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# COVID-19 Vaccine Hesitancy and Early Adverse Events Reported in a Cohort of 7,881 Italian Physicians

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*Key words: Vaccine Hesitancy, Early adverse events, COVID-19, Sars-CoV-2, Physicians*
*Parole chiave: Esitazione Vaccinale, Eventi avversi precoci, COVID-19, Sars-CoV-2, medici*

**Abstract**

***Background.*** *The COVID-19 vaccination campaign began in Italy at the end of December 2020, with the primary aim of immunizing healthcare professionals, using the EMA approved mRNA vaccines (Comirnaty® by Pfizer/BioNTech; mRNA-1273 by Moderna) and recombinant adenoviral vaccine (Vaxzevria® by AstraZeneca). The study aimed at evaluating the prevalence and motivations underlying Vaccine Hesitancy, as well as the incidence and type of adverse events associated with COVID-19 vaccination.*

***Methods.*** *Cross-sectional study. Data were collected January 1st to 28th 2021 using a purposely created online self-administered questionnaire from a selected cohort of Italian physicians.*

***Results.*** *Overall, 7,881 questionnaires were analyzed: 6,612 physicians had received one dose, and 1,670 two doses of Comirnaty®; 30 had received one dose of mRNA-1273. Vaccine Hesitancy rate was 3.6%; it correlated with prior SARS-CoV-2 infection, diabetes, Adverse Eventss at previous vaccinations and refusal of 2020 flu vaccine, and was mainly motivated by concerns about vaccine Adverse Events. Typical Adverse Events were pain/itching/paresthesia at the inoculation site, followed by headache, fever, fatigue and myalgia/arthralgia occurring more frequently after the second dose (77.8 vs 66.9%; p<0.001), and in subjects with a prior SARS-CoV-2 infection.*

***Conclusion.*** *Adherence to COVID-19 vaccination is high among physicians. Adverse Events are typically mild and more frequent in people with a prior SARS-CoV-2 infection.*

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## Background

As of January 30th 2021, more than 2.5 million laboratory-confirmed cases of SARS-CoV-2 infection have been recorded in Italy, with approximately 100,000 affected healthcare workers (HCWs), and more than 300 deaths from COVID-19 (1). Two m-RNA (Tozinameran, Comirnaty® by Pfizer/BioNTech, Germany; and Spikevax® by Moderna, US) and a recombinant adenoviral (Vaxzevria® by AstraZeneca, UK) anti-COVID-19 vaccines have received the European Medical Agency rolling review process for conditional marketing authorization and are currently being administered (2-4). Based on pre-marketing trial results, two vaccine doses are recommended to obtain the maximum effectiveness against symptomatic disease (2-4), while most of reported side effects are mild to moderate and transient (5).

Following the COVAX initiative and the US NASEM recommendations (6), the Italian vaccination campaign started on December 27th 2020, with the aim of covering 1.5 million HCWs by the first trimester of 2021 (3). Because the vaccine supply was not immediately available to immunize all who could benefit from vaccination, the vaccination plan gave the priority to HCWs, nursing home residents and workers and people aged 80 and over (7). Vaccine Hesitancy (VH) (8), reflecting the proportion of subjects unwilling to receive vaccination because of various country- and context-specific concerns (9), is a public health threat that may undermine the efforts to achieve herd immunity reported by 14 to 38% of the people, with regards to COVID-19 vaccines (10-13).

Based on these premises, this study aimed at understanding reasons underlying VH, and monitoring adverse events (AEs) associated with anti-COVID-19 vaccines in a large cohort of Italian HCWs. With regards to side effects, special attention was paid to highlight differences between the first and second dose, and to identify predictors of vaccine reactions.

## Materials and Methods

Data were collected using an online, purposely created, self-administered questionnaire (Supplementary Material – Questionnaire), delivered from January 1st to January 28th 2021 to 100,141 Italian physicians, members of a Facebook private group ("*Coronavirus, Sars-CoV-2 e COVID-19 gruppo per soli medici"*). The group was created during the first wave of COVID-19 pandemic in Italy; medical license was verified before admission. Ethical approval was waived for this study, due to the deidentified nature of the data presented. Participants reviewed information on the study before consenting to participating: by clicking "yes" they communicated their approval to participate in the survey.

