

Association between seasonal flu vaccination and COVID-19 among healthcare workers

M. Belingheri^{1,2}, M. E. Paladino^{1,2}, R. Latocca², G. De Vito¹ and M. A. Riva^{1,2}

¹School of Medicine and Surgery, University of Milano-Bicocca, Monza 20900, Italy, ²Unit of Occupational Medicine, San Gerardo Hospital, ASST Monza, Monza 20900, Italy.

Correspondence to: M. Belingheri, School of Medicine and Surgery, University of Milano-Bicocca, Building U38 (Villa Serena), Via Cadore 48, Monza 20900, Italy. Tel: +39 0264488191; fax: +39 0392332434; e-mail: michael.belingheri@unimib.it

Background	In next fall and winter, SARS-CoV-2 could circulate in parallel with seasonal influenza. The dual epidemics will result in considerable morbidity and mortality; therefore, influenza vaccination may be essential. Recent studies found increased risk of coronavirus in individuals receiving influenza vaccination.
Aims	Our aim is to analyse the association between influenza vaccination and COVID-19 in a population of healthcare workers (HCWs).
Methods	IgG antibodies against SARS-CoV-2 were detected in 3520 HCWs at a large hospital in Northern Italy. For each participant, we collected data on flu immunization status for the last five flu seasons. Logistic regression was used to test associations between seasonal flu vaccination status and a positive serology tests for COVID-19.
Results	During the last five flu seasons, 2492 vaccinations were administered. Serology tests were negative for 3196 (91%) HCWs and residents and only 21 (1%) people had an equivocal test (12.0–15.0 AU/mL). Only 128 (4%) people received a diagnosis of COVID-19, with a positive swab test. No flu vaccinations for the last five flu seasons were specifically associated with diagnosis of COVID-19 or with positive results of serology tests.
Conclusions	Flu vaccinations did not appear to be associated with SARS-CoV-2 infection. Influenza vaccination should continue to be recommended for HCWs and for individuals at increased risk for severe illness from respiratory infection.
Key words	Coronavirus; COVID-19; healthcare workers; influenza; SARS-CoV-2; seasonal flu vaccination.

Introduction

COVID-19 (Coronavirus Disease-2019), caused by the coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2), is an emerging infectious disease, declared pandemic by World Health Organization (WHO). On 11 October 2020, there were >37 000 000 confirmed cases and >1 000 000 death from COVID-19 worldwide. In Europe, Northern Italy was severely affected early on, particularly in Lombardy, the most populous, richest and most productive region in the country. Clinical manifestations of COVID-19 varied; most infected persons have only mild symptoms or even no symptoms, while some patients suffer from severe respiratory failure that requires early and prolonged support by mechanical ventilation. Scientists

around the world are working on several vaccines and treatments for COVID-19. Unless a new treatment is discovered, developing a vaccine is crucial to controlling this infection. In the absence of a vaccine, in fall and winter, SARS-CoV-2 will also circulate in parallel with seasonal influenza [1]. The dual epidemics of COVID-19 and seasonal influenza will result in considerable morbidity and mortality [2]. The confluence of these infectious diseases could have important repercussions for national health systems. For this reason, influenza vaccination could be essential in the next months during the COVID-19 pandemic. According to CDC Vaccination Guidance, healthcare providers should ‘use every opportunity during the influenza vaccination season to administer influenza vaccines to all eligible persons’. In particular, essential workers, individuals at

Key learning points

What is already known about this subject:

- COVID-19 is an emerging infectious disease, declared pandemic by World Health Organization.
- Previous studies were conducted only on benign coronaviruses, and no specific studies on the association between influenza vaccination and COVID-19 have been published.

What this study adds:

- Flu vaccination in the last five flu seasons was not associated with the presence or absence of IgG antibodies against SARS-CoV-2.
- The uptake of flu vaccination in the last five flu seasons was not a protective or risk factor for COVID-19.

