COVID-19 Vaccine Surveillance Report

4

27/12/2020 - 26/04/2021

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AIFA
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 April 2021, 309 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 (75%), which has been the most widely used (70.9% of administered doses), and only to a lesser extent the Vaxzevria vaccine (former COVID-19 Vaccine AstraZeneca; 22%) and the Moderna vaccine (3%)

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

Non-serious adverse events that resolve completely have mainly been reported

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

The evaluation of the Italian cases of intracranial and atypical venous thrombosis in subjects vaccinated with Vaxzevria is in line with the conclusions of the European signaling procedure

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

Reference period: 27/12/2020 - 26/04/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

ADMINISTERED DOSES

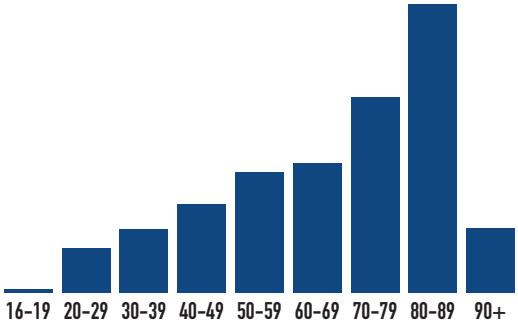
18.148.394

Comirnaty 70,9%
Moderna 7%
Vaxzevria 22%
Janssen 0,1%

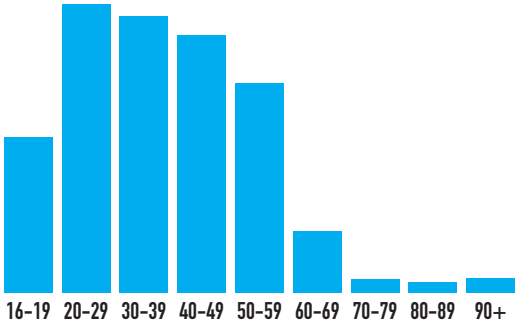
SUSPECTED ADVERSE REACTIONS

56.110

Comirnaty 75%
Moderna 3%
Vaxzevria 22%



ADMINISTRATIONS BY AGE RANGE

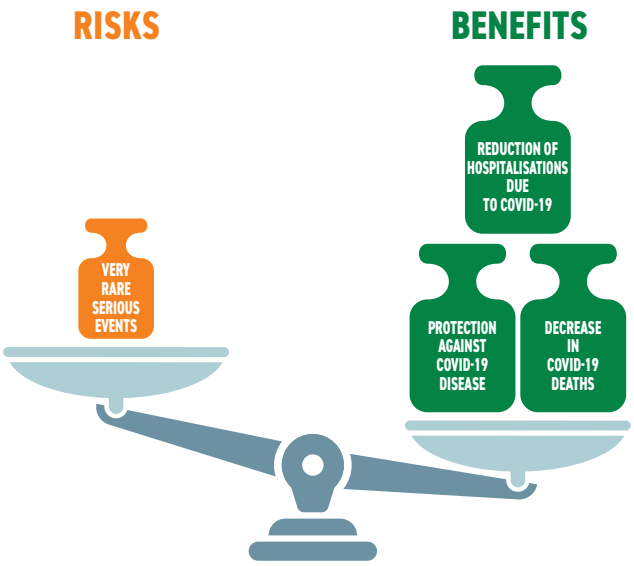


REPORTING RATE BY AGE RANGE

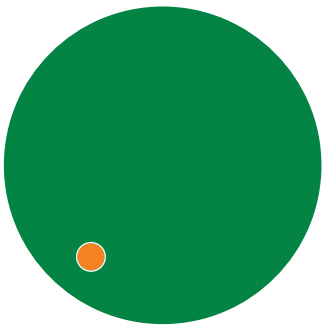
	1st dose	2nd dose
ADMINISTRATIONS PER DOSE	70,8%	29,2%

	1st dose	2nd dose
REPORTING RATE PER DOSE	299	333

VACCINATIONS



SERIOUS/NON-SERIOUS SUSPECTED ADVERSE REACTIONS



SERIOUS **8,6%**

NON-SERIOUS **91,2%**

0.2% OF SUSPECTED ADVERSE REACTIONS ARE NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)
PERIOD UNDER REVIEW: 27/12/2020 - 26/04/2021

During the period considered, **4 vaccines for COVID-19** were authorised and used in Italy, two based on messenger RNA 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 26/04/2021, a total of **18,148,394 vaccine doses** were administered, of which 70.9% Comirnaty, 22% Vaxzevria, 7% COVID-19 Moderna vaccine and 0.1% COVID-19 Janssen vaccine [2]. The number of suspected adverse reaction reports entered in the RNF on the same date is **56,110**, with a **reporting rate of 309 per 100,000 doses administered**.

Most reports refer to the Comirnaty vaccine (75%), followed by Vaxzevria vaccine (22%). Reports for the Moderna vaccine are 3% of the total. As of 26/04/2021, no reports are present relating to COVID-19 Janssen vaccine.
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 26/04/2021	Administered doses as of 26/04/2021	Reporting rate (per 100,000 administered doses)
Comirnaty	42,171	12,872,320	**328**
Moderna	1,649	1,276,863	**129**
mRNA active ingredient (unspecified brand)	14	-	-
Vaxzevria	12,276	3,977,851	**309**
Janssen	-	21,360	-
Total	***56,110***	***18,148,394***	***309***

[2] The number of doses administered as of 26/04/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 29/04/2021.

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.

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*

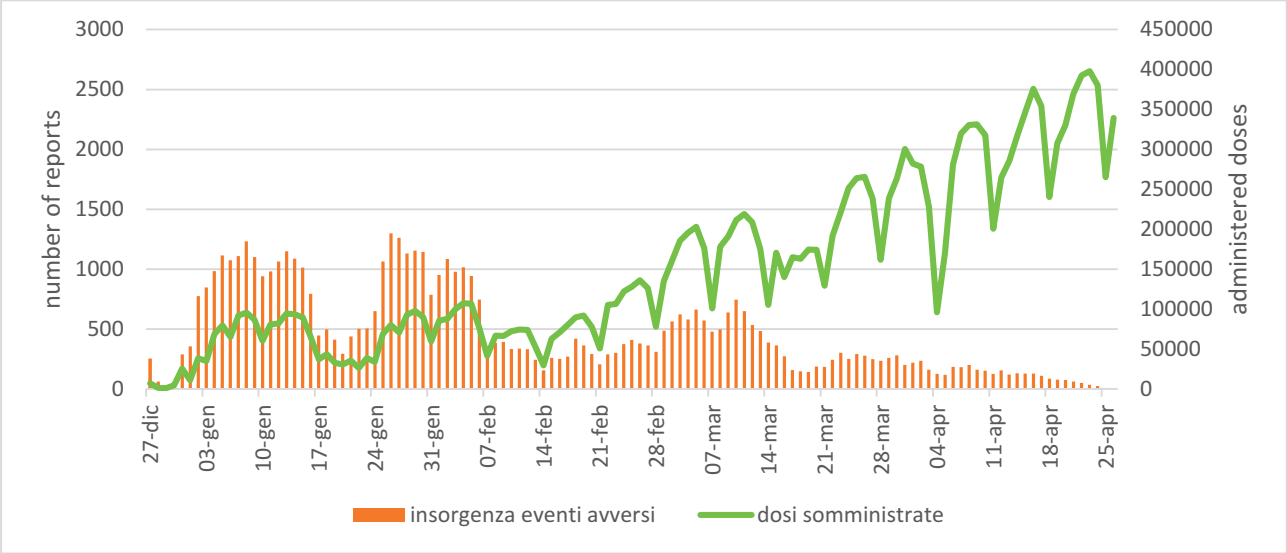
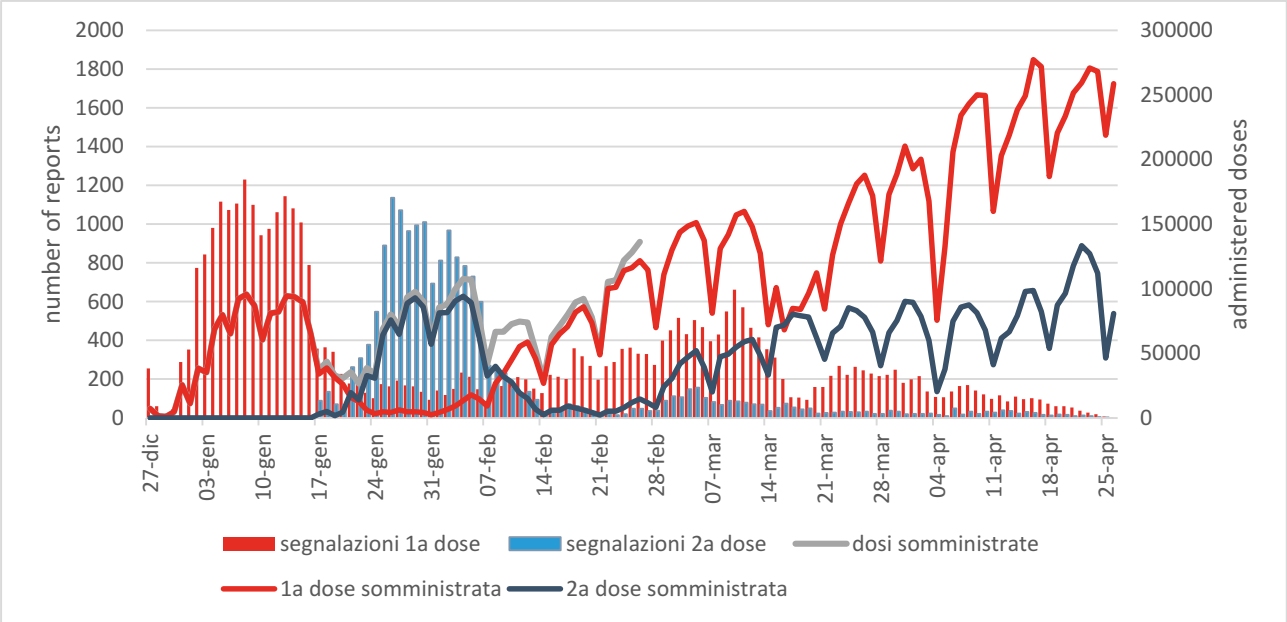


