COVID-19 Vaccine Surveillance Report

2

27/12/2020 - 26/02/2021

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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.

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, 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 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 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**.

HIGHLIGHTS

As of 26 February 2021, 729 reports were entered for every 100.000 doses administered, regardless of the vaccine and dose administered.

The reports mainly concern the Pfizer/BioNTech Comirnaty vaccine (96%), which was the most widely used, and only to a lesser extent the Moderna vaccine (1%) and the Astra Zeneca vaccine (3%).

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

Mostly non-serious adverse events were reported that resolve completely.

For all vaccines, the most reported adverse events are fever, headache, mucle and joint pains, injection site piain, chills and nausea.

As expected, fever was reported more frequently after the second dose rather than after the first dose, followed by headache and asthenia/fatigue.

Events occur mostly the same day as vaccination or the day after (87% of cases).

The reporting trend and its rates in the first two months of the vaccination campaign confirm the trend showed in Report #1.

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 - 26/02/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

DOSES ADMINISTERED

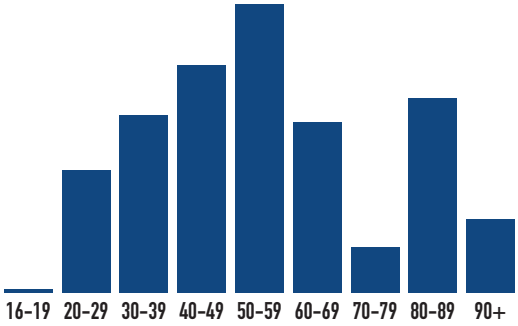
4.118.277

Comirnaty 87%
Vaccino Moderna 4%
Vaccino AstraZeneca 9%

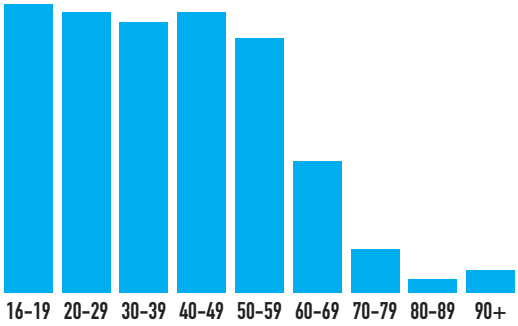
SUSPECTED ADVERSE REACTIONS

30.015

Comirnaty 96%
Vaccino Moderna 1%
Vaccino AstraZeneca 3%



ADMINISTRATIONS BY AGE GROUPS



REPORTING RATE BY AGE GROUPS

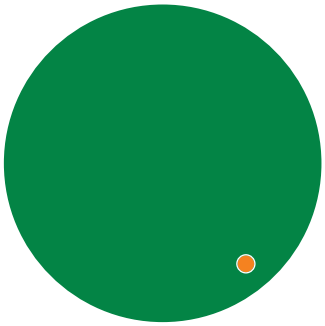
	1st dose	2nd dose
ADMINISTRATIONS PER DOSE	66,4%	33,6%

	1st dose	2nd dose
REPORTING RATE PER DOSE	773	785

MOST REPORTED ADVERSE REACTIONS AFTER THE 2ND DOSE

IN ALMOST 90% OF CASES THE SUSPECTED ADVERSE REACTION OCCURS THE SAME DAY OR THE NEXT DAY AS VACCINATION

SUSPECTED ADVERSE REACTIONS SERIOUS/NON-SERIOUS



NON-SERIOUS **93,6%**

SERIOUS **6,1%**

0.3% OF SUSPECTED ADVERSE REACTIONS ARE NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK-RNF
PERIOD UNDER REVIEW: 27/12/2020 - 26/02/2021

In the period considered, **3 vaccines for COVID-19** were authorised and used in Italy, two based on messenger RNA (mRNA) technology and one on viral vector use:

- the Pfizer/BioNTech mRNA vaccine called Comirnaty (authorised as from 22/12/2020 and used as from 27/12/2020);
- the Moderna mRNA vaccine called COVID-19 Moderna Vaccine (authorised as from 07/01/2021 and used as from 14/01/2021;
- the recombinant viral vector vaccine called COVID-19 AstraZeneca Vaccine (authorised as from 29/01/2021 and used as from 01/02/2021).

As of 26/02/2021 a total of 30,015 reports have been entered in the RNF out of a total of 4,118,277 doses administered for all vaccines, with a reporting rate of 729 per 100,000 doses[1].

Most of the reports (96%) relate to the most widely used vaccine Comirnaty (83% of the administered doses), whereas the reports related to the Moderna and AstraZeneca vaccines are resplectively 1% and 3% of the total, proportional to the administered doses.

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.

The number of reports, the administered doses and the reporting rates of the COVID-19 vaccines currently in use are shown in table 1.

Table 1 *– Reports, administered doses and reporting rates for currently authorised COVID-19 vaccines*

COVID-19 vaccine	Reports as of 26/2/2021	Administered doses as of 26/2/2021	Reporting rate (per 100,000 administered doses)
Comirnaty	28.762	3.741.828	**769**
Moderna	403	120.886	**333**
AstraZeneca	834	255.563	**326**
mRNA active ingredient (unspecified brand)	16		
Total	***30.015***	***4.118.277***	***729***

The lower reporting rates of the Moderna and AstraZeneca vaccines compared to Comirnaty are due to the lower and/or recent use, therefore they will have to be monitored over time.

[1] The number of administered doses as of 26/02/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 02/03/2021

Figure 1a shows the temporal trend of the number of reports for all vaccines and of the number of doses administered in the period considered. Figure 1b shows separately the suspected adverse reactions reported after the 1st or 2nd dose of the vaccine.

