1 (14.3) | 73 (30.2) |
| Malaise | 2 (66.7) | 50 (21.6) | 1 (14.3) | 53 (21.9) |
| Myalgia | 1 (33.3) | 80 (34.5) | 4 (57.1) | 85 (35.1) |
| Nausea | 1 (33.3) | 33 (14.2) | 0 (0.0) | 34 (14.0) |
| Body temperature increased | 1 (33.3) | 7 (3.0) | 2 (28.6) | 10 (4.1) |
| Pyrexia | 2 (66.7) | 27 (11.6) | 0 (0.0) | 29 (12.0) |
| Hyperpyrexia | | | | |
| **Dose 2** | | | | |
| **Subjects with at least one ADR** Number of participants | NA | 114 | 2 | 116 |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | |
| Injection site erythema | NA | 4 (3.5) | 0 (0.0) | 4 (3.4) |
| Injection site haematoma | NA | 1 (0.9) | 0 (0.0) | 1 (0.9) |
| Injection site induration | NA | 0 (0.0) | 0 (0.0) | 0 |
| Injection site inflammation | NA | 14 (12.3) | 2 (100) | 16 (13.8) |
| Injection site pain | NA | 57 (50.0) | 2 (100) | 59 (50.9) |
| Injection site pruritus | NA | 2 (1.8) | 0 (0.0) | 2 (1.7) |
| Injection site reaction | NA | 0 (0.0) | 0 (0.0) | 0 |
| Injection site swelling | NA | 11 (9.6) | 2 (100) | 13 (11.2) |
| Injection site warmth | NA | 11 (9.6) | 2 (100) | 13 (11.2) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | |
| Arthralgia | NA | 18 (15.8) | 0 (0.0) | 18 (15.5) |
| Chills | NA | 25 (21.9) | 0 (0.0) | 25 (21.6) |
| Fatigue | NA | 65 (57.0) | 1 (50.0) | 66 (56.9) |
| Headache | NA | 58 (50.9) | 0 (0.0) | 58 (50.0) |
| Malaise | NA | 41 (36.0) | 0 (0.0) | 41 (35.3) |
| Myalgia | NA | 39 (34.2) | 0 (0.0) | 39 (33.6) |
| Nausea | NA | 24 (21.1) | 0 (0.0) | 24 (20.7) |
| Body temperature increased | NA | 12 (10.5) | 2 (100) | 14 (12.1) |
| Pyrexia | NA | 23 (20.2) | 0 (0.0) | 23 (19.8) |
| Hyperpyrexia | NA | 1 (0.9) | 0 (0.0) | 1 (0.9) |

**Legend:** percentages calculated based on the specific PT Term for solicited ADR over the number of vaccinee-reported solicited and non-solicited ADRs, by COVID-19 vaccine manufacturer. The table include data pooled across countries. **a.** Includes one subject reporting at least one adverse reaction with no recorded age information**. Abbreviations:** ADR = adverse

reaction, MedDRA=Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term, y.o.= years old

**People with a history of allergy**

Among the local solicited ADRs and following the receipt of the first and the second dose, injection site pain was the most frequently reported ADR for all vaccine manufacturers. Among the list of systematic solicited ADR and following the receipt of the first dose, fatigue was the most frequently reported ADR for all vaccines manufacturers, along with headache reported at higher rate following the vaccination with the Janssen vaccine. Following the receipt of the second dose, fatigue was the most frequently ADR for the participants receiving the AstraZeneca and the BioNTech/Pfizer vaccines. Malaise was reported at higher rate for the vaccinees to whom Moderna vaccine was administered.

***Table 30.*** *Frequency of reported local and systemic solicited ADRs in the group of people with a history of allergy by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine*

| Type of ADR | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | AstraZeneca | BioNTech/Pfizer | Janssen | Moderna | Total vaccines |
| **Dose 1** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 1034 (100) | 973 (100) | 310 (100) | 460 (100) | 2777 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 131 (12.7) | 49 (5.0) | 18 (5.8) | 60 (13.0) | 258 (9.3) |
| Injection site haematoma | 71 (6.9) | 36 (3.7) | 13 (4.2) | 35 (7.6) | 155 (5.6) |
| Injection site induration | 14 (1.4) | 12 (1.2) | 3 (1.0) | 12 (2.6) | 41 (1.5) |
| Injection site inflammation | 279 (27.0) | 143 (14.7) | 49 (15.8) | 126 (27.4) | 597 (21.5) |
| Injection site pain | 599 (57.9) | 537 (55.2) | 149 (48.1) | 297 (64.6) | 1582 (57.0) |
| Injection site pruritus | 61 (5.9) | 28 (2.9) | 9 (2.9) | 39 (8.5) | 137 (4.9) |
| Injection site reaction | 1 (0.1) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| Injection site swelling | 230 (22.2) | 142 (14.6) | 52 (16.8) | 109 (23.7) | 533 (19.2) |
| Injection site warmth | 189 (18.3) | 97 (10.0) | 24 (7.7) | 94 (20.4) | 404 (14.5) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 392 (37.9) | 114 (11.7) | 74 (23.9) | 64 (13.9) | 644 (23.2) |
| Chills | 643 (62.2) | 103 (10.6) | 134 (43.2) | 81 (17.6) | 961 (34.6) |
| Fatigue | 748 (72.3) | 441 (45.3) | 206 (66.5) | 222 (48.3) | 1617 (58.2) |
| Headache | 763 (73.8) | 289 (29.7) | 206 (66.5) | 157 (34.1) | 1415 (51.0) |
| Malaise | 752 (72.7) | 294 (30.2) | 193 (62.3) | 145 (31.5) | 1384 (49.8) |
| Myalgia | 674 (65.2) | 409 (42.0) | 146 (47.1) | 215 (46.7) | 1444 (52.0) |
| Nausea | 342 (33.1) | 151 (15.5) | 84 (27.1) | 79 (17.2) | 656 (23.6) |
| Body temperature increased | 66 (6.4) | 25 (2.6) | 20 (6.5) | 18 (3.9) | 129 (4.6) |
| Pyrexia | 514 (49.7) | 65 (6.7) | 114 (36.8) | 45 (9.8) | 738 (26.6) |
| Hyperpyrexia | 13 (1.3) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 14 (0.5) |
| **Dose 2** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 387 (100) | 679 (100) | NA | 354 (100) | 1420 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 23 (5.9) | 46 (6.8) | NA | 70 (19.8) | 139 (9.8) |
| Injection site haematoma | 17 (4.4) | 28 (4.1) | NA | 27 (7.6) | 72 (5.1) |
| Injection site induration | 1 (0.3) | 3 (0.4) | NA | 3 (0.8) | 7 (0.5) |
| Injection site inflammation | 55 (14.2) | 89 (13.1) | NA | 94 (26.6) | 238 (16.8) |
| Injection site pain | 156 (40.3) | 319 (47.0) | NA | 176 (49.7) | 651 (45.8) |
| Injection site pruritus | 8 (2.1) | 25 (3.7) | NA | 23 (6.5) | 56 (3.9) |
| Injection site reaction | 0 (0.0) | 3 (0.4) | NA | 0 (0.0) | 3 (0.2) |
| Injection site swelling | 45 (11.6) | 89 (13.1) | NA | 77 (21.8) | 211 (14.9) |
| Injection site warmth | 36 (9.3) | 72 (10.6) | NA | 98 (27.7) | 206 (14.5) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 33 (8.5) | 113 (16.6) | NA | 81 (22.9) | 227 (16.0) |
| Chills | 47 (12.1) | 121 (17.8) | NA | 149 (42.1) | 317 (22.3) |
| Fatigue | 167 (43.2) | 332 (48.9) | NA | 224 (63.3) | 723 (50.9) |
| Headache | 140 (36.2) | 249 (36.7) | NA | 196 (55.4) | 585 (41.2) |
| Malaise | 121 (31.3) | 271 (39.9) | NA | 235 (66.4) | 627 (44.2) |
| Myalgia | 119 (30.7) | 278 (40.9) | NA | 199 (56.2) | 596 (42.0) |
| Nausea | 51 (13.2) | 99 (14.6) | NA | 107 (30.2) | 257 (18.1) |
| Body temperature increased | 9 (2.3) | 30 (4.4) | NA | 37 (10.5) | 76 (5.4) |
| Pyrexia | 39 (10.1) | 88 (13.0) | NA | 142 (40.1) | 269 (18.9) |
| Hyperpyrexia | 0 (0.0) | 0 (0.0) | NA | 4 (1.1) | 4 (0.3) |

**Legend:** percentages calculated based on the specific PT Term for solicited ADR over the number of vaccinee-reported solicited and non-solicited ADRs, by COVID-19 vaccine manufacturer. The table include data pooled across countries.

**Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term, y.o.= years old

### Immunocompromised

Among the local solicited ADRs and following the receipt of the first and the second dose, injection site pain was the most frequently reported ADR for all vaccine manufacturers. Among the list of systematic solicited ADR and following the receipt of the first and the second dose, fatigue was the most frequently reported ADR for the group of participants receiving either the BioNTech/Pfizer, the Janssen or the Moderna vaccine. Headache was the most frequently reported ADR following the receipt of the AstraZeneca vaccine, for both first and second dose.

