Signals Management Office
Pharmacovigilance Office
Post Marketing Surveillance Department
in cooperation with
International Affairs Department

COVID-19 Vaccine Surveillance Report

Report #8
Period 27/12/2020 – 26/08/2021

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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.
Based on 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 August 2021, 119 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 86.1%) which resolve completely and only to a lesser extent as severe (13.8%), resulting in full recovery or improvement in most cases.
- In the period considered, 45% 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, injection site pain or local reaction, chills and nausea.
- The reporting rate of the mixed vaccine schedule is 41 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 22 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.

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

[infographics – by Press and Communication Office]

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)

PERIOD UNDER REVIEW: 27/12/2020 - 26/08/2021

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 26/08/2021, **91,360 reports of adverse events following immunisation** have been entered in the National Pharmacovigilance Network, out of 76,509,846 **vaccine doses**, with a **reporting rate of 119 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 (16%), Spikevax (11%) and COVID-19 Janssen vaccine (2%) [2]. In line with the previous publications, the distribution of reporting by type of vaccine is similar to the distribution of administered doses (Comirnaty 67%, Vaxzevria 24%, Spikevax 8% 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 of 26/08/2021	Administered doses as of 26/08/2021	Reporting rate (per 100,000 administered doses)	95% Confidence interval
Comirnaty	61,281	54,226,752	***113***	***112-114***
Spikevax	7,056	8,762,697	***80***	***78-82***
Active ingredient mRNA	17			
Vaxzevria	21,790	12,093,073	***180***	***178-182***
Janssen	1,224	1,427,324	***85***	***80-90***
Total	**91.368***	**76,509,846**	***119***	***118-120***

** 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 26/08/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 29/08/2021

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, 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. 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*

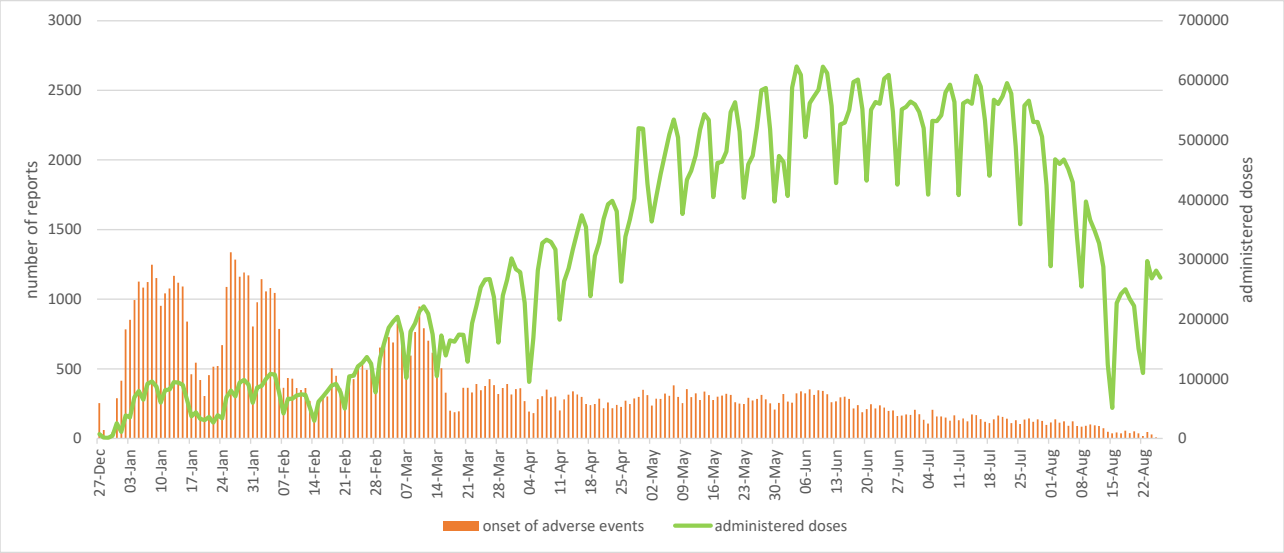
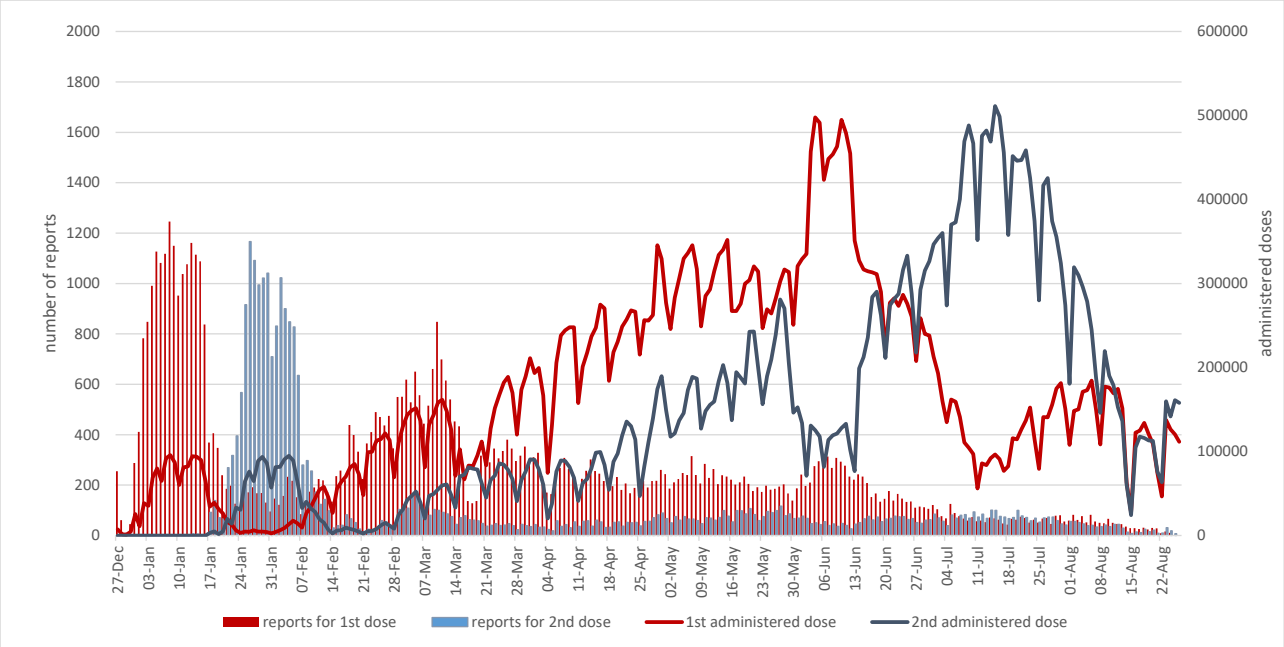


