Norwegian
Medicines Agency

Reported suspected adverse reactions to coronavirus vaccines

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About the report

- A summary is presented below of all assessed reports concerning suspected adverse reactions following coronavirus vaccination from 27 December 2020, the date on which the first vaccine became available.

- The figures are taken from the Norwegian ADR Registry and include reports from healthcare professionals, the general population and Market Authorisation Holders in Norway.

- Only reports which have undergone quality assurance and been assessed in the Norwegian ADR Registry are included in the report. At any one time, there will be reports which are currently being assessed – these reports are not considered further in this summary.

- Reports of serious events are assessed first. The report therefore does not give a true picture of the distribution between serious and non-serious events.

- Symptoms or illnesses that occur after vaccination are reported if there is any *suspicion* of a possible link. As a result, it cannot be assumed that there is a causal relationship between the suspected adverse reaction and the vaccine.

- This report contains all suspected adverse reactions regardless of any possible causal link.

- Additional information from the reporter or new knowledge concerning the vaccine may become available at any time which alters the assessment of the reports.

- The Norwegian Medicines Agency, the European Medicines Agency (EMA), the World Health Organization (WHO) and pharmaceutical companies review the reports of adverse reactions and perform statistical calculations in order to identify unknown adverse reactions (i.e. signal detection). When a signal is identified, a more thorough analysis is carried out to assess whether it could be a new adverse reaction to the drug, or whether any other factors more likely explain the signal. Based on these analyses, it may be appropriate to update the product information with new adverse reactions or introduce measures aimed at minimising the risks.

- Weekly reports are published which summarise the adverse reactions reported following vaccination with the coronavirus vaccines.

Summary

This report is based on reports that are assessed until 1 June 2021. The assessed adverse reaction reports for this week do not provide a basis for revising the current recommendations regarding the use of the vaccines.

Common to all the vaccine types is that most adverse reaction reports following vaccination against COVID-19 concern transient adverse reactions such as headache, fatigue, malaise, fever, nausea and body pain. These usually appear on the first or second day after vaccination and last around 2-3 days. Most people tolerate these transient adverse reactions well, while others experience significant discomfort during the first few days after vaccination. The suspected adverse reactions which have been observed following vaccination are otherwise generally in line with what is described in the product information.

Amongst the reports that have been assessed, there were reported 172 deaths following vaccination. Eight deaths concern persons under the age of 60, but most relate to elderly nursing home residents in need of nursing care. The average age of those concerned is over 83 years. Several of the reporters state that no causal link to vaccination is suspected. The fact that a person dies soon after being vaccinated does not mean that there is a causal relationship. In order to analyse whether there could be a causal relationship, other data sources and advanced analyses are normally required.

In the case of some patients, there is always a possibility that relatively mild adverse reactions following the vaccination of frail elderly people contributed to a deterioration in their underlying illness.

Coronavirus vaccines approved in Norway

Four coronavirus vaccines are approved for use in Norway:

- Comirnaty (BioNTech/Pfizer)
- COVID-19 Vaccine Moderna (Moderna)
- Vaxzevria (COVID-19 Vaccine AstraZeneca)
- COVID-19 Vaccine Janssen (Janssen Cilag International NV)

The Norwegian Government is following the recommendation of the Norwegian Institute of Public Health and the Vorland committee and is removing the AstraZeneca vaccine from the Norwegian vaccination programme. The Janssen vaccine is set on pause while the Norwegian Government considers how to use this vaccine outside the vaccination program.

The mRNA vaccines and Vaxzevria (COVID-19 vaccine AstraZeneca) vaccine are given as two doses a few weeks apart, while the Janssen COVID-19 vaccine is given as a single dose.

Statistics concerning reports of suspected adverse reactions as of 1 June 2021

So far, a total of 14,517 reports of suspected adverse reactions following COVID-19 vaccination; of these, 10,003 (69 %) have been assessed.

By 1 June 2021, over 1,658,000 people had received their first dose of COVID-19 vaccine, and over 1,036,000 people had received the second dose.