***Table 31**. Frequency of reported local and systemic solicited ADRs in the immunocompromised by COVID-19 vaccine manufacturer, following the first and the second dose of vaccine*

| Type of ADR | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | AstraZeneca | BioNTech/Pfizer | Janssen | Moderna | Total vaccines |
| **Dose 1** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 154 (100) | 149 (100) | 20 (100) | 82 (100) | 405 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 23 (14.9) | 13 (8.7) | 1 (5.0) | 8 (9.8) | 45 (11.1) |
| Injection site haematoma | 8 (5.2) | 8 (5.4) | 0 (0.0) | 5 (6.1) | 21 (5.2) |
| Injection site induration | 0 (0.0) | 1 (0.7) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| Injection site inflammation | 48 (31.2) | 25 (16.8) | 0 (0.0) | 18 (22.0) | 91 (22.5) |
| Injection site pain | 93 (60.4) | 83 (55.7) | 11 (55.0) | 49 (59.8) | 236 (58.3) |
| Injection site pruritus | 12 (7.8) | 3 (2.0) | 0 (0.0) | 5 (6.1) | 20 (4.9) |
| Injection site reaction | 2 (1.3) | 1 (0.7) | 0 (0.0) | 0 (0.0) | 3 (0.7) |
| Injection site swelling | 45 (29.2) | 22 (14.8) | 0 (0.0) | 20 (24.4) | 87 (21.5) |
| Injection site warmth | 37 (24.0) | 19 (12.8) | 0 (0.0) | 12 (14.6) | 68 (16.8) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 48 (31.2) | 23 (15.4) | 6 (30.0) | 13 (15.9) | 90 (22.2) |
| Chills | 85 (55.2) | 21 (14.1) | 10 (50.0) | 14 (17.1) | 130 (32.1) |
| Fatigue | 100 (64.9) | 68 (45.6) | 17 (85.0) | 39 (47.6) | 224 (55.3) |
| Headache | 101 (65.6) | 36 (24.2) | 14 (70.0) | 32 (39.0) | 183 (45.2) |
| Malaise | 97 (63.0) | 47 (31.5) | 16 (80.0) | 30 (36.6) | 190 (46.9) |
| Myalgia | 93 (60.4) | 57 (38.3) | 11 (55.0) | 36 (43.9) | 197 (48.6) |
| Nausea | 52 (33.8) | 23 (15.4) | 6 (30.0) | 14 (17.1) | 95 (23.5) |
| Body temperature increased | 7 (4.5) | 7 (4.7) | 1 (5.0) | 4 (4.9) | 19 (4.7) |
| Pyrexia | 61 (39.6) | 8 (5.4) | 6 (30.0) | 9 (11.0) | 84 (20.7) |
| Hyperpyrexia | 4 (2.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (1.0) |
| **Dose 2** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 45 (100) | 108 (100) | NA | 67 (100) | 220 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 4 (8.9) | 9 (8.3) | NA | 8 (11.9) | 21 (9.5) |
| Injection site haematoma | 2 (4.4) | 7 (6.5) | NA | 7 (10.4) | 16 (7.3) |
| Injection site induration | 0 (0.0) | 2 (1.9) | NA | 0 (0.0) | 2 (0.9) |
| Injection site inflammation | 5 (11.1) | 14 (13.0) | NA | 15 (22.4) | 34 (15.5) |
| Injection site pain | 17 (37.8) | 48 (44.4) | NA | 40 (59.7) | 105 (47.7) |
| Injection site pruritus | 1 (2.2) | 4 (3.7) | NA | 6 (9.0) | 11 (5.0) |
| Injection site reaction | 0 (0.0) | - | NA | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 5 (11.1) | 14 (13.0) | NA | 18 (26.9) | 37 (16.8) |
| Injection site warmth | 5 (11.1) | 11 (10.2) | NA | 10 (14.9) | 26 (11.8) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 5 (11.1) | 17 (15.7) | NA | 21 (31.3) | 43 (19.5) |
| Chills | 6 (13.3) | 13 (12.0) | NA | 24 (35.8) | 43 (19.5) |
| Fatigue | 23 (51.1) | 43 (39.8) | NA | 47 (70.1) | 113 (51.4) |
| Headache | 24 (53.3) | 32 (29.6) | NA | 30 (44.8) | 86 (39.1) |
| Malaise | 20 (44.4) | 31 (28.7) | NA | 43 (64.2) | 94 (42.7) |
| Myalgia | 13 (28.9) | 38 (35.2) | NA | 35 (52.2) | 86 (39.1) |
| Nausea | 5 (11.1) | 18 (16.7) | NA | 18 (26.9) | 41 (18.6) |
| Body temperature increased | 2 (4.4) | 4 (3.7) | NA | 6 (9.0) | 12 (5.5) |
| Pyrexia | 3 (6.7) | 11 (10.2) | NA | 28 (41.8) | 42 (19.1) |
| Hyperpyrexia | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 0 (0.0) |

**Legend:** percentages calculated based on the specific PT Term for solicited ADR over the number of vaccinee-reported solicited and non-solicited ADRs, by COVID-19 vaccine manufacturer. The table include data pooled across countries.
**Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term, y.o.= years old

**Pregnant women**

Among the local solicited ADRs and following the receipt of the first and the second dose, injection site pain was the most frequently reported ADR for all vaccine manufacturers. Among the list of systematic solicited ADR and following the receipt of the first and the second dose, fatigue and myalgia were the most frequently reported ADR for group of participants receiving the BioNTech/Pfizer and the Moderna vaccines, respectively.

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

| Type of ADR | COVID-19 vaccine manufacturer | | | | |
|---|---|---|---|---|---|
| | AstraZeneca | BioNTech/Pfizer | Janssen | Moderna | Total vaccines |
| **Dose 1** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 2 (100) | 41 (100) | 2 (100) | 40 (100) | 85 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 0 (0.0) | 1 (2.4) | 0 (0.0) | 3 (7.5) | 4 (4.7) |
| Injection site haematoma | 0 (0.0) | 1 (2.4) | 1 (50.0) | 4 (10.0) | 6 (7.1) |
| Injection site induration | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.5) | 1 (1.2) |
| Injection site inflammation | 2 (100) | 2 (4.9) | 0 (0.0) | 7 (17.5) | 11 (12.9) |
| Injection site pain | 2 (100) | 22 (53.7) | 0 (0.0) | 26 (65.0) | 50 (58.8) |
| Injection site pruritus | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.5) | 3 (3.5) |
| Injection site reaction | 0 (0.0) | 1 (2.4) | 0 (0.0) | - | 1 (1.2) |
| Injection site swelling | 1 (50.0) | 5 (12.2) | 1 (50.0) | 6 (15.0) | 13 (15.3) |
| Injection site warmth | 2 (100) | 2 (4.9) | 0 (0.0) | 4 (10.0) | 8 (9.4) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 1 (50.0) | 1 (2.4) | 1 (50.0) | 2 (5.0) | 5 (5.9) |
| Chills | 2 (100) | 3 (7.3) | 1 (50.0) | 2 (5.0) | 8 (9.4) |
| Fatigue | 1 (50.0) | 20 (48.8) | 2 (100) | 11 (27.5) | 34 (40.0) |
| Headache | 1 (50.0) | 8 (19.5) | 1 (50.0) | 5 (12.5) | 15 (17.6) |
| Malaise | 1 (50.0) | 11 (26.8) | 1 (50.0) | 3 (7.5) | 16 (18.8) |
| Myalgia | 2 (100) | 13 (31.7) | 1 (50.0) | 14 (35.0) | 30 (35.3) |
| Nausea | 0 (0.0) | 5 (12.2) | 0 (0.0) | 3 (7.5) | 8 (9.4) |
| Body temperature increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.5) | 1 (1.2) |
| Pyrexia | 1 (50.0) | 1 (2.4) | 1 (50.0) | 0 (0.0) | 3 (3.5) |
| Hyperpyrexia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Dose 2** | | | | | |
| **Subjects with at least one ADR** Number of participants (%) | 1 (100) | 19 (100) | NA | 36 (100) | 56 (100) |
| **Local solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Injection site erythema | 0 (0.0) | 0 (0.0) | NA | 6 (16.7) | 6 (10.7) |
| Injection site haematoma | 0 (0.0) | 1 (5.3) | NA | 3 (8.3) | 4 (7.1) |
| Injection site induration | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 0 (0.0) |
| Injection site inflammation | 0 (0.0) | 5 (26.3) | NA | 9 (25.0) | 14 (25.0) |
| Injection site pain | 0 (0.0) | 11 (57.9) | NA | 21 (58.3) | 32 (57.1) |
| Injection site pruritus | 0 (0.0) | 1 (5.3) | NA | 0 (0.0) | 1 (1.8) |
| Injection site reaction | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 0 (0.0) | 3 (15.8) | NA | 7 (19.4) | 10 (17.9) |
| Injection site warmth | 0 (0.0) | 2 (10.5) | NA | 6 (16.7) | 8 (14.3) |
| **Systemic solicited ADR (MedDRA PT)** Number of participants (%) | | | | | |
| Arthralgia | 0 (0.0) | 1 (5.3) | NA | 4 (11.1) | 5 (8.9) |
| Chills | 0 (0.0) | 2 (10.5) | NA | 11 (30.6) | 13 (23.2) |
| Fatigue | 1 (100) | 10 (52.6) | NA | 16 (44.4) | 27 (48.2) |
| Headache | 0 (0.0) | 7 (36.8) | NA | 8 (22.2) | 15 (26.8) |
| Malaise | 1 (100) | 4 (21.1) | NA | 18 (50.0) | 23 (41.1) |
| Myalgia | 0 (0.0) | 9 (47.4) | NA | 20 (55.6) | 29 (51.8) |
| Nausea | 0 (0.0) | 1 (5.3) | NA | 5 (13.9) | 6 (10.7) |
| Body temperature increased | 0 (0.0) | 0 (0.0) | NA | 4 (11.1) | 4 (7.1) |
| Pyrexia | 0 (0.0) | 2 (10.5) | NA | 5 (13.9) | 7 (12.5) |
| Hyperpyrexia | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 0 (0.0) |

**Legend:** percentages calculated based on the specific PT Term for solicited ADR over the number of vaccinee-reported solicited and non-solicited ADRs, by COVID-19 vaccine manufacturer. The table include data pooled across countries.
**Abbreviations:** ADR = adverse reaction, MedDRA=Medical Dictionary for Regulatory Activities, NA= not applicable, n=number, PT=preferred term, y.o.= years old

### 1.11.1.3. Vaccinee-reported serious adverse reactions following the first dose

Overall, of 7,057 vaccinees who reported at least one ADR following the first vaccination dose, 17 (0.2%) reported at least one serious ADR. Most of the reported serious ADRs are from the Netherlands; no serious ADRs were reported in the UK.

The list of the reported serious ADRs by COVID-19 vaccine following the first dose of vaccine are depicted in Table 33.