Figure 1b *– Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*



In the first 2 months of the campaign, the reporting trend is proportional to the doses administered. Subsequently, the increase in the number of administrations is not associated with a concomitant increase in reports. This "plateau" effect can be partly attributed to a delay in entering reports with respect to the onset date of the adverse event and/or from vaccine administration (for example, events reported upon booster), partly to the reduction in the number of reports of known and frequent adverse events, following increased knowledge on vaccine safety. Furthermore, the

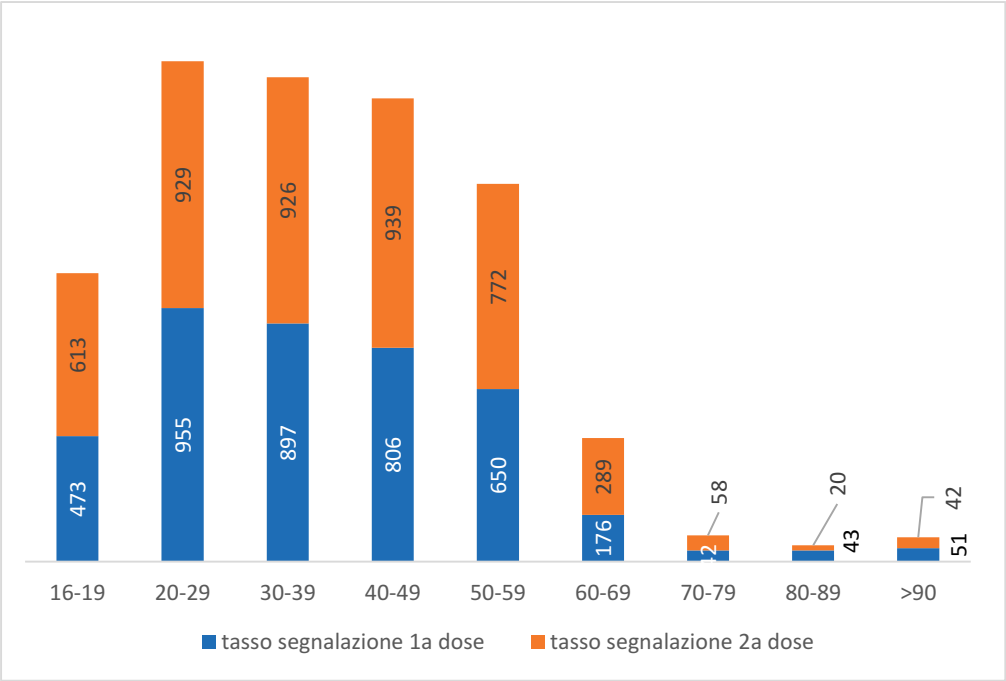
vaccinated population, initially composed mainly of healthcare professionals, more oriented to the reporting of adverse events, is now represented more by citizens who tend to rarely report events through the available methods[3].

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 age, sex and type of reporter

The average age is 47 years (age range 0.5-104 years, median age 47 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. No significant differences are observed between the reporting rates by age group in relation to the number of doses.

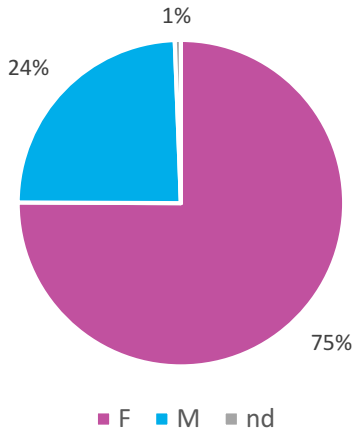
Overall, 8 reports relate to breastfed babies whose mother had been vaccinated, with age ranging from 20 days to 18 months. In addition to the 6 cases already described in the previous Report, 1 non-serious report was entered of aphthous stomatitis in a 9-month-old baby, 1 day after the administration of the second dose of Comirnaty to the mother, which completely resolved a few days later, and 1 non-serious case of irritability and loss of appetite in a 6-month-old girl, which appeared at an unspecified time after administration of the first dose of Comirnaty and resolved completely 3 days after onset.

Compared to a 57% exposure of the doses administered in women and 43% in men, 75% of the reports concern women, with a reporting rate of 404/100,000 doses administered, and 24% men,

[3] https://www.aifa.gov.it/en/content/segnalazioni-reazioni-avverse

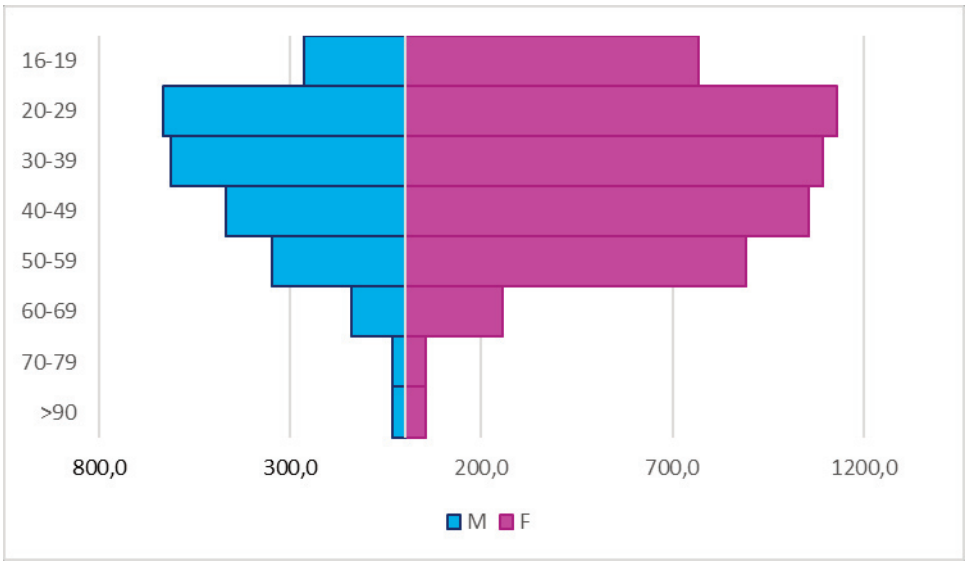
with a reporting rate of 176/100,000 doses administered, regardless of the dose and vaccine administered (gender is not reported in 1% of reports, Fig. 3) This trend is in line with other European countries.