Distribution of reports by gender

Gender	Female	Male	Unknown gender
Number	8330	1667	6

Table 1: Gender breakdown amongst patients in the reports

Distribution of reports by age

	Age group									
	0-29	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**90+**	**Unknown age**	**Total**
Serious reports	151	155	166	157	144	184	190	105	34	1286
Non serious reports	2112	2263	1852	1333	427	195	251	123	161	8717
Total	2263	2418	2018	1490	571	379	441	228	195	10003

Table 2: Age distribution of patients in the reports

Distribution of reports according to severity for each vaccine

Vaccination numbers is per 30 May 2021 – Source: 2021 – *Weekly report from the Norwegian Institute of Public Health*

Vaccine	Number of vaccinated with first dose	Numer of vaccinated with second dose	Total number of reports	Number of reports involving death	Serious reports other than death	Non-serious reports
Comirnaty (Pfizer/BioNTech)	1 338 351	798 861	3190	160	609	2420
COVID-19 Vaccine Moderna (Moderna)	162 106	107 340	477	6	100	371
Vaxzevria (COVID-19 Vaccine AstraZeneca)	136 755	100 818** (mRNA-vaccine)	6336	6	405	5926
Total	**1 637 212**	**1 007 019**	**10 003**	**172***	**1114**	**8717**

Table 3: Distribution of reports of suspected adverse reactions according to severity

** The fact that a person dies soon after being vaccinated does not necessarily mean there is a causal relationship. Read more on page 3.*

***Among these, 99,808 persons have received 1st dose Vaxzevria and Comirnaty for the 2nd dose, and 1738 persons have received Vaxzevria for the 1st dose and COVID-19 Vaccine Moderna for the 2nd dose*

The data concerning the various coronavirus vaccines are not directly comparable. The vaccines have been administered to a different numbers of people with different disease profiles and ages.

Reports on deaths

So far, 172 reports of deaths after vaccination have been assessed. Most deaths have occurred amongst elderly nursing home residents in need of nursing care, but the Norwegian Medicines Agency has also received eight reports of deaths concerning persons under the age of 60.

Reports concerning deaths in elderly persons

Many of the elderly nursing home residents who have been vaccinated are very frail or terminally ill patients. It is therefore to be expected that deaths will occur with a temporal link to vaccination, without there necessarily being any causal link to the vaccine. The reports on many of these deaths in the elderly state that no link with vaccination is suspected, and that the death is being reported for the sake of completeness.

An expert group of geriatric specialists have looked into some of these incidents and assessed the causal relationship with vaccination after reported deaths in this patient group.

Reports concerning thrombosis with thrombocytopenia syndrome (TTS)

In mid-March, cases were reported of a very rare but serious clinical picture involving a combination of blood clots, low blood platelet count and bleeding, now referred to as thrombosis with thrombocytopenia syndrome (TTS) or vaccine-induced immune thrombotic thrombocytopenia (VITT). These symptoms mainly occurred three to twenty-one days after vaccination with Vaxzevria (COVID-19 Vaccine AstraZeneca). As of 1 June 2021, Norway has reported seven confirmed cases of TTS/VITT after the Vaxzevria vaccine, four of which were fatal. In addition, one further suspected case of TTS/VITT has been reported but not confirmed, along with one case which does not meet the diagnostic criteria for TTS according to the Brighton Collaboration. TTS is now listed as a rare adverse reaction in the product information for Vaxzevria and the Janssen COVID-19 vaccine, but more research is needed to clarify what causes this reaction.

Four reports have also been received concerning both thrombosis and thrombocytopenia after vaccination with an mRNA vaccine. These have been reviewed and assessed according to the above-mentioned criteria for TTS from the Brighton Collaboration. The clinical picture for these cases differs from that seen after Vaxzevria vaccination; the patients are all close to 70 or older and have one or more underlying conditions and/or take medication that may increase the risk of thrombocytopenia (such as treatment for cancer) or thrombosis.

