COVID-19 Vaccine Surveillance Report

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27/12/2020 - 26/05/2021

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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 investigatation.

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

HIGHLIGHTS

As of 26 May 2021, 204 reports were entered for any 100,000 doses administered, regardless of the vaccine and the dose administered

The reports mainly concern the Pfizer/BioNTech Comirnaty vaccine, which has been the most widely used, and only to a lesser extent the Vaxzevria vaccine (former COVID-19 Vaccine AstraZeneca) and the Moderna vaccine, whereas the COVID-19 Janssen vaccine is still little used

The trend of the reports and the related rates have substantially decreased compared to the previous report, thus highlighting a plateau effect, which may be due to the greater knowledge about the vaccine and to the different target population of the vaccination campaign, as well as to a delay in entering the reports

Most reported adverse events are classified as non-serious, which resolve completely and only to a lesser extent are reported as severe, resulting in complete recovery or improvement in most cases

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

The most frequently reported vaccination-related serious adverse events refer to an influenza-like syndrome with severe symptoms, more frequent after the second dose of mRNA vaccines and after the first dose of Vaxzevria

The reporting rate of intracranial and atypical venous thrombosis in subjects vaccinated with Vaxzevria is in line with the European reports (1 case per 100,000 first doses administered, no cases after the second dose), mainly occurring in people under 60 years of age

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

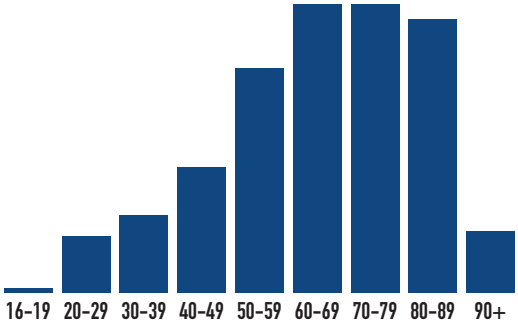
Reference period: 27/12/2020 - 26/05/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

ADMINISTERED DOSES

32.429.611

Comirnaty 68,7%
Moderna 9%
Vaxzevria 20,8%
Janssen 1,5%



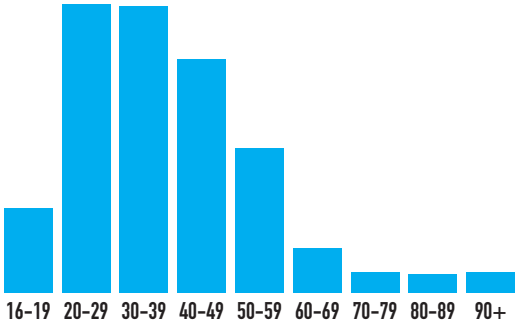
ADMINISTRATIONS BY AGE RANGE

ADMINISTRATIONS PER DOSE	1st dose	2nd dose
	68%	32%

SUSPECTED ADVERSE REACTIONS

66.258

Comirnaty 71,8%
Moderna 3,9%
Vaxzevria 24%
Janssen 0,3%

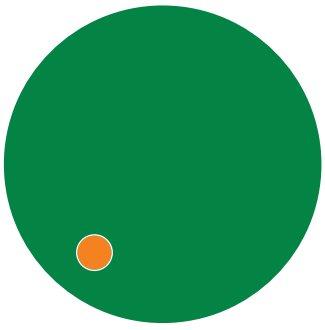


REPORTING RATE BY AGE RANGE

REPORTING RATE PER DOSE	1st dose	2nd dose
	211	189

MORE SAFETY INFORMATION ON VACCINES MAKES IT EASIER TO IDENTIFY RARE OR VERY RARE EVENTS

SUSPECTED ADVERSE REACTIONS SERIOUS/NON-SERIOUS



SERIOUS	NON-SERIOUS
10,4%	89,4%

0.2% OF SUSPECTED ADVERSE REACTIONS ARE NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)
PERIOD UNDER REVIEW: 27/12/2020 - 26/05/2021

During the period considered, **4 vaccines for COVID-19** were authorised and used in Italy, two based on messenger RNA (mRNA) technology and two using a viral vector:

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

As of 26/05/2021, a total of **32,429,611 vaccine doses** were administered, of which 68.7% Comirnaty, 20.8% Vaxzevria, 9% COVID-19 Moderna vaccine and 1.5% COVID-19 Janssen vaccine[2]. The number of suspected adverse reaction reports entered in the RNF on the same date is **66,258**, with a **reporting rate of 204 per 100,000 doses administered**.

As in previous Reports, the distribution of reports by type of vaccine is similar to the distribution of administrations (Comirnaty 71.8%, Vaxzevria 24%, Moderna vaccine 3.9% and Janssen vaccine 0.3%).

The number of reports, the doses administered and the related reporting rates of the different COVID-19 vaccines currently in use are shown in table 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 26/05/2021	Administered doses as of 26/05/2021	Reporting rate (per 100,000 administered doses)	95% Confidence interval
Comirnaty	47,631	22,285,723	***214***	***212-216***
Moderna	2,564	2,901,137	***88***	***85-91***
mRNA active ingredient (unspecified brand)	14	-	-	
Vaxzevria	15,878	6,739,596	***236***	***232-239***
Janssen	171	503,155	***34***	***29-39***
Total	**66,258**	**32,429,611**	***204***	***202-206***

[2] The number of doses administered as of 26/05/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 31/05/2021.

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. Figure 1b shows reports and administrations divided by 1st or 2nd dose. 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*

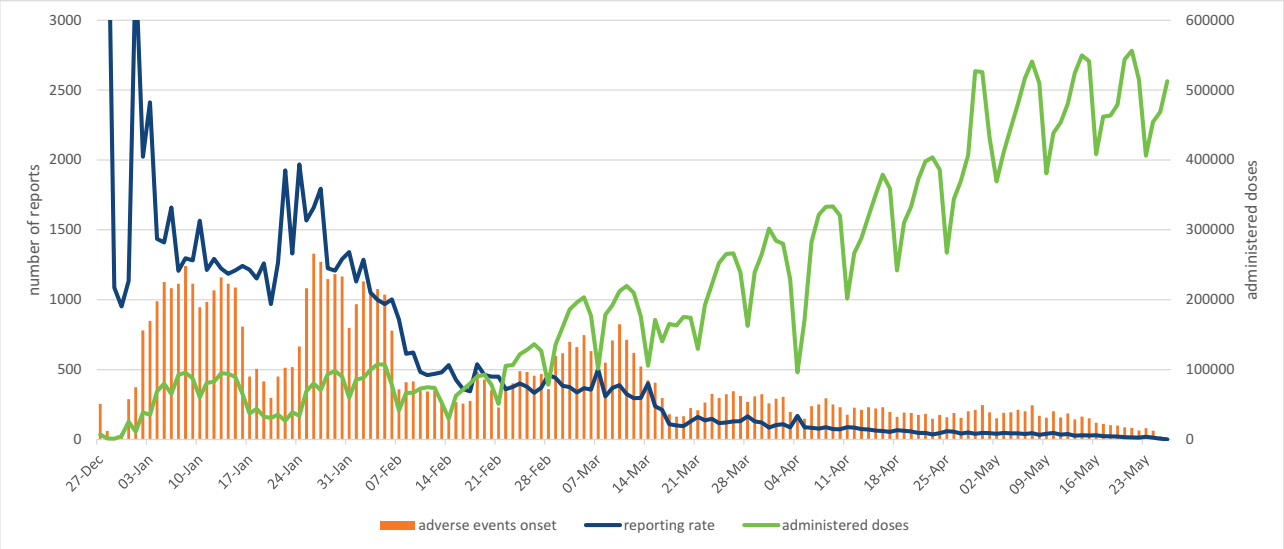
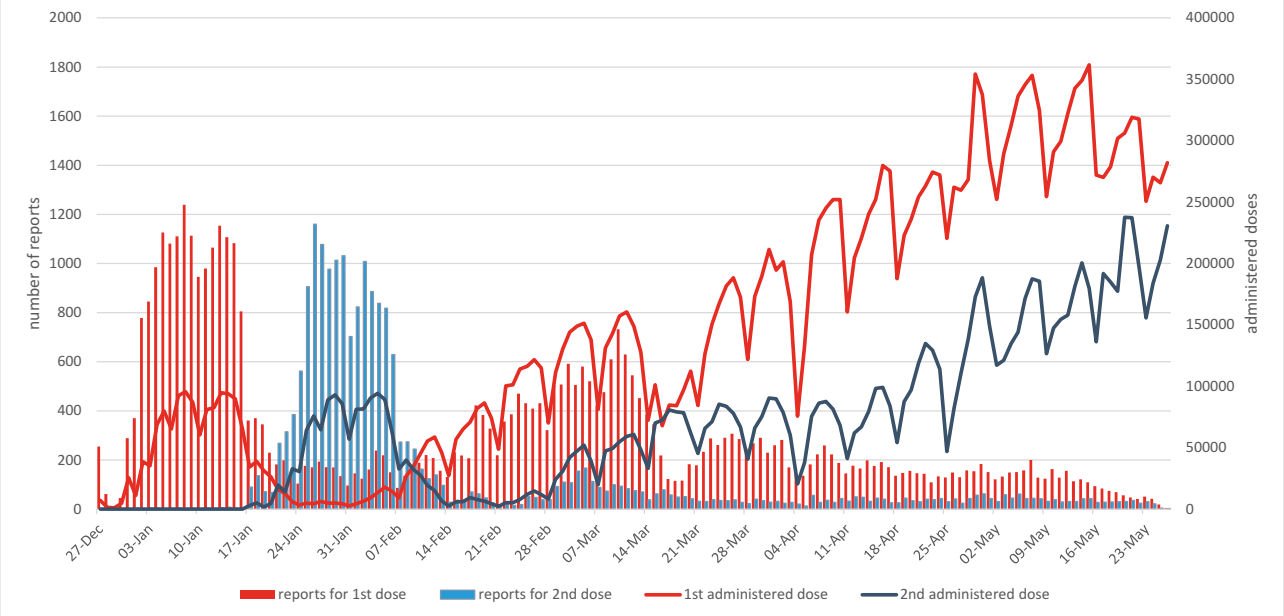


Figure 1b – *Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*

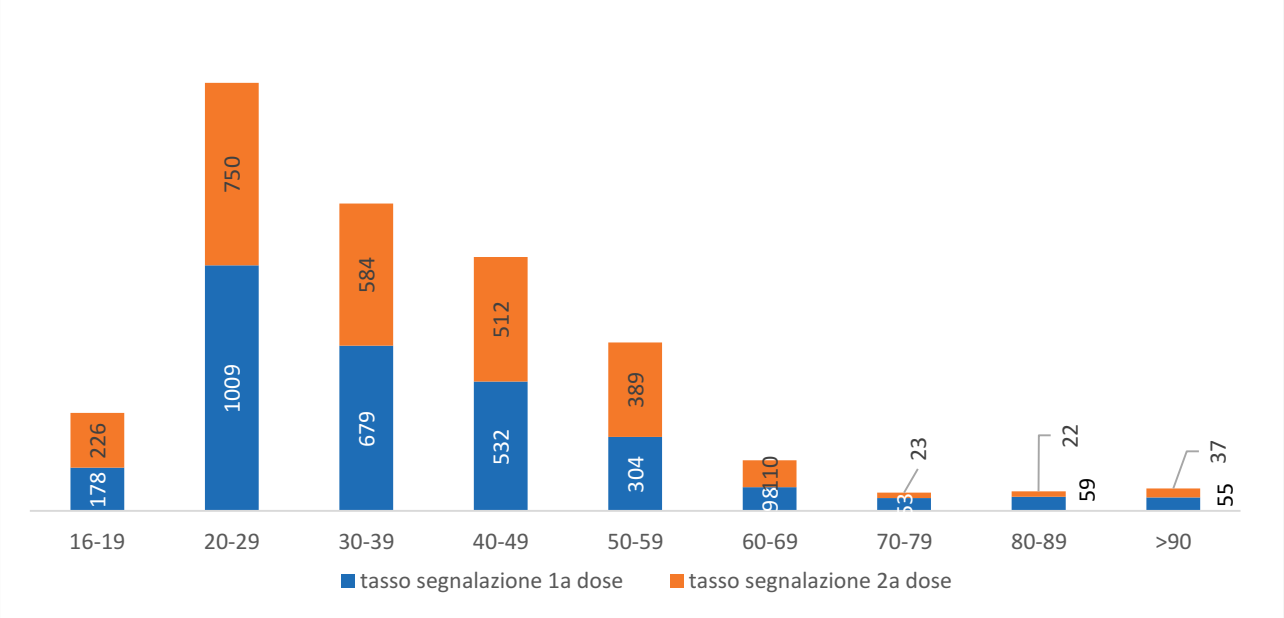


As described in the previous Report, a minor increase in reports (+18%) is confirmed compared to the remarkable increase in the number of administrations (+78%). This “plateau” effect can be observed both in relation to the first and second dose and mainly concerns non-serious, transient and known adverse events, therefore probably attributable to the increased knowledge of safety aspects. This effect is also found in the generalised decrease in reporting rates due to the denominator increase (the administered doses), which is not proportional to the numerator increase (the reports).