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*



This 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[4, 5].

Figure 5 shows the distribution by type of reporter. It should be noted that most of the reports (about 81%) come from healthcare professionals, mainly doctors and pharmacists, while about 18% from patients/citizens. 97% of these reports are spontaneous.

[4] 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

[5] 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*

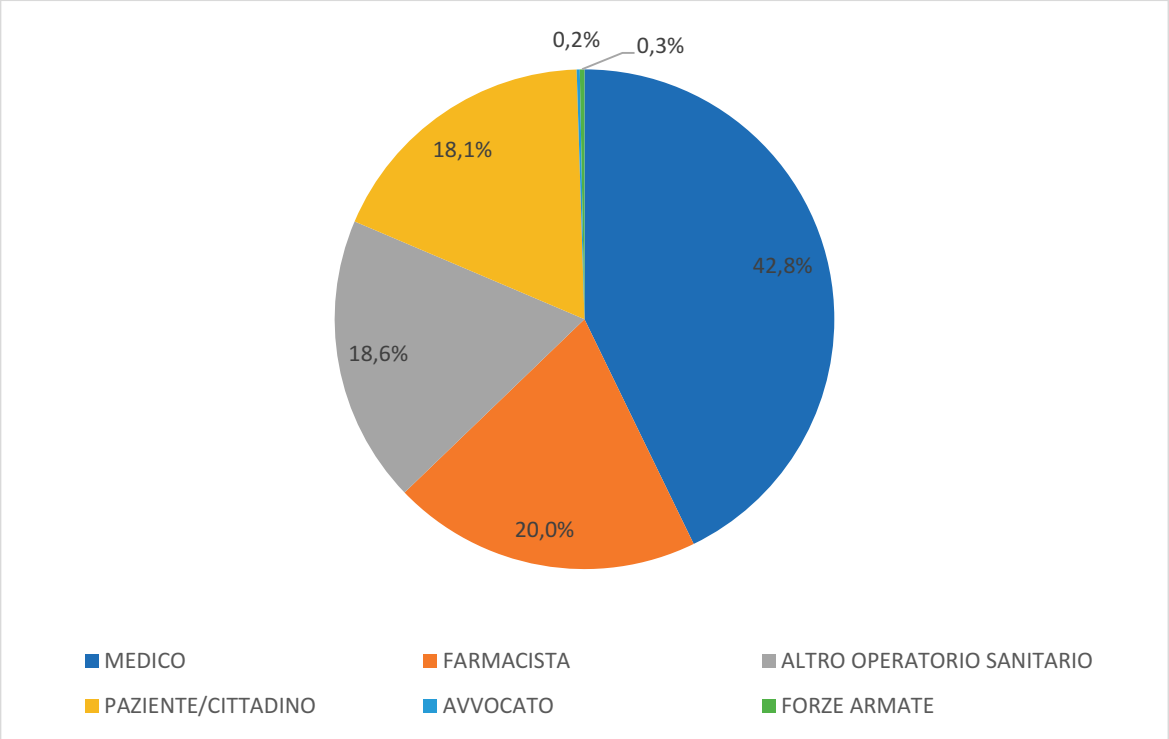


Table 2 shows the report distribution by time of onset from vaccination.

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

ONSET TIME	N° REPORTS	%
0 days	28,715	51.2%
1 day	18,888	33.7%
2-7 days	4,821	8.6%
>7 days	2,086	3.7%
Not definable	1,600	2.9%
Total	***56,110***	***100%***

As in the previous reports, regardless of vaccine, dose and type of event, the reaction occurred on the same day as vaccination or the following day (about 85% of cases). Only rarely did the event occur beyond the following 48 hours.

Distribution by seriousness and outcome

91% of the reports entered as of 26/04/2021 relate to non-serious events, with a reporting rate equal to 282/100,000 administered doses. The figure is similar to the cumulative rate for all the events because non-serious reports represent the majority.

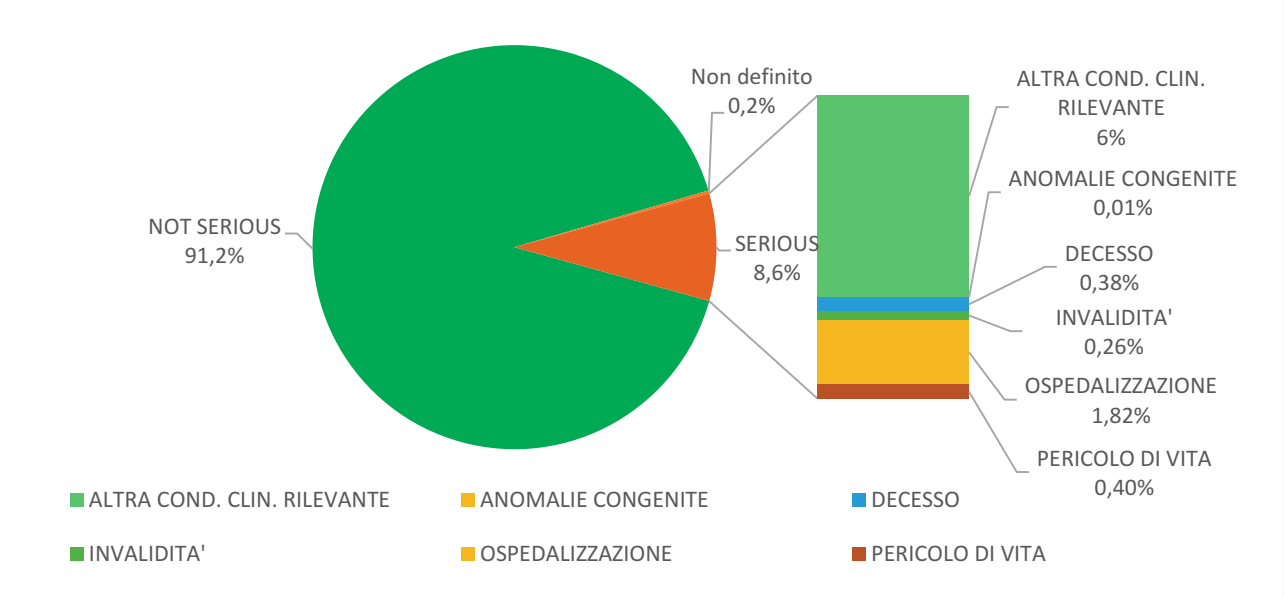
Serious reports are 8.6% of the total, with a rate of 27 serious events per 100,000 administered doses, regardless of the type of vaccine, of the dose administered (1st or 2nd dose) and of the possible causal role of the vaccination. The reporting rates of serious events for each vaccine are 24 (Comirnaty), 18 (Moderna), 39 (Vaxzevria) 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)*



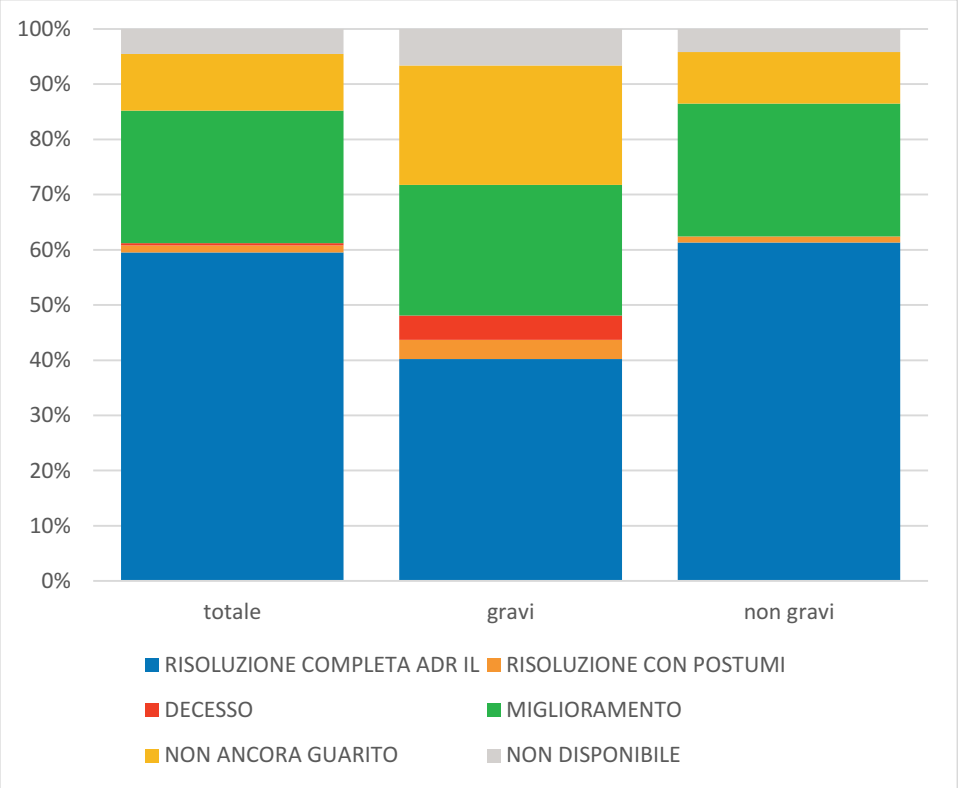
Most serious reports are classified as "other clinically relevant condition", i.e., alerting the subject and/or the reporter without entailing a specific intervention in hospitals.