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 (cumulative)*

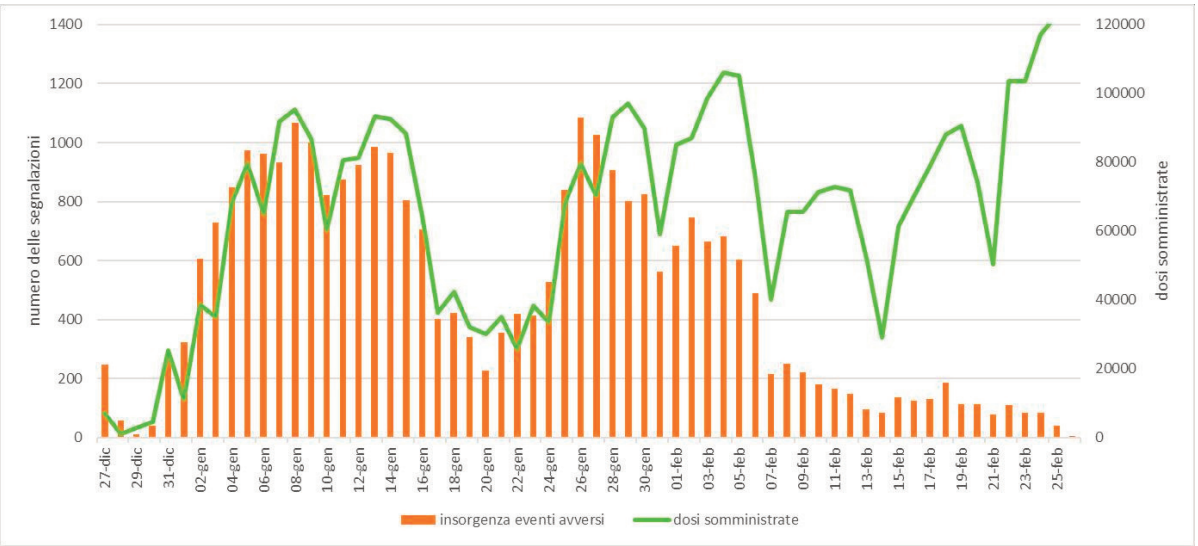
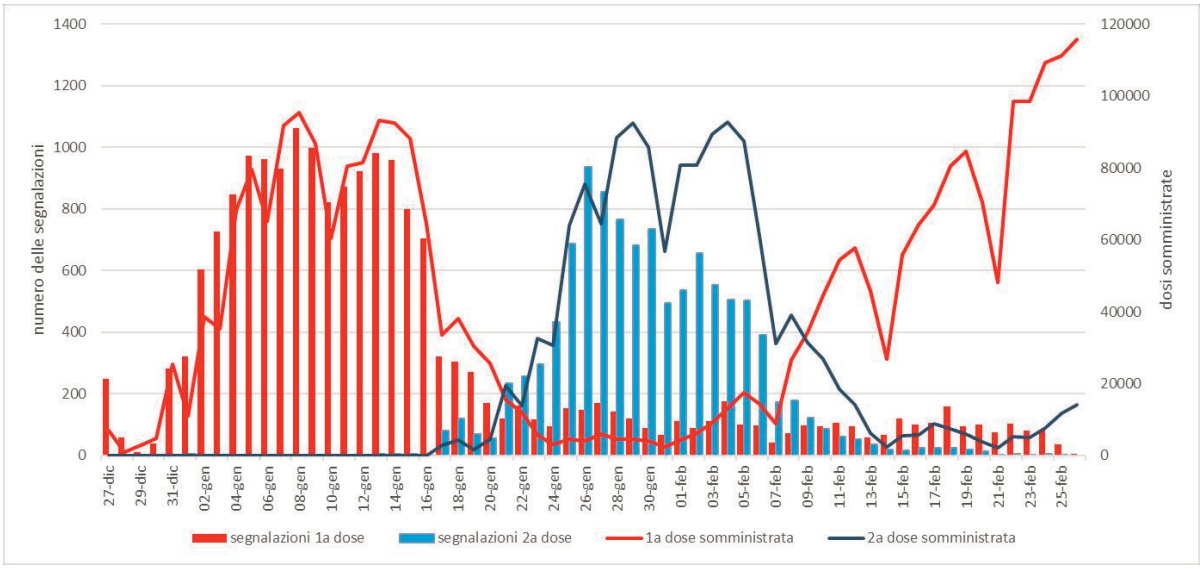


Figure 1b – *Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*

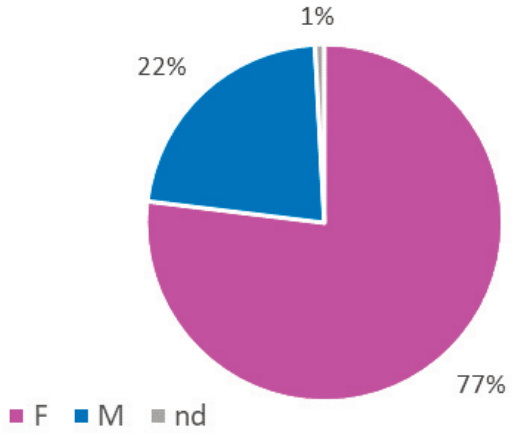


The bimodal trend of the graphs highlights the correspondence between the trend of vaccinations and the trend of reports. The increase in the number of administrations in the last part of the graph does not correspond to a concomitant increase in reports, probably due to the possibility to enter the reports some time after onset of the adverse event and/or vaccine administration (for example, 1st dose reactions communicated and reported upon booster). 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.

Distribution by sex, age and type of reporter

The reporting rate is 907/100,000 doses administered in women (F) and 424/100,000 doses administered in men (M), regardless of the dose and vaccine administered (fig. 2).

Figure 2 *– Distribution by sex of the reports entered in the RNF*



Various factors can influence this difference between the sexes, including the different exposure to vaccines, the greater sensitivity of women to reporting and the different frequency of some adverse reactions between the two sexes. According to some studies the different immune response in women seems to affect the frequency and severity of adverse reactions to vaccination, especially when it comes to fever, pain and inflammation[2, 3].

The average age is 46 years (age range 0.5-104 years, median age 47 years). The reporting rate based on age is shown in Figure 3. The data relating to the age group 16-19 years is to be considered preliminary as it is extrapolated for 100,000 doses administered on the basis of a small number of reports (46) and of doses administered (4,235). The distribution by age group shows how the reporting rate is rather constant and high in subjects up to 60 years, then it decreases in the more older age groups. As already observed in pre-authorisation clinical studies, the older population has a lower predisposition to the onset of adverse events. Gender differences for each age group are in line with the cumulative figure. The 2 reports of infants under one year of age refer to 2 cases of non-serious adverse reaction, with complete resolution, occurring in two breastfed babies whose mother was vaccinated the day before. In the first case, the 5-month-old girl presented two episodes of vomiting without fever or other gastrointestinal symptoms the day after the mother's vaccination, resolved on the day of onset. In the second case, the 18-month-old girl breastfed by her mother presented a fever the day after the mother's vaccination for which further investigations were performed to ascertain other possible causes (urinalysis, urine culture).

There are no significant differences between the reporting rates by age group in relation to the number of doses.

