COVID-19 Vaccine Surveillance Report

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27/12/2020 - 26/07/2021

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ITALIAN MEDICINES AGENCY

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: https://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf?ua=1

HIGHLIGHTS

As of 26 July 2021, 128 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 87.1%) which resolve completely and only to a lesser extent as severe (12.8%), resulting in full recovery or improvement in most cases.

In the period considered, 43% of the overall administered doses was used to complete the vaccination cycle (second doses), mainly with the Comirnaty vaccine.

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.

The reporting rate of the mixed vaccine schedule is 29 reports per 100,000 administered doses. 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 27 adverse events per 100,000 administered doses (as of 26/07/2021, Comirnaty was the only vaccine approved from 12 years of age; Spikevax was approved for the age group 12-17 on 28/07/2021). The distribution by type of adverse events is not substantially different from the one observed for any other age group.

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

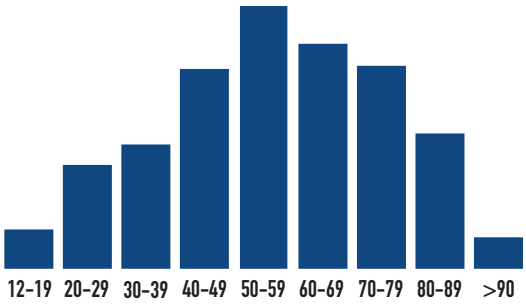
Reference period 27/12/2020 - 26/07/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

DOSES ADMINISTERED

65.926.591

Comirnaty 71%
Spikevax 10%
Vaxzevria 17%
Vaccino Janssen 2%



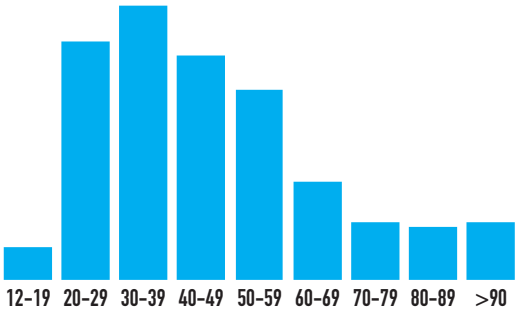
ADMINISTRATION BY AGE GROUP

ADMINISTRATION BY DOSE	First dose	Second dose
	57%	43%

SUSPECTED ADVERSE REACTIONS

84.322

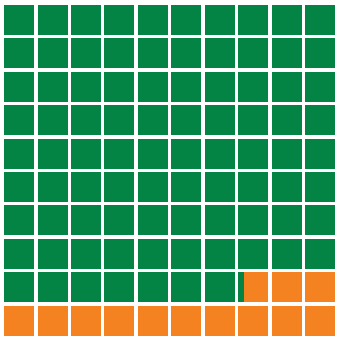
Comirnaty 68%
Spikevax 6%
Vaxzevria 25%
Vaccino Janssen 1%



REPORTING RATE BY AGE GROUP

REPORTING RATE BY DOSE	First dose	Second dose
	160%	86%

SUSPECTED ADVERSE REACTIONS SERIOUS/NON-SERIOUS



NON-SERIOUS 87,1%

SERIOUS 12,8%

0.2% OF SUSPECTED ADVERSE REACTIONS ARE NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)
PERIOD UNDER REVIEW: 27/12/2020 - 26/07/2021

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 26/07/2021, **84,322 reports of adverse events following immunisation** have been entered in the National Pharmacovigilance Network, out of a total of **65,926,591 vaccine doses**, with a **reporting rate of 128 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%), followed by Vaxzevria (17%), Spikevax (10%) and COVID-19 Janssen vaccine (2%)[2]. As in previous Reports, the distribution of reports by type of vaccine is similar to the distribution of administrations (Comirnaty 68%, Vaxzevria 25%, Spikevax 6% and COVID-19 Janssen vaccine 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 26/07/2021	Administered doses as of 26/07/2021	Reporting rate (per 100,000 administered doses)	95% Confidence interval
Comirnaty	57,143	46,710,874	***122***	***121-123***
Spikevax	5,416	6,615,237	***82***	***80-84***
Active ingredient mRNA	15			
Vaxzevria	20,708	11,274,942	***184***	***181-186***
Janssen	1,046	1,325,538	***79***	***74-84***
Total	**84,328***	**65,926,591**	***128***	***127-129***

** 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 six records (after heterologous vaccination)*

[2] The number of doses administered as of 26/07/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 29/07/2021

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 no. 5 and no. 6. A smaller increase in reports is confirmed compared to the higher increase in the number of administrations, with a stable trend in recent 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 vaccine doses administered*

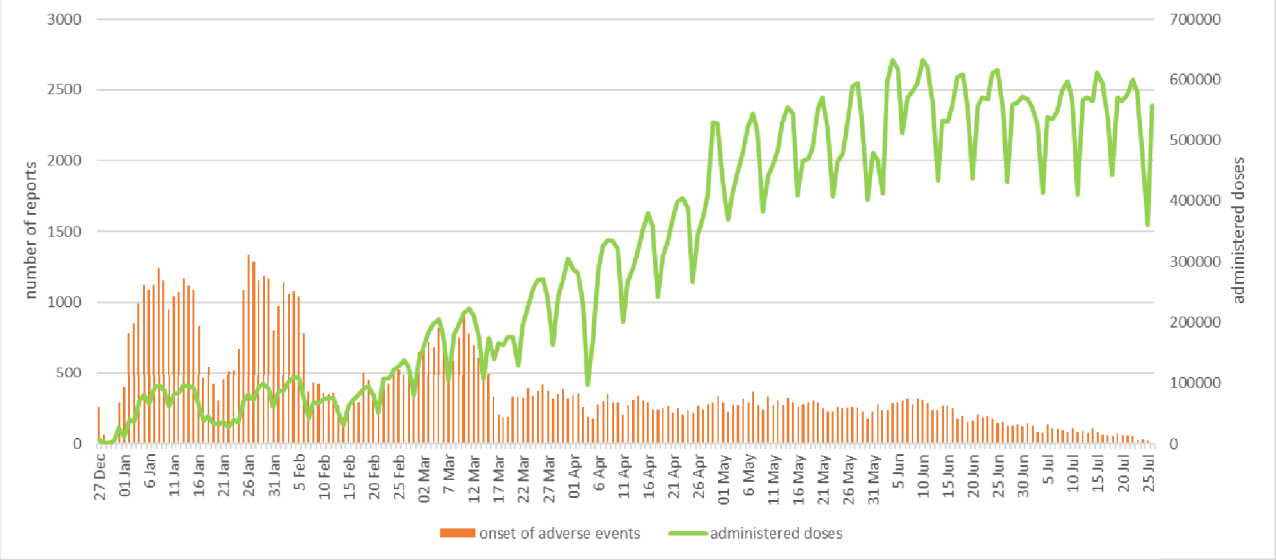
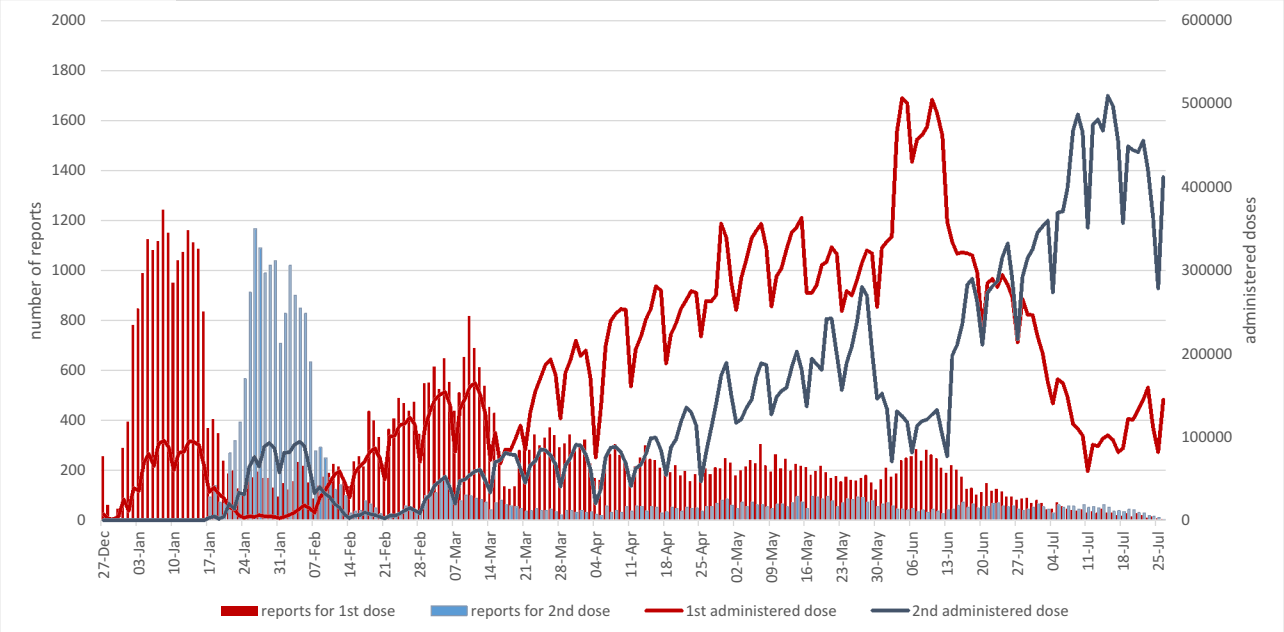


