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SARS-CoV-2 infection and H1N1 vaccination: does a relationship between the two factors really exist? A retrospective analysis of a territorial cohort in Ferrara, Italy

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Abstract. – OBJECTIVE: SARS-CoV-2 has been compared with other strains of coronaviruses, SARS-CoV and MERS-CoV, and with the flu viruses: all of them manifest themselves with respiratory symptoms and, although their genetic patterns are similar, the spread of SARS-CoV-2 infection has quickly reached global dimensions, demonstrating that SARS-CoV-2 is a virus with greater spreading capacity, albeit less lethal. Compared with influenza viruses, coronaviruses have a longer incubation period and the patients with coronaviruses' syndromes develop more severe diseases requiring frequent hospitalizations and intensive care admissions. The aim was to explore the relationships between seasonal influenza vaccination and coronavirus infection and to understand whether this hypothetic role by the flu vaccines modifies SARS-CoV-2 infection's outcomes.

PATIENTS AND METHODS: In this retrospective, multicenter study, we enrolled 952 patients diagnosed with SARS-CoV-2 infection; 448 were admitted to our two main hospitals in Ferrara territory, while the remaining 504 were isolated at home. We compared the group of patients who had been vaccinated for influenza in the previous 12 months to that of unvaccinated patients.

RESULTS: Significant differences were found for both the need for hospitalization and 30-day mortality between vaccinated and unvaccinated patients. We found age to be the only independent risk factor for a worse 30-day prognosis, while gender, influenza vaccinations and age itself were independent risk factors for undergoing hospitalization.

CONCLUSIONS: In our groups of patients, we found a relationship between seasonal influenza vaccinations and SARS-CoV-2 infection. Age seems to be the main risk factor for short-term mortality in COVID-19 inpatients, while the influenza vaccination is, together with gender and age itself, a determining factor in predicting the need for hospitalization.

Key Words:
SARS-CoV-2, Coronavirus, Influenza, H1N1, Seasonal influenza vaccination.

Introduction

Since the spread, in December 2019, of the novel coronavirus pandemic defined COVID-19 (COronaVIrus Disease-2019)[1], many studies have investigated the characteristics of SARS-CoV-2 virus, comparing it to the other coronaviruses (SARS-CoV and MERS-CoV) and to influenza viruses (such as H1N1 virus), all leading to respiratory syndromes.

Differently from SARS and MERS pandemics, which caused 8,094 (with 774 deaths) and 2,494 (with 858 deaths) cases, respectively[2], SARS-CoV-2 infection has rapidly caused a global outbreak with more than 60 million cases and 1,425,000 deaths worldwide as of November 26, despite its genetic similarities with the other two coronaviruses.

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All three coronaviruses have longer incubation periods (time from infection to symptoms onset) than influenza viruses: one study estimated the mean incubation period of SARS-CoV-2 to be 5.8 days, ranging from 1.3 to 11.3 days[3]; another study estimated it to be 5.1 days[4], while a recent Chinese study estimated the mean period to be 5.2 days[3]. For comparison, pandemic influenza in 2009 had a mean incubation period of 2 days.

Differences between the viruses were also found in the proportion of patients requiring hospitalization. Patients with SARS-CoV infection underwent hospitalization in more than 70% of cases against the 20% ca. of patients with SARS-CoV-2 infection; in 2009, the percentage of patients with pandemic influenza who underwent hospitalization was even smaller. Many patients with SARS-CoV infection required an Intensive Care Unit admission (40%), while the proportion of patients in SARS-CoV-2 cohort was 1/16,000 as of June 2020[5]. It is also interesting to underline how the mean age of dead patients was significantly higher in the group of patients with SARS-CoV and SARS-CoV-2 infection: less than 3% of these patients were younger than 65 years against 80% and 95% of dead patients during the influenza pandemics in 2009 and in 1918, respectively[5].

A key point of view to understand differences between SARS-CoV-2 and pandemic influenza seems to be the distribution of illness severity in the different ages: as for the Italian experience, until the 21st of September 2020, the 67% ca. of dead patients with SARS-CoV-2 infection were more than 80 years old; only the 4% of them were less than 50 years old.