Figure 1b – *Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*

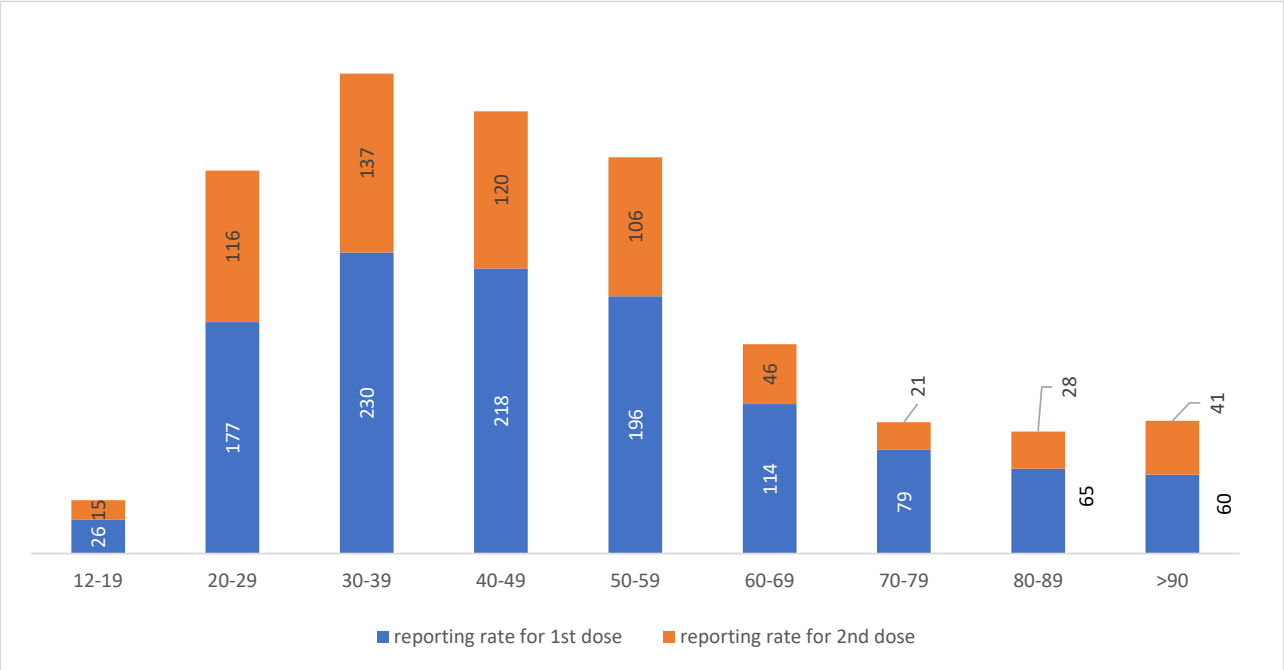


Distribution by age, sex and type of reporter

Distribution by age

The average age of people with a suspected adverse event is 48.3 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*

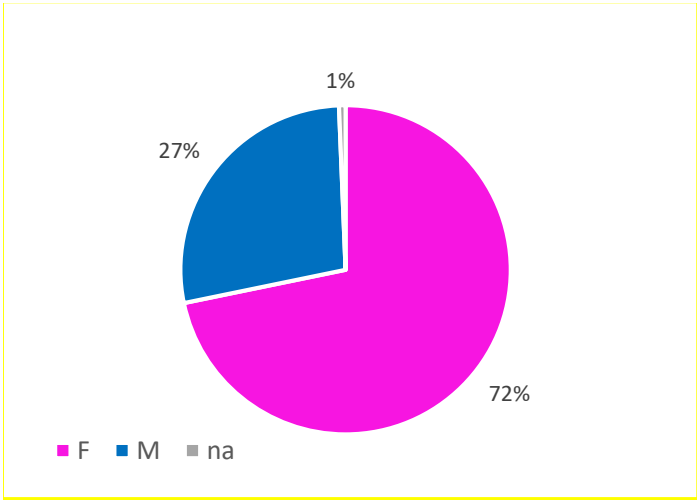


As already observed in pre-authorisation clinical studies and in previous Reports, the reporting rate is higher in the age groups between 20 and 60 years and then decreases in the more advanced and in the youngest age groups, with a similar trend after 1st and 2nd dose.

Distribution by sex

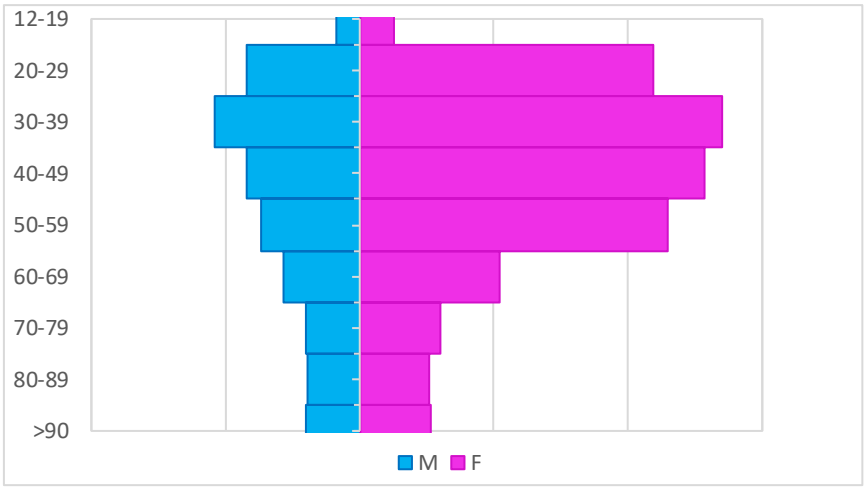
Considering an overlapping exposure of the sexes (52% of the doses administered in women and 48% in men), 72% of the reports concern women (164/100,000 administered doses) and 27% men (69/100,000 administered doses), regardless of the dose and vaccine administered (sex is not reported in 1% of reports, 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 72% of the reports come from healthcare professionals, mainly doctors and pharmacists, while about 27% 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*

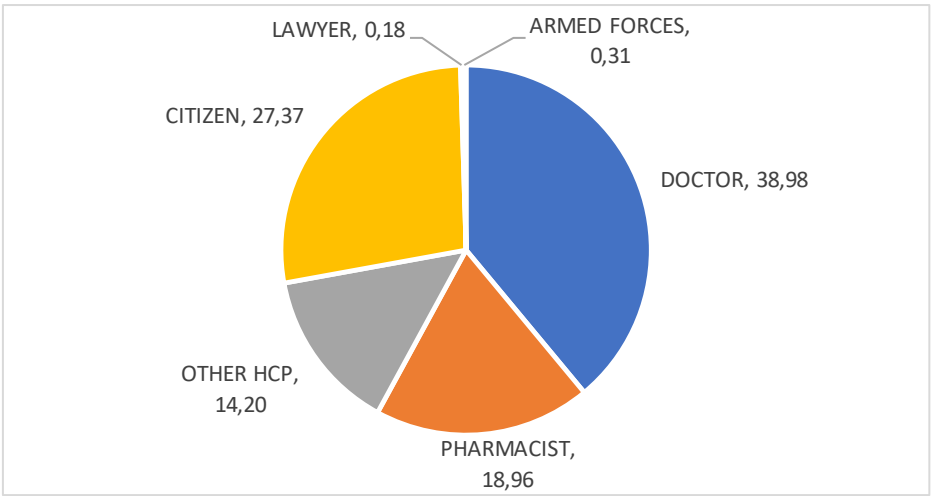


Table 2 shows the report distribution by onset time from vaccination.