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

85% of the reports refer to non-serious adverse events with full recovery or improvement already at the time of reporting. 63% 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 26/04/2021, the causal link according to the WHO algorithm was included in 71% of reports of serious adverse events. Overall, 41% of all serious reports are related to vaccination, with a reporting rate of 11/100,000 doses, regardless of vaccine type and dose number. Full recovery or improvement of the reaction are reported in 84% of reports of relatable serious adverse events. Most of these reports are categorized as "other clinically relevant condition" (82% of all relatable serious reports), with complete resolution or improvement at the time of reporting in 84% of cases and are predominantly represented by fever or high fever with headache and/or muscle and joint pain, in the context of a flu-like syndrome with symptoms of high intensity or duration. These reports rarely include painful or non-painful lymphadenopathy, diffuse skin reactions such as erythema and facial paralysis. Serious reports related to hospitalisation or life-threatening (16% of all serious related) result in full recovery or improvement of the event at the time of reporting in 80% of cases and mainly concern cases of high fever with respiratory symptoms and cases of severe allergic reaction up to anaphylactic shock. In the remaining 20% of cases, the outcome at the time of reporting is mainly reported as "not yet recovered" or "not available" at the time of reporting.

Distribution by number of doses

In the period considered, the number of vaccinees who completed the vaccination cycle remained substantially stable for mRNA vaccines, amounting to 30% of the overall number of administered doses. In contrast, less than 1% of patients who received the first dose of Vaxzevria completed the vaccination course. No differences in reporting rates were observed between the first and second dose of Comirnaty or Moderna vaccine as shown in Table 3. The reporting rate for 2nd dose of Vaxzevria vaccine is strongly influenced by the low number of doses administered and therefore, at moment, it is not reported since it is not significant.

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 first and second dose of the Comirnaty and Moderna vaccine. Evaluation of adverse events after the second dose of Comirnaty confirms a trend of reported suspected adverse events coherent with what described for the first dose, with fever, headache and fatigue frequently reported.

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	315	348	328
Moderna vaccine	132	121	129
Vaxzevria	307	-	309

Distribution by type of event

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

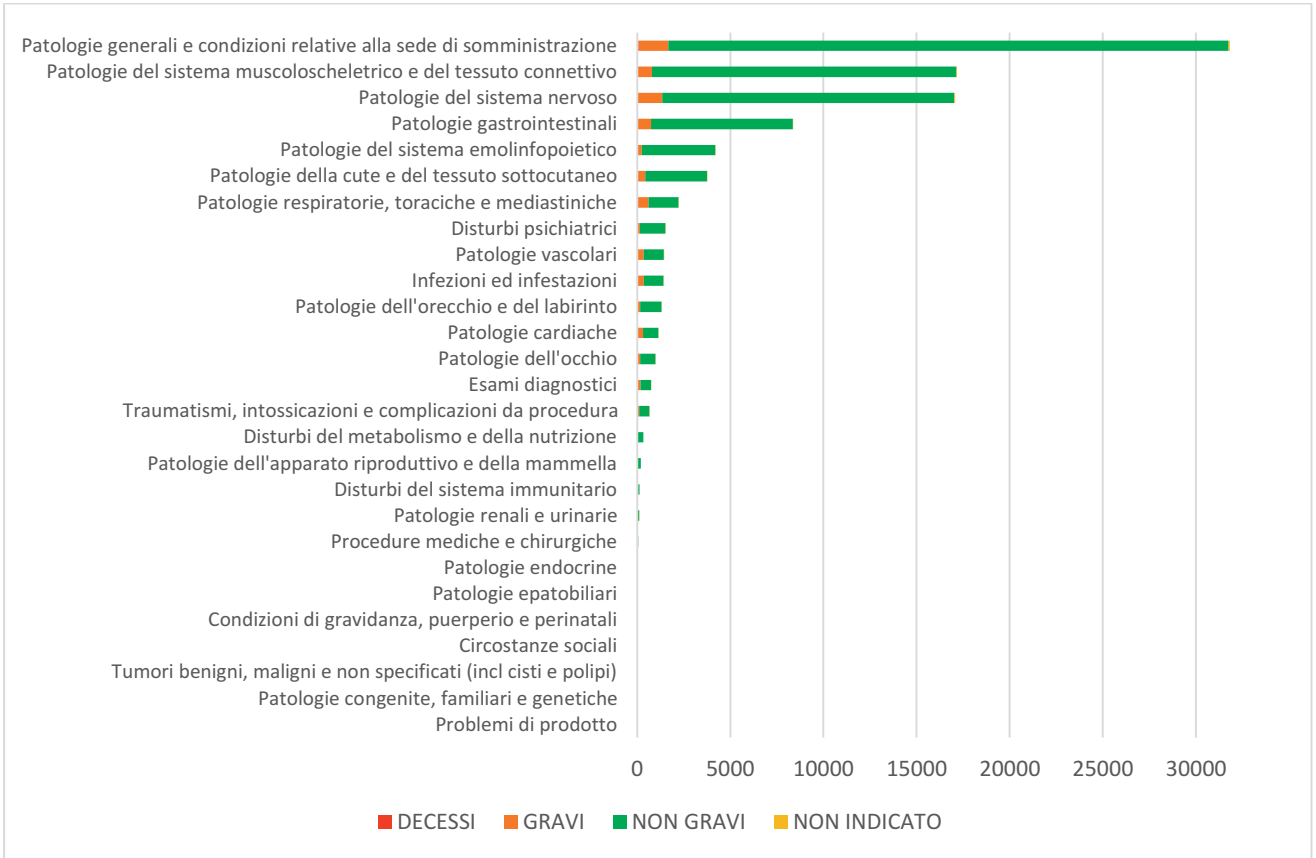
How are adverse events classified in reports?

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 **suspected adverse events following vaccination with Comirnaty** relate to the system organ class of General Disorders and Administration Site Conditions (75%), predominantly fever, injection site pain, asthenia/fatigue and general malaise (non-serious in 94% of cases), followed by pathologies of the musculoskeletal system and connective tissue (41%), especially myalgia, arthralgia and musculoskeletal pain (non-serious in 95% of cases).

