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Effectiveness of repetitive influenza vaccination against SARS-CoV-2 infection among a cohort of health care workers in Portugal

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Abstract Vaccination for influenza has been essential over the years to protect the most vulnerable populations. Moreover, it was recently suggested that influenza vaccination might confer some nonspecific immunity to other viruses and be associated with a lower risk for coronavirus disease 2019 (COVID-19) morbidity and mortality. Therefore, we aimed to assess the effectiveness of repetitive influenza vaccination against SARS-CoV-2 infection in a cohort of health care workers (HCWs). This study was conducted among HCWs at São João University Hospital Center (CHUSJ), Porto, Portugal, a tertiary reference hospital for diagnosis and therapy, one of the largest hospitals in the country with approximately 6000 HCWs. We analyzed databases for influenza vaccination conducted between 2012 and 2019 and COVID-19 laboratory testing retrieved from the first and last registered positive COVID test date before HCW's COVID-19 vaccination started. The study outcome was the incidence of the first SARS-CoV-2 infection, as determined by reverse transcription polymerase chain reaction (RT-PCR). Age and sex were considered potential confounders. We used multivariable Cox regression to estimate odds ratios. Neither the absolute number nor the proportion of influenza shots influenced the risk of getting infected by SARS-CoV-2 (adjusted odds ratio 1.02, 95% CI: 0.9–1.06 and 1.17 95% CI: 0.86–1.58, respectively). Similar findings were observed in most cases when the analysis was restricted by year. The findings from our retrospective observational analysis of a HCWs cohort failed to support any protective effect between repetitive influenza vaccination and SARS-CoV-2 infection.

Keywords: COVID-19, influenza vaccines, health care workers, SARS-CoV-2 infection, vaccination

An Impact Statement: No protective effect between repetitive influenza vaccination and SARS-CoV-2 infection in health care workers.

Introduction

Vaccination for influenza has been essential over the years not only to protect the most vulnerable populations but also to prevent the transmission of infection between health care workers (HCWs) and patients and to try to reduce the work absenteeism of workers at high risk of exposure. The European Center for Disease Prevention and Control recommends the annual vaccination of all health care workers.[1] Moreover, it was recently suggested that influenza vaccination might confer some nonspecific immunity to other viruses and be associated with a lower risk for coronavirus disease 2019 (COVID-19) morbidity and mortality.[2-5] This concept of "trained immunity" has been increasingly studied because it can revolutionize the use of certain vaccines.[6-8] Accordingly, live vaccines, such as the Bacillus Calmette-Guérin (BCG), measles and rubella vaccines, provide nonspecific protection for infections other than those to which the vaccines are directed.[9,10] Depending on the vaccine use, this mechanism reprograms myeloid and lymphoid cells.[11,12] However, this influenza vaccine–induced "trained immunity" reported to protect against SARS-CoV-2 infection, and severe COVID-19 could have arisen because of bias and may not reflect a natural biological effect. Notably, this protection may be due to the healthy user effect, whereby health-aware people are more likely to receive an influenza vaccine and practice healthy behaviors that reduce their risk of acquiring the infection.

Another confounder effect may appear because of the required repeated annual administration of the influenza vaccine. Several reports suggest that repeated vaccination might attenuate the effectiveness.[13,14] In fact, despite no biological mechanism having been found, taking the influenza vaccine in the previous year attenuates the efficacy. Still, somehow repetitive shots over the years seem to confer more protection than not to get any influenza vaccine at all. However, these studies were not relevant enough to change the vaccination guides. The hypothesis of possible vaccination biases still leads to the need for more studies in this area.[14]

Therefore, we aimed to assess the effectiveness of repetitive influenza vaccination against SARS-CoV-2 infection in a cohort of health care workers.

Methods

This study was conducted among health care workers (HCWs) at São João University Hospital Center (CHUSJ), Porto, Portugal, a tertiary reference hospital for diagnosis and therapy in several areas, one of the largest hospitals in the country with

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approximately 6000 health care workers. We analyzed databases for influenza vaccination conducted by HCWs between 2012 and 2019 and COVID-19 laboratory testing retrieved from the date of the first registered positive COVID test (March 2020) and the date of the last positive COVID test (December 2020) before the HCWs COVID-19 vaccination started. These databases include demographic information such as sex and age. All participants had to work at CHUSJ in 2020 and at least one year before to guarantee they had had at least one opportunity to get the influenza vaccination. Therefore, after applying the inclusion criteria, data from 3969 of the 6451 HCWs were analyzed. The study outcome was the incidence of the first SARS-CoV-2 infections, as determined by reverse transcription polymerase chain reaction (RT-PCR) Age and sex were considered potential confounders.

