COVID-19 Vaccine Surveillance Report

6

27/12/2020 - 26/06/2021

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ITALIAN MEDICINES AGENCY

INTRODUCTION TO READING

No medicinal product can ever be considered risk-free. Each one 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 that 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: https://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf?ua=1

HIGHLIGHTS

As of 26 June 2021, 154 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; Spikevax (former COVID-19 Moderna vaccine) and COVID-19 Janssen vaccine are less used.

The reporting trend and the related rates are substantially stable over time.

Most reported adverse events are classified as non-serious (approximately 87.9%) which resolve completely and only to a lesser extent as severe (11.9%), resulting in full recovery or improvement in most cases.

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

It is confirmed that the most frequently reported serious correlated adverse reactions configure a picture of flu-like syndrome with intense symptoms, more frequent after the second dose of mRNA vaccines and after the first dose of Vaxzevria.

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

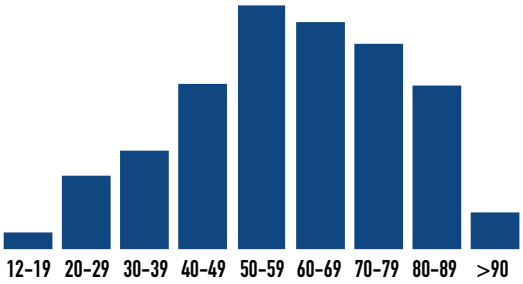
Reference period 27/12/2020 - 26/06/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

DOSES ADMINISTERED

49.512.799

Comirnaty 70,6%
Spikevax 9,6%
Vaxzevria 17,3%
Vaccino Janssen 2,5%



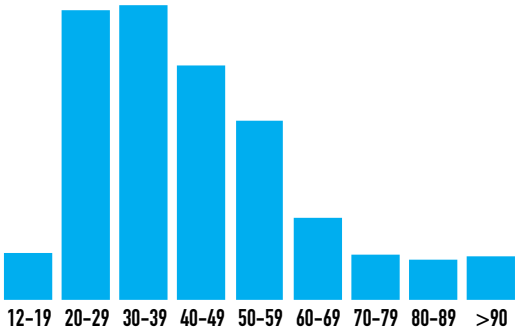
ADMINISTRATION BY AGE GROUP

ADMINISTRATION BY DOSE	First dose	Second dose
	67%	33%

SUSPECTED ADVERSE REACTIONS

76.206

Comirnaty 69,0%
Spikevax 5,2%
Vaxzevria 24,7%
Vaccino Janssen 1,1%



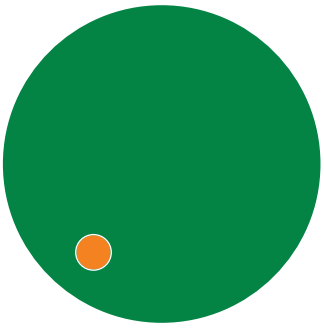
REPORTING RATE BY AGE GROUP

REPORTING RATE BY DOSE	First dose	Second dose
	164	134

VACCINES OFFER MAXIMUM PROTECTION AGAINST COVID-19 WITHIN 2-3 WEEKS OF COMPLETING THE VACCINE COURSE

BOOK AND GET THE 2ND DOSE OF VACCINE IF RECOMMENDED

SUSPECTED ADVERSE REACTIONS SERIOUS/NON-SERIOUS



SERIOUS	NON-SERIOUS
11,9%	87,9%

0.2% OF SUSPECTED ADVERSE REACTIONS ARE NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)
PERIOD UNDER REVIEW: 27/12/2020 - 26/06/2021

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, viral vector vaccine authorised as from 12/03/2021 and used from 22/04/2021.

As of 26/06/2021, 7**6,206 reports of adverse events following immunisation** have been entered in the National Pharmacovigilance Network, out of a total of **49,512,799 vaccine doses**, with a **reporting rate of 154 per 100,000 doses.**

The distribution by type of vaccine is shown in table 1.

Comirnaty is currently the most widely used vaccine in the Italian vaccination campaign (70.6%), followed by Vaxzevria (17.3%), Spikevax (9.6%) and COVID-19 Janssen vaccine (2.5%)[2]. As in previous Reports, the distribution of reports by type of vaccine is similar to the distribution of administrations (Comirnaty 69%, Vaxzevria 24.7%, Spikevax 5.2% and COVID-19 Janssen vaccine 1.1%).

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 of 26/06/2021	Administered doses as of 26/06/2021	Reporting rate (per 100,000 administered doses)	95% Confidence interval
Comirnaty	52,604	34,962,870	***150***	***149-151***
Spikevax	3,947	4,733,984	***83***	***80-85***
mRNA active ingredient (unspecified brand)	14	-	-	
Vaxzevria	18,827	8,600,057	***219***	***216-222***
Janssen	816	1,215,888	***34***	***31-37***
Total	**76.208***	**49,512,799**	***154***	***153-155***

** 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 two records (after heterologous vaccination)*

[2] The number of doses administered as of 26/06/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 30/06/2021

Figure 1a shows the temporal trend of the number of reports for all vaccines compared to the number of doses administered in the period considered, while figure 1b shows the same trend by number of doses (1st or 2nd dose). As described in the previous Report, a minor increase in reports is confirmed compared to the remarkable increase in the number of administrations, with a stable trend in the last few months.

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 vaccine doses administered*

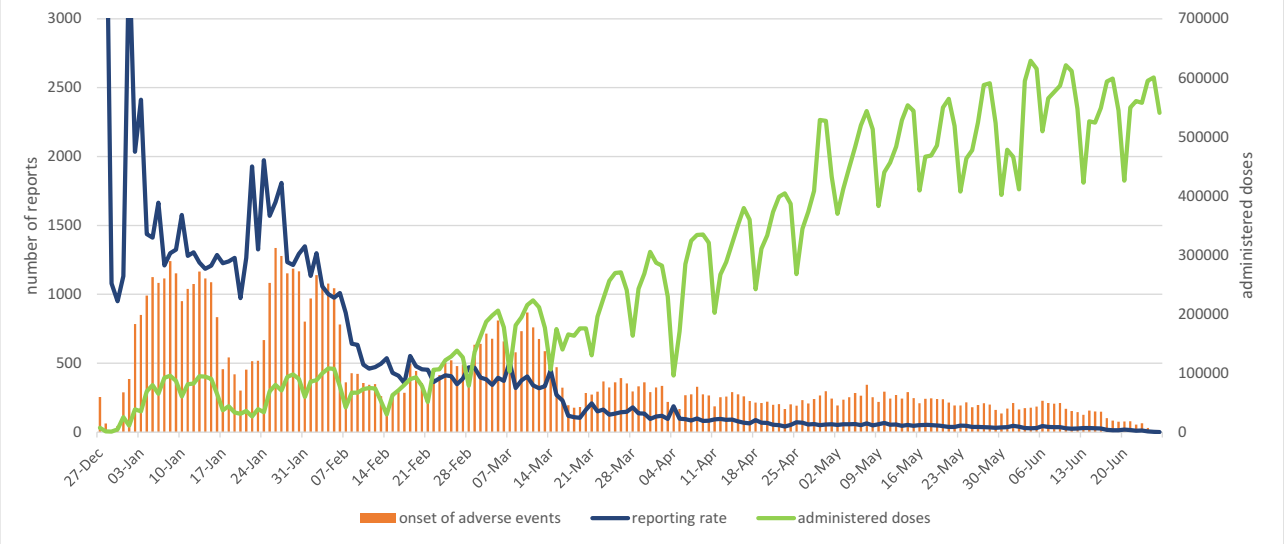
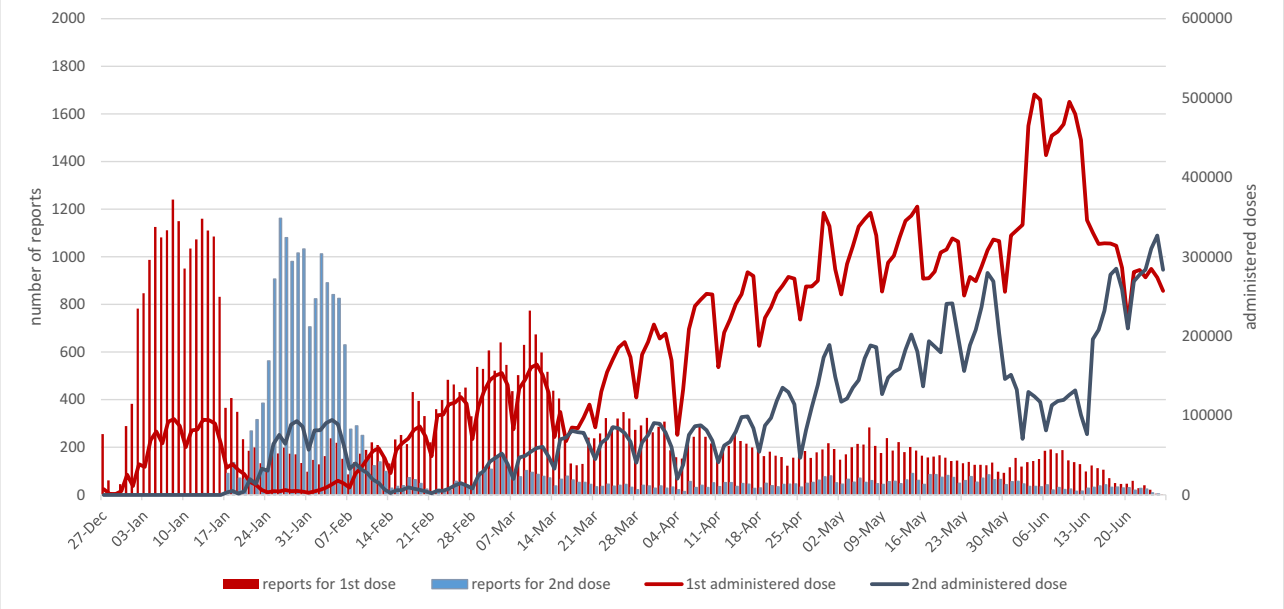


