

Immediate adverse events following COVID-19 immunization. A cross-sectional study of 314,664 Italian subjects

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Abstract. *Background and aim:* The urgency of having rapidly safe and efficient COVID-19 vaccines called for the need to shorten trial phases, reduce sample sizes, and speed-up the approval process by the regulatory Agencies. In light of this, monitoring adverse effects (AEFI) (both immediate and at medium-long term) become of great importance. Aim of this cross-sectional study was to explore the associations between several factors and risk of immediate AEFI. *Methods:* Data come from the electronic dataset developed *ad hoc* to record demographic data, anamnesis and data related to immunization, set-up in the mass vaccination site in Novegro (Milan). Novegro mass vaccination site was one of the mass vaccinations sites with the highest flow in Lombardy Region, with a maximum capacity of 5,000 vaccinations/day. The center opened in April 2021 and closed the 1st of August 2021. A multivariable logistic regression model was used. Odds ratios adjusted (aOR) for age and sex are presented. Statistical significance was set at $p < 0.05$. Analyses were conducting using STATA. *Results:* Among the total of 314,671 subjects vaccinated, 0.5% developed an immediate AEFI, on average 17.0 ± 0.43 minutes after the administration. The three most frequent AEFI recorded were vagal response (30%), anxiety reaction (24%) and dizziness (21%). AEFI were more frequently observed among women [aOR= 2.24 (95%CI= 2.00 - 2.50)], and those with at least one previous disease [aOR= 1.47 (95%CI= 1.22-1.76)]. *Conclusions:* In conclusion, AEFI were less likely to occur for increasing age and after the second dose. Results from this large, complete and representative sample population regarding enrich the interesting scientific debate on potential adverse events following COVID-19 immunization. (www.actabiomedica.it)

Key words: COVID-19, Lombardy, SARS-COV-2, adverse events following immunization, vaccine

Introduction

The SARS-CoV2 virus, responsible for the COVID-19 disease, was firstly identified in Whuan (China) at the end of December 2019, and then rapidly spread worldwide, with Italy the first western country affected (1, 2). Due to its novelty and because of its rapid spread (3, 4), strong containment

and primary preventive measures were firstly adopted (including keep physical distance, hands washing, wearing face mask) (5, 6). However, the high mortality rate (7) and because of the immunological susceptibility of the world population, many efforts were put in rapidly developing new safe and efficient vaccines (8). This urgency called for the need to shorten trial phases, reduce sample sizes, and speed-up the approval process

by the regulatory Agencies. In light of this, monitoring side effects (both immediate and at medium-long term) become extremely needed.

Among more than 200 COVID-19 vaccine candidates, between December 2020 and March 2021, only four have been approved in Europe. The first vaccine to be authorized was the Comirnaty (Pfizer) (9), followed by Moderna (now known as Spikevax) (10), AstraZeneca (now known as Vaxzevria) (11), and Janssen (12). All of them showed satisfactory level of safety and efficacy in clinical trials, requiring two doses for all but Janssen only one. In Italy, and simultaneously in the rest of Europe, the vaccination campaign began in December 2020 (13). All these vaccines were used, albeit with different indications, for the mass vaccination campaign in Italy, and in Europe, during the first half of 2021. Indeed, in order to proceed in an orderly fashion, each countries identified its own vaccination strategy with priority categories. In particular, in Italy, healthcare workers were vaccinated at first, followed by subjects over 80 years, patients affected by various diseases and then vaccination was gradually extended to the entire population over 12 years old (13). The vaccination campaign of the general population necessarily required large spaces also useful for providing clinical support in case of immediate post-vaccine adverse reactions (14, 15). Indeed, according to the vaccine administration guidelines, subjects should be supervised for at least 15 minutes after immunization or even more based on clinical evaluation. Because of this and considering that evidence collected so far only described and assessed medium-term adverse events following immunization (AEFI), with the current study we aimed to explore the associations between several factors and risk of immediate AEFI.