Another point of discussion about differences between viruses is the organ damage following the host immune response after infection. Both adaptive and innate immune responses are required for host protection; the adaptive immune response efficiently recognizes and destroys specific pathogens[6] and thus restricts the spread of pathogens usually without causing significant non-specific inflammation. The innate immune system is responsible for initial responses to pathogens and is critical even in the case of vaccinations against influenza A virus[7]. Studies on mice investigated relations between the severity of coronaviruses and the ability to develop a virus-specific immune response, showing how the organ damage could effectively be a consequence of the hyper-inflammation, an extra-ordinary immune response by the host to the virus[8]. Both COVID-19 and influenza may be accompanied by ARDS.

SARS-CoV-2 infection and influenza can have several ways of clinical presentation, ranging from no symptoms (asymptomatic infection) to severe COVID-19. The most probable transmission pathway is definitely the inter-human one: asymptomatic patients seem to play a crucial role in spreading the infection[9].

Common symptoms include fever, cough, difficult breathing, sore throat, muscle pain, tiredness, hyposmia, headache, vomiting and diarrhea. Mechanisms for preventing viral spread are similar to those of other influenza-like viruses and are represented by the use of a face mask and sanitizing gel, avoiding contact with infected patients and careful hand hygiene[10].

Before the arrival of SARS-CoV-2, several studies found respiratory viral coinfection rates of about 40% in patients presenting with influenza-like illness, suggesting that SARS-CoV-2, as happening for the other members of respiratory viruses' family, could circulate together with the other viruses themselves[11-15]. Whether these viruses have a role in worsening COVID-19 presentation still remains unclear; one Chinese study showed no difference in terms of mortality in patients co-infected with SARS-CoV-2 and H1N1 against patients with SARS-CoV-2 infection only[16]; Wang et al[17] showed a lower mortality rate in co-infected patients, while Zhang et al[18] found higher mortality for patients with viral coinfections.

It is thus still plausible to think of a protective role of other viral infections, such as influenza viruses, against SARS-CoV-2 growth and disease development. This could be a consequence of the stimulation by other viruses of the innate immune response: in this case, response to SARS-CoV-2 would be more rapid, affecting positively the course of COVID-19. Anyway, the role that seasonal influenza vaccinations may play is generally not included in the debate.

Some Italian researchers investigated the relationship between influenza vaccination and COVID-19, finding a moderate to strong negative correlation between the two variables and resulting in a lower mortality rate in this cohort of patients[19].

The aim of this study is to understand whether a relation between seasonal influenza vaccination and SARS-CoV-2 infection exists and how this vaccine affects COVID-19 outcomes.

Patients and Methods

Study Design

This is a multicenter, retrospective cohort study. We enrolled 952 adult patients (≥ 18 years old) with a laboratory diagnosis of SARS-CoV-2 infection. 448 patients were hospitalized between March 15 and June 13, 2020 into the two main hospitals of Ferrara's territory that were set up for COVID-19 inpatients, "Arcispedale S. Anna" in Cona (Fe) and "Ospedale del Delta"in Lagosanto (Ferrara, Italy). The remaining 504 patients were isolated at home and followed by the local Public Health Department until complete recovery or death.

The study population was divided into two groups: 1) the case group, constituted by patients who had been vaccinated (VP) for influenza in the last 12 months and 2) the control group, with unvaccinated patients (UP). Both cohorts of patients had a positive story of SARS-CoV-2 infection.

The primary outcome of the study was to evaluate differences between the two groups in terms of the need for hospitalization, need for intensification of care (inpatients who underwent admission to the Pulmonology department or to Intensive Care Units – ICUs), the mortality rate at the 30th day since hospital admission (when occurred) and time until negativity of oro- and nasopharyngeal swabs for SARS-CoV-2 RNA detection, if possible (meant as two consecutively negative swabs).

