COVID-19 Vaccine Surveillance Report

9

27/12/2020 - 26/09/2021

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INTRODUCTION TO READING

No medicinal product can ever be considered risk-free. Each of us, when deciding to use a medicine or undergo a vaccination, should be aware that what he is doing is balancing the benefits with the risks. Verifying that the benefits of a vaccine outweigh the risks and reducing these to a minimum is the responsibility of the health authorities that regulate the introduction on the market of medicinal products. It is everyone's responsibility to use a medicine in a correct, considered and informed manner.

Italy is provided with a pharmacovigilance system that, for many years now, has paid special attention and a special organisational structure to monitoring what happens after the administration of a vaccine.

It is an open, dynamic system to which everyone (health professionals, patients, parents, and citizens) can send their reports, helping to monitor the safe use of vaccines and medicines in general. In addition, the system is fully transparent and offers access to aggregated data, which can be queried on the AIFA website.

It is thanks to this pharmacovigilance system that it is possible to produce this report, which will be updated on a monthly basis and which will punctually follow the progress of the vaccination campaign against COVID-19.

Correct information is the basis of every conscious choice and this report aims to provide everyone with timely, understandable and consolidated information.

GUIDE TO DATA READING

This document describes the reports of reactions that have been observed after administration of the vaccine. This does not mean that such reactions were caused by the vaccine. They could be a symptom of another disease or they could be associated with another product taken by the person who was vaccinated. Investigating the significance and causes of these reactions is the task of pharmacovigilance. As an aid to orientation in this investigation and analysis process, it is necessary to know that:

- an **adverse event** is any unfavourable episode that occurs after the administration of a medicine or vaccine, but which is not necessarily caused by taking the medicine or having received the vaccine;

- an **adverse reaction**, on the other hand, is a noxious and unintended response to a medicine or vaccine for which it is possible to establish a causal relationship with the medicine or the vaccine itself. In order to distinguish, therefore, whether we are facing an adverse event or an adverse reaction, we have to evaluate whether it is possible to trace a cause related to the medicinal product. It is not enough that the event occurred shortly after vaccination or taking the medicine

- An **undesirable effect** is an unintended effect related to the properties of the medicine or vaccine, which is not necessarily harmful and has been observed in a number of people. This is therefore a known possible effect that has occurred over time and is considered acceptable.

Investigating **every event** that appears after a vaccination, serves to gather as much information as possible and increase the possibility of identifying truly suspicious events whose nature is important to understand, or which have never been observed before, with the aim of ascertaining whether there is a causal link with the vaccination.
In this way, regulatory authorities such as AIFA can verify the safety of vaccines in the real world, confirming what was observed in studies prior to authorisation and possibly identifying new potential adverse reactions, especially if they are rare (1 in 10,000) and very rare (less than 1 in 10,000).
A large number of reports, therefore, does not imply that the vaccine is more dangerous, but is an indication of the **high ability** of the pharmacovigilance system to **monitor safety**.

How to investigate a report
Each report represents a **suspicion** that requires further investigation, through a process that gradually leads to recognizing whether the reaction may have a relationship with vaccine administration. The signal analysis process follows standardized ways so that it is always possible to compare them with other signals and similar processes.

For this reason, the Global Advisory Committee for Vaccine Safety (GACVS) of the World Health Organization has developed a specific algorithm taking into account the following factors:

- temporal relationship between vaccination and the reported reaction;

- presence of possible alternative explanations;
- evidence in favour of the association between vaccination and reaction;
- previous evidence in literature;
- frequency of the event reported in the general population, even if not vaccinated;
- biological plausibility

It is therefore required to collect all available data to define the characteristics of the reported event. The following aspects are further analysed: the plausibility of the temporal and biological relationship with vaccination, the frequency of the event in relation to the vaccine administered compared to the frequency of finding the same event in the general population and the coexistence is assessed of other conditions which can determine or contribute to the onset of the reaction.
On the basis of the available evidence, all these analyses allow to evaluate the **probability** that a vaccine and that a specific associated event over time are linked by a causal relationship, that is, the probability that that a specific reaction was caused by the vaccine[1].

This evaluation process, which allows to gradually discriminate in the large number of signals taken into consideration at the outset, can provide three possible interpretations:

- **related to the event**: the causal association between event and vaccine is considered plausible;
- **unrelated to the event:** other factors can justify the event;
- **indeterminate:** the temporal association is compatible, but the evidence is not sufficient to support a causal link.

Any reports lacking sufficient information, for which further investigation is necessary, are defined as **not classifiable.**

Surveillance of the potential association between a certain event and a vaccine also takes into account more general assessments.
For example, the number of reports of suspected adverse reactions following the administration of the vaccine is compared with the reports of **the same adverse reaction** after the administration of **any other drug**, to highlight whether a certain event is reported more frequently for a certain medicine.
The observed/expected analysis, on the other hand, makes it possible to compare the frequency with which, in a given time window, an event is observed in relation to vaccination, compared to the frequency with which t**he same event is observed in the general population.**
Both evaluations allow to identify the possibility of a potential association, which in that case would require further investigation.

[1](for further information: http://www.who.int/vaccine_safety/publications/AEFI_aide _memoire.pdf?ua=1)

HIGHLIGHTS

As of 26 September 2021, 120 reports were entered for any 100,000 doses administered, regardless of the vaccine and the dose administered.

The reports mainly concern Comirnaty, which has been the most widely used, and only to a lesser extent Vaxzevria and Spikevax (former COVID-19 Moderna vaccine), while COVID-19 Janssen vaccine is used less.

The reporting trend and the related rates are substantially stable over time, with an expected slight decline in the summer period.

Most reported adverse events are classified as non-serious (approximately 85.4%) which resolve completely and only to a lesser extent as severe (14.4%), resulting in full recovery or improvement in most cases.

In the period considered, 46% of the overall administered doses was used to complete the vaccination cycle (second doses), mainly with the Comirnaty vaccine. The administration of the third dose was started for which only one report was made during the period.

For all vaccines, the most reported adverse events are fever, fatigue, headache, muscle/joint pain, injection site pain or local reaction, chills and nausea.

The reporting rate of the mixed vaccine schedule is 40 reports per 100,000 administered doses, mostly non-serious and resulting in full recovery or improvement. The distribution by type of adverse events is not substantially different between the two vaccines used.

The reporting rate in the age group between 12 and 19 years is 24 adverse events per 100,000 administered doses. The distribution by type of adverse event is not substantially different from that observed in any other age group. Rare cardiological events are being investigated.

The data processed and described in these reports should be considered as descriptive of a continuously evolving dynamic process.

Considering the stability of the reporting trend for the various COVID-19 vaccines, the Surveillance Report will no longer be published monthly but quarterly. As usual, all safety information will still be published on the Agency's website, as well as any further information on specific topics of interest. The monthly update of interactive graphs will continue.

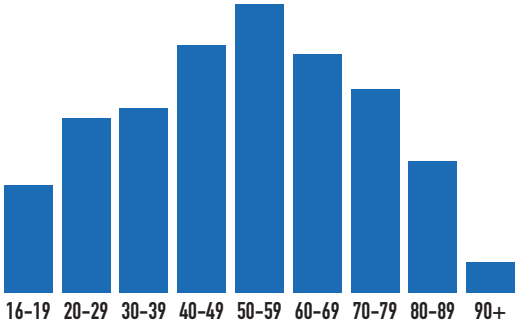
Reference period: 27/12/2020 - 26/09/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

ADMINISTERED DOSES

84.010.605

Comirnaty 71,2%
Spikevax 12,5%
Vaxzevria 14,5%
Janssen Vaccine 1,8%

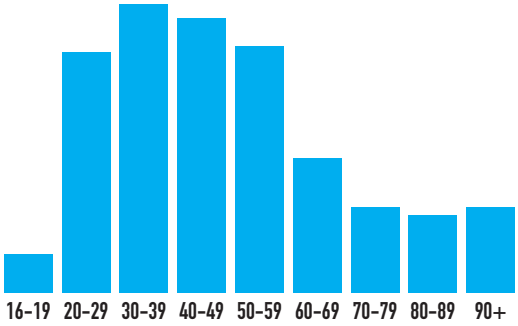


ADMINISTRATIONS BY AGE GROUP

SUSPECTED ADVERSE REACTIONS

101.110

Comirnaty 69%
Spikevax 5,2%
Vaxzevria 24,7%
Janssen Vaccine 1,1%



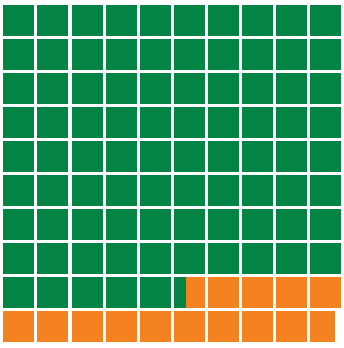
REPORTING RATE BY AGE GROUP

	1st dose	2nd dose	3rd dose
ADMINISTRATIONS BY DOSE	53,43%	46,51%	0,06%

	1st dose	2nd dose
REPORTING RATE BY DOSE	158	77

*3rd dose not applicable

SUSPECTED ADVERSE REACTIONS SERIOUS/NON-SERIOUS



NON-SERIOUS **85,4%**

SERIOUS **14,4%**

0.2% OF SUSPECTED ADVERSE REACTIONS IS NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)

PERIOD UNDER REVIEW: 27/12/2020 - 26/09/2021

The vaccines currently authorised and used in the COVID-19 vaccination campaign are 4:

- Comirnaty (Pfizer/BioNTech), mRNA vaccine authorised as from 22/12/2020 and used from 27/12/2020;
- Spikevax (Moderna), mRNA vaccine authorised as from 07/01/2021 and used from 14/01/2021;
- Vaxzevria (Astrazeneca), recombinant viral vector vaccine, authorised as from 29/01/2021 and used from 01/02/2021;
- COVID-19 Janssen Vaccine (Janssen Cilag), viral vector vaccine authorised as from 12/03/2021 and used from 22/04/2021.

As of 26/09/2021, **101,110 reports of adverse events following immunisation** have been entered in the National Pharmacovigilance Network, out of a total of **84,010,605 vaccine doses**, with a **reporting rate of 120 per 100,000 administered doses.**

The distribution of reports and administered doses by type of vaccine is shown in table 1.