Distribution by age, sex and type of reporter

The average age of people sufferring from a suspected adverse event is 48 years (age range 0.1-107 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*

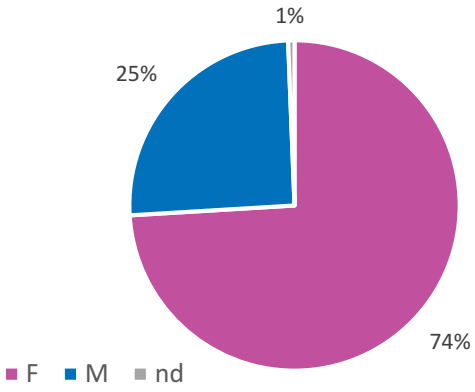


As already observed in the previous Reports, the reporting rate is higher and relatively constant in the younger age groups (up to 60 years), and then decreases in the more advanced age groups, in line with what was reported in pre-authorisation clinical studies. The rates for the 16-19 age group are calculated on a poorly represented population of vaccinated people compared to other age groups and should therefore be considered with caution. No significant differences are observed between the reporting rates by age group in relation to the number of doses.

Overall, 11 reports relate to 9 breastfed babies whose mother had been vaccinated, with age ranging from 20 days to 18 months. In fact, in two of these cases the symptoms (irritability and loss of appetite or crying) have been reported both after the first and after the second dose of the vaccine administered in the nursing mother. Overall, adverse events reported in the breastfed infant are mild and transient, completely recovered or improving as of reporting time.

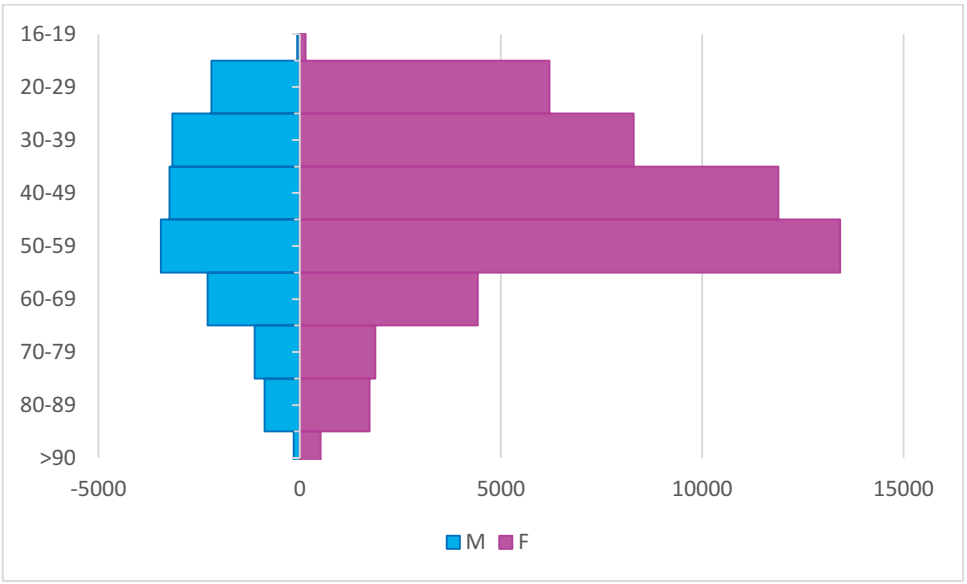
With a 56% exposure of the doses administered in females and 44% in males, 74% of the reports concern women, with a reporting rate of 272/100,000 administered doses, and 25% men, with a reporting rate of 116/100,000 administered doses, regardless of the dose and vaccine administered (sex is not reported 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*



The gender difference can only minimally be attributed to a different exposure to vaccines and needs to be further investigated as to any psycho-social factors (higher predisposition of women to reporting) or biological (different predisposition to adverse reactions), which have already been partially observed[3, 4].

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 20% from patients/citizens. 97% of these reports are spontaneous.

[3] Wen-Han Chang; A review of vaccine effects on women in light of the COVID-19 pandemic; Taiwanese Journal of Obstetrics & Gynecology 59 (2020) 812e820

[4] Patricia Robin McCartney. Sex-Based Vaccine Response in the Context of COVID-19. JOGNN 2020. 49: 405–408.

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

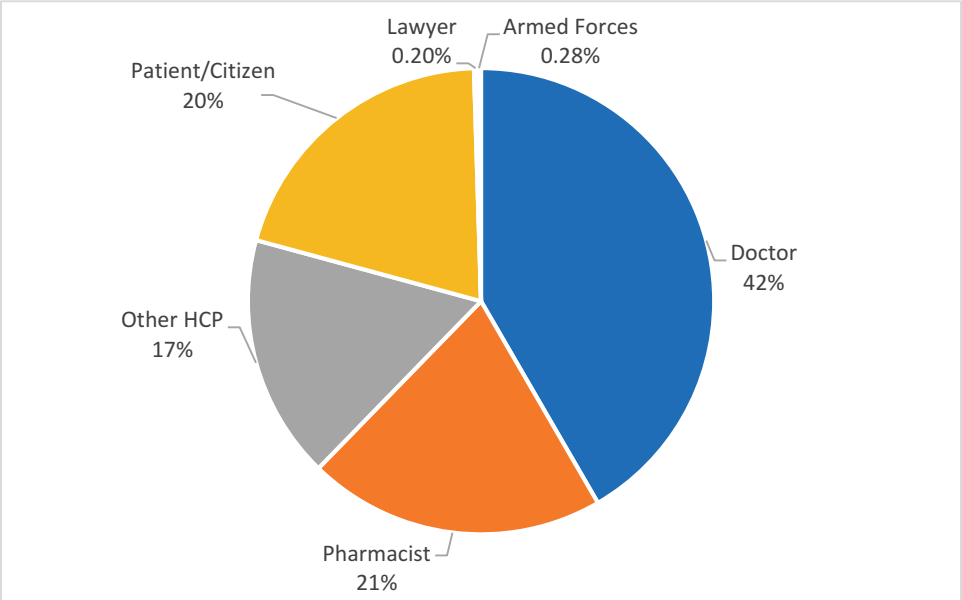


Table 2 shows the report distribution by time of onset from vaccination.

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

ONSET TIME	N° REPORTS	%
0 days	33,261	50.2%
1 day	21,519	32.5%
2-7 days	6,243	9.4%
>7 days	3,164	4.8%
Not definable	2,071	3.1%
Total	***66,258***	***100%***

As previously reported, regardless of the vaccine, the dose and type of event, most reactions (about 83%) occur on the same day as vaccination or on the following day, more rarely beyond the following 48 hours.

Distribution by seriousness and outcome

90% of the reports entered as of 26/05/2021 relate to non-serious events, with a reporting rate equal to 183/100,000 administered doses. The figure is similar to the cumulative rate for all the events because non-serious reports represent the majority.

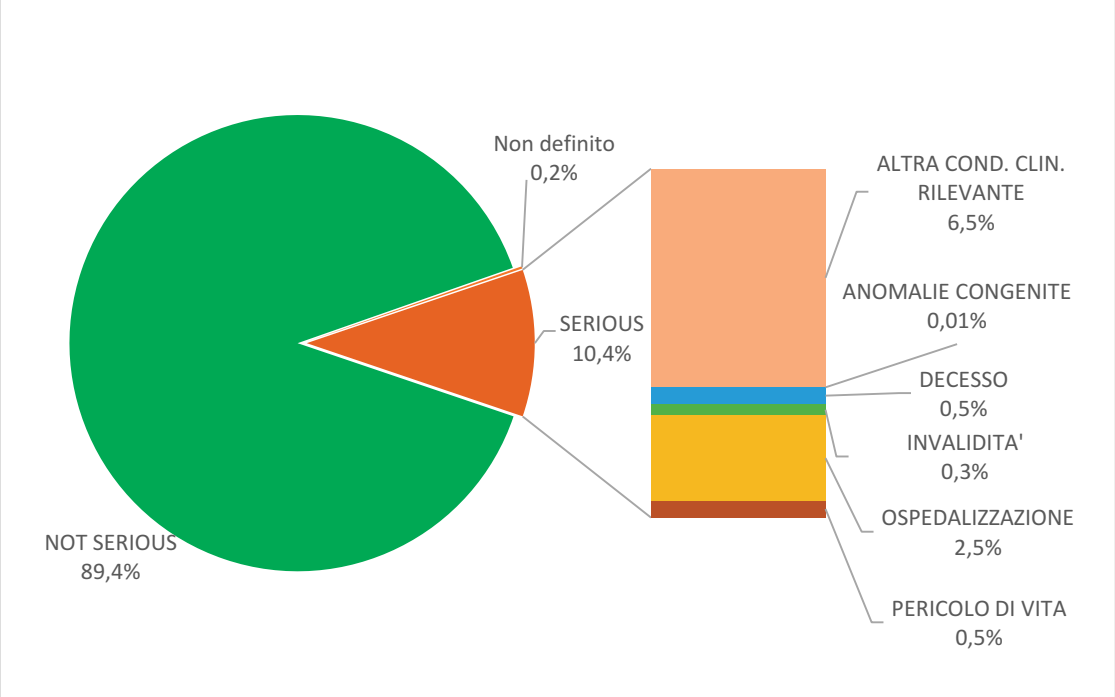
Serious reports are 10,4% of the total, with a rate of 21 serious events per 100,000 administered doses, regardless of the type of vaccine, of the dose administered (1st or 2nd dose) and of the possible causal role of the vaccination. The reporting rates of serious events for each vaccine are 18 (Comirnaty), 13 (Moderna), 36 (Vaxzevria) and 4.6 (Janssen) per 100,000 administered doses. The time distance between vaccine administration and the onset of serious adverse events follows a trend similar to all reports received (see table 2).

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?