Methods

This is a cross-sectional study assessing the association between COVID-19 vaccination and immediate AEFI. Data come from the electronic dataset developed *ad hoc* to record demographic data, anamnesis and data related to immunization, set-up in the mass vaccination site in Novegro (Milan) (16). Novegro mass vaccination site was one of the mass vaccinations sites

with the highest flow in the province of Milan (Lombardy Region, Italy) reaching approximately 5,000 vaccinations/day. The center opened April 21st 2021 and closed August 1st, 2021. The absolute and relative frequencies were calculated for all qualitative variables; Pearson's Chi-square test (χ^2) was used to analyze categorical variables. T-test was used for continuous variables. Category of vulnerability was grouped as follow: healthcare workers (also included healthcare students involved in clinical activities), professional risk (included non-healthcare workers, civilian personnel, laboratory staff, volunteer in health care sector), residents in confined communities (included school personnel, prisoners and patients hosted in long-term care settings), military, pregnant women, general population (included people younger than 60 years, blood donors, people living in a high risk geographical area due to the epidemic, close relative of high risk subjects due to diseases). A multivariable logistic regression model was used. The dependent variable selected was "Having had an immediate AEFI" that was defined as any type of immediate reaction occurred during the observation time (from at least 15 minutes to 120 minutes after immunization) and that required physician intervention or admission in the shock room available at the mass vaccination site. In model 1, adjustment for age and sex was conducted. Results are expressed as adjusted Odds Ratio (aOR) with 95% Confidence Intervals (95% CI). The level of significance chosen for statistical analysis was 0.05. The data was analyzed using statistical software STATA® version 16. As the data used in our analysis were routinely collected and completely anonymized, this study did not require approval by the institutional review board.

Results

A total of 314,671 subjects were vaccinated and recorded in the system, however, 7 subjects were excluded because records were uncompleted. The final sample therefore consisted of 314,664 subjects of with an average age of 47.5 years (standard error 0.03). Table 1 shows the sample description and the results of the bivariate analysis. In total, 1,409 (0.5%) of the total population developed an immediate AEFI, on average

Table 1. Descriptive characteristics of the sample, and bivariate associations. Used Pearson's Chi-square test, and t-test for continuous variables. Pearson's Chi-square test (χ^2) for categorical variables

Variables N (%)	Total population	AEFI (yes)	AEFI (no)	p-value*
Sex				
Women	152,690 (48.5)	946 (0.6)	151,744 (99.4)	<0.001
Men	161,974 (51.5)	463 (0.3)	161,511 (99.7)	
Age (mean \pm SE)	47.5 \pm 0.03	41.9 \pm 0.46	47.5 \pm 0.03	<0.001
Age				
0-19	17,456 (5.5)	134 (0.8)	17,332 (99.2)	<0.001
20-39	85,197 (27.1)	546 (0.6)	84,651 (99.4)	
40-59	130,351 (41.4)	467 (0.4)	129,884 (99.6)	
\geq 60	81,660 (26.0)	262 (0.3)	81,398 (99.7)	
Category of vulnerability				
Age \geq 60	81,660 (26.0)	262 (0.3)	81,398 (99.7)	<0.001
Previous pathology	27,252 (8.7)	172 (0.6)	27,080 (99.4)	
Healthcare workers	1,087 (0.4)	3 (0.3)	1,084 (99.7)	
Residents in confined communities	429 (0.1)	3 (0.7)	426 (99.3)	
Professional risk	361 (0.1)	4 (1.1)	357 (98.9)	
Military	152 (0.1)	3 (2.0)	149 (98.0)	
Pregnant women	40 (0.0)	0 (0.0)	40 (100)	
None (general population)	199,472 (63.4)	945 (0.5)	198,527 (99.5)	
Others	4,211 (1.34)	17 (0.4)	4,194 (99.6)	
Type of vaccine				
Pfizer (Comirnaty)	270,380 (85.9)	1,199 (0.4)	269,181 (99.6)	<0.001
Astrazeneca (Vaxzevria)	21,636 (6.9)	72 (0.3)	21,564 (99.7)	
Moderna (Spikevax)	14,544 (4.6)	85 (0.6)	14,459 (99.4)	
Janssen (Johnson & Johnson)	8,104 (2.6)	53 (0.7)	8,051 (99.3)	
Dosage				
First dose	255,173 (81.1)	1,273 (0.5)	253,900 (99.5)	<0.001
Second dose	59,491 (18.9)	136 (0.2)	59,355 (99.8)	
Latency of AEFI in minutes (mean \pm SD)	n.a.	17.0 \pm 0.43	n.a.	n.a.
Type of AEFI				
Vagal response	n.a.	423 (30.0)	n.a.	n.a.
Anxiety reaction		339 (24.1)		
Dizziness		296 (21.0)		
Paresthesias		99 (7.0)		
Allergic reaction		93 (6.6)		
Hypertensive crisis		78 (5.5)		
Other		81 (5.8)		