Comirnaty is currently the most widely used vaccine in the Italian vaccination campaign (71.2%), followed by Vaxzevria (14.5%), Spikevax (12.5%) and COVID-19 Janssen vaccine (1.8%)[2]. In line with the previous publications, the distribution of reporting by type of vaccine is similar to the distribution of administered doses (Comirnaty 68%, Vaxzevria 22%, Spikevax 9% and COVID-19 Vaccine Janssen 1%).

What is the reporting rate?

The reporting rate is the ratio between the number of reports entered in the Pharmacovigilance system and the number of doses administered at the time of data extraction. This value is reported as the number of reports that are observed every 100,000 doses administered, in order to obtain a standardised and comparable measure of the functioning of the system.

Table 1 *- Reports, doses administered and related rates for currently authorised COVID-19 vaccines*

COVID-19 vaccine	Reports as at 26/09/2021	Administered doses as at 26/09/2021	Reporting rate (per 100,000 administered doses)	95% Confidence interval
Comirnaty	68,444	59,858,216	114	***113-115***
Spikevax	8,863	10,535,649	84	***82-86***
Active ingredient mRNA	19			
Vaxzevria	22,457	12,145,021	185	***183-187***
Janssen	1,347	1,471,719	92	***87-97***
Total	**101.130***	**84,010,605**	**120**	***119-121***

** the total number of reports per commercial vaccine does not correspond to the total number of records in the National Pharmacovigilance Network but is greater as two suspect vaccines are indicated in 20 records (after heterologous vaccination)*

The temporal trend of the number of reports by number of administered doses (figure 1a) and by dose number (1st or 2nd dose; figure 1b) in the period considered is comparable with the trend shown in previous Reports, with a smaller increase in reports than the increase in the number of administrations, also decreasing in August, and has been stable in recent months.

[2] The number of doses administered as of 26/09/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 30/09/2021

Since September, the administration of the 3rd dose of vaccine (46,357 doses) has been underway, in relation to which there is only one report - not serious - in a person infected with HIV. There are about 1.5 million people with previous COVID-19 infection who have received a single dose of vaccine, in accordance with ministerial guidelines, and the related reports are assimilated to those referring to the first dose of vaccine.

Please note that the above trend represents a snapshot of the reports in the National Pharmacovigilance Network at the time of data extraction and may change over time.

Figure 1a *- Distribution of the reports entered in the National Pharmacovigilance Network (RNF) by onset date of the event, according to the overall vaccine doses administered*

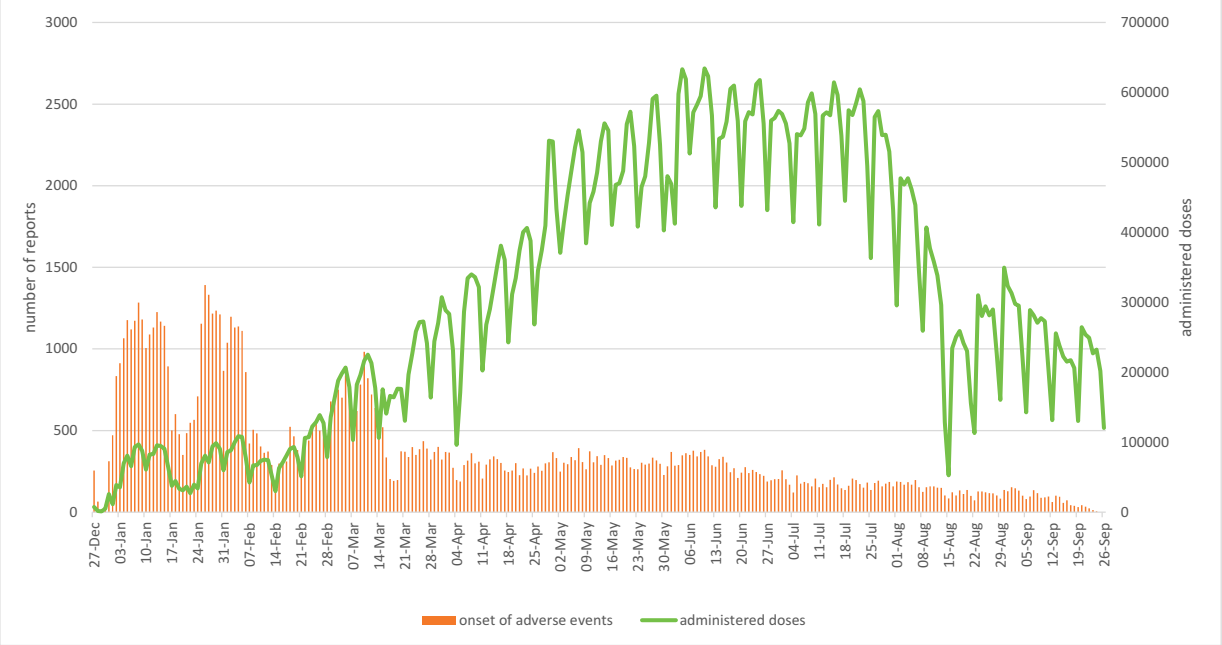
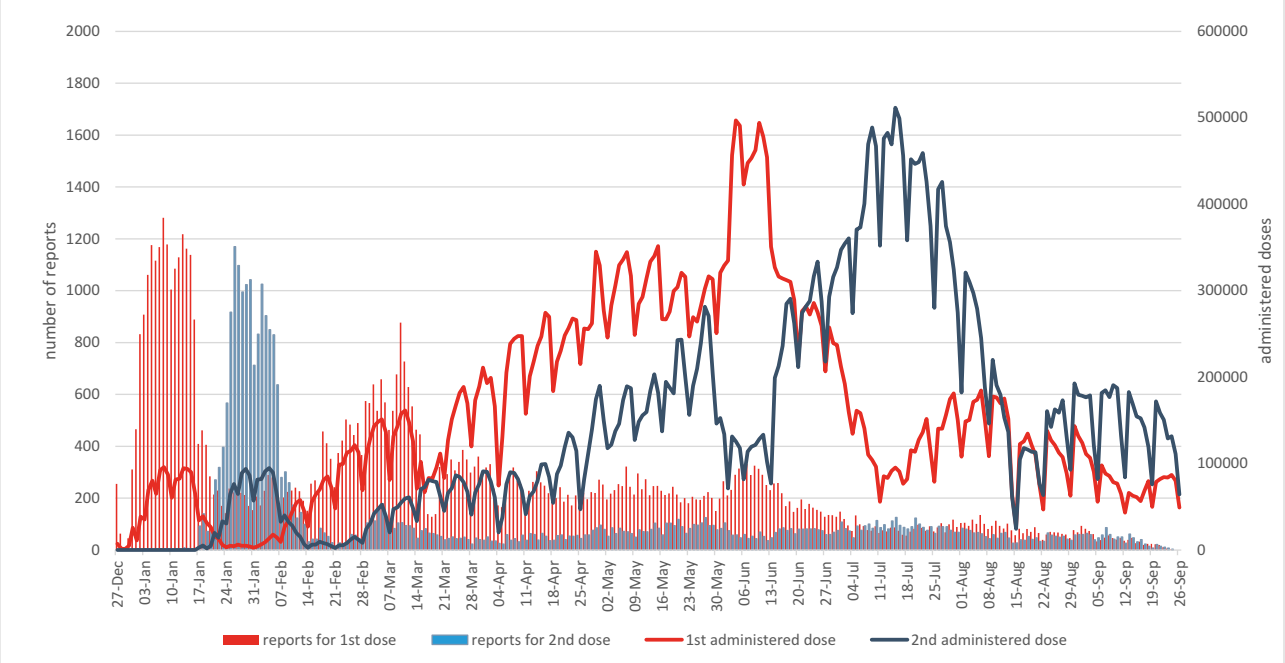


Figure 1b *- Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*

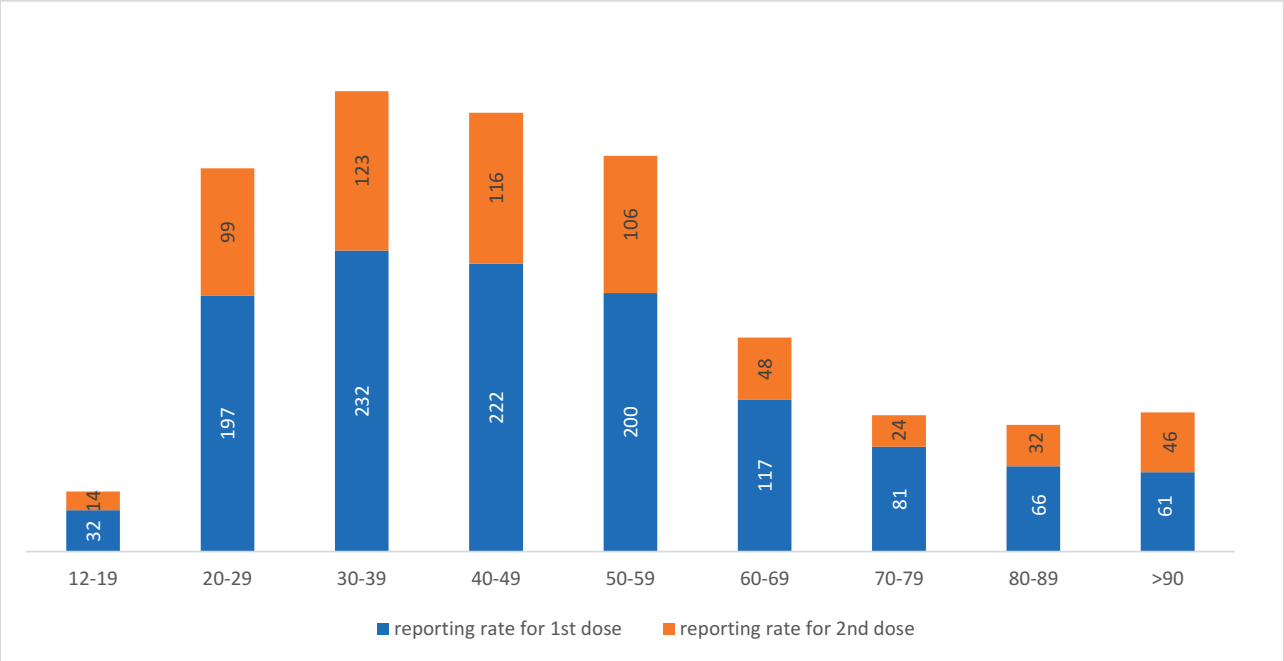


Distribution by age, sex and type of reporter

Distribution by age

The average age of people with a suspected adverse event is 47.8 years (median age 48 years). The reporting rate based on age is shown in Figure 2.

