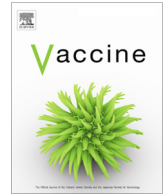




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Influenza and pneumococcal vaccinations are not associated to COVID-19 outcomes among patients admitted to a university hospital



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ABSTRACT

In order to reduce the burden on healthcare systems and to support differential diagnosis with COVID-19, influenza and pneumococcal vaccinations were strongly recommended during the COVID-19 pandemic, especially in vulnerable groups. However, no univocal and conclusive evidence on the relationship between influenza and pneumococcal vaccinations and COVID-19 outcomes exists. We evaluated the association between such vaccinations, COVID-19 hospitalization, intensive care unit admissions and deaths in a cohort (N = 741) of COVID-19 patients who had access to the emergency room of a large Italian University hospital between March 1, 2020 and June 1, 2020. Results show that influenza and pneumococcal vaccinations did not affect hospitalization, intensive care unit admission and deaths in COVID-19 patients in the overall sample and in those ≥ 65 years. The same pattern of results was confirmed considering timing of influenza vaccine administration, vaccination type, and number of uptakes in the last five vaccination campaigns. In conclusion, our study does not support an impact of influenza and pneumococcal vaccinations on COVID-19 outcomes.

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1. Introduction

The influenza virus has annually a high impact in terms of mortality, morbidity and hospitalization all over the world, with about 650,000 deaths associated with seasonal influenza [1,2]. Italy registers about 7 million cases and an average mortality excess rate between 11.6 and 41.2 per 100,000 annually [3]. Despite these figures, the influenza vaccine coverage among elderly and persons with chronic illnesses is lower than 75%, which is the cut-off recommended by the World Health Organization (WHO) [4]. Indeed, in Italy, in 2019/2020 the influenza vaccine coverage was 16.8% in the general population and 54.6% in people ≥ 65 years old [5]. Considering pneumococcal infection, the vaccination reduces mortality, morbidity and hospitalization of invasive disease, especially in elderly and vulnerable persons [6].

During the COVID-19 pandemic, both influenza and pneumococcal vaccinations were strongly recommended [7] in order to protect vulnerable groups of the population. Influenza poses two

different issues: on the one hand, it presents a symptomatology and clinical manifestation similar to COVID-19 [8]. On the other hand, the simultaneous infection of these two viruses is associated with worse clinical outcomes with more than a doubled mortality risk [9]. Therefore, reducing the possibility of influenza transmission translates into a reduced burden, hospitalizations, diagnostic tests for COVID-19, which takes the pressure on healthcare systems [10].

While the importance of influenza and pneumococcal vaccination during the COVID-19 pandemic has been widely discussed [7,10–12], there is no univocal evidence about the relationship between influenza vaccination and COVID-19 risk and related-outcomes [13], and the same holds for pneumococcal vaccination [14,15]. From a biological point of view, the vaccination itself might bring a potential protective effect against COVID-19 risks and outcomes in relation to the stimulation of innate immunity in an antigen-nonspecific manner, which could induce resistance to unrelated pathogens such as SARS-CoV-2, resulting in a reduced all-cause mortality [16]. Instead, disinformation and fake news all over the world reported an opposite effect, with an increased risk of infection and worst COVID-19 clinical outcomes due to influenza vaccination [17,18].

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An example of non-specific protection is represented by the Bacillus Calmette–Guérin (BCG) vaccination, that reduces deaths for pneumonia and respiratory tract infections caused by pathogens other than Mycobacterium tuberculosis [19]. The BCG vaccine, therefore, might have the same effect on SARS-CoV-2 [20]. In particular, BCG vaccine has a non-targeted protective effect against the virus of 2009 pandemic influenza A (H1N1), the Respiratory syncytial virus (RSV) and in general both the acute upper and lower respiratory tract infections. BCG vaccine, indeed, induces, in addition to the normal tuberculosis-specific antibody response, also an adaptive trained immunity based on functional reprogramming of mononuclear phagocytes enhancing the innate immune response, that is responsible of this non-specific protective effect against subsequent infections [19]. However, considering the SARS-CoV-2 infection, WHO currently recommends the use of BCG vaccine only in randomized controlled trails, in order to obtain robust evidences on a potential protective effect of BCG vaccine against COVID-19, and continue to ensure neonatal vaccination in countries and settings with a high incidence of tuberculosis [20,21].

