COVID-19 Vaccine Surveillance Report

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27/12/2020 - 26/03/2021

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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**.

HIGHLIGHTS

As of 26 March 2021, 510 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 (81%), which has been the most widely used (77% of administered doses), and only to a lesser extent the Vaxzevria vaccine (ex-COVID-19 Vaccine AstraZeneca; 17%) and the Moderna vaccine (2%)

The trend in reports and related rates are substantially stable

Non-serious adverse events were mostly reported that resolve completely (87% of cases)

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

The suspected adverse reactions reported are in line with the information already known on vaccines currently used in Italy

Unknown adverse events are continuously monitored at both a national and European level

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

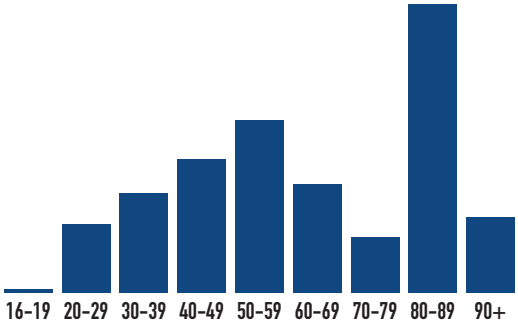
Reference period: 27/12/2020 - 26/03/2021

SUSPECTED ADVERSE REACTIONS TO COVID-19 VACCINES

ADMINISTERED DOSES

9,068,349

Comirnaty 77%
Moderna vaccine 5%
Vaxzevria 18%



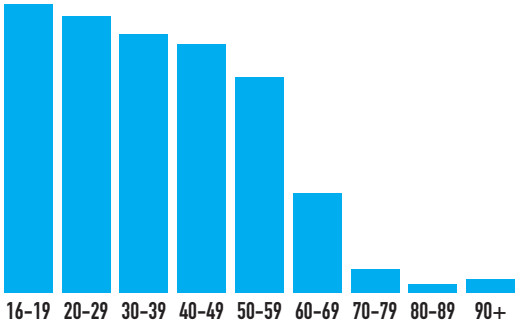
ADMINISTRATIONS BY AGE RANGE

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

SUSPECTED ADVERSE REACTIONS

46,237

Comirnaty 81%
Moderna vaccine 2%
Vaxzevria 17%



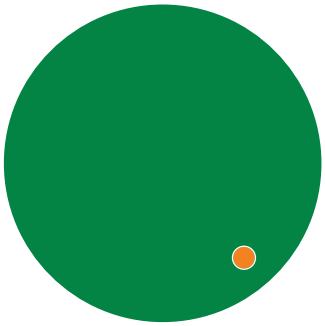
REPORTING RATE BY AGE RANGE

REPORTING RATE PER DOSE	1st dose	2nd dose
	496	540

PLEASE NOTE

- DO NOT OVERLOOK ANY UNUSUAL OR UNEXPECTED EVENT
- PROVIDE ALL USEFUL INFORMATION IN THE REPORT
- NOT ALL ADVERSE EVENTS ARE CAUSED BY THE VACCINE, BUT ALL INFORMATION CONTRIBUTE TO MONITOR THE SAFETY OF THESE DRUGS

SERIOUS/NON-SERIOUS SUSPECTED ADVERSE REACTIONS



NON-SERIOUS **92.7%**

SERIOUS **7.1%**

0.2% OF SUSPECTED ADVERSE REACTIONS ARE NOT DEFINED

DATA ANALYSIS

REFERENCE DATABASE: NATIONAL PHARMACOVIGILANCE NETWORK (RNF)
PERIOD UNDER REVIEW: 27/12/2020 - 26/03/2021

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 adenoviral vector vaccine called COVID-19 Janssen Vaccine (authorised as from 12/03/2021 and not yet used in Italy).

Therefore, the description of the reporting trend in this period will concern the three vaccines currently used. As of 26/03/2021, **46,237 reports** have been entered in the RNF **out of a total of 9,068,349 doses administered for all vaccines, with a reporting rate of 510 per 100,000 doses**[1].

Most reports (81%) refer to the most widely used vaccine Comirnaty (77% of administered doses), with an increase in reports for Vaxzevria vaccine (17%), following the increased use of such vaccine (18% of administered doses). Reports for the Moderna vaccine are 2% of the total, in proportion to the limited number of doses administered (5%).

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 doses administered and the related reporting rates of the different COVID-19 vaccines currently in use are shown in table 1.

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

COVID-19 vaccine	Reports as of 26/3/2021	Doses administered as of 26/3/2021	Reporting rate (per 100,000 doses administered)
Comirnaty	37,397	6,994,739	**535**
Moderna	971	427,731	**227**
Vaxzevria	7,854	1,645,879	**477**
mRNA active ingredient (unspecified brand)	15		
Total	***46,237***	***9,068,349***	***510***

[1] The number of doses administered as of 26/01/2021 is published by the Ministry of Health at the following link: https://github.com/italia/covid19-opendata-vaccini; data extraction was carried out on 30/03/2021.

As expected, the reporting rate of the Vaxzevria vaccine has increased compared to the previous month, approaching Comirnaty, in proportion to the higher use in the vaccination campaign, whereas the reporting rate for the Moderna vaccine remains stable and lower due to lower use.
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)*

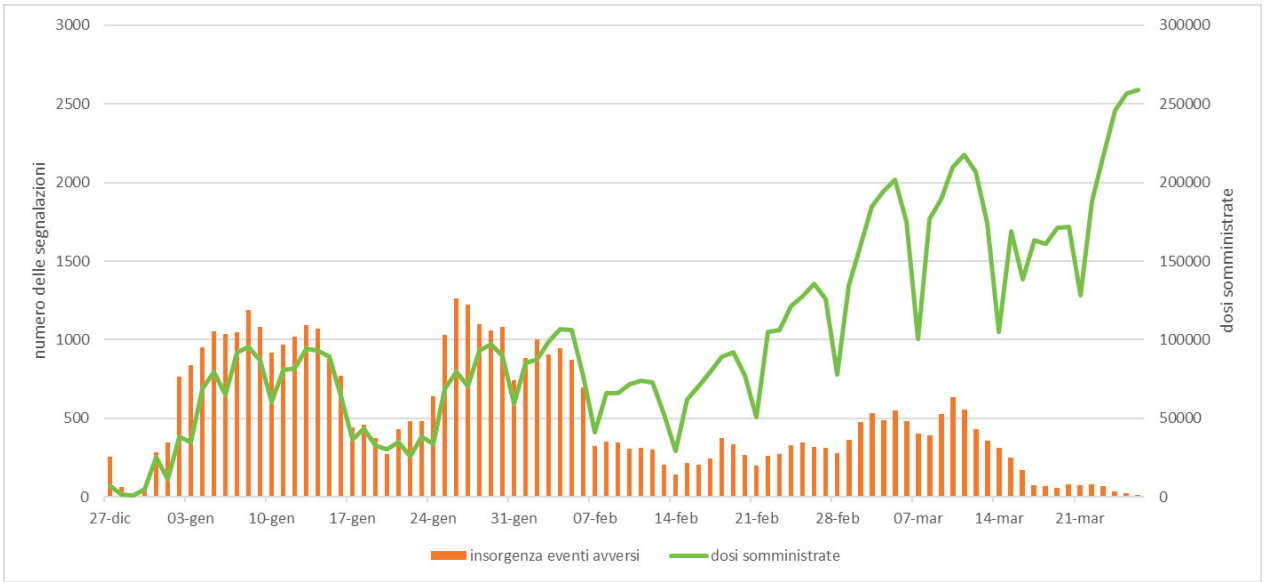
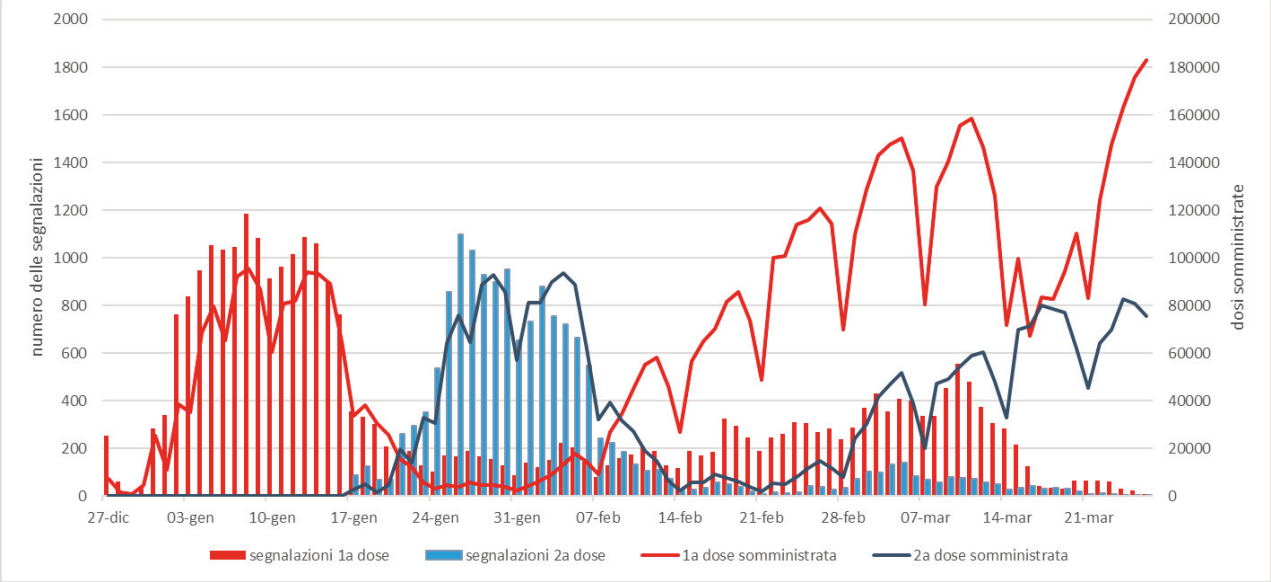