Figure 1b *– Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*

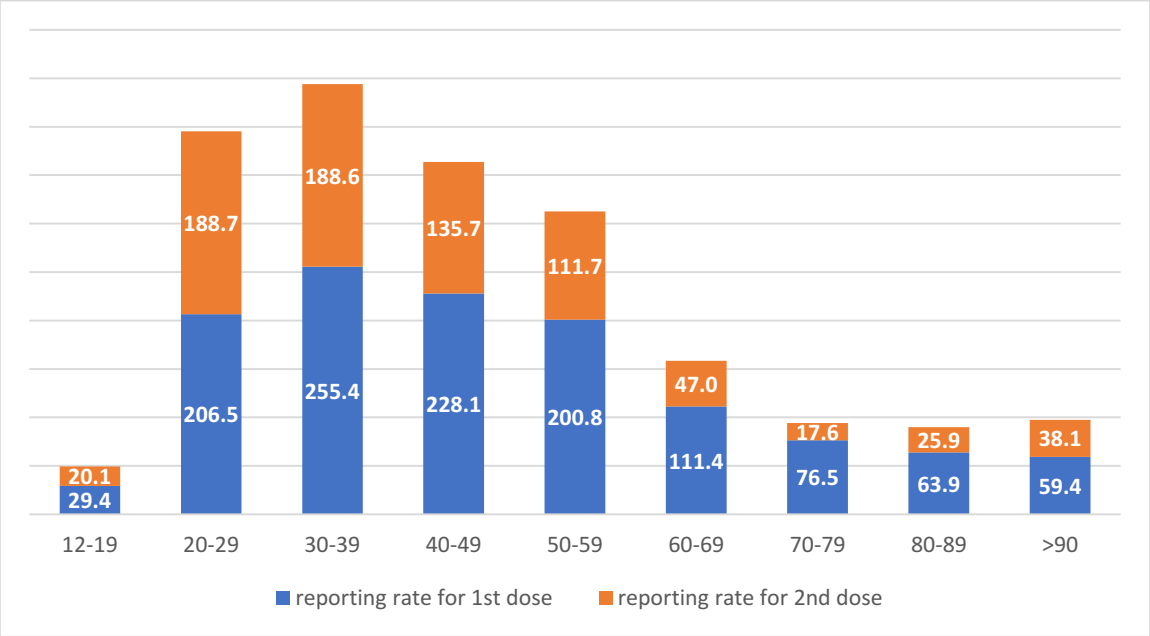


Distribution by age, gender and type of reporter

Distribution by age

The average age of people with a suspected adverse event is 48.5 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*

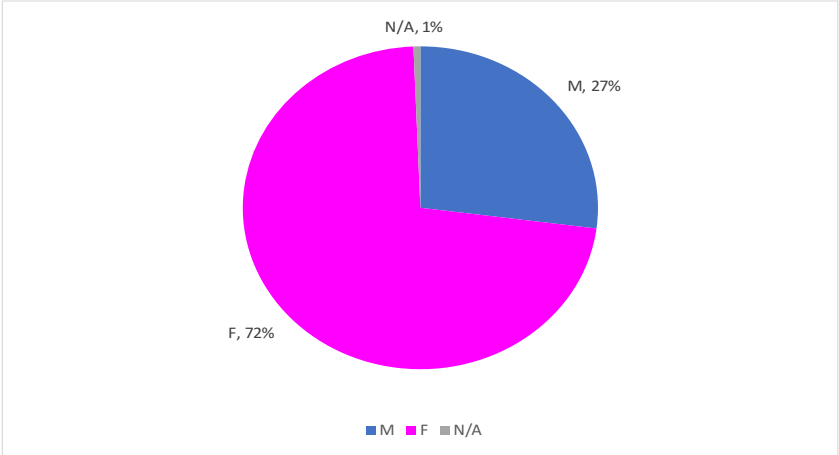


As already observed in the previous Reports, the reporting rate is higher in the age groups between 20 and 60 years and then decreases in the more advanced age groups, with a similar trend after 1st and 2nd dose.

Distribution by gender

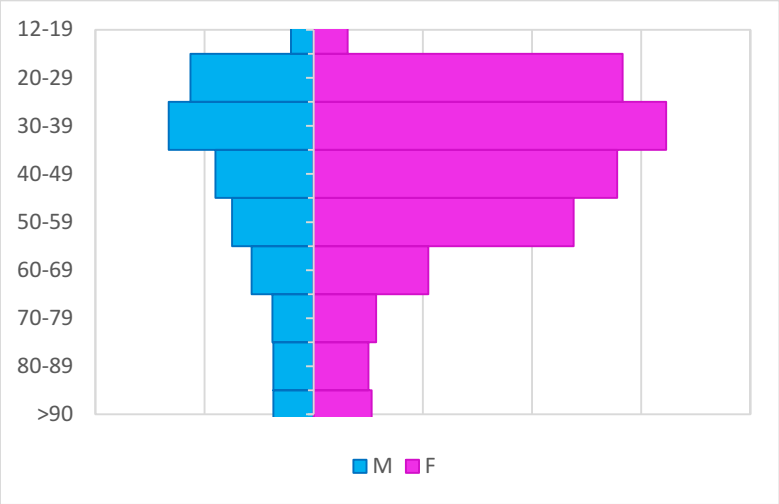
Considering an overlapping exposure of the genders (53% of the doses administered in women and 47% in men), 72% of the reports concern women (175/100,000 administered doses) and 27% men (73/100,000 administered doses), regardless of the dose and vaccine administered (sex is not reported in 1% of reports, Fig. 3). This trend is in line with other European countries.