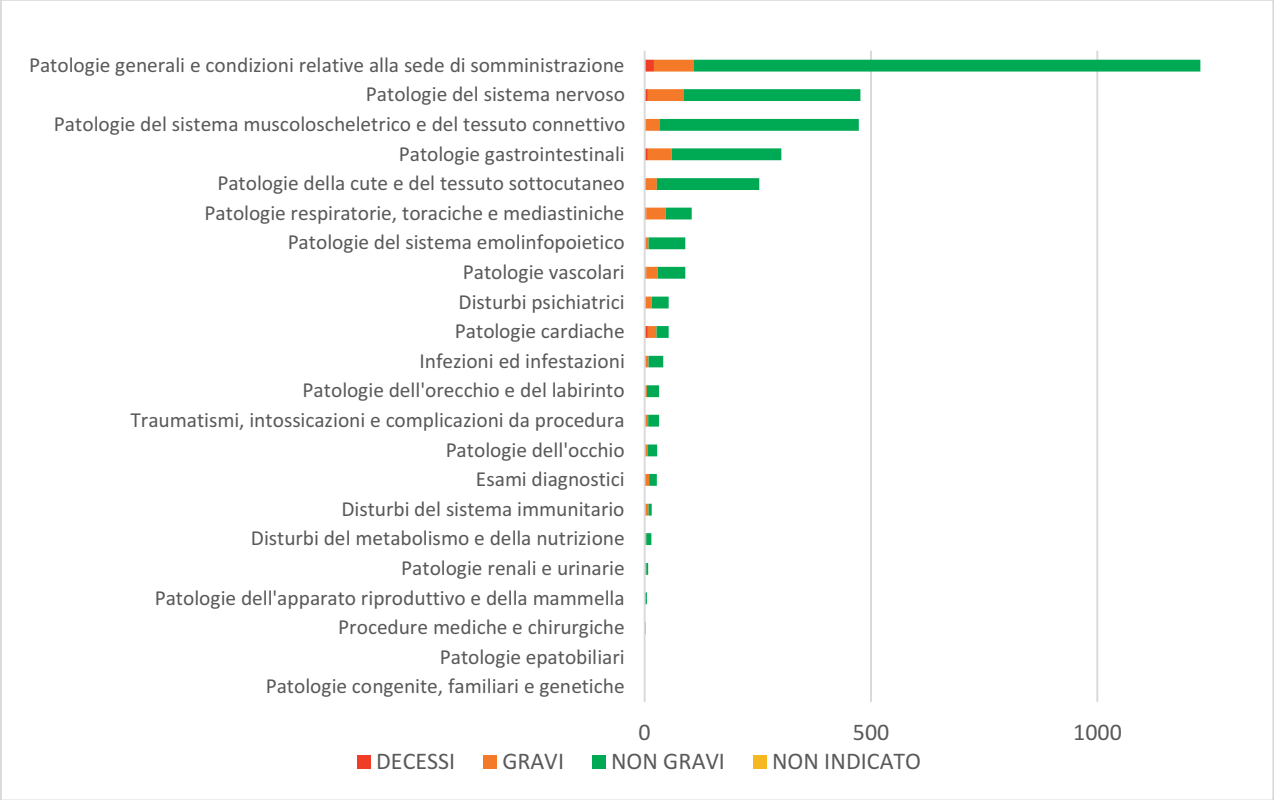
Figure 8 *- Distribution of adverse events after Comirnaty vaccine by system organ class (SOC)*



Overall, 7% of reports for the Comirnaty vaccine were entered as serious. Regardless of whether it is a 1st or 2nd dose and of 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. Less frequently reported are nausea, lymphadenopathy, paraesthesia, vomiting, diarrhea, dizziness and allergic-type reactions; more rarely reported are tachycardia, hypertensive or hypotensive crisis and facial paralysis.

Most of the **events reported for the Moderna vaccine** relate to the system organ class of General Disorders and Administration Site Conditions (74%) and are predominantly fever, asthenia/fatigue and injection site pain, classified as non-serious in 92% of cases. Events falling under Nervous system disorders (29%) follow in order of frequency, especially headache, paraesthesia and dizziness, classified as non-serious in 79% of cases.

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

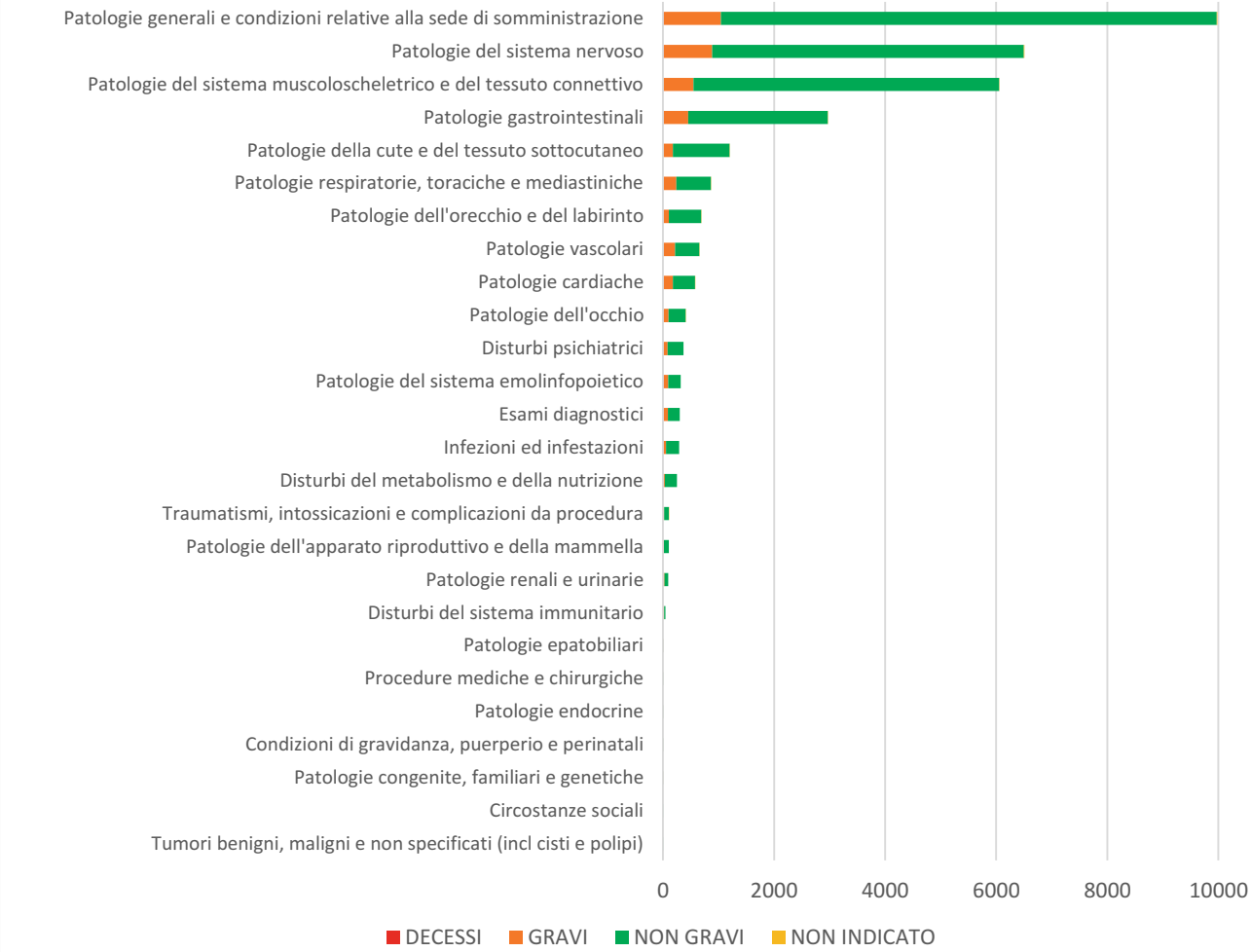


11% of report sheets concerning the Moderna vaccine report serious adverse events. The most frequent serious reactions correspond in part to the distribution of all reports and mainly refer to systemic symptoms and to the musculoskeletal system (high fever, diffuse myalgia and arthralgia, etc.). Other events are reported with a frequency equal to or less than 2 reports.

Most of the **events reported for the Vaxzevria vaccine** are related to the system organ class of General Disorders and Administration Site Conditions (81%) and are mainly fever, chills, injection site pain and asthenia/fatigue. 89% of these reports are classified as non-serious. Following in order of frequency: events falling under Nervous system disorders (53%), especially headache, paraesthesia and dizziness, classified as non-serious in 83% of cases, and under Musculoskeletal

system and connective tissue disorders (49%), mainly represented by widespread muscle and joint pain, classified as non-serious in 90% of cases.

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



12.4% of adverse event reports for this vaccine are classified as severe and mainly refer to severe headache and high fever with any other associated systemic symptoms, mainly arthralgia and myalgia. Other preferred terms reported less frequently are: chills, dizziness, drowsiness, difficulty in breathing and generalised pain.

With regard to anaphylactic reactions, the number of reports in the period was limited, therefore, no additional information is present in this edition of the Report which requires a dedicated focus.