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

ONSET TIME	N° REPORTS	%
0 days	42,968	47%
1 day	26,877	29%
2-7 days	10,694	12%
>7 days	6,840	7%
Not definable	3,981	4%
Total	***91,360***	***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 beyong the following 48 hours.

Distribution by seriousness and outcome

86.1% of reports entered as of 26/08/2021 refer to **non-serious events**, with a reporting rate of 111/100,000 administered doses and **13.8%** to **serious adverse events**, with a reporting rate of 13 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).

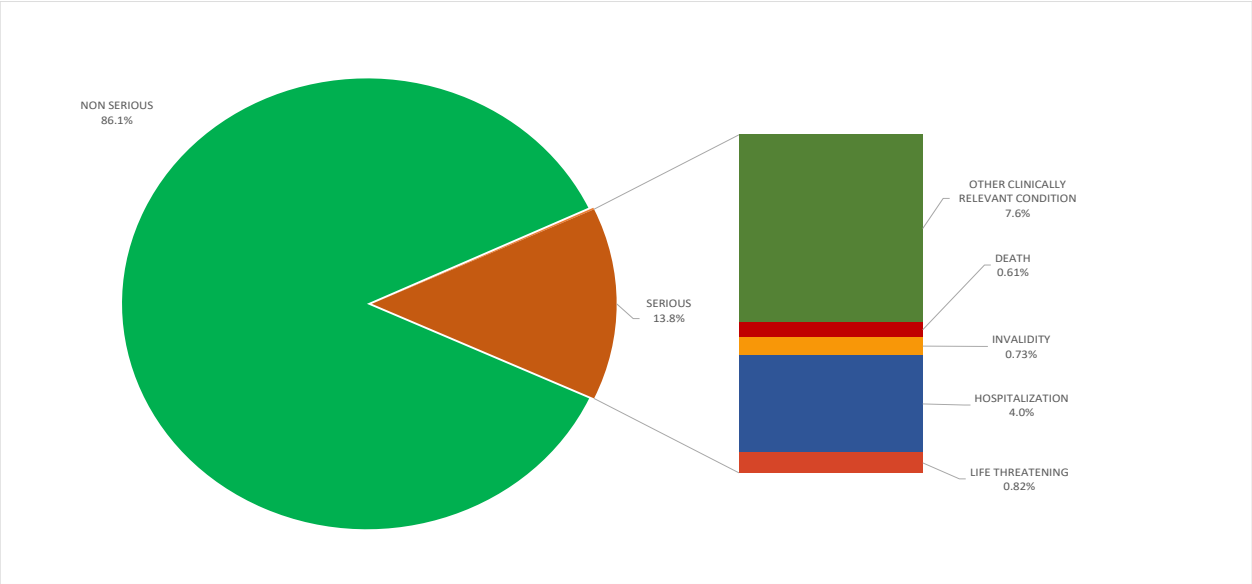
The reporting rates of serious events for each vaccine are as follows: 13 cases per 100,000 doses of Comirnaty, 14 per 100,000 doses of Spikevax, 33 per 100,000 doses of Vaxzevria, and 19 per 100,000 doses of Janssen. As already shown in the previous Reports, the reported serious adverse events occur in the first 48 hours after vaccination (about 53% of cases), more rarely in the following weeks (about 41% of cases). In the remaining 6% 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. 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

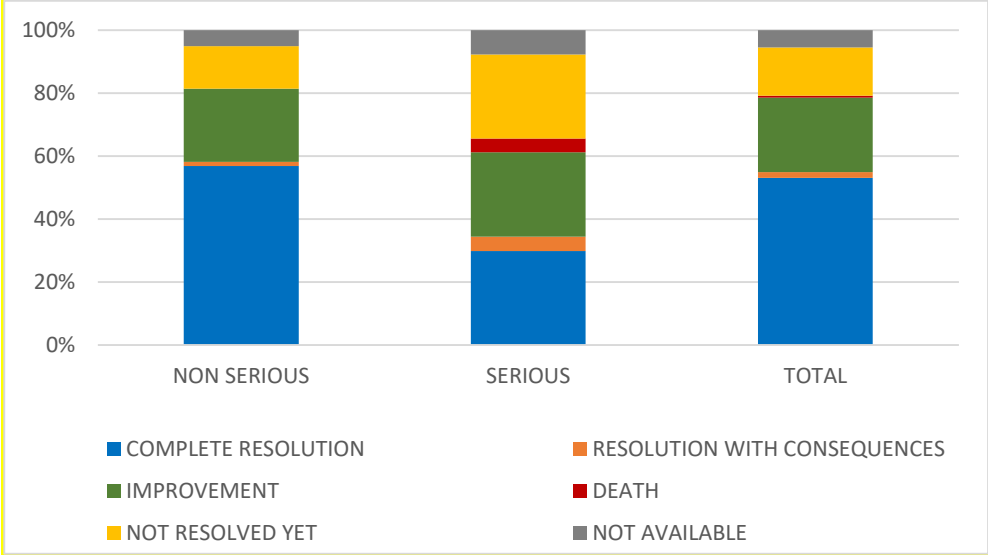
Figure 6 shows the distribution of reports by seriousness, with details of the seriousness parameter for serious reactions relating to all vaccines.

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



As shown in figure 7, most reports (about 70%) refer to non-serious adverse events with full recovery or improvement already at the time of reporting. 56% of serious reports result in full recovery or improvement and 26% 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.

Serious reports and causal link.

At the time of drafting this Report, the causal link according to the WHO algorithm was included in 74% (9,324/12,600) of **reports of serious adverse events**, regardless of the outcome and was found related to vaccination in 42% of all serious reports evaluated (3,909/9,324), indeterminate in 35% (3,302/9,324) and unrelated in 20% (1,845/9,324). 3% (268/9,324) of the reports are unclassifiable, due to lack of sufficient information.

Deaths and causal link.

Overall, 555 of these serious reports (net of duplicates, or cases for which more than one report was entered) reported the "death" outcome with a reporting rate of 0.73/100,000 doses administered, 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.

48.5% of cases concern women, 50.8% men while 0.7% (4 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, where reported. In 381 cases, death is recorded after the first dose, in 174 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	345	0.64
Spikevax	92	1.05
Vaxzevria	94	0.78
Janssen	24	1.68
Total	**555**	**0.73**

71.3% (396/555) of death reports have a causality assessment with the algorithm used in the vaccine surveillance (WHO Algorithm), according to which 58.8% of cases (233/396) is **not related**, 32.3% (128/396) **indeterminate** and 5.3% (21/396) **unclassifiable** due to lack of sufficient information. Overall, 14 cases (3.5%) out of the 396 evaluated were **related** (approximately 0.2 cases per million doses administered), of which 7 have already been described in the previous Reports. The remaining 7 reports refer to 3 patients over eighty with a condition of fragility due to multiple pathologies, who died from COVID-19 after completing the vaccination course (in two cases 3 weeks before and in one case 39 days before the fatal event), 3 patients died from complications of a thrombotic event associated with thrombocytopenia and 1 patient died from complications of thrombotic thrombocytopenic purpura.