In the regulatory field, the reports are classified as serious or non-serious based on 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 (where the acronym IME stands for Important Medical Events). Based on these criteria, it can be considered serious, e.g., a fever ≥ 39°C which may require the administration of a

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



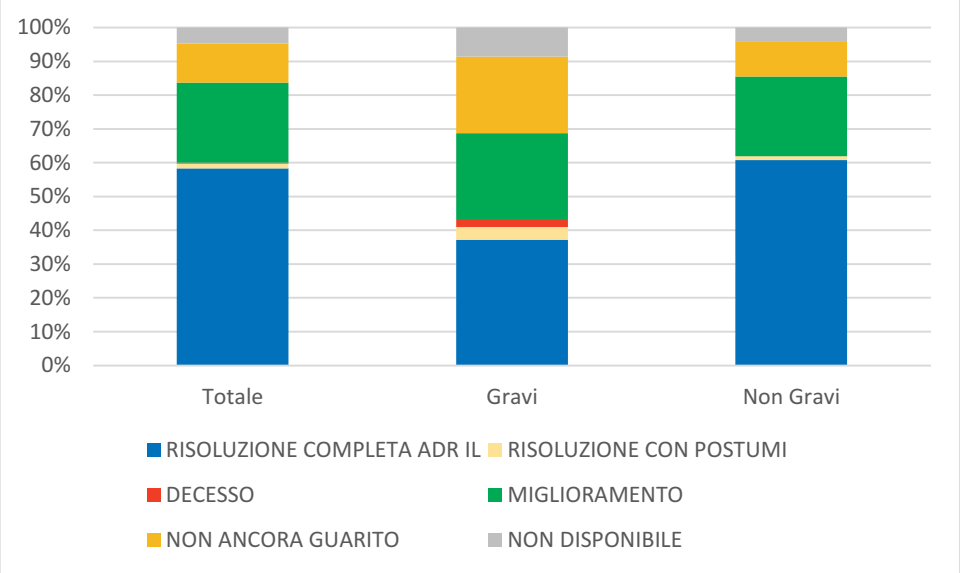
Most serious reports are classified as "other clinically relevant condition", i.e., alerting the subject and/or the reporter without entailing a specific intervention in hospitals.

The distribution by seriousness and outcome of the reports is shown in Figure 7.

About 80% of reports refer to non-serious adverse events with full recovery or improvement already at the time of reporting. 62% of serious reports result in full recovery or improvement and 22% has

not yet recovered. The small number of cases resulting in "recovery with sequelae" refers to subjects undergoing in-depth investigations whose outcome is not yet known.
Please note that the report outcome is continuously being updated, through the request of follow-up information. The cases with outcome "death" are discussed in the specific focus. The distribution by outcome does not show significant differences between the vaccines currently in use.

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



The assessment is currently underway at European level of the causal role of vaccines in serious reports, to determine the probability that a vaccine and a temporally associated event are linked by a causal relationship based on the available evidence.
As of 26/05/2021, the causal link according to the WHO algorithm was included in 74% of reports of serious adverse events (5,087/6,891). Overall, 49% of all serious reports evaluated (2,477/5,087) are related to vaccination, 32% (1,617/5,087) are indeterminate, 17% (877/5,087) are unrelated and 2% (116 / 5,087) unclassifiable.

Distribution by number of doses

In the period considered, 32% 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. No differences in reporting rates were observed between the first and second dose of Comirnaty or Moderna vaccine, in line with the cumulative rate. As for the Vaxzevria vaccine, the reporting rate for the 2nd dose is significantly lower than the 1st dose, probably due to the lower number of second doses of this vaccine administered as of 26/05/2021.

Table 3 *– Report distribution by number of doses*

Vaccine	1st dose reporting rate (per 100,000 administered doses)	95% Confidence interval	2nd dose reporting rate (per 100,000 administered doses)	95% Confidence interval	Cumulative reporting rate (per 100,000 administered doses)	95% Confidence interval
Comirnaty	213	210-215	216	213-219	214	**212-216**
Moderna	95	91-99	74	68-80	88	**85-91**
Vaxzevria	261	257-265	24	20-28	236	**232-239**
Janssen	34	29-39	-	-	34	**29-39**

Distribution by type of event

Graphs 8, 9, 10 and 11 show the types of events reported for the four vaccines used (Comirnaty, Moderna, Vaxzevriaand Janssen), in order of frequency, regardless of the dose administered and the causal link with the vaccination, on the basis of the organ or apparatus concerned, the etiology or scope (System Organ Class or SOC).

How are adverse events classified in reports?

Adverse events following immunisation are entered in the RNF according to internationally codified terminology in a specific dictionary, called MedDRA (Medical Dictionary for Regulatory Activities). In MedDRA, single medical concepts (signs, symptoms, diseases, diagnosis, therapeutic indications, etc.) are reported as preferred terms, subsequently grouped according to equivalence (synonymous terms) and hierarchy relationships. The highest level of organisation is represented by the system organ class (SOC), which groups events by cause (etiology, e.g.: infections and infestations), organ or apparatus involved (site of manifestation, e.g., gastrointestinal disorders) and purpose (e.g., surgical and medical procedures).

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.

Comirnaty vaccine (Pfizer/BioNTech)

Most **suspected adverse events following vaccination with Comirnaty** relate to the system organ class of **General Disorders and Administration Site Conditions** (about 33% of all reported events). The most reported reactions are fever, injection site pain, asthenia/fatigue and general malaise. About 94% of these events are reported as non-serious and 5.4% as serious, mostly resulting in full recovery or improvement.

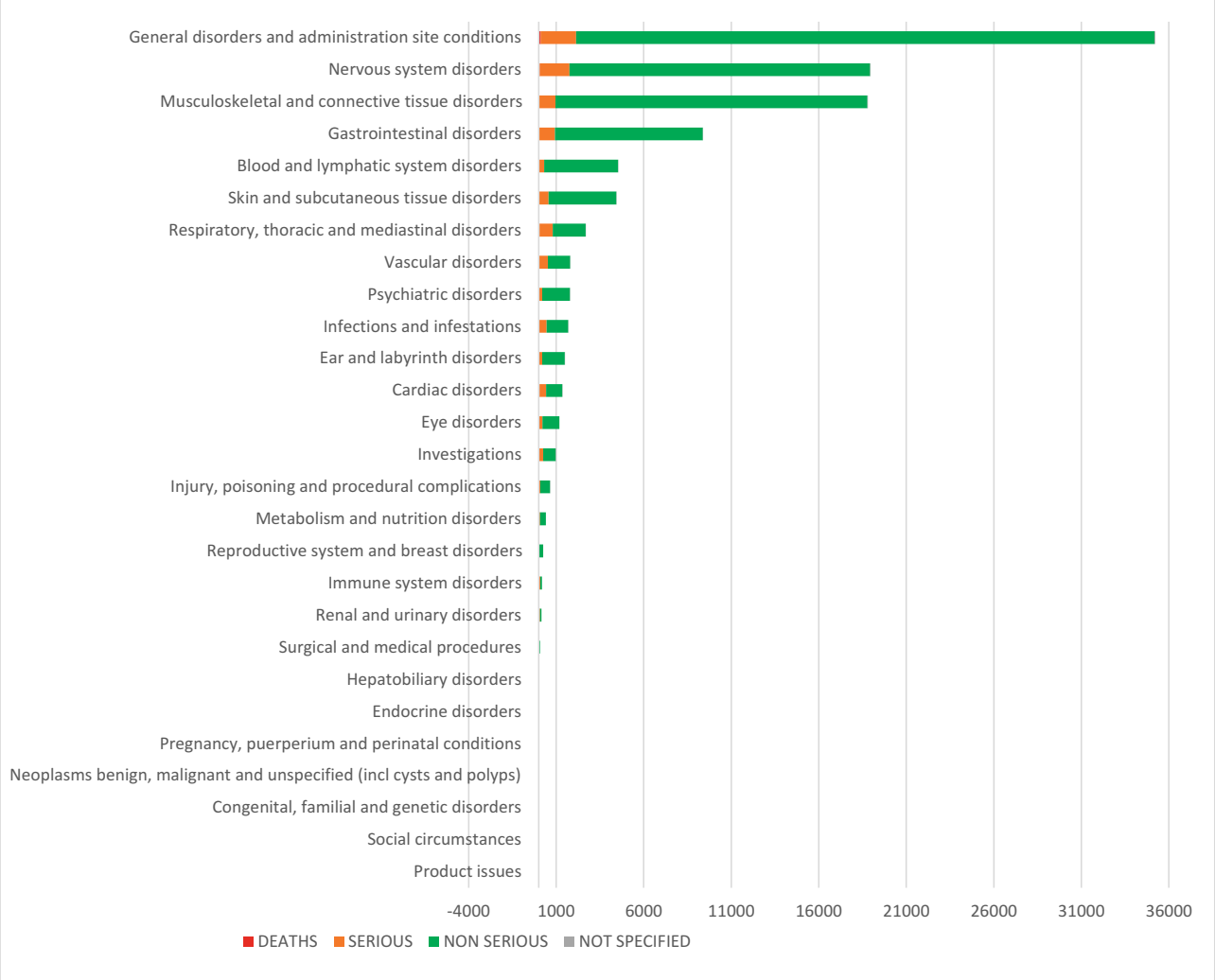
Nervous system disorders follow in order of frequency (about 18% of all reported events), mainly consisting of headache, limb paraesthesia and drowsiness, which are not serious in about 88% of reports and serious in about 11% of cases, followed by **musculoskeletal system and connective tissue disorders** (approximately 17% of all reported events), especially myalgia, arthralgia and musculoskeletal pain (not serious in 94% of cases and serious in 5%).

More rarely, suspected adverse events have been reported which are related to the SOC of **gastrointestinal diseases** have been reported (about 9% of all reported events), more frequently nausea, diarrhea and vomiting (not serious in 90% of cases) and **diseases of the blood and lymphatic system** (about 4% of all reported events), mainly represented by lymphadenopathy (not serious in 92% of cases).

Overall, 8.5% of reports relating to the Comirnaty vaccine were listed as serious. In most cases (about 66%), seriousness is defined as "other clinically relevant condition", while in 22% of cases it depended on hospitalisation or prolonged hospitalisation and in 3% on a condition causing a threat to life.

Regardless of dose number and causation, the most frequent serious adverse events coincide with the distribution of all reactions and are mainly represented by high fever, severe headache, widespread muscle/joint pain and asthenia. Less frequently reported are nausea, lymphadenopathy, paraesthesia, vomiting, diarrhea, dizziness and allergic reactions. Very rarely reported adverse reactions include tachycardia and facial nerve palsy.

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



Comirnaty-related serious adverse events

About 7 reports per 100,000 doses of Comirnaty administered are serious events related to vaccination (6 related serious adverse events per 100,000 first doses administered and 8 related serious adverse events per 100,000 second doses administered). Based on the severity criterion, 82% of these reports were included as "another clinically relevant condition", 14.3% as requiring hospitalisation and 2.2% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 61.5% of cases and improvement in 21.6%.