***Table 33**. List of reported serious ADRs following the first dose in special cohorts by COVID-19 vaccine and country.*

| Country – Special target group | COVID-19 vaccine manufacturer | Reported serious ADR | N. of reported serious ADRs |
|---|---|---|---|
| **Netherlands** | | | |
| People with prior SARS-CoV-2 infection | AstraZeneca | Retinal detachment | 1 |
| | AstraZeneca | Vitreous floaters | 1 |
| | BioNTech/Pfizer | Abortion spontaneous | 1 |
| | BioNTech/Pfizer | Dyspnoea | 1 |
| | BioNTech/Pfizer | Hypersensitivity | 1 |
| | BioNTech/Pfizer | Pruritus | 1 |
| | BioNTech/Pfizer | Rash | 1 |
| People with a history of allergy | AstraZeneca | Dyspnoea | 1 |
| | AstraZeneca | Headache | 1 |
| | AstraZeneca | Pulmonary pain | 1 |
| | BioNTech/Pfizer | Myocardial infarction | 2 |
| | Janssen | Abortion spontaneous | 1 |
| | Janssen | Anaphylactic reaction | 1 |
| | Janssen | Chills | 1 |
| | Janssen | Malaise | 1 |
| | Moderna | Dizziness | 1 |
| | Moderna | Gait disturbance | 1 |
| | Moderna | Hypotension | 1 |
| | Moderna | Loss of consciousness | 1 |
| | Moderna | Vision blurred | 1 |
| Immunocompromised people | AstraZeneca | Asthma | 1 |
| | AstraZeneca | Dyspnoea | 1 |
| | BioNTech/Pfizer | Abortion spontaneous | 1 |
| Pregnant women | BioNTech/Pfizer | Abortion spontaneous | 1 |
| **Italy** | | | |
| People with prior SARS-CoV-2 infection | Moderna | Hyperpyrexia | 1 |
| People with a history of allergy | BioNTech/Pfizer | Dysentery | 1 |
| | BioNTech/Pfizer | Urticaria | 1 |
| Immunocompromised people | Moderna | Malaise | 1 |
| **France** | | | |
| Children and adolescents | BioNTech/Pfizer | Paraesthesia | 1 |
| | BioNTech/Pfizer | Swelling face | 1 |

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

### 1.11.1.4. Vaccinee-reported serious adverse reactions following the second dose

Overall, of 3793 vaccinees who reported at least one ADR following the second vaccination dose, 9 (0.2%) reported at least one serious ADR. Most of the reported serious ADRs are from the Netherlands; no serious ADRs were reported in the UK and France. The list of the reported serious ADRs by COVID-19 vaccine following the second dose are depicted in Table 34.

***Table 34.*** *List of reported serious adverse reactions following the second dose in special target group by COVID-19 vaccine manufacturer and country.*

| Country – Special target group | COVID-19 vaccine manufacturer | Reported serious ADR | N. of reported serious ADRs |
|---|---|---|---|
| **Netherlands** | | | |
| People with prior SARS-CoV-2 infection | BioNTech/Pfizer | Eye haemorrhage | 1 |
| People with a history of allergy | BioNTech/Pfizer | Hypertension | 1 |
| | BioNTech/Pfizer | Lacunar infarction | 1 |
| | BioNTech/Pfizer | Malaise | 1 |
| | Moderna | Arthritis | 1 |
| Immunocompromised people | BioNTech/Pfizer | Hypertension | 1 |
| | BioNTech/Pfizer | Malaise | 1 |
| | Moderna | Arthritis | 1 |
| **Italy** | | | |
| People with a history of allergy | BioNTech/Pfizer | Haematochezia | 1 |
| | BioNTech/Pfizer | Herpes zoster | 1 |
| Children/adolescents | BioNTech/Pfizer | Haematochezia | 1 |

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

### 1.11.1.5. Vaccinee-reported adverse events of special interest following the first and second dose

Overall, out of the total of vaccinees who reported at least one ADR following the first (N= 7,057) and second (N= 3,793) vaccination dose, 25 (0.4%) and 15 (0.4%) vaccinees reported at least one AESI following the first and second vaccination dose, respectively. Most of the data comes from the Netherlands; no AESIs were reported in Italy and the UK. A thorough analysis including age, gender, reported AESIs and outcome will give more insight into these reactions and the participants who have reported these.

Tables 35 and 36 show the list of the reported events of special interest (AESIs) following the first and second dose, respectively.

***Table 35**. List of reported adverse events of special interest following the first dose in special target group by COVID-19 vaccine manufacturer and country.*

| Country – Special target group | COVID-19 vaccine manufacturer | Reported AESI | N. of AESI |
|---|---|---|---|
| **Netherlands** | | | |
| People with prior SARS-CoV-2 infection | AstraZeneca | Arrhythmia | 1 |
| | BioNTech/Pfizer | Hypersensitivity | 1 |
| | Janssen | COVID-19 | 1 |
| | Moderna | Hypersomnia | 1 |
| People with a history of allergy | AstraZeneca | Arrhythmia | 2 |
| | AstraZeneca | COVID-19 | 2 |
| | AstraZeneca | Facial paralysis | 1 |
| | AstraZeneca | Hypersensitivity | 4 |
| | BioNTech/Pfizer | Hypersensitivity | 4 |
| | BioNTech/Pfizer | Myocardial infarction | 2 |
| | Janssen | Anaphylactic reaction | 1 |
| | Janssen | Generalised tonic-clonic seizure | 1 |
| | Moderna | Hypersensitivity | 1 |
| Immunocompromised people | AstraZeneca | COVID-19 | 1 |
| | AstraZeneca | Epilepsy | 1 |
| **France** | | | |
| People with a history of allergy | BioNTech/Pfizer | COVID-19 | 1 |
| | BioNTech/Pfizer | Pericarditis | 1 |

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

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

| Country – Special target group | COVID-19 vaccine manufacturer | Reported AESI | N. of AESI |
|---|---|---|---|
| **Netherlands** | | | |
| People with a history of allergy | AstraZeneca | Arrhythmia | 1 |
| | AstraZeneca | COVID-19 | 4 |
| | AstraZeneca | Hypersensitivity | 1 |
| | BioNTech/Pfizer | Arrhythmia | 2 |
| | BioNTech/Pfizer | COVID-19 | 1 |
| | BioNTech/Pfizer | Hypersensitivity | 3 |
| | Moderna | Arrhythmia | 1 |
| Immunocompromised people | BioNTech/Pfizer | Arrhythmia | 1 |
| | Moderna | Platelet count decreased | 1 |

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

### 1.11.2. Research Online data source

In this section, we present data from the special target populations receiving the first and/or second dose of COVID-19 vaccines collected through the Research Online (RO) web app by five countries: Italy, Romania, Slovakia, Spain, and Switzerland. Table 37 summarizes the recruited special target groups, the total number of inclusions until the 9th of February 2022, and the exact recruitment start date for each country. Please note that a single participant may belong to more special cohorts and therefore, the table should be read across the columns.

The number of recruited participants for the CVM study reflect the state of the vaccination campaign across the participating countries, in which most of the eligible people have already received at least their first dose of vaccine, except for the group of children aged 5-11 years old. For all countries but Switzerland, currently recruiting only pregnant and lactating women, children aged 5-11 years old were recruited in higher numbers compared to all other special target group.

***Table 37.*** *Number of participants belonging to the special target groups who filled in the baseline questionnaire by Country*

| Country | Special target group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection** | **Children 5-11 y.o.** | **Adole-scents 12-17 y.o.** | **People with history of allergy** | **Immuno compro-mised** | **Pregnant women** | **Lactating women** | **Tool** | **Recruitment start date** |
| **Italy** | 23 | 79 | 5 | 22 | 1 | 31 | 17 | RO | 09/10/2021 |
| **Romania** | 11 | 64 | 1 | 5 | 1 | NA | 1 | RO | 01/12/2021 |
| **Slovakia** | 13 | 71 | 1 | 13 | NA | NA | NA | RO | 11/01/2022 |
| **Spain** | NA | 8 | 2 | 1 | NA | NA | NA | RO | 13/12/2021 |
| **Switzerland** | 2 | NA | NA | NA | NA | 1 | 4 | RO | 19/01/2022 |
| **Total** | **49** | **222** | **9** | **41** | **2** | **32** | **22** | | |

**Abbreviations:** NA= not applicable**,** y.o.= years old

#### 1.11.2.1. Baseline characteristics

Table 38 shows the distribution of registered vaccinee by subgroup and vaccine. For each special target group, more than three quarter of the vaccinees have received the Pfizer/BioNTech vaccine. Children and adolescents, here pooled together in the same group, have almost exclusively received the Pfizer/BioNTech (99.1%). Except for the Moderna vaccine, administered to a minority of subjects and in particular in Italy, no other vaccine manufacturer was used across the groups and countries.

When data was pooled together, the majority of participants across the groups of people with prior SARS-CoV-2 infection and people with a history of allergy were females. For the group of children/adolescents the F/M was lower than 1 (0.9).