Reports classified as serious

Reports of adverse reactions are generally classified as serious when the event:

1. results in or extended a stay in hospital
2. results in a prolonged reduction in function level
3. results in life-threatening illness or death
4. results in birth defects/congenital malformations
5. is on the EMA's list of important medical events (the IME list)

In addition to the reports concerning deaths, 1114 reports have so far been assessed which

fulfil one of the other severity criteria listed above.

What types of events are classified as "serious" following COVID-19 vaccination?
Hospital admission is the most common reason why an event is classified as serious, and this applies to 48% of serious reports. In these cases, the descriptions provided by the person submitting the report cover everything from patients who are only kept under observation for a short period of time and go on to recover quickly, to patients with a life-threatening illness which results in permanent injury.

Most of the serious suspected adverse reactions which have been reported concern medical conditions which are relatively common amongst the population and the timing following vaccination may therefore simply be coincidental.

The EMA has compiled a list of important medical events (5) which are always to be classified as serious (the IME list). The summary below lists the conditions on the IME list which are most frequently reported following COVID-19 vaccination.

The most frequently reported conditions on the IME list for all vaccines in descending order

- Blood clot in the lungs
- Fainting (syncope)
- Anaphylactic reaction
- Deep vein thrombosis
- Blood clots or bleeding in the brain
- Pericarditis
- Pneumonia
- Low blood platelet count (thrombocytopenia)
- Cerebral infarction
- Hallucinations

The list shows that numerous serious suspected adverse effects have been reported following COVID-19 vaccination. The challenge is to respond if new combinations of symptoms following vaccination become apparent – or if common medical conditions occur more frequently following vaccination than we would expect. We have a three-pronged approach to identifying these links:

1. **Both health professionals and the government authorities assess individual cases of medical conditions and reports in order to look for unknown combinations of symptoms or to determine whether there are any factors associated with the progression of the conditions which would indicate a link with vaccination.**

   It was a combination of observant doctors at Oslo University Hospital, a robust and fast electronic monitoring system and analyses by the University Hospital of Northern Norway and the Preparedness Register which enabled Norway to help reveal that, in rare cases, Vaxzevria can give rise to a serious combination of symptoms involving blood clotting and low blood platelet counts.

2. **We carry out statistical analyses where we investigate whether the number of reports of a combination of symptoms is higher than expected.**

   Such statistical analyses of reported adverse reactions have shown that serious allergic reactions occur more frequently following COVID-19 vaccination than with vaccination with influenza vaccines. It also forms the basis for the EMA's current investigations aimed at determining whether indications of an increase in the prevalence of immune thrombocytopenia (ITP) are linked to the vaccine.

3. **Health registers are used to assess and investigate further, and to confirm or disprove possible links between vaccination and reported symptoms or diagnoses. This is done in partnership with the Norwegian Institute of Public Health.**

   Further investigation of possible links concerning symptoms reported via the spontaneous reporting system can be carried out by linking the Norwegian Immunisation Register (SYSVAK) to other health registers, such as the Norwegian Patient Registry (NPR) or the Municipal Patient and User Registry (KPR), to see whether any diagnoses occur more frequently following vaccination than is otherwise the case.

   The Norwegian Institute of Public Health and research institutions in many countries are also conducting registry studies to see whether there is any increase in the prevalence of diseases amongst vaccinated people that are not necessarily identified through the adverse reaction reports.

Serious reports concerning persons under the age of 60

Most reports concerning this patient group concern the same types of adverse reactions as are found in the other age groups. The most frequent adverse reactions in this group which are classified as serious are fainting, anaphylactic reactions and blood clot conditions.
The most frequent reason why a report is classified as serious is that the event is included in the EMA's list of important medical events or that it has resulted in hospital admission.

It appears that an equal proportion of serious events have been reported in both the elderly and younger age groups (see Table 2). There may be a number of explanations for this.

