COVID-19 Vaccine Surveillance Report

1

27/12/2020 - 26/01/2021

Signals Management Office
Pharmacovigilance Office
Post Marketing Surveillance Department

in cooperation with:

International Affairs Department

editing, layout & graphic design:

Press and Communication Office

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.

Our country has 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, 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 READING DATA

This report describes the reports of reactions that have been observed after administration of the vaccine. This does not mean that these 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 got 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**.

HIGHLIGHTS

In the first month of the vaccination campaign, 469 reports were entered for every 100,000 doses administered, regardless of the vaccine and dose administered.

The reports mainly concern the first dose of the Pfizer/BioNTech Comirnaty vaccine (99%), which was the most widely used, and only to a lesser extent the Moderna vaccine (1%).

The suspected adverse reactions reported are in line with the information already present in the summary of product characteristics of the two vaccines.

Mostly non-serious adverse events were reported that resolve completely (92%).

For both vaccines the most reported adverse events are injection site pain, fever, asthenia/fatigue, muscle aches.

With Comirnaty were also reported headache, paraesthesia, dizziness, drowsiness and taste disorders, while with the Moderna vaccine were also reported nausea and abdominal pain.

Other local reactions widespread joint pains are less frequent.

As expected, fever was reported more frequently after the second dose rather than after the first dose.

Events occur mostly on the same day as vaccination or on the day after (85% of cases).

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

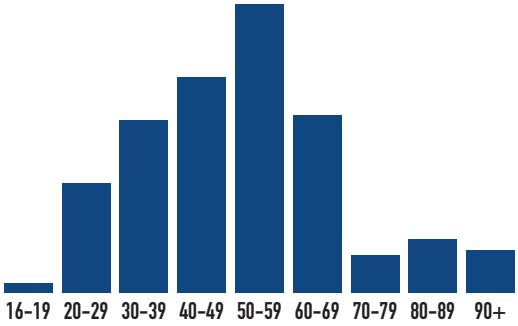
Reference period: 27/12/2020 - 26/01/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

DOSES ADMINISTERED

1.564.090

Comirnaty 99%
Vaccino Moderna 1%



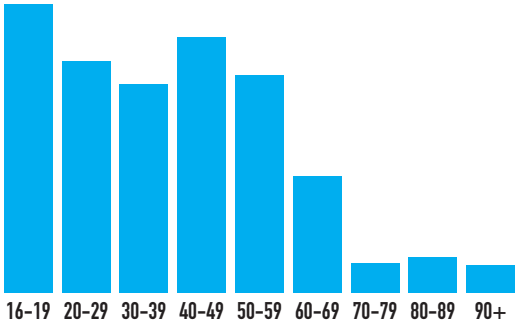
ADMINISTRATIONS BY AGE GROUPS

ADMINISTRATIONS PER DOSE	1st dose	2nd dose
	84,2%	15,8%

SUSPECTED ADVERSE REACTIONS

7.337

Comirnaty 99,5%
Vaccino Moderna 0,5%



REPORTING RATE BY AGE GROUPS

REPORTING RATE PER DOSE	1st dose	2nd dose
	515	225

MOST REPORTED ADVERSE EVENTS

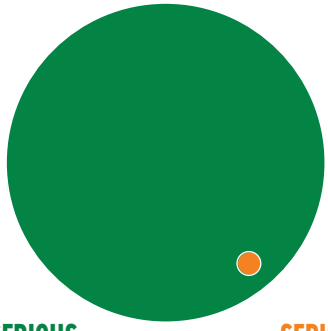

Fever


Headache


Injection site pain


Muscle aches

SUSPECTED ADVERSE REACTIONS SERIOUS/NON-SERIOUS



NON-SERIOUS **92,4%**

SERIOUS **7,3%**

0.3% OF SUSPECTED ADVERSE REACTIONS ARE NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)
PERIOD UNDER REVIEW: 27/12/2020 - 26/01/2021

During the period considered, 2 vaccines for COVID-19 were authorised and used on the national territory, both based on messenger RNA (mRNA) technology:

- the Pfizer/BioNTech mRNA vaccine called Comirnaty (authorised from 22/12/2020 and used from 27/12/2020);
- the Moderna mRNA vaccine called COVID-19 Moderna Vaccine (authorised from 07/01/2021 and used from 14/01/2021).