In our prospective cohort study performed in a large University Hospital in Italy, we aimed at addressing the research question on whether COVID-19 patients experience different clinical outcomes (hospitalization, intensive care unit admission and deaths) in relation to former influenza and pneumococcal vaccinations.

2. Methods

2.1. Patient selection

We included all patients who had a laboratory confirmed SARS-CoV-2 infection at the Fondazione Policlinico Universitario A. Gemelli in Rome, between March 1, 2020 and June 1, 2020. The study cohort included all COVID-19 positive patients who had access consecutively to the emergency room of the hospital, whether they were hospitalized or not. SARS-CoV-2 infection was ascertained by PCR technique applied to the nasopharyngeal swab material, according to the guidelines provided by the Italian National Institute of Health [22]. The study was approved by the local ethics committee (prot. Number 0015439/20).

2.2. Data collection

Trained physicians interviewed each COVID-19 positive patient with a structured questionnaire after accessing the emergency room. Demographics, co-morbidities, travel and COVID-19 exposure history, presenting symptoms were collected using a form for cases of infections from respiratory viruses provided by the Regional Service for Epidemiology, Surveillance and Control of Infectious Diseases (SERESMI) [23]. Family members were interviewed when patients were unable to answer the questionnaire. Concerning comorbidity data, an additional check was made on the hospital information systems in relation to previous admissions or visits. Data about the influenza-co-infection, the hospitalization and intensive care unit admission, disease severity and death attributable to COVID-19 were gathered from the hospital admission information system. According to the definition provided by the Italian National Institute of Health [24], we considered as “deaths attributable to COVID-19” all those that met the following criteria: (i) laboratory diagnosis of SARS-CoV-2 confirmed by PCR technique; (ii) clinical and instrumental evaluation suggestive of COVID-19 (fever, cough, dyspnea and other symptoms typical of the infection); (iii) absence of a clear cause of death other than COVID-19 or otherwise not attributable to SARS-CoV-2

infection; (iv) absence of a period of complete clinical remission between illness and death.

The Lazio Region, through the vaccination registry, provided information about the patients' influenza and pneumococcal vaccination history (from the seasons 2015/16 to 2019/20), timing of the vaccination and type of influenza vaccine (trivalent or quadrivalent) [25].

2.3. Statistical analysis

Descriptive analysis were performed for all variables. We carried out logistic regression analysis to assess the impact of influenza and pneumococcal vaccinations on COVID-19 outcomes (hospitalization for COVID-19 symptoms, intensive care unit admission, and death attributable to the syndrome), with results expressed as odds ratios [OR], 95% CI.

We carried out logistic regression analysis to assess the impact of different types of influenza vaccine (trivalent vs. quadrivalent), timing of vaccine administration (distinguishing those who received immunization in the period October - November 2019 from those vaccinated later, from December 2019 - February 2020), and number of influenza vaccination uptakes (never, one-two, \geq three uptakes, from seasons 2015/16 to 2019/20) on COVID-19 outcomes.

The logistic regression analyses were performed adjusting the estimates for age, gender and comorbidity. All analyses were conducted both on the whole cohort of patients and on patients aged \geq 65, i.e., those who are especially targeted by influenza and pneumococcal vaccination campaigns.

All analyses were performed for a second scenario where missing data on chronic condition variable were handled using multiple imputation [26]. P-values below 0.05 were considered statistically significant. All statistical analyses were performed using Stata software, version 16 (StataCorp LP, College Station, TX).

3. Results

Seven hundred and forty-one patients with a positive COVID-19 test accessed the emergency room during the study period (Table 1). The median age of the patients was 67.5 (IQR = 54–79) years, and males accounted for 61% of the total cohort. Over 40% of the patients had at least one chronic condition. Among them, 76% had a preexisting cardiovascular condition and 32% were previously diagnosed with diabetes mellitus. The prevalence of cancer, respiratory disorders, neurological disorders, and renal disease were 19%, 25%, 6% and 22%, respectively.