We used multivariable Cox regression to estimate odds ratios (ORs) and adjusted odds ratios (reported with 95% CIs) for the association between influenza vaccination and SARS-CoV-2 infection by applying the univariable and multivariable Cox regression, respectively. Influenza vaccination was modeled as a binary time-varying covariate. Individuals were censored if they died or were moved from the hospital. All statistics were performed in R stats packages, version 4.2.2.

The study protocol was approved by the Ethics Committee of CHUSJ (nr 293/22).

TABLE 1

Demographic characteristics for the overall health care workers cohort.

	Overall, n=3969	Female, n= 2986	Male, n=983	*P*
Years of work	6.41 (2.54)	6.38 (2.57)	6.50 (2.44)	.20
Age in 2022	45.0 (10.9)	45.0 (10.7)	45.0 (11.4)	.96
Influenza shots, absolute n (%)				.59
None	1994 (50.2)	1494 (50.0)	500 (50.9)	
1 or 2	951 (24.0)	727 (24.3)	224 (22.8)	
3 or 4	384 (9.7)	279 (9.3)	105 (10.7)	
5 or 6	318 (8.0)	245 (8.2)	73 (7.4)	
7 or 8	322 (8.1)	241 (8.1)	81 (8.2)	
Influenza shots, overall proportion				.43
None	1994 (50.2)	1494 (50.0)	500 (50.9)	
Up to 50%	1276 (32.1)	958 (32.1)	318 (32.3)	
50%–99%	546 (13.8)	424 (14.2)	122 (12.4)	
Higher than 99%	153 (3.9)	110 (3.7)	43 (4.4)	
SARS-CoV-2 infection, n (%)				.06
Negative	3403 (85.7)	2542 (85.1)	861 (87.6)	
Positive	566 (14.3)	444 (14.9)	122 (12.4)	
Time to infection, days	933.1 (254.4)	929.2 (257.8)	944.6 (243.7)	.09

Data presented as mean (SD) unless otherwise stated. Some proportions might not add up to 100% because of rounding.

Results

Most participants included in the analysis were female, median age of 45 years, with about half having at least one influenza shot, and 14% having an episode of SARS-CoV-2 infection (Table 1).

Neither the absolute number nor the proportion of influenza shots influenced the risk of getting infected by SARS-CoV-2 (adjusted OR 1.02, 95% CI: 0.9–1.06 and 1.17, 95% CI: 0.86–1.58, respectively) (Table 2, Fig. 1). Similar findings were observed when the analysis was restricted by year (Table 2).

The time to SARS-CoV-2 infection by the influenza shot group is shown in Fig. 1. Taking more influenza vaccines conferred more protection than not taking the vaccines. However, the results also demonstrated that the number of influenza shots that gave more immunity is variable (Fig. 1A). When applying the proportion of influenza vaccines taken during the years of work (Fig. 1B), it was observed influenza shots were associated with an increased risk for SARS-CoV-2 infection than never getting the influenza vaccination. Being younger and female was a protective factor against illness (Fig. 1C and D).

Discussion

The findings from our retrospective observational analysis of a health care worker cohort failed to support any protective effect between repetitive influenza vaccination and SARS-CoV-2 infection.

Our study has several limitations. First, although we have a relatively large database with 3698 professionals, the investigation takes place at a single center, which may not be representative and lack external validation, particularly to the general population. In addition, there may be potential confounders for which the data were not adjusted, such as comorbidities that we could not consider. Yet our study also has important strengths. Compared with other published studies, our database has an extensive data, 3969 HCWs were included, and our information from influenza vaccination goes back to 2012 till 2019. Furthermore, we considered ten months for a positive COVID test to be registered, something that no other study contemplates.