[2] Wen-Han Chang; A review of vaccine effects on women in light of the COVID-19 pandemic; Taiwanese Journal of Obstetrics & Gynecology 59 (2020) 812 and 820.

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

Figure 3 *– Distribution of the number of reports by age group according to the 1st or 2nd dose administered*

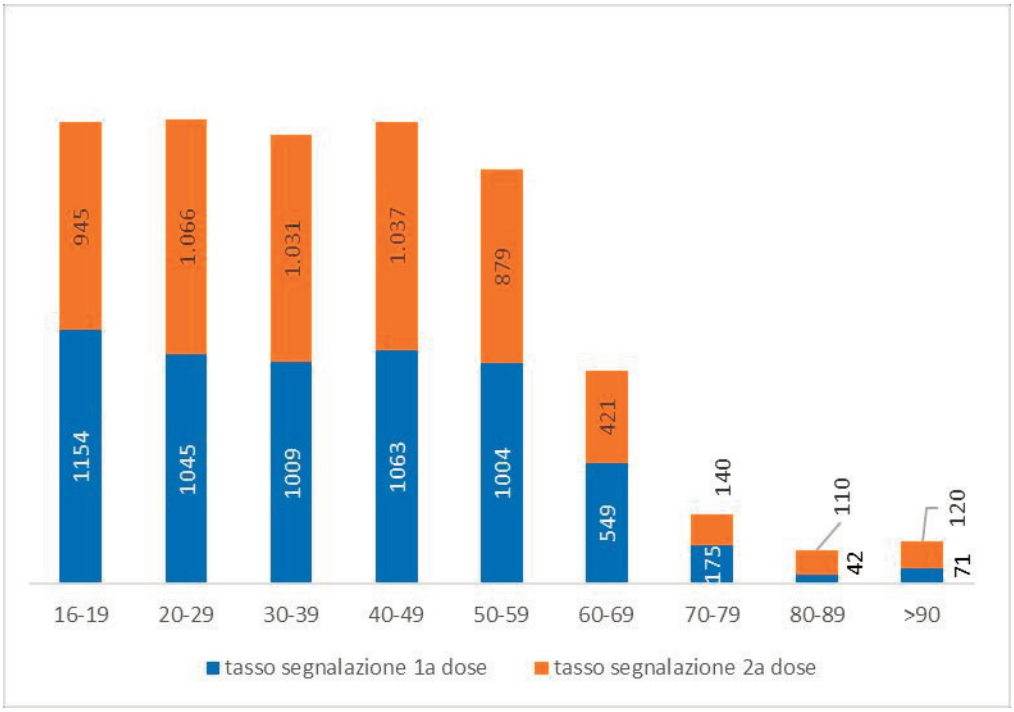
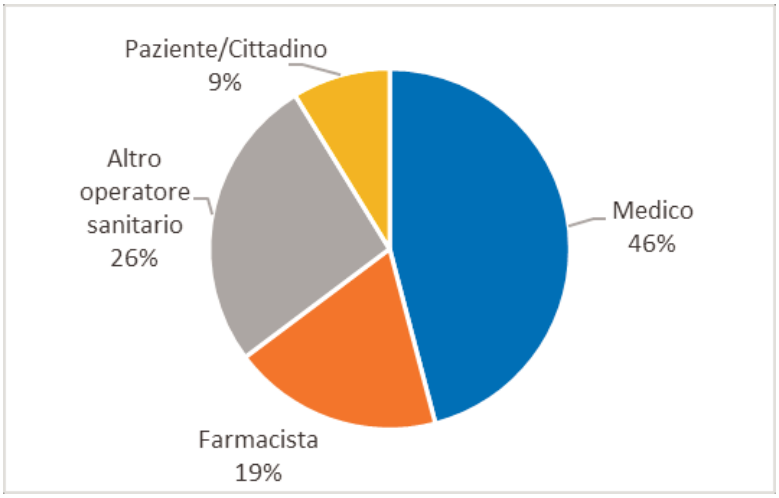


Figure 4 shows the distribution by type of reporter, highlighting that most reports come from health professionals, as expected in this phase of the vaccination campaign.

Figure 4 *– Type of reporter of the reporting sheets entered from the beginning of the vaccination campaign*



The type of reports entered from the beginning of the vaccination campaign is mainly spontaneous (about 99%), while the other reports are prompted by active pharmacovilance projects.
The report distribution by time of onset in relation to vaccination is shown in table 2.

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

ONSET TIME	N° REPORTS	%
0 days	16.474	54,9%
1 day	9.721	32,4%
2-7 days	2.271	7,6%
>7 days	615	2,0%
Not definable	934	3,1%
Total	***30.015***	***100%***

In most cases, the reaction occurred on the same day as vaccination or the following day (about 87% of cases). More rarely, the event occurred beyond the following 48 hours.

Distribution by seriousness and outcome

The reports relating to this period of the vaccination campaign mainly relate to non-serious events (93,6%), with a reporting rate equal to 683/100,000 administered doses.

The figure is similar to the cumulative rate for all the events because non-serious reports represent the majority. The reporting rates of non-serious events of each vaccine are respectively 720 (Comirnaty), 307 (Moderna), 293 (AstraZeneca) per 100,000 administered doses.

Serious reports represent 6,1% of the total, with a rate of 44 serious events per 100,000 administered doses, regardless of the type of vaccine, of the administered dose (1st or 2nd dose) and of the possible causal role of vaccination. The time distance between vaccine administration and the onset of serious adverse events follows a trend similar to all reports received (see table 2).