The survey consisted of three sections. The first section aimed at collecting demographic and other epidemiological data (i.e., age, gender, region of residency, etc.) of the physician and his/her family; positivity to SARS-CoV-2 tests; adherence to vaccination for seasonal influenza; AEs to previous vaccinations). The second section focused on the physician's attitude towards COVID-19 vaccination, while the third explored the occurrence, type, severity, time of onset and duration of AEs occurring after the administration of the first and the second dose of anti-COVID-19 vaccine.

Subjects were considered "*vaccine hesitant*" either if they answered "*unsure*" or "*extremely or somewhat unlikely to get vaccinated*". Exceptions were considered for those with "*certified contraindications*", who were hence excluded from the final analysis.

All subjects were asked to complete the survey only at the resolution of the adverse

events, or 72 hours after vaccination, if they did not experience any symptom.

Wilcoxon and Chi2 tests were used to assess between-group differences for dimensional and categorial variables, respectively. A multivariate analysis was performed for VH, imputing all variables significantly associated with VH at univariate analysis as putative moderators ($p<0.05$), and using a stepwise logistic regression model. A sensitivity analysis, excluding previous vaccination for seasonal influenza, was performed to explore and avoid collinearity.

Subgroup analyses were performed in subjects reporting AEs after the first vaccine dose, stratifying the study sample for gender, age (≤60 years or > 60 years), prior COVID-19 infection and history of adverse reactions at previous vaccinations, to identify potential risk factors. The intensity and duration of each of the reported AEs was also analysed in these patients. All the analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

## Results

The study sample consisted of 7,881 Italian physicians, after excluding from the initial cohort 99 subjects that denied giving informed consent to participate in the study (Table 1). Of them, 6,242 had already received only the first vaccine dose, while 1,670 had received also the second. All but 30 patients (receiving the Spikevax® for the first dose) received the Comirnaty® as first and second vaccine dose.

## Vaccine Hesitancy

Overall, 282 (3.6%) physicians were "*hesitant*" toward vaccination, while 192 (2.4%) did not want to receive the vaccine despite the absence of "*certified contraindications*". According to univariate analysis, VH was more common among physicians living in Northern Italy, among the older ones, and those living with elderly subjects. VH was also associated with prior SARS-CoV-2 infection, diabetes, and adverse reactions at previous vaccinations. In addition, the majority of those unwilling to receive COVID-19 vaccine had refused the 2020 flu vaccine (Supplementary table 1). These associations were confirmed at multivariate analysis (Figure 1, panel A), and using an alternative model for collinearity exploration, except for the association with the refusal of 2020 flu vaccine (Figure 1, panel B).

## Reported adverse events in vaccinated individuals

The complete list of reported AEs is summarized in Table 2. Pain/itching/paraesthesia at the site of vaccine inoculation was the most common reported AEs after both first and second dose, of mild intensity in 85% of the cases. AEs were more frequent, although not more severe, after the second dose (77.8 vs. 66.9%; $p<0.001$), especially for myalgia/arthralgia, headache, fever, lymphadenopathy and diarrhoea, while the incidence of local pain was similar between the two doses (Table 2, Supplementary Fig. 1). Less frequent AEs are all reported in Supplementary Table 2.

Five subjects (0.06%) required hospitalization, 2 after the first dose - one for anaphylactic shock and the other for severe generalized urticaria, and 3 after the second dose – one for anaphylactic shock, another for tachyarrhythmia, and the last for severe generalized urticaria. Detailed information is reported in Supplementary Table 3.

Local and systemic AEs reported after the first vaccine dose were significantly more frequent and of higher intensity in subjects aged <60 years. Overall, the incidence and

Table 1 – Main sample features (n=7,881)