What impact this may have on practice or policy:

- Although no association was found, flu vaccination is highly recommended for healthcare workers and for at-risk groups, in order to reduce hospitalization and to help in the differential diagnosis with COVID-19.

increased risk for severe illness from COVID-19 (those 65 years and older, nursing home residents, those with underlying medical conditions), and other individuals at high risk of influenza complications should receive the flu vaccine [3]. In the last few months, the relationship between influenza vaccination and coronavirus infections has been discussed, based on the phenomenon of vaccine-associated virus interference; that is, vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the non-specific immunity associated with natural infection [4]. In particular, natural infection activates the innate immune response that could temporarily reduce the risk of infection for other respiratory viruses. Flu vaccines reduce the probability of contracting flu infection and then avoid the activation of the innate immune response [4]. Studies have so far only been conducted on benign coronaviruses. In particular, in 2013, Sundaram *et al.* did not show an association between influenza vaccination and detection of coronavirus [5]. More recently, a study conducted by Wolff found increased risk of coronavirus in individuals receiving influenza vaccination. In this study, virus interference trends were found for coronavirus, thus reopening the international debate [6]. These studies were conducted only on benign coronaviruses, and no specific researches on association between influenza vaccination and COVID-19 were published. Recently, Marín-Hernández *et al.* found an association between the higher uptake of influenza vaccination and lower deaths from COVID-19 in Italy [7]. This association was found, studying the relationship between the percentage of vaccinated adults >65 years old and the percentage of COVID-19 deaths from each region in Italy. Thus, the authors concluded that further epidemiological, observational and vaccination studies are needed. Our aim is to analyse the association between influenza vaccination and infection by SARS-CoV-2 in a population of healthcare workers (HCWs) in a hospital in Lombardy, the epicentre of Italy's coronavirus outbreak.

Methods

The study included 3520 HCWs and medical residents at a large university hospital located in Northern Italy. All the participants were tested for IgG antibodies against SARS-CoV-2, as part of a screening promoted by the regional health authority. The test used was the LIAISON® SARS-CoV-2 S1/S2, which uses chemiluminescence immunoassay (CLIA) technology to quantitatively determine the anti-S1- and anti-S2-specific IgG antibodies in human serum or plasma samples [8]. Serology tests have been performed in May 2020. The database with serology data also included information on a previous diagnosis of COVID-19, performed with the polymerase chain reaction (PCR) diagnostic test on nasal swabs.

Every year, all HCWs were invited to get vaccinated by the Occupational Medicine (OM) service of the hospital. For each participant, we collected data on the flu immunization status of the last five flu seasons (2015/16, 2016/17, 2017/18, 2018/19 and 2019/20), from the immunization record of the OM service. Flu vaccines administered were quadrivalent vaccines and complied with the recommended compositions of influenza virus vaccines for use in the Northern hemisphere, in each influenza season [9–12]. In particular, the quadrivalent vaccine of the last flu season contained the following: an A/Brisbane/02/2018 (H1N1)pdm09-like virus, an A/Kansas/14/2017 (H3N2)-like virus, a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) and a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) [13].

Our database, which included both serology and flu status information, was anonymized. We also included data on age and gender, as possible confounders.

Data were analysed using SAS (SAS institute, Cary, NC, USA) statistical software. The age was tested both as a continuous variable and as a categorical variable, grouping it in different age ranges.

For the descriptive analysis, we used Wilcoxon–Mann–Whitney test for age since it is a continuous variable and does not follow normal distribution. We used

Table 1. Characteristics distribution of the overall population ($n = 3520$)