The vaccines have been shown to trigger more of the common adverse reactions in young adults than in the elderly. Younger people have a more responsive immune system and often respond better to vaccines than elderly people, and this is thought to cause more severe reactions. We know from influenza vaccinations that adverse reactions are reported more frequently in younger adults than in older adults. This may be because younger adults suffer more adverse reactions to vaccines, because more attention is paid to symptoms in younger people, or because younger people are more likely to report symptoms in order to find out whether they are actually adverse reactions.

If one considers the proportion of serious reports in relation to non-serious reports in the youngest age groups (under 60), serious reports account for 10% or less of reports. Amongst the age groups over 60, the percentage of serious reports lies between 24% and 47%. In

addition, the processing of serious reports is given greater priority, and there will therefore be a skewed distribution between serious and non-serious reports.

Reports of deaths of persons under the age of 60

As of 1 June 2021, four deaths have been reported of persons under the age of 60 after vaccination with Vaxzevria due to the very rare but serious adverse reaction, thrombosis with thrombocytopenia syndrome (TTS). TTS is described above.

Four deaths have also been reported of persons under the age of 60 after vaccination with an mRNA-vaccine, and these are not related to this rare syndrome. The causal relationship with vaccination in these four cases is uncertain.

Severe allergic reactions to COVID-19 vaccines

As of 2 June 2021, Norway has reported 45 cases of suspected anaphylactic reactions as adverse reactions after vaccination of persons aged from 20 to 92. The 45 cases comprised 38 women and 7 men. 30 cases have been reported with the Comirnaty (Pfizer) vaccine, 12 with the Vaxzevria (AstraZeneca) vaccine and 3 with the Moderna vaccine. All the patients had recovered or were recovering when the reports were submitted.

Severe allergic reactions are extremely rare. Such reactions usually occur shortly after vaccination, can be life-threatening and require immediate treatment. The number of cases with the mRNA vaccines appear to be somewhat higher than with other vaccines, such as the influenza vaccine. Preparedness for anaphylaxis is a requirement at all vaccination sites.

Reactions which health professionals should be aware of

Other serious events have also been observed following vaccination where no causal relationship has been established. The Norwegian Medicines Agency wishes healthcare professionals to be aware of the following conditions in persons who are vaccinated:

- elevated blood sugar levels in people with diabetes
- high INR values in patients taking warfarin (Marevan)
- chest pain and breathing difficulties suspected as being due to blood clots
- numbness
- absence or reduced sensation and paralysis
- exacerbation of autoimmune diseases
- persistent headache
- inflammation of the pericardium (pericarditis)

Some of these symptoms were also observed in studies which formed the basis for the temporary authorisation of the vaccines, but insufficient data is currently available to establish any link to the vaccine. A number of the reactions have been included in the list of possible adverse reactions of particular interest which the pharmaceutical authorities in Europe are closely monitoring.

Number of suspected adverse reactions according to category

A single adverse reaction report can include a number of suspected adverse reactions or symptoms. Suspected adverse reactions are presented below, grouped according to the

category to which they belong for each vaccine type and the types of suspected adverse reactions which have been reported most frequently. The categories are the highest level in a hierarchical, standardised medical terminology which is used internationally (MedDRA). Using this terminology makes it possible compare reports internationally.

Suspected adverse reactions to mRNA vaccines

- Comirnaty (Pfizer/BioNTech)
- COVID-19 Vaccine Moderna (Moderna)

The most frequently reported symptoms following vaccination with the mRNA vaccines primarily consist of known adverse reactions within the general symptoms category, and include reactions at the vaccine injection site, decreased general condition, fever and general malaise. Headache, dizziness and drowsiness after vaccination are also frequently reported, as well as gastrointestinal symptoms such as diarrhoea, nausea and vomiting. The symptoms have arisen within 1-2 days after vaccination and have generally disappeared within a few days. Some reports have been received where the patient has developed infections such as pneumonia and influenza. As the mRNA vaccines are not live, they cannot cause conditions which are being vaccinated against or other infections.