Secondary outcomes were: 1) to determine the role of seasonal influenza vaccination as a predictor of mortality for patients in both the total cohort and the hospitalized cohort; 2) to determine whether seasonal influenza vaccination could be an independent predictor of needing hospitalization.

We followed STROBE guidelines (Strenghtening the Reporting of Observational Studies in Epidemiology) for reporting observational studies as for the compilation of this manuscript.

The local Ethics Committee approved the protocol of this study (code: 520/2020/Oss/AOUFe).

Data Collection

Demographic and clinical data of patients were entered into an electronic case report form. Data included the following: demographic characteristics (age and sex), need for hospital admission, need for intensification of cares, the mortality rate at the 30th day since hospital admission, time until recovery (double consecutively negative swabs).

Diagnoses of patients infected with COVID-19 were confirmed by at least one positive oro- and nasopharyngeal swab to SARS-CoV-2 RNA detection.

The Public Health Department of Ferrara collected data about patients' seasonal influenza vaccinations.

An informed consent was obtained after the nature and possible consequences of the study had been fully explained.

Statistical Analysis

Data analyses were performed by using SPSS 26.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA) software. The normal distribution of the continuous variables was analyzed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables not normally distributed were log-transformed before entering the parametric statistical analyses. Categorical variables were summarized by using frequencies and percentages, and continuous data were presented as mean± standard deviation (SD). The Mann-Whitney U test was used for continuous variables, and the χ^2 test or the Fisher exact test were used for categorical variables. Variables with a p-value < 0.05 in the univariate analysis were entered into multivariate logistic regression analysis. All p-values < 0.05 are considered statistically significant.

Results

Between March 15 and June 13, a number of 952 patients got a laboratory diagnosis of SARS-CoV-2 infection in the territory of Ferrara, Italy. Of these patients, 448 were hospitalized, while the remaining 504 were isolated at home until full recovery or death; the prevalence of vaccinated patients was 40%.

Table I illustrates the characteristics of the population, which was divided into vaccinated patients (VP) and unvaccinated patients (UP). Statistically significant differences were found for all the evaluated variables apart from gender. First, as we could expect from epidemiological data, the age of vaccinated patients was significantly higher than that of unvaccinated patients (75±17 *vs.* 51±19 years; p<0.001).

Differences were found also in the need for hospitalization between the two groups (255 VP *vs.* 193 UP; p<0.001), in the 30-days mortality rates (53 VP *vs.* 25 UP; p<0.001) and in the time until negativity of swabs (33±11 days for VP *vs.* 30±10 for UP; p=0.001).

We further evaluated the specifics of patients who needed hospitalization, dividing the population into two groups as for Table I. Table II il-

Table I. Characteristics of the whole population. VP population (vaccinated patients) compared to UP population (unvaccinated patients).

N=951	VP (371)	UP (581)	p (between groups)
Men	157 (42.3%)	241 (41.6%)	0.81
Women	214 (57.7%)	339 (58.4%)	
Age (mean±SD)	75±17	51±19	<0.001
Need for hospitalization	255 (68.7%)	193 (33.2%)	<0.001
30-days mortality	53 (14.3%)	25 (4.3%)	<0.001
Time until negativity of swabs (mean±SD)	33±11	30±10	0.001

lustrates the characteristics of vaccinated (ViP) and unvaccinated inpatients (UiP). Significant differences were found as for the age of patients: ViP patients were substantially older than UiP patients, as it happened for the total population (79±13 *vs.* 64±18 years; $p<0.001$); groups were also different in terms of 30-day mortality rate ($p=0.03$), while no significant difference concerned time until negativity of swabs.

Multivariate logistic regression analysis was performed to exclude any confounding factor and to understand whether seasonal influenza vaccinations could effectively modify 30-day prognosis of patients with SARS-CoV-2 infection. Moreover, we checked whether variables such as age, gender and influenza vaccination were modifying the probability of requiring a hospitalization.

The multivariate logistic regression analysis of 30-day mortality, in the whole population (Table III) and in the hospitalized population (Table IV), showed that the only variable slightly related to the 30-day prognosis was the age of patients.