Variables	Total	Serology test results (IgG ab SARS-CoV-2)			COVID-19 diagnosis (with swab test)		
		>15.0 AU/mL	≤15.0 AU/mL	<i>P</i> -value	Yes	No	<i>P</i> -value
Age							
Median (interquartile range)	47 (35–55)	48 (36–55)	47 (35–55)	NS	49 (39–55)	47 (35–55)	NS
Age ≥ 60 years old							
Yes	381 (11)	32 (11)	349 (11)	NS	13 (10)	368 (11)	NS
No	3139 (89)	271 (89)	2868 (89)		115 (90)	3024 (89)	
Gender							
Male	986 (28)	90 (30)	896 (28)	NS	38 (30)	948 (28)	NS
Female	2534 (72)	213 (70)	2321 (72)		90 (70)	2444 (72)	
Number of flu vaccinations per season							
2015/16	212 (9)	21 (7)	191 (6)	NS	10 (8)	202 (6)	NS
2016/17	284 (11)	25 (8)	259 (8)	NS	13 (10)	271 (8)	NS
2017/18	429 (17)	33 (11)	396 (12)	NS	16 (13)	413 (12)	NS
2018/19	750 (30)	63 (21)	687 (21)	NS	30 (23)	720 (21)	NS
2019/20	817 (33)	61 (20)	756 (24)	NS	28 (22)	789 (23)	NS
Number of flu vaccination uptakes (seasons 2015/16 to 2019/20)							
None (never vaccinated)	2399 (68)	215 (71)	2184 (68)	NS	84 (66)	2315 (68)	NS
One	426 (12)	31 (10)	395 (12)		18 (14)	408 (12)	
Two	317 (9)	23 (8)	294 (9)		10 (8)	307 (9)	
Three	175 (5)	18 (6)	157 (5)		9 (7)	166 (5)	
Four	108 (3)	8 (3)	100 (3)		3 (2)	105 (3)	
Five (always vaccinated)	95 (3)	8 (3)	87 (3)		4 (3)	91 (3)	

The data represent n (%). NS, not significant.

a chi-square test for the categorical variables, such as gender, age ≥60 years old, number of flu vaccinations per season and number of flu vaccination uptakes (from seasons 2015/16 to 2019/20). Results with P -values > 0.05 were considered not to be statistically significant.

Logistic regression was used in both univariable and multivariable models, to test associations between (i) seasonal flu vaccination status and a positive serology tests (>15.0 AU/mL), and (ii) seasonal flu vaccination status and COVID-19. Odds ratio (OR) and 95% confidence interval (CI) were reported. We tested associations between serology tests and flu vaccination in season 2015/16, flu vaccination in season 2016/17, flu vaccination in season 2017/18, flu vaccination in season 2018/19, flu vaccination in season 2019/20 and number of vaccinations in the last 5 years (regardless the specific flu season). The variables included in multivariable model were age, gender and an interaction term between age and the vaccination intake in the last flu vaccination season 2019/20. The same associations were tested for COVID-19 diagnosis.

Results

A total of 3520 people were included and tested to detect IgG antibodies against SARS-CoV-2. The main characteristics of the study population are presented in [Table 1](#).

Table 2. Positive serology test and COVID-19 diagnosis per 1000 people, by number of flu vaccination uptakes

Number of flu vaccination uptakes (seasons 2015/16 to 2019/20)	Positive serology test (IgG ab SARS-CoV-2)		COVID-19 diagnosis (with swab test)	
	n per 1000 people	<i>P</i> -value	n per 1000 people	<i>P</i> -value
None (never vaccinated)	90		35	
One	73	NS	42	NS
Two	73		32	
Three	102		51	
Four	74		28	
Five (always vaccinated)	84		42	

NS, not significant.

The median age was 47 years old (interquartile range 35–55); 381 (11%) participants were aged 60 years or older; and 72% of participants were female. No difference in terms of age or gender was found between people with a positive serology test and people with negative serology test (P -value > 0.05), as well as no difference

was found between people with COVID-19 and people without COVID-19 (P -value > 0.05).

During the last five flu seasons, 2492 vaccinations were administered; and 1121 (32%) people were vaccinated at least once. **Table 1** reports the number of vaccinations per year. In details, 2399 (68%) participants refused flu vaccinations, so they were not vaccinated in the last 5 years; 426 (12%) people were vaccinated during only one flu season; 317 (9%) were vaccinated during two flu seasons; 175 (5%) during three flu seasons; 108 (3%) during four flu seasons; and 95 (3%) were vaccinated in all the five flu seasons considered in the study. Serology tests were negative for 3196 (91%) HCWs and residents and only 21 (1%) people had an equivocal test (12.0–15.0 AU/mL). Only 128 (4%) people received a diagnosis of COVID-19, with a positive swab test. No

difference was found considering different serology test results or diagnosis of COVID-19 (P -value > 0.05).