Figure 3 *– Distribution by gender 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*



Distribution by type of reporter and onset time

Figure 5 shows the distribution by type of reporter. About 74% of the reports come from healthcare professionals, mainly doctors and pharmacists, while about 25% 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*

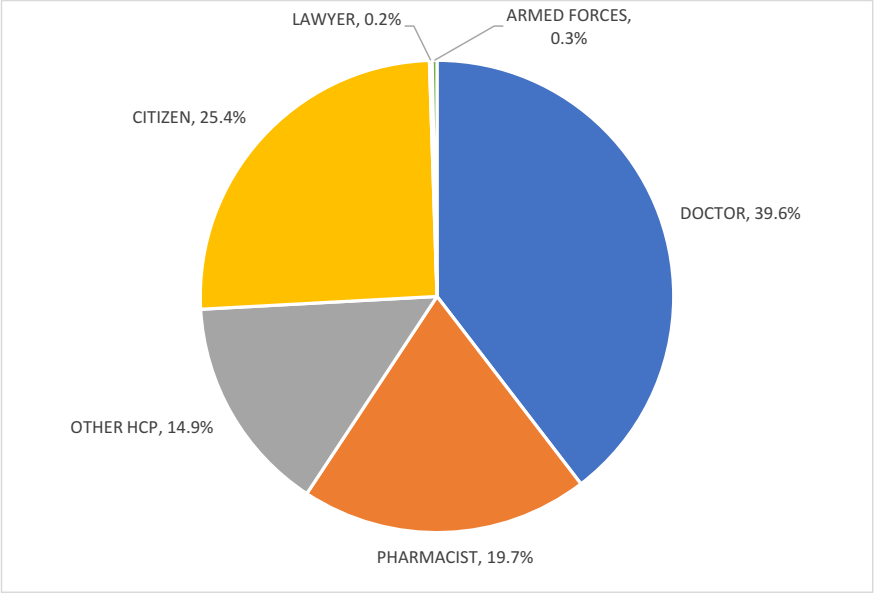


Table 2 shows the report distribution by onset time from vaccination.

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

ONSET TIME	N° REPORTS	%
0 days	41,302	49%
1 day	25,459	30.2%
2-7 days	9,361	11.1%
>7 days	5,471	6.5%
Not definable	2,729	3.2%
Total	***84,322***	***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

87.1% of reports entered as of 26/07/2021 refer to **non-serious events**, with a reporting rate of 111/100,000 administered doses and **12.8%** to **serious adverse events**, with a reporting rate of 16 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 0.1% of reports).

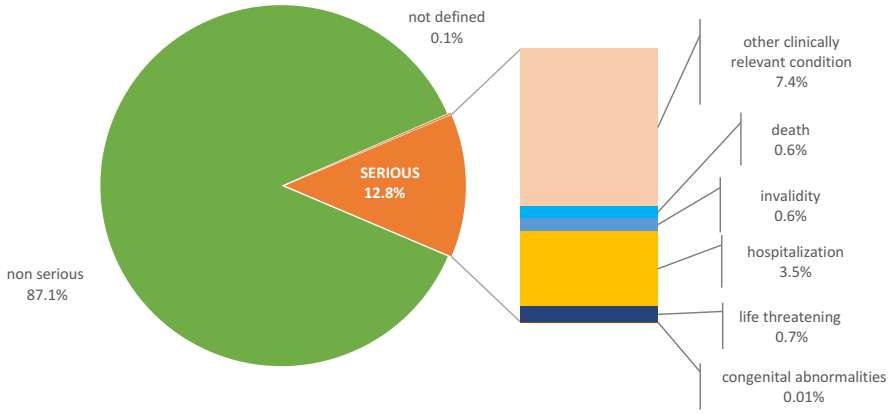
The reporting rates of serious events for each vaccine are 13 (Comirnaty), 13 (Spikevax), 32 (Vaxzevria) and 15 (Janssen) per 100,000 administered doses. As already shown in the previous Reports, the reported serious adverse events occur in the first 48 hours after vaccination (about 60% of cases), more rarely in the following weeks (about 37% of cases). In the remaining 3% of cases, the information is insufficient to establish the onset time 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).

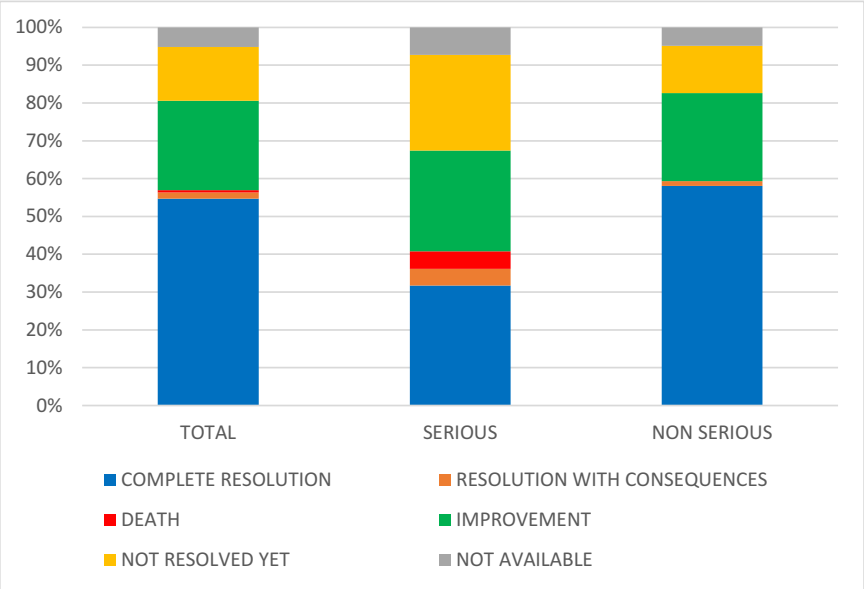
Figure 6 – *Distribution by seriousness of the reports entered in the period considered (0.1% of reports do not indicate seriousness)*



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, 81% of the reports refer to non-serious adverse events with full recovery or improvement already at the time of reporting. 58% of serious reports result in full recovery or improvement and 25% has not yet recovered upon reporting.

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 26/07/2021, the causal link according to the WHO algorithm was included in 74% of reports of serious adverse events (8,032/10,805). Overall, 43% of all serious reports evaluated (3,453/8,032) are related to vaccination, 35% (2,800/6,306) are indeterminate, 19% (1,562/8,032) are unrelated and 3% (215/8,032) unclassifiable.

Regardless of the type of vaccine, the number of doses and the causal link, 498 reports show a "death" outcome with a reporting rate of 0.75/100,000 administered doses, with a slight decrease compared to previous reports. The distribution of such fatal cases by type of vaccine is shown in table 3.

49.8% of cases concern women, 49.8% men while 0.4% (2 sheets) do not report this data. The mean age is 76 years (range 18-104 years). The time between vaccine administration and death varies from two hours up to a maximum of 133 days. In 343 cases death is recorded after the first dose, in 145 after the second (not specified in 10 reporting sheets).

No deaths were reported 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	307	0.66
Spikevax	86	1.30
Vaxzevria	88	0.78
Janssen	17	1.28
Total	**498**	**0.75**

At the time of writing, 59% of death reports have a causality assessment with the algorithm used in the vaccine surveillance (WHO Algorithm), according to which 59.9% of cases is **not correlable**, 33.2% **undetermined** and 4.5% **unclassifiable** due to lack of information necessary for the application of the algorithm.
In seven cases (2.4% of the total), causality is **correlated**. All cases have already been described in previous reports.

Distribution by dose number

In the period considered, 43% of the overall administered doses was used to complete the vaccination cycle (second doses), mainly with the Comirnaty vaccine.
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)	95% Confidence interval	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	104	103-105	122	**121-123**
Spikevax	98	95-101	60	57-63	82	**80-84**
Vaxzevria	304	300-308	21	20-22	184	**181-186**
Janssen	79	74-84	-	-	79	**74-84**

As in previous reports, no differences in reporting rates were observed between the 1st and the 2nd 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 the rate for the 1st dose.