Figure 2 *- Distribution of the reporting rate by age group according to the 1st or 2nd dose administered*

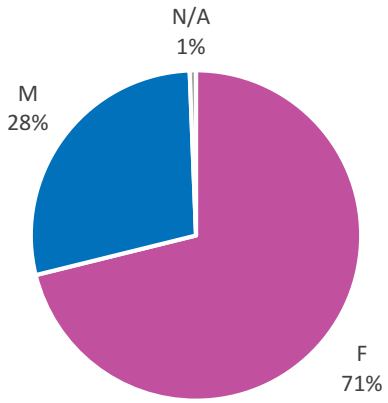


As already observed in the previous Reports, the reporting rate is higher in the age groups between 20 and 60 years and then decreases in the more advanced age groups and in the very young, with a lower reporting rate after the 2nd dose.

Distribution by sex

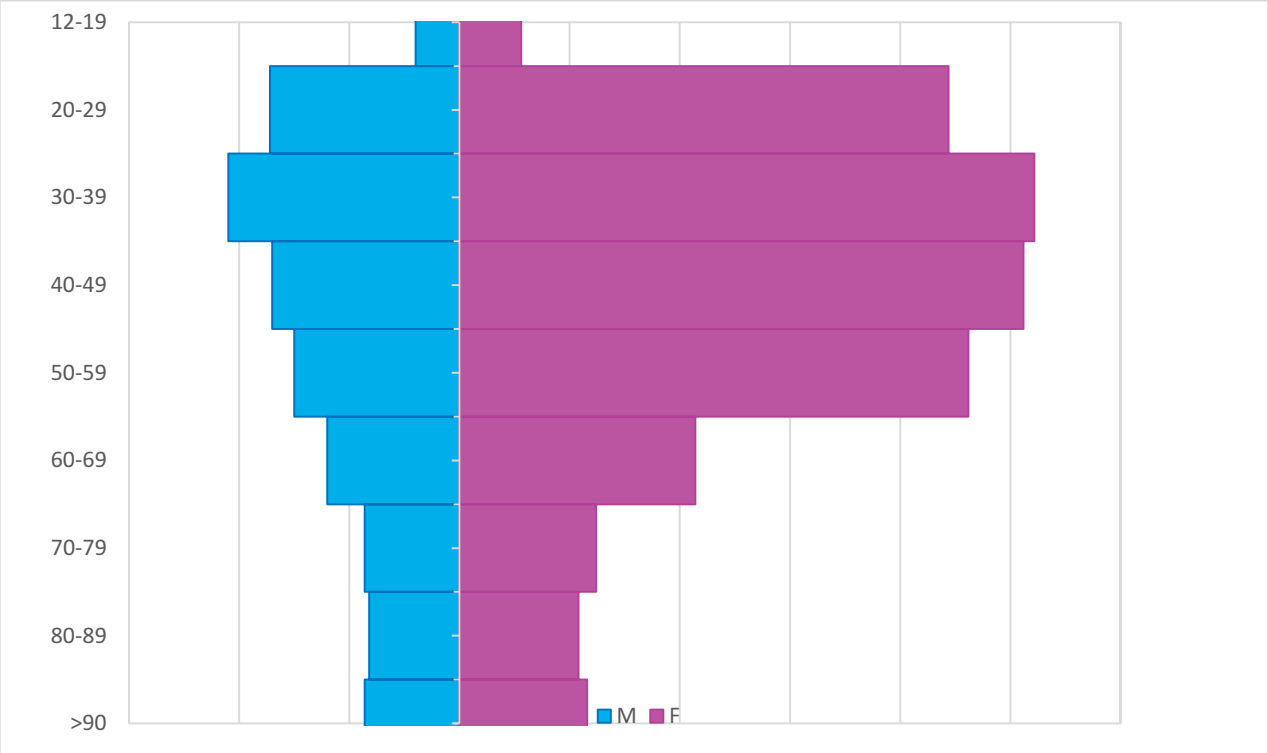
Considering an overlapping exposure of the sexes (52% of the doses administered in women and 48% in men), 71% of the reports concern women (166/100,000 administered doses) and 28% men (70/100,000 administered doses), regardless of the dose and vaccine administered (sex is not reported in 1% of reports, Fig. 3). This trend is in line with other European countries.

Figure 3 *- Distribution by sex of the reports entered in the RNF*



This difference remains almost constant in the various age groups (Fig. 4).

Figure 4 *- Distribution by sex of the reports entered in the RNF*



Distribution by type of reporter and onset time

Figure 5 shows the distribution by type of reporter. About 68% of the reports come from healthcare professionals, mainly doctors and pharmacists, while about 31.5% from patients/citizens, with a slight increase compared to the previous months. About 96% of these reports are spontaneous.

Figure 5 *- Type of reporter of the reporting sheets entered from the beginning of the vaccination campaign*

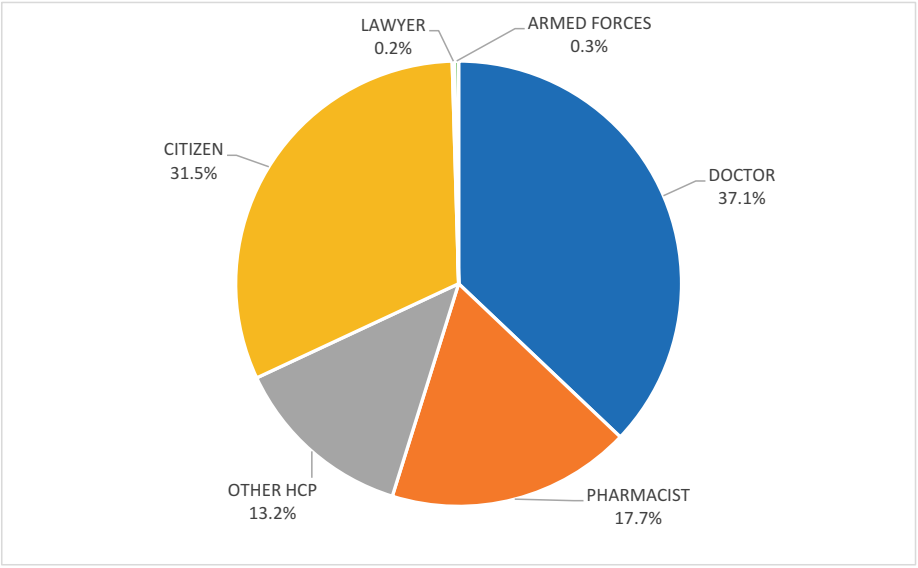


Table 2 shows the report distribution by onset time from vaccination.

Table 2 *- Report distribution by onset time of symptoms from vaccination date*

ONSET TIME	N° REPORTS	%
0 days	48,770	48.2%
1 day	28,365	28.1%
2-7 days	11,979	11.8%
>7 days	8,368	8.3%
Not definable	3,628	3.6%
Total	***101,110***	***100%***

As previously reported, regardless of the vaccine, the dose and type of event, most reactions (about 76%) occur on the same day as vaccination or on the following day, more rarely beyond the following 48 hours.

Distribution by seriousness and outcome

85.4% (no. 86,361) of reports entered as of 26/09/2021 refer to **non-serious events**, with a reporting rate of 103/100,000 administered doses and **14.4%** (no. 14,605) to **serious adverse events**, with a reporting rate of 17 serious events per 100,000 administered doses, regardless of the type of vaccine, the administered dose (1st or 2nd dose) and of the possible causal role of vaccination (seriousness is not reported in 0.2% of reports, no. 144).

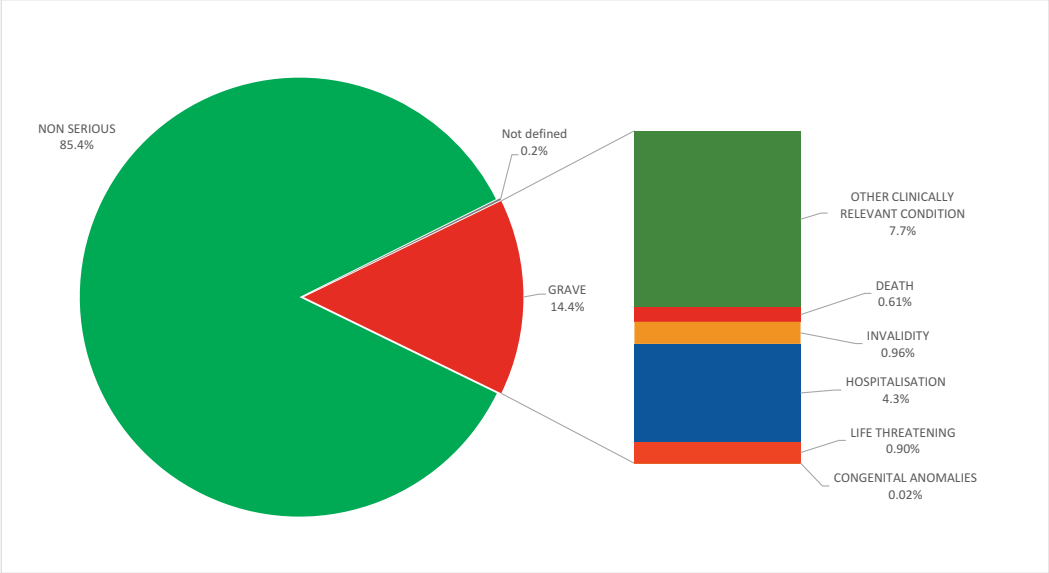
The reporting rates of serious events for each vaccine are as follows: 14 cases per 100,000 doses of Comirnaty, 15 per 100,000 doses of Spikevax, 35 per 100,000 doses of Vaxzevria, and 22 per 100,000 doses of Janssen. As already shown in the previous Reports, the reported serious adverse events occur in the first 48 hours after vaccination (about 57% of cases, no. 8,275), more rarely in the following weeks (about 37% of cases, no. 5,382). In the remaining 6% of cases (no. 948), the information is insufficient to establish the onset time of the adverse event with regard to the report, despite the follow-up requests. Most serious reports are classified as "other clinically relevant condition", i.e., alerting the subject and/or the reporter without entailing a specific intervention in hospitals.