Figure 1b *– Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*



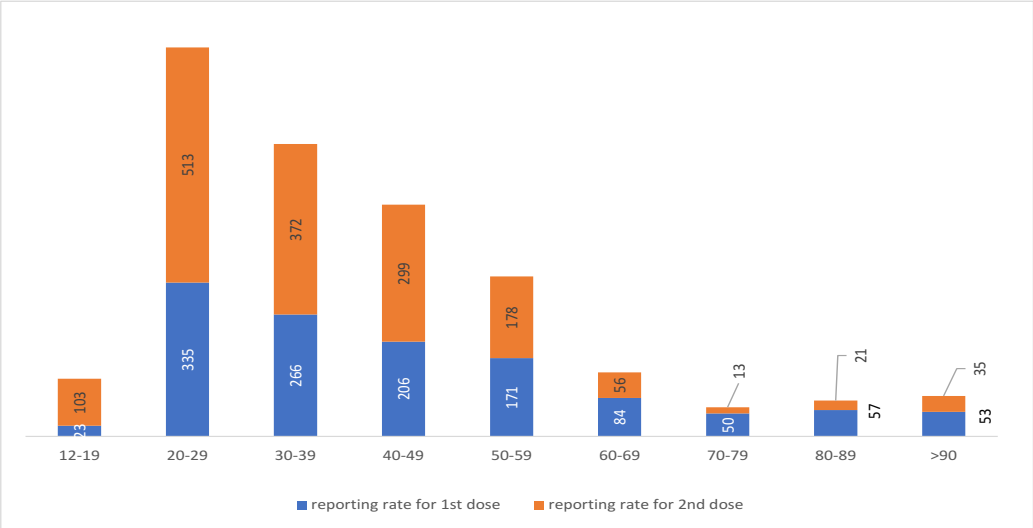
Distribution by age, sex and type of reporter

Two important events are to be reported in the period under monitoring:

1. extension of the indication of the Comirnaty vaccine to adolescents aged 12-15 years;
2. introduction of heterologous vaccination for vaccinated people <60 years after first dose of Vaxzevria.

The average age of people with a suspected adverse event is 49 years (median age 48 years). The reporting rate based on age is shown in Figure 2. The first age group includes adolescents from 12 to 19 years.

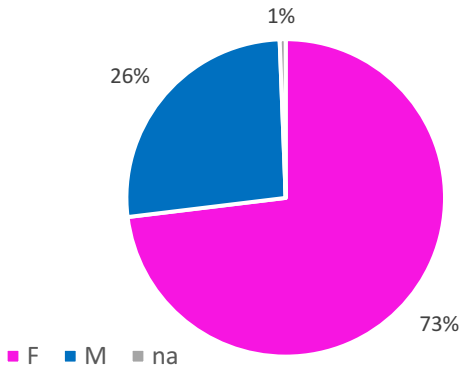
Figure 2 *– Distribution of the reporting rate by age group according to the 1st or 2nd dose administered*



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. The rates for the 12-19 age group are calculated on a poorly represented population of vaccinated people compared to other age groups and should therefore be considered with caution. Reporting rates for the second dose are higher between 20 and 50 years, as expected.

Considering an overlapping exposure of the sexes (54% of the doses administered in females and 46% in males), 73% of the reports concern women (209/100,000 administered doses) and 26% men (88/100,000 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 gender of the reports entered in the RNF*

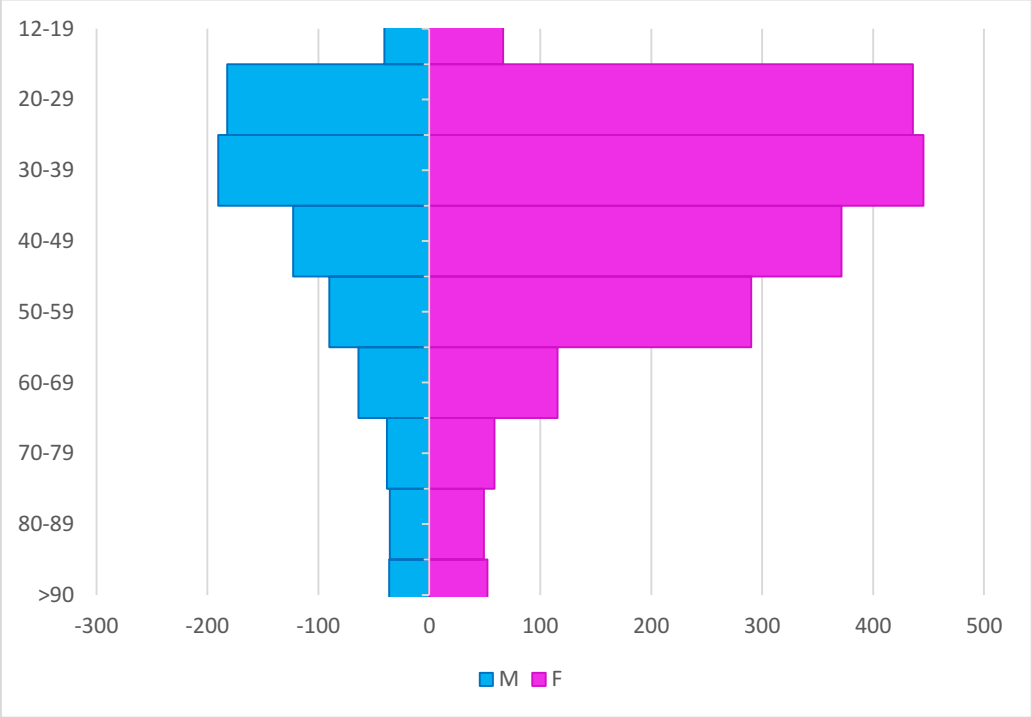


Figure 5 shows the distribution by type of reporter. It should be noted that about 80% of the reports come from healthcare professionals, mainly doctors and pharmacists, while about 23% from patients/citizens. 97% of these reports are spontaneous.