Distribution by type of event

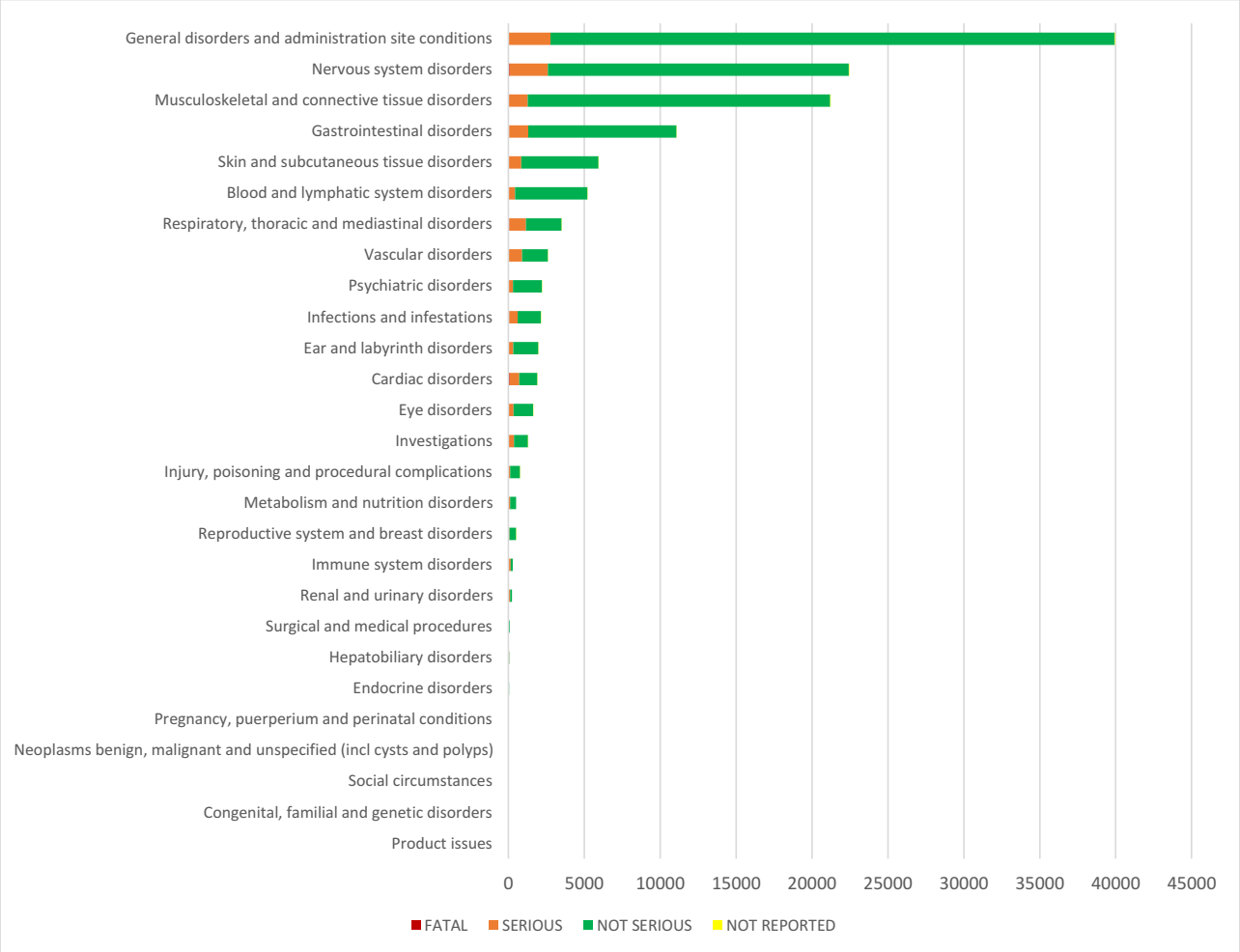
Graphs 8, 9, 10 and 11 report in order of frequency the types of events reported according to the System Organ Class (SOC) for the four vaccines used, regardless of the dose and causality link. It should be noted that a single report sheet can include multiple events, therefore the total number of events 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.
Most reports fall into the system organ class of **general pathologies and administration site conditions**, especially injection site reactions, fever and fatigue/asthenia. Next in order of frequency are **pathologies of the nervous system**, mainly headache, paraesthesia and sleep disorders, **pathologies of the musculoskeletal system and connective tissue**, mostly myalgia, arthralgia and musculoskeletal pain, and **gastrointestinal pathologies**, usually nausea, vomiting and diarrhoea.

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



About 89% of the reports were entered as non-serious and 10% as serious (in 0.1% of cases the severity is not defined). The distribution by type of serious adverse events does not differ significantly from that of all events.

Comirnaty-related serious adverse events

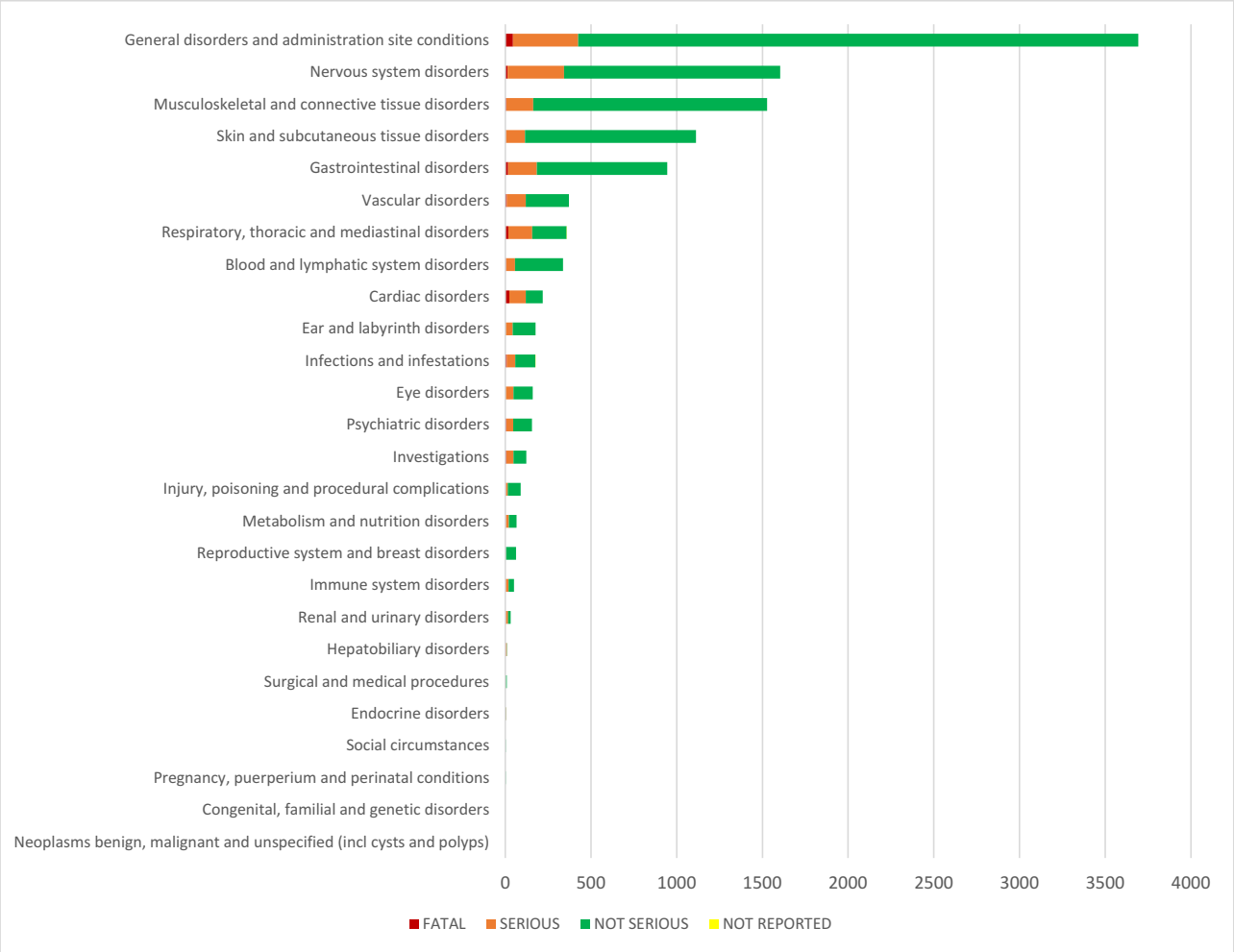
About 4 reports per 100,000 doses of Comirnaty administered are serious events related to vaccination (the reporting rate of serious adverse reactions related to vaccination per every 100,000 first and second doses administered corresponds to the overall rate). Based on the seriousness criterion, 77% of these reports were included as “serious - other clinically relevant condition", 18.2%