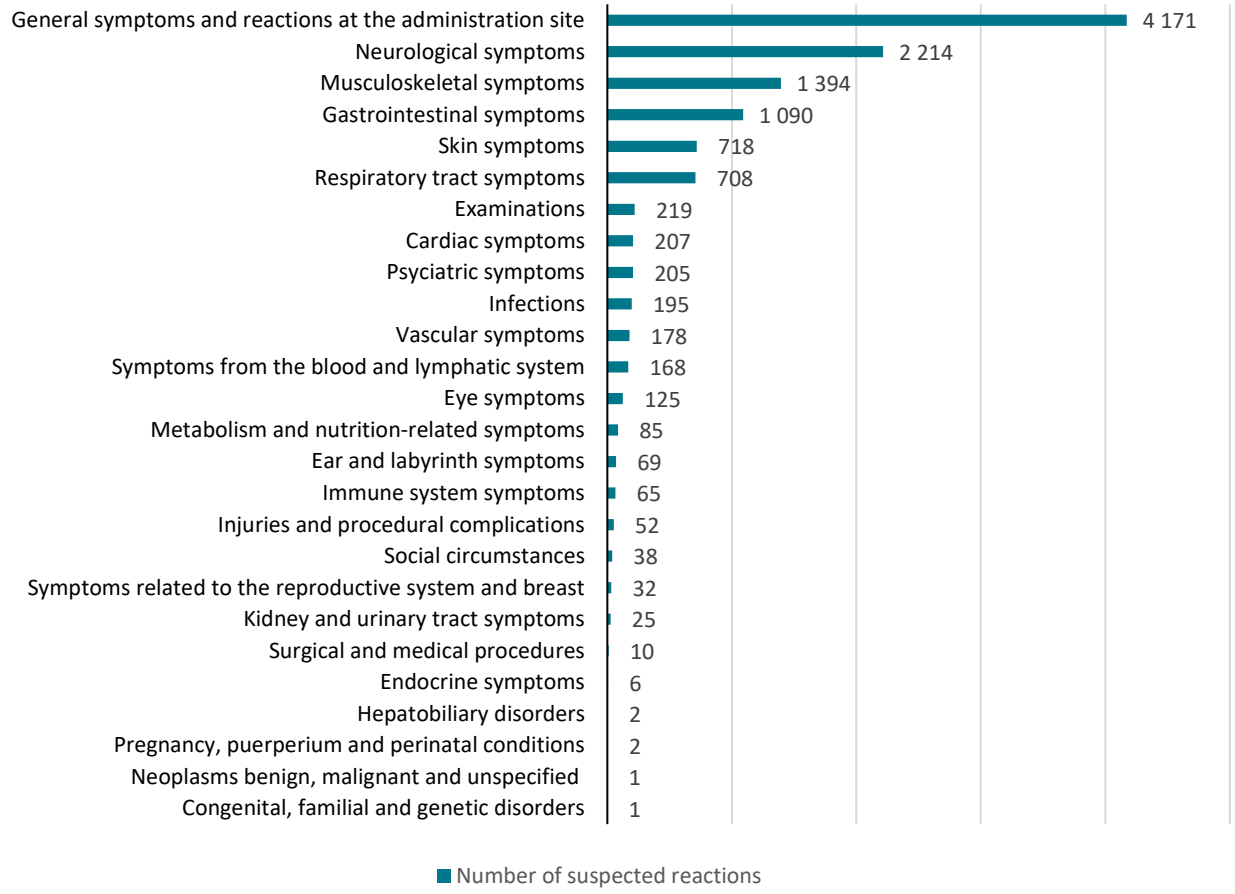

Figure 1: Reported suspected adverse reactions by category for mRNA vaccines (Comirnaty and COVID-19 Vaccine Moderna)