As of 26/01/2021 a total of **7,337 reports** have been entered in the RNF **out of a total of 1,564,090 doses administered for both vaccines, with a reporting rate of 469 per 100,000 doses**[1]. Most of the reports are related to the most widely used vaccine Comirnaty (7,294 out of 1,550,019 doses administered) with a cumulative reporting rate, i.e., not distinguishing between first and second dose, of approximately 471 reports per 100,000 doses administered. The lower number of reports entered for the Moderna vaccine (39 out of a total of 14,071 doses administered, with a reporting rate of approximately 277 per 100,000 doses) is due to its recent introduction on the market and the consequent lower use.

These **preliminary values** will have to be re-evaluated over time and do not allow to compare the safety profile of the two vaccines.

It is important to remember, in fact, that a **high reporting rate** is indicative of a **high sensitivity to reporting** and the importance that this act has for the study of drug safety.

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.

Figure 1A shows the trend over time in the number of reports for both vaccines and the number of doses administered in the period under review. In figure 1B the suspected adverse reactions reported after the 1st or 2nd dose of the vaccine are represented separately.

During the period under review, the first doses of the vaccination cycle were mainly administered with the Comirnaty vaccine, and only about 15% of the administered doses of this vaccine were used for boosters, whose administration began around 16/01/2021. Consequently, the reporting rate for the first dose of this vaccine is very similar to the cumulative rate (517/100,000 doses administered), while the reporting rate for the second dose is much lower (278/100,000 doses administered).

[1] The number of doses administered as of 26/01/2021 is made available by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 30/01/2021.

Also in this case, the two values are not currently comparable because they are too influenced by the low total number of doses used for boosters and by the dynamic nature of the pharmacovigilance database, in which reports can be entered also after some time from onset of the adverse event, as required by law. This trend, therefore, represents a snapshot of what can be found in the National Pharmacovigilance Network at the time of data extraction, or rather as of 26/01/2021 and may change over time.

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

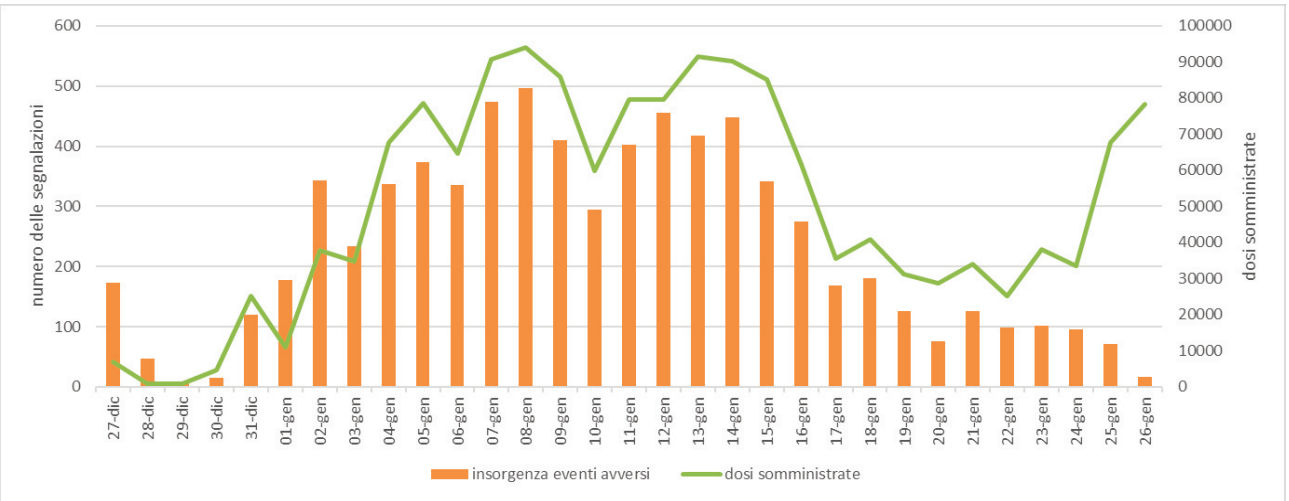
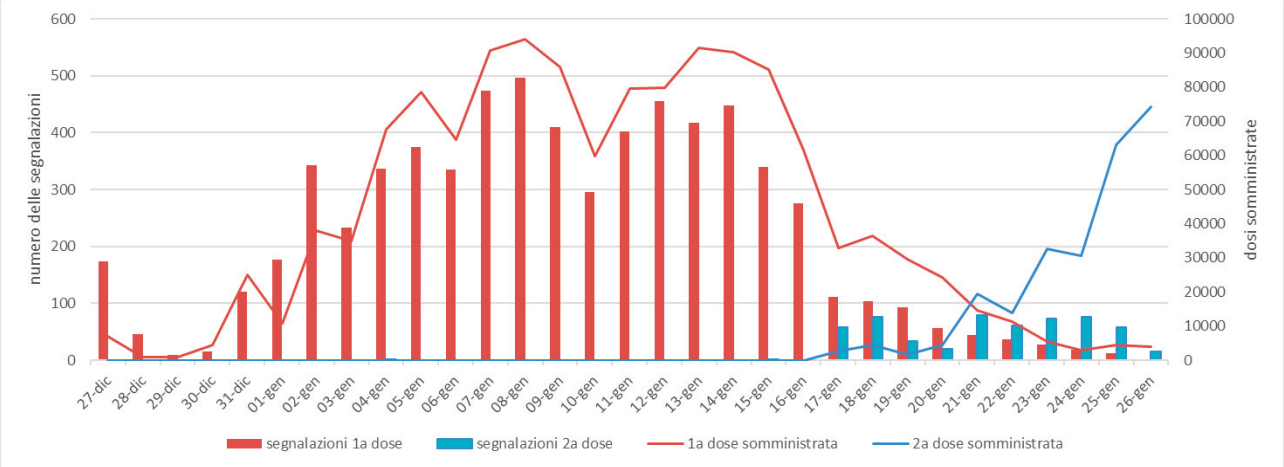