Figure 1b *– Distribution of the reports entered in the RNF by onset date of the event, relating to the 1st or 2nd dose, according to the vaccine doses administered*

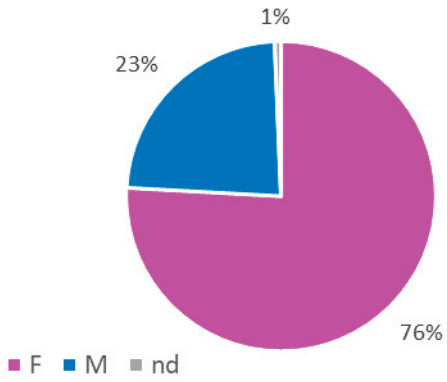


The graph trend highlights the correspondence between the vaccination trend and the reporting trend, especially until mid-February. Later on, the increase in administrations does not correspond to a concomitant increase in reports, which may be due to report entering some time after onset of the adverse event and/or vaccine administration (e.g., reactions to 1st dose reported upon booster), as well as to higher knowledge on vaccine safety. 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 645/100,000 administered doses in women (F) and 299/100,000 administered doses in men (M), regardless of the administered dose and vaccine (fig. 2).

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



Such difference between sexes seems to depend on different exposure to vaccines (mainly administered to women), on higher sensitivity to reporting shown by women and on 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 46 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 based on a small number of both reports (112) and administered doses (10,037). The distribution by age group confirms that the reporting rate is rather constant and high in subjects up to 60 years, later to decrease in the 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. 6 reports relate to breastfed babies whose mother had been vaccinated, with age ranging from 20 days to 18 months. Besides the two cases described in the previous report (vomiting in a 5-month baby girl and fever in another 18-month baby girl), the other

[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) 812e820
[3] Patricia Robin McCartney. Sex-Based Vaccine Response in the Context of COVID-19. JOGNN 2020. 49: 405–408.

four cases reported concern a skin rash reaction in a 20-day-old baby occurred 5 days after the mother's vaccination, febrile seizures in a 16-month-old baby, which was not deemed related to the mother's vaccination and two cases of agitation of the infant occurred the night following the mother's vaccination. Five reporting sheets refer to adverse events in the breastfeeding mother, which were non-serious and completely resolved.
No significant differences are observed between the reporting rates by age group in relation to the number of doses.

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

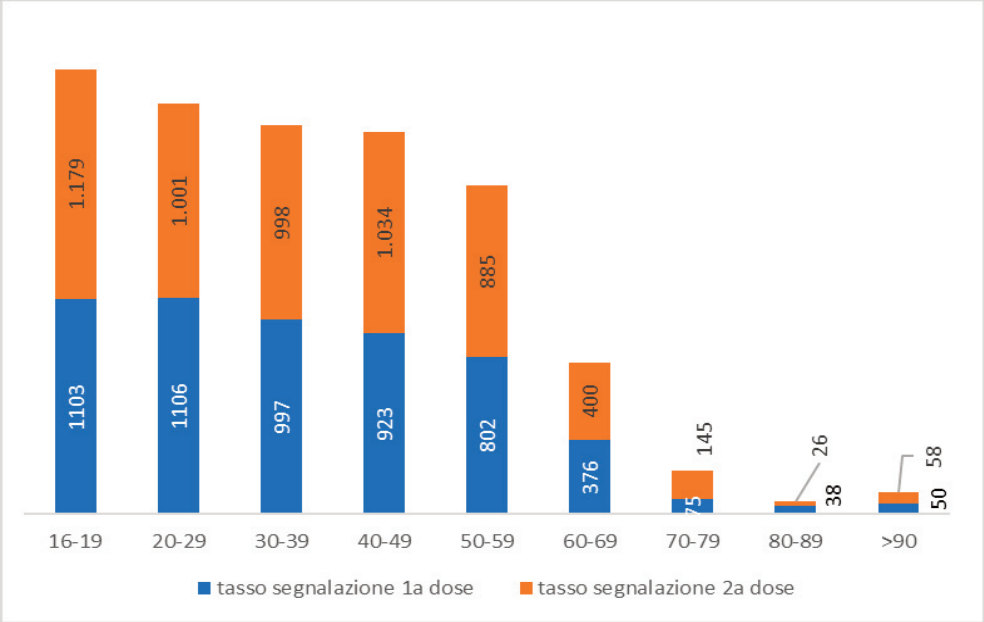
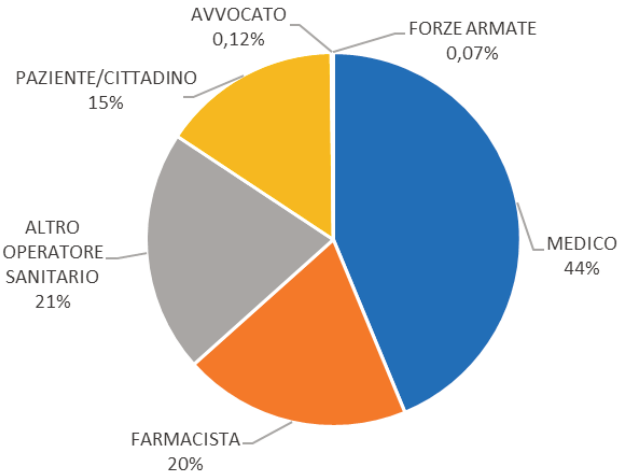


Figure 4 shows the distribution by type of reporter, highlighting that most reports are submitted by health professionals, but 15% are submitted by the vaccinated persons themselves.

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 98%), while the other reports are prompted by other regional initiatives.

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	24,430	52.8%
1 day	15,950	34.5%
2-7 days	3,437	7.4%
>7 days	1,173	2.5%
Not definable	1,247	2.7%
Total	***46,237***	***100%***

As in the previous reports, 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 (92,7%), with a reporting rate equal to 473/100,000 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 for each vaccine are respectively 500 (Comirnaty), 204 (Moderna), 426 (Vaxzevria) per 100,000 administered doses.

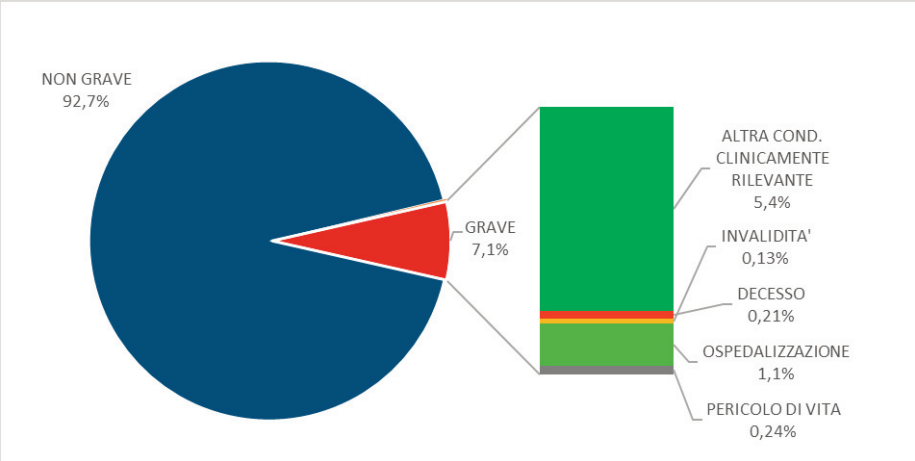
Serious reports are 7,1% of the total, with a rate of 36 serious events per 100,000 administered doses, regardless of the type of vaccine, of the dose administered (1st or 2nd dose) and of the possible causal role of the vaccination. The reporting rates of serious events for each vaccine are 33 (Comirnaty), 22 (Moderna), 50 (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).

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 medicine.

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 (0.2% of reports do not indicate seriousness)*



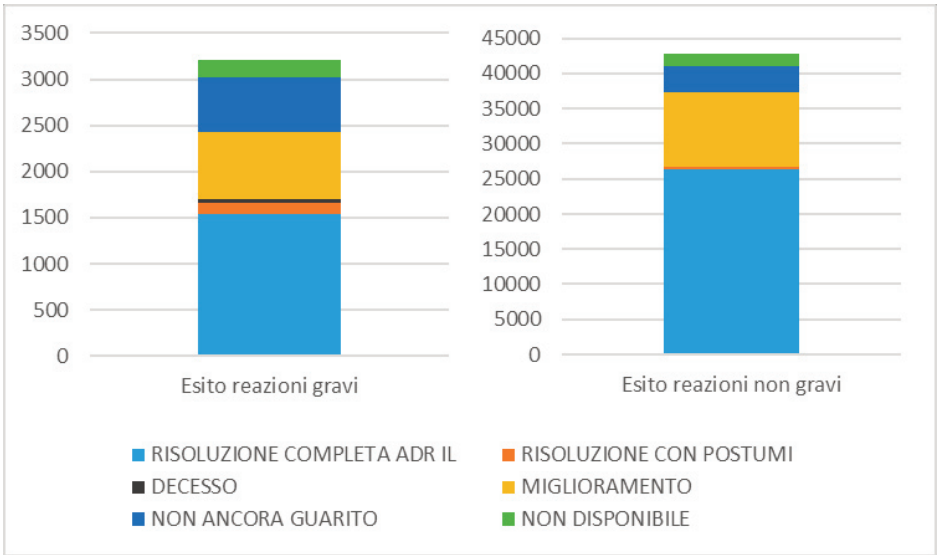
Most serious reports are classified as “other clinically relevant condition”, i.e., alerting the subject and/or the reporter without entailing a specific intervention in hospitals.

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



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.

Distribution by number of doses

The period considered saw an increase in the number of vaccinated persons who completed the vaccination cycle, amounting to 32% of the overall number of administered doses. No differences in reporting rates were observed between the first and second dose of Comirnaty or Moderna vaccine as shown in Table 3. As for Vaxzevria vaccine, currently no data are available to perform such evaluation.

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	525	549	535
Moderna vaccine	216	264	227

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.
As for the Vaxzevria vaccine, it is not possible to make evaluations as vaccinees have not yet been administered the second dose.

Distribution by type of event

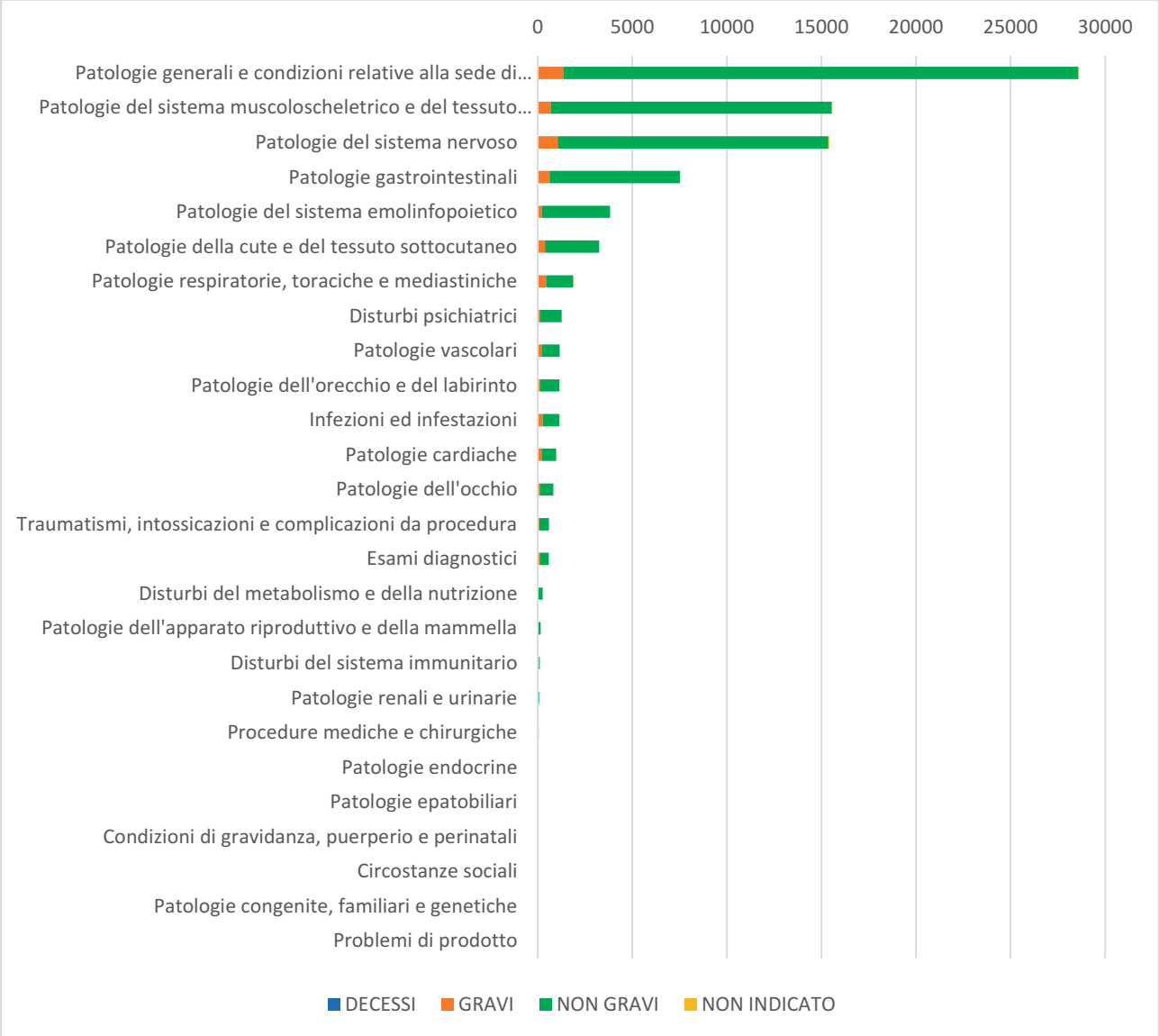
Graphs 7, 8 and 9 show the types of events reported for the three vaccines used, Comirnaty, Moderna and Vaxzevria, in order of frequency, regardless of the dose administered and the causal link with the vaccination, on the basis of the organ or apparatus concerned, the etiology or purpose (System Organ 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 (77%) and are predominantly fever, injection site pain, asthenia/fatigue and chills, classified as non-serious in 96% of cases. Following in order of frequency: events falling under the Musculoskeletal system and connective tissue disorders (42%), 95% of which non-serious, mainly widespread muscle and joint pain, Nervous System disorders (41%), 93% of which non-serious, mainly headache and paraesthesia and the events falling under the Gastrointestinal disorders (20%), 92% of which non-serious, mostly nausea and diarrhoea.

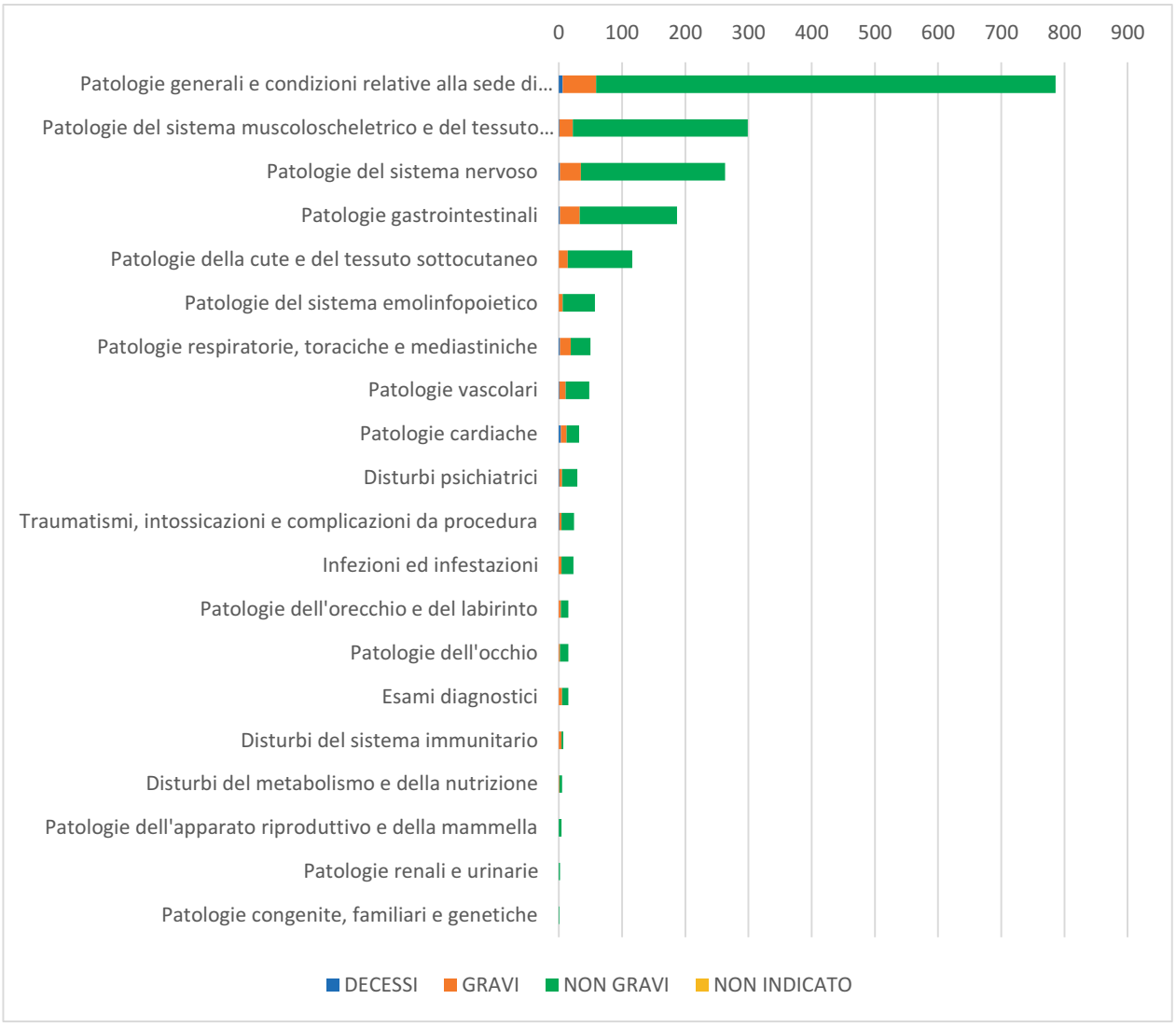
***Figure 7** – Distribution of adverse events after Comirnaty vaccine by system organ class (SOC)*



Overall, 2,262 serious reports relate to the Comirnaty vaccine. 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. 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 (81%) and are predominantly fever, asthenia/fatigue and injection site pain, classified as non-serious in 92% of cases. Following in order of frequency: the events falling under the Musculoskeletal system and connective tissue disorders (31%), especially widespread muscle and joint pain, classified as non-serious in 93% of cases; Nervous System disorders (23%), mostly headache, classified as non-serious in 87% of cases and Gastrointestinal disorders (19%), mainly nausea and vomiting, classified as non-serious in 82% of cases.

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

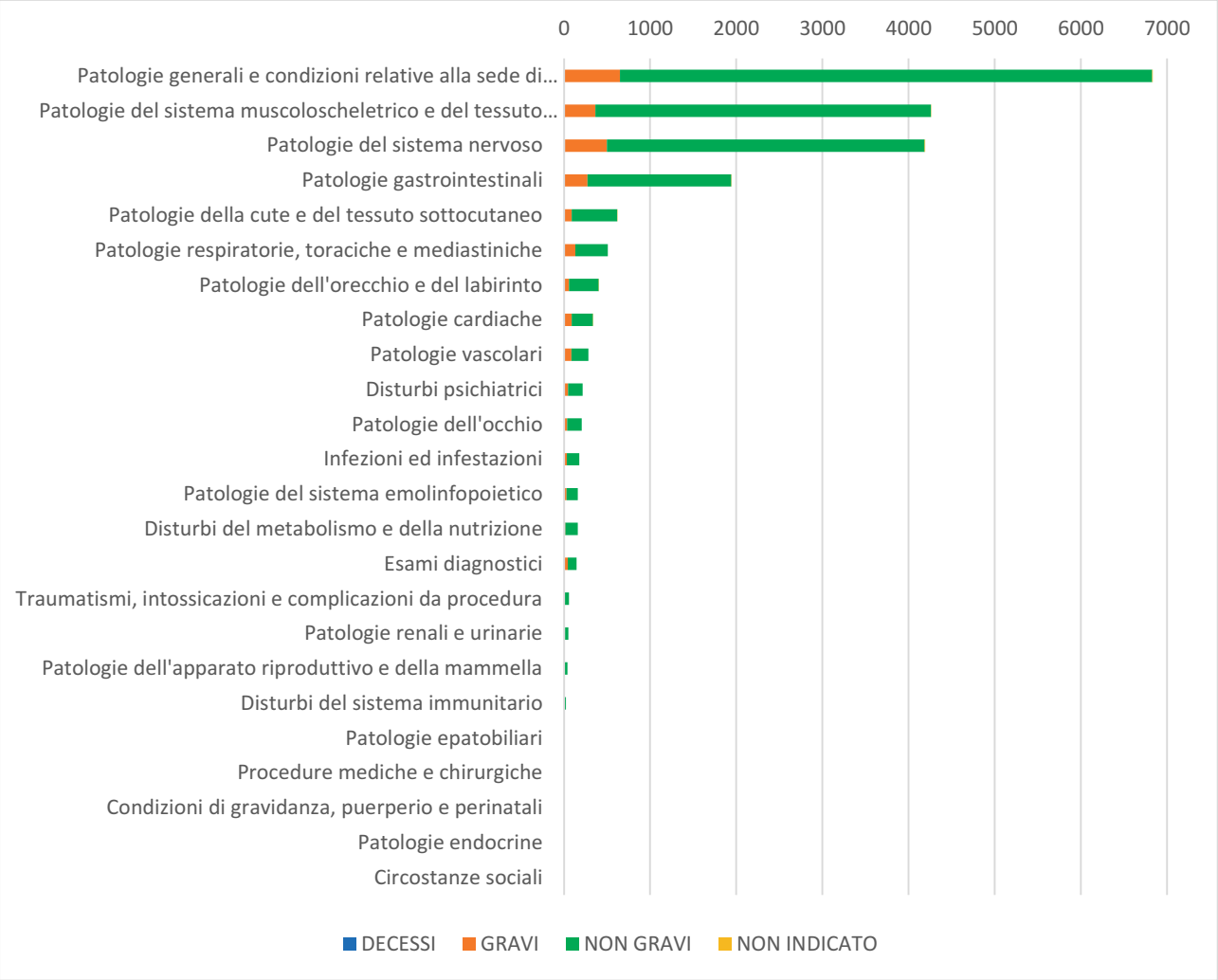


In 85 report sheets concerning the Moderna vaccine, adverse events considered serious were reported. Also for this vaccine, the most frequent serious reactions correspond to the distribution of all reports and refer mainly to systemic symptoms (high fever, diffuse myalgia and arthralgia, etc.). Other events are reported with a frequency equal to or less than 2 reports.

Most of the **events reported for the Vaxzevria vaccine** are related to the system organ class of General Disorders and Administration Site Conditions (87%) and are mainly fever, chills, asthenia/fatigue and injection site pain. 90% of these reports are classified as non-serious. Following

in order of frequency are events falling under the Musculoskeletal System and Connective Tissue Diseases (54%), mainly represented by diffuse muscle and joint pain. Again, 90% of cases are classified as non-serious. These are followed by events falling under the Nervous System disorders (53%), especially headache, classified as non-serious in 90% of cases, and by events falling under the Gastrointestinal disorders (25%), mainly nausea and vomiting, classified as non-serious in 85% of cases.

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



Most of the 824 reports of serious adverse events for this vaccine refer to high fever with any other associated systemic symptoms. Other preferred terms reported less frequently are chills, dizziness, excessive sweating, drowsiness, difficulty in breathing, generalised pain.

Fatal cases after COVID-19 vaccination

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

As of 26 March 2021, 102 reports with a "death" outcome have been entered in the National Pharmacovigilance Network, of which 2 duplicates that were excluded from the analysis, for a reporting rate of 1.1 cases per 100,000 doses administered. 53.9% of cases were women and 42.2% men (sex was not reported in 3.9% of cases, 4). The median age is 81.4 years (range 32-104 years) and 80% of cases occurred in people over the age of 75. The distribution by type of vaccine is shown in table 4.

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

VACCINE	Fatal cases	Rates per 100.000 doses
Comirnaty	76	1.1
Moderna	12	2.8
AstraZeneca	12	0.7
Total	100	1.1

This different distribution by type of vaccine depends in part on the different number of doses administered for the various vaccines in the various age groups. The time between vaccine administration and death varies from two hours up to a maximum of 28 days, with an average of 4 days (median one day). Death occurred after the 1st dose in 74 cases and after the 2nd dose in 25 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, while cardiovascular events are often reported in patients with a history of previous diseases or cardiovascular risk factors. Fatal cases have been also reported which are related to thrombo-embolic problems and are discussed in the dedicated focus available in this report.

The evaluations of the cases with detailed and complete information suggest that the vaccine was not responsible for most cases, as they often occurred in subjects with existing or previous pathologies and in polytherapy, with clinical frailties such as: cardiovascular diseases (high blood pressure, previous MI, heart failure,

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 vaccine vigilance, 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)

cardiomyopathy), metabolic diseases (diabetes, dyslipidaemia), oncological diseases, autoimmune diseases, neurodegenerative diseases (Alzheimer's disease), respiratory and mediastinal diseases (COPD, emphysema), renal, hepatic, pancreatic diseases, diseases of the lymphopoietic system (thrombocytopenia, coagulation defects).

Consequently, both the assessment of the cause of death and the attribution of the causal link are complex. For this reason, each case is carefully investigated and the reporter is always asked to provide as soon as possible further clinical and diagnostic information (clinical and pharmacological history, medical record, any investigations carried out and autopsy). However, it is not always possible to find these details and some report sheets often show important gaps that cannot be filled in the follow-up phase.

At the time of writing, 64% of reports with a fatal outcome (64) have been assessed using the WHO algorithm and 36% have not yet been assessed. Compared to the total number of reports with a fatal outcome, the causal link was not correlated in 38% of cases, indeterminate in 22% and unclassifiable due to lack of information necessary for the application of the algorithm in 3%.

The causal link is correlated in a single report concerning a 79-year-old man with a clinical history of high blood pressure, previous surgery for triple aortocoronary bypass and pacemaker implantation, moderate-severe heart failure (NYHA class III), monoclonal gammopathy of undetermined significance (MGUS), prostatic hypertrophy and retinopathy. The description of the adverse reaction shows that the drug caused a hyperpyrexia resistant to antipyretics, which decompensated the patient, causing his death three days after the first dose of the mRNA vaccine. The high fever event is related to vaccination and triggered other events that caused the bad outcome in an already extremely compromised patient.

On the basis of the available data, it is possible that some events expected for vaccines may have clinically relevant consequences in some frail elderly subjects, especially if they occur with particular intensity (e.g. hyperpyrexia), against an undoubted benefit of vaccination in that segment of the population.

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

During the periodic monitoring of suspected adverse reaction reports at national and European level, on 08/03/2021, Austria reported to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) two serious cases (one with fatal outcome) of thromboembolic events after administration of Vaxzevria, batch ABV5300 - not distributed in Italy.

After this report, a collection of data was initiated on adverse reactions reported both for the specific lot of the vaccine and for all thromboembolic events in the various EU countries. The investigation in the National Pharmacovigilance Network did not reveal any reports for the Austrian batch (not distributed in Italy) but revealed the presence of two reports of a suspected thromboembolic event for the same vaccine, both referring to the same batch (ABV2856) and entered close to the Austrian communication. On 09/03/2021, the Austrian National Authority suspended the use of the batch ABV5300, a decision subsequently taken by other European countries where the batch had been distributed. Similarly, on 11/03/2021, upon request of the Public Prosecutor's Office of Siracusa, AIFA ordered a ban on the use of batch ABV2856 and proceeded to sample the same batch and other batches for comparison, for the appropriate investigations at the Istituto Superiore di Sanità, which is the official medicines control laboratory (OMCL) for Italy. Pending the necessary feedback, both on specific batches and in general on cases of thromboembolic events, most European nations, including Italy, have in the meantime precautionarily suspended vaccination with the Vaxzevria vaccine. On 12/03/2021, the PRAC began the scientific evaluation of the reported cases, confirming a possible safety signal relating to thromboembolic events, also starting a careful analysis of all cases included in the European pharmacovigilance database Eudravigilance. In this first phase of the evaluation, all the reports were investigated of thrombotic and embolic events of any nature, entered up to 11/03/2021, for a total of 269 cases (258 of which classified as serious), of which 224 from the United Kingdom, 30 from EU/EEA countries (1 from Italy) and 15 from non-European countries.

What is the PRAC?

The Pharmacovigilance Risk Assessment Committee (PRAC) consists 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.

What is an OMCL?

OMCLs (Official Medicines Control Laboratories) are state laboratories that support all national and European regulatory authorities (such as AIFA and EMA) in the quality control of human and veterinary medicines available on the market. The collection of all reference laboratories for the various European Member States constitutes a network coordinated by the European Directorate for the Quality of Medicines (EDQM). The activities of these laboratories consist in performing analytical controls validated according to shared protocols that allow mutual recognition within the network, conducted independently of pharmaceutical companies. For vaccines, these controls are conducted batch by batch before distribution.

The analysis conducted by the PRAC and the EMA included information shared by the UK regulatory agency MHRA (which, as of 16/03/2021, reported about 11 million doses administered). The PRAC noted that for most of the thrombotic and embolic events reported, the number of cases observed after vaccination with Vaxzevria was lower than the number of cases that would be expected in the general population, unrelated to the vaccination and based on frequency of the various pathologies examined. This type of analysis, defined as observed/expected, is important to understand if there is a potential statistical association between a medicine and an event. When the number of cases observed after the administration of a medicine is lower than or equal to the number of cases that would have occurred independently of it, in fact, the association between the medicine and the event is unlikely and probably incidental. On the contrary, when the administration of a medicine determines a number of cases higher than those that would be expected independently of it, the association is potentially causal.

What is a safety signal?

A 'safety signal' is essentially 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, such as an increased frequency. 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 European Medicines Agency.

It is important to emphasise that this type of analysis is indicative of the statistical "strength" of the temporal correlation between an event and the administration of a medicine and does not provide direct information on the causal link, which necessarily requires a clinical evaluation of individual cases. In this first phase of evaluation, which ended on 19/03/2021, the EMA determined that the benefits of the vaccine in preventing COVID-19 disease (which in turn causes clotting problems) still outweighed the risks, that the vaccine did not increase the overall risk of thromboembolic events and that there are no issues related to specific batches or particular production sites.

The only thromboembolic events for which the observed/expected analysis did not allow to completely exclude a role of the vaccine were represented by very rare events for which it was very difficult to estimate the number of expected cases regardless of the vaccine. These events are essentially thrombosis of the vessels draining blood from the brain (thrombosis of the intracranial venous sinuses or CSVT, for a total of 18 cases) and thrombosis of several blood vessels (in atypical site and with disseminated intravascular coagulation or DIC, for a total of 7 cases), in some cases associated with low platelet levels (thrombocytopenia). The analysis of these events was carried out on the data up to 16/03/2021 and concluded that further investigations were necessary. Most of

the cases have been reported mainly in women under the age of 55, but it is unclear whether this is due to the fact that the vaccine was mainly administered to this category of people[4].

As a result, the PRAC has included this new information in the Summary of Product Characteristics and Package Leaflet of Vaxzevria and provided guidance on these events to patients and healthcare professionals through an important information note, while continuing to closely monitor reports of blood coagulation disorders, contacting the vaccine company with a list of requests to acquire all data and information useful for the evaluation and proceeding to a further review of these risks, including the analysis relating to other types of COVID-19 vaccines. On the basis of these recommendations, on 19/03/2021 AIFA issued a provision to revoke the previously issued ban on the use of the Vaxzevria vaccine.

The new review of the CSVT and DIC cases by the PRAC began on 03/04/2021 and was based on the reports entered in Eudravigilance until 22/03/2021. In detail, a total of 62 cases of CSVT were evaluated, of which 44 from EU/EEA countries (7 from Italy), 15 from the United Kingdom and 3 from non-European countries, 24 cases of thrombosis of multiple vessels in atypical sites (including 7 cases of DIC), of which 17 from EU/EEA countries (4 from Italy) and 7 from the United Kingdom. Eighteen of these cases had a fatal outcome (2 of CSVT and 2 of thrombosis of multiple blood vessels in atypical site observed in Italy). These cases occurred on a total of 25 million people who received Vaxzevria and it is currently unclear whether this increase in the number of cases compared to the first review is due to an increase in reports or to an actual higher frequency of the event. The PRAC evaluation also considered the advisory opinion expressed by an interdisciplinary group of qualified European experts convened on 29/03/2021.

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.

Following this second evaluation, completed on 08/04/2021, 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.

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

[4] https://www.aifa.gov.it/-/covid-19-vaccine-astrazeneca-benefits-still-outweigh-the-risks-despite-possible-link-to-rare-blood-clots-with-low-blood-platelets1

studies and modifications to the ongoing clinical trials and will continue to monitor these events with further possible revisions of the data[5].

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[6].

The PRAC, EMA and AIFA will continue to monitor this risk and more generally all COVID-19 vaccines. Any new information will be promptly disclosed through official channels.

[5] 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

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

Anaphylaxis

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

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[7, 8, 9, 10]. 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[11]. 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[12, 13].

With the introduction of the new vaccines against Covid-19, as expected, some cases of post-vaccine anaphylaxis have occurred, and they have been 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 of 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[14]. 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 the pre-vaccination clinical history[15, 16].

Viral vector vaccines (adenovirus) have been introduced more recently and, at the moment, only the Vaxzevria vaccine, which does not contain PEG, is available in Italy. There is polysorbate 80 among the excipients of this vaccine, which is also present in other vaccines in use for many years and for which anaphylaxis is a very rare event.

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[7] McNeil MM et al. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018;141 (2):463-472.

[8] Guide to the evaluation of adverse reactions observable after vaccination: http://www.agenziafarmaco.gov.it/sites/default/files/Guida_valutazione_reazioni_avverse_osservabili_dopo_vaccinazione_2.pdf

[9] Castells M C et al. Maintaining Safety with SARS-CoV-2 Vaccines. N Engl J Med 2021; 384: 643-9.

[10] 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.

[11] 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.

[12] Nilsson L et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr Allergy Immunol. 2017; 28 (7): 628-640.

[13] Kelso JM et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol 2012;130:25-43.

[14] 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.

[15] 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.

[16] Sellaturay P et al. Polyethylene Glycole-Induced Systemic Allergic Reactions (Anaphylaxis). J Allergy Clin Immunol 2021; 9 (2): P670 – 675.

Data analysis

All the reports entered from the start of the vaccination campaign to 26/03/2021 that contained at least one term from the Standardised MedDRA Query (SMQ) "Anaphylactic reactions" of the MedDRA dictionary were extracted from the National Pharmacovigilance Network. The reports were then subjected to the independent evaluation of two medical experts in vaccine vigilance and classified according to the definition of the Brighton Collaboration, which identifies three levels of decreasing diagnostic certainty.

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

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

Out of a total of 410 cases extracted with this methodology, 80 reports clearly referred to cases of anaphylaxis to all COVID-19 vaccines. In all cases, the event occurred on the day of vaccination, specifically within one hour of administration in approximately half of the cases (the onset interval in hours was present in 66% of reports and not reported in 44%). The overall reporting rate, regardless of vaccine type, is 8.8 cases per million doses, with a higher frequency in females (13.2). The characteristics of the reports are shown in table 5. In detail, 85% of cases (68) occurred after vaccination with Comirnaty (median age: 46 years), mainly in women and in relation to the first dose. 2.5% (2) of cases occurred after vaccination with the Moderna vaccine (median age: 62 years) and 12.5% (10) after vaccination with Vaxzevria (median age: 48 years) with an overlapping distribution by sex and number of doses.

This distribution largely depends on the different exposure to the 3 different vaccines, ie on the fact that the number of vaccinated women is higher than the number of men and that Comirnaty was mainly used, followed by Vaxzevria. More recent literature data have shown a much higher rate of anaphylactic reactions for mRNA vaccines[17].

However, this adverse event remains under observation, to verify its trend over time and its incidence in relation to recent and future vaccines. In fact, further investigations on the cases of anaphylaxis are currently underway both at national and European level by the Pharmacovigilance Risk Assessment Committee (PRAC).

[17] Blumenthal KG et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA 8/3/2021: E1 – E3 online

Table 5 - *Characteristics of reports of anaphylaxis after COVID-19 vaccine entered in the PhV system in the period 27/12/2020 – 26/03/2021*

CHARACTERISTICS	COMIRNATY	MODERNA	VAXZEVRIA	TOTAL
Number of reports	68	2	10	80
Median age (range)	46 (20 - 82)	62 (47 - 76)	48 (20 - 57)	47 (20 - 82)
Women (%)	91 % (n. 62)	100 % (n. 2)	80 % (n. 8)	90 % (n. 72)
Rate per million doses administered	9.7	4.7	6.1	8.8
Rate per million vaccinated women	14.7	7.9	8.1	13.2
Rate per million vaccinated men	2.2	0.0	3.0	2.2
Hypotension	26 % (n. 18)	50 % (n. 1)	10 % (n. 1)	25 % (n. 20)
Adrenalin administration	25 % (n. 17)	50 % (n. 1)	30 % (n. 3)	26 % (n. 21)
Onset of symptoms ≤ 15 minutes	31 % (n. 21)	50 % (n. 1)	50 % (n. 5)	34 % (n. 27)
Onset of symptoms ≤ 60 minutes	49 % (n. 33)	50 % (n. 1)	60 % (n. 6)	50 % (n. 40)
Interval in minutes not specified (same day)	44 % (n. 30)	50 % (n. 1)	40 % (n. 4)	44 % (n. 35)
Allergies or allergic reactions to foods, inhalants or insects	29 % (n. 20)	50 % (n. 1)	20 % (n. 2)	29 % (n. 23)
Allergies or allergic reactions to medicines or vaccines	37 % (n. 25)	50 % (n. 1)	20 % (n. 2)	35 % (n. 28)
Previous anaphylaxis	6 % (n. 4)	0 % (n. 0)	0 % (n. 0)	5 % (n. 4)
Rate per million of first doses	10,9	0,0	6,1	9,0
Rate per million of second doses	6,1	19,8	0,0	6,6
Anaphylaxis classification (according to Brighton Collaboration)				
Level 1	58.8 % (n. 40)	50 % (n. 1)	40 % (n. 4)	56.3 % (n. 45)
Level 2	32.4 % (n. 22)	50 % (n. 1)	60 % (n. 6)	36.3 % (n. 29)
Level 3	8.8 % (n. 6)	0 % (n. 0)	0 % (n. 0)	7.5 % (n. 6)
Total	68	2	10	80

Neurological adverse events and subjective sensory disorders

With the collaboration of the Regional Pharmacovigilance Centers and the Prevention Departments of Lazio, Puglia, Tuscany and Umbria.

In the current pandemic context, confidence in COVID-19 vaccination appears to be more strongly correlated with the perception of vaccine safety than with understanding the risk of contracting the disease[18]. As with other vaccines, neurological reactions are among the adverse events following vaccinations that most frighten public opinion and are most debated in the context of vaccine misinformation, contributing to vaccination hesitation[19, 20]. In fact, already during the vaccine development phase, the onset of some adverse neurological events during clinical trials had a notable media coverage, contributing to the spread of false news and unfounded fears about vaccines[21].

In fact, although relatively frequent both pre- and post-marketing, most of the neurological adverse events following vaccinations for COVID-19 observed so far are not serious and completely resolve in most cases. As reported in the Summary of Product Characteristics of the 3 vaccines currently authorised and used in Italy, the main neurological reactions observed in clinical studies are:

- for mRNA vaccines (Comirnaty and Covid-19 Vaccine Moderna), headache as very common and acute peripheral facial paralysis as rare;
- for the viral vector vaccine (Vaxzevria), headache as very common and dizziness and drowsiness as uncommon.

However, the frequency of facial paralysis observed in mRNA vaccine licensing studies was comparable to that reported in the general population. The data collected by the pharmacovigilance systems after the conditional authorisation of these vaccines are being studied both nationally and internationally. As reported in the section "Distribution by type of event" of this Report, the adverse events that fall within the systemic-organic class "Nervous system disorders" are the third in order of frequency to be reported for the three vaccines currently used in Italy and they are largely represented by headache.

Data analysis

As of 26/03/2021, a total of 17,333 neurological events have been reported for all vaccines, representing 38% of all reported events, with a reporting rate of 191 events per 100,000 doses administered, regardless of the type of vaccine.

92.7% of these events are non-serious and 7% serious (severity was not defined in about 0.3% of cases), regardless of the type of vaccine and causation. The reporting rate of serious neurological adverse events after COVID-19 vaccines is 13.5 per 100,000 doses administered, with no substantial differences between the first and second dose.

[18] Karlsson LC et al. Fearing the disease or the vaccine: The case of COVID-19. Personality and Individual Differences, 2921; 172: 110590

[19] Larson HJ et al. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007-2012. Vaccine 2014; 32 (19): 2150-9.

[20] Loomba S et al. Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA. Nat Hum Behav 2021; 5 (3): 337-348.

[21] https://www.lescienze.it/news/2020/06/05/news/diffusione_fake_news_twitter_controllo-4739653/

The distribution of neurological adverse events by vaccine type, regardless of severity and causation is shown in Table 6.

Table 6 *- Distribution of neurological adverse events by type of vaccine*

VACCINE	Neurological AEFI	Rates per 100.000 doses
Comirnaty	13,345	190
Moderna	208	49
Vaxzevria	3,780	230
Total	17,333	191

86.3% of all neurological events resolved completely or were improving at the time of data extraction, with no substantial differences between the 3 vaccines.
The distribution of neurological adverse events by type of reaction and type of vaccine, regardless of severity and causation is shown in table 7.

Table 7 *- Distribution of neurological adverse events by type of reaction and type of vaccine*

	Comirnaty	Rates per 100.000 doses	Vaxzevria	Rates per 100.000 doses	Moderna	Rates per 100.000 doses
Headaches	11,865	169.85	3,415	208.07	167	39.14
Sleep disorders	1,047	14.99	250	15.23	22	5.16
Dizziness/Vertigo	383	5.48	174	10.60	9	2.11
Paraesthesia	147	2.10	42	2.56	12	2.81
Ageusia/Dysgeusia	169	2.42	23	1.40	2	0.47
Cranial Nerve Paralysis	79	1.13	13	0.79	2	0.47
Seizures	49	0.70	6	0.37	7	1.64
Anosmia	48	0.69	3	0.18	0	0.00

The most reported neurological adverse event for all vaccines currently used in Italy is headache, frequently associated with other systemic symptoms such as fever, asthenia and widespread osteo-joint or muscle pain. As expected, dizziness and vertigo were observed more frequently after Vaxzevria.
The distribution of serious neurological adverse events by type of vaccine, regardless of causation is shown in table 8.

Table 8 *- Distribution of neurological adverse events by type of vaccine*

VACCINE	Severe neurological AEFI	Rates per 100.000 doses
Comirnaty	790	11.3
Moderna	22	5.1
Vaxzevria	410	24.9
Total	1,222	13.5

At the time of extraction, 75% of reports of serious neurological adverse events reported complete resolution of the reaction or improvement, with no substantial differences between the 3 vaccines. The distribution of serious neurological adverse events by type of reaction and type of vaccine, regardless of causality is shown in table 9.

Table 9 *- Distribution of neurological adverse events by type of reaction and type of vaccine*

	Comirnaty	Rates per 100.000 doses	Vaxzevria	Rates per 100.000 doses	Moderna	Rates per 100.000 doses
Headaches	508	7.27	310	18.89	12	2.81
Sleep disorders	44	0.63	44	2.68	3	0.70
Dizziness/Vertigo	40	0.57	26	1.58	4	0.94
Paraesthesia	60	0.86	4	0.24	1	0.23
Cranial Nerve Paralysis	49	0.70	6	0.37	1	0.23
Cognitive Disorders	17	0.24	6	0.37	6	1.41
Ageusia/Dysgeusia	21	0.30	3	0.18	0	0.00
Seizures	14	0.20	4	0.24	2	0.47

Even considering only serious reports, the most reported neurological adverse event for all vaccines currently used in Italy is headache, reported as severe in intensity and/or duration and often associated with other systemic symptoms. Very rarely (about 1 case in every 500,000 doses administered), seizures have been reported that refer to events of various kinds, including epileptogenic syncopes, i.e. fainting caused by other factors (low blood pressure, response to vaccination stress) that can occur with convulsive-type shocks.

Subjective sensory disorders

Paraesthesias and dysesthesias are among the most frequently reported neurological adverse events for all vaccines currently used in Italy. The term "paraesthesia" refers to the appearance of different types of sensations ranging from tingling to the feeling of falling asleep, to itching, pinpricks and burning, which appear regardless of stimulation. Usually, these symptoms occur more or less suddenly, especially in the extremities, but they can also include other parts of the body and affect both the skin and mucous membranes. The term "dysesthesia" instead describes distorted perceptions, often abnormal and unpleasant, of normal stimuli or spontaneous sensations of altered sensitivity. They are often described as burning or pain, a feeling of excessive cold or heat in one part of the body, or stiffness-like sensations in a limb.
Paraesthesias and dysesthesias can persist for a variable time and can have various clinical meanings, since they do not always represent a neurological symptom but can also be caused by circulatory problems, can be among the symptoms of anaphylaxis and can have a psychogenic cause. Neurological causes can also be different and range from peripheral nerve disorders (for example, compression, trauma, infection or inflammation of a nerve) to central nervous system injury (for example, ischemic stroke or multiple sclerosis). The pathologies of the peripheral nerves that are most frequently associated with paraesthesia or dysesthesia include diabetic neuropathy and

inflammatory polyradiculoneuritis. Therefore, with a view to properly assessing these adverse events following vaccination, it is particularly important to evaluate the other symptoms and signs in the adverse reaction report.

Data analysis

In the period considered there were 1,549 reports containing preferred terms referable to subjective sensory disorders[22], with a reporting rate of 17 cases per 100,000 doses administered. No significant differences were observed between the first and second dose.
The distribution of paraesthesia/dysesthesia by type of vaccine, regardless of severity and causation is shown in table 10.

Table 10 *- Distribution of paraesthesia/dysesthesia by type of vaccine*

VACCINE	Paraesthesia/Dysesthesia	Rates per 100.000 doses
Comirnaty	1,383	19.7
Moderna	21	4.9
Vaxzevria	145	8.8
Total	1,549	17

The mean age of the affected patients is approximately 45 years for the mRNA vaccines (range 19-93) and 43 years for the Vaxzevria vaccine (range 19-59), with a clear prevalence in women (1269/1549, 82%) compared to men (269/1549, 8%). Considering the total number of reports, the adverse event occurred on the same day of vaccine administration in 64.4% of cases (977/1549), after 24-48 hours in 18.4% (285/1549) of cases and after 48 hours in 12.7% (198/1549) of cases.
Most of the reports (86.7%) are non-serious; serious reports (13.3%, 206/1549) refer to "other clinically relevant condition" in 77.2% of cases and hospitalisation in 19.9% of cases. A life-threatening condition was reported in 6 cases, in which the set of coded adverse reactions was compatible with anaphylaxis. The outcome reported at the time of reporting was complete resolution or improvement in 81.45% of cases.
The distribution by site is shown in table 11.

Table 11 *- Distribution of paraesthesia/dysesthesia by type of vaccine*

SITE	COMIRNATY	MODERNA	VAXZEVRIA	Total
limbs	303 (18.8%)	3 (14.2%)	56 (38.9%)	**362 (23.4%)**
extremities	164 (15%)	3 (14.2%)	18 (12.4%)	**185 (11.9%)**
face	286 (20.7%)	2 (9.5%)	15 (10.3%)	**303 (19.6%)**
not specified	167 (12)	7 (33.5%)	20 (13.8%)	**194 (12.5%)**
mouth-tongue-throat	119 (8.6%)	1 (4.8%)	15 (10.3%)	**135 (8.7%)**

[22] The following preferred terms (PT) were used to search for reports: paraesthesia, dysesthesia, hypoesthesia, synaesthesia and hyperesthesia, anaesthesia. For PT synaesthesia and hyperesthesia no reports were identified.

mixed	128 (9.3%)	3 (14.2%)	8 (5.6%)	**139 (9.0%)**
generalised	100 (7.2%)	1 (4.8%)	4 (2.8%)	**105 (6.8%)**
lips	73 (5.3%)	1 (4.8%)	5 (3.4%)	**79 (5.1%)**
perioral	24 (1.7%)	0	0	**24 (1.54%)**
injection site	19 (1.4%)	0	4 (2.8%)	**23 (1.48%)**
TOTAL	**1,383 (100%)**	**21 (100%)**	**145 (100%)**	**1,549 (100%)**

Overall, the set of signs and symptoms associated with paraesthesias/dysesthesias showed a picture compatible with an allergic or hypersensitivity reaction in 15.1% (234 / 1,549) of the reported cases. In the remaining number of cases, paraesthesias were present alone or in association with other systemic symptoms and only very rarely with other neurological symptoms.
The Pharmacovigilance Risk Assessment Committee (PRAC) is investigating also such adverse events both at national and European level.

Reactivation of latent infections

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

Latent infections are caused by viruses that remain in the host cell without causing the disease and can remain in this state for a long time, sometimes even for years, until a stimulus to the immune system causes it to reactivate. The best known viral agents capable of remaining latent in the human body are the Herpes Simplex type 1 and 2 viruses, the Varicella/Zoster virus and the infectious mononucleosis virus, which, after a first infection during which the pathogen penetrates our body, remain quiescent within specific target cells and can reactivate under specific conditions, causing a "reactivation pathology". The exact biological mechanisms underlying this latency are not fully known and may depend both on tolerance phenomena on the part of our immune system and on specific virus strategies. The best known example is the varicella-zoster virus (VZV) infection which, after the primary infection called chickenpox, very common in children, remains latent in the spinal ganglia attached to the posterior horns of the spinal cord. The reactivation of this virus occurs only in 10-20% of people who have had chickenpox, especially in old age and is responsible for herpes zoster. Herpes zoster represents the "reactivation pathology" of VZV infection and can arise spontaneously or in relation to physical and psychological trauma, fever and some pathologies or therapies that induce immunosuppression or in any case, a "modulation" of the immune system (e.g. diabetes, HIV infection, prolonged therapy with cortisone or immunosuppressants). In more recent times, cases of reactivation of VZV during SARS-CoV-2 infection are also described, probably due to the reduction of lymphocytes, in particular of the so-called CD4+ lymphocytes induced by the COVID-19 virus[23, 24, 25, 26]. The median time described between the diagnosis of COVID-19 and the onset of herpes zoster is approximately 5.5 days (1-5).
Very rarely, some cases of reactivation of latent viral infections have also been described in temporal relationship with vaccinations in general but, at the present state of knowledge, there is no conclusive evidence on the causal role of vaccines. More in detail, about three cases of herpes virus reactivation after immunisation with inactivated influenza, hepatitis A and Japanese rabies/encephalitis vaccines and only one case of VZV reactivation after immunisation with inactivated anti-COVID-19 vaccine in a 78-year-old patient have been reported in the literature[27].

Data analysis

In the period considered, 279 reports contain preferred terms referable to viral infections, of which 272 can be evaluated for analysis after the exclusion of duplicates and cases of infections of other nature or arising before vaccination, with a reporting rate of 2.9 cases per every 100,000 doses administered[28]. Two hundred and ten reports (77.2%) concerned women and 59 (21.6%) men; in 3

[23] Saati A et al. Herpes zoster co-infection in an immunocompetent patient with COVID-19. Cureus. 2020; 12 (7): e8998.
[24] Ferreira ACAF et al. COVID-19 and herpes zoster co-infection presenting with trigeminal neuropathy. Eur J Neurol. 2020; 27 (9): 1748-1750.
[25] Tartari F et al. Herpes zoster in COVID-19-positive patients. Int J Dermatol. 2020; 59 (8): 1028-1029.
[26] Zheng M et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020; 17 (5): 533-535.
[27] Walter R et al. Reactivation of herpesvirus infections after vaccinations? Lancet. 1999; 353 (9155): 810.
[28] Preferred terms related to "viral infection" and containing the name of the viruses (e.g., "Herpes") were used to search for reports.

cases (1.1%), the patient's sex was not specified. The mean age was 50.3 years, with the majority of patients in the age group below 65 years (n = 233; 86.0%) and the lowest percentage being 65 years or older (n = 38; 14.0%). Most reports were made by a healthcare professional (n = 228, 83.9%) and only to a lesser extent by citizen/patient (n = 44, 16.1%).

As expected in relation to the number of doses administered, most of these reports of suspected adverse event occurred in relation to the Comirnaty vaccine (n = 231; 85%), with a reporting rate of 3.3 cases per 100,000 doses administered, mainly after the first dose (n = 137, 59.5%) and to a lesser extent after the second dose (n = 87, 37.5%). More rarely, they have been observed after Vaxzevria vaccine (n = 34, 12.4%), with a reporting rate of 2.1 cases per 100,000 doses administered, and after Moderna vaccine (n = 7, 2.6%), with a reporting rate of 1.6 cases per 100,000 doses administered, all after the administration of the first dose.

Regardless of the type of vaccine, almost all reports refer to herpetic infections (n = 270; 99.3%; mean age 50.4 years).

The Herpes simplex virus is the most frequently involved in these reports (n = 179; 66.3%), followed by Herpes Zoster (n = 90; 33%). In most of these cases, the event occurred 1-4 days after the administration of the vaccine (see table 12). In 82.8% (n = 226) of cases the adverse event was not serious and resolved or improved in most cases (n = 178; 65.2%).

Table 12 - *Distribution of reports by time of symptom onset (herpetic infections) compared to vaccination date (for Comirnaty distinguished by I and II dose)*

Time lapse in days between vaccination and event	Comirnaty I dose	Comirnaty II dose	Vaxzevria	Moderna
0	28	26	9	1
1-4	63	38	21	3
5-7	17	8	2	1
>7	27	12	2	2
AVERAGE	**3.8**	**3.8**	**3.6**	**4.4**
Total*	135	84	34	7

At the current state of knowledge, the role of anti-COVID-19 vaccination in causing viral activation/re-activation, in particular related to herpes viruses, remains indeterminable at the moment and is difficult to establish, considering the mechanism of action of vaccines and the potential coexistence of other risk or predisposing factors that cannot always be excluded at the individual level.

Vaccines in general, in fact, including anti-COVID-19 ones, involve an activation of the immune system and not a possible suppression. Therefore, it is not clear how this activation could possibly interfere with the complex immunological tolerance mechanisms, still not fully known, which allow some viruses to remain latent.

Moreover, at both clinical and biological levels, it is difficult to assess the impact of conditions such as immunisation stress (immunisation stress-related responses), stress closely related to the pandemic condition or other psychosocial factors and some para-physiological conditions that may induce a state of transient immunodepression.