* p-value estimated comparing subjects who developed immediate AEFI compared to those without
SE: standard error; n.a.: not applicable

17.0 \pm 0.43 minutes after administration. The three most frequent AEFI recorded were vagal response (n= 423, 30%), anxiety reaction (n= 339, 24%) and dizziness (n= 296, 21%). All cases were promptly managed with clinical symptomatology solved in short time. Generally speaking, AEFI affected more frequently women compared to men, they occurred in younger subjects (on

average at 41.9 \pm 0.46 years), and more approximately 2-times more often after the first shot rather than the second one (0.5% vs 0.2%, respectively). Table 2 shows the unadjusted and adjusted odds ratios. From the multivariate logistic regression analysis our data confirm a significant higher risk of AEFI among women [aOR= 2.24 (95%CI= 2.00- 2.50; p<0.001)], among those

Table 2. Multivariable logistic regression. Crude Odds Ratio (OR) and Adjusted OR (aOR for sex and age) are presented.

	Dependent variable: AEFI (Yes)				
		OR (95% CI)	p-value	aOR* (95% CI)	p-value
Sex	Men	1		1	
	Women	2.17 (1.94-2.43)	0.000	2.24 (2.00- 2.50)	<0.001
Age	As the unit increases	0.98 (0.97-0.98)	0.000	0.98 (0.97-0.98) [^]	<0.001
Age	0-19	1		1	
	20-39	0.83 (0.68- 1.01)	0.060	0.85 (0.71-1.03) [^]	0.104
	40-59	0.46 (0.38-0.56)	0.000	0.47 (0.39-0.57) [^]	0.000
	≥ 60	0.42 (0.34-0.51)	0.000	0.40 (0.33-0.50) [^]	0.000
Type of vulnerability categories	Other	1		1	
	Age ≥ 60	0.65 (0.57-0.75)	0.000	0.62 (0.54-0.71) [^]	<0.001
	Previous pathology	1.26 (1.05-1.51)	0.011	1.47 (1.22-1.76)	<0.001
Type of vaccine	Pfizer (Comirnaty)	1		1	
	Astrazeneca (Vaxzevria)	0.75 (0.59-0.95)	0.018	1.19 (0.92-1.53)	0.176
	Moderna (Spikevax)	1.32 (1.06-1.65)	0.014	1.35 (1.09-1.69)	0.007
	Janssen (Johnson & Johnson)	1.48 (1.12-1.95)	0.006	2.06 (1.52-2.67)	<0.001
Dosage	First dose	1		1	
	Second dose	0.46 (0.38-0.55)	0.000	0.55 (0.46-0.66)	<0.001

* The model was adjusted for sex and age

[^] Only adjusted for sex

with at least one previous disease [aOR= 1.47 (95%CI= 1.22-1.76; p<0.001)]. Considering the type of vaccine administered, no differences were detected among Pfizer and Astrazeneca, whereas we found an increased risk for Janssen and Moderna vaccines. Nevertheless, since Janssen was the only vaccine with one administration dose required (instead of two as for all the other assessed vaccines), we performed a sensitivity analysis further adjusting for the dosage. However, even if the aOR decreased, the differences remained significant [aOR= 1.78 (95%CI= 1.34-2.36; p<0.001)]. On the contrary we found a lower risk of AEFI at the increasing of age and when the second dose was administered. In particular, for each year more, the aOR decreased of 2% [aOR= 0.98 (95%CI= 0.97-0.98)], whereas, the risk of AEFI was [aOR= 0.55 (95%CI= 0.46-0.66)] in case of second dose compared to the first dose.

Discussion

To the best of our knowledge this is one of the first study describing type and characteristics of immediate AEFI after COVID-19 vaccination, in a very

large population. Moreover, factors associated with higher risk of immediate AEFI were analyzed. In particular, sex, age, category of vulnerability, type of vaccines and dosage were considered. In our study, only a very small percentage of the total vaccinated subjects developed immediate AEFI, on average 17.0 ± 0.43 minutes after administration. AEFI affected more frequently women, younger subjects, or subjects with at least one previous disease, and as a consequence of the first immunization dose. Results were confirmed in the multivariable logistic regression adjusted for age and sex. Moreover, when comparing type of vaccines and AEFI it emerged that in the crude model, Astrazeneca seemed associated with a lower risk of AEFI when compared with Pfizer. However, this association was not confirmed in the model adjusted for age and sex. In fact, after Ministry of Health decree, Astrazeneca was primary administered to people older than 60 years (13). This is an important element that should be taken into account, indeed according to our analysis the risk of AEFI was lower in older people. Whereas an increased risk of immediate AEFI was detected when Moderna and Janssen were compared with Pfizer. These results were found in both crude and adjusted