Table 2 reported the prevalence of positive serology test per 1000 people by the number of flu vaccination uptakes. No difference was found between the group who never received flu vaccines and the groups who received one or more flu vaccines in the last flu seasons. **Table 2** also showed the prevalence of COVID-19 diagnosis per 1000 people by flu vaccination uptakes. Similar to previous data, no difference was found into those groups.

The association between a positive serology test and seasonal flu vaccination is reported in **Table 3**. The flu vaccination in the last flu season 2019/20 was not associated with the serology test result (OR 0.82, 95% CI: 0.61–1.10). Similarly, no flu vaccines of the last five flu seasons were associated with the presence or absence of

Table 3. Logistic regression results showing the ORs for the association between seasonal flu vaccination and positive results to serology test

Variables	Univariate model			Multivariate model		
	OR	95% CI		OR	95% CI	
Age	1.01	0.99	1.02	1.00	0.99	1.02
Age ≥ 60 years old						
Yes	Ref	–	–			
No	1.03	0.70	1.51			
Gender						
Male	Ref	–	–	Ref	–	–
Female	0.91	0.71	1.18	0.91	0.70	1.17
Flu vaccination in season 2019/20						
No	Ref	–	–	Ref	–	–
Yes	0.82	0.61	1.10	0.89	0.29	2.79
Flu vaccination in season 2018/19						
No	Ref	–	–			
Yes	0.97	0.72	1.29			
Flu vaccination in season 2017/18						
No	Ref	–	–			
Yes	0.87	0.60	1.27			
Flu vaccination in season 2016/17						
No	Ref	–	–			
Yes	1.03	0.67	1.58			
Flu vaccination in season 2015/16						
No	Ref	–	–			
Yes	1.18	0.74	1.88			
Number of flu vaccination uptakes						
None (never vaccinated)	Ref	–	–			
One	0.80	0.54	1.18			
Two	0.80	0.51	1.24			
Three	1.17	0.70	1.94			
Four	0.81	0.39	1.69			
Five (always vaccinated)	0.93	0.45	1.95			
Interaction term (Age * Flu vaccination 2019/20)				1.00	0.97	1.02

The multivariate model includes age, gender, flu vaccination in season 2019/20, and the interaction term between age and vaccination uptake in the last flu season 2019/20.

IgG antibodies against SARS-CoV-2. Furthermore, no associations were found between the number of flu vaccinations and the serology test result. In details, no difference was found between people who always received flu vaccines and people who have never been vaccinated. Age and gender seem to be not associated with a different immune response against coronavirus. [Table 3](#) also showed the multivariable model results that included the interaction term between age and the last flu vaccination (season 2019/20). As well as for the univariable logistic regression, we did not find any association between flu vaccination and the serology test result.

Furthermore, we assessed the association between a diagnosis of COVID-19 and seasonal flu vaccination. Results of the logistic regression are reported in [Table 4](#). The uptake of flu vaccination in the last flu season was not

found as a protective or risk factor for COVID-19 since no association was reported (OR 0.92, 95% CI: 0.60–1.42). Correspondingly, no flu vaccinations of the last five flu seasons were specifically associated with COVID-19. We did not find any association with the number of flu vaccinations and the diagnosis of COVID-19. Finally, as well as for serology test, we did not find any association between age or gender and COVID-19. No association was found using the same multivariable logistic regression model that we used to assess associations between flu vaccination and serology test results. Data are shown in [Table 4](#).