| **Feature** (n, %) | N, % | |
|---|---|---|
| **Age** | | |
| 18-30 years | 890 | (11.3) |
| 31-40 years | 2,319 | (29.4) |
| 41-50 years | 1,991 | (25.3) |
| 51-60 years | 1,486 | (18.9) |
| 61-70 years | 1,120 | (14.2) |
| 71-80 years | 66 | (0.8) |
| 81+ years | 9 | (0.1) |
| **Gender** | | |
| Females | 6,015 | (76.3) |
| Males | 1,866 | (23.7) |
| **Italy region** | | |
| Northern | 1,824 | (23.1) |
| Central | 4,001 | (50.8) |
| Southern | 2,056 | (26.1) |
| **Live with subject/s aged≥ 65 years** | | |
| Yes | 1,673 | (21.2) |
| No | 6,208 | (78.8) |
| **Diabetes mellitus** | | |
| Yes | 254 | (3.2) |
| No | 7,627 | (96.8) |
| **Previous confirmed COVID-19** | | |
| Yes | 524 | (6.6) |
| No | 7,357 | (93.4) |
| **Vaccination for influenza (2020/21)** | | |
| Yes | 5,764 | (73.1) |
| No | 2,117 | (26.9) |
| **Adverse events (AEs) to previous vaccinations** | | |
| Yes | 931 | (11.8) |
| *severe AE* | 57 | (0.7) |
| *non severe AE* | 874 | (11.1) |
| No | 6,702 | (85.0) |
| Not known/no answer | 248 | (3.1) |
| **COVID vaccination** | | |
| Already vaccinated | 6,242 | (79.2) |
| Unsure | 20 | (0.3) |
| Extremely or somewhat likely | 1,359 | (17.2) |
| Extremely or somewhat unlikely, because: | 252 | (3.2) |
| The vaccine might have dangerous side effects | *93* | *(1.2)* |
| I am already immune from a past COVID-19 infections | *46* | *(0.6)* |
| I had COVID infection and I will wait for vaccination | *16* | *(0.2)* |
| COVID infection is not so dangerous | *2* | *(0.1)* |
| I am against vaccinations | *5* | *(0.1)* |
| I have certified contraindications | *90* | *(1.1)* |
| No answer | 8 | (0.1) |

Supplementary Table 1 – Predictors of COVID-19 vaccine adherence (n=7,707)

| | Adherence to be vaccinated* | |
|---|---|---|
| Feature | n (%) | p |
| **Age** | | <0.001 |
| 18-30 years | 873 (98.1) | |
| 31-40 years | 2,287 (98.6) | |
| 41-50 years | 1,959 (98.4) | |
| 51-60 years | 1,444 (97.2) | |
| 61+ years | 1,144 (95.7) | |
| **Gender** | | 0.062 |
| Females | 5,889 (97.9) | |
| Males | 1,818 (97.4) | |
| **Italy region** | | 0.030 |
| Northern | 1,772 (97.1) | |
| Central | 3,920 (98.0) | |
| Southern | 2,015 (98.0) | |
| **Live with subject/s aged ≥ 65 years** | | <0.001 |
| Yes | 1,608 (96.1) | |
| No | 6,099 (98.2) | |
| **Diabetes mellitus** | | <0.001 |
| Yes | 237 (93.5) | |
| No | 7,470 (97.9) | |
| **Prior Sars-CoV-2 infection** | | <0.001 |
| Yes | 472 (90.0) | |
| No | 7,235 (98.3) | |
| **Vaccination for 2020 flu (2020/21)** | | <0.001 |
| Yes | 5,702 (98.9) | |
| No | 2,005 (94.7) | |
| **Adverse events (AEs) to previous vaccinations**** | | <0.001 |
| Yes | 871 (93.6) | |
| No | 6,587 (98.3) | |

* "Unsure" and "extremely or somewhat unlikely to get vaccinated" (with the exception of "I have certified contraindications" that was excluded from the analysis) was considered as vaccination hesitant respondents and compared with the rest of the sample.
** Not known (n=248)