Five-hundred forty-one (73%) patients required hospitalization, of which 57% \geq 65 years. Ninety-nine (13%) patients required intensive care and 97 (13%) patients died, of which 92% \geq 65 years (Table 1). Forty-two patients among the hospitalized group (7.7%) were also tested for influenza virus (A and B) and none of these patients tested positive.

Two hundred forty (32%) COVID-19 patients had received influenza vaccine during the last campaign (2019–2020) and eighty-one individuals (11%) were vaccinated against pneumococcal disease (Table 1).

Concerning influenza vaccine, 83.3% were vaccinated between October and November 2019 (over 93% before mid-December 2019) (Table 2). Regarding type of influenza vaccine, trivalent and quadrivalent were almost equally represented. Considering the influenza vaccination history, 50% of the individuals vaccinated during the last campaign were vaccinated also in the previous four campaigns. Considering people \geq 65, the coverage rate of the influenza and pneumococcal vaccinations was 47% and 15%, respectively. Table 3 reports adjusted OR and 95% CI of the

Table 1
Characteristics of eligible patients (N = 741).

Variable	Category	N	%
Age		67.5 years (IQR = 54–79)*	
	0–18	5	0.67
	18–45	73	9.85
	46–64	257	34.68
	≥ 65	406	54.79
Gender	Female	289	39.00
	Male	452	61.00
Chronic condition	No	160	21.59
	Yes	302	40.76
	Unknown	279	37.65
Hospitalizations for COVID-19 symptoms	No	199	26.86
	Yes	542	73.14
Admissions to intensive care units	No	642	86.64
	Yes	99	13.36
Deaths attributable to COVID-19	No	644	86.91
	Yes	97	13.09
Influenza vaccination	Not vaccinated	501	67.61
	Yes	240	32.39
Pneumococcal vaccination	Not vaccinated	660	89.07
	Yes	81	10.93

* Median; Interquartile range (IQR).

Table 2
Characteristics of COVID-19 patients who received influenza and pneumococcal vaccination.

Variable	Category	N	%	
Influenza (N = 240)				
Age	≥ 65	201	83.75	
	Timing of influenza vaccination	October–November 2019	200	83.33
		December 2019–February 2020	40	16.67
Composition of influenza vaccine 2019	Trivalent	129	53.75	
	Quadrivalent	111	46.25	
Number of influenza vaccine uptake	Only 2019	54	22.50	
	2 years (2018–2019)	0	0.00	
	3 years (2017–2019)	46	19.17	
	4 years (2016–2019)	22	9.17	
	5 years (2015–2019)	118	49.17	
Pneumococcal (N = 81)				
Age	≥ 65	73	90.12	
Type of vaccine	PCV13, Prevenar	81	100	

relationships between influenza pneumococcal vaccinations and the COVID-19 outcomes.

Influenza vaccination is not associated to COVID-19 related hospitalization, intensive care unit admissions, and death attributable to COVID-19 both in the overall sample (OR = 1.03 [0.66–1.62]; OR = 1.26 [0.74–2.21]; OR = 1.33 [0.77–2.31]) and in those aged ≥ 65 years (OR = 0.98 [0.58–1.68]; OR = 1.54 [0.80–2.94]; OR = 1.41 [0.80–2.49]). The same pattern of results was confirmed considering timing of influenza vaccine administration, vaccine type, and number of uptakes in the last five seasons.

Similarly, there was no association between pneumococcal vaccination and hospitalization, intensive care unit admission, and death in the overall sample (OR = 0.96 [0.53–1.78]; OR = 0.75 [0.35–1.61]; OR = 1.11 [0.56–2.21]) and in those aged ≥ 65 years (OR = 1.00 [0.53–1.91]; OR = 0.74 [0.33–1.66]; OR = 1.16 [0.58–2.32]). Moreover, no combined effects of the two vaccinations on COVID-19 outcomes were detected (data not shown). Multiple imputation analysis confirmed the absence of association between

vaccinations and clinical outcomes reported for the entire cohort (data not shown).

4. Discussion

Our results show that both vaccinations did not affect hospitalization, intensive care unit admission, and deaths among COVID-19 patients among patients admitted to a university hospital.