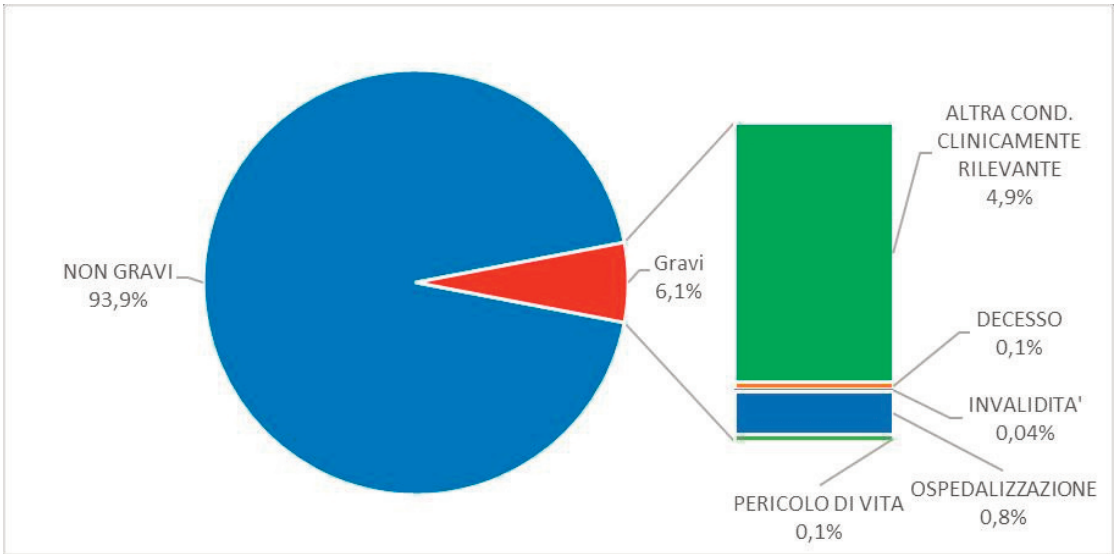
When is a report considered serious?

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.

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 relating to all vaccines.

Figure 5 – *Distribution by seriousness of the reports entered in the period considered (0,3% of reports do not indicate seriousness)*



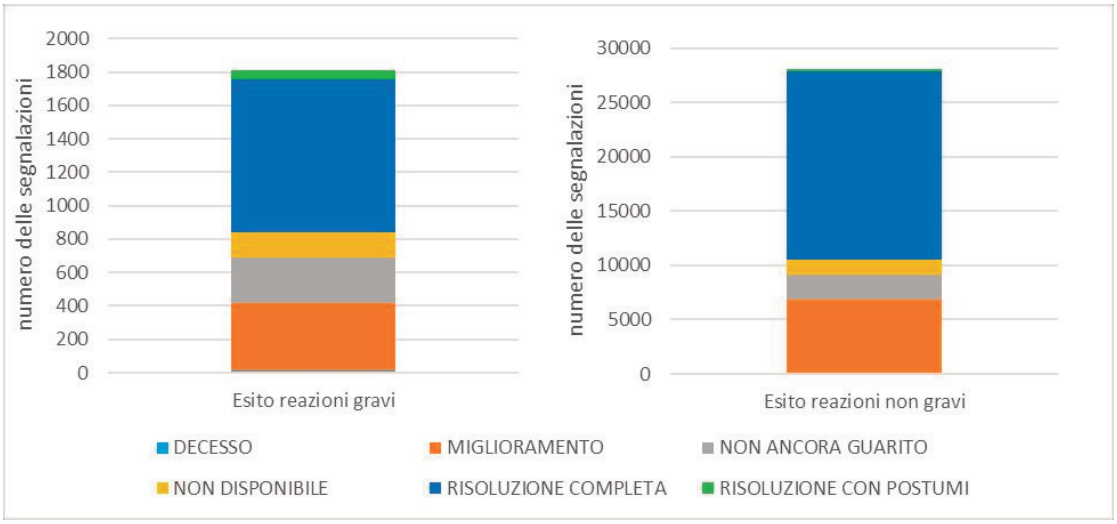
Most serious reports are classified as "other clinically relevant condition", i.e., alerting the subject and/or the reporter without entailing a specific intervention in hospitals.

The distribution by seriousness and outcome of the reports is shown in Figure 6. 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. Please note that the report outcome is continuously being updated, through the request of follow-up information. The cases with outcome “death” were discussed in the specific focus. The distribution by outcome does not show significant differences when the three vaccines are examined separately.

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 reports entered in the period considered*



Distribution by number of doses

In the period under examination, 34% of vaccinated subjects completed the vaccination cycle, mainly with the Comirnaty vaccine, for which the number of reports is currently such that initial comparative evaluations can be carried out. No differences in reporting rates were observed between the 1st and 2nd dose of Comirnaty or Moderna vaccine as shown in Table 3.

Table 3 *– Distribution of reports by number of doses*

	Reporting rate of the 1st dose (per 100,000 administered doses)	Reporting rate of the 2nd dose (per 100,000 administered doses)	Cumulative reporting rate (per 100,000 administered doses)
Comirnaty	756	790	769
Moderna Vaccine	335	322	333

The single-dose reporting rates are consistent with the cumulative rate reported in Table 1. No difference is shown in the distribution by severity or outcome criteria between the 1st and 2nd dose of the Comirnaty vaccine (the number of reports after the 2nd dose of Moderna vaccine is still too low).
Evaluation of adverse events after the 2nd dose of Comirnaty confirms a greater number of events related to "fever" or related terms (rise in temperature, high temperature, 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 one described for the 1st dose, with headache and asthenia being reported frequently.
For the AstraZeneca vaccine it is not possible to make evaluations as vaccinees have not yet been administered the second dose.

Distribution by type of event

Graphs 7, 8 and 9 show the types of events reported for the three vaccines used, Comirnaty, Moderna and AstraZeneca, 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 purpose (System Organ Class or SOC).