Table V shows the relations between the same variables and the need for hospitalization in the whole population; in this case, all three variables were independently associated with the need for hospitalization, suggesting how the seasonal influenza vaccination could be considered as an independent predictor of needing hospitalization in our cohort of patients with SARS-CoV-2 infection (OR 1.44; 95% CI 1.01-2.05; $p=0.04$), but the two strongest factors leading to hospital admission were the older age of patients (OR 1.06; 95% CI 1.05-1.07; $p<0.001$) and male gender (OR 2.40; 95% CI 1.75-3.29; $p<0.001$).

We performed the same analysis eliminating the extreme values for age (0-17 and 86-100 years), but the final results did not change (table not shown).

Discussion

In our study, there was a higher prevalence of unvaccinated patients (UP) compared to that of vaccinated patients (VP) (581 UP *vs.* 371 VP; 60% *vs.* 40%). This proportion was not observed as we evaluated the group of patients who underwent hospitalization, with 255 VP *vs.* 193 UP. As predictable, the age of VP and UP was significantly different from each other: VP were older than UP and the same happened as for ViP and UiP (Table I and II).

Table II. Characteristics of the inpatients' population. ViP population (vaccinated inpatients) compared to UiP population (unvaccinated inpatients).

N=448	ViP (n=255)	UiP (n=193)	p (between groups)
Age (mean±SD)	79±13	64±18	**<0.001**
30-days mortality	53 (20.8%)	25 (13.0%)	0.03
Time until negativity of swabs (mean±SD)	33±12	32±12	0.61

Table III. Multivariate analysis results in the whole population. Variables independently associated with 30-days mortality.

Variables	OR	95% CI	p
Age	1.08	1.06-1.10	**<0.001**
Gender (M)	0.79	0.48-1.32	0.37
H1N1 Vaccination	1.06	0.60-1.88	0.85

Table IV. Multivariate analysis results in the hospitalized population. Variables independently associated with 30-days mortality.

Variables	OR	95% CI	p
Age	1.07	1.04-1.10	**<0.001**
Gender (M)	1.08	0.64-1.82	0.79
H1N1 vaccination	1.15	0.65-2.04	0.64

Table V. Multivariate analysis results in the whole population. Variables independently associated with the need for hospitalization.

Variables	OR	95% CI	p
Age	1.06	1.05-1.07	<0.001
Gender (M)	2.40	1.75-3.29	<0.001
H1N1 Vaccination	1.44	1.01.-2.05	0.04

We investigated then the 30-day mortality rate in the whole population, with 53 deaths in the VP (14.3%) and 25 deaths (4.3%) in the UP: this difference between groups was statistically significant ($p<0.001$), as it happened in the inpatients' population ($p=0.03$).

Significant differences ($p<0.001$) were found also in the time until the negativity of swabs in the whole population (33±11 days in the VP *vs.* 30±10 days in the UP), data not detected in the inpatients' group.

In order to find the possible causes of such differences between groups in terms of 30-days mortality, we performed multivariate analysis for the whole group of patients and for the inpatients' group. We tried to understand whether there were confounding factors that could make seasonal influenza vaccination a predictive factor for a worse prognosis in the cohort of patients with SARS-CoV-2 infection.

We chose age, gender and H1N1 vaccination as variables of this analysis. Age was the only independent risk factor to be found for a worse 30-day prognosis in our groups of patients (in either the whole population or the inpatients' population, $p<0.001$).

We further performed a multivariate analysis with the same three variables (age, gender, H1N1 vaccination) to check whether a relationship with the risk of undergoing a hospitalization in patients with SARS-CoV-2 infection existed. In this case, we found age, gender and influenza vaccination to be independent risk factors for undergoing hospitalization ($p<0.001$ for both age and gender; $p=0.04$ for H1N1 vaccination).

The current literature has still poor evidence of relations between SARS-CoV-2 infection and seasonal influenza vaccinations. Data that could prove a significant improvement or worsening of coronavirus infection by influenza vaccination are still missing and only a few retrospective studies searching for any relationship between these two factors exist.