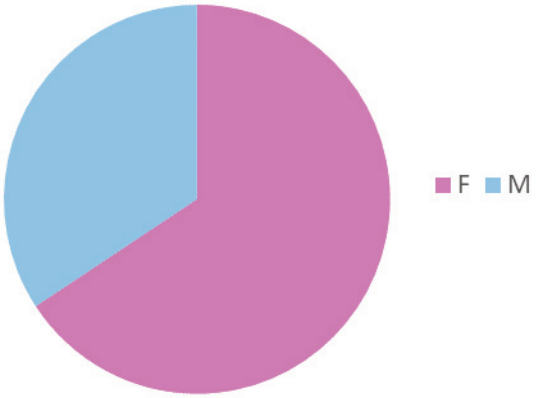
Figure 1b *- Distribution of the reports entered in the National Pharmacovigilance Network by date of onset of the event divided by first and second dose*



Distribution by sex, age and type of reporter

The reporting rate is 561/100,000 doses administered in females and 293/100,000 doses administered in males, regardless of the dose and vaccine administered (Fig. 2). These values could be affected by the **higher sensitivity to reporting by vaccinated women**, a phenomenon already found in the spontaneous pharmacovigilance of other vaccines and medicines.

Figure 2 *- Distribution by sex of the rate of reports entered in the RNF.*



The average age of the subjects is 46.2 years (age range 18-109 years, median age of 47 years). The reporting rate based on age is shown in Figure 3. The distribution by age groups shows how the reporting rate is rather constant and high in subjects up to 60 years, and then decreases in the more advanced age groups. This difference reflects the trend of the vaccination campaign which mainly concerned health professionals aged between 20 and 60, more sensitive to reporting and only to a lesser extent the predominantly institutionalised elderly population. Differences by sex for each age group are in line with the cumulative figure.

Figure 3 *- Distribution of the number of reports (curve) and of the reporting rates (histograms) by age group (indicated in years)*