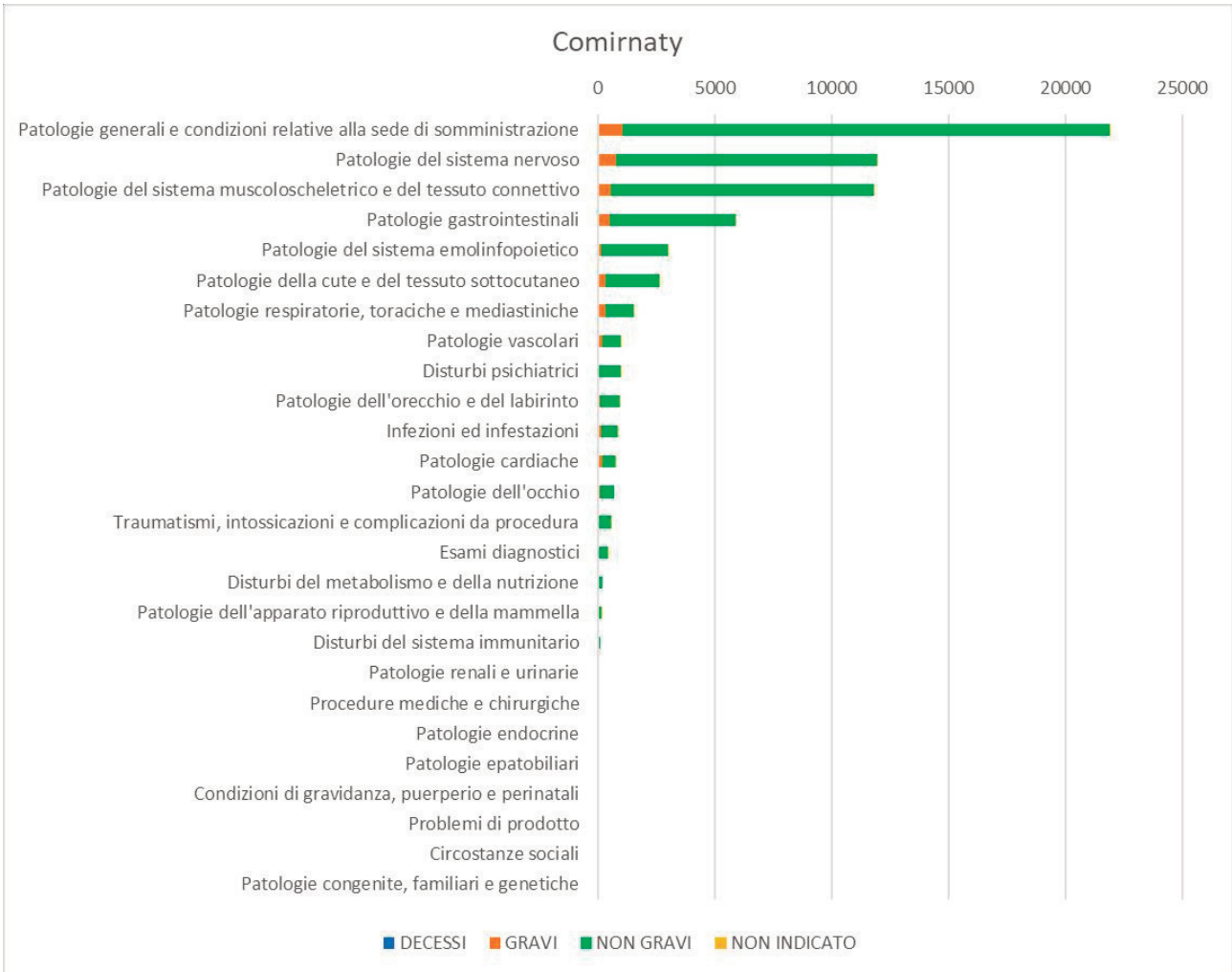
How are adverse events classified in reports?

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.

Most of the **events reported for the Comirnaty vaccine** relate to the system organ class of General Disorders and Administration Site Conditions and are predominantly fever, injection site pain, asthenia/fatigue and chills, classified as non-serious in 95% of cases. Following in order of frequency: the events falling under the Nervous System Disorders, for 93% of a non-serious type, mainly represented by headache and paraesthesia; the events falling under the Musculoskeletal system and connective tissue disorders, for the 95% non-serious, mainly represented by widespread muscle and joint pain and the events falling under the gastrointestinal disorders, 91% non-serious, mainly represented by nausea and diarrhea.

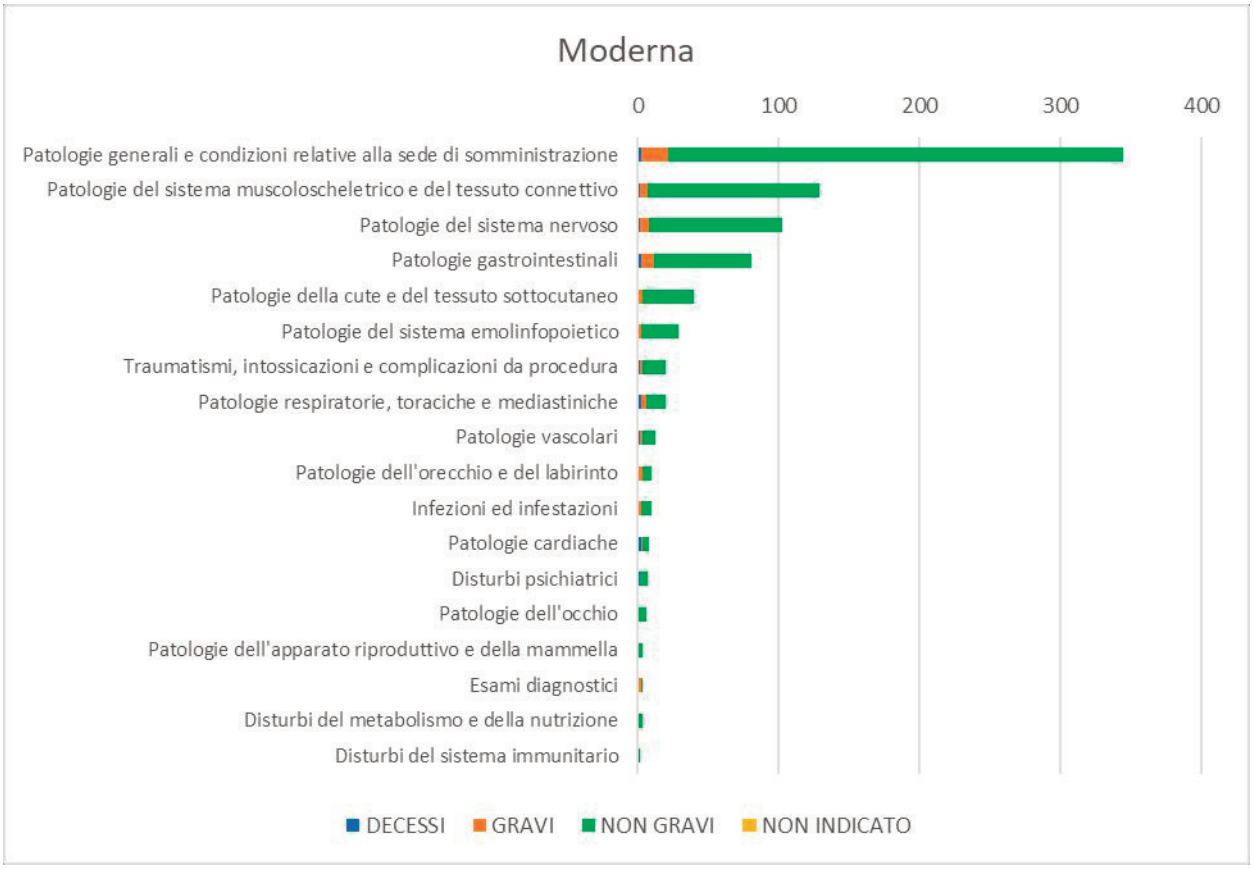
Figure 7 *- Distribution of adverse events after Comirnaty vaccine by system organ class (SOC)*



Overall, there are 1,700 serious reports on the Comirnaty vaccine. Regardless of whether it is a 1st or 2nd dose and the causal link, the most frequent reactions coincide with the distribution of all reactions and are mainly represented by high fever, severe headache, widespread muscle/joint pain and asthenia. In addition, allergic-type reactions, lymphadenopathy, paraesthesia, tachycardia and hypertensive crisis and facial paralysis are less frequently reported.