***Table 38.*** *Number of participants belonging to the special target groups by COVID-19 vaccine manufacturer for each country*

| Country/ COVID-19 vaccine manufacturer | Distribution | Special target group | | | | | |
|---|---|---|---|---|---|---|---|
| | | People with prior SARS-CoV-2 infection | Children and Adolescents (5-17 y.o.) | People with a history of allergy | Immuno-compromised | Pregnant women | Lactating women |
| **Italy** | | | | | | | |
| BioNTech/ Pfizer | n vaccinees (%) | 17 (73.9) | 82 (97.6) | 17 (77.3) | 1 (100) | 27 (87.1) | 15 (88.2) |
| | F/M ratio | 1.4 | 0.7 | 0.9 | - | - | - |
| Moderna | n vaccinees (%) | 6 (26.1) | 2 (2.4) | 5 (22.7) | NA | 4 (12.9) | 2 (11.8) |
| | F/M ratio | 5 | 1 | 4 | NA | - | - |
| **All vaccines** | **n vaccinees (%)** | **23 (100)** | **84 (100)** | **22 (100)** | **1 (100)** | **31 (100)** | **17 (100)** |
| | **F/M ratio** | **1.9** | **0.8** | **1.2** | **-** | **-** | **-** |
| **Romania** | | | | | | | |
| BioNTech/ Pfizer | n vaccinees (%) | 11 (100) | 65 (100) | 5 (100) | 1 (100) | NA | 1 (100) |
| | F/M ratio | 0.6 | 0.8 | 1.5 | 0 | NA | - |
| **All vaccines** | **n vaccinees (%)** | **11 (100)** | **65 (100)** | **5 (100)** | **1 (100)** | NA | **1 (100)** |
| | **F/M ratio** | **0.6** | **0.8** | **1.5** | **0** | NA | **-** |
| **Slovakia** | | | | | | | |
| BioNTech/ Pfizer | n vaccinees (%) | 13 (100) | 72 (100) | 13 (100) | NA | NA | NA |
| | F/M ratio | 0.9 | 1.1 | 1.2 | NA | NA | NA |
| **All vaccines** | **n vaccinees (%)** | **13 (100)** | **72 (100)** | **13 (100)** | **NA** | **NA** | **NA** |
| | **F/M ratio** | **0.9** | **1.1** | **1.2** | **NA** | **NA** | **NA** |
| **Spain** | | | | | | | |
| BioNTech/ Pfizer | n vaccinees (%) | NA | 10 (100) | 1 (100) | NA | NA | NA |
| | F/M ratio | NA | 1.5 | 0 | NA | NA | NA |
| **All vaccines** | **n vaccinees (%)** | **NA** | **10 (100)** | **1 (100)** | **NA** | **NA** | **NA** |
| | **F/M ratio** | **NA** | **1.5** | **0** | **NA** | **NA** | **NA** |
| **Switzerland** | | | | | | | |
| BioNTech/ Pfizer | n vaccinees (%) | 1 (50.0) | NA | NA | NA | 1 (100) | 3 (75.0) |
| | F/M ratio | - | NA | NA | NA | - | - |
| Moderna | n vaccinees (%) | 1 (50.0) | NA | NA | NA | NA | 1 (25.0) |
| | F/M ratio | - | NA | NA | NA | NA | - |
| **All vaccines** | **n vaccinees (%)** | **2 (100)** | **NA** | **NA** | **NA** | **1 (100)** | **4 (100)** |
| | **F/M ratio** | **-** | **NA** | **NA** | **NA** | **-** | **-** |
| **All countries** | | | | | | | |
| BioNTech/ Pfizer | n vaccinees (%) | 42 (85.7) | 229 (99.1) | 36 (87.8) | 2 (100) | 28 (87.5) | 19 (86.4) |
| | F/M ratio | 1 | 0.9 | 1 | 1 | - | - |
| Moderna | n vaccinees (%) | 7 (14.3) | 2 (0.9) | 5 (12.2) | NA | 4 (12.5) | 3 (13.6) |
| | F/M ratio | 6 | 1 | 4 | NA | - | - |
| **All vaccines** | **n vaccinees (%)** | **49 (100)** | **231 (100)** | **41 (100)** | **2 (100)** | **32 (100)** | **22 (100)** |
| | **F/M ratio** | **1.2** | **0.9** | **1.2** | **1** | **-** | **-** |

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

Table 39 shows the number of participants belonging to the special target group by age group and sex following the first dose of the vaccine. Most of participants belonging to the groups of people with prior SARS-CoV-2 infection, with history of allergy, and immunocompromised, were aged between 5 and 11 years. Most of pregnant women and lactating women were between 30 and 39 years at the time they filled in the baseline questionnaire.

***Table 39.*** *Number of participants belonging to the special target groups by age group and sex following the first dose of vaccine.*

| Characteristics | Special target group | | | | | |
|---|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection** | **Children/ Adolescents (5-17 y.o.)** | **People with history of allergy** | **Immuno-Compromised** | **Pregnant Women** | **Lactating women** |
| **N of participants (%)** | 49 (100) | 231 (100) | 41 (100) | 2 (100) | 32 (100) | 22 (100) |
| **Age group (y.o.)** | **n (%)** | | | | | |
| 5 – 11 | 30 (61.3) | 222 (96.1) | 24 (58.5) | 2 (100) | 0 (0.0) | 0 (0.0) |
| 12 – 17 | 1 (2.0) | 9 (3.9) | 4 (9.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 18 – 24 | 2 (4.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.5) |
| 25 – 29 | 1 (2.0) | 0 (0.0) | 2 (4.9) | 0 (0.0) | 8 (25.0) | 1 (4.5) |
| 30 – 39 | 7 (14.3) | 0 (0.0) | 6 (14.6) | 0 (0.0) | 18 (56.2) | 19 (86.5) |
| 40 – 49 | 7 (14.3) | 0 (0.0) | 4 (9.8) | 0 (0.0) | 6 (18.8) | 1 (4.5) |
| 50 – 59 | 0 (0.0) | 0 (0.0) | 1 (2.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 60 – 69 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 70 – 79 | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| >80 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Sex** | **n (%)** | | | | | |
| Female | 27 (55.1) | 108 (46.8) | 22 (53.7) | 1 (50.0) | 32 (100) | 22 (100) |
| Male | 22 (44.9) | 123 (53.2) | 19 (46.3) | 1 (50.0) | NA | NA |

**Abbreviations:** N=total number; n=number; y.o.=years old

### 1.11.2.2. Vaccinee-reported adverse reactions

Table 40 provides an overview of the frequency of all reported ADRs (solicited and unsolicited), with their percentages calculated based on the number of participants reporting ADRs over the number of vaccinees receiving a specific vaccine. The frequency of the reported ADRs across all countries is depicted by special cohort, vaccine manufacturer, and following the first dose of vaccine.

More than half of lactating women and participants with prior SARS-CoV-2 infection have reported at least one adverse reaction at a rate of 59.2% and 59.1%, respectively. A rate lower or equal than 50% was observed for all other groups. Among 222 children aged 5-11 years old, 72 reported at least one ADR following the administration of the first dose of the Pfizer/BioNTech vaccine.

We also reported in Table 41 the frequency of all reported ADRs, with their percentages calculated based on the number of reported ADRs over the number of vaccinees having completed both the baseline questionnaire and the questionnaire 1. Similarly, to Table 40, the frequency of the reported ADRs across all countries is depicted by special cohort, vaccine manufacturer, and following the first dose of vaccine. Across all groups, the percentage of reported ADRs increases if considering only the number of people having filled in both baseline questionnaire and questionnaire 1, with highest reporting rate still observed for lactating women and people with prior SARS-CoV-2 infection.

***Table 40.*** *Overview of the number of vaccinee-reported solicited and non-solicited adverse reactions in questionnaire 1 over the number of vaccinees having filled in the baseline questionnaire*

| **COVID-19 vaccine manufacturer** | **Special target group** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection**<br><br>Any ADR/ Any vaccinees (%) | **Children (5-11 y.o.)**<br><br>Any ADR/ Any vaccinees (%) | **Adolescents (12-17 y.o.)**<br><br>Any ADR/ Any vaccinees (%) | **People with history of allergy**<br><br>Any ADR/ Any vaccinees (%) | **Immuno-compro-mised**<br><br>Any ADR/ Any vaccinees (%) | **Pregnant Women**<br><br>Any ADR/ Any vaccinees (%) | **Lactating women**<br><br>Any ADR/ Any vaccinees (%) |
| BioNTech/Pfizer | 20/42 (47.6) | 72/222 (32.4) | 1/7 (14.3) | 13/36 (36.1) | 1/2 (50.0) | 12/28 (42.9) | 12/19 (63.2) |
| Moderna | 5/7 (71.4) | NA | 2/2 (100) | 5/5 (100) | NA | 3/4 (75.0) | 1/3 (33.3) |
| **All vaccines** | **25/49 (51.0)** | **72/222 (32.4)** | **3/9 (33.3)** | **18/41 (43.9)** | **1/2 (50.0)** | **15/32 (46.9)** | **13/22 (59.1)** |

**Legend:** percentages calculated based on the number of solicited and non-solicited adverse reactions reported in questionnaire 1 over the number of vaccinees having filled in the baseline questionnaire, by COVID-19 vaccine manufacturer. The table include data pooled across countries. **Abbreviations:** N=total number, NA=not applicable, n=number, y.o.=years old

***Table 41.*** *Overview of the number of vaccinee-reported solicited and non-solicited adverse reactions in questionnaire 1 over the number of vaccinees having filled in the baseline questionnaire and questionnaire 1.*

| **COVID-19 vaccine manufacturer** | **Special target group** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **People with prior SARS-CoV-2 infection**<br><br>Any ADR/ Any vaccinees (%) | **Children (5-11 y.o.)**<br><br>Any ADR/ Any vaccinees (%) | **Adolescents (12-17 y.o.)**<br><br>Any ADR/ Any vaccinees (%) | **People with history of allergy**<br><br>Any ADR/ Any vaccinees (%) | **Immuno-compromised**<br><br>Any ADR/ Any vaccinees (%) | **Pregnant Women**<br><br>Any ADR/ Any vaccinees (%) | **Lactating women**<br><br>Any ADR/ Any vaccinees (%) |
| BioNTech/Pfizer | 20/34 (58.8) | 72/180 (40.0) | 1/5 (20.0) | 13/27 (48.1) | 1/1 (100) | 12/21 (57.1) | 12/15 (80.0) |
| Moderna | 5/5 (100) | NA | 2/2 (100) | 5/5 (100) | NA | 3/4 (75.0) | 1/2 (50.0) |
| **All vaccines** | **25/39 (64.1)** | **72/180 (40.0)** | **3/7 (42.9)** | **18/32 (56.3)** | **1/1 (100)** | **15/25 (60.0)** | **13/17 (76.5)** |

**Legend:** percentages calculated based on the number of solicited and non-solicited adverse reactions reported in questionnaire 1 over the number of vaccinees having filled in the baseline questionnaire, by COVID-19 vaccine manufacturer. The table include data pooled across countries. **Abbreviations:** N=total number, NA=not applicable, n=number, y.o.=years old

## 1.12. Discussion: Monitoring of the special target groups receiving a first (and possibly second) dose of any COVID-19 vaccine

### 1.12.1. Key findings

This study focuses on first dose vaccinees with special conditions: prior SARs-Cov-2, history of allergies, Children, adolescents, immunocompromised, and pregnant and lactating women. Data were collected using the LIM app or Croatian system (as reported above) and through Research Online in eight countries.