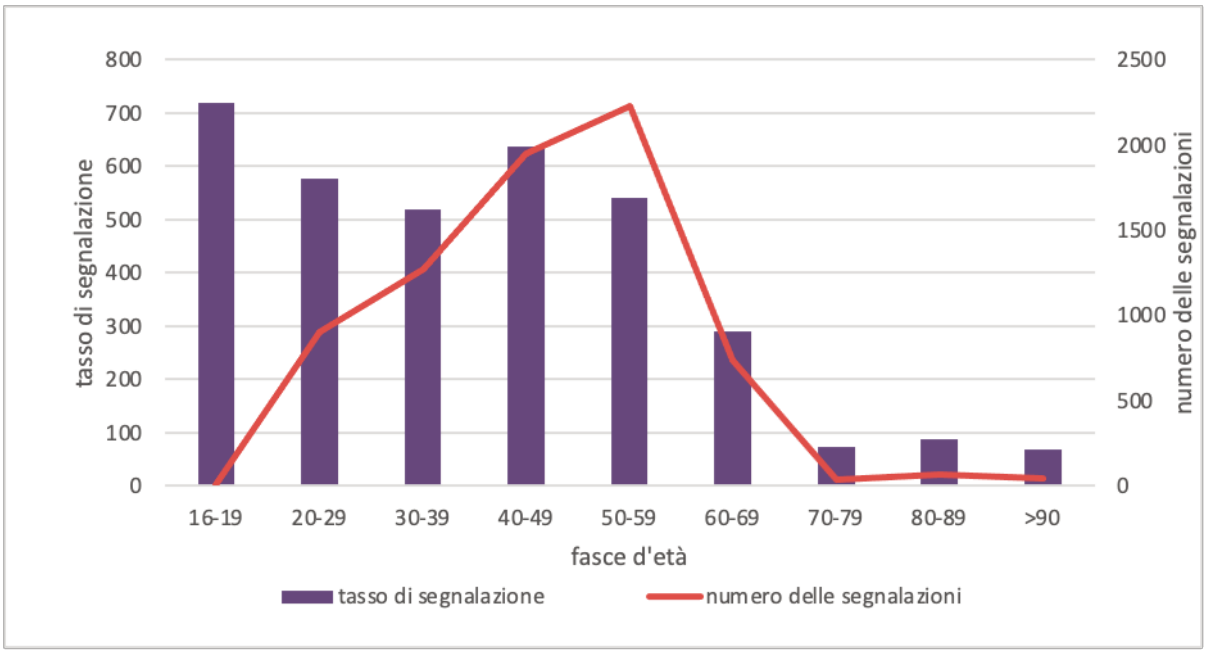
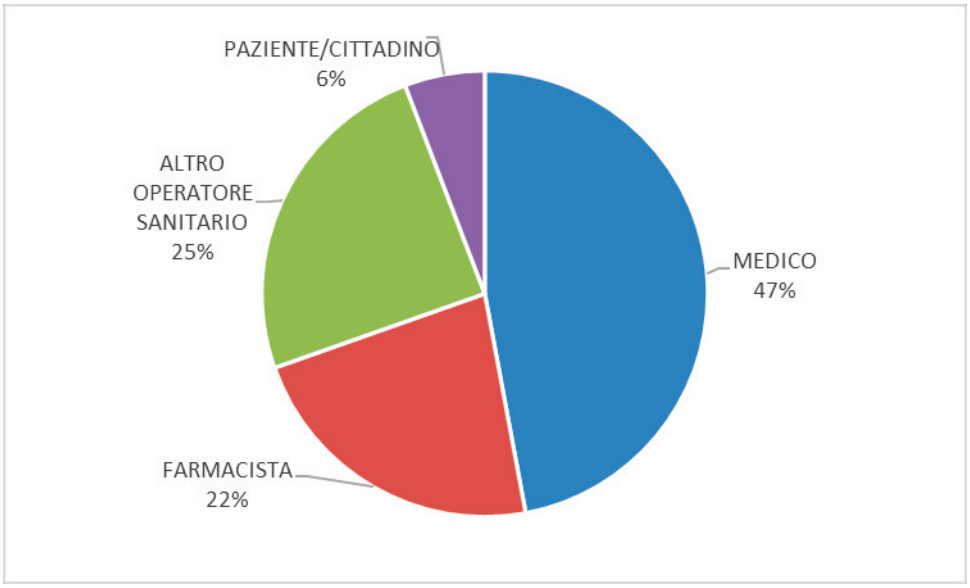


Figure 4 shows the distribution by type of reporter which highlights how most of the reports come from health professionals, as expected in this phase of the vaccination campaign.

Figure 4 *- Type of reporter of the reporting forms inserted from the start of the vaccination campaign.*



The type of reports entered from the start of the vaccination campaign is mainly spontaneous (about 96%). About 4% of the reports are due to active pharmacovigilance projects which prompt reporting.

The distribution of reports by time of onset in relation to vaccination is shown in Table 1.

Table 1 *- Distribution of reports by time of onset of symptoms by vaccination date*

TEMPO DI INSORGENZA	N° SEGNALAZIONI	%
0 giorni	4.497	61.3%
1 giorno	1.693	23.1%
2-7 giorni	668	9.1%
>7 giorni	134	1.8%
Non definibile	345	4.7%
Totale	***7.337***	***100%***

In most cases, the reaction occurred on the same day as vaccination or the day after (approximately 85% of cases). More rarely, the event occurred beyond the following 48 hours. In just under 5% of cases, further information is awaited in order to precisely define the temporal relationship between vaccination and the occurrence of the reported event.