The existence of a protective effect of influenza vaccination against SARS-CoV-2 infection based on innate immunity training has been suggested by a few studies. According to a study conducted in a tertiary acute-care hospital in Italy using a database of 2561 HCWs vaccinated for influenza in 2020/2021, a lower risk for SARS-CoV-2 infection was observed.[2] In addition, in Italy, another study using a public database of influenza vaccination in 2019/2020 in an older population (older than 66 years) confirmed that higher influenza vaccination has been associated with fewer deaths from COVID-19.[3] In a study taking place in an Italian province using a database of 17,608 residents who were tested for SARS-CoV-2, an analysis was made of the ones that take the influenza vaccine, and although a possible protective effect was observed, there was no association between the influenza vaccination and the reduction of hospitalizations.[4] In Canada, a study that evaluated the possible protective effect of taking two consecutive influenza vaccines (2019/2020 and 2020/2021) in a population older than 66 years concluded that the ones who were vaccinated had less infection by SARS-CoV-2. However, they assumed a possible healthy vaccine bias.[14] At last, a study taking place in the Netherlands, with a population of 6856 HCWs in the first wave of the pandemic and 10899 HCWs in the second wave, evaluated a possible association between the influenza vaccination in 2019 and 2020, respectively, and the SARS-CoV-2 infection. They concluded that the ones who had the influenza vaccine had lower COVID-19 incidence.[15]

However, our results are in line with studies that demonstrate that repetitive influenza vaccination can affect effectiveness, and, consequently, there is no innate immunity response built that would provide some kind of protection against SARS-CoV-2 infection.[13] This could happen for multiple reasons, and some studies evaluated the duration of the effect of the influenza vaccine.[16]

Our findings may be partially explained by health-related behavior factors. Although the COVID-19 pandemic changed in

TABLE 2

Analyses of the risk of getting infected by SARS-CoV-2

Crude				Adjusted for sex and age			
Predictors	**Odds Ratios**	**CI**	***P***	**Predictors**	**Odds Ratios**	**CI**	***P***
Years of work	0.91	0.89–0.94	<.001	Years of work	0.95	0.91–0.99	.018
Influenza shots, absolute n	0.98	0.95–1.02	.358	Influenza shots, absolute n	1.02	0.98–1.06	.396
Influenza shots, overall proportion	0.93	0.69–1.24	.642	Influenza shots, overall proportion	1.17	0.86–1.58	.316
2012	1.06	0.84–1.32	.626	2012	1.27	1.00–1.60	.049
2013	0.77	0.60–0.96	.026	2013	0.90	0.70–1.14	.379
2014	0.84	0.67–1.05	.133	2014	1.00	0.79–1.26	.998
2015	0.98	0.78–1.21	.831	2015	1.15	0.91–1.43	.230
2016	0.83	0.65–1.04	.117	2016	0.96	0.75–1.22	.720
2017	0.93	0.74–1,16	.514	2017	1.07	0.84–1.34	.587
2018	0.90	0.72–1.11	.321	2018	1.01	0.81–1.25	.960
2019	1.13	0.92–1.39	.227	2019	1.26	1.02–1.55	.028