Fatal cases after COVID-19 vaccination

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

In Italy, as of 26 April 2021, 223 reports with a "death" outcome have been entered, with a reporting rate of cases with a fatal outcome of 1.23/100,000 doses for all vaccines. 55.6% of cases concern women, 43.4% men while 0.89% (2 cards) do not report this data. The mean age is 79.1±15.9 years (range 26-104 years). The number of cases and the relative reporting rates for each type of vaccine is shown in Table 4 and is in line with what emerged in previous Reports.

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

Vaccine	Fatal cases	Rates per 100,000 administered doses
Comirnaty	150	1.17
Moderna	39	3.05
Vaxzevria	34	0.85
Total	**223**	**1.23**

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. For the purposes of a correct interpretation of these data it is therefore important to take into account that:

1) the Comirnaty vaccine is the most widely administered vaccine, in a population that is more heterogeneous in age in comparison to the Moderna vaccine, and, therefore, has the greatest weight in calculating the rate of death reports of the entire vaccinated population;
2) the Moderna vaccine was mainly administered to older or very frail patients, resulting in a higher probability of coincident fatal events;
3) the Vaxzevria vaccine was used, on average, in a younger and less fragile population during the period under review, resulting in a lower reporting rate of deaths.

The reporting rates observed in Italy are in line with those reported internationally, especially by the United Kingdom Regulatory Agency (MHRA - Medicines and Healthcare products Regulatory Agency), which has extensively used and monitored three of the four vaccines currently administered on our territory. In fact, according to data updated to 29/04/2021, the reporting rate of fatal events in the United Kingdom, regardless of causation, is equal to 1.9/100,000 doses administered for the Pfizer/BioNTech vaccine (347 reports for 18 million doses administered), 3.1/100,000 for AstraZeneca vaccine (685 reports for 26.4 million doses), 2/100,000 for Moderna vaccine (2 for 0.1 million doses)[6].

As for the Italian cases, the fatal event was reported after the first dose in 141 cases and after the second dose in 59 cases (the data is missing in 23 reports), with a time lapse between the administration of the vaccine and the reported date of death ranging from two hours up to a

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

maximum of 28 days. There are no cases of death as a result of anaphylactic shock or major allergic reactions, while cardiovascular events are often reported in patients with a history of previous diseases or cardiovascular risk factors.
In fact, out of 223 total cases reported, 191 reports are related to frail patients with one or more existing or previous pathologies and in polytherapy, especially cardiovascular diseases, metabolic diseases, oncological diseases, neurodegenerative diseases (Alzheimer's disease), respiratory diseases, severe renal or hepatic diseases and diseases of the haemolymphopoietic system.
58.7% of the cards (131 out of 223) had a WHO algorithm causality assessment at the time of card extraction from the pharmacovigilance database. On the basis of the outcome of this assessment, the causal link was not correlated in 56% of cases, indeterminate in 39% and unclassifiable in 3% due to lack of information necessary for the application of the algorithm.
The reports found to be correlated are 3 (2%), of which one case already described in the previous Report and two new cases referring to a 46-year-old man and a 32-year-old woman, who died 12 days after the administration of the 1st dose of Vaxzevria vaccine for thrombotic events and concomitant thrombocytopenia, detailed in the dedicated focus.
A preliminary epidemiological assessment was carried out to verify whether the cases with a fatal outcome observed after vaccination were different from the expected number of deaths based on ISTAT 2019 data. This analysis confirmed that the number of observed events is significantly lower than expected, considering both the age range and the time elapsed between vaccination and death. As for this assessment, please note that: (a) pharmacovigilance databases are not registers but a collection of all spontaneous reports in which the reporter believes that there may be a suspicion of a relationship to be investigated between vaccination and adverse event that deserves further study (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. Regardless of that, it is confirmed that the number of reports with a fatal outcome after vaccination is significantly lower than expected by age group and time elapsed after vaccination. The reported cases represent a suspicion of a causal relationship between vaccination and adverse event which, as discussed in detail, is confirmed only in very few cases and which represents for most of the reports only a temporal concomitance between the two events.

In conclusion, the reporting trend of cases with a fatal outcome is proportional to the number of vaccinated subjects. In most of the reports, information on individual cases makes it possible to exclude a correlation with vaccination. Furthermore, the number of cases observed is significantly lower than the expected deaths in the various age groups and time windows after vaccination. In this sense, the collection of information continues to allow the causal or temporal association of vaccines to be assessed as accurately as possible and the careful monitoring of reported cases for the continuous evaluation of the safety profile of these medicines.

Thromboembolic events and Vaxzevria (formerly COVID-19 Vaccine AstraZeneca)

As illustrated in the previous report, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) evaluated a signal related to thromboembolic events following vaccination with Vaxzevria in March 2021.

On the basis of the available data, the only events for which a role of the vaccine could not be completely excluded were thrombosis of the vessels draining blood from the brain (thrombosis of the intracranial venous sinuses or CSVT) and thrombosis of several blood vessels in atypical site and in some cases associated with low platelet levels (thrombocytopenia). These are very rare adverse events, reported mainly in women under the age of 55, which have also been evaluated with the support of an interdisciplinary group of independent European experts.

What is the PRAC?
The PRAC is a committee consisting of 2 representatives from each Member State of the European Union and the European Economic Area, as well as 6 experts in various fields, appointed by the European Commission and representatives of health professions and patient associations; it is responsible for the evaluation and monitoring of the safety of medicinal products for human use. The PRAC is responsible for identifying and assessing the risk of adverse reactions and, more generally, for periodically reassessing the benefit-risk balance of all medicinal products authorised in Europe, as well as for risk minimisation measures, risk communication, and the design and evaluation of post-authorisation safety studies. On these issues, the PRAC provides recommendations to the other EMA Committees and the European Commission.

Following this second evaluation, the EMA concluded that overall the benefits of the vaccine outweigh the risks and that venous thrombotic events in unusual sites, especially in the cerebral veins (cerebral venous sinus thrombosis - CVST) and abdominal veins (splanchnic vein thrombosis), associated with low platelet levels should be listed as very rare side effects of Vaxzevria. Although most cases have occurred in women under the age of 60, it has not been possible to confirm predisposing risk factors related to age and sex, also taking into account that this vaccine has mainly been administered to people under the age of 60 and predominantly women. Furthermore, it was not possible to identify specific predisposing conditions for these very rare adverse events.

What is a safety signal?
A 'safety signal' is a hypothesis of a potential causal association between a medicinal product and a previously unobserved event or group of events, or a new aspect of an already known association. When this hypothesis is considered sufficiently possible to justify further investigation, the signal is confirmed and evaluated on the basis of all available information, in order to intervene with appropriate prevention, minimisation or risk communication actions and to make the use of the drug safer. The set of all these activities is part of the process called Signal Management, which involves the EMA, all the Regulatory Authorities of the Member States (including AIFA) and the Marketing Authorisation Holders, which are obliged to perform continuous monitoring of the data recorded in the European database of suspected adverse reaction reports (Eudravigilance), cooperate in monitoring data and inform each other of any new risks or if the risks already known have changed and if the benefit/risk ratio of the drug is modified. The assessment of pharmacovigilance signals is collegial and involves the PRAC, which provides recommendations that are regularly published on the website of the EMA.

The EMA has also recommended that the use of Vaxzevria during national vaccination campaigns should consider the pandemic situation and the availability of vaccines in individual countries. At the present state of knowledge, the mechanism underlying these thromboses associated with thrombocytopenia is unknown and an immune-related phenomenon is hypothesised similar to that

observed very rarely during treatment with heparin (heparin-induced thrombocytopenia or HIT). For this reason, the monitoring of these events will continue and the PRAC has requested new studies and modifications to the ongoing clinical trials and will continue to monitor these events with further possible revisions of the data[7]. In any case, following this further assessment, the EMA has further updated the safety information in the Summary of Product Characteristics and Package Leaflet of the Vaxzevria vaccine, in the sections on side effects and on the warnings and precautions for use.

At the end of this further evaluation phase, on 07/04/2021, the Ministry of Health, through the publication of Circular no. 0014358-07/04/2021-DGPRE and following the opinion expressed by AIFA's Scientific-Technical Committee on 07/04/2021, recommended a preferential use of the Vaxzevria vaccine in people over 60 years of age, even if this is still approved from 18 years of age, on the basis of current evidence, considering the low risk of adverse reactions of the thromboembolic type compared to the high mortality rate from COVID-19 in older age groups. In the same circular, it is also stated that, based on the data available to date, those who have already received a first dose of the Vaxzevria vaccine can complete the vaccination cycle with the same vaccine[8].