Distribution by seriousness and outcome

The reports of the first month of the vaccination campaign mainly relate to non-serious events (92.4%), with a reporting rate equal to 434/100,000 doses administered. Also in this case, the rate for the Comirnaty vaccine is comparable to the cumulative figure, since 99% of the reports and doses administered can be attributed to this vaccine (the reporting rate of non-serious events for the Moderna vaccine is 270/100,000 doses administered, extrapolated on the basis of only 14,000 doses actually administered).

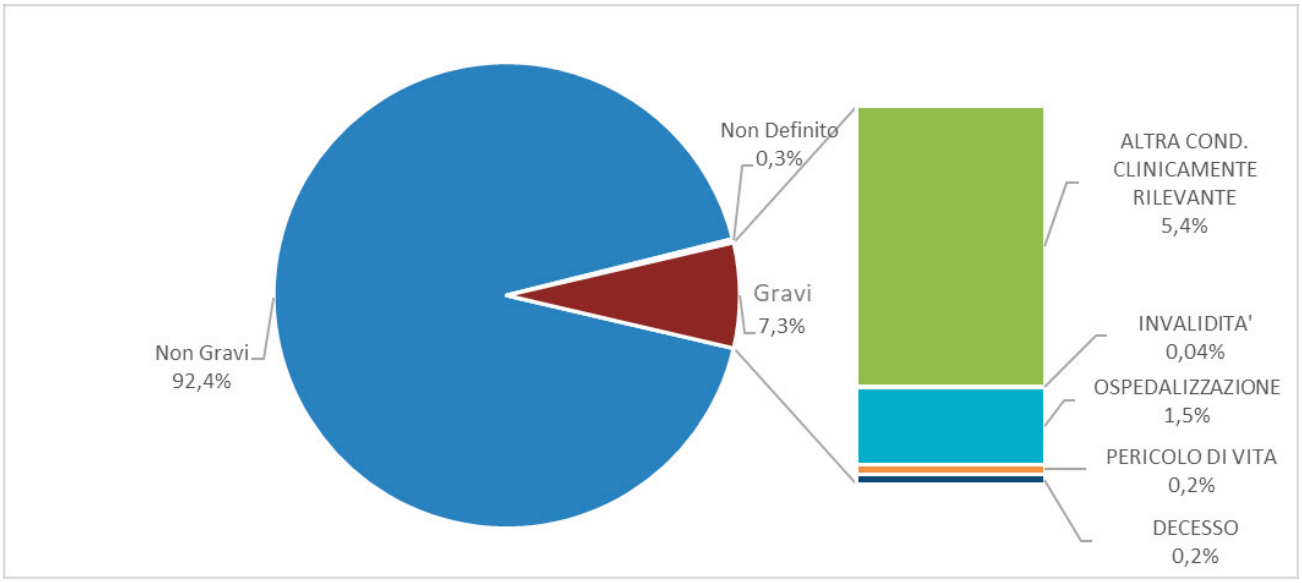
When is a report considered serious?

In the regulatory field, the reports are classified as serious or non-serious on the basis of internationally standardised criteria which 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, other clinically relevant conditions. Furthermore, some adverse events are considered serious regardless of the clinical consequences if present in a list which 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 medicine.

Serious reports represent 7.3% of the total, with a rate of 34 serious events per 100,000 doses administered, regardless of the type of vaccine, of the administered dose (I or II dose) and of the possible causal role of the vaccination. The time distance between vaccine administration and the onset of serious adverse events follows a trend similar to all reports received (see table 1). The evaluation of the causal role of vaccines in such reports is currently ongoing and requires specific investigation for each individual case, possibly requesting further information from the reporter to determine if a vaccine and a temporally associated event are linked by a causal relationship based on available evidence.

Figure 5 shows the distribution of reports by seriousness, with details of the seriousness parameter for serious reactions.

Figure 5 *- Distribution by seriousness of the reports entered in the period considered.*



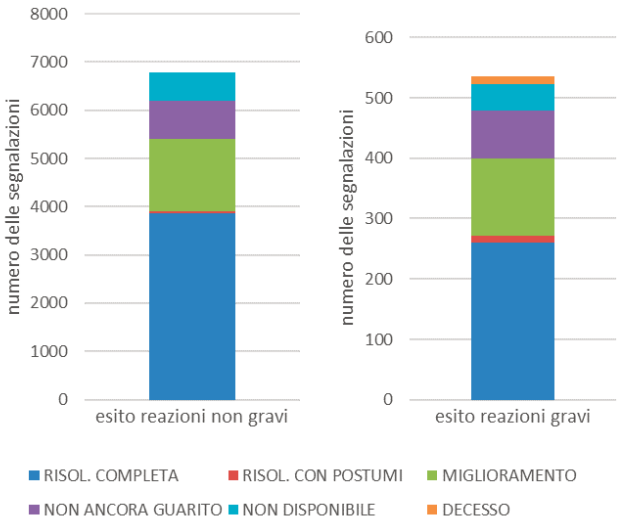
Most serious reports are classified as "other clinically relevant condition" (about 74%), i.e., alerting the subject and/or the reporter without entailing a specific intervention in hospitals.