When is a report considered serious?

Seriousness of reports is defined according to internationally standardised criteria that do not always coincide with the real clinical seriousness of the reported event. Any event is always considered serious if it involved hospitalisation/first aid, immediate life threatening, disability, congenital anomalies, death, and other clinically relevant conditions. Furthermore, some adverse events are considered serious regardless of the clinical consequences if present in a list that is published and periodically updated by the European Medicines Agency, under the name of IME list (Important Medical Events, e.g. high temperature).

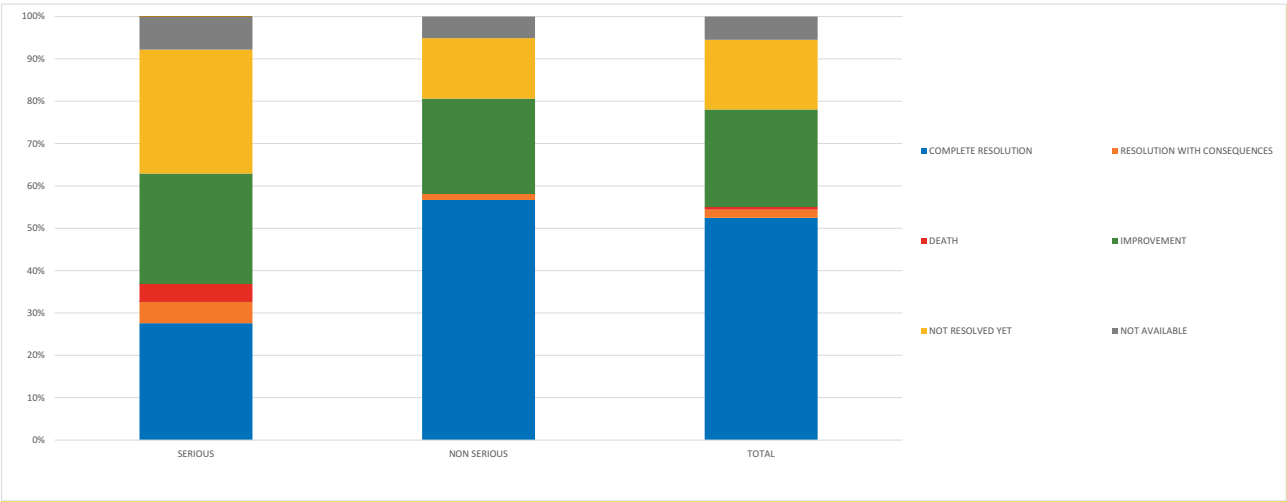
Figure 6 shows the distribution of reports by seriousness, with details of the seriousness parameter for serious reactions relating to all vaccines.

Figure 6 - *Distribution by seriousness of the reports entered in the period considered (0.2% of reports do not indicate seriousness)*



About 70% of reports refer to non-serious adverse events with full recovery or improvement already at the time of reporting. 53.6% of serious reports result in full recovery or improvement and 29% has not yet recovered upon reporting (Fig. 7).

Figure 7 - *Distribution by outcome of reports entered in the period considered*



Please note that the report outcome is continuously being updated, through the request of follow-up information. The distribution by outcome does not show significant differences between the vaccines currently in use.

Serious reports and causal link

At the time of drafting this Report, the causal link according to the WHO algorithm was included in 73% (10,681/14,605) of **reports of serious adverse events**, regardless of the outcome and was found related to vaccination in 40.3% of all serious reports evaluated (4,301/10,681), indeterminate in 36% (3,848/9,324) and unrelated in 20.5% (1,845/9,324). 3.2% (339/10,681) of the reports are unclassifiable, due to lack of sufficient information.

Deaths and causal link

Overall, after checking the presence of duplicates, or cases for which more than one report has been entered, 608 serious reports report the "death" outcome at the time of reporting or as information acquired after the follow-up. The reporting rate is 0.72/100,000 administered doses, regardless of the type of vaccine, dose number and causal link, with a rate similar to the one recorded in the previous Report. The distribution of such fatal cases by type of vaccine is shown in table 3.
48.2% (293) of cases concern women, 50.8% (309) men while 0.7% (6 sheets) do not report this data. The mean age is 76 years. The time between vaccine administration and death varies from two hours up to a maximum of 189 days, where reported. In 397 cases death is recorded after the first dose, in 211 after the second.
No deaths were reported as a result of anaphylactic shock or major allergic reactions, while it is common that death occurs as a result of complications from diseases or conditions already present before vaccination.

Table 3 *- Distribution of death reports by type of vaccine*

VACCINE	Fatal cases	Rates per 100,000 administered doses
Comirnaty	391	0.65
Spikevax	96	0.91
Vaxzevria	98	0.81
Janssen	23	1.56
Total	**608**	**0.72**

71.5% (435/608) of death reports have a causality assessment with the algorithm used in the vaccine surveillance (WHO Algorithm), according to which 59.5% of cases (259/435) is not related, 30.6% (133/435) indeterminate and 6.2% (27/435) unclassifiable due to lack of sufficient information. Overall, 16 cases (3.7%) out of the 435 evaluated were related (approximately 0.2 cases per million administered doses), of which 14 have already been described in the previous Reports. The remaining 2 reports refer to 2 patients aged 76 and 80 with a condition of fragility due to multiple pathologies, who died from COVID-19 after completing the vaccination course.

Distribution by dose number

In the period considered, 46% of the overall administered doses was used to complete the vaccination cycle (second doses), mainly with the Comirnaty vaccine, and less than 2% of the administered doses were used for single administration in patients with previous Sars-CoV-2 infection (situation similar to the completion of the vaccination course).

Regarding the administration of the third dose which started in September, only one report was made, compared to approximately 46,000 administered doses. Table 4 shows the reporting rates of suspected adverse events by vaccine type and dose number.

Table 4 *- Distribution of reports by dose number*

Vaccine	Reporting rate relating to the 1st dose (per 100,000 administered doses)	Interval 95% Confidence	Reporting rate relating to the 2nd dose (per 100,000 administered doses)	95% Confidence interval	Cumulative reporting rate (per 100,000 administered doses)	95% Confidence interval
Comirnaty	137	136-138	89	92-94	114	*113-115*
Spikevax	104	101-107	62	58-63	84	*82-86*
Vaxzevria	320	316-324	28	22-24	185	*183-187*
Janssen	92	87-97	-	-	92	*87-97*
All vaccines	158	157-159	77	76-78	120	*119-121*

As already noted in previous Reports, the reporting rates for the 2nd dose are lower than those for the 1st dose, with a marked difference for the Vaxzevria vaccine.

Distribution by type of event

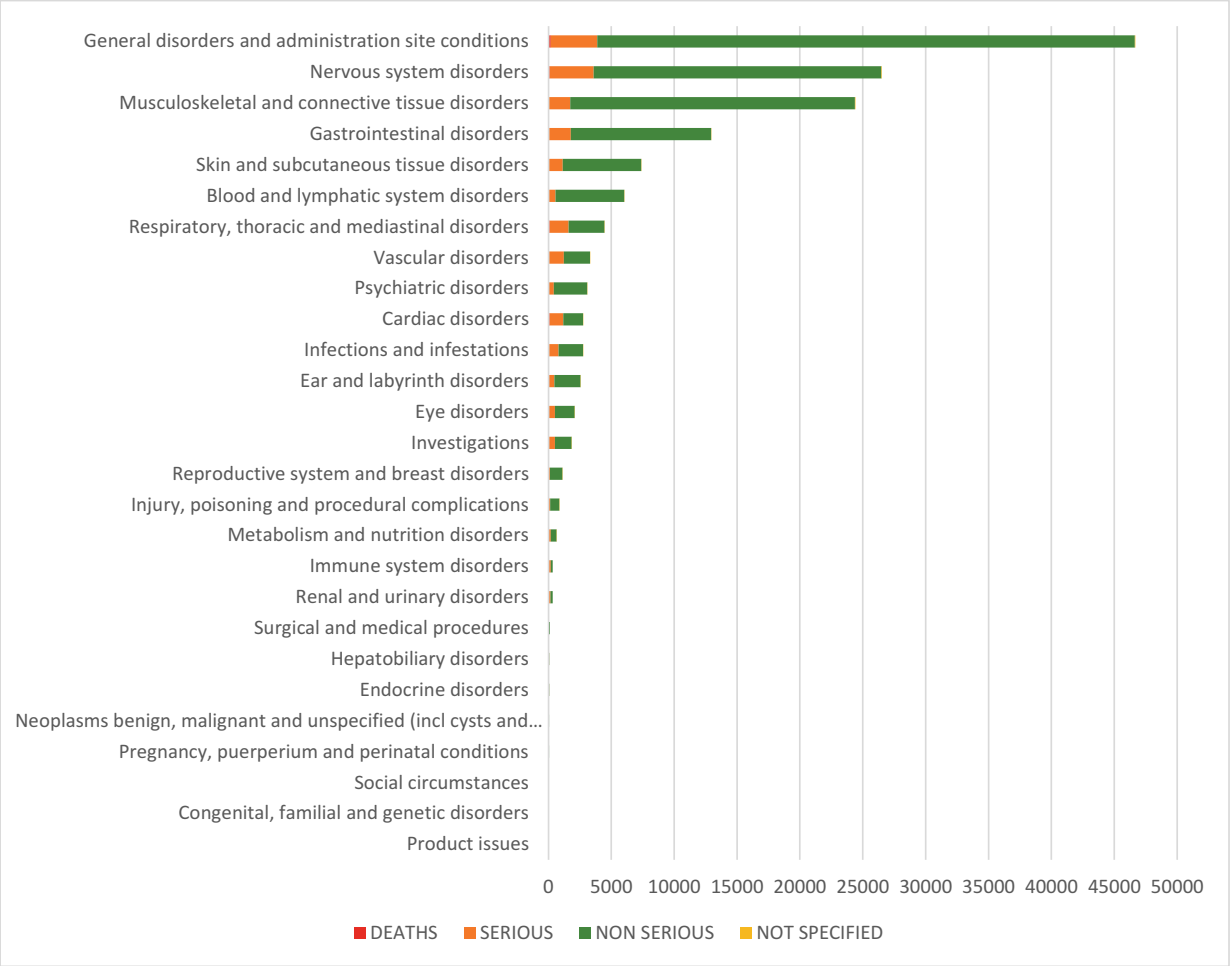
Graphs 8, 9, 10 and 11 report in order of frequency the types of events reported according to the System Organ Class (SOC) for the four vaccines used, regardless of the dose and causal link. It should be noted that a single report sheet can include multiple events, therefore the total number of events is higher than the total number of reports.