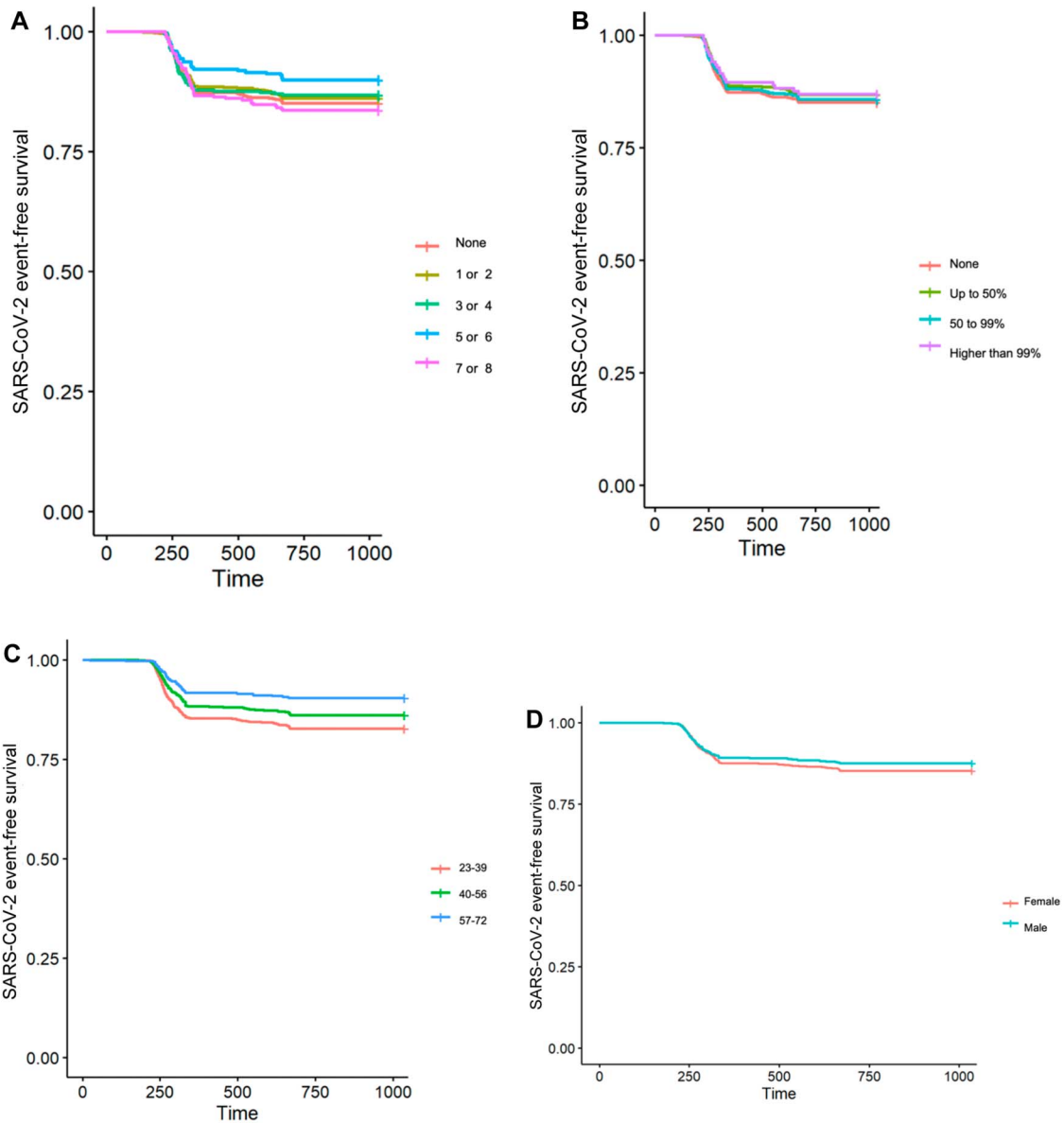

Figure 1. Time to SARS-CoV-2 infection by the absolute (A) or overall proportion (B) of influenza shots or according to age interval (in years) (C) and sex (D).

a good way how HCWs looked at vaccination and started to adhere more to influenza vaccination[17-19] on the one hand, we can hypothesize that vaccinated HCWs are more exposed to risk factors for SARS-CoV-2 infection because they feel more protected by the vaccination. Still, on the other hand, there is a possibility of a healthy user effect. This means a healthy, aware person is likelier to receive the influenza shot and behave healthier. The "health status and health awareness" can be "related to both the probabilities of vaccination and of seeking medical care."[20] This is a crucial point for our discussion because we may assume that our results were affected by these circumstances.

In conclusion, although our findings failed to support any relevant effect of repetitive influenza vaccination on the SARS-CoV-2 infection risk, it continues to be fundamental for the protection of health care workers and the more vulnerable population.[21] Although there may be a reduction in effectiveness with repetitive influenza vaccination over the years, this always provides more protection than lack of any vaccination.

Conflicts of interest

None.

References

[1] (ECDC) ECfDPaC. Expert opinion on priority risk groups for influenza vaccination. Available from: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/0808_GUI_Priority_Risk_Groups_for_Influenza_Vaccination.pdf.

[2] Domnich A, Orsi A, Sticchi L, et al. Effect of the 2020/21 season influenza vaccine on SARS-CoV-2 infection in a cohort of Italian healthcare workers. Vaccine. 2022;40(12):1755–60.