The distribution by outcome of reports divided by seriousness is shown in Figure 6. The trend is very similar regardless of the seriousness of the report. In fact, in most cases, the reports entered refer to non-serious adverse events with full recovery or improvement already at the time of reporting. The small number of cases resulting in "recovery with sequelae" refers to subjects undergoing in-depth investigations whose outcome is not yet known. The low number of cases without information on the outcome indicate the good quality of the reports submitted.

What is the outcome of a report?

The outcome of suspected adverse reactions is information on the status of the adverse event described at the time of reporting and internationally coded as: "full recovery", "improvement", "not yet recovered", "recovery with sequelae" and "death". This information may change over time, due to further update by the reporter.

Figure 6 *- Distribution by outcome of the reports entered in the period considered*



Overall, 13 cases of fatal outcome from the Comirnaty vaccine were included in the period considered, with a reporting rate of 0.8/100,000 doses administered. Most death reports contain a lot of information, mostly already present at the time of entry into the RNF or obtained with follow-up requests.

54% of these cases concern female subjects and 46% male, with an average age of 86.5 years (median age: 90 years), mainly living in retirement homes. The distribution by sex and age is compatible with the demographic characteristics of the elderly population in Italy.

In all cases, these subjects were affected by one or more basic pathologies, of a chronic and complicated nature and undergoing polytherapy. Death occurred in a range from hours to 12 days after vaccination. It should be underlined that the temporal relationship alone is not in itself sufficient to establish a causal role of the vaccine.

For each of these cases, additional clinical information was requested for a correct evaluation of the event. In the more detailed and complete reports of follow-up data, the events reported were not related to vaccination and are largely attributable to the underlying condition of the vaccinated subject. In the remaining cases, the required updates and investigations are still in progress, however no particular security issues arise on the basis of the information available.

Distribution by type of event

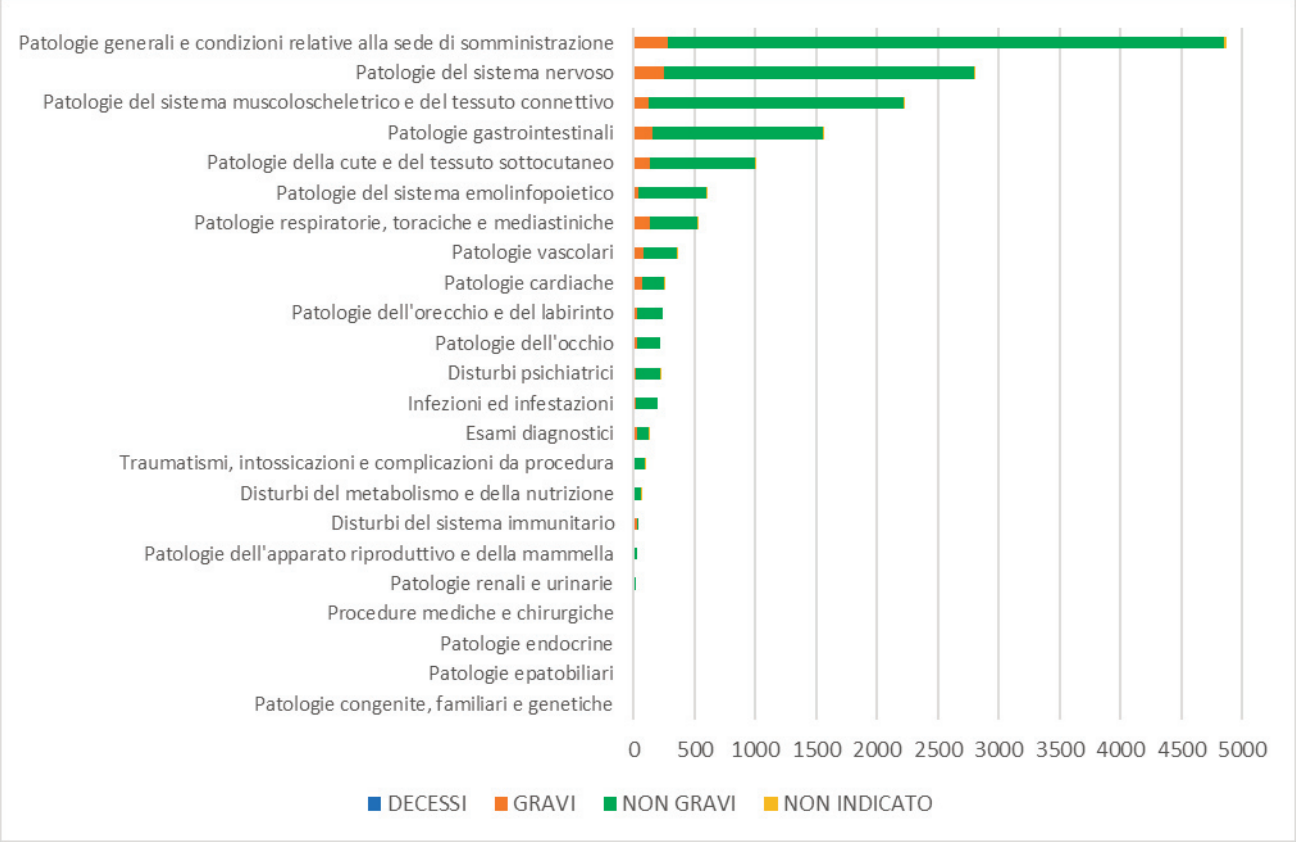
The following graphs show the types of events reported in order of frequency for the two vaccines used, regardless of the causal link with the vaccination, on the basis of the organ or apparatus concerned, the etiology or purpose (System Organ Class or SOC).
It should be noted that a single report sheet can include multiple events, therefore the total number of events is higher than the total number of reports.