How are adverse events classified in reports?
AEFIs are entered into RNF according to a specific dictionary, called MedDRA (Medical Dictionary for Regulatory Activities), which includes preferred terms (unique medical concepts such as signs, symptoms, diseases, etc.), subsequently grouped according to equivalence relationships (synonymous terms) and hierarchy. The highest level of organisation is represented by the system organ class (SOC), which groups events by cause (e.g.: infections and infestations), location (e.g. gastrointestinal disorders) and purpose (e.g.: medical and surgical procedures).

Comirnaty vaccine (Pfizer/BioNTech)

The analysis of the distribution by type of adverse events following vaccination with Comirnaty did not observe substantial differences compared to previous Reports.
The most reported suspected adverse events fall within **general disorders and administration site conditions** (especially fever, injection site pain, fatigue/asthenia), followed by **nervous system disorders** (mainly headache and paraesthesia), by **musculoskeletal and connective tissue disorders** (mostly musculoskeletal pain) and by **gastrointestinal disorders** (generally nausea, vomiting and diarrhoea).

***Figure 8** - Distribution of adverse events after Comirnaty vaccine by system organ class (SOC)*



The proportion between serious reports (about 12%) and non-serious (about 87%) remains unchanged. In 1% of cases seriousness is not defined). The distribution by type of serious adverse events does not differ significantly from that of all events.

Comirnaty-related serious adverse events

About 4 reports per 100,000 doses of Comirnaty administered are serious events related to vaccination (4.5 related serious adverse events per 100,000 first doses administered and 3.5 per 100,000 second doses administered). Based on the seriousness criterion, 73% of these reports were included as “serious - other clinically relevant condition", 21% as “serious - hospitalisation or prolonged hospitalisation” and 3% as “serious - life threatening”. Full recovery of the adverse reaction is reported as an outcome in 52% of these reports and improvement in 26%.

The most commonly reported related serious adverse event is hyperpyrexia (about 1.6 cases per 100,000 administered doses), followed by headache (about 1.4 cases per 100,000 administered doses) and paraesthesia (about 1.3 cases per 100,000 administered doses). Frequent reports also include of joint pain, muscle pain and asthenia, all with a rate of approximately 1 case per 100,000 administered doses. Less frequent are nausea with or without vomiting, skin rashes, dizziness and anxious reactions to vaccination (more often lipothymic reactions), each with a frequency of approximately 0.8 cases per 100,000 administered doses. More rarely, general malaise, major local reactions at the injection site and diarrhoea are observed with a frequency of approximately 0.5 cases per 100,000 administered doses.

The related symptoms most frequently associated with each other in the reporting sheets are high fever, headache, asthenia, and joint and muscle pain in a flu-like syndrome, regardless of the dose number. Other associations of symptoms observed are: lymphadenopathy and hyperpyrexia with asthenia; headache and paraesthesia with joint and muscle pain; skin rashes and general malaise; lipothymia, general malaise and dizziness.

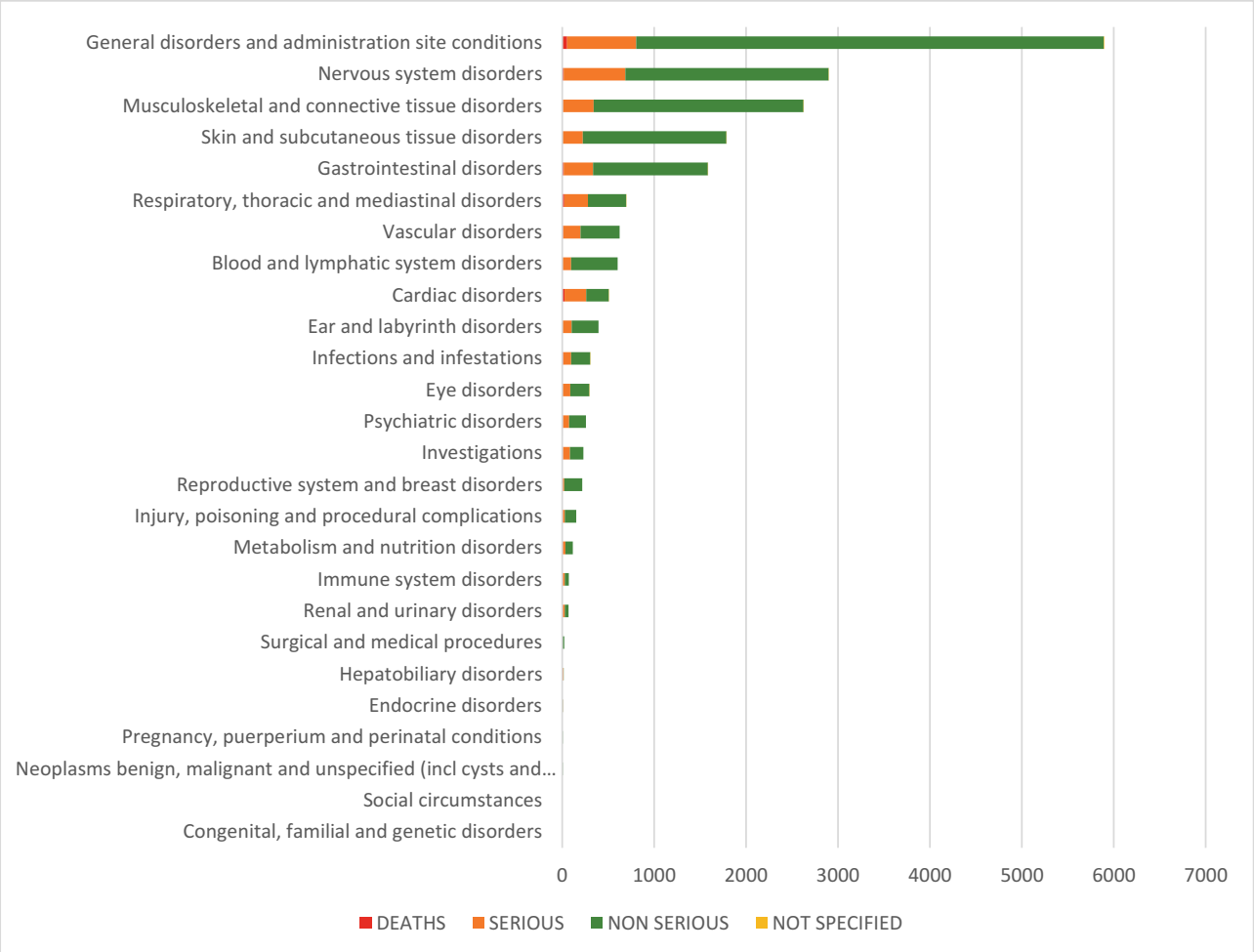
Very rare are myocarditis/pericarditis (6 cases per million administered doses), anaphylactic reactions (3 cases per million administered doses) and facial nerve paralysis (2 cases per million administered doses).

Spikevax (formerly COVID-19 Vaccine Moderna)

The distribution by type of adverse events following vaccination with Spikevax is comparable to that observed in previous Reports.

Most of the suspected adverse events reported are related to **general disorders and administration site conditions**, mainly fever, injection site pain, fatigue/asthenia, followed by **nervous system disorders**, mostly headache, by **musculoskeletal and connective tissue disorders**, such as myalgia, arthralgia and musculoskeletal pain, and by **skin and subcutaneous tissue disorders**, mainly erythema, redness and urticarial reactions. **Gastrointestinal disorders**, such as nausea, vomiting and diarrhoea, are reported more rarely.

Figure 9 *- Distribution of adverse events after Spikevax vaccine by system organ class (SOC)*



Non-serious reactions represent about 82.8% of the total reports and serious reactions represent 18.1% (in 1% of cases seriousness is not defined), in line with the findings of the previous Report. The distribution by type of serious adverse events does not differ significantly from that of all events.