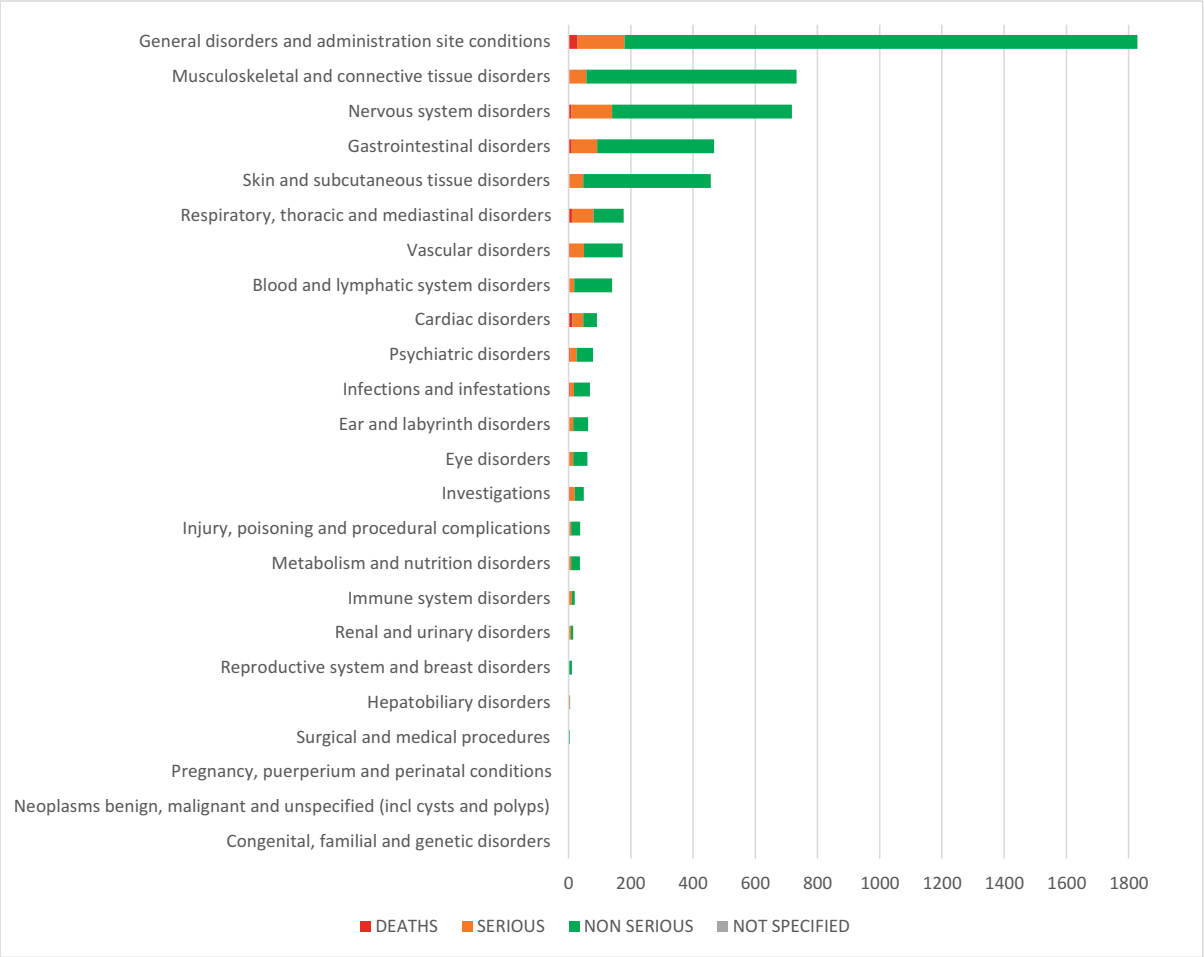
The most commonly reported correlated serious adverse events are hyperpyrexia and headache, with a reporting rate for both reactions of 2 cases per 100,000 administered doses. Joint and muscle pain and anxious reactions to vaccination follow, with a rate of 1.3 cases per 100,000 administered doses. Frequently, hyperpyrexia, headache, joint and muscle pain are associated within an influenza-like syndrome, more often reported as a “serious - other clinically relevant condition" reaction and after the second dose of Comirnaty. Anxious reactions to vaccination include different types of events ranging from anxious state to panic attack, up to pre-lipothymic phenomena and more generally to vagal reactions occurring immediately after vaccination, more often after the 1st dose.

Less frequently, lymphadenopathies are reported as serious adverse events (1 case per 100,000 administered doses). Rarely, facial nerve palsies have been reported, occurring with a frequency of less than 0.5 cases per 100,000 administered doses.

COVID-19 Moderna vaccine

Most of the **suspected adverse events following vaccination with COVID-19 Moderna Vaccine** are related to the SOC of **general diseases and conditions related to the administration site** (approximately 40% of all reported events). The most reported reactions are fever, injection site pain, asthenia/fatigue and general malaise. About 91% of these events are reported as non-serious and 7.5% as serious, in the majority of cases resulting in full recovery or improvement.
In order of frequency, about 35% of all reported events fall within the **musculoskeletal system and connective tissue diseases**, especially myalgia, arthralgia and pain in the vaccinated limb (not serious in 92% of cases and serious in 7%). These are followed by **pathologies of the nervous system** (about 32% of all reported events), mainly consisting of headache, limb paraesthesia and dizziness, which are not serious in about 77% of reports and serious in about 21% of cases, and by **gastrointestinal disorders** (about 25% of all reported events), most frequently nausea, vomiting and diarrhea (not serious in 80% of cases).
About 15% of reports to COVID-19 Moderna vaccine have been entered as serious. Seriousness is defined as "other clinically relevant condition" in most cases (approximately 47%), while hospitalisation/prolonged hospitalisation is reported in 29% of cases and threat to life in 6%. Regardless of dose number and causality, the most frequent serious adverse events coincide with the distribution of all reactions, predominantly high fever, severe asthenia and widespread muscle/joint pain.

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



Serious Adverse Events Related to COVID-19 Moderna vaccine

Approximately 3 reports per 100,000 administered doses of COVID-19 Moderna Vaccine are serious events related to vaccination (2.6 related serious adverse events per 100,000 first doses administered and 2.8 related serious adverse events per 100,000 second doses administered). Based on the seriousness criterion, 80% of these reports were included as "other clinically relevant condition", 13% as requiring hospitalisation and 3.6% as life threatening. Full recovery of the adverse reaction is reported as an outcome in 52% 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 2 cases per 100,000 administered doses. These are followed by anxious reactions to vaccination, with a rate of 1.5 cases per 100,000 administered doses. Frequently, hyperpyrexia, joint and muscle pain are associated with each other and more often reported as a “serious - other clinically relevant condition" reaction. Also for this vaccine, anxious reactions to vaccination include different types of events ranging from anxious state to panic attack, up to pre-lipothymic phenomena and more generally to vagal reactions occurring immediately after vaccination, more often after the 1st dose.

The less frequently reported related serious adverse events include headache and lymphadenopathy (1 case per 100,000 administered doses).

Vaxzevria Vaccine (AstraZeneca)

Most **suspected adverse events following vaccination with Vaxzevria** relate to the SOC of **general disorders and administration site conditions** (approximately 39% of all reported events). The most frequently reported reactions are fever, fatigue/asthenia, chills and pain at the injection site. About 87% of these events are reported as non-serious and 12% as serious, in most cases with full recovery or improvement.

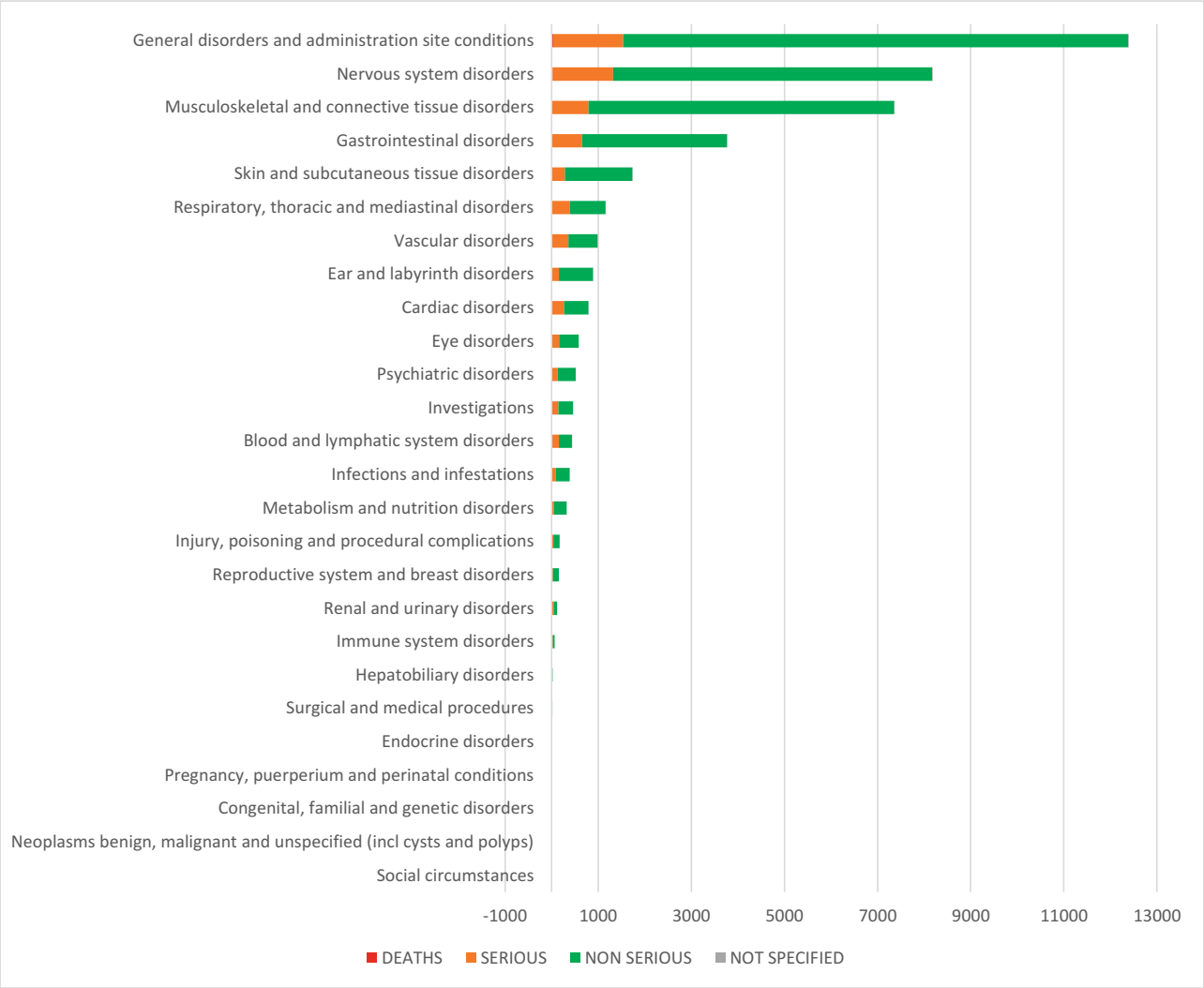
These are followed in order of frequency by **nervous system disorders** (about 38% of all reported events), mainly headache and dizziness, which are not serious in about 81% of the reports and serious in about 18% of cases and by **musculoskeletal system and connective tissue disorders** (about 16% of all reported events), especially myalgia, arthralgia and muscle stiffness (not serious in 88% of cases and serious in 11%).

An overall 15% of reports of the Vaxzevria vaccine have been entered as serious. Seriousness is defined as "other clinically relevant condition" in most cases (about 60%), while in 27% of cases it was due to hospitalisation or prolonged hospitalisation and in 7% to a life-threatening condition.

The distribution of the most frequent suspected serious adverse reactions by type of event coincide with the distribution of all reactions, regardless of dose number and causality. Mostly reported have been severe high fever, profuse asthenia, severe headache and dizziness. Less frequently reported are diffuse muscle/joint pains, paraesthesia and allergic-type reactions.

Serious adverse events in Vaxzevria also include cases of **cerebral venous thrombosis and/or venous thrombosis in atypical location**, with a reporting rate of approximately 1 event per 100,000 administered doses, currently observed exclusively after administration of the 1st dose and mainly under 60 years old. This rare adverse event is constantly monitored at EU level and has resulted in a change in the product information (both the Summary of Product Characteristics and the Package Leaflet).