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

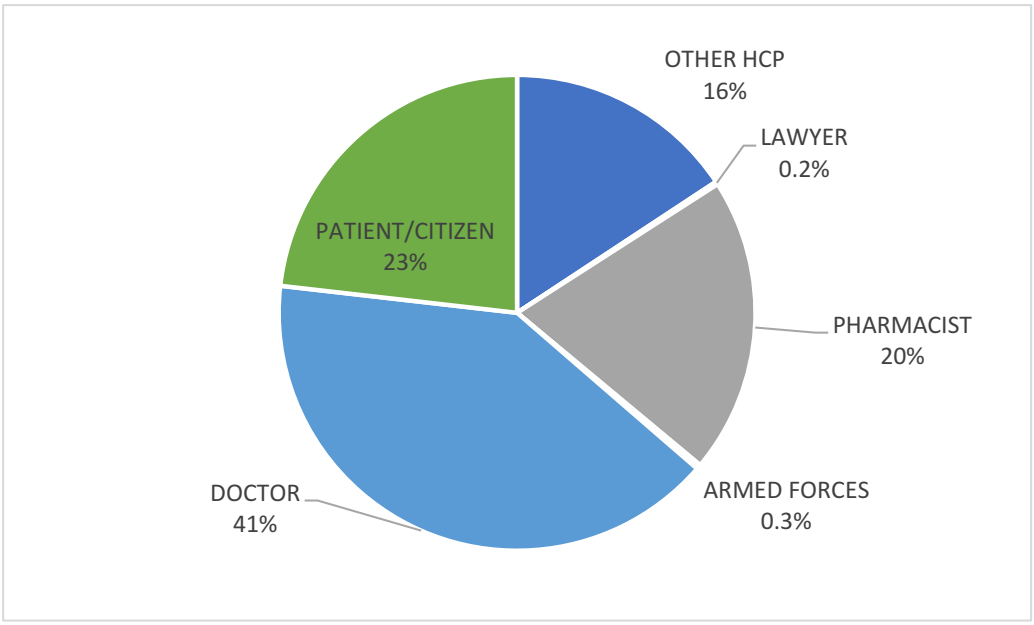


Table 2 shows the report distribution by time of onset from vaccination.

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

ONSET TIME	N° REPORTS	%
0 days	37,388	49.1%
1 day	23,710	31.1%
2-7 days	7,875	10.3%
>7 days	4,378	5.7%
Not definable	2,855	3.7%
Total	***76,206***	***100%***

As previously reported, regardless of the vaccine, the dose and type of event, most reactions (about 80%) occur on the same day as vaccination or on the following day, more rarely beyond the following 48 hours.

Distribution by seriousness and outcome

87.9% of reports entered as of 26/06/2021 refer to **non-serious events**, with a reporting of 135/100,000 administered doses and **11.9%** to **serious adverse events**, with a reporting rate of 18 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).

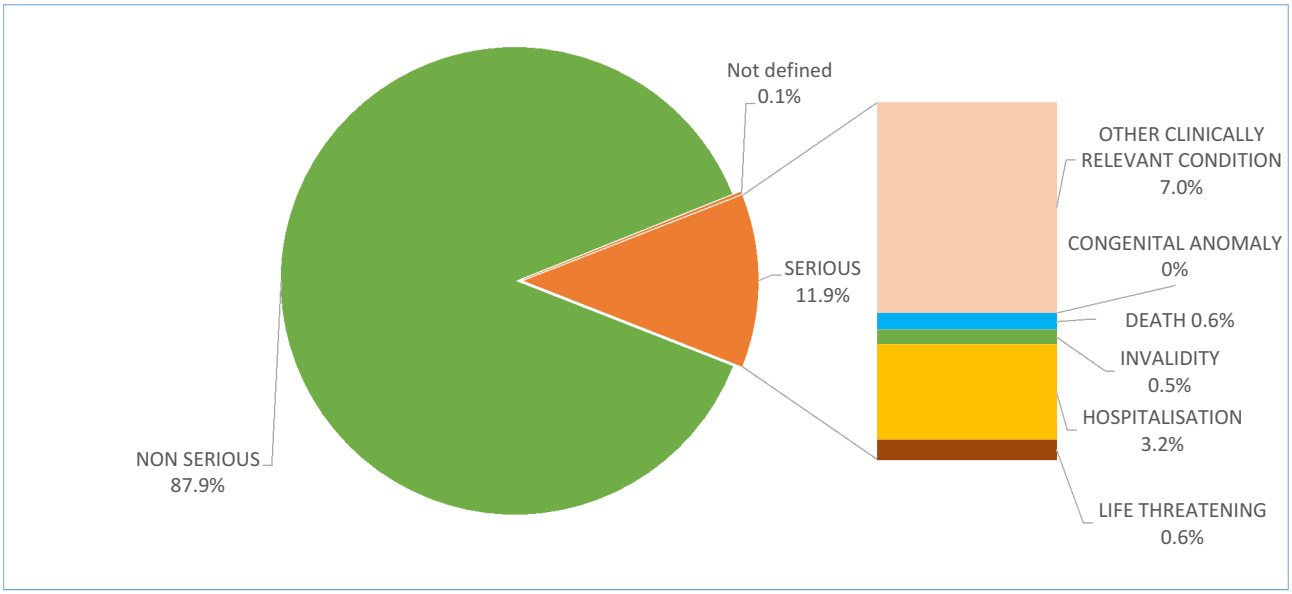
The reporting rates of serious events for each vaccine are 14 (Comirnaty), 14 (Spikevax), 37 (Vaxzevria) and 12 (Janssen) per 100,000 administered doses. In 60% of cases, serious adverse events reported occur in the first 48 hours after vaccination, while, in approximately 37% of cases, in the first week (18%) or in the following weeks (19%). In the remaining 3% of cases, the information is insufficient to establish the time of onset of the adverse event with regard to the report, despite the follow-up requests.

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

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 – *Distribution by seriousness of the reports entered in the period considered (0.1% of reports do not indicate seriousness)*



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.
As shown in figure 7, 82% of the reports refer to non-serious adverse events with full recovery or improvement already at the time of reporting. 60% of serious reports result in full recovery or improvement and 24% has not yet recovered.

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.

As of 26/06/2021, the causal link according to the WHO algorithm was included in 69% of reports of serious adverse events (6,306/9,087). Overall, 46% of all serious reports evaluated (2,882/6,306) are related to vaccination, 33% (2,097/6,306) are indeterminate, 19% (1,175/6,306) are unrelated and 2% (152/6,306) unclassifiable.

Regardless of the type of vaccine, the number of doses and the causal link, 423 reports show a "death" outcome with a reporting rate of 0.85/100,000 administered doses, with a slight decrease compared to previous reports. The distribution of such fatal cases by type of vaccine is shown in table 4.

51.5% of cases concern women, 48% men while 0.5% (2 sheets) do not report this data. The mean age is 77 years (range 18-104 years). The time between vaccine administration and death varies from two hours up to a maximum of 78 days. In 244 cases death is recorded after the first dose, in 127 after the second (not specified in 52 reporting sheets).

There are no cases of death as a result of anaphylactic shock or major allergic reactions, while the correlation with previous pathologies is frequent.

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

VACCINE	Fatal cases	Rates per 100,000 administered doses
Comirnaty	262	0.75
Spikevax	75	1.58
Vaxzevria	72	0.84
Janssen	14	1.15
Total	**423**	**0.85**

The different reporting rate of events with a fatal outcome is largely dependent on the different target population of the individual vaccines and on the different exposure.

The cases accompanied by detailed and complete information report alternative causes to the vaccine, in particular complications of existing or previous pathologies, in subjects with clinical frailties and polytherapy. At the time of writing, 63.4% of death reports have a causality assessment with the algorithm used in the vaccine surveillance (WHO Algorithm), according to which 59.6% of cases is **not correlatable,** 33.6% **undetermined** and 4.2% **unclassifiable** due to lack of information necessary for the application of the algorithm.

In four cases (2.6% of the total), causality is **correlated**. Three cases have already been described in previous reports. Two of the new cases refer to possible vaccination failures in 2 patients with respiratory symptoms and positive swab after respectively 45 and 35 days from completion of the vaccination course, who died from complications of interstitial pneumonia. Both patients had clinical conditions and therapies compatible with a state of immunosuppression. The third case refers to a fragile patient who experienced fever and vomiting after the administration of the first dose of vaccine, events related to vaccination, which triggered a decompensation of the clinical conditions up to death, which occurred 2 days later.