Overall, of 7,057 special population vaccinees using the LIM app or Croatian system who reported at least one ADR following the first vaccination dose, 17 (0.2%) reported at least one serious ADR, this is the same as for the overall population reported above. Overall, of 3,793 vaccinees who reported at least one ADR following the second vaccination dose, 9 (0.2%) reported at least one serious ADR. Out of the total of vaccinees who reported at least one ADR following the first (N= 7,057) and second (N= 3,793) vaccination dose, 25 (0.4%) and 15 (0.4%) vaccinees reported at least one AESI following the first and second vaccination dose, respectively. On the basis of the Research Online app that was used in Italy, Romania, Slovakia, Spain and Switzerland, 377 first dose vaccinees with one of the special conditions were included mostly children and persons with prior Sars-Cov-2 infection. More than half of lactating women and participants with prior SARS-CoV-2 infection reported at least one adverse reaction at a rate of 59.2% and 59.1%, respectively. A rate lower or equal than 50% was observed for all other special groups. Among 222 children aged 5-11 years old, 72 (32.4%) reported at least one ADR following the administration of the first dose of the Pfizer/BioNTech vaccine.

The most reported solicited local adverse reaction among all the COVID-19 vaccine brands, special cohorts, and between 1$^{st}$ and 2$^{nd}$ dose is injection site pain. This is in line with the general population observations (and with previously published works). Among the solicited systemic adverse reactions, fatigue, headache, malaise, and myalgia, were the most frequently reported events, which is consistent with total populations.

Serious adverse reactions and AESI were uncommon among each of the special cohorts, although sample size differs. This is also in line with the general populations' pivotal clinical trials and this study's results in general populations.

Considering fragile cohorts of special interest like children and pregnant women, some preliminary findings with the data in our hands can be stated:

**Pregnant Women:**

- Serious ADRs following COVID-19 vaccination are uncommon
- 8 cases in total (referring to both general population section) of spontaneous abortion were observed. However, only one case is recorded as a pregnant woman at baseline at the date of vaccination.
- No AESI were observed.

**Children/adolescents:**

- Serious ADRs following COVID-19 vaccination are uncommon
- No cases of myocarditis and pericarditis have been reported.

- No AESI were observed.

**Immunocompromised, people with history of allergy, people with prior COVID-19:**

- Serious ADRs and AESI after COVID-19 vaccinations are uncommon
- Among the observed AESI, COVID-19 infection, hypersensitivity, and arrhythmia, have been the most frequently reported.

### 1.12.2. Limitations

Several limitations need to be considered LIM web app data and those from RO could not yet be combined for this interim report, and are therefore reported separately. Although the questionnaires used in the LIM system were used as a blueprint for the RO questionnaires, there are important differences in the data of both systems. First of all, RO as tool is developed with a different technical approach compared to the LIM system which leads to different implementations of forms and sometimes questions in the forms. Second, RO and the LIM system focus on different populations. LIM focused on ADRs in the general population with a later addition of some cohort information. The RO system primarily focused on the special cohorts when registering the 1st/2nd vaccination ADRs. For the Booster, RO had to combine the focus on special cohorts as well as on the general population. As a result, in RO, more detailed cohort specific questions were added which only partially overlap with LIM data. But also, the link between participant registration and data collection is different in both systems. Third, the participation in the LIM system was restricted by the rule of a completed baseline and Q1 form in all subjects. In RO this restriction was not implemented. One of the reasons not to use this rule was the pregnancy questionnaire. In fact, important parts of this questionnaires were placed and planned in Q6. With a strict participation rule like in the LIM system, the number of subjects filling in any forms in Q6 would have been strongly reduced. A less initial strict participation rule allows for a rigorous restriction at the backend of the system, in order to mimic the LIM system. This strategy also allows for more data to be captured. Unfortunately, it also complicates to obtain an exact copy of the LIM participation rules. Finally, some of the LIM questions were modified and/or made obligatory in RO before the start of the study.

Merging LIM and RO data demands a common data model, which is being developed and will be in place for the final report.

Lactating women are a special target group for the CVM WP1 study, but their data could not be collected through the LIM web app. In the LIM web app, there are no questions to identify lactating women. Conversely, RO has been designed to identify lactating women among the other specific population. However, considering the state of the current vaccination campaign, it is very unlikely that more lactating women will be recruited following the receipt of the first dose of vaccine. The LIM web app was also not design to collect specific information regarding pregnant women. Therefore, women may have not indicated they were pregnant when filling in the baseline questionnaire, meaning that we might have underestimated the number of pregnant women registered to the study while pregnant.

In terms of chances of enrolling people in the study, it is also very unlikely that more immunocompromised subjects will be recruited, unless they are subjects aged between 5 and 11 years.

RO has been active since October 2021 to recruit individuals receiving a first dose of vaccine. However, for each special cohort, the number of subjects recruited as of the 9th of February 2022 is less than 100, except for the group of children aged between 5 and 11 years. There is also a considerable number of participants not completing Q1 and, therefore, not providing information of possible ADRs experienced. This will prevent us from making more insightful consideration of the data collected through the RO web app until we combine them with the data collected through the LIM web app.

For this report, we used PTs to describe the medical conditions for each special target group as only PTs were available in our LIM web app dataset. Because more than one LLT may relate to the same PT, we could not calculate the percentage of the number of participants having a specific medical history condition over the number of total participants. Moreover, since the data are available on the aggregated level only and that LLTs are yet included in the dataset used for this report, we were only able to provide raw data. Data on the aggregated level prevented us to better characterize the subject who experienced an AESI or a serious ADR.

Some subjects belonging to the children and adolescents' group might not have been identified if the parents, or the legal representative who filled in the questionnaire on their behalf, have erroneously indicated not their children and adolescents' date of birth.

### 1.12.3. Discussion

We show in this preliminary analysis that the safety profile for the vaccines after first dose does not differ substantially between the general population and the special populations. Solicited reactions are common whereas serious reactions and AESI are uncommon to rare, across each of the special populations. However, conclusion should be cautious as the sample size in each of the special groups is limited

Pfizer/BioNTech and Moderna are the only two COVID-19 vaccines authorized in the 12-17 age group. In addition, Pfizer/BioNTech is also authorized for the age group 5-11. Given the vaccination campaign, vaccinees receiving Moderna vaccine and registering to the study are still low compared to the ones receiving Pfizer/BioNTech vaccine. Considering the state of the current vaccination strategy in the majority of the countries included in the CVM study, it is unlikely that more adolescents will be recruited following the receipt of a first dose of vaccine. Conversely, the number of participants aged 5-11 years old may still increase, since, as of February 2022, only a minority have received their first dose. Moreover, from the end of February 2022, an extension of indication for the Moderna vaccine use for children aged 6 to 11 has been granted by the EMA. In consideration of the differences between participants aged 5 to 11 and those aged 12 to 17, the group of children/adolescents has been split into two groups where possible. This distinction was also necessary due to the different dosage of Pfizer/BioNTech for children aged 5 to 11 than the dosage offered to individuals aged 12 to 17.

Generally, most of the participants were females. While the difference between the number of female and male registered to the RO web app is not striking, for the LIM web app data female represents three-quarters of the overall participants across the people, with prior SARS-CoV-2 infection, those with a history of allergy, and the immunocompromised. Higher frequency of immunologic diseases and allergic conditions among females is expected in the general population. (Gleicher et al, Vollenhoven, Kvien et al.) A possible explanation for the sex gap between participants observed in this study could relate to the propensity of females to report drug's adverse reactions more often than

males (Watson et al. De Vries et al).The less pronounced difference in the female/male ratio in the group of children and adolescents may be explained by the fact that these subjects require a legal representative to register and fill the questionnaires for them. Therefore, the number of children/adolescents should not reflect the tendency of women to be overrepresented in studies based on spontaneous reporting systems.

Age differed widely among the different vaccine recipients participating in this study; older participants represent only a narrower study population. In terms of time, the probability to enroll these subjects in the study was low as the vaccination campaign prioritized the vaccination of fragile people, such as the elderly. Moreover, older people may face difficulties using technologies like smartphones and computers, which are essential tools for filling in the questionnaires.

Regarding data collected through the LIM web app, the ADRs (solicited and unsolicited) are reported at a similar rate across the special target groups of people with prior SARS-CoV-2 infection, a history of allergy, immunocompromised, and pregnant women, when individual COVID-19 vaccine manufacturers are considered. While the low number of participants registered to the RO web app prevent us to make similar consideration for these specific groups of participants, we observed that the percentage of reported ADRs for the children and adolescents' group was the lowest in both the LIM and the RO web app.

According to the available information collected through the LIM web app on the solicited ADRs in general population and to already published studies (Mac Donald et al) injection site pain as a local reaction and headache, fatigue, myalgia, and malaise as systemic reactions were the most frequently reported-ADRs experienced following both the first and the second dose among all the special cohorts. Overall, of 10850 ADRs reported following first and second dose vaccination, 0.2% were considered serious, across all special cohorts and for all vaccines' manufacturers. Concerning the AESI, an overall rate of 0.4% was reported among people with history of allergy, a prior SARS-CoV-2 infection, and immunocompromised, for all vaccine manufacturers and for both doses one and two. In the special group of children/adolescents, most ADRs are solicited, with injection site pain and fatigue being the most frequently reported, as seen in pivotal clinical trials (Frenck et al, Ali et al, Walter et al.). Serious ADRs are rare, with no reported cases of myocarditis and pericarditis, and no AESI were observed in children/adolescents. Similar findings were observed in the special groups of pregnant and lactating women. 8 cases of spontaneous abortion were observed among general and special cohort data, but only 1 case has been recorded as a pregnant woman at baseline at the date of vaccination. Further investigation is needed to disclose if these can be associated with the COVID-19 vaccines. Except for children, results from specific clinical pivotal trials about the safety of the EU marketed COVID-19 vaccines in most of the special populations' cohorts of this observational study are not published, limiting the comparisons between our and other reliable sources of data. On the other side, this lack of clinical trials in special cohorts confers more emphasis on the COVID-19 vaccines' safety information that can be extrapolated by this study about these populations.