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



Serious adverse events related to Vaxzevria

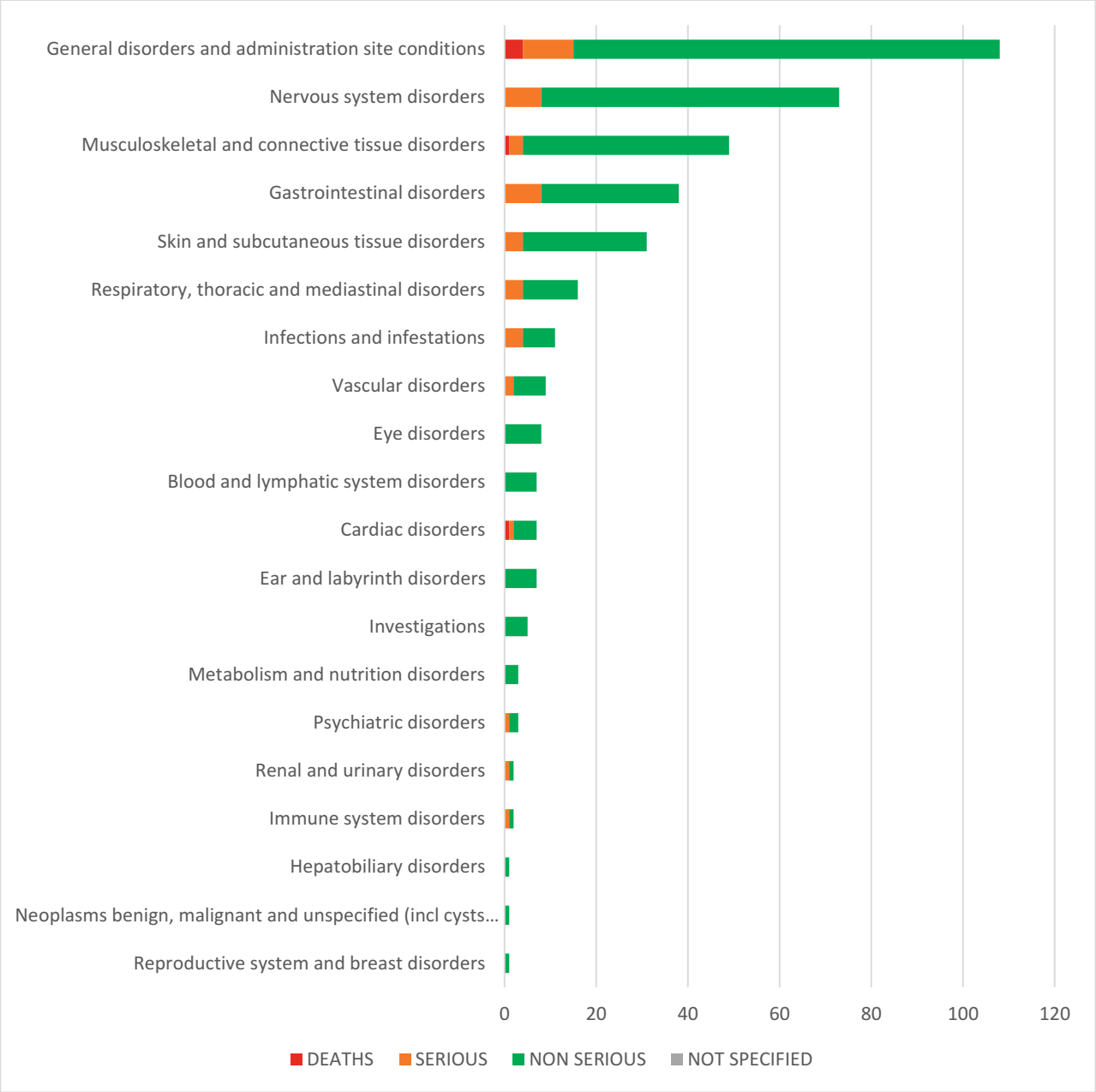
Approximately 13 reports in every 100,000 administered doses of Vaxzevria are serious - related to vaccination. The difference in this value between 1st and 2nd dose is not indicative at the moment, due to the limited number of second doses administered as of 26/05/2021. Based on the seriousness criterion, 75% of these reports have been entered as "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 43.6% of these reports and improvement in 32.3%.
The most commonly reported related serious adverse event is hyperpyrexia, with a reporting rate of 9 cases per 100,000 administered doses, followed by headache (5 cases per 100,000 administered doses) and joint and muscle pain (3 cases per 100,000 administered doses). More rarely reported have been anxious reactions to vaccination, mainly with lipothymia and vagal reactions with syncope (approximately 1 case per 100,000 administered doses). Also for this vaccine, hyperpyrexia, headache, joint and muscle pain are frequently associated within an influenza-like syndrome, more often reported as a "serious - other clinically relevant condition" reaction and after the 1st dose.

COVID-19 Janssen vaccine

Most of the **suspected adverse events following vaccination with COVID-19 Janssen vaccine** are related to the SOC of **general diseases and conditions related to the administration site** (approximately 34% of all reported events), mainly fever, fatigue/asthenia, chills and pain at the injection site. About 86% of these events are reported as not serious and 12% as serious, in most cases with full recovery or improvement.

These are followed in order of frequency by **nervous system disorders** (about 18% of all reported events), mainly headache, which are not serious in about 85% of reports and serious in about 14% of cases, and by **musculoskeletal system and connective tissue disorders** (about 12.5% of all reported events), especially myalgia and arthralgia (not serious in 93% of cases and severe in 5%).

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



About 13% of reports of COVID-19 Janssen vaccine were entered as serious and defined as "other clinically relevant condition" in most cases (approximately 56%) while in 21% of cases it was due to hospitalisation or prolonged hospitalization and in 4% to a life-threatening condition.
The distribution of the most frequent suspected serious adverse reactions by type of event coincide with the distribution of all reactions, regardless of dose number and causality. Mostly, high fever, asthenia, severe headache and dizziness have been reported as serious reactions. Diffuse muscle/joint pains, paraesthesia and allergic-type reactions are less frequently reported.
Out of the **total serious reports**, only 3 were **related** to vaccination, all referred to an influenza-like reaction, with a reporting rate of 0.5 cases per 100,000 administered doses. This data is currently poorly reliable due to the small number of doses administered so far.

Fatal cases after COVID-19 vaccination

With the collaboration of the Regional Pharmacovigilance Centers of Lombardy and Tuscany.

In Italy, as of 26 May 2021, 328 reports with a "death" outcome have been entered with a reporting rate 1/100,000 doses administered, regardless of causality.
Based on the type of vaccine, 213 deaths were reported after Comirnaty, 58 after Covid-19 Vaccine Moderna, 53 after Vaxzevria and 4 dopo after COVID-19 Vaccine Janssen (table 4).
53.4% of cases concern women, 46% men while 0.6% (2 cards) do not report this data; the average age is 78.6 years (range 26-104 years). The time between vaccine administration and death varies from two hours up to a maximum of 55 days. In 211 cases death is recorded after the first dose, in 98 after the second (where specified in the report form).
There are no cases of death as a result of anaphylactic shock or major allergic reactions, while the correlation with cardiovascular causes (eg hypovolemic and cardiogenic shock) is frequent in patients with pathologies of this apparatus.

Table 4 *– Distribution of death reports by type of vaccine*

VACCINE	Fatal cases	Rates per 100,000 administered doses
Comirnaty	213	0.96
Moderna	58	1.99
Vaxzevria	53	0.79
Janssen	4	0.79
Total	**328**	**1.01**

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. Rates are decreasing for the three vaccines already in use since the previous analysis, as well as the overall rate.
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, which make the evaluation of the cause of death and the causal relationship complex. At the time of writing, 68.6% of the forms (225 out of 328) have a causality assessment with the algorithm used in the vaccine surveillance (WHO Algorithm), according to which 57.8% of cases is **not related**, 36.9% **undetermined** and 3.6% **unclassifiable** due to lack of information necessary for the application of the algorithm.
In four cases (1.8% of the total), causality is **related**. Three cases have already been described in previous reports. The fourth case refers to a 58-year-old man (suffering from hypercholesterolemia and previously undergoing thyroidectomy), who died 17 days after the first dose of the vaccine, due to thrombosis of the splanchnic veins with thrombocytopenia, splenomegaly, haemoperitoneum and consequent splanchnic ischemia. The case was interpreted as suspected atypical thrombosis associated with thrombocytopenia in a patient vaccinated with Vaxzevria and evaluated as correlable, pending further information from the autopsy examination.
Here is briefly an update of the international databases:

- the "Weekly Summary of Yellow Card reporting" of the United Kingdom Regulatory Agency (MHRA - Medicines and Healthcare products Regulatory Agency), updated on 19/05/2021, reports a total of 1,213 reports with a fatal outcome on a total of approximately 59 million doses

administered Comirnaty, Vaxzevria and Moderna vaccines, with a reporting rate of approximately 2 cases per 100,000 doses administered[5];

- the Vaccine Adverse Event Reporting System (VAERS) in the United States reports as of 24 May 2021, 4,863 death reports among people who have received at least one vaccine dose out of a total of more than 285 million doses of COVID-19 vaccines (reporting rate 1.7/100,000 doses administered)[6];
- the latest periodic report from Swissmedic dated 21/05/2021, prepared in collaboration with the regional pharmacovigilance centers, reports 84 reports with fatal outcome out of a total of 2269 notifications of suspected adverse reactions and 3.7 million doses of the Comirnaty and Covid-19 Vaccine Moderna vaccines (currently used in Switzerland), with a rate of 2.3 reports per 100,000 doses administered[7].

Even in these reports, despite the temporal association with vaccination, the cases with a fatal outcome mainly involved frail people with significant comorbidities and there are no indications confirming a causal link with the vaccine, since the causes of death reported (infections, cardiovascular/pulmonary events) occur in relation to the pathologies reported in the medical history and regardless of vaccination.

The evaluation of the literature and the communications of the other regulatory agencies do not reveal situations that are particularly different from those observed in Italy.

[5]https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

[6]https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html#:~:text=Over%20285%20million%20doses%20of,received%20a%20COVID%2D19%20vaccine

[7]https://www.swissmedic.ch/swissmedic/it/home/news/coronavirus-covid-19/nebenwirkungen-covid-19-impfungen-update-6.html

Comparison analysis between expected deaths and deaths observed after first and second dose of COVID-19 vaccines

With the collaboration of the Economic Strategy of Pharmaceutical Products Department of AIFA.

Methodology

The analysis between observed and expected deaths was conducted starting from spontaneous reports with fatal outcome (**observed deaths**) in the 14 days following the first or second administration of COVID-19 vaccines in the population over 30 years and inserted in the RNF until 26 May 2021. Reports with missing data for date of administration, date of reaction, sex and age and a single report outside the age group considered were excluded.

For the calculation of the **expected deaths**, the probability of death of the population over 30 years old, reported in the ISTAT mortality tables of 2019 specific for sex and five-year age groups, was applied to the vaccinated population as of 26 May 2021[8]. Since the ISTAT tables relate to the probability of death at 5 years, these values have been re-proportioned to obtain the probability of death at 1 and 2 weeks, assuming a constant probability over 5 years. The deaths observed within the first and second week after administration of the first or second doses were related to the expected deaths, calculating the Standardized Mortality Ratios (SMR) and the relative 95% confidence intervals (95% CI) all within the age groups 30-69 and 70+ years, both in the total population and in the population stratified by sex. At the end of this analysis, there are 3 possibilities:

What is the observed/expected analysis?