Distribution by dose number

In the period considered, 45% 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	131	130-132	93	92-94	113	**112-114**

Spikevax	94	91-97	61	58-63	80	**78-82**
Vaxzevria	314	310-318	23	22-24	180	**178-182**
Janssen	86	81-91	-	-	86	**81-91**
All vaccines	153	152-154	78	77-79	119	**118-120**

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

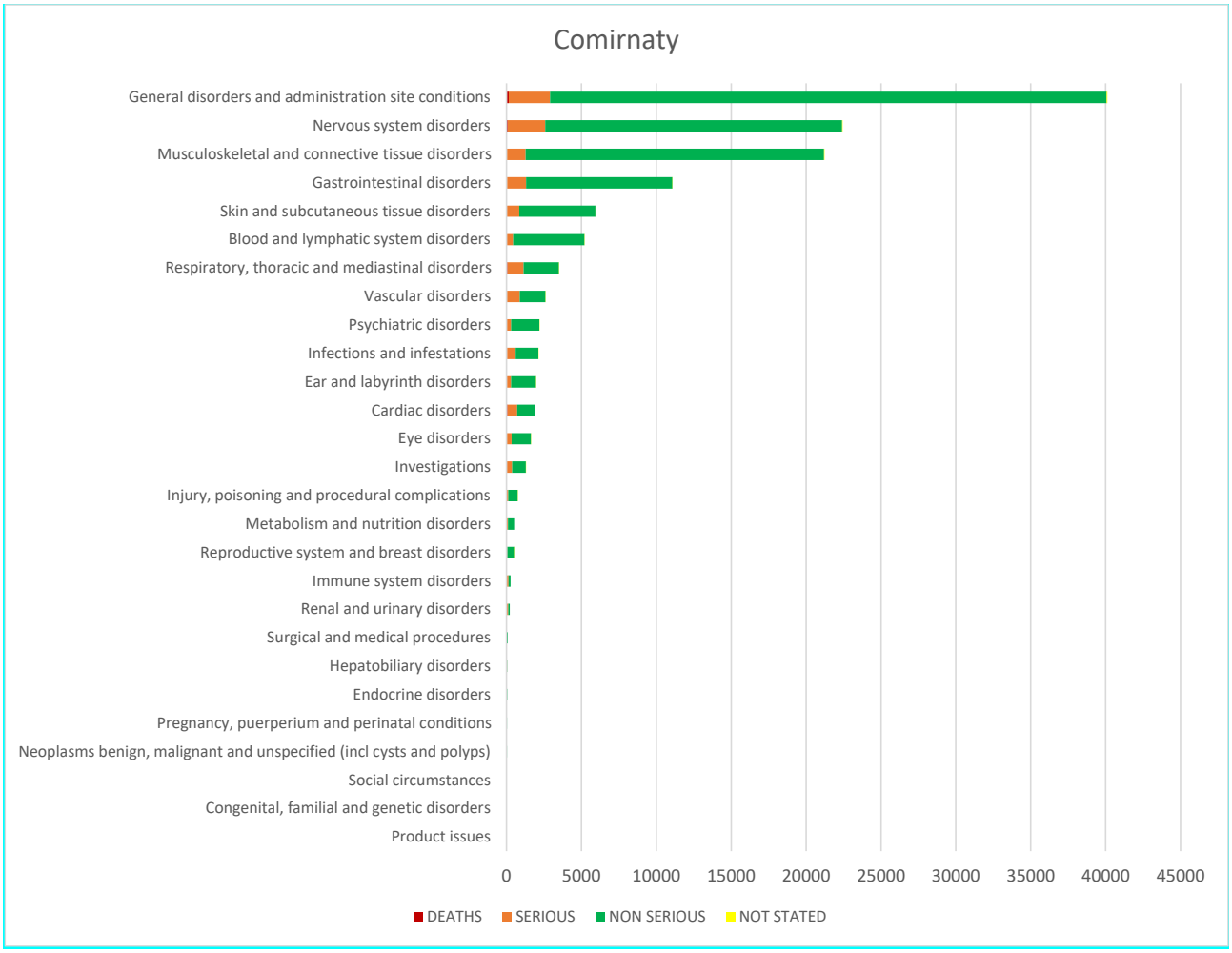
Graphs 8, 9, 10 and 11 report in order of frequency the types of events reported according to the System Organ Class (SOC) for the four vaccines used, regardless of the dose and causal link. It should be noted that a single report sheet could include multiple events; therefore, the total number of events 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 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 musculoskeletal pain) and by **gastrointestinal diseases** (generally nausea, vomiting and diarrhea).

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



The proportion between serious reports (about 10%) and non-serious (about 89%) 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

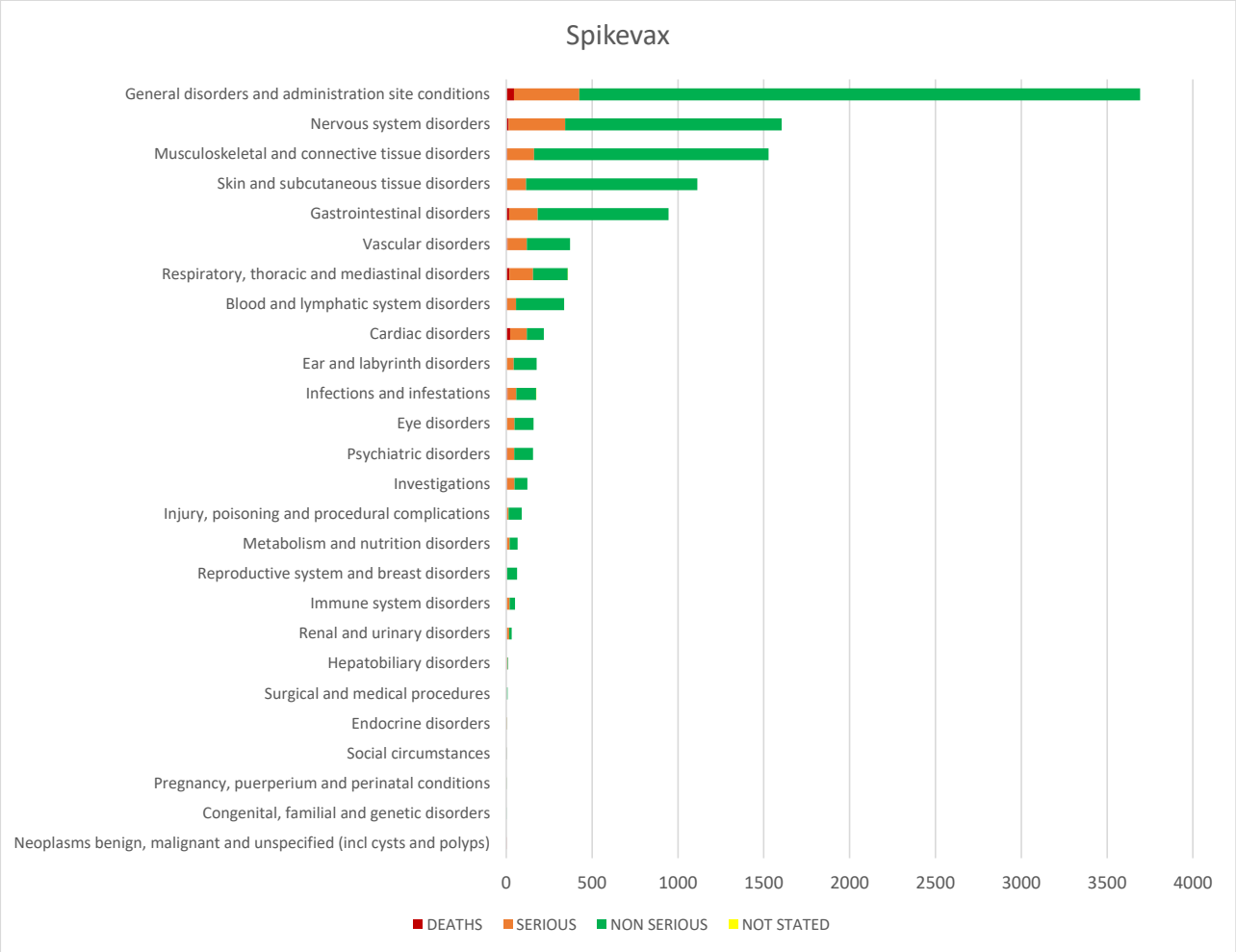
About 4 reports per 100,000 doses of Comirnaty administered are serious events related to vaccination (4 related serious adverse events per 100,000 first doses administered and 3 per 100,000 second doses administered). Based on the seriousness criterion, 74% of these reports were included as “serious - other clinically relevant condition", 20% as requiring hospitalisation and 3% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 54% of these reports and improvement in 26%.