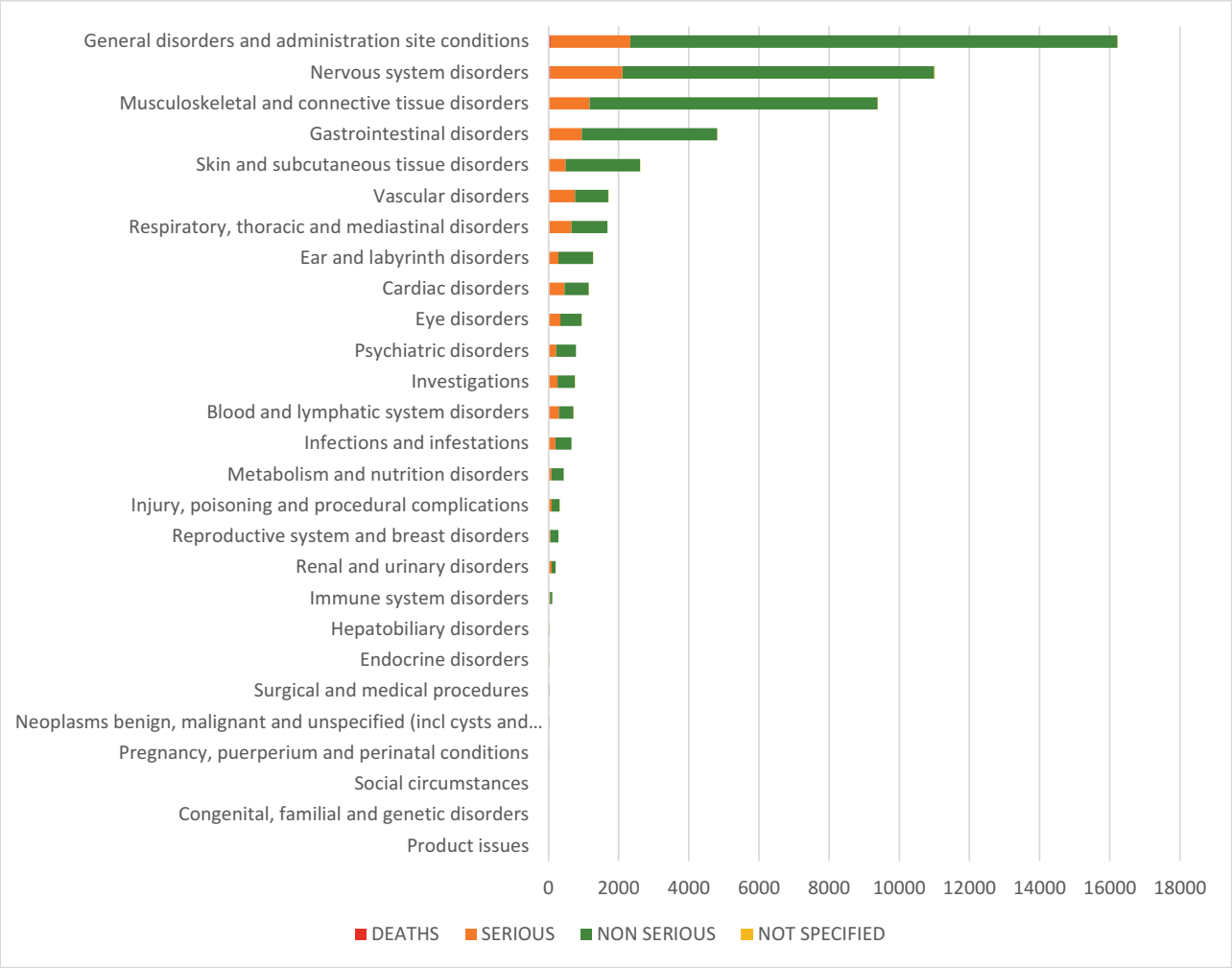
Spikevax-related serious adverse events

About 3 reports per 100,000 administered doses of Comirnaty are serious events related to vaccination (4 related serious adverse events per any 100,000 first doses administered and 3 per any 100,000 second doses administered).
Based on the seriousness criterion, 63% of these reports were included as “serious - other clinically relevant condition", 28% as “requiring hospitalisation” and 5% as “life threatening”. Full recovery of the adverse reaction is reported as an outcome in 38% of these reports and improvement in 31%.
Hyperpyrexia confirms as the most commonly reported related serious adverse event, (about 1.5 cases per 100,000 administered doses), followed by headache, nausea/vomiting, with a reporting rate of about 1 case per any 100,000 administered doses. Rarely reported are asthenia, joint and muscle pain, paraesthesia, lymphadenopathies, skin rashes and anxious reactions to vaccination (especially lipothymia or vegetative reaction), all with a reporting rate of approximately 0.5 case per 100,000 doses administered.
The related symptoms most frequently associated with each other in the reporting sheets are high fever, headache, asthenia, and joint and muscle pain in a flu-like syndrome, regardless of the dose number.
Other associations of symptoms observed are: headache and paraesthesia; asthenia with joint and muscle pain; skin rashes and hyperpyrexia; lipothymia and asthenia.
Very rare are myocarditis/pericarditis (11 cases per million administered doses), anaphylactic reactions (2 cases per million administered doses) and facial nerve paralysis (2 cases per million administered doses).

Vaxzevria Vaccine (AstraZeneca)

Also for the Vaxzevria vaccine, the distribution of **suspected adverse events following vaccination** is in line with that reported in previous Reports.
The most reported suspected adverse events fall within **general disorders and administration site conditions** (especially fever, injection site pain, fatigue/asthenia), followed by **nervous system disorders** (mainly headache), by **musculoskeletal and connective tissue disorders** (mostly musculoskeletal pain), generally associated with each other and with the increase in body temperature.

***Figure 10** - Distribution of adverse events after Vaxzevria vaccine by system organ class (SOC)*



About 81% of the reports of the Vaxzevria vaccine were entered as non-serious and 18% as serious (in 1% of cases seriousness is not defined), with a distribution by type of event that does not differ significantly from the one shown in figure 10.

Serious adverse events related to Vaxzevria

About 11 reports per 100,000 doses of Vaxzevria administered are serious events related to vaccination (11 per 100,000 first doses administered and 1 per 100,000 second doses administered). 71% of these reports are classified as “serious - other clinically relevant condition”, 20% as “hospitalisation” and 5.8% as “life threatening”. Full recovery of the adverse reaction is reported in 44% of these reports and improvement in 30%.

The most commonly reported related serious adverse events are hyperpyrexia (about 7 cases per 100,000 administered doses) and headache (approximately 4 cases per 100,000 administered doses). Relatively frequent are nausea and vomiting (about 2 cases per 100,000 administered doses), asthenia, chills and muscle/joint pain (approximately 2 cases per 100,000 administered doses). More rarely reported are lipothymias and vagal reactions (1 case per 100,000 administered doses).

The related symptoms most frequently associated with each other in the reporting sheets are high fever, headache, asthenia, and joint and muscle pain in a flu-like syndrome, mainly after the first

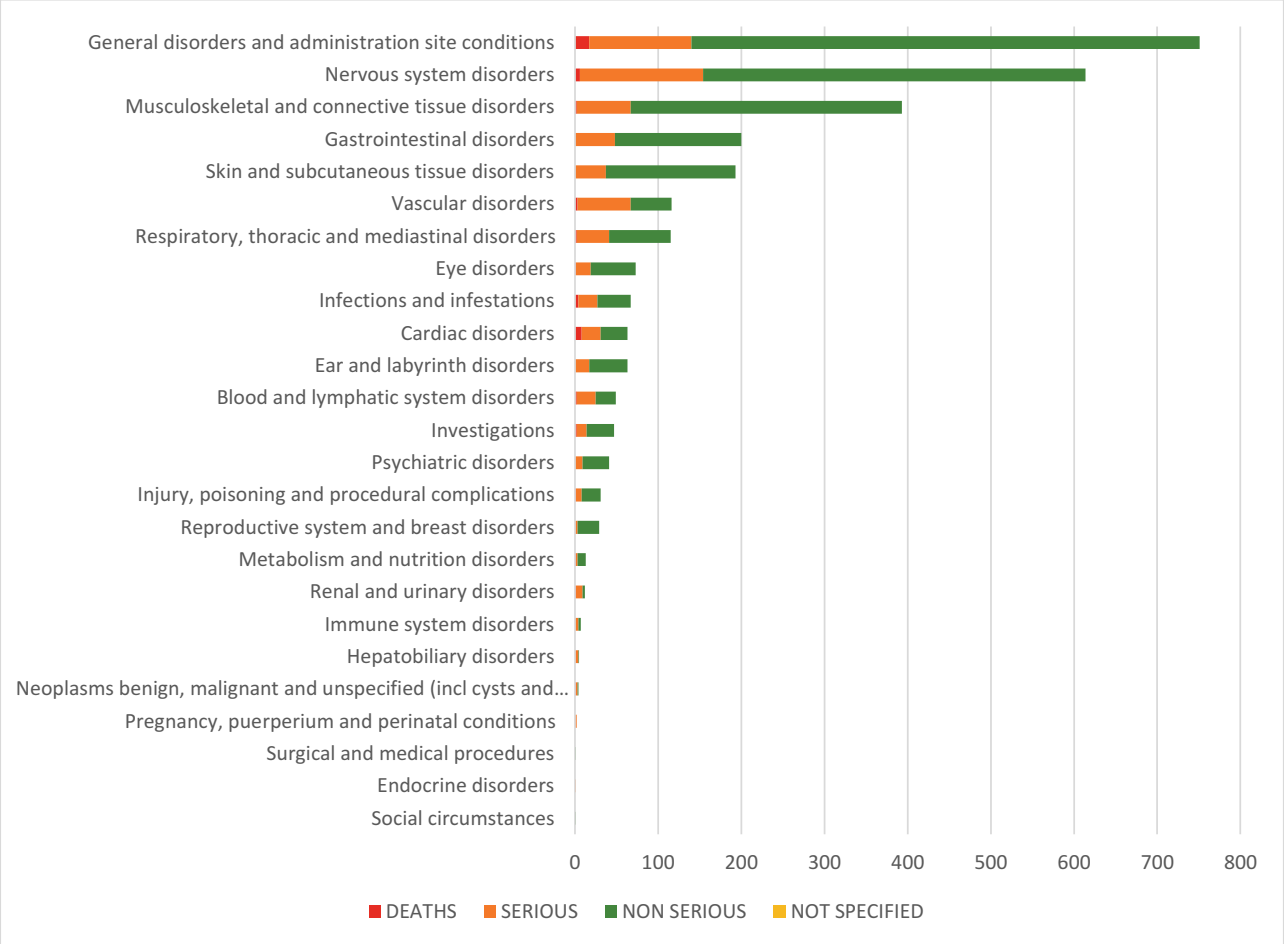
dose. Other associations of symptoms observed are: headache and dizziness; nausea and dizziness; asthenia, headache and muscle/joint pain.

Some adverse events continue to be very rare, with a stable reporting rate of around 2 cases of anaphylactic reaction per million administered doses and around 1 case per 1,000,000 administered doses for acute and subacute neuropathies (including the Guillain-Barré syndrome), intracranial or atypical venous thrombosis with thrombocytopenia (VITT) and idiopathic thrombocytopenia, which continue to be monitored at national and European level.

COVID-19 Janssen vaccine

The distribution by type of **suspected adverse events following vaccination with COVID-19 Janssen vaccine** also remains comparable to previous Reports, with most of the reports falling under **general disorders and administration site conditions** (such as fever, local injection site reactions and fatigue/asthenia, followed by **nervous system disorders** (mainly headache) and by **musculoskeletal system and connective tissue disorders** (mostly myalgia and arthralgia).

Figure 11 *- Distribution of adverse events after COVID-19 Janssen vaccine by system organ class (SOC)*



76% of reports of the COVID-19 Janssen vaccine were entered as non-serious and 24% as serious, with no substantial differences in the distribution by type of reaction.