as requiring hospitalisation and 2.5% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 56% of these reports and improvement in 24%.
Headache, hyperpyrexia and joint and muscle pain 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 follows, with a rate of approximately 1 case per 100,000 doses administered. Less frequently, anxious reactions to vaccination (more often lipothymic reactions), diffuse paraesthesia and lymphadenopathies are reported as correlated serious adverse events, each with a frequency of approximately 1 case in 100,000 doses administered. Facial paralysis, anaphylactic reactions and myocarditis/pericarditis are very rare (their rate is respectively 5, 4 and 3 cases per million doses administered).

Spikevax (formerly COVID19 Vaccine Moderna)

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

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



Most of the suspected adverse events reported are related to the system organ class of **general diseases and conditions related to the administration site**, mainly 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 tissue pathologies**, mainly erythema, redness and urticarial reactions. Rarer are the reactions that fall within the **pathologies of the gastrointestinal system** (essentially nausea and vomiting).
Non-serious reactions represent about 83% of the total reports and serious reactions represent 16% (in 1% of cases the severity is not defined), and that is in line with what was observed in the previous Report. The distribution by type of serious adverse events does not differ significantly from that of all events.

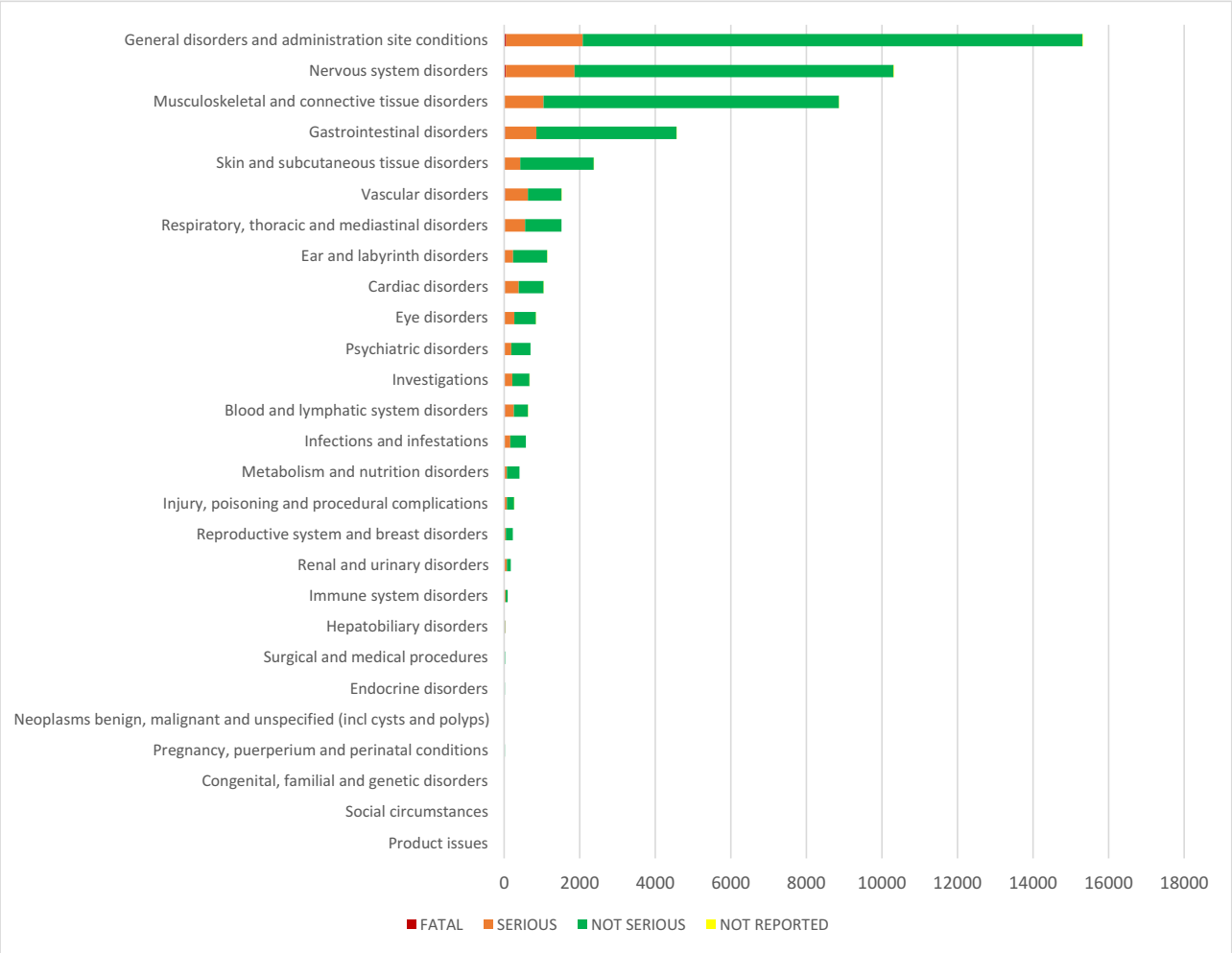
Spikevax-related serious adverse events

About 2.7 reports per 100,000 doses of Spikevax administered are serious events related to vaccination (3 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, 70% of these reports were included as “serious - other clinically relevant condition", 21% as requiring hospitalisation and 6% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 41% of these reports and improvement in 34%.
The most commonly reported related serious adverse events are hyperpyrexia, joint pain and muscle pain, with a reporting rate of approximately 1.5 cases per 100,000 administered doses. Headache, lymphadenopathy and anxious reactions to vaccination (especially lipothymia or vegetative reaction) 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. Anaphylactic reactions are very rare, with a reporting rate of approximately 2.6 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.
In fact, most reports fall into the system organ class of **general pathologies and administration site conditions**, and mainly report fever, local reactions at the injection site and fatigue/asthenia. Next in order of frequency are **pathologies of the nervous system**, mainly headache, **pathologies of the musculoskeletal system and connective tissue**, mostly widespread joint pain and musculoskeletal pain, often in association with each other and with the increase in temperature.
More rarely, adverse events have been reported that fall within **gastrointestinal pathologies**, generally nausea, vomiting and diarrhoea and **skin and subcutaneous tissue pathologies**, especially diffuse erythematous-type reactions.