Hyperpyrexia confirms as the most commonly reported related serious adverse event, (about 1.5 cases per 100,000 administered doses), followed by joint and muscle pain, headache and fatigue (all with arond 1 case per 100,000 administered doses). These symptoms are very often associated with each other in an influenza-like syndrome, with no substantial differences between the first and second dose. Less frequently reported are anxious reactions to vaccination (more often lipothymic reactions), diffuse paraesthesia and lymphadenopathies, each with a frequency of approximately 0.5 cases per 100,000 administered doses. Very rare are anaphylactic reactions (3 cases per million doses administered) and myocarditis/pericarditis (2 cases per million doses administered) and facial nerve paralysis (1 case 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.

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



Most of the suspected adverse events reported are related to **general pathologies 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.

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

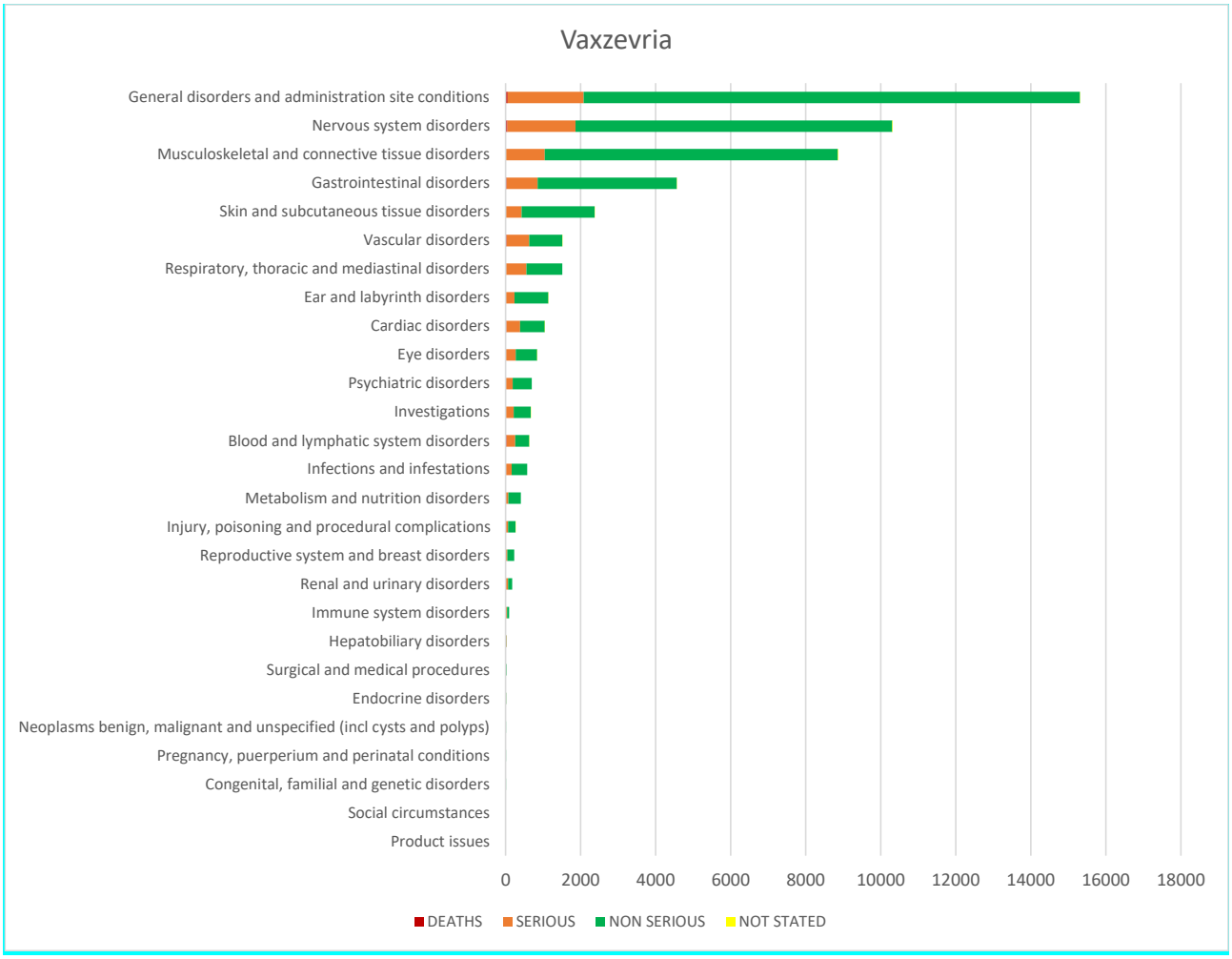
Approximately 3 reports in every 100,000 administered doses of Vaxzevria are serious related to vaccination, with no difference between first and second dose.

Based on the seriousness criterion, 68% of these reports were included as “serious - other clinically relevant condition", 23% as requiring hospitalisation and 5% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 44% of these reports and improvement in 30%.
Hyperpyrexia confirms as the most commonly reported related serious adverse event, (about 1.5 cases per 100,000 administered doses), followed by headache, joint and muscle pain and anxious reactions to vaccination (especially lipothymia or vegetative reaction), all with a reporting rate of about 1 case per 100,000 administered doses. Also for the Spikevax vaccine, hyperpyrexia, joint and muscle pain and headache are often associated with each other within an influenza-like syndrome, with no substantial difference between first and second dose. More rarely reported are fatigue and lymphoadenopathies, with a rate of 0.5 cases per 100,000 administered doses. Anaphylactic reactions are very rare, with a reporting rate of approximately 2 cases per million doses administered and myocarditis/pericarditis with a reporting rate of about 1 case 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 pathologies and conditions related to the administration site** (especially fever, injection site pain, fatigue/asthenia), followed by **pathologies of the nervous system** (mainly headache), by **pathologies of the musculoskeletal system and of the connective tissue** (mostly musculoskeletal pain), generaly 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). 72% of these reports are serious - other clinically relevant condition, 19% requiring hospitalisation and 5.4% life threatening. Full recovery of the adverse reaction is reported in 44% of these reports and improvement in 30%.