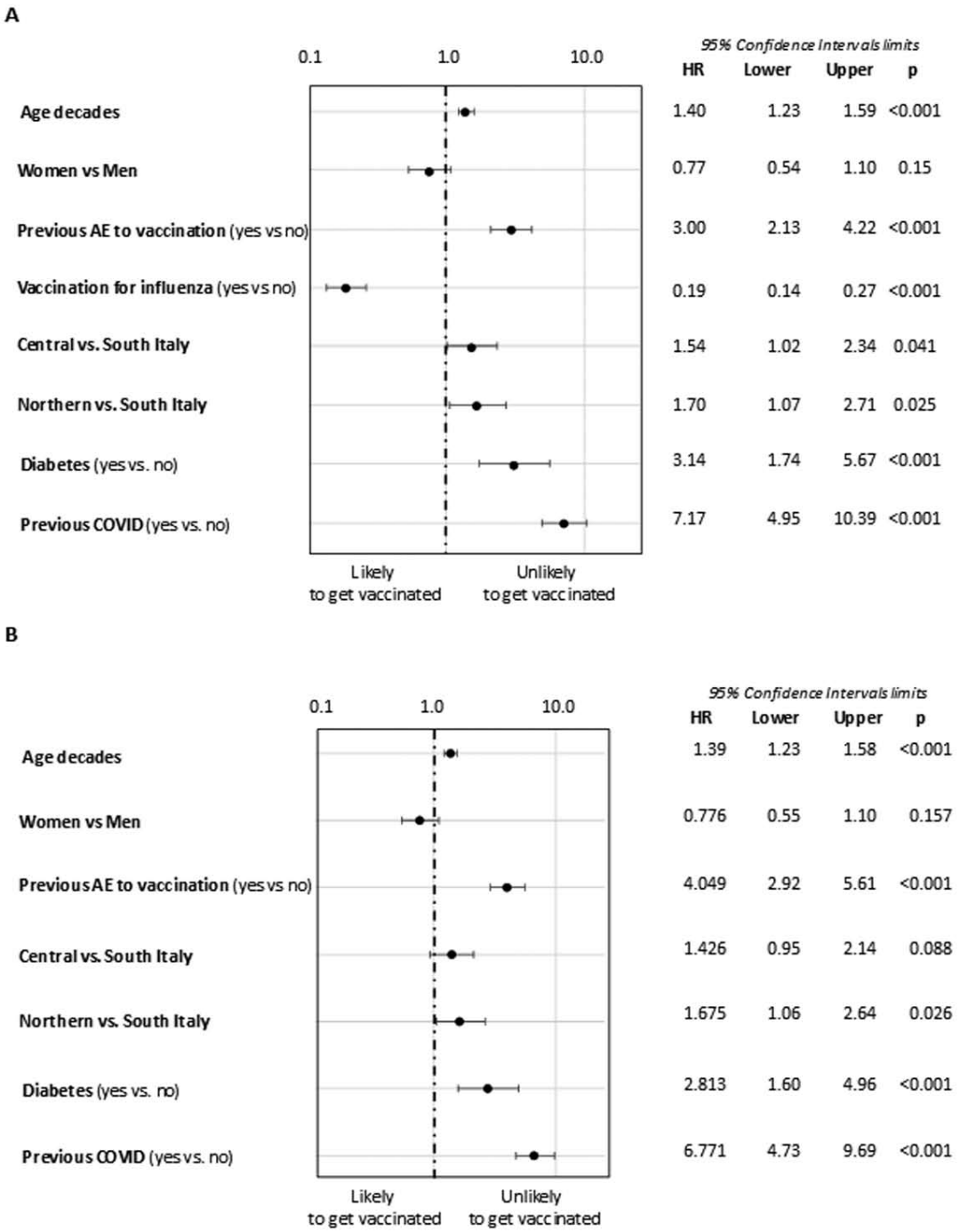
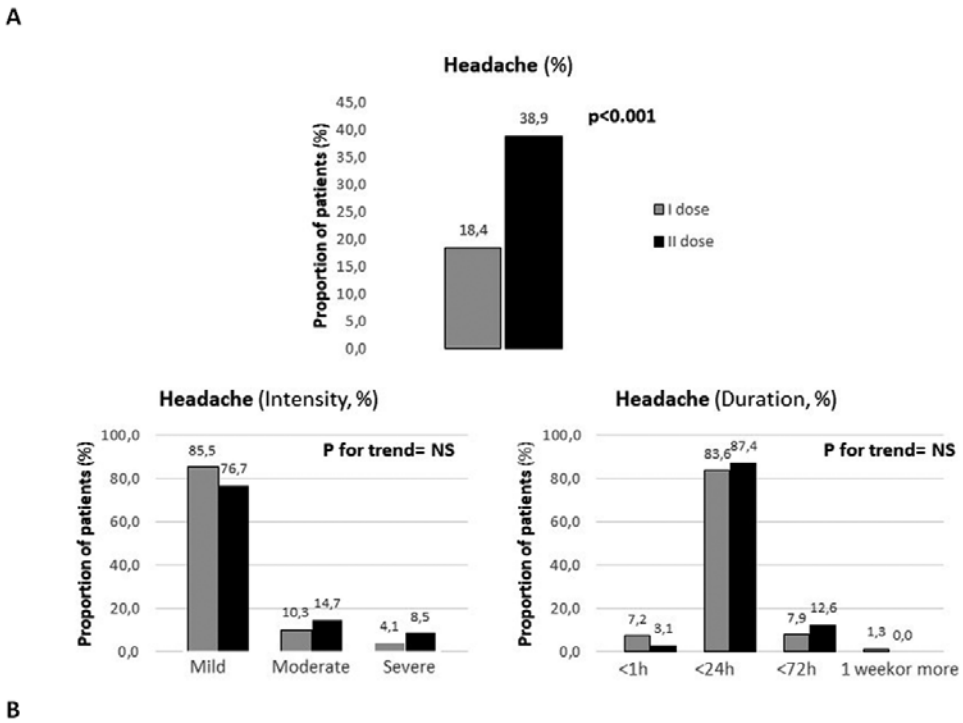