During this ongoing SARS-CoV-2 pandemic, some reports on the significant association of influenza vaccines with an increased risk of coronavirus infection appeared in both media and academic circles. Speculation of vaccines increasing the risk of other viral infections originated probably during 2009 influenza A (H1N1pdm09) pandemic when some Canadian studies showed an increased risk of influenza A infection following a seasonal influenza vaccination[20]. The proposed mechanism behind this phenomenon was called "original antigenic sin": it suggested that the infection by a virus, only slightly different in antigens from that against which the person had been vaccinated (the "original" strain), could induce the immune system to produce antibodies against the "original" strain through high-affinity memory B cells, resulting in an inhibition of naïve B cells and in a weaker immune response against the new infecting virus.

Moreover, it is to consider how a sort of interference between viruses exists. There is enough evidence of this, in showing how this interference can decrease[21,22] or increase[23,24] the spread of other viral outbreaks. Vaccinated individuals could be at increased risk of developing other viral infections because they do not receive the non-specific immunity associated with natural infection.

Wolff et al[25] recently performed a large study to investigate respiratory virus interference during the 2017–2018 influenza season by comparing respiratory virus status with their influenza vaccination status. They concluded that, overall, receipt of influenza vaccination was not associated with virus interference among the study popula-

tion. However, vaccine-derived virus interference by specific respiratory viruses was significantly associated with coronavirus and human metapneumovirus.

In our population, we did not find influenza vaccination to be independently predictive for a worse 30-day prognosis, even if we found a significant difference in the 30-day mortality rate between VP and UP, and between ViP and UiP.

Besides, we found age, gender and influenza vaccination to be independent risk factors for hospitalization, suggesting how a possible relation between seasonal influenza vaccination and this new coronavirus infection could exist, but age remains (together with male gender in our study) the strongest factor influencing the worse prognosis and the need for hospitalization: vaccinated patients were older than unvaccinated patients and they underwent with more frequency a hospitalization or died within 30 days since SARS-CoV-2 infection diagnosis.

This is to underline how further and larger studies on relations between SARS-CoV-2 infection and seasonal influenza vaccination are required for understanding whether and how influenza vaccinations modify the immune response to SARS-CoV-2 infection.

The main limitations of the study are related to its retrospective nature and to the little number of patients with SARS-CoV-2 infection enrolled.

The role of seasonal influenza vaccination in the development of COVID-19 disease remains for these reasons unclear.

Conclusions

A relation between seasonal influenza vaccination and SARS-CoV-2 infection, in our cohort of patients, seems to exist. In our study, significant differences were found for both the need for hospitalization between vaccinated and unvaccinated patients and in 30-day mortality rate between these patients. Nevertheless, it is not possible to ignore how both outcomes (hospitalization and 30-day death) are strongly influenced by patients' age: apart from professional reasons, H1N1 vaccinations are usually recommended to older patients (>65 years old) and we still believe that this kind of recommendation has to be kept for older patients and for healthcare professionals. In our study, vaccinated patients were on average older than unvaccinated patients and this made age (and male gender as for this population) the real only predictive factor for a worse prognosis and for the need of hospitalization in patients with SARS-CoV-2 infection. Further and larger studies are obviously required to deepen this (still unexplored aspect) of SARS-CoV-2 infection.

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Author Statement

Greco Salvatore: acquisition, analysis and interpretation of data; drafting the article.
Bella Alessandro: acquisition, analysis and interpretation of data; drafting the article.
Bonsi Beatrice: acquisition, analysis and interpretation of data.
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Chessa Paola: acquisition and analysis of data.
Zuliani Giovanni: revising the article critically for important intellectual content.
Manfredini Roberto: revising the article critically for important intellectual content.
De Giorgi Alfredo: acquisition, analysis and interpretation of data.
Passaro Angelina: the conception and design of the study; drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted.

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Conflict of Interests

The authors have declared that no competing interests exist.

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