multivariate analysis, and even after adjustment for vaccination dose (sensitivity analysis not reported in table). This is an unexpected result, since trials studies did not find significant differences in AEFI among the used vaccines (17). Our first hypothesis was that since Janssen is the only vaccine that require one dose, the increased risk could be attributable to the fact the first dose is associated with higher risk of AEFI. However, after adjusting for dose, the risk was lower but still significant. Consequently, the real interpretation of this result is still unclear. Future studies can further investigate this association, confirming or rejecting this observation.

Generally speaking, our results are in line with previous similar studies (18-21). In particular, two studies conducted in the United States, assessed the prevalence of immediate AEFI, but only focusing on the risk of allergic reactions following the first dose of COVID-19 immunization of Pfizer's Comirnaty (19), and Moderna (20) vaccines. In this study, authors detected 0.2% of allergic reaction after Pfizer and 0.03% after Moderna injection. Allergic reactions were most frequently detected in women, as in our study, and the median age was 40 years and 47 years, respectively for subjects who received Pfizer and Moderna, in line with our data. The median interval from vaccine receipt and immediate allergic reactions onset was slightly lower compared to what we found, being 13 min for subjects who received Pfizer and 7.5 minutes among those who received Moderna. Moreover, in agreement with literature, our results confirm that AEFI are more frequently associated with the first dose. Further, the majority of immediate AEFI were vagal response, anxiety reaction and dizziness, that can be generally attributable to fear of needles and immunization stress-related response (22). Moreover, fear of needles is also one of the barriers affecting vaccine acceptance, that needs to be addressed during the pre-vaccination counselling (23), both for increasing vaccination acceptance (24-26) and prevent potential AEFI (27). In this respect, a recent published guideline (28), highlighted the importance in preventing immunization stress-related response as for instance by means of educational materials, reassuring subjects using calm voice and simple messages, or distracting subjects during the injection.

This study has some certain limitations: as a cross-sectional study it is affected by the intrinsic limitation of the study design; the exposure and outcome are simultaneously measured, reducing the possibility to establish a true cause and effect relationship. In fact, even if the AEFI recorded immediately happened after the vaccine injection, it is not possible to unequivocally demonstrate a causality. Moreover, since we used administrative data routinely collected, some level of data cleaning was needed (29). Further, the level of details and quality of the data might be lower compared to data collected *ad hoc* for a predefined research question (29). Actually, even if we assessed the association between immediate AEFI, and demographic data, category of vulnerability and type and dose of vaccine, many other potential related factors could be explored, as for instance type of previous disease, history of allergy, medical prescription or previous vaccination status. Nevertheless, this study has important strengths. Firstly, it is based on a very large population study that helped in assessing also eventually rarer immediate AEFI. Secondly, we were able to estimate the prevalence of immediate AEFI. This is extremely important in public health for at least three main reasons. First, these data help in defining vaccine safety, second help in assessing the burden of potential immediate AEFI, and third they are useful in planning the development and implementation of a vaccination site; in other word in better allocating resources (both in terms of human and financial resources). Lastly, because of the cross-sectional design the current study was also relatively quick, cheap and easy to conduct, providing timely data ready to be used by public health experts and policy makers.

Conclusions

To conclude, we assessed the association between immediate AEFI and COVID-19 vaccination for each of the four vaccines approved in Italy (Pfizer, Astrazeneca, Moderna, and Janssen). Our data confirms the safety profile of the COVID-19 vaccines used, even if a higher risk of immediate AEFI were detected for Moderna and Janssen vaccines. Future studies should be performed in order to eventually

confirm these results, as well as identify possible reasons. All the subjects who experienced an AEFI received a prompt treatment by physicians presented in the shock room and available at the vaccination site. All cases had a quick resolution of the symptomatology. Immediate AEFI were more frequently recorded in young, women, in subjects with previous disease and after the first dose. Vagal response, anxiety reaction and dizziness were the most frequently reported AEFI. Results from this large, complete and representative sample population enrich the interesting scientific debate on potential adverse events following COVID-19 immunization.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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