The observed/expected analysis relating to a suspected adverse event, temporally related to a medicine or a vaccine, compares the number of cases that are "observed" after administration of the product with the number of cases that are “expected” in the population, regardless of the use of the medicine or vaccine. This type of analysis is important to understand if there is a potential statistical association between a medicine and an event. When the number of cases observed after the administration of a medicine is lower than the number of cases that would have occurred independently of it, the association between the medicine and the event is unlikely and likely coincident. On the contrary, when the administration of a medicine determines a number of cases higher than those that would be expected independently of it, the association is potentially causal. It is important to emphasise that this type of analysis is indicative of the statistical "strength" of the temporal correlation between an event and the administration of a medicine and does not provide direct information on the causal link.

1. the 95% confidence interval (95% CI) contains the numerical value 1: the frequencies of observed and expected deaths are not significantly different;
2. the lower end of the 95% confidence interval (95% CI) is greater than 1: the observed deaths are significantly greater than the expected deaths;
3. the upper end of the 95% confidence interval (95% CI) is less than 1: the observed deaths are significantly lower than the expected deaths.

[8] http://demo.istat.it/tvm2016/index.php?lingua=ita

Data analysis

A total of 277 reports with fatal outcome events were included in the analysis as observed deaths, including 213 following the first dose and 64 following the second dose. Overall, as of 26/05/2021, 21,069,268 people over the age of 30 have received the first dose and 9,952,833 the second dose of a COVID-19 vaccine, regardless of the type of vaccine.

The Standardized Mortality Ratios (SMRs) and the related 95% confidence intervals (95% CI) are shown in Tables 5 and 6. The number of deaths observed in the vaccinated population within the first and second week after the first or second dose are significantly lower than the expected deaths (the upper end of the 95% confidence interval (95% CI) is much less than 1). This result is also confirmed by stratifying by sex, age group and type of vaccine (data not shown).

Table 5 – *Observed-Expected Analysis (as of 26/05/2021) relating to vaccinated with first dose, considering the total number of vaccinated people or stratified by gender*

age group	total	deaths expected in 1 week	deaths observed in 1 week	SMR (95% CI) * 1 week	deaths expected in 2 weeks	deaths observed in 2 weeks	SMR (95% CI)* 2 week
30-69	12,079,539	2,034	35	0.017 (0.011 - 0.023)	4,069	51	0.012 (0.009 - 0.016)
70+	8,989,729	13,511	137	0.010 (0.008 - 0.011)	27,022	162	0.006 (0.005 - 0.006)

age group	men	deaths expected in 1 week	deaths observed in 1 week	SMR (95% CI) * 1 week	deaths expected in 2 weeks	deaths observed in 2 weeks	SMR (95% CI) * 2 week
30-69	5,507,755	1,227	27	0.022 (0.014 - 0.032)	2,453	33	0.013 (0.009 - 0.019)
70+	3,968,595	6,338	62	0.010 (0.007 - 0.012)	12,676	70	0.005 (0.004 - 0.006)

age group	women	deaths expected in 1 week	deaths observed in 1 week	SMR (95% CI) * 1 week	deaths expected in 2 weeks	deaths observed in 2 weeks	SMR (95% CI)* 2 week
30-69	6,571,784	773	8	0.010 (0.004 - 0.020)	1,545	18	0.011 (0.006 - 0.018)
70+	5,021,134	7,077	75	0.010 (0.008 - 0.013)	14,153	92	0.006 (0.005 - 0.007)

*Fisher Exact Test. https://www.openepi.com/SMR/SMR.htm

Table 6 – *Observed-Expected Analysis (as of 26/05/2021) relating to vaccinated with second dose, considering the total number of vaccinated people or stratified by gender*

age group	total	deaths expected in 1 week	deaths observed in 1 week	SMR (95% CI) * 1 week	deaths expected in 2 weeks	deaths observed in 2 weeks	SMR (95% CI)* 2 week
30-69	4,487,144	660	7	0.010 (0.004 - 0.021)	1,319	10	0.007 (0.003 - 0.013)
70+	5,465,689	10,127	50	0.005 (0.004 - 0.006)	20,255	54	0.003 (0.002 - 0.003)

age group	men	deaths expected in 1 week	deaths observed in 1 week	SMR (95% CI) * 1 week	deaths expected in 2 weeks	Deaths observed in 2 weeks	SMR (95% CI) * 2 week
30-69	2,020,636	395	2	0.005 (0.0006 - 0.018)	790	4	0.005 (0.001 - 0.013)
70+	2,316,556	4,513	22	0.005 (0.003 - 0.007)	9,026	24	0.003 (0.002 - 0.004)

age group	women	deaths expected in 1 week	deaths observed in 1 week	SMR (95% CI) * 1 week	deaths expected in 2 weeks	deaths observed in 2 weeks	SMR (95% CI)* 2 week
30-69	2,466,508	252	5	0.020 (0.006 - 0.046)	505	6	0.011 (0.004 - 0.026)
70+	3,149,133	5,540	28	0.005 (0.003 - 0.007)	11,080	30	0.003 (0.002 - 0.004)

*Fisher Exact Test. https://www.openepi.com/SMR/SMR.htm

For a correct interpretation of these results, please note that:

a. pharmacovigilance databases are not clinical registers but collections of spontaneous reports of events in which a reporter believes that there may be a suspicion of a relationship to be investigated between vaccination and adverse event;
b. ISTAT 2019 data does not take into account the increase in mortality from COVID-19 disease occurred in 2020, which affects the risk assessment, underestimating the expected events.

Anaphylaxis

With the collaboration of the Regional Pharmacovigilance Centers and the Prevention Departments of Veneto and Lombardy.

Vaccine anaphylaxis is a rare but potentially life-threatening reaction. Its frequency after vaccinations is very low (about one case per million doses)[9]. Covid-19 vaccines, particularly mRNA vaccines, have been associated with an increased risk of anaphylaxis. Spontaneous reporting data in the United States reported a reporting rate of 4.7 cases of anaphylaxis per million doses administered for Comirnaty vaccine and 2.5 cases per million doses administered for Moderna vaccine. A more recent prospective surveillance study suggested an even higher incidence[10, 11].
For these vaccines, the main suspected allergen is polyethylene glycol (PEG), present in the lipids surrounding the mRNA but also in many medicines and other commonly used products. In the case of viral vector vaccines, which do not contain PEG, a possible triggering agent for anaphylaxis could be the excipient polysorbate 80.
This paragraph is an update of the situation with the cases reported as of 26 May 2021, compared to what is reported in the third Report. Also in this case, for a correct evaluation, the reports were evaluated and classified according to the case definition formulated by the Brighton Collaboration, which combines clinical criteria to establish the level of diagnostic certainty. The Brighton Collaboration classification has 5 levels. Level 1 represents the highest level of diagnostic certainty for a reported case of anaphylaxis; levels 2 and 3 represent progressively lower levels. Level 4 defines an anaphylaxis report which does not fit within the Brighton definition; finally, level 5 defines a case that is not explicitly reported as anaphylaxis nor falls within the definition of the Brighton[12].

Data analysis

All the reports entered since the start of the vaccination campaign that contained terms specifically linked to the Standardized MedDRA Query (SMQ) of the MedDRA dictionary "Anaphylactic reactions" were extracted from the National Pharmacovigilance Network. The SMQ defines both a list of terms specifically related to anaphylactic reactions and a combination of symptoms that could define an anaphylactic reaction.

What is a Standardized MedDRA Query (SMQ) from the MedDRA dictionary?

The Standardized MedDRA Query is a tool developed to facilitate the querying of pharmacovigilance databases and retrieval of data through a pre-determined and validated grouping of synonymous and non-synonymous terms that are compatible with one or more signs and symptoms of a given condition. These terms are grouped after extensive review, testing, analysis, and expert discussion.

As of 26 May 2021, 651 cases have been selected using this methodology, which have been independently evaluated by three experts in vaccinovigilance and allergology and classified according to the definition of the Brighton Collaboration. Only reports with

[9] McNeil MM et al. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018;141 (2):463-47.
[10] Shimabukuro TT et al. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA 2021. doi: 10.1001/jama.2021.196
[11] Blumenthal KG et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA. 2021 Apr 20;325(15):1562-1565.
[12] Rüggeberg JU et al, Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5675-84.

a diagnostic certainty level classification from 1 to 3 were included in the analysis, excluding only the cards with an onset beyond 24 hours after administration.

In total, 125 cases were defined as anaphylaxis, of which 97 associated with the Comirnaty vaccine, 19 with the Vaxzevria vaccine, 8 with the Moderna vaccine and 1 case with the Janssen vaccine. Almost all the reports were fully documented with follow-up carried out by the Pharmacovigilance Managers of the structures involved. This allowed for an accurate selection of cases based on the Brighton criteria and reaffirms the high quality of the information contained in the reports of the Italian spontaneous reporting system, already reported in the literature[13].

Table 7 lists the characteristics of the cases (reporting of the Janssen vaccine was excluded, as this is a single notification).

Table 7 *– Characteristics of reports of anaphylaxis after COVID-19 vaccine entered in the PhV system as of 26/05/2021*

	COMIRNATY	MODERNA	VAXZEVRIA	TOTAL
Number of reports	97	8	19	124
	47 (20-91)	**57 (47-85)**	**49 (27-77)**	
First Doses administered	13,507,773	1,984,158	6,009,238	21,501,169
Second Doses administered	8,783,270	919,051	731,353	10,433,674
Total doses administered	22,291,043	2,903,209	6,740,591	31,934,843
First dose reports	77 (79%)	5 (63%)	18 (95%)	100 (81%)
Second dose reports	20 (11%)	3 (37%)	1 (5%)	24 (19%)
Rate per million of first doses	5.7	2.5	3.0	4.7
Rate per million of second doses	2.3	3.3	1.4	2.3
Total rate per million doses	4.4	2.8	2.8	3.9
Women (%)	89 (92%)	8 (100%)	17 (89%)	114 (92%)
Number of doses for women	12,467,576	1,629,324	3,685,541	17,782,441
Number of doses for men	9,823,467	1,273,885	3,055,050	14,152,402
Reports per million doses - women	7.1	4.9	4.6	6.4
Reports per million doses - men	0.8	-	0.7	0.7
Hypotension	23 (24%)	1 (13%)	3 (16%)	27 (22%)
Adrenaline administered	25 (26%)	1 (13%)	5 (26%)	31 (25%)
Symptoms onset <15 minutes	35 (36%)	3 (38%)	8 (42%)	46 (37%)
symptoms onset <60 minutes	49 (51%)	5 (63)	10 (53%)	64 (52%)

[13] Bergvall T et al. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Saf 2014; 37)1=: 6577.

previous food or drug allergies	46 (47%)	5 (63%)	7 (37%)	58 (47%)
Classification according to Brighton Collaboration:				
Level 1	52 (54%)	3 (38%)	11 (58%)	66 (54%)
Level 2	34 (35%)	4 (50%)	7(37%)	45 (36%)
Level 3	11 (11%)	1 (12%)	1 (5%)	13 (10%)

The overall reporting rate has decreased compared to the previous data and is equal to 3.9 cases of anaphylaxis per million doses administered, with a higher value for Comirnaty (4.4 cases per million) than for Vaxzevria (2.8) and Moderna (2.8). It should be emphasised that the reporting rate for the Vaxzevria viral vector vaccine is not very far from the mRNA vaccines, with a higher value than that reported in the literature for vaccines in general.