The same results were confirmed considering timing of influenza vaccine administration (distinguishing between those who received the vaccination in the period October – November 2019 and those in the period December 2019 – February 2020), type of vaccine (trivalent vs quadrivalent), and number of uptakes in the last five vaccination campaigns.

Although it was anticipated that influenza vaccination does not affect the risk of contracting other viral respiratory infections (the phenomenon of vaccine-associated virus interference) [27], SARS-CoV-2 is a new virus and possible interactions between influenza vaccination, COVID-19 infection and prognosis are not unequivocal.

A recent systematic review reported that there is no evidence to suggest that the influenza vaccination would have a negative impact on patients in terms of COVID-19 infections, illness, or deaths [13]. However, to date limited studies have evaluated the relationship between influenza vaccination and COVID-19 prognosis [28–37] with controversial results. Some of these reported a potential protective role of influenza vaccination on COVID-19 outcomes in the general population [28–30,32,33,38] and, albeit marginally, in elderly [37], while others reported a lack of association [31,34–36,38]. Recently, Conlon et al. reported that COVID-19 patients vaccinated against influenza were less likely hospitalized or mechanically ventilated and had a shorter hospital length of stay, although significant differences between the group of unvaccinated patients in terms of mortality or intensive care unit admission were not reported [38]. Authors admitted that residual confounding by a number of missing information on different covariates might have affected the results.

The timing of vaccine administration is another issue under debate [28,32]. In Italy, the 2019–2020 influenza vaccination campaign ended before the start of the pandemic and over 80% of the patients under study received the vaccine before December 2019. Fink et al. reported a significant mortality reduction among COVID-19 patients who received the influenza vaccine at time of clinical symptom onset or shortly thereafter, but not for individuals vaccinated earlier. This could suggest that if a beneficial effect of influenza vaccination exists, it does not last long, which calls the role of innate immunity into question [28]. In our study, the vast majority of patients received the vaccination well in advance to the onset of COVID-19. Consequently, we were unable to test this hypothesis in our sample.

Concerning the pneumococcal vaccination, an Italian survey based on a self-administered questionnaire documented that participants aged < 65 years old, who had reported receiving a pneumococcal vaccination, were less likely to test positive for SARS-CoV-2 than those not vaccinated [14]. Recently Jehi et al. confirmed a lower risk of contracting COVID-19 in vaccinated patients, while no study evaluated the association between pneumococcal vaccination and COVID-19 outcomes [15,39]. Our study did not report an association between pneumococcal vaccination and COVID-19 clinical outcomes.

Influenza vaccination and pneumococcal vaccinations are two fundamental public health interventions to reduce the pressure on the healthcare system during the first wave of the COVID-19 pandemic [11,12]. Although evidences about the effects of these vaccinations on clinical symptoms of COVID-19 are not univocal,

Table 3

Adjusted OR and 95% CI of the relationships between influenza and pneumococcal vaccinations and COVID-19 outcomes in whole cohort of COVID-19 patients (N = 741), and in the age group > 65 years (N = 406).