How are adverse events classified in reports?

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).

The distribution of adverse events by system organ class (SOC) after Comirnaty vaccine, regardless of the dose administered and the causal link with vaccination is shown in Figure 7.

Figure 7 *- Distribution of adverse events after Comirnaty vaccine by system organ class (SOC)*

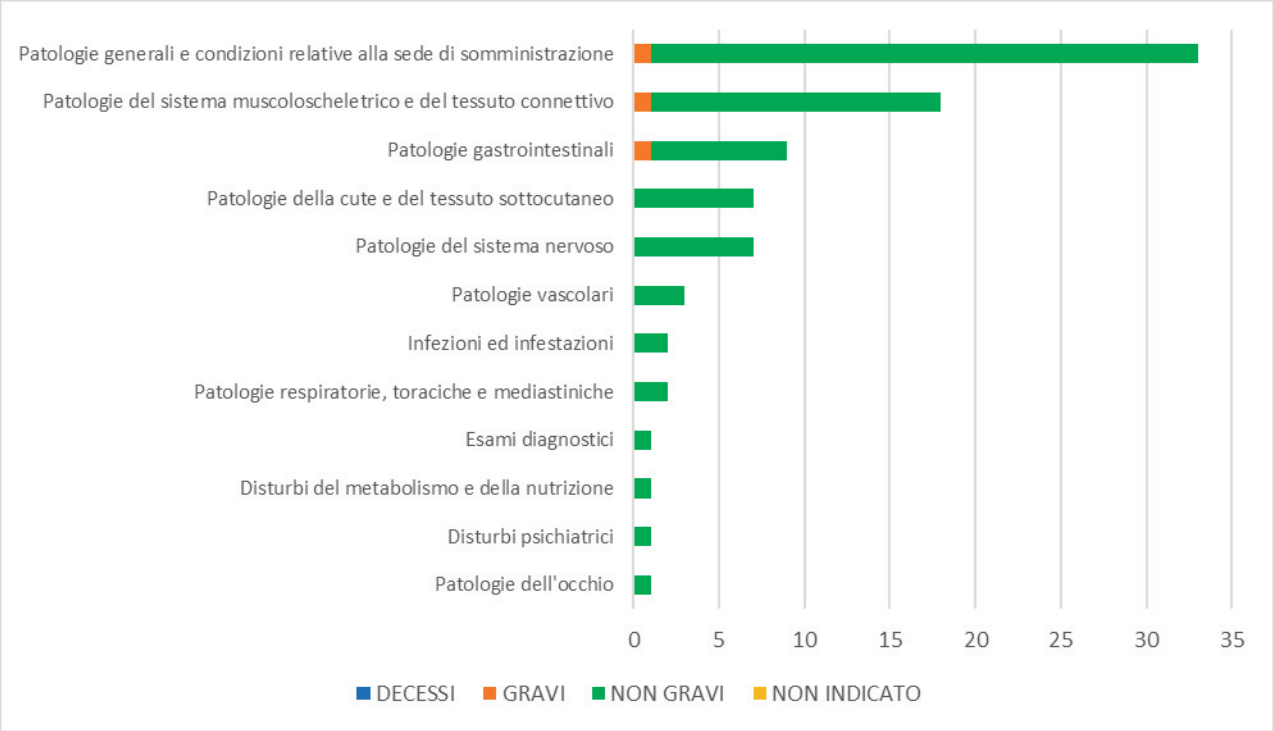


Most **events reported for Comirnaty vaccine** relate to the system organ class of General Disorders and Administration Site Conditions and are predominantly injection site pain, fever, asthenia/fatigue and local reactions, classified as non-serious in 94% of cases.

The events falling under the Nervous System Disorders follow in order of frequency, 91% of which are non-serious, mainly represented by headache, paraesthesia, dizziness, drowsiness and taste disorders; as for the events falling under the Musculoskeletal and connective tissue disorders, 94% are non-serious, mainly represented by widespread muscle and joint pain.

The distribution of adverse events by system organ class (SOC) after Moderna vaccine, regardless of dose number and causal link with vaccination is shown in Figure 8.

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



Most **events reported for Moderna vaccine** relate to the system organ class of General Disorders and Administration Site Conditions and are predominantly fever, asthenia/fatigue and injection site pain, 97% of which are classified as non-serious. The events falling under the musculoskeletal system and connective tissue disorders follow in order of frequency, especially widespread muscle and joint pain, classified as non-serious in 94% of cases, while among gastrointestinal disorders, mainly nausea and abdominal pain, classified as non-serious in 90% of cases.

During the period considered, 14 **reports of anaphylaxis/anaphylactic shock** to the Comirnaty vaccine were reported, of which 1 duplicate case entered by both the vaccinator and the company. Twelve cases relate to female subjects and 1 case to a male subject, with an average age of about 45 years. All reports refer to events occurring immediately after the administration of the first dose of vaccine. At the time of reporting, the outcome was full recovery or improvement in 85% of cases.

According to the reported description of the event, all cases were quickly assisted and treated at the vaccination centre where the vaccination took place or promptly referred to an emergency