Most of the **events reported for the 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, classified as non-serious in 94% of cases. Following in order of frequency: the events falling under the Musculoskeletal system and connective tissue disorders, especially widespread muscle and joint pain, classified as non-serious in 95% of cases; the events falling under the Nervous System Disorders, especially headache, classified as non-serious in 92% of cases and those falling under the Gastrointestinal Disorders, mainly nausea and vomiting, classified as non-serious in 86% of cases.

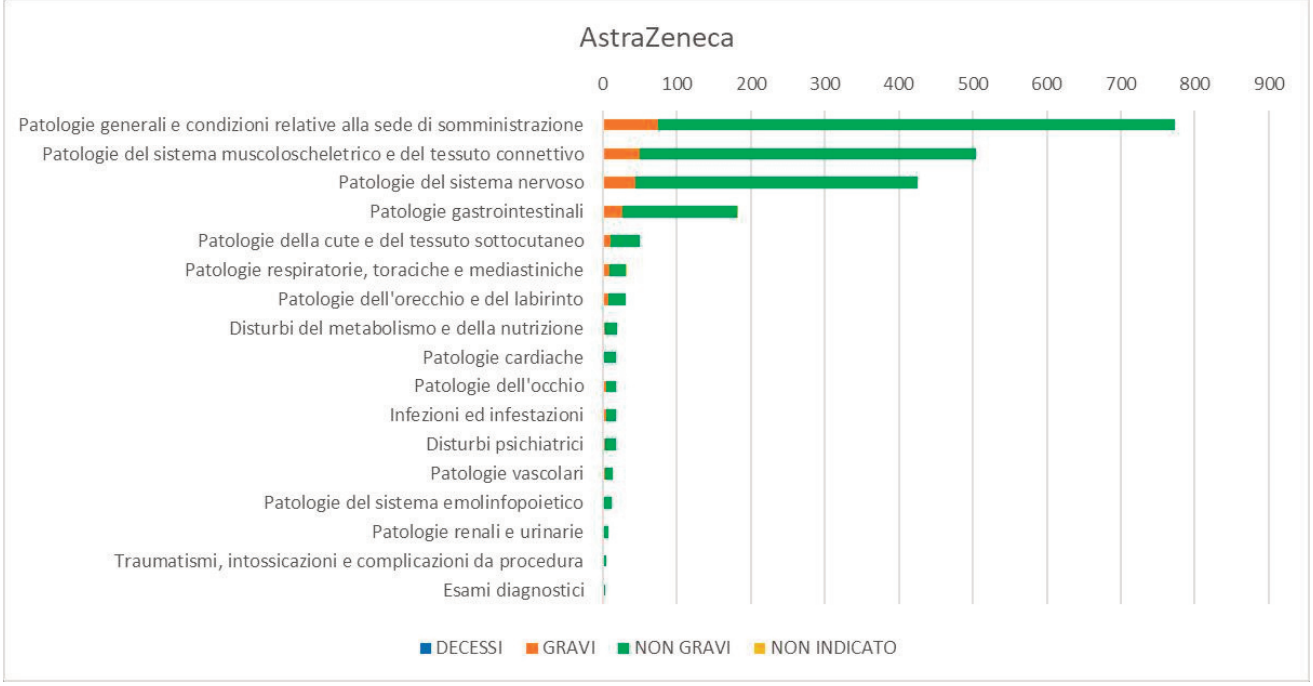
Figure 8 *- Distribution of adverse events after Moderna vaccine by system organ class (SOC)*



In 32 report sheets concerning the Moderna vaccine, adverse events considered serious were reported. Also for this vaccine, the most frequent serious reactions correspond to the distribution of all reports and refer mainly to systemic symptoms (high fever, diffuse myalgia and arthralgia, etc.). Other events are reported with a frequency equal to or less than 2 reports.

Most of the **events reported for the AstraZeneca vaccine** are related to the system organ class of General Disorders and Administration Site Conditions and are mainly fever, chills, asthenia/fatigue and injection site pain. 90% of these reports are classified as non-serious. This is followed in order of frequency by events falling under the Musculoskeletal System and Connective Tissue Diseases, mainly represented by diffuse muscle and joint pain. Again, 90% of cases are classified as non-serious. This is followed in order of frequency by events falling under the disorders of the nervous system, mainly headaches, classified as non-serious in 90% of cases, and under the gastrointestinal disorders, mainly nausea and vomiting, classified as non-serious in 85% of cases.

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



Most of the 79 reports of serious adverse events for this vaccine refer to high fever with any other associated systemic symptoms. Other preferred terms reported less frequently than 10 reports are: chills, dizziness, excessive sweating, drowsiness, difficulty in breathing, generalised pain.

Fatal cases after Covid-19 vaccination

With the collaboration of the Regional Pharmacovigilance Centres of the Lombardy and Tuscany Regions.

As of 26 February 2021, 40 reports with a "death" outcome have been entered for a reporting rate of approximately 0.97 per 100,000 doses administered.
The evaluations of the cases with detailed and complete information indicate that the vaccine was not responsible, because these people had previous pathologies and were taking several medicines at the same time.
Out of 40 reports, 29 report sheets showed an assessment of the causal link at the time of writing this document: the causal link was considered unrelated in 66% of cases, undetermined in 27% of cases and unclassifiable due to lack of information necessary to carry out the algorithm in 7% of cases.
60% of cases were women and 32.5% men (sex was not reported in 7.5% of cases), in line with the general trend of reported adverse reactions by sex. The median age of fatal cases differed significantly from other adverse reactions and was 86 years (range 41-104). The time to death after vaccine administration ranged from two hours to a maximum of 21 days, with a median of two days. Death occurred after the 1st dose in 25 cases and after the 2nd dose in 14 cases (in 1 case the dose is not reported). There are no cases of death as a result of anaphylactic shock or major allergic reactions. Very often death is linked to cardiovascular causes in patients who had basic cardiovascular disease.
Fatal cases have also been reported and investigated in other countries after the implementation of anti-COVID-19 vaccination programs: many of them are elderly people over 75 of age.
In the US report published by the CDC, 113 deaths were reported out of 13,794,904 doses administered of which 78 (65%) among institutionalised patients. Information available from death certificates, autopsy reports, medical records and clinical descriptions does not suggest any causal relationship between COVID-19 vaccination and death[4].