Figure 1 – Factors associated to vaccine hesitancy (VH) in a full adjusted multivariate analysis (Panel A) and in an alternative model after excluding "vaccination for influenza" (Panel B).

Table 2 – Reported adverse reactions after the first dose and the second dose.

| Symptom | First dose (n=6,242) n (%) | | Second dose (n=1,671) n (%) | | p |
|---|---|---|---|---|---|
| Pain, itching, paraesthesia (vaccination site) | 3,164 | (50.7) | 811 | (48.5) | 0.11 |
| Fatigue | 1,435 | (23.0) | 871 | (52.1) | <0.001 |
| Headache | 1,148 | (18.4) | 650 | (38.9) | <0.001 |
| Myalgia/Arthralgia | 800 | (12.8) | 797 | (47.7) | <0.001 |
| Fever | 285 | (4.6) | 275 | (16.5) | <0.001 |
| Tachycardia/Tachyarrhythmia | 254 | (4.1) | 168 | (10.1) | <0.001 |
| Lymphadenopathy | 237 | (3.8) | 184 | (11.0) | <0.001 |
| Diarrhoea | 138 | (2.2) | 93 | (5.6) | <0.001 |
| Facial/perioral paraesthesia | 114 | (1.8) | 37 | (2.2) | 0.35 |
| Nausea/Vomiting | 111 | (1.8) | 34 | (2.0) | 0.55 |
| Flushing | 68 | (1.1) | 168 | (10.1) | <0.001 |
| Urticaria | 40 | (0.6) | 14 | (0.8) | 0.40 |
| Dizziness | 39 | (0.6) | 14 | (0.8) | 0.90 |
| Shivering | 25 | (0.4) | 25 | (1.5) | <0.001 |
| Limb paraesthesia | 15 | (0.2) | 5 | (0.3) | 0.18 |
| Syncope | 7 | (0.1) | 34 | (2.0) | <0.001 |
| Other | 81 | (1.3) | 21 | (1.3) | <0.001 |




Supplementary Fig. 1 – Most frequently reported systemic adverse events (AEs) after first (grey bars) and second (black bars) dose.

Supplementary table 2 – Distribution of rare adverse events (AEs) in 7,881 subjects.

| Symptom | First Dose N (%) | Second Dose N (%) |
|---|---|---|
| Insomnia | 13 (16.0) | 3 (14.3) |
| Confusion | 7 (8.6) | 3 (14.3) |
| Cough | 7 (8.6) | 2 (9.5) |
| Rashes/dermatitis | 7 (8.6) | 2 (9.5) |
| Conjunctivitis/Photophobia | 6 (7.4) | 2 (9.5) |
| Herpes simplex/zoster reactivation | 6 (7.4) | 0 (0.0) |
| Vasomotor rhinitis | 6 (7.4) | 1 (4.8) |
| Upper and lower limbs hyposthenia | 5 (6.2) | 1 (4.8) |
| Thoracic oppression | 5 (6.2) | 1 (4.8) |
| Anosmia/Dysgeusia | 3 (3.7) | 1 (4.8) |
| Neuralgia | 3 (3.7) | 0 (0.0) |
| Tinnitus/Otalgia | 3 (3.7) | 0 (0.0) |
| Hypertensive crisis | 1 (1.2) | 1 (4.8) |
| Shock | 1 (1.2) | 1 (4.8) |
| Dyspnoea | 1 (1.2) | 0 (0.0) |
| Increased blood sugar | 1 (1.2) | 0 (0.0) |
| Laryngospasm | 1 (1.2) | 0 (0.0) |
| Mild agitation | 1 (1.2) | 0 (0.0) |
| Nystagmus | 1 (1.2) | 0 (0.0) |
| Sacroiliitis relapse | 1 (1.2) | 0 (0.0) |
| Sore throat | 1 (1.2) | 0 (0.0) |
| Sudden unilateral hypoacusia | 1 (1.2) | 0 (0.0) |
| Profuse sweating | 0 (0.0) | 2 (9.5) |
| Cystitis | 0 (0.0) | 1 (4.8) |
| Total | 81 | 21 |

severity of AEs was significantly higher in females, in people with a prior SARS-CoV-2 infection, and in those reporting AEs to previous vaccinations (Table 3).