Serious adverse events related to COVID-19 Janssen vaccine

Approximately 5 reports per 100,000 doses were found to be serious related to vaccination, 46% of which were entered as “serious - other clinically relevant condition", 41% as requiring hospitalisation and 8% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 22% of these reports and improvement in 41%.
The number of related serious reports is still very low (71 reports), due to the limited number of doses currently administered. Therefore, the reporting rates continue to be affected by the low exposure, they have not changed compared to the previous Report and are not currently consolidated. Despite this, the most frequently observed correlated serious adverse reaction is hyperpyrexia (approximately 3 cases per 100,000 administered doses), followed by diffuse arthromyalgia (approximately 2 cases per 100,000 administered doses), frequently associated with each other. The number of cases of cerebral or atypical site venous thrombosis with or without thrombocytopenia, acute or subacute polyneuropathies or severe allergic reactions is very small and results in a reporting rate of less than 1 cases per 1,000,000 administered doses, unchanged compared to the previous Report.

Heterologous vaccination

In total, as of 26/09/2021, 644,428 so-called heterologous vaccinations have been administered on people under 60 years of age who had received the Vaxzevria vaccine as their first dose (about 39,563 more heterologous vaccinations compared to 26/08/2021). To complete the vaccination course, the Comirnaty vaccine was used in 76% of cases and the Spikevax vaccine in 24%.
Compared to this mixed-schedule modality of vaccination, 262 reports were entered, with a reporting rate of 40 per 100,000 administered doses. 77% of reactions occurred with Comirnaty (36 reports per 100,000 doses administered) and 23% with Spikevax (33 reports per 100,000 doses administered). Unlike the general distribution of adverse events, approximately 54% of reports come from citizens and 46% from healthcare professionals.
77% of the reports are reported as non-serious and 23% as serious. The full recovery outcome at the time of reporting was entered in 45% of cases and improvement in 21% of cases.
The distribution by type of adverse events is not substantially different between the two vaccines used and is consistent with reports of mRNA vaccines. The most frequently reported adverse events are fever, injection site reactions, paraesthesia and widespread joint/muscle pain. More rarely reported are nausea/vomiting, diffuse lymphadenopathy and generalised skin rashes. Fever associated with joint/muscle pain and headache, paraesthesia associated with headache and diffuse lymphadenopathy are reported in most serious reports.

Vaccination in the age group 12-19 years

As at 26/09/2021, Comirnaty (whose indication was extended from 12 years from 31/05/2021) and Spikevax (approved from 12 years of age from 28/07/2021) were used for vaccination in adolescents, while the Vaxzevria and COVID-19 Janssen vaccine are authorised from the age of 18. By the same date, 5,623,932 doses of vaccine have been administered in adolescents aged 12-19

years, of which 56% were first doses and 44% second doses. Approximately 87.7% of the doses used in this age group are related to the Comirnaty vaccine, 11.3% to the Spikevax vaccine, 0.3% to the Vaxzevria vaccine and 0.7% to the Janssen vaccine.
Overall, 1.358 reports of suspected adverse events were entered in the age group 12-19 years with a reporting rate of 24 adverse events per 100,000 administered doses (1.000 reports after the 1st dose, with a reporting rate of 32 adverse events per 100,000 administered doses, and 358 reports after the 2nd dose, with a reporting rate of 14 adverse events per 100,000 administered doses). 76.7% of the reports (no. 1,041) were recorded as not serious and 23.1% (no. 314) as serious (0.2% of the reports do not include this information). About 71% of serious reports include complete resolution or improvement at the time of reporting.

The distribution by type of adverse event is not substantially different from that observed in any other age group. In particular, the most frequently reported adverse events are headache, fatigue, fever and local reactions at the injection site, regardless of vaccine type, dose number and seriousness.
Considering the low number of serious reports received (5 cases per 100,000 administered doses), the assessment of the distribution by type of event and the related evaluation of the causal link is currently still unreliable. Approximately 1 report in every 100,000 administered doses was found to be serious related to vaccination, with no substantial differences at the present time compared to the previous Report. Most of these reports report a clinical picture characterised by fever, joint/muscle pain, headache and, more rarely, myocarditis, pericarditis or myopericarditis/perimyocarditis after administration of mRNA vaccines, mainly after the second dose and in men. The latter reactions are being studied in depth at national and European level.

General considerations on data

The time trend of the main parameters analysed in the different reports published so far is summarised in table 5.

Table 5 *- Summary data Report#1 - Report#9*

	Report #1	Report #2	Report #3	Report #4	Report #5	Report #6	Report #7	Report #8	Report #9
	as at 26/01/2021	as at 26/02/2021	as at 26/03/2021	as at 26/04/2021	as at 26/05/2021	as at 26/06/2021	as at 26/07/2021	as at 26/08/2021	as at 26/09/2021
administered doses	1,564,090	4,118,277	9,068,349	18,148,394	32,429,611	49,512,799	65,926,591	76,509,846	84,010,605
reporting of adverse events	7,337	30,015	46,237	56,110	66,258	76,208	84,322	91,360	101,110
reports in the period	7,337	22,678	16,222	9,873	10,148	9,950	8,114	7,038	9,750
reporting rate	469	729	510	309	204	154	128	119	120
reporting rate for men	293	424	299	176	116	88	73	69	70
reporting rate for women	561	907	645	404	272	209	175	165	166
reporting rate for first dose	515	773	496	299	211	164	160	153	158
reporting rate for second dose	225	785	540	333	190	134	86	78	77
reporting rate of serious adverse reactions	34	44	36	27	21	18	16	16	17
reporting rate of serious adverse reactions for men	22	28	23	18	15	13	12	12	13
reporting rate of serious adverse reactions for women	42	54	44	33	26	23	20	20	21
reporting rate of serious adverse reactions without “clinically relevant” cases	8.9	8.1	8.5	8.8	7.9	7.5	7.0	7.0	8.0

	Report #1	Report #2	Report #3	Report #4	Report #5	Report #6	Report #7	Report #8	Report #9
	as at 26/01/2021	as at 26/02/2021	as at 26/03/2021	as at 26/04/2021	as at 26/05/2021	as at 26/06/2021	as at 26/07/2021	as at 26/08/2021	as at 26/09/2021
reporting rate of deaths	0.8	0.97	1.1	1.23	1.0	0.8	0.75	0.73	0.72
Source of reporting									
Doctor	47%	46%	44%	42%	42%	40.5%	39.5%	39%	37%
Pharmacist	22%	19%	20%	20%	20.5%	20%	20%	19%	18%
Other healthcare professional	25%	26%	21%	19%	17%	16%	15%	14.2%	13%
Patient/Citizen	6%	9%	15%	18%	20%	23%	25%	27.3%	31.5%
Lawyer	0%	0%	0.12%	0.20%	0.2%	0.2%	0.2%	0.2%	0.2%
Armed Forces	0%	0%	0.07%	0.30%	0.3%	0.3%	0.3%	0.3%	0.3%
Comirnaty									
reporting rate	471	769	535	328	214	150	122	113	114
reporting rate for first dose	517	756	525	315	212	144	137	131	137
reporting rate for second dose	278	790	549	348	216	161	104	93	89
reporting rate of serious adverse reactions	na	45	33	24	18	15	13	13	14
Spikevax									
reporting rate	277	333	227	129	88	83	82	80	84
reporting rate for first dose	277	335	216	132	95	94	98	94	104
reporting rate for second dose	-	322	264	121	73	65	60	61	61
reporting rate of serious adverse reactions	na	26	22	18	13	14	13	14	15
Vaxzevria									
reporting rate	-	326	477	309	236	219	184	180	185
reporting rate for first dose	-	326	477	307	261	281	304	314	320

	Report #1	Report #2	Report #3	Report #4	Report #5	Report #6	Report #7	Report #8	Report #9
	as at 26/01/2021	as at 26/02/2021	as at 26/03/2021	as at 26/04/2021	as at 26/05/2021	as at 26/06/2021	as at 26/07/2021	as at 26/08/2021	as at 26/09/2021
reporting rate for second dose	-	-	-	-	24	31	21	23	28
reporting rate of serious adverse reactions	-	31	50	39	36	37	32	33	35
Janssen									
reporting rate	-	-	-	-	34	67	79	86	91
reporting rate of serious adverse reactions	-	-	-	-	5	12	15	19	22

Figure 12 describes the trend in reports, rates and doses over time. There are fluctuations in rates compared to previous reports, which may be partly due to the expected drop in reports in the summer period. On the other hand, a constant increase is observed in reports from citizens for active pharmacovigilance projects (Fig. 13).

Figure 12 *– Trend in reports, rates and doses over time*

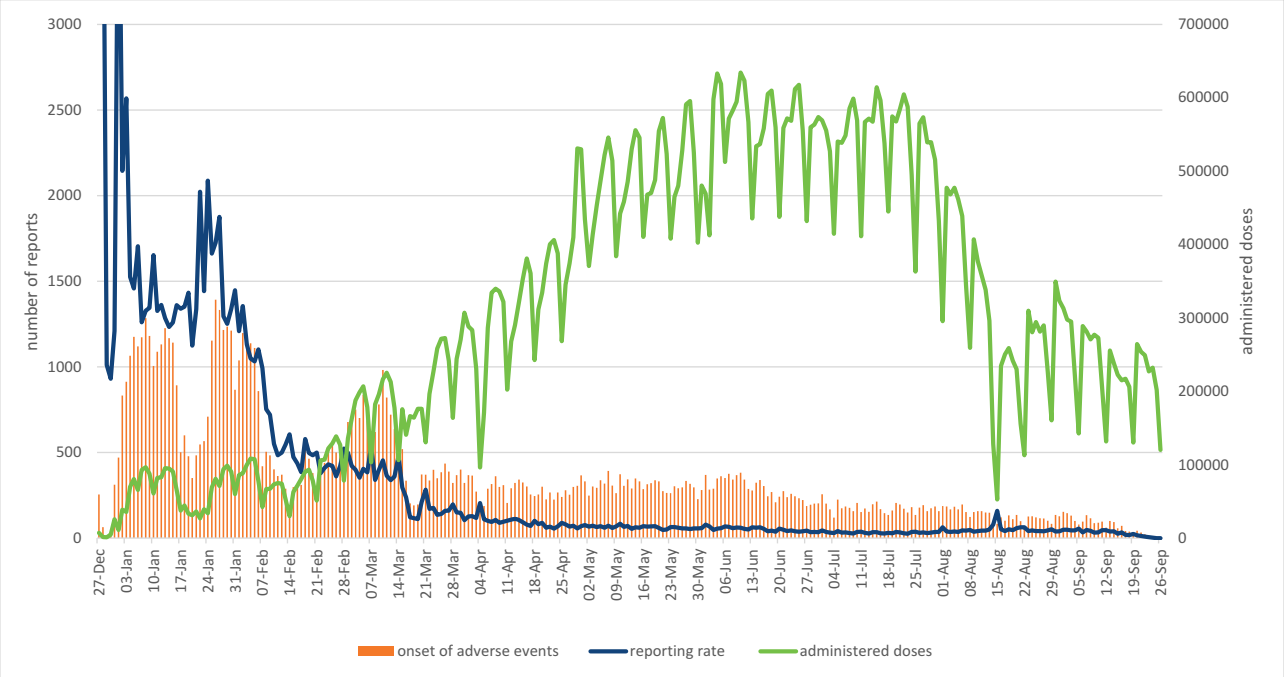


Figure 13 *– Trend in reporting rates by gender, number of doses, severity and fatal events over time*