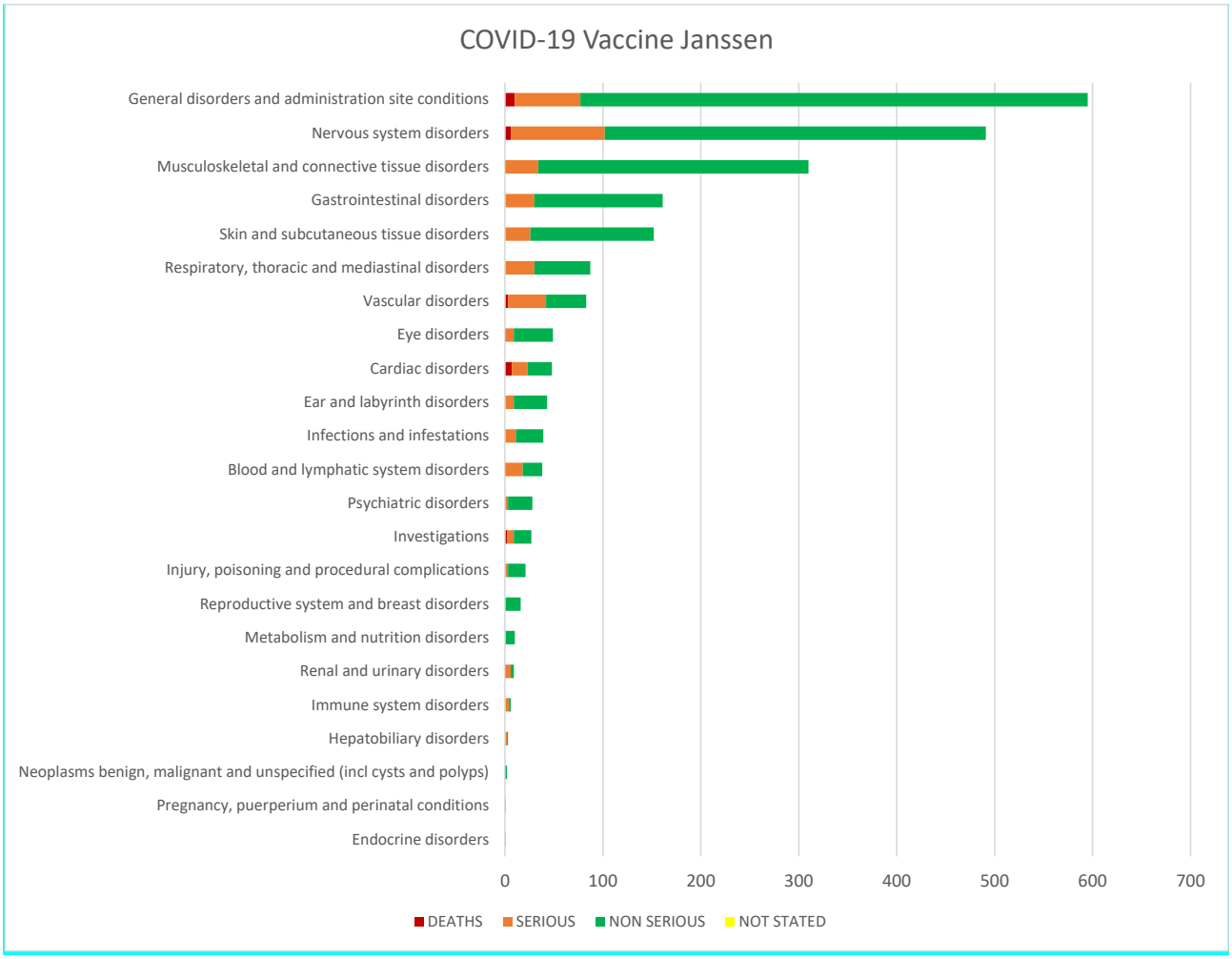
The most commonly reported related serious adverse events are hyperpyrexia (7 cases per 100,000 administered doses), headache and joint/muscle pain, both with approximately 4 cases per 100,000 administered doses. Fatigue is also relatively frequent, with a reporting rate of approximately 2 cases per 100,000 administered doses. As with other vaccines, these symptoms are often associated with each other in an influenza-like syndrome that 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 include acute and subacute neuropathies (including Guillain-Barré's syndrome) and intracranial or atypical venous thrombosis with or without thrombocytopenia, which is the subject of more extensive investigations at European level. For all three adverse reactions, a nationwide reporting rate is estimated of approximately 1 case in

1,000,000 administered doses. The reporting rate for anaphylactic reactions is comparable to that reported in the previous Reports (2 cases per million administered doses).

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 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 Vaccine Janssen by system organ class (SOC)*



78% of reports of the COVID-19 Janssen vaccine were entered as non-serious and 19% as serious (in 1% of cases seriousness was not defined), with no substantial differences in the distribution by type of reaction.

Serious adverse events related to COVID-19 Janssen vaccine

Approximately 4 reports per 100,000 doses were found to be serious related to vaccination, 48% of which were entered as “serious - other clinically relevant condition", 40% as requiring hospitalisation and 8% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 25% of these reports and improvement in 42%.

The number of related serious reports is still very low (27 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), and 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.

Heterologous vaccination

In total, as of 26/08/2021, 604,865 so-called heterologous vaccinations have been administered on people under 60 years of age who had received the Vaxzevria vaccine as their first dose. 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, 248 reports were entered, with a reporting rate of 41 per 100,000 administered doses. 80% of reactions occurred with Comirnaty (43 reports per 100,000 administered doses) and 20% with Spikevax (33 reports per 100,000 administered doses). Unlike the general distribution of adverse events, approximately 51% of reports come from citizens and 49% from healthcare professionals.

83% of the reports are entered as non-serious and 17% as serious. The full recovery outcome at the time of reporting was entered in 48% of cases and improvement in 22% 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 12-19 years age group

As of 26/08/2021, 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 vaccines are authorised from the age of 18. By the same date, 3,798,938 doses of vaccine had been administered in adolescents aged 12-19 years, of which 77% were first doses and 23% second doses. Approximately 89.6% of the doses used in this age group are related to the Comirnaty vaccine, 9% to the Spikevax vaccine, 0.4% to the Vaxzevria vaccine and 1% to the Janssen vaccine.