## Discussion and conclusions

Immunization of HCWs still represents a priority of the Italian strategic roadmap for COVID-19 vaccination, considering that the actual vaccine coverage depends also on HCWs' propensity to be vaccinated and to encourage vaccination.

Our study, based on a large nationwide online survey, demonstrated an overall high propensity of Italian physicians toward anti-COVID-19 vaccines, being the estimated rate of VH considerably lower than those reported by previous surveys performed not only among the general population (10-16), but also among HCWs (17). These observations could be explained by the fact that the large majority of physicians perceive themselves at very high risk of contracting SARS-CoV-2 infection, and of developing severe, life-threatening complications.

Since the investigation of the motivations underlying VH is extremely important in order to prepare specific informative interventions for each vaccination plan, so to maximize vaccine coverage (21), participants

Supplementary table 3 – Main features of subjects admitted to the hospital for severe adverse events (AEs) after 2nd dose of COVID-19 vaccine.

| Hospitalization | Age (years) | Gender | Diabetes | Priori Sars-CoV-infection | 2020 flu vaccine | AEs at previous vaccinations | Symptoms at first COVID-19 vaccine dose |
|---|---|---|---|---|---|---|---|
| First dose | | | | | | | |
| *Anaphylactic shock* | 61-70 | F | No | No | No | No | - |
| *Urticaria* | 51-60 | F | No | No | Yes | Yes, mild | - |
| **Second dose** | | | | | | | |
| *Urticaria* | 51-60 | F | No | No | No | Unknown | *Headache, Fever, Myalgia, Urticaria (mild), Fatigue, Tachycardia* |
| *Anaphylactic shock* | 41-50 | F | No | No | No | No | *Headache, Lymphadenopathy, Myalgia, Facial/perio-ral paraesthesia, Fatigue, Local pain.* |
| *Tachyarrhythmia* | 41-50 | F | No | No | No | No | *Headache, Myalgia, Fatigue, Pain, Tachycardia* |

Legend to table: F = female

Table 3 – Prevalence of adverse events (AEs) occurred after first dose in the different subgroups

| **Adverse event (AEs)** (%) | **≤60 yrs** n=5,315 | **>60 yrs** n=867 | **p** | **Female** n=4,754 | **Male** n=1,428 | **p** | **COVID-19 –** n=5,809 | **COVID-19 +** n=373 | **p** | **Vaccine AR –** n=5,267 | **Vaccine AR +** n=915 | **p** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Local | | | | | | | | | | | | |
| Local pain | 54.0 | 31.3 | <0.001 | 52.8 | 44.0 | <0.001 | 50.9 | 50.1 | 0.79 | 48.9 | 61.5 | <0.001 |
| Lymphadenopathy | 4.2 | 1.0 | <0.001 | 4.2 | 2.4 | 0.002 | 3.5 | 9.0 | <0.001 | 3.4 | 6.1 | <0.001 |
| Systemic | | | | | | | | | | | | |
| Fatigue | 25.0 | 11.1 | <0.001 | 24.7 | 17.4 | <0.001 | 22.1 | 37.3 | <0.001 | 21.0 | 35.0 | <0.001 |
| Headache | 20.2 | 7.3 | <0.001 | 20.3 | 12.0 | <0.001 | 17.6 | 31.5 | <0.001 | 16.7 | 28.3 | <0.001 |
| Myalgia/Arthralgia | 13.8 | 7.4 | <0.001 | 13.4 | 11.3 | 0.04 | 11.8 | 30.4 | <0.001 | 11.5 | 20.8 | <0.001 |
| Fever | 7.0 | 5.5 | 0.29 | 6.7 | 7.2 | 0.62 | 5.2 | 28.8 | <0.001 | 6.2 | 9.7 | <0.001 |
| Tachycardia | 4.4 | 2.1 | <0.001 | 4.4 | 2.7 | 0.004 | 3.9 | 6.3 | 0.023 | 3.0 | 6.3 | <0.001 |
| Facial/perioral par. | 2.8 | 1.5 | 0.06 | 2.9 | 1.8 | 0.05 | 2.6 | 2.8 | 0.84 | 2.5 | 3.6 | 0.12 |
| Flushing | 1.3 | 0.2 | 0.009 | 1.3 | 0.6 | 0.03 | 1.1 | 0.8 | 0.63 | 0.9 | 2.1 | 0.002 |
| Diarrhea | 2.3 | 1.7 | 0.28 | 2.4 | 1.7 | 0.11 | 2.1 | 3.6 | 0.07 | 2.1 | 2.8 | 0.18 |
| Nausea/Vomiting | 2.0 | 0.4 | 0.001 | 2.2 | 0.4 | <0.001 | 1.7 | 3.1 | 0.05 | 1.4 | 3.9 | <0.001 |
| Urticaria | 0.7 | 0.2 | 0.11 | 0.7 | 0.4 | 0.25 | 0.6 | 0.8 | 0.64 | 0.6 | 0.9 | 0.31 |
| Dizziness | 0.5 | 1.3 | 0.1 | 0.7 | 0.5 | 0.44 | 0.7 | 0.3 | 0.39 | 0.6 | 1.1 | 0.06 |
| At least one AE | 69.6 | 58.0 | <0.001 | 66.4 | 76.0 | <0.001 | 64.2 | 82.7 | <0.001 | 70.6 | 44.2 | <0.001 |