The analysis of the reports revealed a short interval between the administration of the vaccine and the onset of symptoms. In 40% of cases, symptoms started within the first 15 minutes after vaccination. Almost all reports refer to female subjects, despite the presence of a similar distribution of doses in the two sexes, with a reporting rate per million doses almost 10 times higher in females than in males. As already noted in the third Report, a high percentage of cases (about 50%) involve people with a history of allergy to food, inhalants, drugs or other vaccines.

The reporting rate of these events after the second dose is lower than after the first dose and this difference is somewhat unexpected. A sensitization with the first dose, in fact, could favor the onset of more serious allergic events at the second exposure. A possible explanation for the difference observed could be represented by greater caution in administering the second dose to subjects with allergic reactions to the first dose, modifying the method of administration (eg in a protected environment) or suspending vaccination in these subjects. About 10 reports of anaphylaxis, however, relate to the administration of the second dose in people who had experienced an allergic reaction to the first dose of the vaccine. This data recalls the importance of a thorough pre-vaccination history and surveillance of subjects at risk of allergic reactions.

Adverse events related to sense organ dysfunction after Covid-19 vaccination

With the collaboration of the Regional Pharmacovigilance Centers of Liguria, Emilia Romagna and Valle d'Aosta.

Eye disorders

As of 26/05/2021, a total of 952 suspected adverse events concerning eye diseases were reported for all vaccines, representing 1.4% of all reports in the National Pharmacovigilance Network for COVID-19 vaccines. The reporting rate is 2.9 events per 100,000 vaccine doses administered, regardless of vaccine type and causation.
Table 8 shows the distribution by type of vaccine with relative reporting rate and by dose number (1st or 2nd dose). The value for the Janssen vaccine depends on the short period of use of the vaccine and the low number of doses currently administered.

Table 8 *– Number of reports relating to eye disorders, divided by vaccine and dose number*

	eye disorders			reporting rate (per 100,000 doses)
	first dose	*second dose*	total	
COMIRNATY	387	223	610	2.7
VAXZEVRIA	302	3	305	4.5
MODERNA	28	6	34	1.2
JANSSEN	3	0	3	0.6
Total	720	232	952	2.9

77.1% of the events were recorded as not serious and 22.9% as serious. The distribution by type of vaccine according to the severity criterion and the relative reporting rate of serious adverse events are shown in Table 9.

Table 9 *– Distribution of reports relating to eye disorders by severity and type of vaccine*

	COMIRNATY	VAXZEVRIA	MODERNA	JANSSEN	Total
NOT SERIOUS	492	217	22	3	734
SERIOUS	118	88	12	0	218
Total	610	305	34	3	952
% serious on the total	19.3%	28.9%	35.3%	0.0%	22.9%
serious adverse event reporting rate (per 100,000 doses)	0.36	0.27	0.04	-	0.67

At the time of extraction, 68% of reports report complete resolution of the reaction or improvement as a result, regardless of the dose of the vaccination cycle and the severity attributed to the reaction, with the following data by type of vaccine: Comirnaty 71%, Vaxzevria 68%, Moderna 62%.
The distribution of the most frequently reported adverse events affecting the visual apparatus, divided by type of reaction and by vaccine, regardless of causation is shown in table 10.

Table 10 *– Distribution of reports relating to eye disorders by type of reaction and vaccine*

	total	Comirnaty	rates per 100,000 doses	Vaxzevria	rates per 100,000 doses	Moderna	rate per 100,000 doses	Janssen	rate per 100,000 doses
Eye pain	136	77	0.35	56	0.83	3	0.1	-	-
Photophobia	129	96	0.43	30	0.45	3	0.1	-	-
Visual disturbance NAS	85	35	0.16	46	0.68	3	0.1	1	0.2
Lacrimation	67	54	0.24	12	0.18	1	0.03	-	-
Diplopia	66	47	0.21	17	0.25	2	0.07	-	-
Eyelid edema	53	42	0.19	10	0.15	1	0.03	-	-
Diminished vision	36	25	0.11	7	0.1	4	0.14	-	-
Impaired vision	31	20	0.09	11	0.16	-	-	-	-
Eye redness	26	20	0.09	5	0.07	1	0.03	-	-

The most reported adverse event is eye pain, followed by photophobia, visual disturbances not otherwise specified and lacrimation. The higher number of cases was observed after administration of the Comirnaty vaccine, probably related to the higher exposure.
Among serious adverse reactions, the most reported adverse event is diplopia (33), frequently associated with other neurological symptoms, followed by eyelid edema (17), mostly associated with other signs and symptoms of hypersensitivity. Rarely, some cases of retinal vascular thrombosis (arterial or venous, 12) have also been reported. These are in the phase of investigation and follow-up for the purpose of assessing the causal link.

Hearing disturbances and dizziness

As of 26 May 2021, in the RNF there are 2,249 reports relating to the **first dose** of COVID-19 vaccine with ADR falling within the SOC "hearing disorders and dizziness" (of which 323 serious, 1922 non-serious and 4 undefined) and 770 relating to **second dose** (of which 96 serious, 645 non-serious and 1 undefined).
As for SOC, severity and type of vaccine present in the report, the data are reported in table 11.

Table 11 *– Reports divided by Vaccine, dose number and severity*

Vaccine	Dose	SERIOUS	NON SERIOUS	Undefined
Comirnaty	1	142	1008	2
Comirnaty	2	96	645	1
Vaxzevria	1	169	860	2
Vaxzevria	2	3	7	/
Moderna	1	12	47	/
Moderna	2	4	14	/
Janssen	1 (single dose)	/	7	/

Regardless of severity and causation, the distribution of adverse events for “ear and labyrinth” SOC is shown in Table 12.

Table 12 *– Distribution of "ear and labyrinth" SOC adverse events*

Vaccine	"ear and labyrinth" SOC
Comirnaty	1942
Vaxzevria	1089
Moderna	80
Janssen	7
Total	3118

Adverse events by type of reaction and by vaccine, regardless of severity and causation, are shown in table 13.

Table 13 *– Distribution by type of reaction and vaccine of adverse reactions affecting the ear and labyrinth*

	Comirnaty	Rate per 100.000 doses	Vaxzevria	Rate per 100.000 doses	Moderna	Rate per 100.000 doses	Janssen	Rate per 100.000 doses
Vertigo	916	4.11	533	7.91	46	1.59	2	0.40
Dizziness	582	2.61	293	4.35	22	0.79	1	0.20
Dizziness	135	0.61	112	1.66	3	0.10	2	0.40
Otalgia	45	0.20	14	0.21	2	0.07	/	/
Tinnitus	43	0.19	26	0.39	/	/	1	0.20
Dizzy syndrome	39	0.17	14	0.21	/	/	/	/
Ringing in the ears	31	0.14	21	0.31	/	/	1	0.21

Table 14 shows the distribution of serious adverse reactions related to ear and labyrinth disorders with the related reporting rates. There were no reports of this type for the Janssen vaccine during the period under review.

Table 14 *– Distribution by type of vaccine of serious adverse reactions affecting the ear and labyrinth*

	Comirnaty	Rates per 100.000 doses	Vaxzevria	Rates per 100.000 doses	Moderna	Rates per 100.000 doses
Vertigo	93	0.42	90	1.34	11	0.38
Dizziness	71	0.32	44	0.65	3	0.10
Dizziness	15	0.07	8	0.12	/	/
Hypoacusis	12	0.05	8	0.12	2	0.07
Otalgia	10	0.07	5	0.07	/	/
Tinnitus	9	0.04	6	0.09	/	/
Ringing in the ears	31	0.14	6	0.09	/	/
Buzzing in the ears	29	0.13	6	0.09	/	/

The most frequently reported adverse events affecting the ear and labyrinth are related to the synonymous terms "vertigo", "dizziness" and "dizziness". Most of the reports that report these events are spontaneous and refer to subjective disorders, for which it is difficult to establish the real relevance and trace the exact nature of the disorder. 64% of serious adverse reactions affecting the ear and labyrinth report complete resolution of the event or improvement as a result.

Disorders of taste and smell

Taste and smell disturbances are unwanted effects, usually not serious, associated with various medicines, including antibiotics, analgesics, antidepressants and chemotherapy drugs. These events are part of the disorders of the nervous system and, to date, the mechanisms of their onset are not fully known.

Anosmia (loss of smell) and ageusia (loss of taste) are very frequently reported symptoms in association with Sars-CoV-2 infection, the pathogenesis of which could be due to the interaction of the virus with the ACE2 receptor and/or with sialic acid receptors that would interfere with the activity of non-neuronal cells of the oral and nasal mucosa, whose dysfunction would impact on receptor and nerve functions[14].

For this reason, anosmia and ageusia have been selected among the Adverse Events of Special Interest (AESI) for COVID-19[15] vaccines, for which it is necessary to carry out monitoring and in-depth analysis. Among the criteria for the selection of these AESIs there is the known association to immunization events in general or to the use of technological platforms for the generation of vaccines. It is also necessary to monitor events that may be peculiar to the clinical course of natural Sars-CoV-2 infection or complications of the infection. It is possible that adverse events may occur after vaccination with an immunopathogenic mechanism similar to that of natural infection and it is in this category of neurological AESIs that taste and smell disorders fall.

The SmPC of the four currently authorised COVID-19 vaccines does not mention taste and smell disorders[16], nor is there evidence in the literature referring to these types of events after vaccination.

Nonetheless, adverse effects on taste and smell have been reported during post-marketing surveillance. In Eudravigilance the most frequent of these is *dysgeusia* which, between Comirnaty and Vaxzevria, counts 2,736 cases out of 447,914 reports collected[17].

Data analysis

A total of 650 reports were included in the RNF as of 26 May 2021 (478 after the first dose and 172 after the second) which reported a total of 751 adverse events attributable to taste and smell disorders, 13.8% serious. with a reporting rate of 2.3 adverse events per 100,000 doses administered.

[14] Vaira LA, Salzano G, Deiana G et al. ENT Today, doi: 10.1002/lary.28692. Anosmia and ageusia: common findings in COVID19 patients. Otolaryngological manifestations in COVID-19.
[15] https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf
[16] SmPC Comirnaty, Vaxzevria, Moderna and Janssen.
Banca Dati Farmaci AIFA https://www.aifa.gov.it/trova-farmaco (accessed on 1 June 2021).
[17] Adrreports: http://www.adrreports.eu/en/search_subst.html# (data updated to 29/05/2021)

The distribution by vaccine type of adverse events reported, with evidence of the reporting rate and frequency of serious events is shown in Table 15.

Table 15 *– Distribution of adverse events related to taste and smell by type of vaccine with relative rate of reporting e frequency*

	Number of events	***Reporting rate (cases per 100,000 doses)***	***Severe AEFI frequency (%)***
Comirnaty	601	2.7	12.8%
Vaxzevria	130	1.9	19.2%
Moderna	15	0.5	13.3%
Janssen	5	1.0	0.0%
Total	*751*	*2.3*	*13.8%*

Overall, considering all vaccines and serious and non-serious cases, the most frequently reported event is the *metallic taste*, followed by *dysgeusia* and *bitter taste*.
Table 16 shows the distribution of serious adverse events by type of vaccine, excluding the Janssen vaccine due to the small number of cases.

Table 16 *– Distribution of serious adverse events affecting taste and smell by type of vaccine*

AEFI	***Comirnaty***	***Vaxzevria***	***Moderna***
Metallic taste	115	12	1
Dysgeusia	98	17	4
Bitter taste	80	14	3
Ageusia	73	13	1
Anosmia	67	11	1
Alteration of taste	54	17	1

In most of the reports entered as serious, the severity criterion is mainly determined by other adverse events reported together with those related to taste and smell, since the severity of the case is currently attributed by the reporter to the adverse event deemed most serious. In some cases, moreover, the onset of taste and smell disorders is part of a more complex syndromic picture. For example, in 10 cases, infection with Sars-CoV-2, which is known to be associated with these symptoms, was reported at the same time. In about 67% of serious adverse events affecting taste and smell, the outcome at the time of reporting is complete resolution or improvement.