Distribution by number of doses

In the period considered, 33% of the overall administered doses was used to complete the vaccination cycle (second doses), mainly with the Comirnaty vaccine.
Table 3 shows the reporting rates of suspected adverse events by vaccine type and dose number.

Table 4 *– Distribution of reports by number of doses*

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)	Interval 95% Confidence	Cumulative reporting rate (per 100,000 administered doses)	Interval 95% Confidence
Comirnaty	144	142-145	161	159-163	150	**149-151**
Spikevax	94	91-97	65	61-69	83	**80-86**
Vaxzevria	281	277-285	31	29-33	219	**216-222**
Janssen	67	62-72	-	-	67	**62-72**

No differences in reporting rates were observed between the first and second dose of Comirnaty or Spikevax vaccine, in line with the cumulative rate. As for the Vaxzevria vaccine, the reporting rate for the 2nd dose is significantly lower than that for the 1st dose. This difference could in part be attributed to the lower number of second doses administered of this vaccine as of 26/06/2021, in part it could depend both on the greater distance between the first and second dose of Vaxzevria than other vaccines, and on a smaller number of adverse events associated with the second dose of this vaccine (lower reactogenicity).

In total, 233,034 so-called heterologous vaccinations were given to persons under 60 who had received Vaxzevria as their first dose. The administration of mRNA vaccines for the second dose involved Comirnaty in 86% of cases and Spikevax in 14%. Compared to this modality of vaccination with a mixed schedule, 27 reports were entered, in the same proportion of the mRNA vaccines administered, with a reporting rate of 12 per 100,000 doses administered. Three of the reactions were rated as serious by the reporter, mainly related to pain at the injection site and improving already at the time of reporting. The remaining reports report the expected and most frequently reported symptoms.

Distribution by type of event

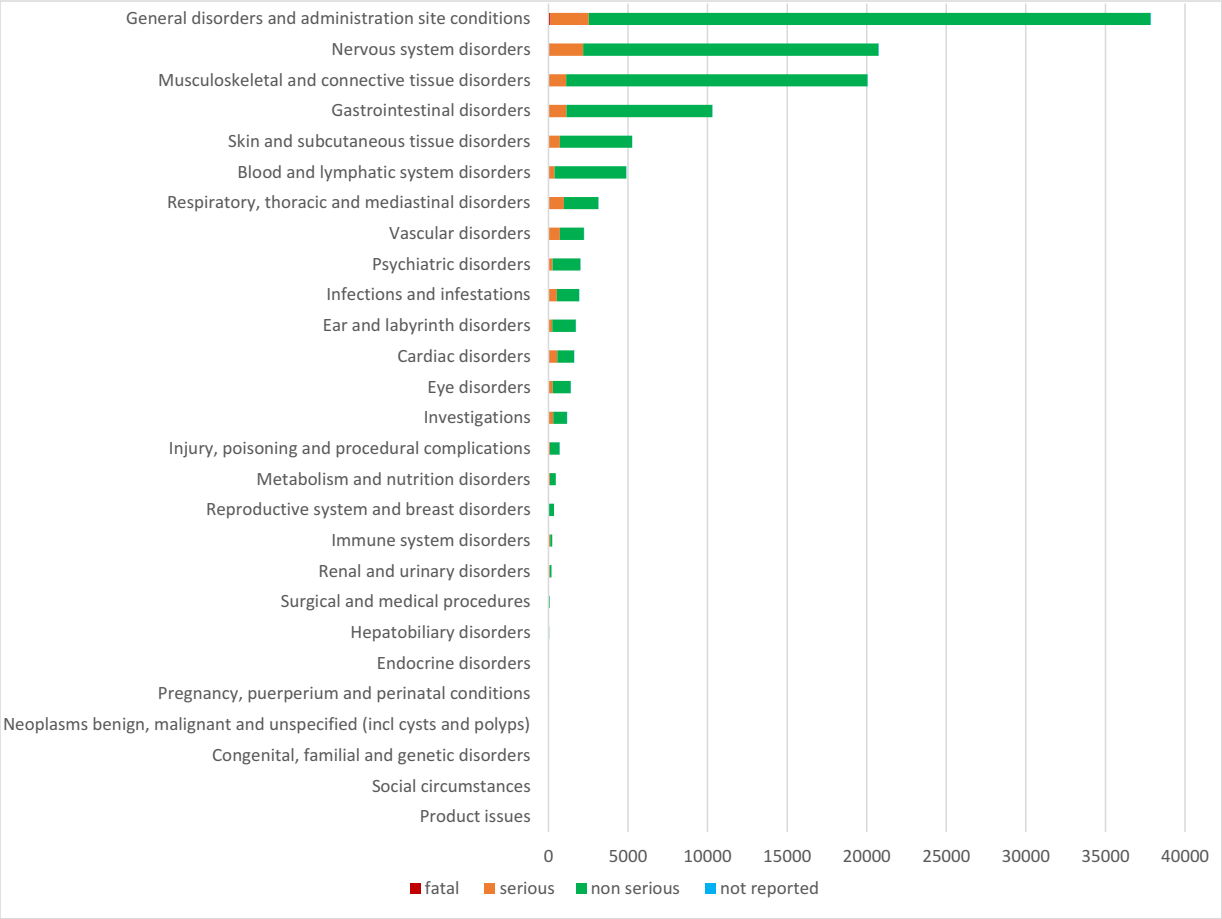
Graphs 8, 9, 10 and 11 report in order of frequency the types of event reported based on the organ or apparatus involved, the aetiology or purpose (Systemic-Organic Class or SOC) for the four vaccines used (Comirnaty, Spikevax, Vaxzevria and Janssen), regardless of the dose and the causal link. It should 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)

Consistent with previous Reports, most of the **suspected adverse events following vaccination with Comirnaty** are related to the organ-system class of **general diseases and conditions related to the administration site** (especially fever, injection site pain, fatigue/asthenia), followed by **pathologies of the nervous system** (mainly headache and paraesthesia), by **pathologies of the musculoskeletal system and of the connective tissue** (mostly myalgia, arthralgia and musculoskeletal pain) and by **gastrointestinal diseases** (generally nausea, vomiting and diarrhoea).
About 90% of the reports were entered as non-serious and 9.6% as serious (in 0.4% of cases the severity is not defined). The distribution by type of serious adverse events does not differ significantly from that of all events.
Among serious adverse reactions, 14 cases of **myocarditis** (mean age 32.3 years, median age 30 years) and 55 cases of **pericarditis** (mean age 52.6 years, median age 52 years) were reported with a reporting rate of 0.03 cases and 0.1 cases per 100,000 doses administered. Reports of myocarditis occurred after the 1st dose in 50% of cases and after the 2nd dose in the remaining 50% of cases. 92% of reports of pericarditis occurred after the 1st dose and approximately 8% after the 2nd dose. Both adverse events resulting from vaccination with Comirnaty are under discussion as a signal to the European Medicines Agency's Committee for Pharmacovigilance Risk Assessment (PRAC) and will be examined in detail in the next report, in relation to the outcome of the signal at the level European.

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



Comirnaty-related serious adverse events

About 5 reports per 100,000 doses of Comirnaty administered are serious events related to vaccination (4 related serious adverse events per 100,000 first doses administered and 6 related serious adverse events per 100,000 second doses administered). Based on the seriousness criterion, 80% of these reports were included as “serious - other clinically relevant condition", 15.6% as requiring hospitalisation and 2.3% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 60% of these reports and improvement in 23%.