Discussion

Our study aimed to assess the possible association between influenza vaccination and infection by

Table 4. Logistic regression results showing the ORs for the association between seasonal flu vaccination and diagnosis of COVID-19

Variables	Univariate model			Multivariate model		
	OR	95% CI		OR	95% CI	
Age	1.01	0.99	1.03	1.01	0.99	1.03
Age ≥ 60 years old						
Yes	Ref	–	–			
No	1.08	0.60	1.93			
Gender						
Male	Ref	–	–	Ref	–	–
Female	0.92	0.62	1.35	0.93	0.63	1.37
Flu vaccination in season 2019/20						
No	Ref	–	–	Ref	–	–
Yes	0.92	0.60	1.42	0.41	0.07	2.39
Flu vaccination in season 2018/19						
No	Ref	–	–			
Yes	1.14	0.75	1.72			
Flu vaccination in season 2017/18						
No	Ref	–	–			
Yes	1.03	0.60	1.76			
Flu vaccination in season 2016/17						
No	Ref	–	–			
Yes	1.30	0.72	2.34			
Flu vaccination in season 2015/16						
No	Ref	–	–			
Yes	1.34	0.69	2.59			
Number of flu vaccination uptakes						
None (never vaccinated)	Ref	–	–			
One	1.22	0.72	2.05			
Two	0.90	0.46	1.75			
Three	1.49	0.74	3.03			
Four	0.79	0.25	2.53			
Five (always vaccinated)	1.21	0.44	3.38			
Interaction term (Age * Flu vaccination 2019/20)				1.02	0.98	1.06

The multivariate model includes age, gender, flu vaccination in season 2019/20, and the interaction term between age and vaccination uptake in the last flu season 2019/20.

SARS-CoV-2. We used a population of HCWs, since flu vaccination is highly recommended in HCWs and, at the same time, they have an increased risk of contracting COVID-19 [14–17].

As far as we know, this is the first study that examined the association between influenza vaccination and SARS-CoV-2 infection, considering flu vaccination status, serology test result and diagnosis of COVID-19. Although Marin-Hernández *et al.* have already studied the relationship between flu vaccination and COVID-19, actually they only considered the percentage of vaccinated adults (>65 years old) and the percentage of COVID-19 deaths by region in Italy [7]. Our study is the first that considered the flu vaccination status of the last five influenza seasons and examined the association between novel coronavirus and previous vaccination uptakes. We considered two different variables as outcomes: the result of the serology test to detect IgG antibodies and the diagnosis of COVID-19 with PCR on swab samples. Our analysis did not show any association between flu vaccination in the last 5 years and serology test results. Similarly, we did not find any association between vaccines and diagnosis of COVID-19, probably because there is no interference in immunological mechanisms between flu vaccines and other respiratory viruses. It was not possible to compare our results with other studies since there are not similar investigations. However, our findings were consistent with previous studies that showed a non-association among flu vaccination and other coronavirus [5]. Although we did not find any association, influenza vaccination should be highly recommended for HCWs and for individuals at increased risk for severe illness from respiratory illness, especially during the outbreak of COVID-19. Indeed, flu vaccination may reduce the number of people who need hospitalization and may help in the differential diagnosis in case of fewer and other flu-like symptoms.

It is important not to underestimate the role of flu vaccination and the important disease burden. Indeed, seasonal influenza results in ~3–5 million cases of severe illness and up to 650 000 respiratory deaths worldwide [18].

The main limit of this study is that participants might have been vaccinated in other settings other than the OM service. However, this is unlikely as the OM service provided vaccination in the workplace, free of charge and without any loss of time.

In conclusion, we found no association between flu vaccination and infection by SARS-CoV-2, both considering serology antibodies and confirmed diagnosis of COVID-19. Flu vaccination is highly recommended for HCWs and for at-risk groups to reduce hospitalization and to help in the differential diagnosis with COVID-19.

Acknowledgements

The authors would like to thank Professor Maria Grazia Valsecchi for her valuable suggestions.

Competing interests

None declared.