[3] Marín-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. 2021;93(1):64–5.

[4] Ragni P, Marino M, Formisano D, et al. Association between exposure to influenza vaccination and COVID-19 diagnosis and outcomes. Vaccines (Basel). 2020;8(4):675.

[5] Wang R, Liu M, Liu J. The association between influenza vaccination and COVID-19 and its outcomes: a systematic review and meta-analysis of observational studies. Vaccines (Basel). 2021;9(5):529.

[6] Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20(6):375–88.

[7] Brueggeman JM, Zhao J, Schank M, Yao ZQ, Moorman JP. Trained immunity: an overview and the impact on COVID-19. Front Immunol. 2022;13:837524.

[8] Sánchez-Ramón S, Conejero L, Netea MG, Sancho D, Palomares Ó, Subiza JL. Trained immunity-based vaccines: a new paradigm for the development of broad-spectrum anti-infectious formulations. Front Immunol. 2018;9:2936.

[9] Pawlowski C, Puranik A, Bandi H, et al. Exploratory analysis of immunisation records highlights decreased SARS-CoV-2 rates in individuals with recent non-COVID-19 vaccinations. Sci Rep. 2021;11(1):4741.

[10] Ten Doesschate T, Moorlag S, van der Vaart TW, et al. Two Randomized Controlled Trials of Bacillus Calmette-Guérin Vaccination to reduce absenteeism among health care workers and hospital admission by elderly persons during the COVID-19 pandemic: a structured summary of the study protocols for two randomised controlled trials. Trials. 2020;21(1):481.

[11] Netea MG, Schlitzer A, Placek K, Joosten LAB, Schultze JL. Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. Cell Host Microbe. 2019;25(1):13–26.

[12] Mosaddeghi P, Shahabinezhad F, Dorvash M, Goodarzi M, Negahdaripour M. Harnessing the nonspecific immunogenic effects of available vaccines to combat COVID-19. Hum Vaccin Immunother. 2021;17(6):1650–61.

[13] Jones-Gray E, Robinson EJ, Kucharski AJ, Fox A, Sullivan SG. Does repeated influenza vaccination attenuate effectiveness? A systematic review and meta-analysis. Lancet Respir Med. 2023;11(1):27–44.

[14] Hosseini-Moghaddam SM, He S, Calzavara A, Campitelli MA, Kwong JC. Association of influenza vaccination with SARS-CoV-2 infection and associated hospitalization and mortality among patients aged 66 years or older. JAMA Netw Open. 2022;5(9):e2233730.

[15] Debisarun PA, Gössling KL, Bulut O, et al. Induction of trained immunity by influenza vaccination—impact on COVID-19. PLoS Pathog. 2021;17(10):e1009928.

[16] Young B, Sadarangani S, Jiang L, Wilder-Smith A, Chen MI. Duration of influenza vaccine effectiveness: a systematic review, meta-analysis, and meta-regression of test-negative design case-control studies. J Infect Dis. 2018;217(5):731–41.

[17] Amato M, Werba JP, Frigerio B, et al. Relationship between influenza vaccination coverage rate and COVID-19 outbreak: an Italian Ecological Study. Vaccines (Basel). 2020;8(3):535.

[18] Domnich A, Grassi R, Fallani E, et al. Changes in attitudes and beliefs concerning vaccination and influenza vaccines between the first and second COVID-19 pandemic waves: a longitudinal study. Vaccines (Basel). 2021;9(9):1016.

[19] Dini G, Toletone A, Sticchi L, Orsi A, Bragazzi NL, Durando P. Influenza vaccination in healthcare workers: a comprehensive critical appraisal of the literature. Hum Vaccin Immunother. 2018;14(3):772–89.

[20] Ainslie KEC, Haber M, Orenstein WA. Bias of influenza vaccine effectiveness estimates from test-negative studies conducted during an influenza pandemic. Vaccine. 2019;37(14):1987–93.

[21] Doornekamp L, van Leeuwen L, van Gorp E, Voeten H, Goeijenbier M. Determinants of vaccination uptake in risk populations: a comprehensive literature review. Vaccines (Basel). 2020;8(3):480.