Category	Number of suspected adverse reactions
General symptoms and reactions at the vaccine administration site E.g.: Pain and reactions at the injection site, discomfort, fever, fatigue, decreased general condition	4171
Neurological symptoms E.g.: Headache, dizziness, drowsiness, syncope	2214
Musculoskeletal symptoms E.g.: Muscle pain, joint pain, muscle stiffness, pain in the extremities	1394
Gastrointestinal symptoms E.g.: Stomach pain, nausea, vomiting, diarrhoea	1090
Skin symptoms E.g.: Rash, itching, redness, cold sweats	718
Respiratory tract symptoms E.g.: Difficulty breathing, shortness of breath, cough, irritation of the respiratory	708
Examinations E.g.: Abnormal and raised heart rate, decreased blood pressure, decrease in oxygen saturation	219
Cardiac symptoms E.g.: Bradycardia, tachycardia, pericarditis	207
Psychiatric symptoms E.g.: Sleep abnormalities, restlessness, lethargy, hallucination	205
Infections E.g.: Pneumonia, cold symptoms	195
Vascular symptoms E.g.: Flushes, pallor, low blood pressure	178
Symptoms from the blood and lymphatic system E.g.: Swollen lymph nodes	168
Eye symptoms E.g.: Blurred vision, twitch	125
Metabolic and nutrition-related symptoms E.g.: Reduced appetite	85
Ear and labyrinth symptoms E.g.: Discomfort in the ear	69
Immune system symptoms E.g.: Allergic reaction	65
Injuries and procedural complications E.g.: Fall	52
Social circumstances E.g.: Bedridden	38
Symptoms relating to the reproductive organs and breast E.g.: Breast pain	32
Kidney and urinary tract symptoms E.g.: Urinary tract infection	25
Surgical and medical procedures E.g.: Oxygen therapy, revaccination with other Covid-19 vaccine	10
Endocrine symptoms E.g.: Hypothyroidism	6

Hepatobiliary disorders	2
Pregnancy, puerperium and perinatal conditions	2
Neoplasms benign, malignant and unspecified	1
Congenital, familial and genetic disorders	1

Table 4: Reported suspected adverse reactions by category for mRNA vaccines (Comirnaty and COVID-19 Vaccine Moderna). A report can cover several adverse reactions and there will therefore be many more adverse reactions than reports.

Suspected adverse reactions to viral vector vaccines

- Vaxzevria (COVID-19 Vaccine AstraZeneca)(AstraZeneca)

Viral-vector vaccines are not part of the Norwegian vaccination programme. See separate paragraph on reports concerning thrombosis with thrombocytopenia syndrome (TTS).

Many people have reported significant reactions after the first dose of Vaxzevria, and most reports concern known adverse reactions, such as reactions around the injection site, headache, fever, fatigue and deterioration in general condition.