General considerations on data

The time trend of the main parameters analysed in the different reports published so far is summarised in table 17.

Table 17 *– Summary data of Report#1-Report#5*

	Report#1	Report#2	Report#3	Report#4	Report#5
	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
administered doses	1,564,090	4,118,277	9,068,349	18,148,394	32,429,611
reporting of adverse events	7,337	30,015	46,237	56,110	66,258
reporting rate	469	729	510	309	204
reporting rate for men	293	424	299	176	116
reporting rate for women	561	907	645	404	272
reporting rate for first dose	515	773	496	299	211
reporting rate for second dose	225	785	540	333	190
reporting rate of serious adverse reactions	34	44	36	27	21
reporting rate of serious adverse reactions for men	22	28	23	18	15
reporting rate of serious adverse reactions for women	42	54	44	33	26
reporting rate of serious adverse reactions with no “clinically relevant” cases	8.9	8.1	8.5	8.8	7.9
reporting rate of deaths	0.8	0.97	1.1	1.23	1.0
Source of reporting					
Doctor	47%	46%	44%	42%	42%
Pharmacist	22%	19%	20%	20%	20.5%
Other healthcare professional	25%	26%	21%	19%	17%
Patient/Citizen	6%	9%	15%	18%	20%
Lawyer	0%	0%	0.12%	0.20%	0.2%
Armed Forces	0%	0%	0.07%	0.30%	0.3%

Comirnaty					
reporting rate	471	769	535	328	214
reporting rate for first dose	517	756	525	315	212
reporting rate for second dose	278	790	549	348	216
reporting rate of serious adverse reactions	na	45	33	24	18
Moderna vaccine					
reporting rate	277	333	227	129	88
reporting rate for first dose	277	335	216	132	95
reporting rate for second dose	-	322	264	121	73
reporting rate of serious adverse reactions	na	26	22	18	13
Vaxzevria					
reporting rate	-	326	477	309	236
reporting rate for first dose	-	326	477	307	261
reporting rate for second dose	-	-	-	-	24
reporting rate of serious adverse reactions	-	31	50	39	36
Janssen vaccine					
reporting rate	-	-	-	-	34
reporting rate of serious adverse reactions	-	-	-	-	5

As observed in the previous report, the trend in the reporting rate for all vaccines shows a peak in the second month of observation, and then decreases in the two subsequent months (Figure 12). Overall, rates by type of vaccine and for the first and second dose continue to decrease, while rates of severe and fatal reactions remain stable (Figure 13).

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

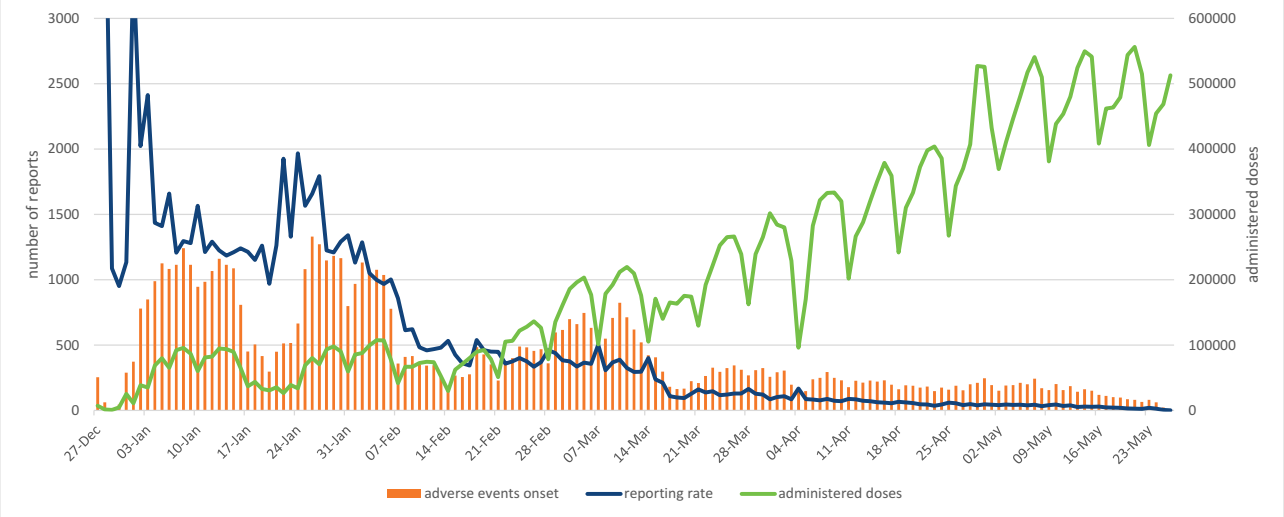
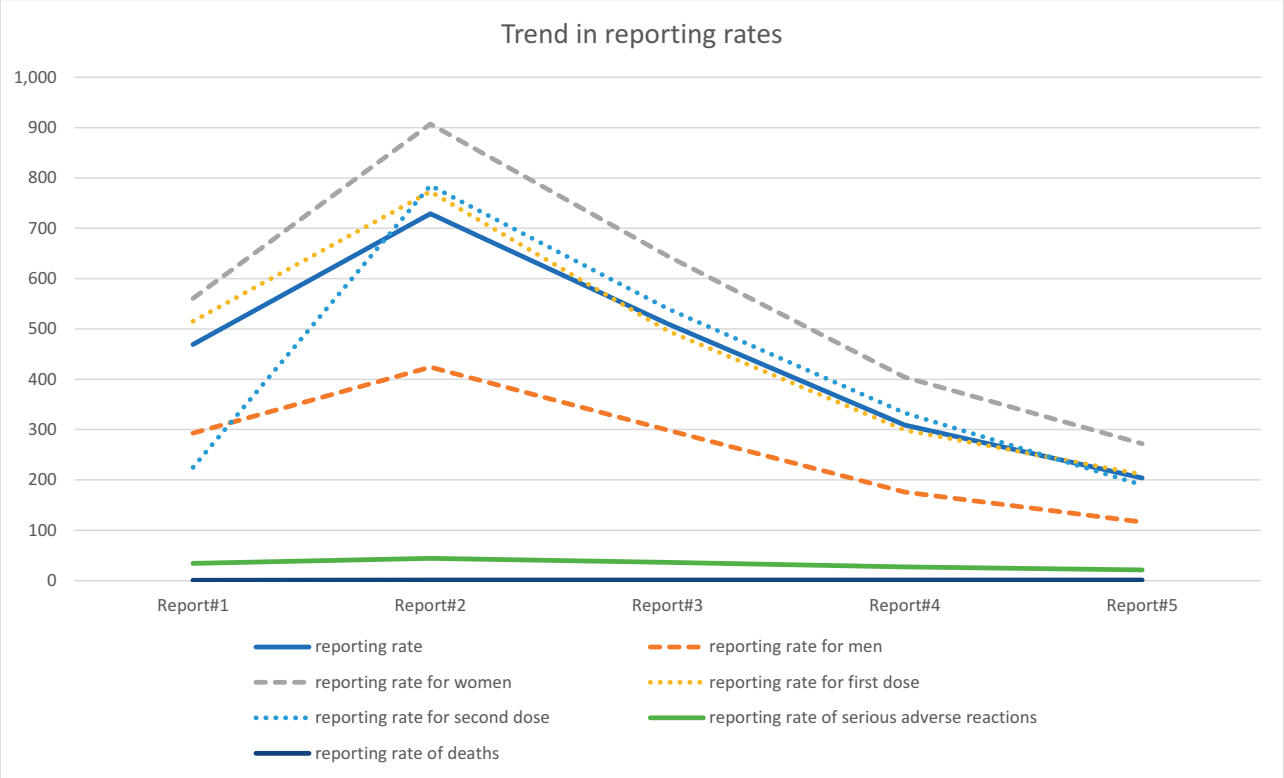
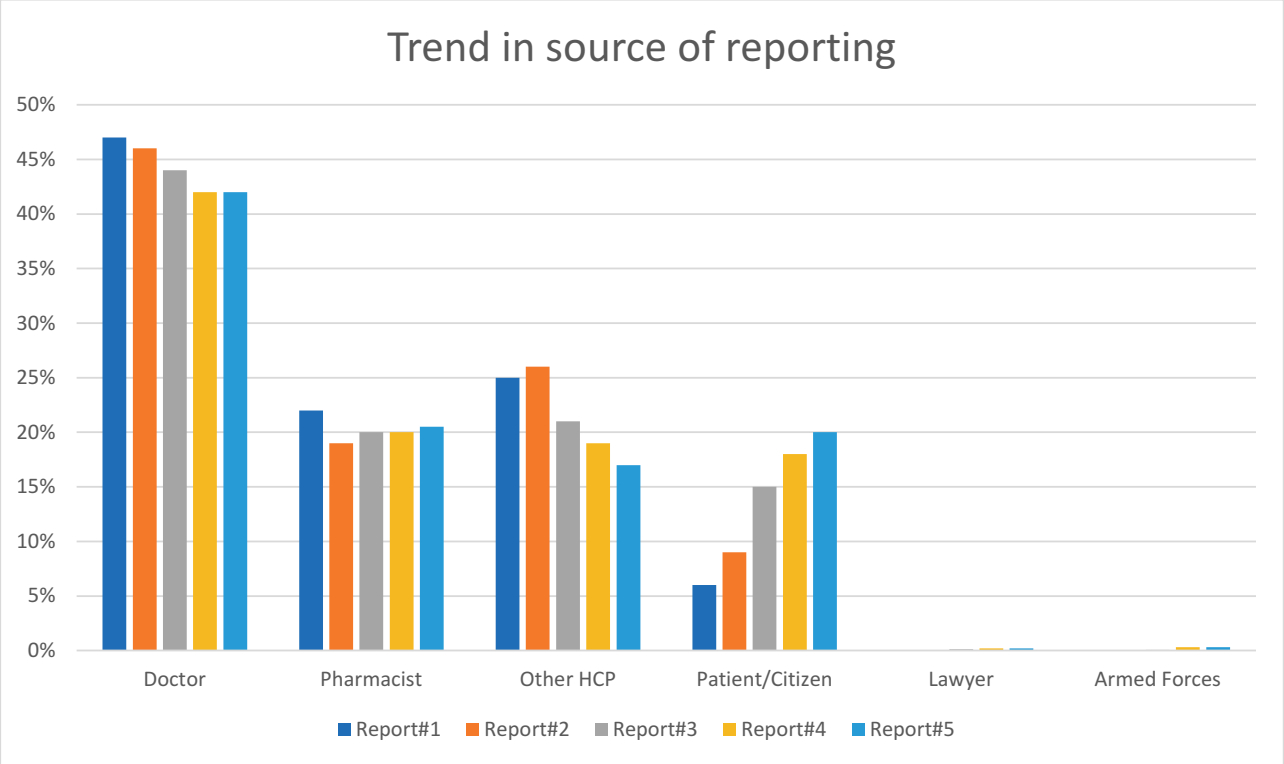


Figure 13 *– Trend in reporting rates by gender, number of doses, severity and fatal events over time*



The highest number of reports comes from doctors (range 47% — 42%). In general terms, reports from doctors and pharmacists are stable, while the number of reports from other healthcare professionals has registered a decrease (down from 25% to 17%). The number of reports by patients has increased from 6% to 20% (Figure 14).

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



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