## 1.13. Conclusions: Monitoring of the special target groups receiving a first (and possibly second) dose of any COVID-19 vaccine

This section summarized the data that were available as of the 9th of February 2022, including data from two sources, the LIM web app and the RO web app, and from eight different countries. The most reported solicited local adverse reaction among all the COVID-19 vaccine brands, special cohorts, and

between 1st and 2nd dose is injection site pain. This is in line with the general population observations (and with previously published works). Among the solicited systemic adverse reactions, fatigue, headache, malaise, and myalgia, were the most frequently reported events, which is consistent with total populations.

Serious adverse reactions and AESI were uncommon among each of the special cohorts, although sample size and power to detect differs. This is also in line with the general populations' pivotal clinical trials and this study's results in general populations.

Caution should be taken in interpreting the data as analysis considering participants' baseline characteristics and the adverse reaction they reported has not yet been conducted.

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

### 1.14.1. Research Online data source

Table 42 summarizes the total number of participants who belong to the special cohorts and the general population receiving a booster dose up to the 9th of February 2022, including those participants with missing vaccine manufacturer information. Although Portugal has started recruiting participants from February 5, 2022, there are no Portuguese data available for this Interim report. The next result sections only consider the subjects providing the vaccine manufacturer information. Please note that a single participant may belong to more special cohorts and that the general population group include participants that belong to the special cohorts. Therefore, the table should be read across the columns. Moreover, even if some countries are not intentionally enrolling participants belonging to some cohorts, it may still happen that a participant belonging to a targeted group for that country has characteristics that are specific for other groups too.

The cohort of children and adolescents was identified based on the age indicated by the parent/legal representative filling in the baseline questionnaire on their behalf. We excluded the subjects in the age group 0-4 years old (n=8 subjects), since we believe that some subjects may have indicated an erroneous date of birth when filling in the baseline questionnaire. Moreover, vaccination against COVID-19 was not yet approved for children aged 0-4 years old. This will require to be further investigated.

Overall, 8493 subjects belonging to the general population registered to the RO webapp and filled in the baseline questionnaire. The highest number of subjects was registered in France (n=4912) followed by Italy (n=2384). Similarly, France and Italy recruited most of the subjects belonging to the special cohorts, specifically subjects with prior SARS-CoV-2 infection and with a history of allergy. A major contribution for the group of pregnant women comes from Ireland, with 174 subjects having indicated they were pregnant at the time they filled the baseline questionnaire. For the group of children and adolescents, the majority of subjects were registered in Italy. However, considering that the vaccination campaign in Italy for those aged 5-11 started from December 2021, we did not expect a higher number of subjects aged 5-11 than those aged 12-17 years old.

***Table 42.*** *Number of Research Online (RO)participants who received the booster dose of any vaccine and filled in the baseline questionnaire by country*

| Country | Special target group | | | | | | | General population | Start recruiting date |
|---|---|---|---|---|---|---|---|---|---|
| | People with prior SARS-CoV-2 infection | Children 5-11 y.o. | Adolescents 12-17 y.o. | People with a history of allergy | Immunocompromised | Pregnant women | Lactating women | | |
| **France** | 416 | 3 | 17 | 577 | 78 | 42 | 32 | 4912 | 02/12/2021 |
| **Ireland** | 14 | NA | NA | 15 | 2 | 174 | 12 | 199 | 20/12/2021 |
| **Italy** | 234 | 47 | 26 | 297 | 100 | 61 | 40 | 2384 | 27/10/2021 |
| **Romania** | 39 | NA | 2 | 15 | 3 | 3 | 3 | 170 | 01/12/2021 |
| **Slovakia** | NA | NA | NA | 2 | NA | NA | 1 | 2 | 11/01/2022 |
| **Spain** | 22 | NA | NA | 20 | 3 | 2 | 5 | 158 | 13/12/2021 |
| **Switzerland** | 3 | NA | NA | 1 | NA | 14 | 8 | 21 | 19/01/2022 |
| **United Kingdom** | 172 | NA | 1 | 47 | 32 | 4 | 18 | 647 | 15/12/2021 |
| **Total** | **900**[a] | **50** | **46** | **974**[a] | **218** | **300** | **119**[a] | **8493**[a] | |

**Legend:** a. at least one subject did not report vaccine manufacturer information. **Abbreviations**: NA= not applicable; y.o.= years old.

## 1.14.2. Baseline characteristics

Table 43 shows the distribution of registered vaccinees by subgroup and vaccine manufacturer, for each country. As expected, participants were almost exclusively vaccinated with the BioNTech/Pfizer and the Moderna vaccines, the only two vaccines currently authorised by the EMA for the booster vaccination. Most of participants in each cohort received the BioNTech/Pfizer vaccine, especially vaccinees belonging to the cohorts of pregnant women and children/adolescents (74% and 99%, respectively). Overall, most of participants in the special target groups and in the general population were female. When stratifying by vaccine manufacturer and country, some variability is observed. When information from all countries and for all vaccine manufacturers are pooled together, the highest F/M ratio was found in the group of people with a history of allergy (2.4), while the lowest in the group of children/adolescents. Please note that Ireland should recruit only females, therefore the eligibility of the male subject registered to the study from Ireland should be validated.

***Table 43**. Number of participants and ratio female/male (F/M) by COVID-19 vaccine manufacturer and for all COVID-19 vaccine manufacturer, for each country and for all countries*

| Country/ COVID-19 vaccine manufacturer | Distribution | Special target group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Prior SARS-CoV-2 infection | Children/ Adolescents (5-17 y.o.) | People with a history of allergy | Immuno-Compro-mised | Pregnant women | Lactating women | General population |
| **France** | | | | | | | | |
| AstraZeneca | n vaccinees (%) | NA | NA | NA | NA | NA | NA | 6 (0.1) |
| | F/M ratio | NA | NA | NA | NA | NA | NA | 0.2 |
| BioNTech/ Pfizer | n vaccinees (%) | 185 (44.5) | 20 (100) | 255 (44.3) | 37 (47.4) | 24 (57.1) | 9 (28.1) | 2113 (43.0) |
| | F/M ratio | 1.8 | 1.5 | 2 | 1.1 | - | - | 1.6 |
| Janssen | n vaccinees (%) | NA | NA | NA | NA | NA | NA | 1 (0.0) |
| | F/M ratio | NA | NA | NA | NA | NA | NA | NA |
| Moderna | n vaccinees (%) | 231 (55.5) | NA | 321 (55.7) | 41 (52.6) | 18 (42.9) | 23 (71.9) | 2791 (56.9) |
| | F/M ratio | 1.4 | NA | 2.3 | 1.3 | - | - | 1.3 |
| **All vaccines** | n vaccinees (%) | **416 (100)** | **20 (100)** | **576 (100)** | **78 (100)** | **42 (100)** | **32 (100)** | **4911 (100)** |
| | F/M ratio | **1.6** | **1.5** | **2.2** | **1.2** | **-** | **-** | **1.4** |
| **Ireland** | | | | | | | | |
| AstraZeneca | n vaccinees (%) | NA | NA | NA | NA | NA | NA | 1 (0.5) |
| | F/M ratio | NA | NA | NA | NA | NA | NA | NA |
| BioNTech/ Pfizer | n vaccinees (%) | 11 (78.6) | NA | 11 (73.3) | 1 (50.0) | 140 (80.5) | 10 (83.3) | 157 (78.9) |
| | F/M ratio | - | NA | - | - | - | - | 156 |
| Moderna | n vaccinees (%) | 3 (21.4) | NA | 4 (26.7) | 1 (50.0) | 34 (19.5) | 2 (16.7) | 41 (20.6) |
| | F/M ratio | - | NA | - | - | - | - | - |
| **All vaccines** | n vaccinees (%) | **14 (100)** | NA | **15 (100)** | **2 (100)** | **174 (100)** | **12 (100)** | **199 (100)** |
| | F/M ratio | - | NA | - | - | - | - | **198** |
| **Italy** | | | | | | | | |
| AstraZeneca | n vaccinees (%) | 1 (0.4) | NA | 1 (0.3) | NA | NA | NA | 18 (0.8) |
| | F/M ratio | 0 | NA | 0 | NA | NA | NA | 1.3 |
| BioNTech/Pfizer | n vaccinees (%) | 166 (71.0) | 72 (98.6) | 179 (60.5) | 66 (66.0) | 50 (82.0) | 25 (62.5) | 1456 (61.2) |
| | F/M ratio | 1.8 | 1 | 3.2 | 2.1 | - | - | 1.8 |
| Janssen | n vaccinees (%) | NA | NA | NA | NA | NA | NA | 5 (0.2) |
| | F/M ratio | NA | NA | NA | NA | NA | NA | 0.7 |
| Moderna | n vaccinees (%) | 67 (28.6) | 1 (1.4) | 116 (39.2) | 34 (34.0) | 11 (18.0) | 15 (37.5) | 901 (37.8) |
| | F/M ratio | 1.3 | 0 | 2.7 | 1.8 | - | - | 1.2 |
| **All vaccines** | n vaccinees (%) | **234 (100)** | **73 (100)** | **296 (100)** | **100 (100)** | **61 (100)** | **40 (100)** | **2380 (100)** |
| | F/M ratio | **1.6** | **1.0** | **2.9** | **2.0** | - | - | **1.6** |
| **Romania** | | | | | | | | |
| BioNTech/Pfizer | n vaccinees (%) | 27 (69.2) | 2 (100) | 12 (80.0) | 2 (66.7) | 3 (100) | 2 (66.7) | 114 (67.1) |
| | F/M ratio | 0.9 | 1 | 0.7 | 0 | - | - | 1 |
| Janssen | n vaccinees (%) | NA | NA | NA | NA | NA | NA | 1 (0.6) |
| | F/M ratio | NA | NA | NA | NA | NA | NA | 0 |
| Moderna | n vaccinees (%) | 12 (30.8) | NA | 3 (20.0) | 1 (33.3) | NA | 1 (33.3) | 55 (32.3) |
| | F/M ratio | 1.4 | NA | - | - | NA | - | 1.5 |
| **All vaccines** | n vaccinees (%) | **39 (100)** | **2 (100)** | **15 (100)** | **3 (100)** | **3 (100)** | **3 (100)** | **170 (100)** |
| | F/M ratio | **1.1** | **1.0** | **1.4** | **0.5** | - | - | **1.1** |
| **Slovakia** | | | | | | | | |
| BioNTech/Pfizer | n vaccinees (%) | NA | NA | 1 (50.0) | NA | NA | NA | 1 (50.0) |
| | F/M ratio | NA | NA | 0 | NA | NA | NA | 0 |
| Moderna | n vaccinees (%) | NA | NA | 1 (50.0) | NA | NA | 1 (100) | 1 (50.0) |
| | F/M ratio | NA | NA | - | NA | NA | - | - |
| **All vaccines** | n vaccinees (%) | NA | NA | **2 (100)** | NA | NA | **1 (100)** | **2 (100)** |
| | F/M ratio | NA | NA | **1.0** | NA | NA | - | **1.0** |
| **Spain** | | | | | | | | |
| AstraZeneca | n vaccinees (%) | NA | NA | NA | NA | NA | NA | 1 (0.6) |
| | F/M ratio | NA | NA | NA | NA | NA | NA | 0 |
| BioNTech/Pfizer | n vaccinees (%) | 7 (31.8) | NA | 4 (20.0) | NA | NA | NA | 40 (25.3) |
| | F/M ratio | 2.5 | NA | - | NA | NA | NA | 2.1 |
| Moderna | n vaccinees (%) | 15 (68.2) | NA | 16 (80.0) | 3 (100) | 2 (100) | 5 (100) | 117 (74.1) |
| | F/M ratio | 2.0 | NA | 1.7 | 2.0 | - | - | 1.5 |
| **All vaccines** | n vaccinees (%) | **22 (100)** | NA | **20 (100)** | **3 (100)** | **2 (100)** | **5 (100)** | **158 (100)** |
| | F/M ratio | **2.1** | NA | **2.3** | **2.0** | - | - | **1.6** |