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



About 82% of the reports of the Vaxzevria vaccine were entered as non-serious and 17% as serious (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.

Serious adverse events related to Vaxzevria

About 18 reports per 100,000 doses of Vaxzevria administered are serious events related to vaccination (11 related serious adverse events per 100,000 first doses administered and 1 related serious adverse event per 100,000 second doses administered). 75% of these reports are “serious - other clinically relevant condition", 19% requiring hospitalisation and 5.8% life threatening. Complete resolution of the adverse reaction is reported in 45.6% of these reports and improvement in 32%.

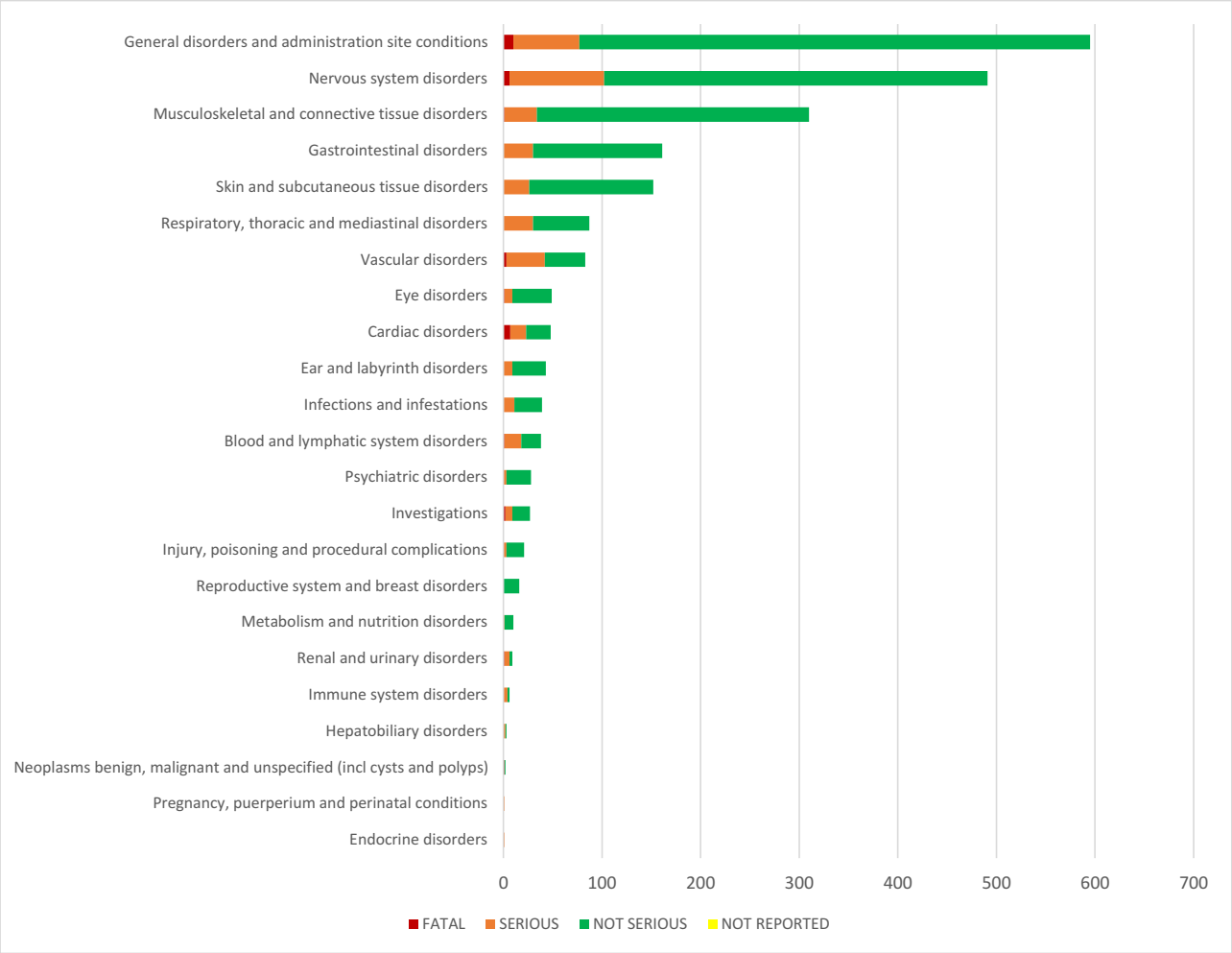
The most commonly reported correlated serious adverse events are hyperpyrexia (3 cases per 100,000 doses administered), headache (2 cases per 100,000 doses administered) and joint and muscle pain (2 cases per 100,000 doses administered), often associated with each other in a flu-like syndrome which appears more frequently after the first dose. More rarely, lipothymias and vagal reactions have been reported (1 case per 100,000 doses administered). Very rare adverse events (<1 case/100,000 doses administered) include acute and subacute neuropathies (including Guillain-Barrè syndrome) and intracranial or atypical venous thrombosis with or without thrombocytopenia.

Both suspected adverse reactions are being further investigated, both at national and European level, with the aim of verifying the actual frequency in the various age groups or on the basis of sex and to identify any risk factors.
The reporting rate for anaphylactic reactions is comparable to that reported in the previous Reports (2.7 cases per million doses administered).

COVID-19 Janssen vaccine

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** (such as fever, local injection site reactions and fatigue/asthenia, 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 Janssen vaccine by system organ class (SOC)*



80% of reports of the COVID-19 vaccine Janssen vaccine were entered as non-serious and 19% as severe (in 1% of cases the severity was not defined), with no substantial differences in the distribution by type of reaction.

Serious adverse events related to COVID-19 Janssen vaccine

Approximately 3 reports per 100,000 doses were found to be serious related to vaccination, 63% of these reports were included as “serious - other clinically relevant condition", 32% as requiring hospitalisation and 7% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 30% of these reports and improvement in 44%.
The number of reports is still low, due to the limited number of doses currently administered. Therefore, reporting rates continue to be affected by low exposure and are not currently consolidated. Despite this, the most frequently observed correlated serious adverse reaction is hyperpyrexia (approximately 3 cases per 100,000 doses administered), followed by diffuse arthromyalgia (approximately 2 cases per 100,000 doses administered), 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 2 cases per 1,000,000 doses administered.

Heterologous vaccination

In total, as of 26/07/2021, 396,952 so-called heterologous vaccinations have been carried out on people under 60 years of age who had received the Vaxzevria vaccine as their first dose. The Comirnaty vaccine was used in 82.6% of cases and the Spikevax vaccine in 17.4%.
Compared to this modality of vaccination with a mixed schedule, 114 reports were entered, with a reporting rate of 29 per 100,000 doses administered. 78% of reactions occurred with Comirnaty (27 reports per 100,000 doses administered) and 22% with Spikevax (27 reports per 100,000 doses administered). Unlike the general distribution of adverse events, approximately 53% of reports come from citizens and 47% from healthcare professionals.
83% of the reports are reported as non-serious and 17% as serious. The complete resolution outcome at the time of reporting was reported in 54% of cases and improvement in 20% of cases.
The distribution by type of adverse events is not substantially different between the two vaccines used. Consistent with reports of mRNA vaccines, the most frequently reported adverse events are fever, injection site reactions, and widespread joint and muscle pain. More rarely, diffuse lymphadenopathy and generalised rash have been reported.