How is causal link assessed?

The assessment of the causal link of a suspected adverse reaction evaluates the probability that a vaccine and a temporally associated event are causally linked on the basis of the available evidence.
In the context of vaccinovigilance, a specific algorithm is used, constructed and validated by the World Health Organisation (WHO), which uses a systematic and standardised method that takes into account the temporal relationship between vaccination and event, the presence of evidence in favour or possible alternative explanations for the association, literature and pharmacovigilance evidence and biological plausibility.
The assessment of suspected adverse reaction reports containing adequate information can produce 3 possible interpretations:

- with a possible correlation, so that the causal association between event and vaccine is considered plausible;
- without a possible correlation, due to the presence of other factors that can justify the event;
- indeterminate, whereby the temporal association is compatible, but the evidence is insufficient to support a causal link.

Reports of suspected adverse reactions for which further investigation is required as they lack sufficient information to carry out the assessment, are categorised as non-classifiable in this transition phase.
(for further information:
http://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf?ua=1)

[4] Gee J et al. First Month of COVID-19 Vaccine Safety Monitoring - United States, December 14, 2020-January 13, 2021. MMWR. Morbidity and mortality weekly report.

The investigation by the Swiss agency, Swissmedic, revealed that the six deaths reported occurred in patients with pre-existing diseases aged between 85 and 92 years and were due to diseases such as infections, cardiovascular events or lung and respiratory tract diseases, which are common in this age group. Despite the coincidence in time with the vaccination, in none of the cases there is any concrete evidence that the vaccination was the cause of death[5].

The reports of deaths in nursing homes collected by the Norwegian Medicines Agency mainly concerned very frail or terminally ill patients and were reviewed by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency. The review did not reveal any safety concerns and the deaths were attributable to pre-existing conditions in people with serious diseases and/or undergoing palliative care[6].

Further evaluations of fatal case reports have also been carried out by regulatory agencies in other European countries (e.g. Belgium, Denmark and Germany) and, to date, no causal relationship with COVID-19 vaccines has been established[7, 8, 9].

[5] https://www.swissmedic.ch/swissmedic/it/home/news/coronavirus-covid-19/verdachtsmeldungen-covid-19-update.html
[6] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-january-2021_en.pdf
[7] https://www.fagg.be/nl/news/coronavirus_wekelijks_overzicht_bijwerkingen_covid_19_vaccins_van_4_februari_2021
[8] https://laegemiddelstyrelsen.dk/da/nyheder/temaer/Indberettede%20bivirkninger%20ved%20COVID-19%20vacciner/#total
[9] https://www.pei.de/SharedDocs/Downloads/DE/newsroom/dossiers/sicherheitsberichte/sicherheitsbericht-27-12-bis-26-02-21.pdf?__blob=publicationFile&v=6

Anaphylaxis

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

Vaccine anaphylaxis is a serious, potentially life-threatening and rare adverse event that occurs on average with a frequency of about 1 case per million, with symptoms rapidly affecting the respiratory tract or cardiovascular system, very often associated with symptoms affecting the skin and mucous membranes[10,11,12,13]. For a correct evaluation of these cases reported to the pharmacovigilance systems, a precise definition by the Brighton Collaboration Group is used which combines major and minor clinical criteria referring to the organs involved and, if available, to the blood values of an enzyme known as tryptase during the most acute phase of the reaction[14]. The most appropriate time interval to correlate anaphylaxis to a specific trigger is usually 1 hour, while for vaccines the time window is about 4 hours, according to international guidelines and recommendations[15,16].

With the introduction of the new vaccines against Covid-19, as expected, some cases of post-vaccine anaphylaxis have occurred, rapidly evaluated in order to verify their real frequency, understand their mechanisms and identify possible causes and risk factors. Currently, according to published US data, the reporting rate for mRNA vaccines is 4.7 cases of anaphylaxis per million doses administered for Pfizer vaccine and 2.5 cases per million doses administered for Moderna vaccine, most of which occurred after the 1st dose, within 30 minutes as administration, almost all in women and in most cases in people with a history of allergies or allergic reactions to other substances or a history of anaphylaxis[17]. The major accusation was against polyethylene glycol (PEG), also called macrogol, one of the components present in the lipids that surround mRNA and which is also present in other medicines and non-pharmaceutical products of common daily use. On the basis of the available data, hypersensitivity reactions to PEG are rare and difficult to investigate because no standardised tests are available for diagnosis. For the moment, therefore, the evaluation of vaccination risk in people with suspected allergy to PEG should be based essentially on clinical history[18, 19].

The pre-vaccination medical history is required by the vaccination plan for each person to be vaccinated and aims to detect the presence of any contraindications or precautions to vaccination. In addition, all vaccinated persons should remain under observation for at least 15 minutes after vaccination, but in the presence of risk factors for severe allergic reactions they should be observed for a longer time (60 minutes), as reported in the Vaccination Contraindications Guide.

[10] McNeil MM et al. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018;141 (2):463-472.
[11] Guida alla valutazione delle reazioni avverse osservabili dopo vaccinazione: http://www.agenziafarmaco.gov.it/sites/default/files/Guida_valutazione_reazioni_avverse_osservabili_dopo_vaccinazione_2.pdf
[12]Castells M C et al. Maintaining Safety with SARS-CoV-2 Vaccines. N Engl J Med 2021; 384: 643-9.
[13] Muraro A et al. EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014; 69 (8):1026-45.
[14] 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.
[15] Nilsson L et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr Allergy Immunol. 2017; 28 (7): 628-640.
[16] Kelso JM et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol 2012;130:25-43.
[17] 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.2021.1967.
[18] Turner PJ et al. WAO Anaphylaxis Committee. COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organ J. 2021; 14 (2): 100517.
[19] Sellaturay P et al. Polyethylene Glycole-Induced Systemic Allergic Reactions (Anaphylaxis). J Allergy Clin Immunol 2021; 9 (2): P670 – 675.