| Country/ COVID-19 vaccine manufacturer | Distribution | Special target group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Prior SARS-CoV-2 infection | Children/ Adolescents (5-17 y.o.) | People with a history of allergy | Immuno-Compro-mised | Pregnant women | Lactating women | General population |
| **Switzerland** | | | | | | | | |
| BioNTech/Pfizer | n vaccinees (%) | 1 (33.3) | NA | NA | NA | 3 (21.4) | 2 (25.0) | 5 (23.8) |
| | F/M ratio | - | NA | NA | NA | - | - | - |
| Moderna | n vaccinees (%) | 2 (66.7) | NA | 1 (100) | NA | 11 (78.6) | 6 (75.0) | 16 (76.2) |
| | F/M ratio | - | NA | - | NA | - | - | - |
| **All vaccines** | n vaccinees (%) | **3 (100)** | NA | **1 (100)** | NA | **14 (100)** | **8 (100)** | **21 (100)** |
| | F/M ratio | - | NA | - | NA | - | - | - |
| **United Kingdom** | | | | | | | | |
| AstraZeneca | n vaccinees (%) | 2 (1.2) | NA | 2 (4.2) | NA | NA | NA | 9 (1.4) |
| | F/M ratio | 0 | NA | - | NA | NA | NA | 0.8 |
| BioNTech/Pfizer | n vaccinees (%) | 105 (62.1) | 1 (100) | 35 (74.5) | 28 (87.5) | 2 (50.0) | 12 (70.6) | 400 (62.5) |
| | F/M ratio | 2.2 | - | 1.5 | 1.0 | - | - | 1.9 |
| Moderna | n vaccinees (%) | 62 (36.7) | NA | 10 (21.3) | 4 (12.5) | 2 (50.0) | 5 (29.4) | 231 (36.1) |
| | F/M ratio | 4.6 | NA | 1 | 1.0 | - | - | 1.9 |
| **All vaccines** | n vaccinees (%) | **169 (100)** | **1 (100)** | **47 (100)** | **32 (100)** | **4 (100)** | **17 (100)** | **640 (100)** |
| | F/M ratio | **2.7** | - | **1.5** | **1.0** | - | - | **1.9** |
| **All countries** | | | | | | | | |
| AstraZeneca | n vaccinees (%) | 3 (0.3) | NA | 3 (0.3) | NA | NA | NA | 35 (0.4) |
| | F/M ratio | 0 | NA | 2.0 | NA | NA | NA | 0.8 |
| BioNTech/Pfizer | n vaccinees (%) | 502 (56.0) | 95 (99.0) | 497 (51.1) | 134 (61.5) | 222 (74.0) | 60 (50.8) | 4286 (50.5) |
| | F/M ratio | 1.9 | 1.1 | 2.3 | 1.4 | - | - | 1.8 |
| Janssen | n vaccinees (%) | NA | NA | NA | NA | NA | NA | 7 (0.1) |
| | F/M ratio | NA | NA | NA | NA | NA | NA | 0.8 |
| Moderna | n vaccinees (%) | 392 (43.7) | 1 (1.0) | 472 (48.6) | 84 (38.5) | 78 (26.0) | 58 (49.2) | 4153 (49.0) |
| | F/M ratio | 1.7 | 0 | 2.4 | 1.5 | - | - | 1.3 |
| **All vaccines** | n vaccinees (%) | **897 (100)** | **96 (100)** | **972 (100)** | **218 (100)** | **300 (100)** | **118 (100)** | **8481 (100)** |
| | F/M ratio | **1.8** | **1.1** | **2.4** | **1.5** | - | - | **1.5** |

**Legend:** percentages are calculated based on the number of participants receiving any vaccine by country and all countries. A F/M ratio > 1 indicates that the number of female participants is higher than the number of male participants. **Abbreviations**: F=female, M=male, NA=not applicable, n=number, y.o.=years old.

The age distribution of all participants belonging to the special cohorts and the general population group is depicted in Table 44. In the group of the general population, which includes participants belonging to the special cohorts, almost 70% of the participants were in the age group 30 – 59. Similarly, most of the vaccinees belonging to the cohorts of people with prior SARS-CoV-2 infection (76.4%) and people with history of allergy (69.5%) were aged between 30 and 59 years. 68.8% of the immunocompromised were represented by vaccinees aged between 40 and 69 years. Overall, pregnant and lactating women were aged between 18 and 49 years. The majority of vaccinees were aged between 30 and 39 years, with 82.1% of the pregnant women and 72.9% of the lactating women being 30-39 years old.

***Table 44.*** *Demographics of participants receiving the booster dose vaccine, by group, age group, sex.*

| | Special target group | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Prior SARS-CoV-2 infection** | **Children/ Adolescents (0-17 y.o.)** | **People with a history of allergy** | **Immuno-compromised** | **Pregnant women** | **Lactating women** | **General population** |
| **Number of participants (%)** | 897 (100) | 96 (100) | 972 (100) | 218 (100) | 300 (100) | 118 (100) | 8481 (100) |
| **Age group (y.o.)** | **n (%)** | | | | | | |
| 5 – 11 | 2 (0.2) | 50 (52.1) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 50 (0.6) |
| 12 – 17 | 5 (0.6) | 46 (47.9) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 46 (0.5) |
| 18 – 24 | 95 (10.6) | 0 (0.0) | 64 (6.6) | 10 (4.5) | 1 (0.3) | 2 (1.7) | 666 (7.9) |
| 25 – 29 | 96 (10.7) | 0 (0.0) | 81 (8.3) | 13 (6.0) | 25 (8.4 | 11 (9.3) | 700 (8.3) |
| 30 – 39 | 200 (22.3) | 0 (0.0) | 213 (21.9) | 29 (13.3) | 247 (82.3) | 86 (72.9) | 1869 (22.0) |
| 40 – 49 | 199 (22.2) | 0 (0.0) | 252 (25.9) | 47 (21.6) | 27 (9.0) | 19 (16.1) | 1928 (22.7) |
| 50 – 59 | 196 (21.8) | 0 (0.0) | 211 (21.8) | 65 (29.8) | 0 (0.0) | 0 (0.0) | 1746 (20.6) |
| 60 – 69 | 86 (9.6) | 0 (0.0) | 127 (13.1) | 38 (17.4) | 0 (0.0) | 0 (0.0) | 1164 (13.7) |
| 70 – 79 | 18 (2.0) | 0 (0.0) | 15 (1.5) | 15 (6.9) | 0 (0.0) | 0 (0.0) | 278 (3.3) |
| >80 | 0 (0.0) | 0 (0.0) | 3 (0.3) | 1 (0.5) | 0 (0.0) | 0 (0.0) | 34 (0.4) |
| **Sex** | **n (%)** | | | | | | |
| Female | 572 (63.8) | 50 (52.1) | 682 (70.2) | 130 (59.6) | 300 (100) | 118 (100) | 5154 (60.8) |
| Male | 325 (36.2) | 46 (47.9) | 290 (29.8) | 88 (40.4) | NA | NA | 3327 (39.2) |

**Abbreviations:** NA= not applicable; N= total number; n= number; y.o.= years old

### 1.14.3. Vaccinee-reported adverse reactions

Table 44 provides an overview of the frequency of all reported ADRs (solicited and unsolicited), with their percentages calculated based on the number of participants receiving the booster dose of a specific vaccine by special cohort and general population.