Vaccination in the age group 12-19 years

As of 26/07/2021, the Comirnaty vaccine is the only one approved from the age of 12, while the Spikevax, Vaxzevria and COVID-19 Vaccine Janssen vaccines are authorised from the age of 18 (the Spikevax vaccine was approved for the age group between 12 and 17 years on 28/07/2021). By the same date, 1,986,221 doses of vaccine had been administered in adolescents aged 12-19 years, of which 71% were first doses and 29% second doses. As expected, approximately 93.7% of the doses used in this age group are related to the Comirnaty vaccine, 3.7% to the Spikevax vaccine, 0.6% to the Vaxzevria vaccine and 2% to the Janssen vaccine.
Overall, 530 reports of suspected adverse events were entered in the age group 12-19 years with a reporting rate of 27 adverse events per 100,000 doses administered (414 reports after the 1st dose,

with a reporting rate of 29 adverse events per 100,000 doses administered, and 116 reports after the 2nd dose, with a reporting rate of 20 adverse events per 100,000 doses administered). About 77% of the reports were entered as non-serious and 22% as serious (1% of the reports do not report this information). Approximately 67% of serious reports report complete resolution or improvement at the time of reporting.

The distribution by type of adverse events is not substantially different from the one observed for any other age group. In particular, the most frequently reported adverse events are fever and local reactions at the injection site, followed by headache and lymphadenopathy, regardless of vaccine type, dose number and severity. Given the low number of doses administered and the small number of reports received, the assessment of the distribution by type of event is currently still unreliable. Approximately 1 report per 100,000 doses administered was found to be a serious vaccination-related report, the most frequent of which was flu-like syndrome (1 case per 100,000 doses administered). Very rare adverse events include myocarditis and acute pericarditis (3 cases per million doses administered). No cases of anaphylaxis have been reported in this age group.

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#7*

	Report#1	Report#2	Report#3	Report#4	Report#5	Report#6	Report#7
	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	as of 26/07/2021
administered doses	1,564,090	4,118,277	9,068,349	18,148,394	32,429,611	49,512,799	65,926,591
reporting of adverse events	7,337	30,015	46,237	56,110	66,258	76,208	84,322
reporting rate	469	729	510	309	204	154	128
reporting rate for men	293	424	299	176	116	88	73
reporting rate for women	561	907	645	404	272	209	175
reporting rate for first dose	515	773	496	299	211	164	128
reporting rate for second dose	225	785	540	333	190	134	160
reporting rate of serious adverse reactions	34	44	36	27	21	18	16
reporting rate of serious adverse reactions for men	22	28	23	18	15	13	12
reporting rate of serious adverse reactions for women	42	54	44	33	26	23	20

	Report#1	Report#2	Report#3	Report#4	Report#5	Report#6	Report#7
	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	as of 26/07/2021
reporting rate of serious adverse reactions with no “clinically relevant” cases	8.9	8.1	8.5	8.8	7.9	7.5	7.0
reporting rate of deaths	0.8	0.97	1.1	1.23	1.0	0.8	0.75
Source of reporting							
Doctor	47%	46%	44%	42%	42%	40.5%	39.5%
Pharmacist	22%	19%	20%	20%	20.5%	20%	20%
Other healthcare professional	25%	26%	21%	19%	17%	16%	15%
Patient/Citizen	6%	9%	15%	18%	20%	23%	25%
Lawyer	0%	0%	0.12%	0.20%	0.2%	0.2%	0.2%
Armed Forces	0%	0%	0.07%	0.30%	0.3%	0.3%	0.3%
Comirnaty							
reporting rate	471	769	535	328	214	150	122
reporting rate for first dose	517	756	525	315	212	144	137
reporting rate for second dose	278	790	549	348	216	161	104
reporting rate of serious adverse reactions	na	45	33	24	18	15	13
Spikevax							
reporting rate	277	333	227	129	88	83	82
reporting rate for first dose	277	335	216	132	95	94	98
reporting rate for second dose	-	322	264	121	73	65	60
reporting rate of serious adverse reactions	na	26	22	18	13	14	13
Vaxzevria							
reporting rate	-	326	477	309	236	219	184
reporting rate for first dose	-	326	477	307	261	281	304
reporting rate for second dose	-	-	-	-	24	31	21
reporting rate of serious adverse reactions	-	31	50	39	36	37	32
Janssen							
reporting rate	-	-	-	-	34	67	79
reporting rate of serious adverse reactions	-	-	-	-	5	12	15

The decrease in overall reporting rates continues (Fig. 12). Rates for individual vaccines also show a downward trend, with the exception of Janssen, used since 22 April 2021. Rates of serious reactions are maintained, in particular when excluding the category of "clinically relevant" cases. Additionally, rates of fatal cases continue to decline, with a peak observed in April (1.23 cases per 100,000 doses administered vs the current figure of 0.75 cases per 100,000 doses administered). The reporting rate for second dose is the only one recording a slight increase, in line with the higher percentage of second doses administered over the period compared with the previous months (43% in July vs 33% in June) (Fig. 13).

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

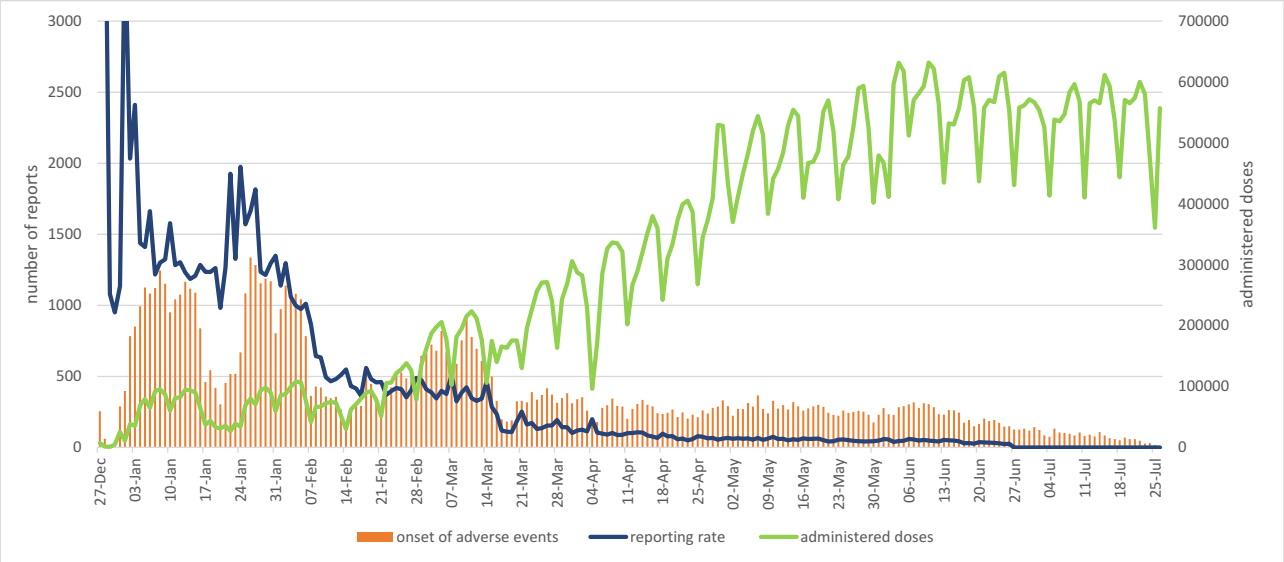


Figure 13 *– Trend in reporting rates by gender, number of doses, severity and fatal events over time*