Overall, 838 reports of suspected adverse events were entered in the age group 12-19 years with a reporting rate of 22 adverse events per 100,000 administered doses (645 reports after the 1st dose, with a reporting rate of 26 adverse events per 100,000 doses administered, and 193 reports after the 2nd dose, with a reporting rate of 15 adverse events per 100,000 doses administered). 76.5% of the events were recorded as not serious and 23.4% as serious (0.1% of the reports do not include this information). About 62% of serious reports includes complete resolution or improvement at the time of reporting.

The distribution by type of adverse event is not substantially different from the one 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 (frequently influenza-like syndrome, more rarely vasovagal reactions and myocarditis or pericarditis).

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#8*

	Report #1	**Report #2**	**Report #3**	**Report #4**	**Report #5**	**Report #6**	**Report #7**	**Report #8**
	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**
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
reporting of adverse events	7,337	30,015	46,237	56,110	66,258	76,208	84,322	91,360
reporting rate	469	729	510	309	204	154	128	119
reporting rate for men	293	424	299	176	116	88	73	69
reporting rate for women	561	907	645	404	272	209	175	165
reporting rate for first dose	515	773	496	299	211	164	160*	153
reporting rate for second dose	225	785	540	333	190	134	86*	78
reporting rate of serious adverse reactions	34	44	36	27	21	18	16	16
reporting rate of serious adverse reactions for men	22	28	23	18	15	13	12	12
reporting rate of serious adverse reactions for women	42	54	44	33	26	23	20	20
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	7.0

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

	Report #1	Report #2	Report #3	Report #4	Report #5	Report #6	Report #7	Report #8
	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
reporting rate for first dose	-	326	477	307	261	281	304	314
reporting rate for second dose	-	-	-	-	24	31	21	23
reporting rate of serious adverse reactions	-	31	50	39	36	37	32	33
Janssen								
reporting rate	-	-	-	-	34	67	79	86
reporting rate of serious adverse reactions	-	-	-	-	5	12	15	19

*typo corrected from Report#7

Reporting rates continue to decrease, similarly to those for individual vaccines. Reporting rates of serious adverse reactions are maintained, in particular when excluding the category of "clinically relevant" cases. The reporting rate for the first dose has remained almost stable since Report#6, just like that of fatal cases (0.7 out of 100,000 doses in July and August) (Fig. 13).

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

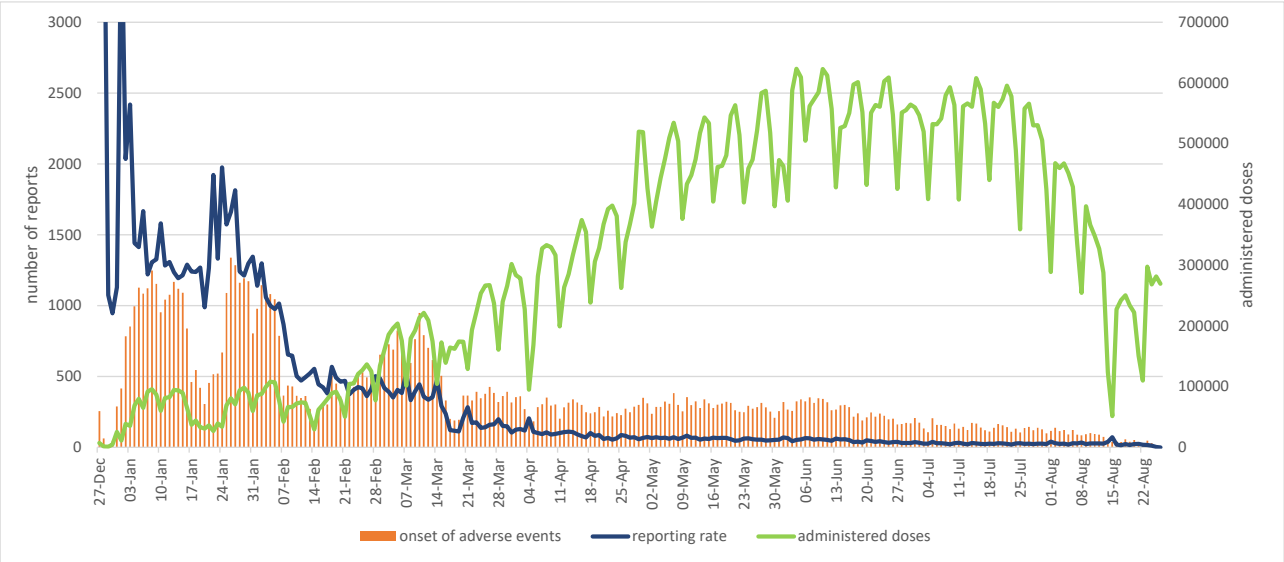


Figure 13 *– Trend in reporting rates by gender, number of doses, severity and fatal events over time*