The lowest rate of reported ADRs was observed in the group of children and adolescents (altogether 28.2%), while the highest was observed in the group of lactating women (56.8%). In the general population, approximately one participant out of two reported at least one ADR within 15 days after the vaccination. For the special cohorts and the general population, the percentage of vaccinees-reported ADRs following the receipt of the Moderna vaccine was higher than the one reported following the receipt of the BioNTech/Pfizer vaccine.

Since the number of participants filling in the baseline questionnaire is higher than the number of participants filling in the follow-up questionnaires, there might be an underestimation of the number of at least one ADR experienced. It is also possible that those not completing questionnaire 1 may have not experienced any ADR, meaning that there is a possibility we are overestimating the number of at least one ADR experienced. In Table 45 we reported the frequency of all ADRs, with the percentages calculated on the number of reported ADRs over the number of vaccinees filled in both, the baseline questionnaire and the questionnaire 1. Among those completing questionnaires 1, approximately three quarter belonging to the lactating women and to the allergic people reported at least one ADR.

***Table 44.*** *Overview of the number of vaccinee-reported solicited and non-solicited adverse reactions in questionnaire 1 over the number of vaccinees having filled in the baseline questionnaire by COVID-19 vaccine manufacturer*

| COVID-19 vaccine manu-facturer | Special target group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Prior SARS-CoV-2 infection** Any ADR/ Any vaccinees (%) | **Children (5-11 y.o.)** Any ADR/ Any vaccinees (%) | **Adole-scents (12-17 y.o.)** Any ADR/ Any vaccinees (%) | **People with a history of allergy** Any ADR/ Any vaccinees (%) | **Immuno-compro-mised** Any ADR/ Any vaccinees (%) | **Pregnant Women** Any ADR/ Any vaccinees (%) | **Lactating women** Any ADR/ Any vaccinees (%) | **General popu-lation** Any ADR/ Any vaccinees (%) |
| Astra-Zeneca | 2/3 (66.7) | NA | NA | 1/3 (33.3) | NA | NA | NA | 12/35 (34.3) |
| BioNTech/ Pfizer | 207/502 (41.2) | 10/50 (20.0) | 17/45 (37.8) | 247/497 (49.7) | 46/134 (34.3) | 87/222 (39.2) | 30/60 (50.0) | 1795/4286 (41.9) |
| Janssen | NA | NA | NA | NA | NA | NA | NA | 1/7 (14.3) |
| Moderna | 211/392 (53.8) | NA | 0/1 (0.0) | 287/472 (60.8) | 39/84 (46.4) | 36/78 (46.2) | 37/58 (63.8) | 2026/4153 (48.8) |
| **All vaccines** | **420/897 (46.8)** | **10/50 (20.0)** | **17/46 (37.0)** | **535/972 (55.0)** | **85/218 (39.0)** | **123/300 (41.0)** | **67/118 (56.8)** | **3834/8481 (45.2)** |

**Legend:** percentages calculated based on the number of solicited and non-solicited adverse reactions reported in questionnaire 1 over the number of vaccinees having filled in the baseline questionnaire, by COVID-19 vaccine manufacturer. The table include data pooled across countries. **Abbreviations:** ADR= adverse reaction, NA= not applicable, y.o.= years old

***Table 45.*** *Overview of the number of vaccinee-reported solicited and non-solicited adverse reactions in questionnaire 1 over the number of vaccinees having filled in questionnaire 1 and having filled in the baseline questionnaire.*

| COVID-19 vaccine manu-facturer | Special target group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Prior SARS-CoV-2 infection** Any ADR/ Any vaccinees (%) | **Children (5-11 y.o.)** Any ADR/ Any vaccinees (%) | **Adole-scents (12-17 y.o.)** Any ADR/ Any vaccinees (%) | **People with a history of allergy** Any ADR/ Any vaccinees (%) | **Immuno-compromised** Any ADR/ Any vaccinees (%) | **Pregnant Women** Any ADR/ Any vaccinees (%) | **Lactating women** Any ADR/ Any vaccinees (%) | **General popu-lation** Any ADR/ Any vaccinees (%) |
| Astra-Zeneca | 2/3 (66.7) | NA | NA | 1/3 (33.3) | NA | NA | NA | 12/27 (44.4) |
| BioNTech / Pfizer | 207/337 (61.4) | 10/28 (35.7) | 17/33 (51.5) | 247/355 (69.6) | 46/92 (50.0) | 87/185 (47.0) | 30/43 (69.8) | 1795/3039 (59.1) |
| Janssen | NA | NA | NA | NA | NA | NA | NA | 1/4 (25.0) |
| Moderna | 211/289 (73.0) | NA | NA | 287/365 (78.6) | 39/61 (63.9) | 36/60 (60.0) | 37/42 (88.1) | 2026/3118 (65.0) |
| **All vaccines** | **420/629 (66.8)** | **10/28 (35.7)** | **17/33 (51.5)** | **535/723 (74.0)** | **85/153 (55.6)** | **123/245 (50.2)** | **67/85 (78.8)** | **3834/6188 (62.0)** |

**Legend:** percentages calculated based on the number of solicited and non-solicited adverse reactions reported in questionnaire 1 over the number of vaccinees receiving a specific vaccine and having filled in questionnaire 1 and the baseline questionnaire. The table include data pooled across countries. **Abbreviations:** ADR= adverse reaction, NA= not applicable, y.o.= years old.

## 1.15. Discussion: Monitoring of the special target groups and general population receiving a booster dose of any COVID-19 vaccine

### 1.15.1. Key findings

A total of 11,100 persons registered for participation in the booster dose using the RO application

- BioNTech/Pfizer and Moderna are the most commonly administered COVID-19 vaccines among included persons that received a booster
- Reporting of any (solicited or non-solicited) ADR is common in each of the populations for the booster dose similar to first doses.
- Among the different populations, lactating women reported the highest rate of any ADRs (56.8%) in this booster vaccination study.
- Informative details about the type of the reported ADRs are not yet reported for these booster dose data since follow-up is short.

### 1.15.2. Limitations

A high number of participants did not fill the questionnaire 1 after completing the registration and having filled in the baseline questionnaire. The number of participants having experienced at least one adverse reaction might have been either underestimated or overestimated, depending if the participants not filling in questionnaire 1 have or have not experienced at least one adverse reaction within 15 days from the vaccination date.

The children and adolescents' group was selected based on the indicated date of birth in the baseline questionnaire. They were considered <12 years old or <18 years old if at the moment of the vaccination they were <12 years old and <18 years old. We found a considerable number of children whose age was indicated to be <12 years. The vaccination for children aged 5-11 years old has only been recommended by the EMA on the 25$^{th}$ of November 2021, and therefore, it is very unlikely that this specific group has already received a booster dose. Therefore, for this section we might have overestimated the number of children aged 5-11 years.

Although the definition of a booster dose has been provided in the registration page for most of the participating countries, there is still a chance that some participants have registered to the study after the receipt of their second dose of vaccine. This is a possible explanation for the high number of subjects in the group of children aged 5-11 years old.

Some subjects belonging to the children and adolescents' group might not have been identified if the parent or the legal representative who filled in the questionnaire on their behalf have erroneously indicated not their children and adolescents' date of birth but their own.

Ireland should only have recruited female participants, but a subject has registered indicated their sex as male. This will need to be further investigated.

More informative details regarding the type of the reported ADRs (AESI, serious, solicited/unsolicited) are not yet available from Research Online. These stratifications on booster vaccination ADRs will be

available in the next reporting activities, paving the way for a more detailed discussion regarding the safety of these vaccines.

### 1.15.3. Discussion

As expected, most of the participants have recorded to have received either the BioNTech/Pfizer or the Moderna vaccines, the first two vaccines that were recommended by the EMA to be used as additional doses for the booster vaccination.

Only a small proportion of participants was older than 70 years old and/or immunocompromised. Despite some countries have started to recruit participants at the beginning of the COVID-19 booster campaign, we might have missed the peak of the campaign for the fragile people, such as the elderly and/or the immunocompromised. Moreover, older people may face difficulties using technologies like smartphones and computers, which are essential tools for filling in the questionnaires.

Females represented most of the participants of the booster study, with some less pronounced differences in the female/male ratio for the group of children and adolescents. The less pronounced difference in the female/male ratio in the group of children and adolescents may be explained by the fact that these subjects require a legal representative to register and fill the questionnaires for them. Therefore, the number of children/adolescents should not reflect the tendency of women to be overrepresented in studies based on spontaneous reporting systems.

As mentioned in the limitation section, we might have underestimated or overestimated the number of the number of participants reporting at least one ADR, since a considerable number of participants have not filled in questionnaire 1. However, the variability observed among the different special target group ADR reporting rate based on the number of participants filling in a baseline questionnaire was consistent with the variability observed for the ADR reporting rate based on the number of participants filling in questionnaire 1. Children and adolescents reported the lowest rate of ADRs when compared to that of the general population, in which all participants receiving a booster dose of vaccine were included.

## 1.16. Conclusions: Monitoring of the special target groups and general population receiving a booster dose of any COVID-19 vaccine

This section summarized the COVID-19 vaccine booster vaccination information available until the 9$^{th}$ of February 2022 from the Research Online system, including data from seven out of the eight participating countries. Portugal has started to recruit participants on February 5, 2022; therefore, their data are not yet available for this Interim Report. This data overview has been exclusively used for the interim study report update and it has not yet been included in the dashboard.

Given the limitations we have highlighted for the booster study, we recommend interpreting the data reported within this section with caution, especially those regarding children aged 5 to 11 years. A more detailed classification of the booster vaccination dose observed adverse reactions will be available with the next reporting activities.

# 2. Overall conclusion

This interim report summarizes the safety evidence of COVID-19 vaccines in more than 550,000 persons from both the general and special populations that were included after first dose, and booster doses combining data coming from a total of eleven countries and four different data sources.

Collectively the data show that solicited adverse reactions are common, especially injection site reactions across all populations, with differences between vaccines, which can be related to the populations they were channeled to. Serious adverse reactions and AESI are uncommon for all vaccines, after 1$^{st}$ doses, booster and in the general as well as special populations.

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