In line with the same guide, people suffering from severe allergy with severe persistent bronchial asthma should be vaccinated in a protected environment, i.e. under the supervision of medical staff trained to intervene with advanced cardio-pulmonary assistance.

Data analysis

In the period considered, 28 case reports were entered containing preferred terms clearly referable to anaphylactic/anaphylactoid shock/reaction, including 3 duplicate cases entered by both the vaccinating doctor and the company.
The 25 reports considered are all related to the Comirnaty vaccine and have been detailed according to the Brighton Collaboration case definition. Sixteen cases are compatible with a diagnosis of anaphylactic reaction ranging from 1 to 3 (anaphylaxis with decreasing diagnostic certainty). In 4 cases, the information is not sufficient to properly classify them (level 4) and 4 cases cannot be confirmed as anaphylaxis (level 5). One case was excluded because the symptoms appeared at a time distance incompatible with vaccination and following another triggering cause.
The characteristics of the 16 confirmed anaphylaxis cases (first 3 levels of the Brighton Collaboration Group case definition) are summarised in Table 4.

Table 4 *– Characteristics of anaphylaxis reports after Pfizer mRNA vaccine submitted to the Pharmacovigilance system in the period 27/12/2020 – 26/2/2021*

CHARACTERISTICS	**N. (%) of reports (Total 16)**
Age, median (range)	46 YEARS (37 – 58)
Female (%)	81 % (13 out of 16)
Hypotension	38 % (6 out of 16)
Adrenaline ADMINISTERED	31 % (5 out of 16)
Onset of symptoms, min.< 15	50 % (8 out of 16)
Within 60 minutes	63 % (10 out of 16)
Interval in minutes not specified*	37 % (7 out of 16)
Allergies or allergic reactions to foods, inhalants or insects	19 % (3 out of 16)
Allergies or allergic reactions to drugs or other vaccines	13 % (2 out of 16)
Previous anaphylaxis	6 % (1 out of 16)
First dose	81 % (13 out of 16)
Rate for one million first doses	5,5
Second dose	19 % (3 out of 16)
Rate for one million second doses	2,2
Anaphylaxis Classification (according to Brighton Collaboration)	
Level 1	37,5 % (6 out of 16)
Level 2	25 % (4 out of 16)
Level 3	37,5 % (6 out of 16)
Reporting rate (cases per million doses)	4,3

The reporting rate is 4.3 cases per million doses with a higher frequency in women, broadly in line with the data reported in the literature. At the time of reporting, the reported outcome was complete resolution or improvement in 85% of cases. Based on what is reported in the 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. The role of the clinical history of allergies or with previous allergic reactions as a risk factor needs further evaluation.

Further investigations on anaphylaxis cases are currently underway both at national and European level by the Pharmacovigilance Risk Assessment Committee (PRAC). At the moment no reports are present of anaphylaxis/anaphylactic shock to the Moderna and AstraZeneca vaccines, probably in relation to the limited number of doses administered.

Vaccination failure

With the collaboration of the Regional Pharmacovigilance Centres of the Regions Campania and Lombardy and the Prevention Department of the Region Lombardy

Whether someone vaccinated for COVID-19 has tested positive for coronavirus or has symptoms of the disease is not enough to say that the vaccine did not work. Each individual case should be evaluated on the basis of the characteristics of the virus (incubation period), the type of vaccine and the immune response (time it takes for the vaccine to determine a protective immune response) and the method of vaccination (correct administration of the vaccine). In general terms, we speak of vaccine failure when a complete and appropriate vaccination does not lead to an adequate immune response (*immunological vaccination failure*) or does not protect against the disease it intends to prevent (*clinical vaccination failure*), taking into account the biological characteristics of the infectious agent to be protected against, the methods of administration and the mechanism of action of the vaccine[20]. At the moment, there is not yet enough information to define immunological vaccination failure, because the immunological markers of protection are not yet clear. On the other hand, it is possible to define clinical vaccination failure which is particularly relevant in light of the indications of the vaccines and the goals of the vaccination campaign. The currently authorised COVID-19 vaccines, in fact, are *all indicated for active immunisation for the prevention of COVID-19, a disease caused by the SARS-CoV-2 virus*.
In the absence of a globally agreed case definition, we can speak of **clinically confirmed vaccination failure** when COVID-19 disease occurs as a result of the following 4 conditions:

Condition 1 – correct and appropriate immunisation according to the Summary of Product Characteristics and the National Immunisation Plan guidelines.
Condition 2 – adequate time interval from the administration of the second dose, taking into account the incubation time of SARS-CoV-2.
Condition 3 – laboratory diagnosis: the molecular test with RT-PCR using a nasopharyngeal swab must be positive (other types of tests are currently not sufficiently reliable).
Condition 4 – clinical definition of disease: systemic or respiratory symptoms consistent with a diagnosis of COVID-19 must be present.

When conditions 3 and 4 are not fully satisfied, we speak of SUSPECTED CLINICAL VACCINAL FAILURE.
It is important to clarify that these definitions may change over time as new information becomes available.

[20] Definition and Application of Terms for Vaccine Pharmacovigilance - Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance" (https://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf).

Analysis of cases of suspected vaccination failure entered in the National Pharmacovigilance Network

As of 26/02/2021, there were 49 reports in the National Pharmacovigilance Network referring to a possible lack of vaccination efficacy, all following the administration of two doses of Comirnaty vaccine. In 29 of these reports, condition 2 was not met, i.e. the swab result or symptom onset was observed immediately after administration of the second dose. These cases were excluded because the infection probably occurred before the administration of the 2nd dose or before the time necessary for an adequate immune response had elapsed.

Overall, 6 reports meet the 4 criteria for the definition of clinically confirmed vaccination failure with a reporting rate of 0.43 cases per 100,000 doses administered, relating only to subjects who have completed the vaccination cycle.

A further 14 reports are compatible with a definition of clinically suspected vaccine failure, including 3 with non-positive molecular swab (lack of laboratory diagnosis of COVID-19) and 11 without symptoms compatible with COVID-19 disease (lack of clinical diagnosis of disease).

These data refer to cases of vaccination failure reported in the context of the National Pharmacovigilance Network and are not representative of the real efficacy of vaccines in the field, which needs to be investigated with dedicated studies, currently underway in various countries. Further insights into this type of reporting are carried out as part of the post-marketing surveillance procedures required by legislation at European level and through efficacy studies in the field.