Variable	Category	Hospitalizations for COVID-19 symptoms		Admissions to intensive care units		Deaths attributable to COVID-19	
		OR [95% CI]	P value	OR [95% CI]	P value	OR [95% CI]	p value
Whole cohort (N = 741)							
Influenza vaccination (season 2019/2020)	No	–	–	–	–	–	–
	Yes	1.03 [0.66–1.62]	0.89	1.26 [0.74–2.21]	0.38	1.33 [0.77–2.31]	0.31
Timing	No	–	–	–	–	–	–
	October–November 2019	0.89 [0.55–1.44]	0.64	1.19 [0.66–2.15]	0.55	1.44 [0.82–2.53]	0.21
	December 2019–February 2020	1.84 [0.83–4.10]	0.14	1.64 [0.63–4.22]	0.30	0.80 [0.25–2.53]	0.70
Type of vaccine	No	–	–	–	–	–	–
	Trivalent	1.10 [0.63–1.93]	0.73	1.12 [0.56–2.26]	0.73	1.08 [0.57–2.05]	0.82
	Quadrivalent	0.97 [0.56–1.68]	0.92	1.42 [0.74–2.71]	0.29	1.76 [0.88–3.52]	0.11
Influenza vaccination uptakes	None	–	–	–	–	–	–
	1–2	1.77 [0.85–3.71]	0.13	1.06 [0.40–2.79]	0.91	0.42 [0.13–1.31]	0.13
	≥3	1.34 [0.75–2.40]	0.33	0.87 [0.54–1.42]	0.59	1.61 [0.92–2.84]	0.10
Pneumococcal vaccination	No	–	–	–	–	–	–
	Yes	0.96 [0.53–1.78]	0.91	0.75 [0.35–1.61]	0.46	1.11 [0.56–2.21]	0.76
Age ≥ 65 (N = 406)							
Influenza vaccination (season 2019/2020)	No	–	–	–	–	–	–
	Yes	0.98 [0.58–1.68]	0.96	1.54 [0.80–2.94]	0.20	1.41 [0.80–2.49]	0.24
Timing	No	–	–	–	–	–	–
	October–November 2019	0.95 [0.55–1.64]	0.86	1.42 [0.73–2.78]	0.31	1.54 [0.86–2.76]	0.15
	December 2019–February 2020	1.29 [0.43–3.88]	0.65	2.67 [0.79–8.95]	0.11	0.65 [0.18–2.32]	0.51
Type of vaccine	No	–	–	–	–	–	–
	Trivalent	1.15 [0.63–2.11]	0.65	1.27 [0.59–2.73]	0.54	1.08 [0.56–2.10]	0.82
	Quadrivalent	0.78 [0.39–1.58]	0.50	1.92 [0.88–4.18]	0.11	2.08 [1.00–4.33]	0.05
Influenza vaccination uptakes	None	–	–	–	–	–	–
	1–2	1.52 [0.59–3.89]	0.39	1.64 [0.52–5.14]	0.40	0.45 [0.14–1.45]	0.18
	≥3	0.91 [0.52–1.58]	0.73	1.52 [0.77–2.97]	0.22	1.69 [0.94–3.05]	0.08
Pneumococcal vaccination	No	–	–	–	–	–	–
	Yes	1.00 [0.53–1.91]	0.99	0.74 [0.33–1.66]	0.47	1.16 [0.58–2.32]	0.67

it is important to encourage campaigns for such vaccinations to reduce the number of hospitalizations, diagnostic tests for COVID-19 and healthcare system saturations. Moreover, these vaccinations may prevent influenza or pneumococcal coinfection with SARS-CoV-2, thereby reducing mortality from COVID-19 [40].

Our study might have some limitations. Firstly, it is based on a relatively small sample size, so that might be underpowered to detect a robust association between influenza and pneumococcal vaccinations and the outcome under investigation. Secondly, we know that COVID-19 patients with a number of comorbidities experience the worst clinical outcomes, and that in Italy these subjects are usually overrepresented in the group of vaccinated persons. In our study, we had almost 40% missing data on baseline chronic conditions, which might have affected residual confounding of our results. The multiple imputation analysis on ‘chronic conditions’ variable, however, confirms the absence of association between vaccinations and clinical outcomes. Thirdly, we missed information on ‘socio-economic’ variables and on ‘date of onset of symptoms’ that might affect clinical outcomes so that additional residual confounding might exist.

Our study is the first considering the influenza vaccination status of the last five influenza seasons, the pneumococcal vaccination and examined individual and combined effect with clinical outcomes of COVID-19. According to our findings, influenza and pneumococcal vaccinations did not affect hospitalization, intensive care unit admission, and deaths in COVID-19 patients in the overall sample and in those aged ≥ 65 years. However, further studies are needed to investigate the possible protective effect of vaccinations carried out during the pandemic (especially the 2020–2021 influenza campaign) to analyze the hypothesis that influenza and pneumococcal vaccinations could stimulate a strong immune response (through cross-protection, cross-reactivity and immunostimulation linked to the vaccines) with a potentially lower severity of COVID-19 infection.

Declarations

Funding

No funding was received for this study.

Ethics approval

The study was approved by the Ethics Committee of the Policlinico Universitario A. Gemelli IRCCS. (prot. Number 0015439/20).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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