The investigation at national level of the reports from Italy was conducted with the support of a "Working Group for the evaluation of thrombotic risks from anti-COVID-19 vaccines", made up of some of the leading national experts in thrombosis and haemostasis.

Data analysis

As of 26 April 2021, a total of 29 reports of intracranial venous thrombosis and 5 cases of venous thrombosis in unusual sites for the vaccine Vaxzevria have been entered in the National Pharmacovigilance Network. Most of these events (22 cases, 65%) involved women with an average age of about 48 years and only about 1/3 of the cases involved men (12 cases, 35%) with an average age of about 52 years. The mean time to onset was approximately 8 days after administration of the 1st dose of the Vaxzevria vaccine. Overall, in about 53% of cases, the thrombotic event is associated with a reduction in the total number of platelets.

In most cases of intracranial venous thrombosis, the onset symptom was headache, more often widespread, very intense and associated with at least one other symptom including general malaise, drowsiness and vomiting. The cases of venous thrombosis in an atypical site, on the other hand, only involved the abdominal venous structures (mesenteric vein, portal vein, etc.) with a clinical presentation characterized mainly by important gastrointestinal symptoms (especially abdominal pain). In about 30% of cases (10), the outcome reported at the time of reporting was resolution of the adverse reaction or improvement, while 23% of cases were not yet cured at the time of reporting.

The causal link assessed with the WHO algorithm was found not to be correlated in 2 cases (1 of which with death), due to the presence of other alternative causes of the event, indeterminate in 14 cases, due to the presence of confounding factors that do not allow to completely attribute the event to the vaccine or to exclude its role, and correlated in 5 cases (including 2 deaths described above), due to the absence of alternative explanations to the event. One case was found to be

[7] https://www.aifa.gov.it/-/vaccino-covid-19-astrazeneca-ema-trova-un-possibile-collegamento-con-casi-molto-rari-di-trombi-inusuali-associati-a-bassi-livelli-di-piastrine

[8] https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=79629&parte=1%20&serie=null

unclassifiable due to the inability to find useful information for evaluating the case and 12 cases, for which further data is pending, have not yet been evaluated.
On the base of the anamnestic information obtained at the follow-up, thanks to the prompt collaboration of the Regional Centers and the Local Pharmacovigilance Managers, at the moment no specific risk factors have been identified for the onset of intracranial or atypical venous thrombosis temporally associated with the Vaxzevria vaccine.

General considerations on data

The time trend of the main parameters analysed in the different reports published so far is summarised in table 5.

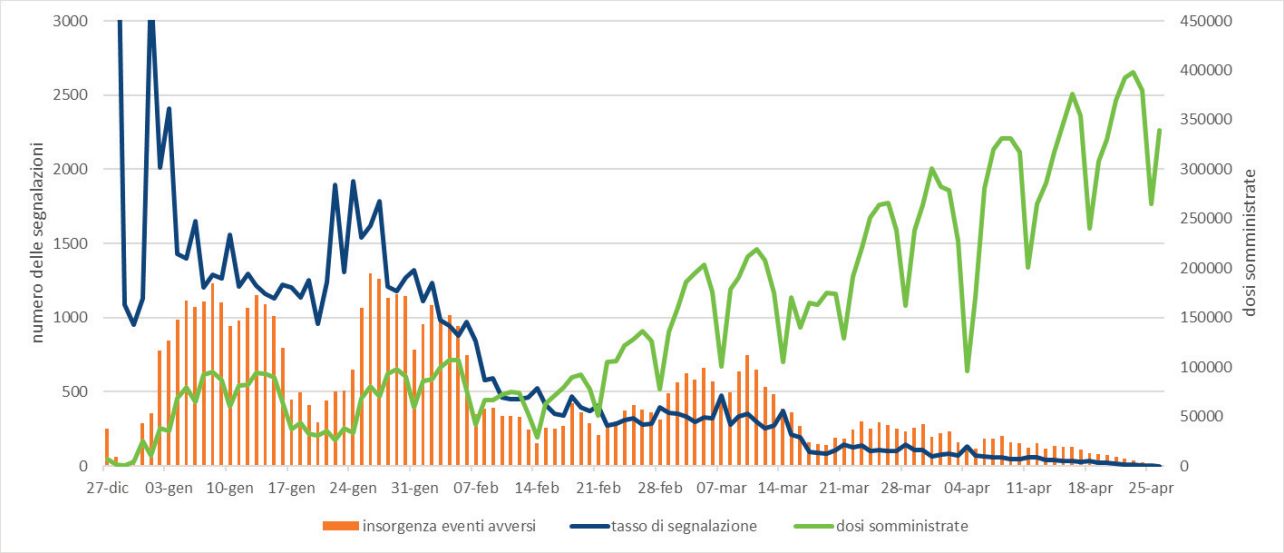
Table 5 *– Summary data Report#1 - Report#4*

	Report#1	**Report#2**	**Report#3**	**Report#4**
	as of 26/01/2021	**as of 26/02/2021**	**as of 26/03/2021**	**as of 26/04/2021**
administered doses	1,564,090	4,118,277	9,068,349	18,148,394
reporting of adverse events	7,337	30,015	46,237	56,110
reporting rate	469	729	510	309
reporting rate for men	293	424	299	176
reporting rate for women	561	907	645	404
reporting rate for first dose	515	773	496	299
reporting rate for second dose	225	785	540	333
reporting rate of serious adverse reactions	34	44	36	27
reporting rate of serious adverse reactions for men	22	28	23	18
reporting rate of serious adverse reactions for women	42	54	44	33
reporting rate of serious adverse reactions with no “clinically relevant” cases	8.9	8.1	8.5	8.8
reporting rate of deaths	0.8	0.97	1.1	1.23
Source of reporting				
Doctor	47%	46%	44%	42%
Pharmacist	22%	19%	20%	20%
Other healthcare professional	25%	26%	21%	19%
Patient/Citizen	6%	9%	15%	18%
Lawyer	0%	0%	0.12%	0.20%
Armed Forces	0%	0%	0.07%	0.30%
Comirnaty				
reporting rate	471	769	535	328
reporting rate for first dose	517	756	525	315
reporting rate for second dose	278	790	549	348

reporting rate of serious adverse reactions	na	45	33	24
Moderna vaccine				
reporting rate	277	333	227	129
reporting rate for first dose	277	335	216	132
reporting rate for second dose	-	322	264	121
reporting rate of serious adverse reactions	na	26	22	18
Vaxzevria				
reporting rate	-	326	477	309
reporting rate for first dose	-	326	477	307
reporting rate for second dose	-	-	-	-
reporting rate of serious adverse reactions	-	31	50	39

The trend in the reporting rate for all vaccines shows a peak in the second month of observation (where only 2 vaccines were available against COVID-19). It then decreases in the two subsequent months (Figure 11), while the rates of serious adverse reactions and fatal cases remain stable (Figure 12).