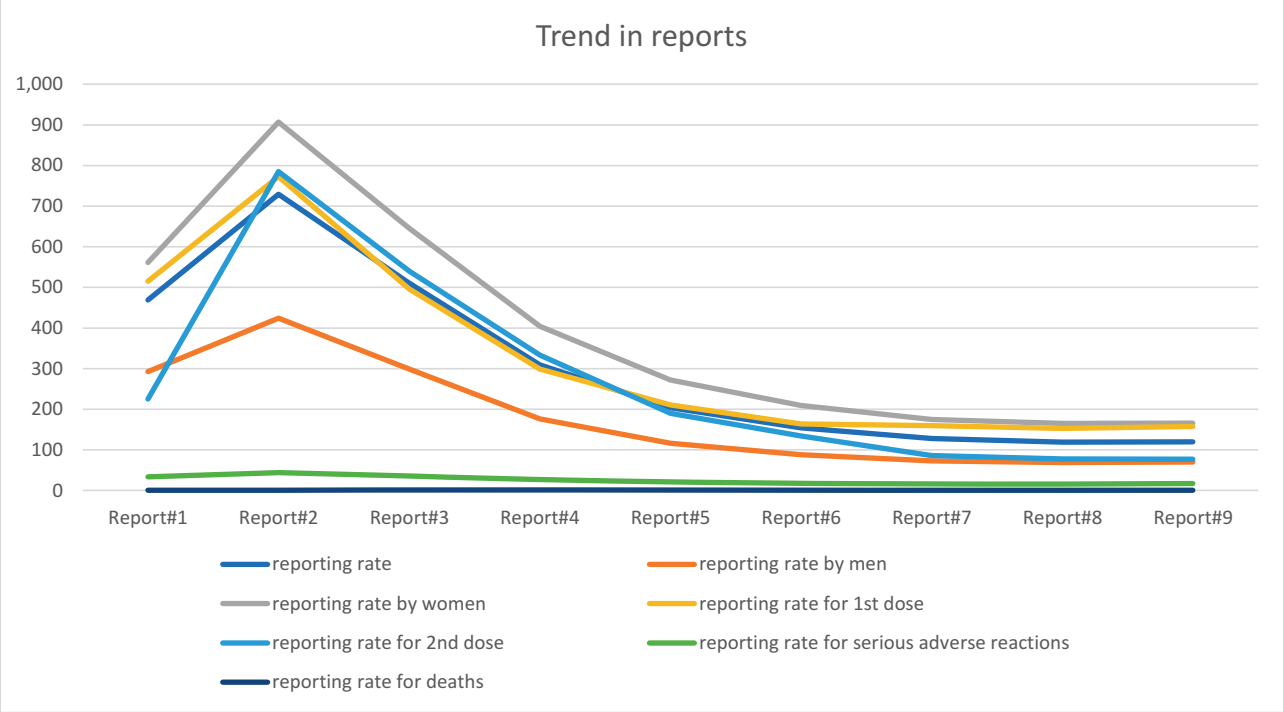
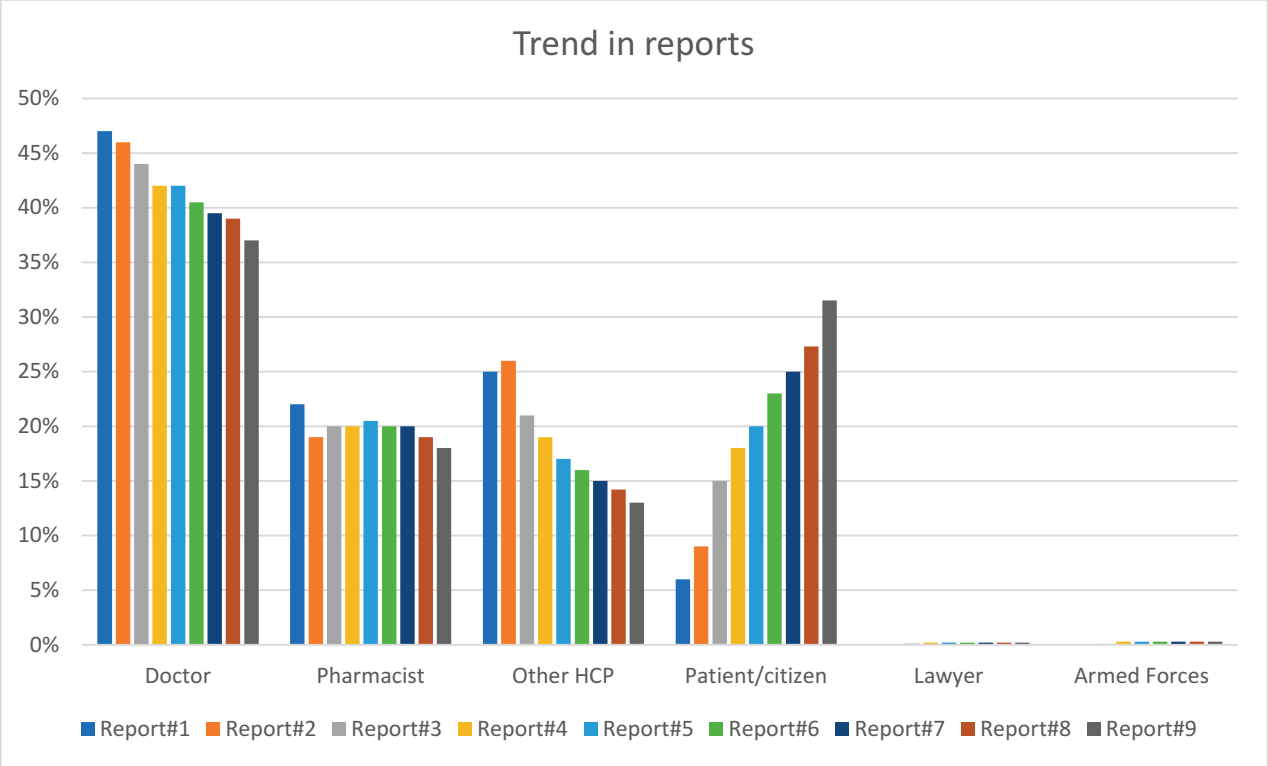


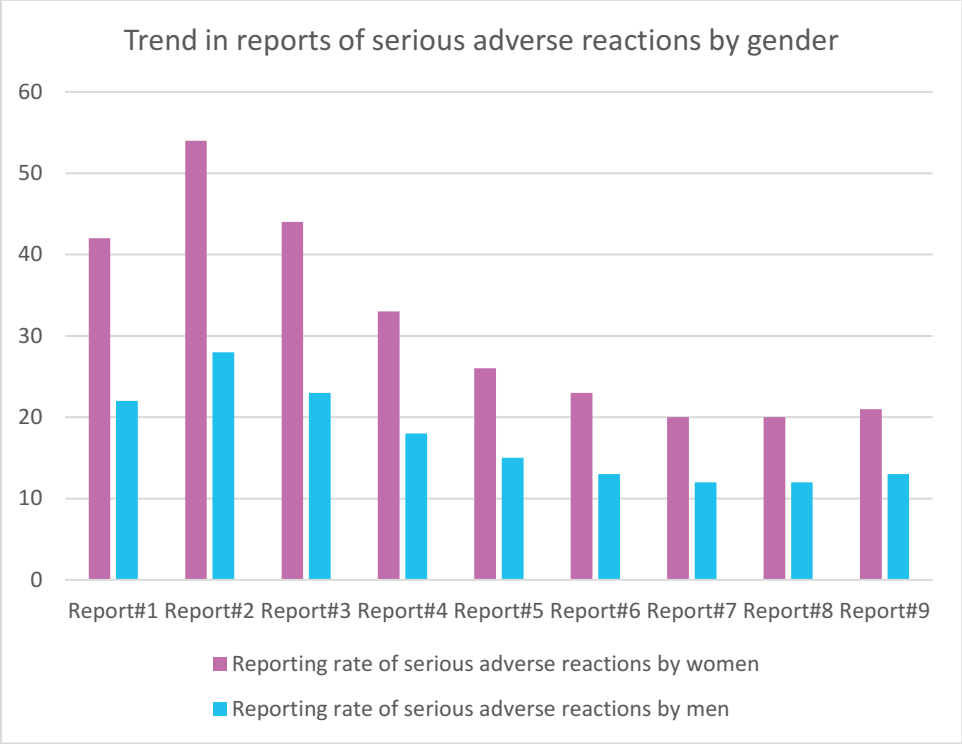
Figure 14 shows the trend by source of reporting; the largest number of reports come from doctors, while reports from pharmacists remain stable. Compared to previous periods, the increase in reports from citizens is more marked while those from doctors decrease (Fig. 14).

Figure 14 *– Trend in the type of source of reporting over time*



The ratio between women/men reports is constant (Fig. 15).

Figure 15 *– Trend in reporting rates of serious adverse reactions by gender*



Concluding remarks

Considering the stability of the reporting trend for the various COVID-19 vaccines, the Surveillance Report will be published quarterly. As usual, all safety information will still be published on the AIFA website, as well as any further information on specific topics of interest. The monthly update of interactive graphs will continue.

How to report a suspected adverse reaction?

Information for reporting a suspected adverse reaction following vaccination is available at the following link: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse