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Revisiting the Benefit–Risk Profile of COVID-19 Vaccines of the Italian Vaccination Campaign

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Abstract

Vaccination against COVID-19 represented one of the main public health strategies to reduce mortality, hospitalizations, and complications. In this context, pharmacovigilance played an essential role in the continuous monitoring of the benefit-risk profile of authorized vaccines, enabling the timely identification of rare adverse events and the implementation of risk minimization measures. This work revisits the post-marketing surveillance system for COVID-19 vaccines in Italy, with particular attention to signal detection mechanisms, risk management, and the main safety signals that emerged during the first year of the vaccination campaign. Data from the National Pharmacovigilance Network, periodic safety reports, EMA/PRAC documents, and AIFA communications were considered. The analysis highlights how, following the widespread use of mRNA and adenoviral vector vaccines, adverse events of special interest emerged, including vaccine-induced immune thrombotic thrombocytopenia, myocarditis/pericarditis, and other rare events, which led to updates of the Summary of Product Characteristics, the Package Leaflet, and communications to healthcare professionals. The data confirm that the benefit-risk ratio of COVID-19 vaccines remained favorable. The study emphasizes the effectiveness of the regulatory and pharmacovigilance architecture implemented in Italy and Europe in supporting rapid, evidence-based decisions in the context of a pandemic emergency.

Keywords: COVID-19; Vaccines; Adverse reactions

Introduction

COVID-19 is an acute respiratory infection caused by SARS-CoV-2, first identified in Wuhan in December 2019, whose rapid global spread and excess mortality led the World Health Organization to declare a pandemic in March 2020. Despite social distancing, mandatory mask use and lockdowns, healthcare systems faced severe pressure, and vaccination quickly

emerged as the most effective strategy to reduce morbidity and relieve hospitals. In the European Union, the EMA used rolling review and conditional marketing authorisation to rapidly approve several COVID-19 vaccines (Comirnaty, Spikevax, Vaxzevria, COVID-19 Vaccine Janssen), while maintaining a positive benefit–risk balance through post authorisation safety studies and enhanced adverse event reporting [1]. This framework required a reinforced pharmacovigilance system, with PRAC, the EMA COVID-19 task force (COVID-ETF) and specific risk management plans defining AESIs and risk minimisation activities [2]. In Italy, the national vaccination campaign started on 27 December 2020 and, in its first year, exceeded 108 million administered doses, representing a real life stress test for the National Pharmacovigilance Network. AIFA intensified surveillance, periodic safety reports and safety communications, as several Important Information Notes (NII) on safety as part of the risk minimisation strategy, in line with EMA decisions. In this scenario, post marketing pharmacovigilance became crucial to confirm the vaccines' benefit–risk profile and to identify rare or unexpected adverse events [1]. This narrative review revisits and summarizes the first year safety data of COVID-19 vaccines used in Italy, focusing on adverse event patterns, the safety profile of individual vaccines and the adaptation of pharmacovigilance tools during the pandemic, considering the evidence and regulatory experience accumulated in subsequent years.

Materials and Methods

In this work, a narrative review approach was chosen because it is suitable for synthesizing regulatory documents, observational data and post marketing surveillance reports from multiple sources over a clearly defined time frame (27 December 2020–26 December 2021). The primary data source was the first Italian annual report on the safety of COVID-19 vaccines published by the Italian Medicines Agency (AIFA), which summarizes all reports of suspected adverse reactions recorded in the National Pharmacovigilance Network (RNF) during the first year of the vaccination campaign. Regulatory documents from European and national authorities were also analysed, including updates to product information, PRAC assessment reports and direct healthcare professional communications published in 2021 for Comirnaty, Spikevax, Vaxzevria and COVID-19 Vaccine Janssen. Particular attention was paid to Core RMP19 guidance and Good Pharmacovigilance Practices (GVP) Modules V [3], VI [4] and VIII [5], which provide standardised recommendations on safety specifications, pharmacovigilance activities and risk minimisation measures. AESIs were defined according to Brighton Collaboration criteria, based on five levels of diagnostic certainty, and lists of them, prepared before marketing authorization including the SPEAC list for COVID-19 vaccines, guided the selection of outcomes to be monitored. Scientific literature on the safety of COVID-19 vaccines was identified through PubMed, focusing on epidemiological studies, observed versus expected analyses and the self controlled case series study conducted by the Italian National Institute of Health and AIFA. RNF data were coded using MedDRA terminology, allowing for uniform and standardized coding of clinical manifestations. Causality was assessed with the WHO-UMC algorithm and mortality was analysed using the observed versus expected methodology applied in Summary Safety Reports.

Results

General surveillance data: first year of the Italian vaccination campaign

During the first year of the national COVID-19 vaccination campaign in Italy (from 27 December 2020 to 26 December 2021), a total of 108,530,987 doses were administered. The campaign began with Comirnaty (Pfizer/BioNTech) and later included

Spikevax (Moderna), Vaxzevria (AstraZeneca) and the COVID-19 Vaccine Janssen. Overall, Comirnaty was the most widely used vaccine (69.1% of all doses), followed by Spikevax (18.3%), Vaxzevria (11.2%) and Janssen (1.4%) [1]. This heterogeneous distribution reflects both the staggered timing of authorisations and regulatory recommendations limiting the use of adenoviral vector vaccines to specific age groups, after the identification of certain AESIs. During the same period, the Italian National Pharmacovigilance Network (RNF) received 117,920 individual case safety reports, corresponding to an overall reporting rate of 109 events per 100,000 administered doses. A higher prevalence of reports from females (70%) compared to males (29%) was observed, and reporting rates were higher among individuals aged between 20 and 60 years. Regarding the source of reports, 65% were submitted by healthcare professionals, while 34.5% came from citizens **(Figure 1)**. From a methodological point of view, most events (94.8%) originated from passive surveillance, with only a small portion generated by active pharmacovigilance projects. Most adverse events occurred shortly after vaccination, clustering on the day of administration or the following day [1].

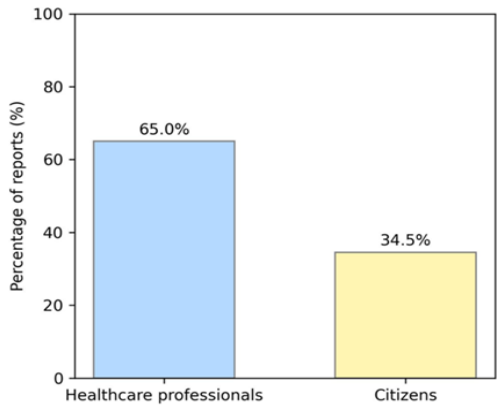

Figure 1: Source of reports during the first year of the vaccination campaign.

Classification of severity and causality assessment

During the first year of the vaccination campaign, clinical evaluation of reported events confirmed an overall favorable safety profile. Of the 117,920 individual safety reports, 83.7% were classified as non-serious (91 per 100,000 doses) and 16.3% as serious (17.6 per 100,000 doses) **(Figure 2)**. Serious adverse reactions generally occurred shortly after vaccination, most often within 48 hours and only rarely after the first week. Causality was assessed using the WHO-UMC algorithm, and only a minority of serious events were considered plausibly related to vaccination. Particular attention was paid to reports with fatal outcomes. Cross analysis of data from AIFA, U.S. pharmacovigilance databases and PRAC reviews found no solid evidence of an increased mortality risk associated with COVID-19 vaccines. In the few fatal cases reported, severe pre-existing diseases were identified as the determining factor in the outcome, often in elderly patients in advanced stages of illness in whom systemic reactions led to the fatal decompensation of an already severely compromised clinical condition. Observed versus expected analysis further confirmed that, during the 14-day period following vaccine administration, mortality in the vaccinated population consistently remained below expected levels in a matched unvaccinated reference cohort by age and sex [1].

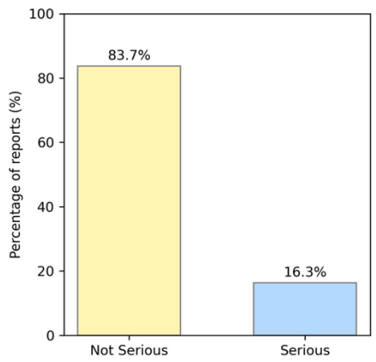

Figure 2: Percentage of reports according to severity.

Safety profile of individual vaccine preparations

For *Comirnaty* (Pfizer/BioNTech), most reported reactions involved "General disorders and administration site conditions", "Nervous system disorders" and "Musculoskeletal and connective tissue disorders"; most events were non-serious, and serious vaccine related cases were rare (about 4.4 per 100,000 doses), with overall adverse events classified as "rare" or "very rare". For *Spikevax* (Moderna), the pattern was similar, with general, nervous system and connective tissue reactions predominating; around 80% of reports were non-serious, serious events were about 12 per 100,000 doses (3.3 per 100,000 related), and myocarditis and pericarditis were identified as AESI for both mRNA vaccines. For *Vaxzevria* (AstraZeneca), "general disorders and administration site conditions" and "Musculoskeletal and connective tissue disorders" were most common; about 80.2% of events were non-serious and 19.8% serious, with a serious event rate of 38 per 100,000 doses and rare or very rare events including anaphylaxis, Guillain Barré syndrome, immune thrombocytopenia and venous thrombosis (VITT). For *COVID-19 Vaccine Janssen*, reactions mainly involved "General disorders and administration site conditions"; about 73% of events were non-serious and 27% serious, with roughly 28 adverse reactions per 100,000 doses (6.5 serious and related), and AESIs included immune thrombocytopenia, and anaphylaxis [1].

Analysis of adverse events of special interest (AESIs)

Anaphylaxis

Anaphylaxis was one of the first adverse events of special interest to be systematically monitored during the Italian vaccination campaign, with cases classified according to Brighton Collaboration definitions based on standardized clinical criteria [6]. The overall reporting rate was approximately 2.8 cases per million doses, corresponding to a "very rare" frequency. The mechanism was mainly linked to hypersensitivity to excipients such as Polyethylene Glycol (PEG) in mRNA vaccines and polysorbate 80 in adenoviral vector vaccines, with a predominance of cases in females and in subjects with a history of allergies to drugs, foods or other vaccines. In more than one third of cases, onset occurred within the first 15 minutes after administration, consistent with IgE mediated anaphylaxis and with the recommended post vaccination observation period. The incidence of episodes after the second dose was lower than after the first, largely because individuals with significant reactions to the first dose were excluded from further exposure or vaccinated under protected clinical conditions, supporting the effectiveness of risk minimisation measures [1].

Vaccine-induced immune thrombotic thrombocytopenia (VITT)

The first cases of Vaccine induced Immune Thrombotic Thrombocytopenia (VITT) after Vaxzevria administration were reported in March 2021, leading regulatory authorities to identify a very rare risk of thrombotic events with thrombocytopenia, observed mainly in women under 55 years of age, while confirming an overall positive benefit–risk profile for the vaccine. These data were incorporated into the Summary of Product Characteristics and Package Leaflet of Vaxzevria and communicated to healthcare professionals through AIFA safety communications; similar warnings were later extended to COVID-19 Vaccine Janssen following PRAC and CHMP evaluations, which lead to the preferential use of these vaccines in individuals aged 60 years or older. In Italy, suspected VITT cases were classified using Brighton Collaboration definitions, resulting in 107 confirmed cases, with a higher incidence for Vaxzevria than for Janssen, and an average onset interval around 12 days after vaccination. The overall VITT reporting rate was approximately 1 case per 200,000 doses, particularly among women aged 30–49 years, indicating a rare but clearly identifiable risk concentrated in specific demographic groups [1].

Guillain-Barré syndrome

Guillain Barré Syndrome (GBS) is a rare immune mediated disease causing inflammation of peripheral nerves and, in severe cases, paralysis. In August 2021, the PRAC identified a safety signal of possible increased GBS risk with adenoviral vector vaccines (Vaxzevria and COVID-19 Vaccine Janssen) and classified it as a "very rare" reaction, requesting additional data and adding a warning to the product information for Vaxzevria. Data from italian reports were classified according to Brighton Collaboration definitions, and the analysis identified 124 evaluable cases, mostly with symptom onset within 42 days after vaccination and all considered serious; only one fatal case occurred in a patient with pre-existing autoimmune disease. The overall reporting rate was about 1 case per 1,000,000 administered doses, clearly lower than the natural incidence of GBS in the general population and consistent with a favourable benefit–risk profile, possibly influenced by strict risk minimisation measures, including age based restrictions on adenoviral vector vaccines [4]. Nevertheless, GBS was included among the risks listed in the Summary of Product Characteristics and package leaflet of the adenoviral vector vaccines, in line with a precautionary, transparency oriented approach [7].