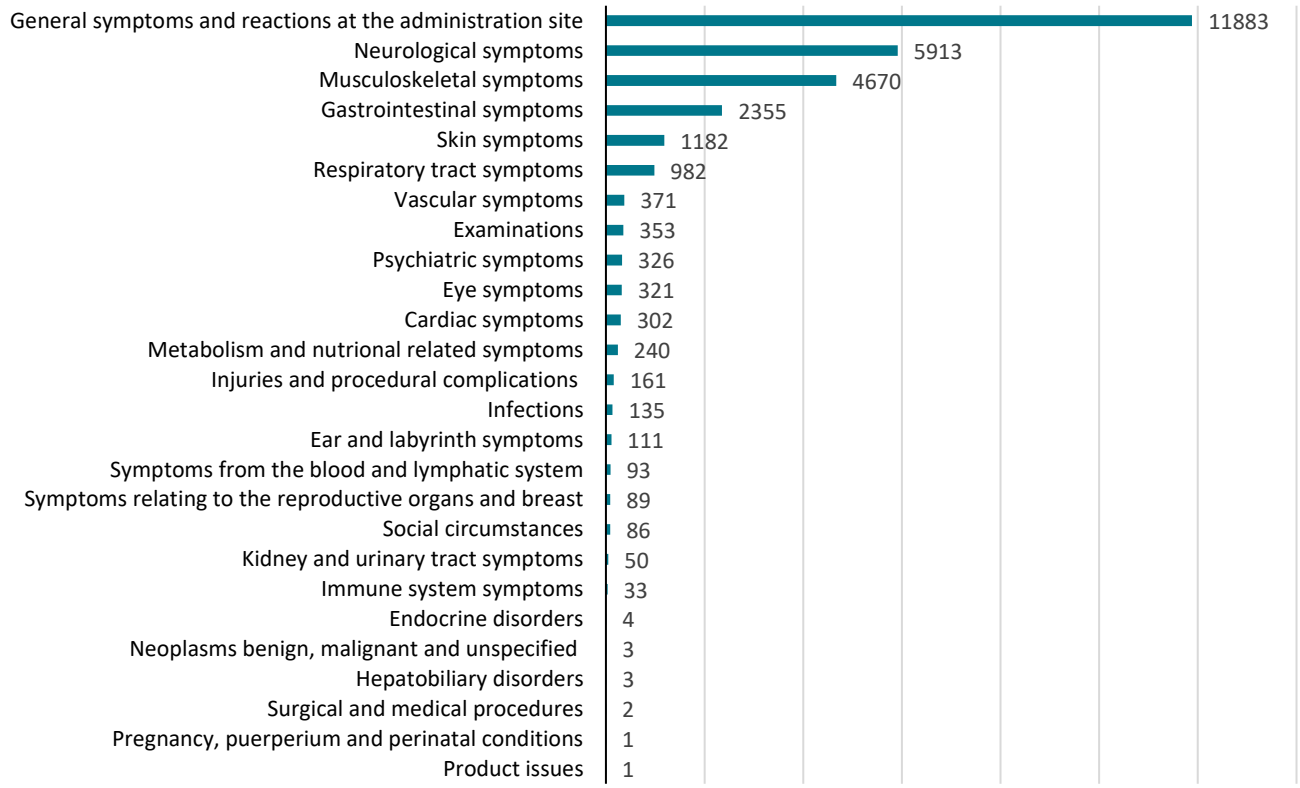

Figure 2: Number of reported suspected adverse reactions by category for viral vector vaccines (COVID-19 Vaccine AstraZeneca)

Category	Number of reported adverse reactions
General symptoms and reactions at the vaccine administration site E.g.: Pain and reactions at the injection site, discomfort, fever, fatigue, decreased general condition	11883
Neurological symptoms E.g.: Headache, dizziness, drowsiness, numbness	5913
Musculoskeletal symptoms E.g.: Muscle pain, joint pain, back pain	4670
Gastrointestinal symptoms E.g.: Stomach pain, nausea, vomiting, diarrhoea	2355
Skin symptoms E.g.: Rash, skin pain, cold sweats	1182
Respiratory tract symptoms E.g.: Difficulty breathing, hyperventilation, nasal congestion, pain and swelling of pharynx	982
Vascular symptoms E.g. Flushing	371
Examinations E.g.: Abnormal and raised heart rate	353
Psychiatric symptoms E.g.: Sleep abnormalities, insomnia	326
Eye symptoms E.g.: Blurred vision, twitch, eye pain	321
Cardiac symptoms E.g.: Palpitations	302
Metabolic and nutrition-related symptoms E.g.: Reduced appetite	240
Injuries and procedural complications E.g. Contusion	161
Infections E.g. Sinus infection, cold symptoms	135
Ear and labyrinth symptoms E.g.: Discomfort in the ear, sound sensitivity	111
Symptoms from the blood and lymphatic system E.g.: Swollen lymph nodes	93
Symptoms relating to the reproductive organs and breast: E.g. Pain in reproductive organs and nipples	89
Social circumstances E.g.: Bedridden	86
Kidney and urinary tract symptoms E.g.: Frequent urination	50
Immune system symptoms	33

E.g.: anaphylactic reaction, allergic reaction	
Endocrine disorders	4
Neoplasms, benign, malignant and unspecified	3
Hepatobiliary disorders	3
Surgical and medical procedures	2
Pregnancy, puerperium and perinatal conditions	1
Product issues	1

Table 4: Reported suspected adverse reactions by category for viral vector vaccines (COVID-19 Vaccine AstraZeneca). A report can cover several adverse reactions and there will therefore be many more adverse reactions than reports.