References

1. Grech V, Borg M. Influenza vaccination in the COVID-19 era. *Early Hum Dev* 2020;**148**:105116.
2. Gostin LO, Salmon DA. The dual epidemics of COVID-19 and influenza: vaccine acceptance, coverage, and mandates. *J Am Med Assoc* 2020;**324**:335–336.
3. Centers for Disease Control and Prevention. Vaccination Guidance During a Pandemic [Internet]. <https://www.cdc.gov/vaccines/pandemic-guidance/index.html> (20 July 2020, date last accessed).
4. Cowling BJ, Fang VJ, Nishiura H *et al.* Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. *Clin Infect Dis* 2012;**54**:1778–1783.
5. Sundaram ME, McClure DL, VanWormer JJ, Friedrich TC, Meece JK, Belongia EA. Influenza vaccination is not associated with detection of noninfluenza respiratory viruses in seasonal studies of influenza vaccine effectiveness. *Clin Infect Dis* 2013;**57**:789–793.
6. Wolff GG. Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017–2018 influenza season. *Vaccine* 2020;**38**:350–354.
7. Marin-Hernández D, Schwartz RE, Nixon DF. Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy. *J Med Virol* 2020, doi:10.1002/jmv.26120.
8. DiaSorin. LIAISON® SARS-CoV-2 S1/S2 IgG. https://www.diasorin.com/sites/default/files/allegati/m0870004366_a_liaison_sars-cov-2_lr.pdf (20 July 2020, date last accessed).
9. World Health Organization. Recommended Composition of Influenza Virus Vaccines for Use in the 2015–2016 Northern Hemisphere Influenza Season [Internet]. 2015. https://www.who.int/influenza/vaccines/virus/recommendations/201502_recommendation.pdf?ua=1 (20 July 2020, date last accessed).
10. World Health Organization. Recommended Composition of Influenza Virus Vaccines for Use in the 2016–2017 Northern Hemisphere Influenza Season [Internet]. 2016. https://www.who.int/influenza/vaccines/virus/recommendations/201602_recommendation.pdf?ua=1 (20 July 2020, date last accessed).
11. World Health Organization. Recommended Composition of Influenza Virus Vaccines for Use in the 2017–2018 Northern Hemisphere Influenza Season [Internet]. 2017. https://www.who.int/influenza/vaccines/virus/recommendations/201703_recommendation.pdf?ua=1 (20 July 2020, date last accessed).
12. World Health Organization. Recommended Composition of Influenza Virus Vaccines for Use in the 2018–2019 Northern Hemisphere Influenza Season [Internet]. 2018. https://www.who.int/influenza/vaccines/virus/recommendations/201802_recommendation.pdf?ua=1 (20 July 2020, date last accessed).
13. World Health Organization. Addendum to the Recommended Composition of Influenza Virus Vaccines

- for Use in the 2019–2020 Northern Hemisphere Influenza Season [Internet]. 2019. https://www.who.int/influenza/vaccines/virus/recommendations/201902_recommendation_addendum.pdf?ua=1 (20 July 2020, date last accessed).
14. Belingheri M, Paladino ME, Riva MA. COVID-19: health prevention and control in non-healthcare settings. *Occup Med* 2020;**70**:82-83
 15. Belingheri M, Paladino ME, Riva MA. Beyond the assistance: additional exposure situations to COVID-19 for healthcare workers. *J Hosp Infect* 2020;**105**:353.
 16. Belingheri M, Paladino ME, Riva MA. Working schedule, sleep quality and susceptibility to COVID-19 in healthcare workers. *Clin Infect Dis* 2020, doi:10.1093/cid/ciaa499.
 17. Belingheri M, Paladino ME, Riva MA. Risk exposure to coronavirus disease 2019 in pregnant healthcare workers. *J Occup Environ Med* 2020;**62**:e370.
 18. World Health Organization. Seasonal Influenza [Internet]. 2018. [https://www.who.int/en/news-room/fact-sheets/detail/influenza-\(seasonal\)](https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)) (20 July 2020, date last accessed).

doi:10.1093/occmed/kqaa215

Filler articles

Occupational Medicine seeks authors to write interesting or amusing filler articles for its white spaces. We welcome contributions on topics related to occupational medicine or medical matters. Or you may have an interesting story

to tell about why you became an occupational physician or an occupational health practitioner. All contributions must be less than 500 words. If you have something to contribute, please contact us at om@som.org.uk