Myocarditis and Pericarditis

From April 2021, surveillance data highlighted a very rare risk of myocarditis and pericarditis following mRNA vaccines (Comirnaty, Spikevax), which were included among AESI and requiring careful differential diagnosis with MIS-C in children and young people [8]. Onset usually occurred within 14 days (about 10 days in Italy), with myocarditis mainly in young males and pericarditis in slightly older adults; EudraVigilance and RNF data showed a predominantly benign clinical course with rapid resolution. A nationwide self controlled case series conducted by ISS and AIFA in about 3 million individuals under 40 years confirmed increased risk of myocarditis/pericarditis after the second dose of Comirnaty and both doses of Spikevax, especially in males aged 18–29 years, while adenoviral vector vaccines showed no increased risk. By 26 December 2021, applying Brighton levels 1–4, 318 suspected myocarditis and 645 suspected pericarditis cases had been identified across all vaccines, with overall reporting rates of about 1.4 myocarditis and 2 pericarditis cases per 1,000,000 doses, consistent with "very rare" events; despite these signals, ongoing monitoring confirmed that the benefit–risk balance of mRNA vaccines remained overall positive, with absolute risks far outweighed by the protection against severe COVID-19 [1].

Discussion

During the first year of the Italian SARS-CoV-2 vaccination campaign, pharmacovigilance data supported an overall favorable benefit–risk profile for the vaccines, despite 117,920 reports in a context of intense media and institutional attention that may have increased reporting of already known events. Media coverage may contribute to the nocebo effect, whereby symptoms not fully explainable by the pharmacology, are influenced by individual expectations. The main limitation is the risk of overestimating the frequency of highly visible AESI such as VITT or myocarditis [9], but this does not invalidate the identified signals. It highlights the need to integrate spontaneous reporting with robust analytical studies. Each platform showed a coherent risk profile: mRNA vaccines were associated with myocarditis/pericarditis mainly in young males after the second dose, a signal confirmed and quantified by the large ISS–AIFA self controlled case series study, while adenoviral vector vaccines showed specific thrombotic (VITT) and neurological (GBS) risks that remained very rare. The PRAC played a central role by rapidly evaluating signals and updating recommendations, and AIFA translated these into timely safety communications and product information changes, enabling age based restrictions, strengthened screening and protected vaccination settings. The low incidence of anaphylaxis, VITT and GBS compared with background rates, together with the substantial protection against severe COVID-19, confirms a favorable benefit–risk balance, while the inclusion of these risks in Summary of Product Characteristics and package leaflets exemplifies the European principle of transparent, evidence based risk communication.

Conclusions

Overall, the Italian experience during the first year of the COVID-19 vaccination campaign demonstrated the maturity and responsiveness of its pharmacovigilance infrastructure. The RNF, integrated with EudraVigilance and supported by accelerated timelines for transmitting vaccine-related reports, enabled real-time signal generation at the national level while simultaneously contributing to the European regulatory response. The system demonstrated that safety signals can be rapidly identified, confirmed through analytical studies, and managed through targeted regulatory measures, while maintaining a benefit in preventing severe disease, hospitalizations, and deaths that remained clearly greater than the observed risks. The Italian experience highlights the need to increasingly integrate spontaneous reporting with structured post-authorization studies; the effectiveness of risk minimization measures when translated into concrete clinical protocols; and the central role of transparency in preserving public trust. Overall, the pharmacovigilance architecture put in place proved capable not only of promptly detecting and mitigating risks, but also of strengthening the credibility of the vaccination program and representing a model for the future monitoring of other vaccines and innovative therapies, to be integrated ever more rigorously with post-authorization safety studies that allow monitoring of the safety profile of medicinal products.

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