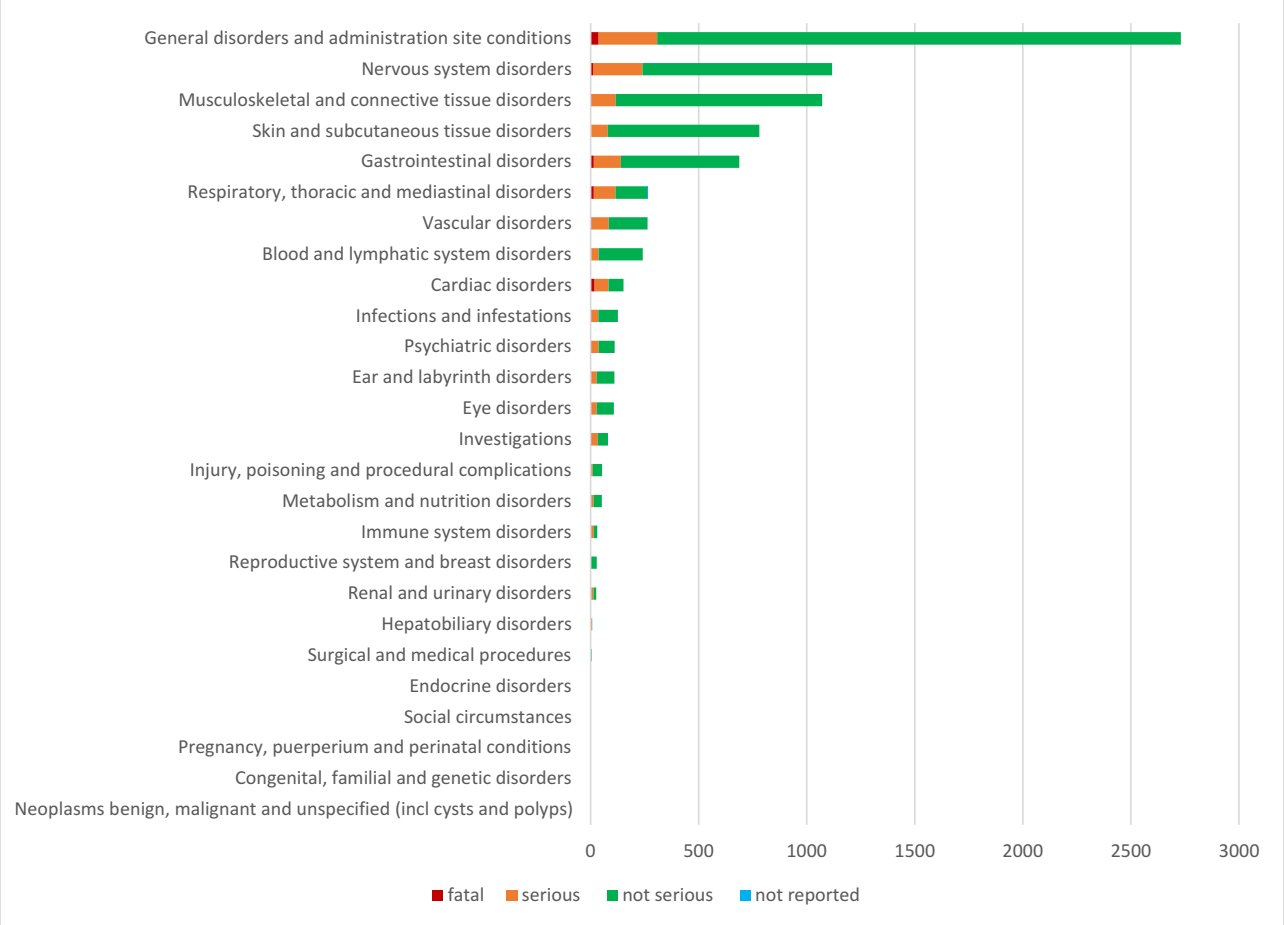
Compared to the previous Report, headache and hyperpyrexia are confirmed as the most commonly reported correlated serious adverse events, with a reporting rate for both reactions of approximately 2 cases per 100,000 doses administered. Fatigue and joint pain follow, with a rate of approximately 1 case per 100,000 doses administered. These symptoms are often associated with each other in the context of flu-like syndromic pictures, more frequent after the second dose.

Less frequently, anxious reactions to vaccination (more often pre-lipothymic reactions), diffuse paraesthesia and lymphadenopathies are reported as correlated serious adverse events. There have been 0.5 cases per 100,000 administered doses of mostly transient facial nerve palsy. A frequency of about 4 cases of anaphylaxis per million doses administered is confirmed.

Spikevax (formerly COVID19 Vaccine Moderna)

Most of the **suspected adverse events following vaccination with Spikevax** are related to the organ-system class of **general diseases and conditions related to the administration site** (especially fever, injection site pain, fatigue/asthenia), followed by **pathologies of the nervous system** (mostly headache), by **pathologies of the musculoskeletal system and of the connective tissue** (such as myalgia, arthralgia and musculoskeletal pain) and by **skin and subcutaneous pathologies** (mainly erythema, redness and urticarial reactions). Rarer are the reactions that fall within the **pathologies of the gastrointestinal system** (essentially nausea and vomiting).

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



Non-serious reactions represent about 83% of the total reports and 16% of the serious ones (in 1% of cases the severity is not defined). The distribution by type of serious adverse events does not differ significantly from that of all events.

Cases of **myocarditis** and **pericarditis** have also been reported for Spikevax, respectively 5 (mean age 29 years, median age 25 years) and 9 (mean age 51 years, median age 56 years), with a reporting rate of 0.1 and 0.2 cases per 100,000 doses administered, under discussion as a signal to the European Medicines Agency's Committee for Pharmacovigilance Risk Assessment (PRAC).