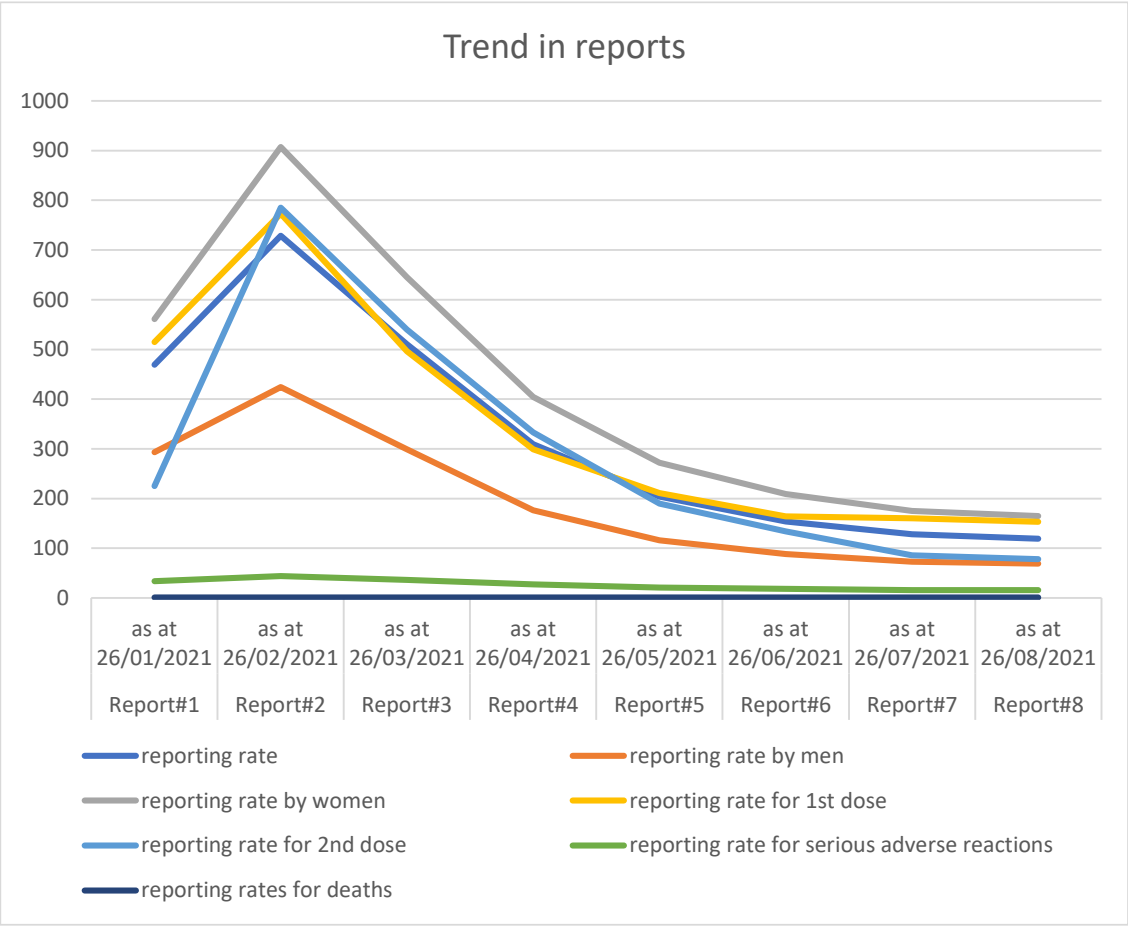


Figure 14 shows the trend by source of reporting; the largest number of reports come from doctors, while reports from pharmacists remain stable. Reports from doctors and other healthcare professionals continue to decrease slowly (from 47% to 39% for doctors and from 25% to 14% for other healthcare professionals). Conversely, reports from patients increase (from 6% to 27%).
The trend in reporting rates by gender has been almost stable since Report#5, after reaching a peak in Report#2, especially for female reporting (Figure 15).

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

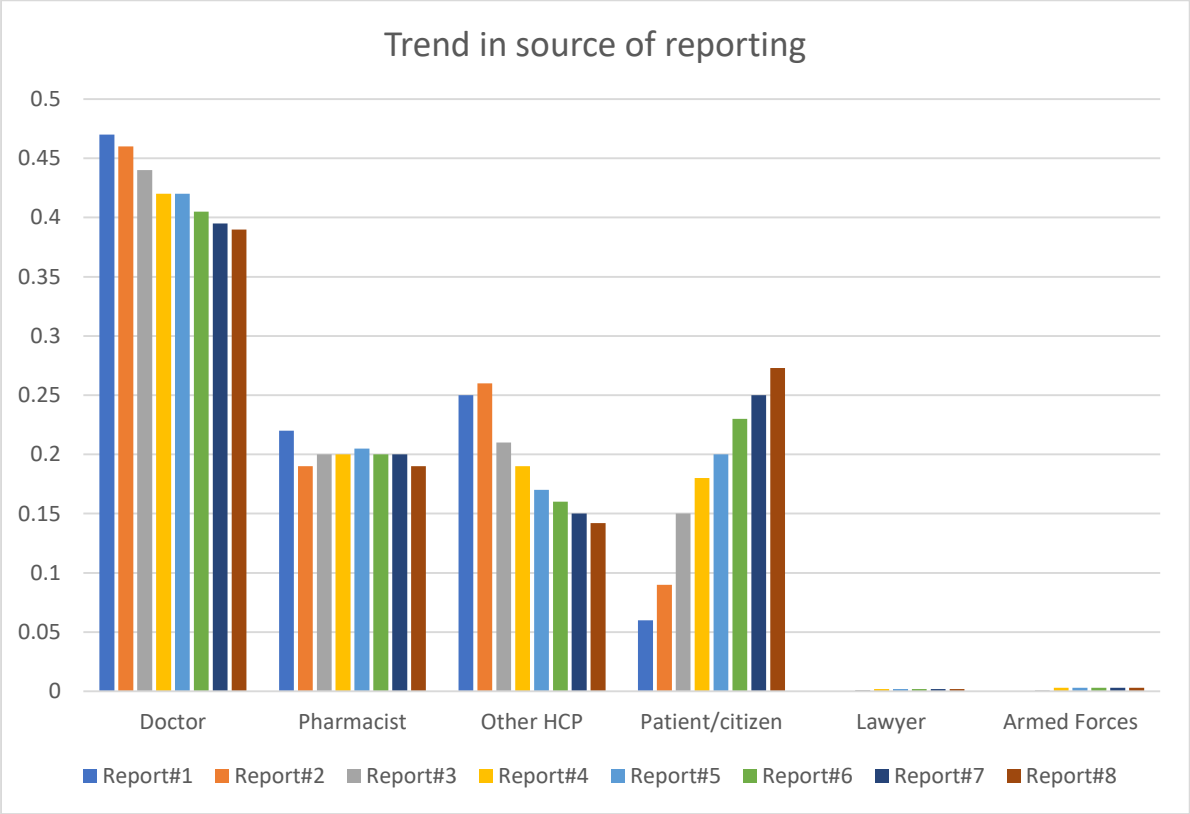
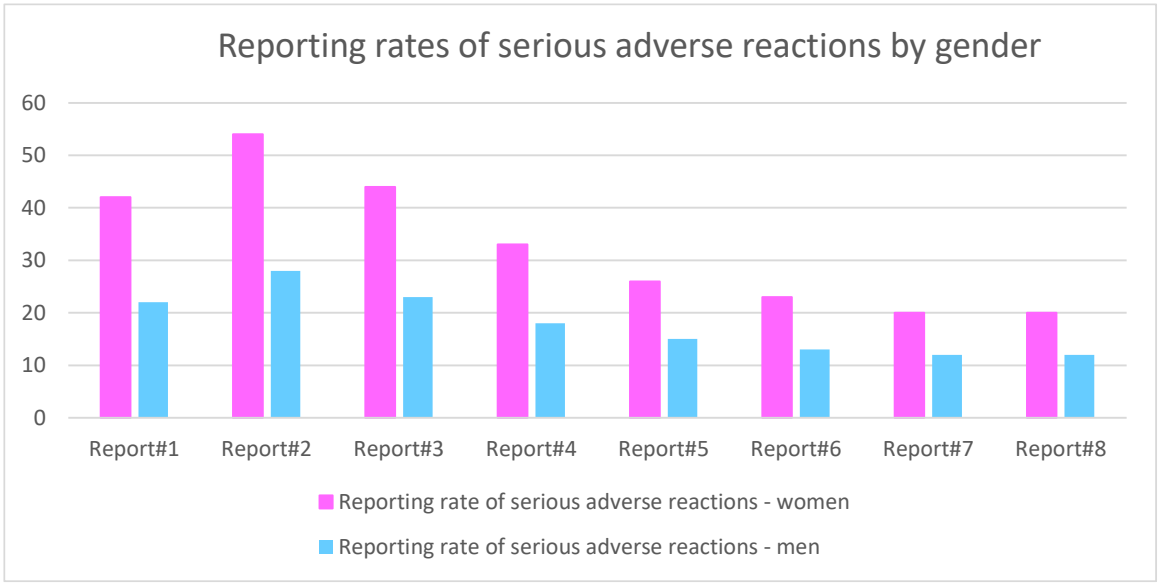


Figure 15 *– Trend in reporting rates of serious adverse reactions by gender*


Reporting rates of serious adverse reactions by gender
60
50
40
30
20
10
0
Report#1
Report#2
Report#3
Report#4
Report#5
Report#6
Report#7
Report#8
Reporting rate of serious adverse reactions - women
Reporting rate of serious adverse reactions - men

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