Par.: Paresthesia; COVID+: previous COVID infection; COVID-: no previous COVID infection; yrs: years; AR: previous vaccine adverse reactions.
Symptoms indicated as ‘others’ and described in the open box of the questionnaire were included - where possible - within the other symptom categories listed.

to the survey were asked to argument about VH. Interestingly, VH for COVID-19 vaccine was higher among physicians who had also refused 2020 flu vaccine, suggesting distrust towards vaccines in general, rather than specifically towards COVID-19 vaccines. On the other hand, unwillingness to undergo COVID-19 vaccination was mainly due to fear of side effects and could be justified by the speed of their development (22) and scanty safety data (23). As expected, VH was more frequent in physicians who had developed AEs at previous vaccinations. Finally, physicians with prior SARS-CoV-2 infection were more prone to avoid or, at least, to delay vaccination. This attitude could be explained by the perception of a reduced vaccine usefulness together with a presumptive higher risk of AEs in subjects who had already developed a specific immune response after infection.

Indeed, our data demonstrate a significantly higher incidence of vaccine AEs in subjects with prior infection, excluded from pre-marketing trials on mRNA COVID-19 vaccines (2-3), but not from the vaccination campaign plans. Data collected from the Italian Medicines Agency support our results (24).

Some considerations are worth to be formulated at this regard. First, the presence of acquired immunity developed after infection can exacerbate the inflammatory response to vaccination, therefore eliciting systemic adverse reactions. Second, even if revaccination after wild type disease has been historically used after the introduction of a new vaccine (i.e. measles vaccination (25)), we do not yet have consistent data on the durability of the antibody response after SARS-CoV-2 infection (26), nor its effectiveness, especially against new virus variants (27), as current assumptions derive from previous studies in patients with SARS-CoV-2 (28-29) and seasonal coronavirus 229E (30). Therefore, a careful assessment of the risk/benefit ratio and of immune coverage durability should be performed for the correct prioritization of vaccination.

Concerning vaccine safety, the overall incidence of early AEs recorded in our study is low, but increased after the second dose, with AEs rates occurring after the first and second dose similar to those reported by the randomized pre-marketing trial of BNT162B2 (2). Moreover, AEs are typically mild to moderate, while severe events requiring hospitalization occurred only in 5 cases (0.01%) and consisted of anaphylactic shock and generalized urticaria. The promising safety of m-RNA vaccine profile seems to largely depend on the presence of the lipid capsule, which is probably capable of ensuring high immunogenicity but lower or similar reactogenicity to that of more classical vaccine formula (31, 32). The risk of adverse events is higher in females, in younger subjects, as previously reported (2), and in those referring adverse reactions to previous vaccinations. These data should be interpreted cautiously, since differences among subgroups could be partly due to a reporting bias; in particular, subjects who had experienced AEs at previous vaccinations could be more sensitive to side effects and more prone to report them, although an individual predisposition to AEs (especially allergic reactions) cannot be excluded *a priori*.