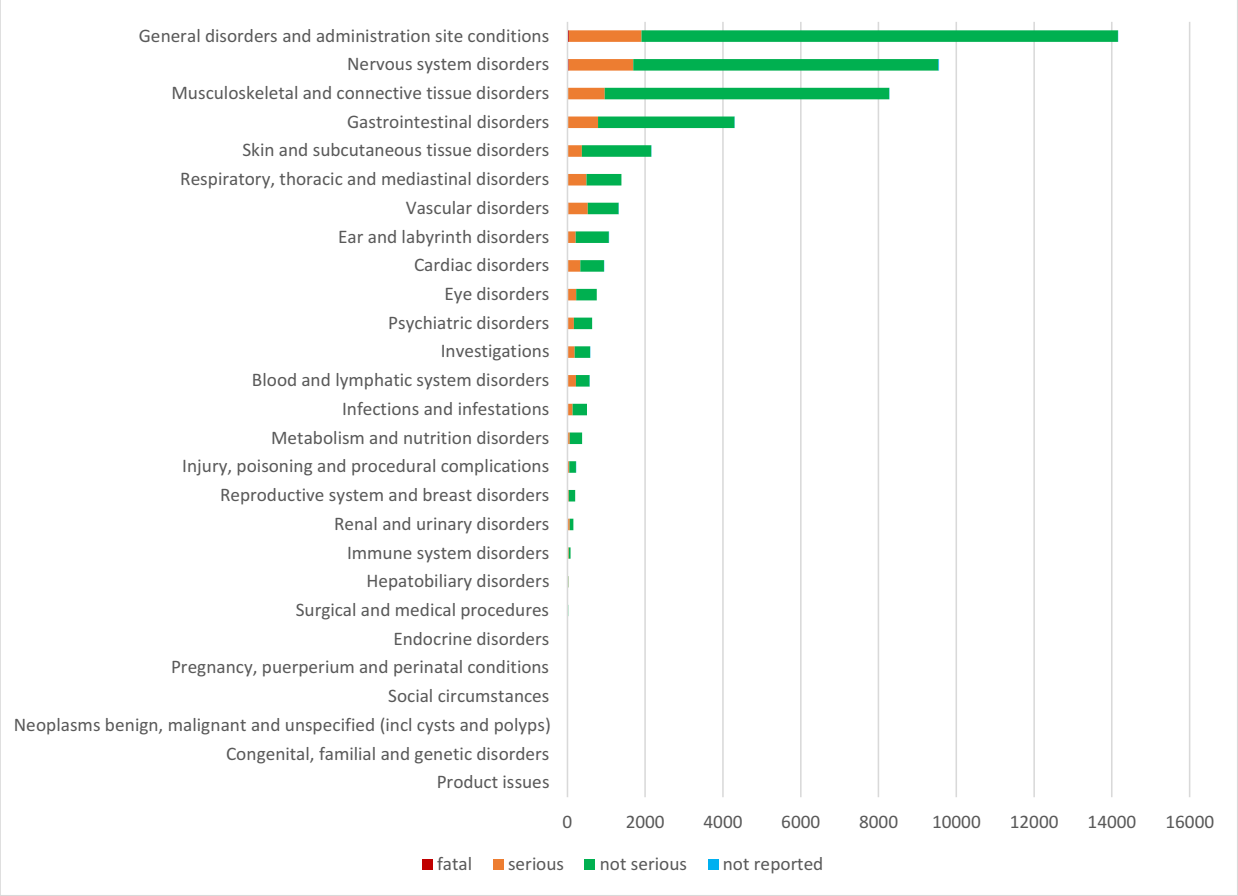
Spikevax-related serious adverse events

About 2.5 reports per 100,000 doses of Spikevax administered are serious events related to vaccination (2.7 related serious adverse events per 100,000 first doses administered and 2 related serious adverse events per 100,000 second doses administered). Based on the seriousness criterion, 77% of these reports were included as “serious - other clinically relevant condition", 14.5% as requiring hospitalisation and 5% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 48% of these reports and improvement in 31%.
The most commonly reported related serious adverse events are hyperpyrexia and joint pain and muscle pain, which confirm a reporting rate of approximately 2 cases per 100,000 administered doses. Headache, lymphadenopathy and anxious reactions to vaccination follow (all with a reporting rate of approximately 1 case per 100,000 doses administered). Also for the Spikevax vaccine, hyperpyrexia, joint and muscle pain and headache are often associated with each other in a picture of flu-like syndrome, more frequent after the second dose. The reporting rate for anaphylactic reactions also remained unchanged at around 2.5 cases per million doses administered.

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, with most reports related to the organ-systemic class of **general diseases and conditions related to the administration site** (especially fever, injection site pain, fatigue/asthenia), followed by **pathologies of the nervous system** (mainly headache and paraesthesia), **pathologies of the musculoskeletal system and of the connective tissue** (mostly myalgia, arthralgia and musculoskeletal pain) and by **gastrointestinal diseases** (usually nausea, vomiting and diarrhoea).

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



About 82% of the reports of the Vaxzevria vaccine were included as non-serious and 17% as severe (in 1% of cases the severity is not defined), with a distribution by type of event that does not differ significantly from that shown in figure 9.

Among the serious adverse reactions were included 55 reports of suspected **cerebral venous thrombosis and/or venous thrombosis in atypical site with or without thrombocytopenia**, after administration of the 1st dose, mainly affecting people under the age of 65 years (mean age 49 years, median age 47 years). The reported cases are not all attributable to vaccination with Vaxzevria and need to be carefully and appropriately evaluated in the light of new information available. This very rare adverse event, in fact, has already been investigated by the Committee for the Evaluation of Risks in Pharmacovigilance (PRAC) of the European Medicines Agency and the international scientific community, which have identified some clinical characteristics and some data of laboratory that allow to distinguish between related cases and those not related to vaccination. Therefore, further clinical details have been requested that will be submitted to the evaluation of the Working Group for the evaluation of thrombotic risks from anti-COVID-19 vaccines, in order to identify cases of vaccination-induced thrombocytopenia (suspected VITT - Vaccine-Induced Thrombotic Thrombocytopenia).

Serious adverse events related to Vaxzevria

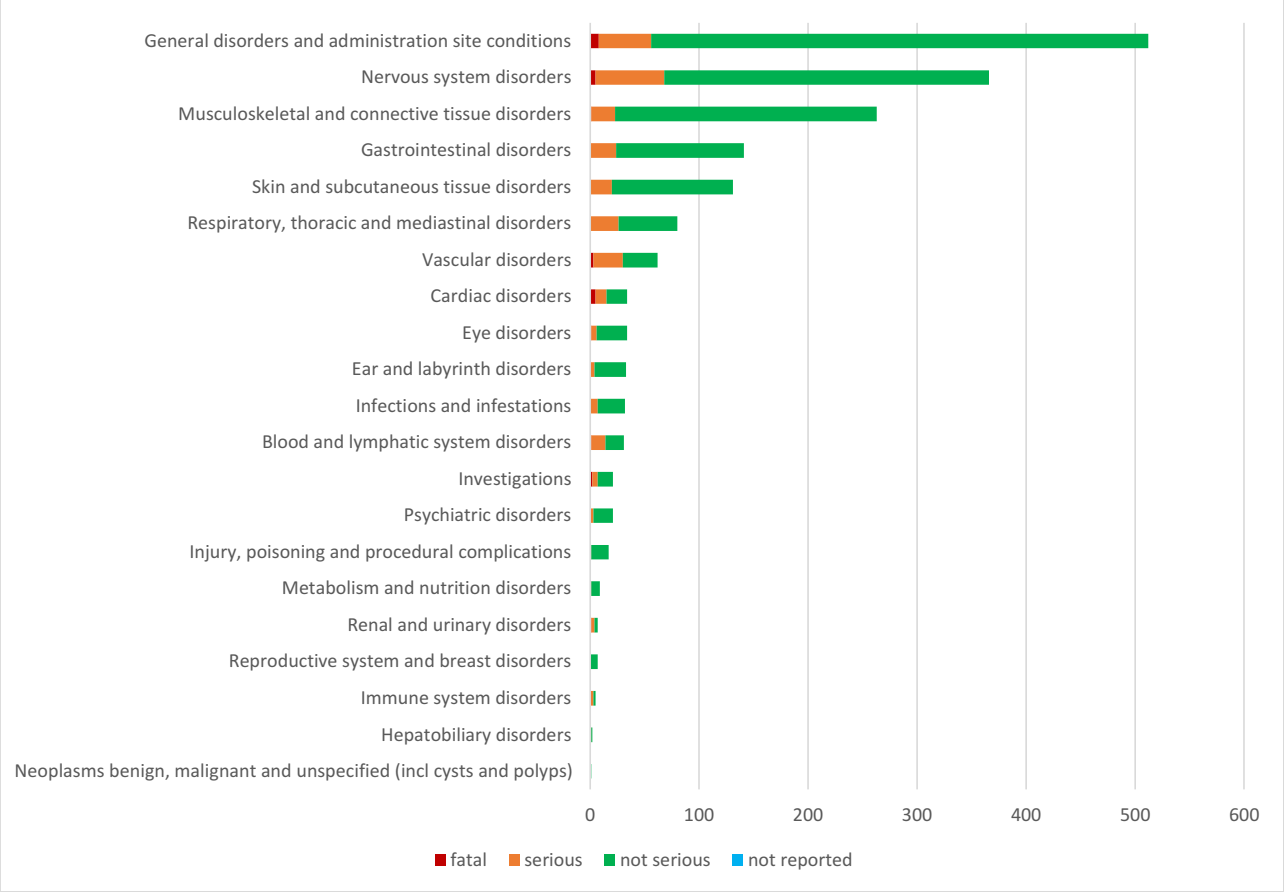
About 12 reports per 100,000 doses of Vaxzevria administered are serious events related to vaccination (15 related serious adverse events per 100,000 first doses administered and 1 related serious adverse events per 100,000 second doses administered). 74% of these reports were included

as “serious - other clinically relevant condition", 17% as requiring hospitalisation and 5.5% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 43.3% of these reports and improvement in 32%.
The most commonly reported correlated serious adverse events are hyperpyrexia (7 cases per 100,000 doses administered), headache (6 cases per 100,000 doses administered) and joint and muscle pain (5 cases per 100,000 doses administered), often associated with each other in a flu-like syndrome which appears more frequently after the first dose. More rarely, lipothymias and vagal reactions have been reported (respectively 3 and 2 cases per 100,000 doses administered). The reporting rate for anaphylactic reactions is comparable to that reported in the previous Report (2.8 cases per million doses administered).

COVID-19 Vaccine Janssen

The distribution by type of **suspected adverse events following vaccination with COVID-19 Vaccine Janssen** is comparable to that reported in the previous Report. The largest number of cases falls under **general diseases and conditions related to the administration site** (mainly fever, fatigue/asthenia, chills and pain at the injection site), followed by **pathologies of the nervous system** (mainly headache) and by **pathologies of the musculoskeletal system and of the connective tissue** (mostly myalgia and arthralgia).