room. In 3 cases, the subjects reported a clinical history of allergy, mainly to pollen and food, whereas in 1 case, the subject reported a previous allergic reaction to another vaccine. The frequency of anaphylaxis is being studied at a European level by the Pharmacovigilance Risk Assessment Committee (PRAC).

As of today, no cases have been reported of anaphylaxis/anaphylactic shock to the Moderna vaccine, probably due to the limited number of doses administered.

In the same period, 18 **reports of paralysis/paresis of the facial nerve** were entered after administration of the Comirnaty vaccine, 12 of which in female subjects and 6 in male subjects, with an average age of about 49 years. Twelve cases were classified as “serious - other clinically relevant condition”, 1 case as “serious - hospitalisation” and 5 cases as non-serious. In 10 cases the outcome reported at the time of reporting was full recovery or improvement, while in 6 cases the event has not yet been cured.

In 50% of cases, the facial nerve deficit began in the hours immediately following vaccination, often incomplete and with full recovery within the following 24 hours, regardless of the administration of specific therapy. In 15% of cases, the disorder appeared the day after vaccination and recovered in a few days with adequate therapy. In the remaining 35% of cases, facial paresis appeared from 48 hours to 9 days after the administration of the vaccine and in some cases, it occurred in subjects with concomitant pathologies or conditions. At the moment, further follow-up information is still awaited, especially for cases with a later onset, in order to correctly frame the cases. The frequency of facial paralysis and its possible correlation with the Comirnaty vaccine is also being studied at a European level by the Pharmacovigilance Risk Assessment Committee (PRAC).

The evaluation of the reports referring to the administration of the second dose of Comirnaty vaccine (No. 568), although their number is still limited, as this phase of the vaccination campaign is in its early stage, confirms the expected figure of a greater number of reported events referring to "fever" or related terms (rise in temperature, high temperature, fever chills, etc.). This information is already reported in the Package Leaflet and in the Summary of Product Characteristics of the Comirnaty vaccine, available on the AIFA website. The remaining suspected adverse reactions reported show a trend in line with the above description.