Major strengths of the study are represented by the high size, homogeneity and spontaneous selection of the study cohort, that, differently from the pre-marketing trials (2), also included subjects with prior SARS-CoV-2 infection, and, finally, the systematicity of data collection. On the other hand, some limitations should also be acknowledged. First, the survey was performed shortly after the beginning of the vaccination campaign in Italy, thus only data on very early AEs, but no information on long-term vaccine safety, could be collected. Second, the study cohort includes physicians only on the basis of spontaneous

adherence to a social network, thus could be not representative of the whole medical community and, consequently, of the entire Italian population. In addition, we do not know the characteristics of those who declined the invitation to this survey, who could have been used for comparison. Due to these reasons, and taking into account that physicians might perceive higher level of risk of infection, we acknowledge that the VH prevalence in this cohort may be underestimated. Moreover, those subjects who developed symptoms after vaccination may have been more prone to participate to the survey, so leading to a potential overestimation of side effects. Furthermore, since all features explored by this survey are self-reported, the frequency and the severity of adverse reactions could reflect subjective perceptions rather than actual reliable clinical features, even if participants are physicians.

In conclusion, the results of this survey suggest a high adherence of Italian physicians to the COVID-19 vaccination campaign. Vaccine hesitancy is largely confined to subjects with prior SARS-CoV-2 infection and/or adverse reactions to previous vaccinations and is mainly related to concerns avbout vaccine tolerability and safety. Early adverse events are unusual, generally mild and mostly occurring after the second vaccine dose. However, prior SARS-CoV-2 infection sensibly increases – according to responses - the risk of adverse events. Careful long-term monitoring of patients is required to confirm the promising safety of vaccine profile, while defining a more accurate roadmap of prioritization of worldwide vaccination campaign.

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**Contributors**

**MM**, **DG, EM** were involved in each of the following points:
1. Design
2. Data collection
3. Data Analysis
4. Manuscript draft
5. Manuscript revision

**FG, MM, BN** were involved in each of the following points:
Data collection
Manuscript writing
Manuscript revision

**RB** was involved in manuscript revision.

## Riassunto

***Esitazione Vaccinale anti-COVID19 ed Eventi Avversi Precoci in una Coorte di 7.881 medici italiani***

**Premessa.** La campagna di vaccinazione anti-COVID-19 è iniziata in Italia a fine dicembre 2020 con l'obiettivo primario di immunizzare gli operatori sanitari, utilizzando i vaccini a mRNA (Comirnaty® di Pfizer/BioNTech; mRNA-1273 di Moderna) e adenovirali ricombinanti (Vaxzevria® di AstraZeneca) approvati dall'EMA. Lo studio ha valutato la prevalenza e le motivazioni alla base dell'esitazione vaccinale, così come l'incidenza e il tipo di eventi avversi associati alla vaccinazione verso COVID-19.

**Metodi.** Studio trasversale. I dati sono stati raccolti dal 1° al 28 gennaio 2021 utilizzando un questionario online appositamente creato ed autosomministrato in una coorte selezionata di medici italiani.

**Risultati.** Complessivamente sono stati analizzati 7.881 questionari; 6.612 medici avevano ricevuto una dose e 1.670 due dosi di Comirnaty®; 30 avevano ricevuto una dose di mRNA-1273. Il tasso di esitazione vaccinale è stato del 3,6% ed era prevalentemente correlato a: precedente infezione da SARS-CoV-2; diabete; aver avuto effetti collaterali in seguito a precedenti vaccinazioni; aver rifiutato il vaccino antinfluenzale 2020. Le principali preoccupazioni riportate riguardavano gli effetti collaterali del vaccino. Gli effetti collaterali tipici sono stati dolore/prurito/parestesie nel sito di inoculazione, seguiti da cefalea, febbre, affaticamento e mialgia/artralgia. Questi eventi si sono verificati più

frequentemente dopo la seconda dose (77,8 vs 66,9%; p<0,001), e nei soggetti con una precedente infezione da SARS-CoV-2.

**Conclusioni.** L'adesione alla vaccinazione anti-COVID-19 è elevata tra i medici. Gli eventi avversi sono tipicamente lievi e più frequenti nei soggetti con una precedente infezione da SARS-CoV-2.

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