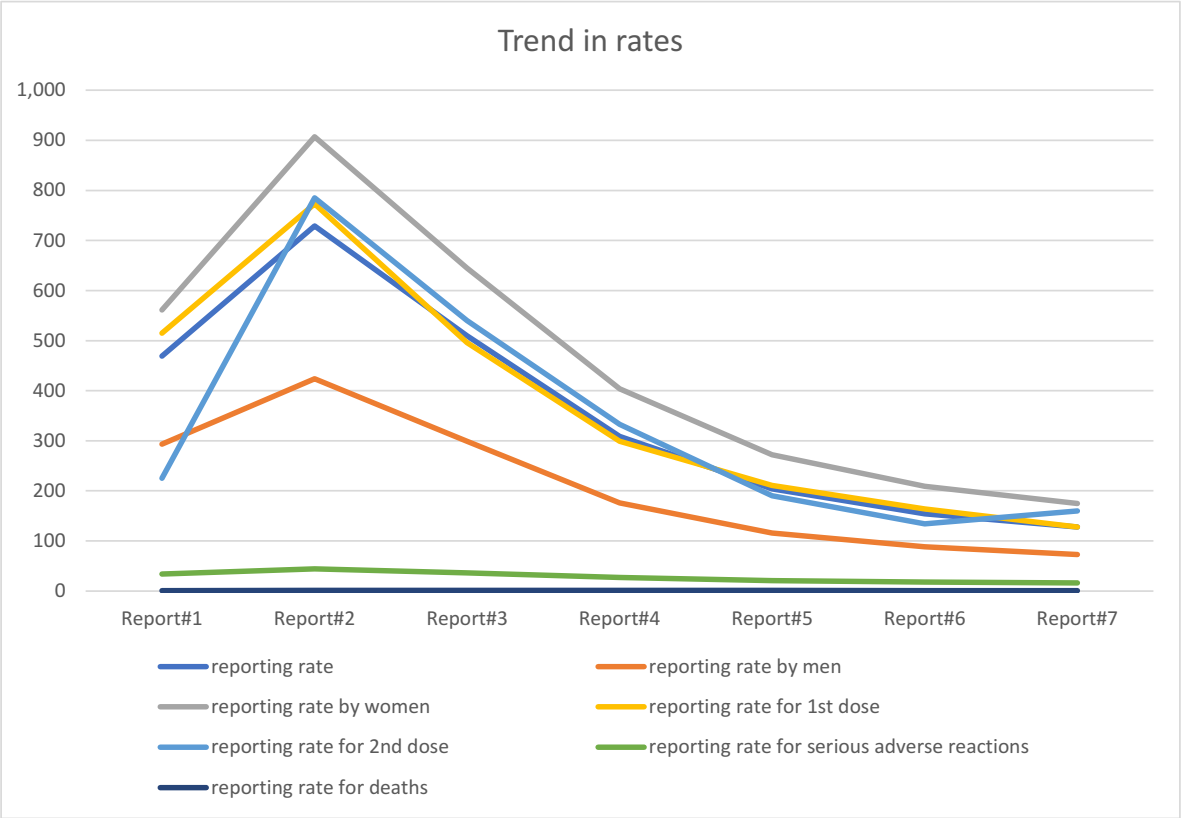


Figure 14 shows the distribution by type of reporter. The largest number of reports comes from doctors, while those from pharmacists remain stable. The already described downward trend in reports from doctors and other healthcare professionals (from 47% to 39.5% for doctors and from 25% to 15% for other healthcare professionals) as well as the increase in reports from patients (from 6% to 25%) are 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). The ratio of serious reactions between women and men is decreasing (from 1.90 to 1.66).

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

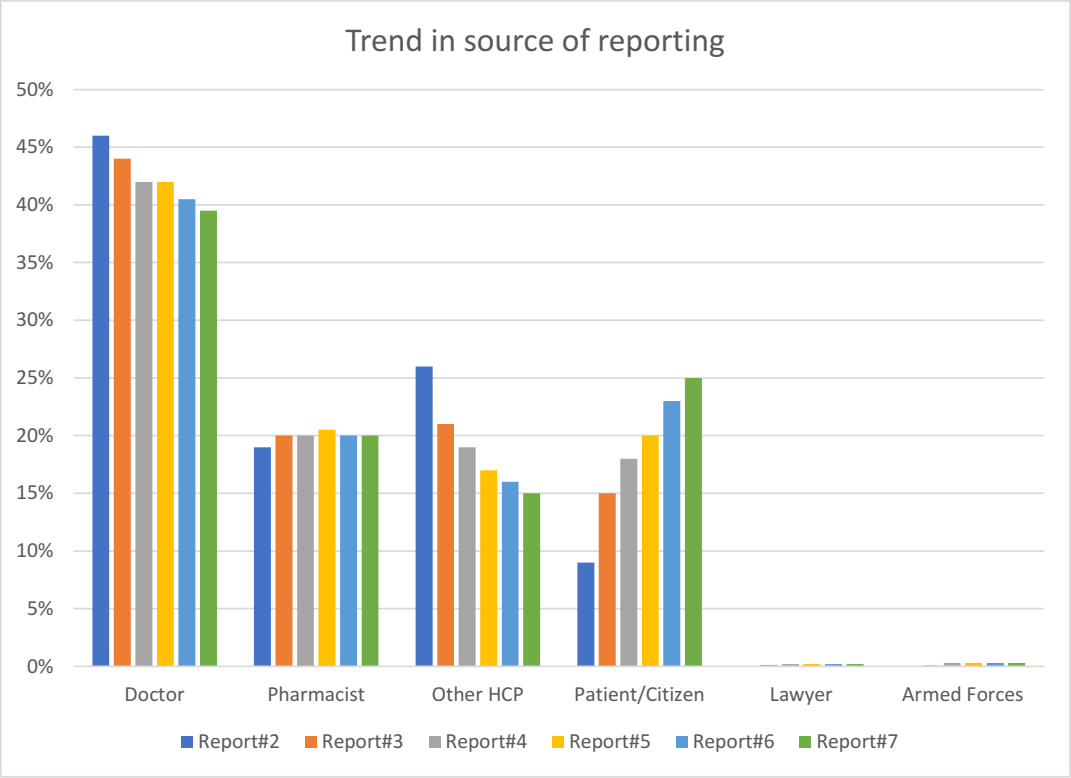
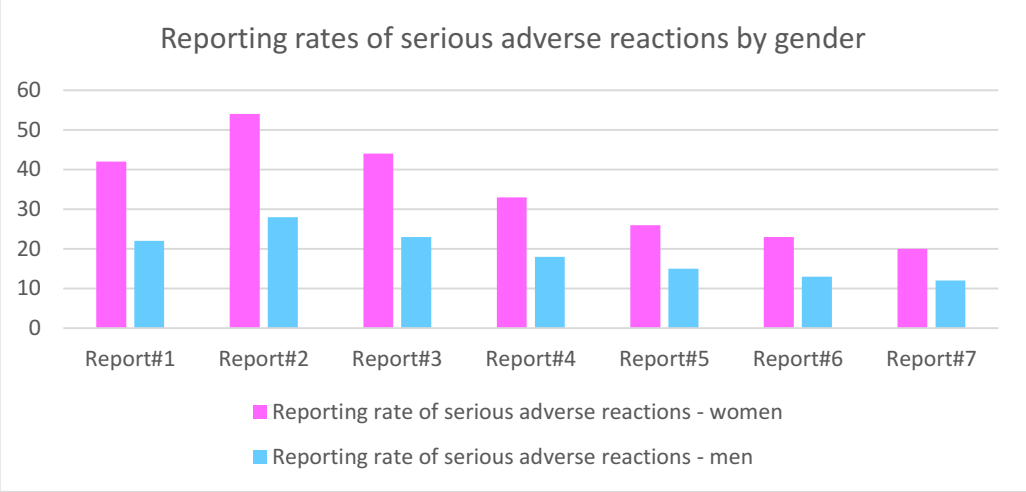


Figure 15 *– Trend in reporting rates of serious adverse reactions by gender*



How to report a suspected adverse reaction?

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