Figure 11 *– Trend in reports, rates and doses over time*

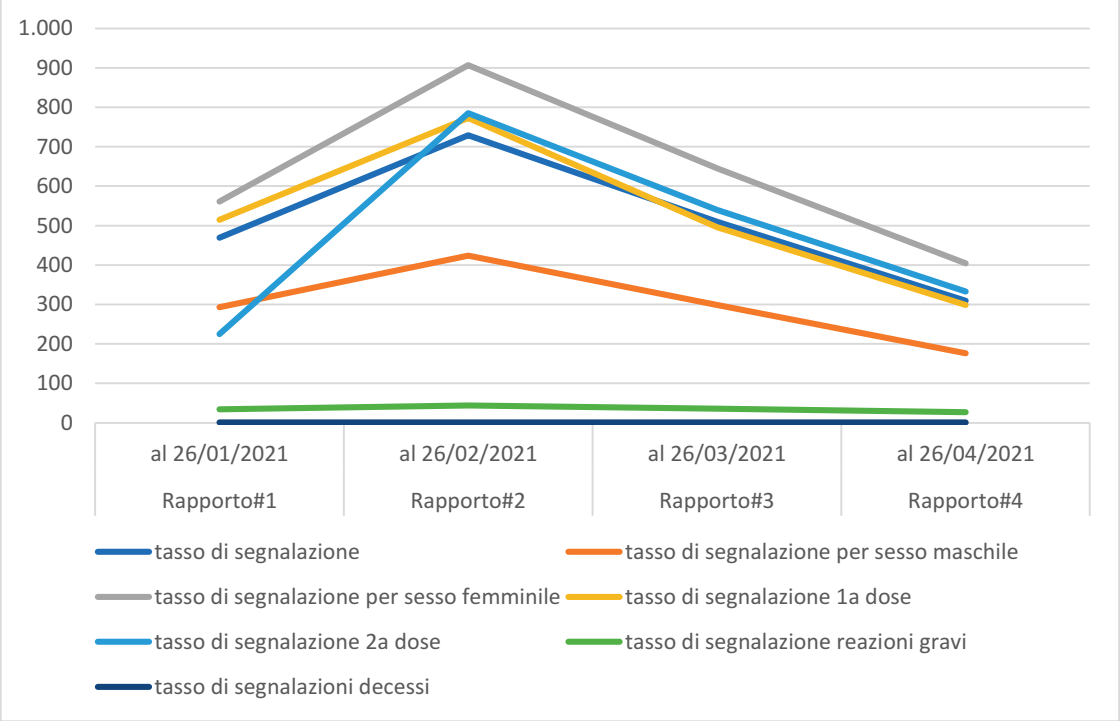


A downward trend is also observed for reporting rates for number of doses and gender (Figure 12). Such changes may be due to an increased knowledge on vaccines, leading to a reduction in reports of non-serious adverse events and expected reactions, as assumed by the Weber effect[9]. This phenomenon, described in the 80s, provides for an increased reporting of suspected adverse reactions at the early stages of the authorisation of a medicinal product. This is likely to be caused

[9] Weber JCP. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. In: Rainsford KD, Velo GD, editors. Side-effects of Anti-inflammatory Drugs, Advances in Inflammation Research. New York: Raven Press; 1984:1–7

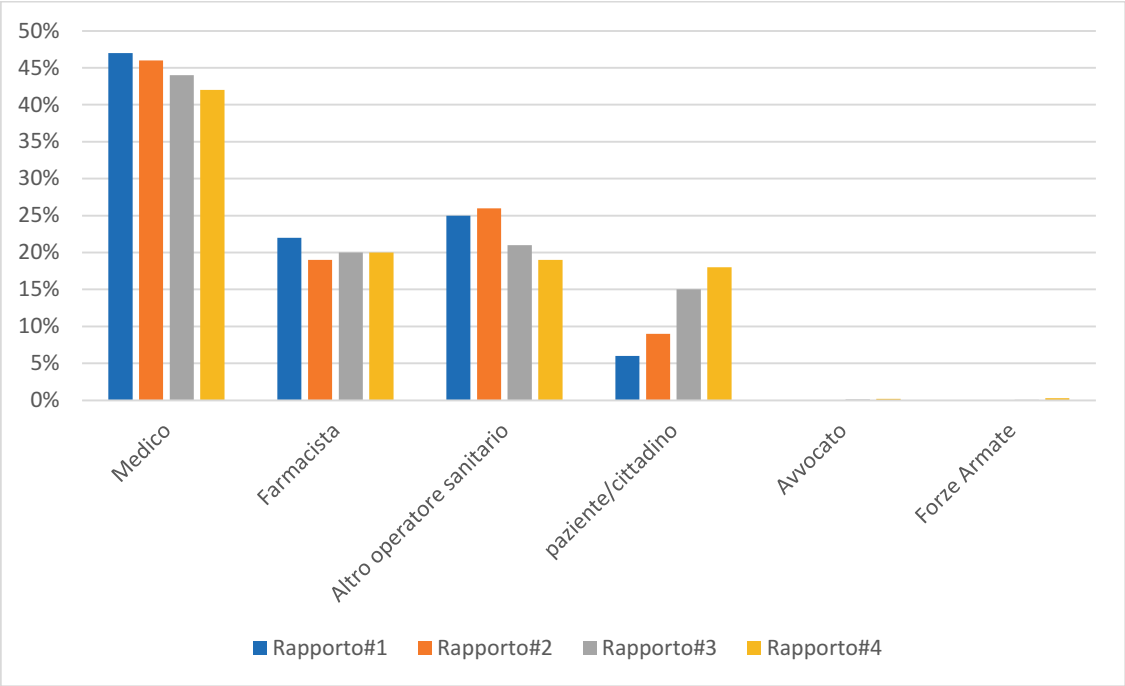
by a lower level of knowledge of the product at the beginning of the "real world" use, leading to a greater focus on reporting. The reporting then decreases rapidly over time. In general, the Weber effect for new medicines authorised under non-emergency conditions is generally observed in the second year after their introduction on the market. In the current pandemic scenario and under mass vaccination conditions, a Weber effect pattern for COVID-19 vaccines has been observed over a significantly shorter period of time, also in relation to the high number of doses administered and the different information disseminated.

Figure 12 *– 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%), as expected given the administration of these vaccines in hospitals and the role of the vaccinator or GP (Fig. 13). The higher percentages of reports from healthcare professionals (HCPs) observed in the first 2 reports may also depend on the fact that HCPs were the main target of the first phase of the vaccination campaign. Conversely, the increase in the number of citizen reports (from 6% to 18%) is in line with them being increasingly targeted by the vaccination campaign.

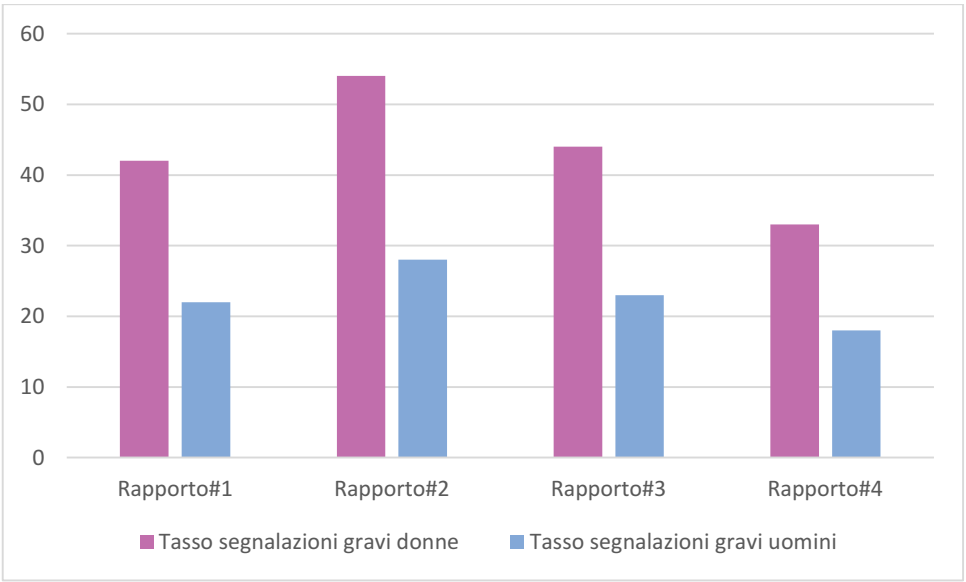
Figure 13 *– Trend in the type of source of reporting over time*



Despite being numerically small, reports by Armed Forces show an increasing trend over time. In addition, COVID-19 vaccine reports account for around 70% of all reports coming from this source of reporting.

The trend in reporting rates by gender is maintained over time, with a figure approximately twice as high for women as for men, both overall and for serious reactions alone (Figure 14).

Figure 14 *– Trend in reporting rates of serious adverse reactions by gender*



This finding is in line with what is described in the reports of other regulatory authorities, such as the French and German, and could be indicative of a gender difference, the characteristics of which require further analysis[10] [11].

[10] https://ansm.sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-contre-la-covid-19-periode-du-16-04-2021-au-22-04-2021

[11] https://www.pei.de/SharedDocs/Downloads/EN/newsroom-en/dossiers/safety-reports/safety-report-27-december-2-april-2021.pdf?__blob=publicationFile&v=4