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



82% of reports of the COVID-19 vaccine Janssen vaccine were entered as non-serious and 17% as severe (in 1% of cases the severity was not defined), with no substantial differences in the distribution by type of reaction.

Overall, for the COVID-19 vaccine Janssen vaccine, 9 reports of suspected **cerebral venous thrombosis and/or venous thrombosis in atypical site with or without thrombocytopenia** (mean age 45 years, median age 48 years) were included among the serious adverse reactions. Also for this vaccine, the reported cases are not all attributable to vaccination with Vaxzevria and need to be carefully and appropriately evaluated in the light of the new information available. This is a very rare adverse event, which has already been investigated by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency and the international scientific community. Vaccination-related cases should be distinguished from non-correlatable cases based on clinical characteristics and laboratory data identified to define thrombosis associated with viral vector vaccines. Therefore, further clinical details have been requested that will be submitted to the evaluation of the Working Group for the evaluation of thrombotic risks from anti-COVID-19 vaccines, in order to identify cases of vaccination-induced thrombocytopenia (suspected VITT - Vaccine-Induced Thrombotic Thrombocytopenia).

Approximately 2 reports per 100,000 doses were found to be serious related to vaccination, 62% of these reports were included as “serious - other clinically relevant condition", 24% as requiring hospitalisation and 9% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 39% of these reports and improvement in 38%. In approximately 2 cases in every 100,000 doses administered, the correlated serious adverse reaction is represented by hyperpyrexia

with muscle and joint pain. In 3 cases in every 1,000,000 doses, severe allergic-type reactions were reported but no cases of anaphylactic reaction. It should be noted that, due to the limited number of doses currently administered, the number of reports is low and data on reporting rates are currently unreliable.

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#6*

	Report#1	**Report#2**	**Report#3**	**Report#4**	**Report#5**	**Report#6**
	as of 26/01/2021	**as of 26/02/2021**	**as of 26/03/2021**	**as of 26/04/2021**	**as of 26/05/2021**	**as of 26/06/2021**
administered doses	1,564,090	4,118,277	9,068,349	18,148,394	32,429,611	49,512,799
reporting of adverse events	7,337	30,015	46,237	56,110	66,258	76,208
reporting rate	469	729	510	309	204	154
reporting rate for men	293	424	299	176	116	88
reporting rate for women	561	907	645	404	272	209
reporting rate for first dose	515	773	496	299	211	164
reporting rate for second dose	225	785	540	333	190	134
reporting rate of serious adverse reactions	34	44	36	27	21	18
reporting rate of serious adverse reactions for men	22	28	23	18	15	13
reporting rate of serious adverse reactions for women	42	54	44	33	26	23
reporting rate of serious adverse reactions with no “clinically relevant” cases	8.9	8.1	8.5	8.8	7.9	7.5
reporting rate of deaths	0.8	0.97	1.1	1.23	1.0	0.8
Source of reporting						
Doctor	47%	46%	44%	42%	42%	40.5%

	Report#1	Report#2	Report#3	Report#4	Report#5	Report#6
	as of 26/01/2021	as of 26/02/2021	as of 26/03/2021	as of 26/04/2021	as of 26/05/2021	as of 26/06/2021
Pharmacist	22%	19%	20%	20%	20.5%	20%
Other healthcare professional	25%	26%	21%	19%	17%	16%
Patient/Citizen	6%	9%	15%	18%	20%	23%
Lawyer	0%	0%	0.12%	0.20%	0.2%	0.2%
Armed Forces	0%	0%	0.07%	0.30%	0.3%	0.3%
Comirnaty						
reporting rate	471	769	535	328	214	150
reporting rate for first dose	517	756	525	315	212	144
reporting rate for second dose	278	790	549	348	216	161
reporting rate of serious adverse reactions	na	45	33	24	18	15
Spikevax						
reporting rate	277	333	227	129	88	83
reporting rate for first dose	277	335	216	132	95	94
reporting rate for second dose	-	322	264	121	73	65
reporting rate of serious adverse reactions	na	26	22	18	13	14
Vaxzevria						
reporting rate	-	326	477	309	236	219
reporting rate for first dose	-	326	477	307	261	281
reporting rate for second dose	-	-	-	-	24	31
reporting rate of serious adverse reactions	-	31	50	39	36	37
Janssen vaccine						
reporting rate	-	-	-	-	34	67
reporting rate of serious adverse reactions	-	-	-	-	5	12

As already observed in the analysis of previous Reports, the decrease in general reporting rates continues (Fig. 12). Rates for individual vaccines also decrease, with the exception of the Janssen vaccine, in use since 22/04/2021, while the rates of serious reactions continue to remain constant, in particular excluding the category of "clinically relevant" and fatal cases, for which a slight flexion is observed (fig. 13).

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

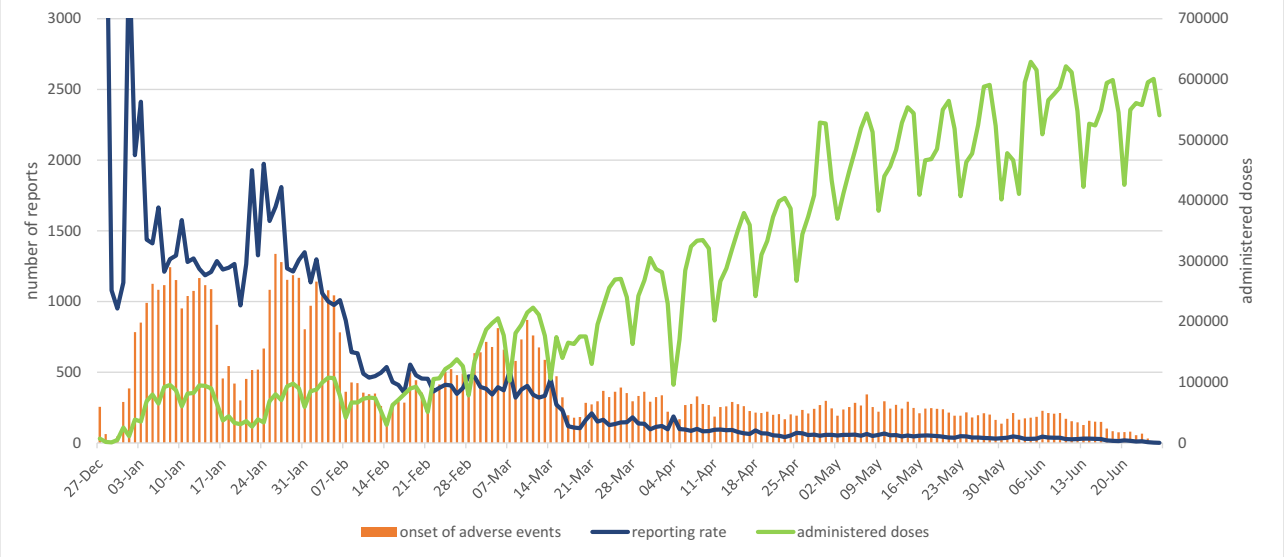
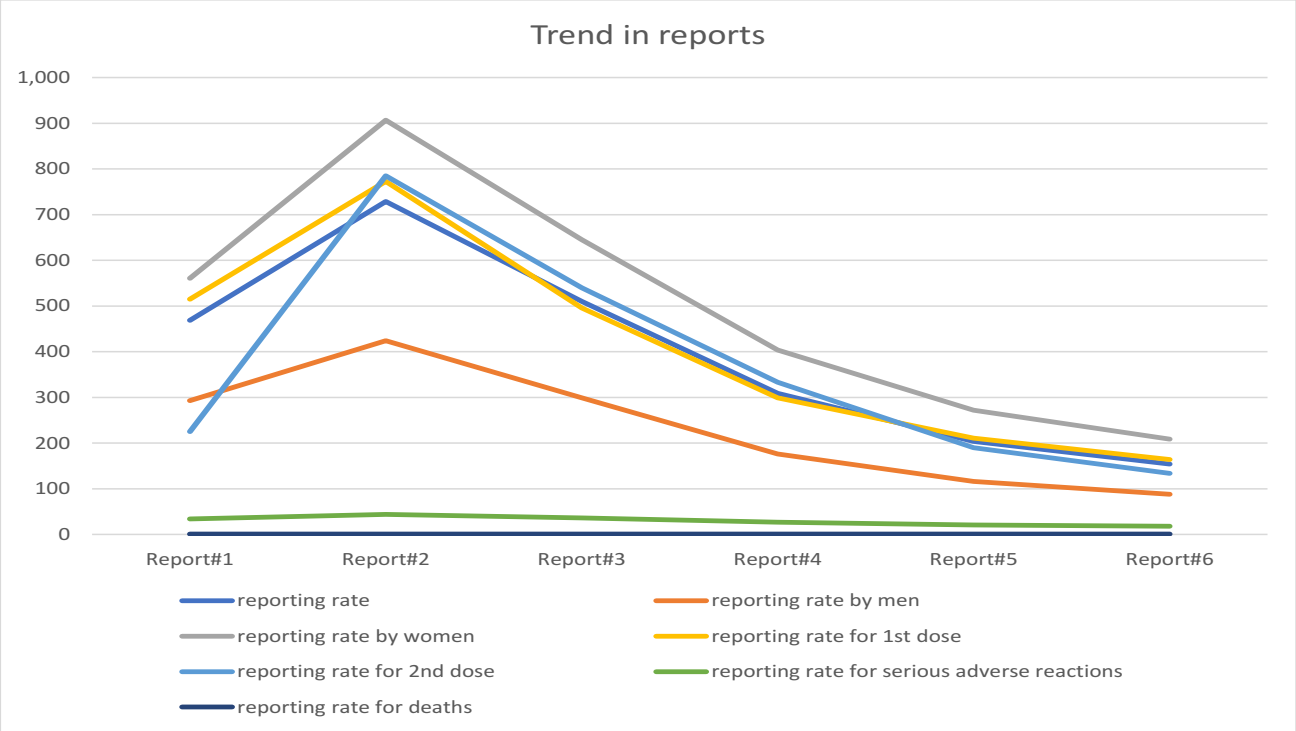


Figure 13 *– Trend in reporting rates by gender, number of doses, severity and fatal events over time*



As shown in Figure 14, the largest number of reports come from doctors, while those from pharmacists remain stable. The trend already observed of a decrease in reports from doctors and other health professionals (from 47% to 40.5% for doctors and from 25% to 16% for other health professionals) and an increase in reports from patients (from 6% to 23%) is confirmed.

The trend in reporting rates by gender is generally maintained over time, with a figure approximately twice as high for women as for men, both overall and for serious reactions alone (Figure 15).

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

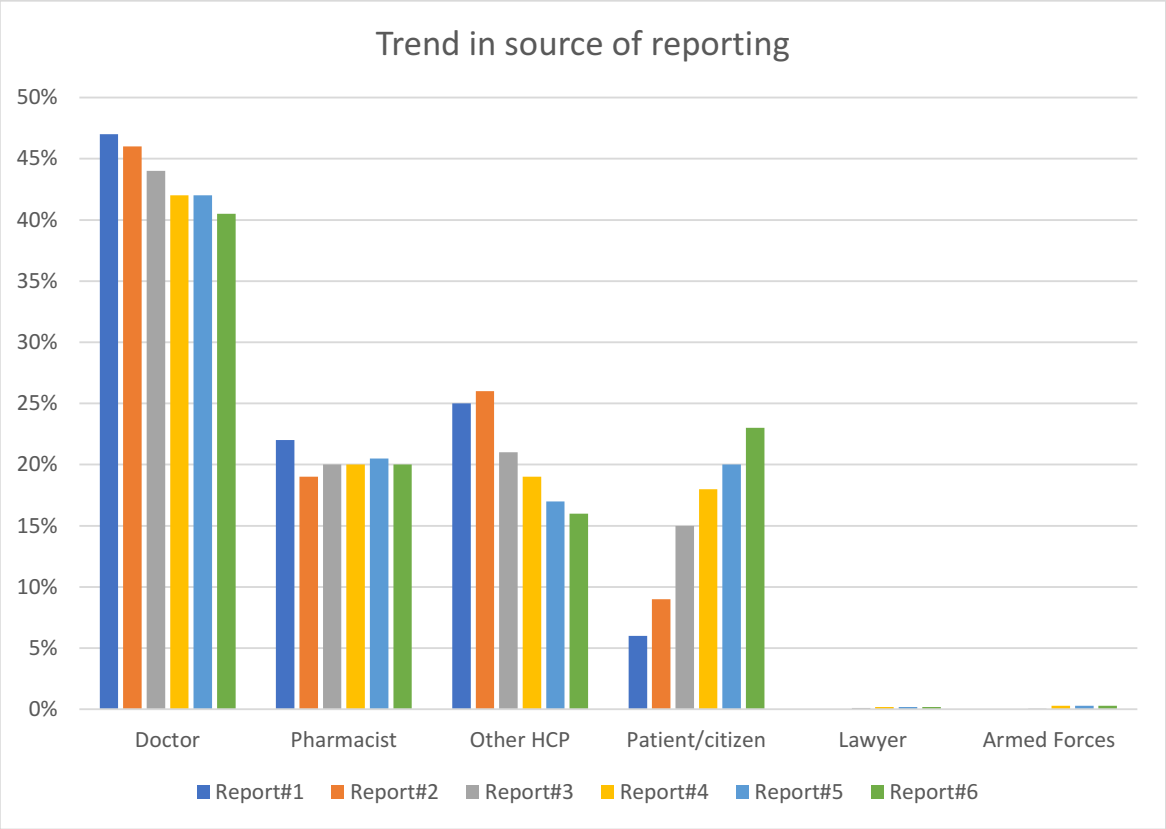
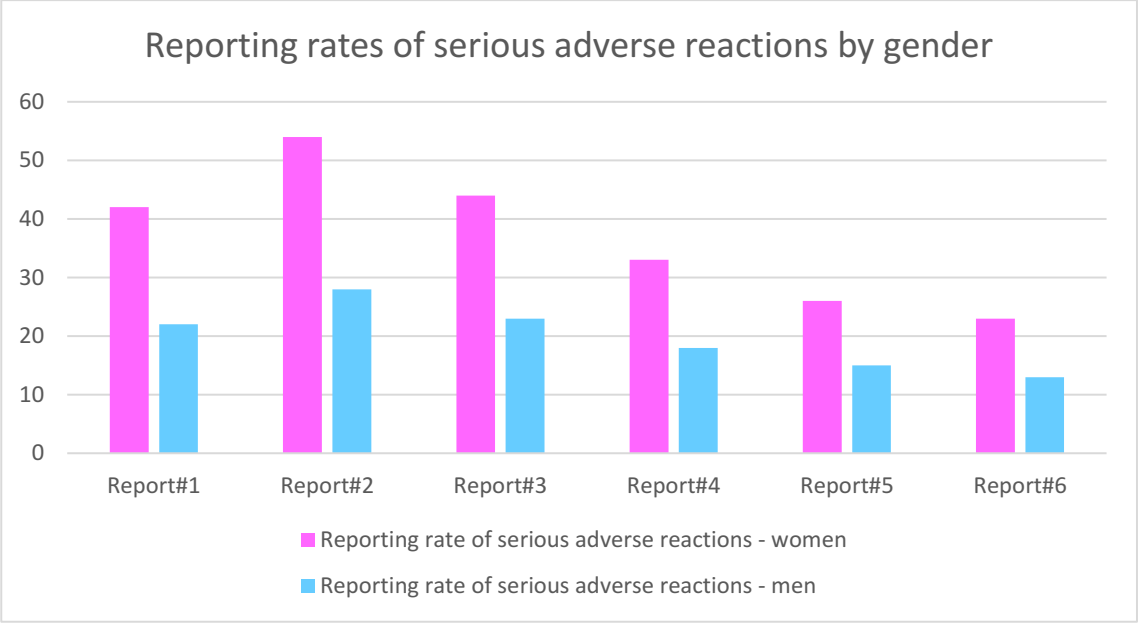


Figure 15 *– Trend in reporting rates of serious adverse reactions by gender*



How to report a suspected adverse reaction?

All the information to report a suspected adverse reaction following vaccination is available at the following link: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse