

## Evaluating the effectiveness of influenza vaccines in reducing COVID-19 in healthcare workers: a historical cohort study

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COVID-19 will remain present, therefore specific prevention, diagnosis, and treatment strategies similar to those used for other diseases will be required. There is ongoing concerns about the future of SARS-CoV-2 due to mutations and the emergence of new strains. This study aimed to evaluate the effectiveness of the influenza vaccine in reducing COVID-19 incidence among healthcare workers. Participants were divided into two groups: those who had received the influenza vaccine and those who had not. The efficacy of the influenza vaccine against COVID-19 was assessed over 3 months in all subjects. The diagnosis of COVID-19 was established using a computed tomography scan and RT-PCR testing. A total of 252 individuals participated in this study, with a mean age of  $33.90 \pm 7.58$  years (range: 20 - 59). Of the total, 101 (40.08 %) were male, and 151 (59.92 %) were female. Our findings demonstrate that the prevalence of COVID-19 infection among medical staff who received the influenza vaccination was significantly lower (80.1 % vs 45.0 %) ( $P < 0.001$ ). The duration of COVID-19 was significantly shorter for vaccine recipients compared to non-recipients, at 2 weeks or less (72.5 % vs 26.6 %) ( $P < 0.001$ ). The vaccinated cohort had a 55 % lower likelihood of contracting COVID-19 than the unvaccinated cohort (relative risk, RR: 0.45; 95 % confidence interval, CI: 0.34 - 0.59). Further analysis revealed that in severe COVID-19 cases necessitating hospitalization, there is no substantial difference between vaccinated and unvaccinated patients ( $P=0.2$ ). A recent survey suggested that the influenza vaccine may help improve COVID-19 management. The cytokine profile of the examined patient before the influenza vaccine is the ideal selection.

**Keywords:** COVID-19; SARS-CoV-2; vaccination; influenza.

### Introduction

The acute phase of the COVID-19 pandemic has concluded, mainly due to achieving herd immunity through comprehensive vaccination campaigns. However, the legacy of the pandemic persists, including concerns about emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants and the

virus's long-term trajectory. These concerns were previously exacerbated by vaccine hesitancy, particularly among key groups such as healthcare workers (HCWs).<sup>(1)</sup> Prior evidence suggests that COVID-19 will persist, requiring specific preventive, diagnostic, and therapeutic measures similar to those for other diseases.<sup>(2)</sup> This leads to increased research in this domain.

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Risk factors for COVID-19, including hypertension, diabetes, and cardiovascular lead to acute respiratory distress syndrome (ARDS), septic shock, and metabolic acidosis.<sup>(3)</sup> Antiviral medications to combat and manage the infection remain unavailable. According to the guidelines, respiratory therapy is the primary treatment approach. Recent studies have investigated the potential effectiveness of the influenza vaccine in reducing the risk of SARS-CoV-2 infection. In rare cases, vaccination has been associated with an altered immune response that may theoretically increase susceptibility to other respiratory infections, a phenomenon investigated in contexts such as vaccine-associated enhanced respiratory disease (VAERD).<sup>(4)</sup> Whether influenza vaccination alters susceptibility to non-influenza viruses is an active area of research, with current evidence yielding inconsistent conclusions.<sup>(5)</sup> Healthcare professionals, including nurses and physicians, face a higher risk of COVID-19 exposure. They are more susceptible to viruses due to frequent exposure and higher viral loads compared to the general population.<sup>(6)</sup>

The influenza vaccination is expected to considerably reduce the infection rate or lessen the severity of COVID-19 by decreasing the production of angiotensin-converting enzyme II (ACE2).<sup>(7)</sup> Multiple studies evaluated the efficacy of the influenza vaccine in preventing COVID-19.<sup>(8,9,10)</sup> Recent research has challenged this assumption, producing contradictory results.<sup>(11,12)</sup> Candeli *et al*<sup>(11)</sup> conducted a study suggesting that the influenza vaccine could reduce COVID-19 mortality. While previous research has collected data on influenza vaccination in infected cohorts,<sup>(12)</sup> it has also underscored the need for more definitive studies on the vaccine's effect.

HCWs, including nurses and doctors, are at a higher risk of COVID-19 exposure. They are more likely to be exposed to viruses due to frequent contact and higher viral loads than the general population. Given the prevalence of viral infections such as influenza A (H1N1) in the country in recent years and the vaccination of most HCWs against this virus, we evaluated the effectiveness of the influenza vaccine in reducing the incidence of COVID-19 among HCWs.

## Materials and Methods

### Study design

This historical cohort study was conducted at Golestan Hospital in Ahvaz, one of the primary COVID-19 treatment centers in southwestern Iran. The study was approved by the Ethics Committee of Medical Sciences (IR.AJUMS.REC.1399.841). Written consent was obtained from each participant. Data were obtained from hospital vaccination records, electronic health systems, laboratory and radiology databases, human resources records, and structured staff interviews.

### Inclusion and exclusion criteria

Eligible participants were required to have continuous employment and active status within the hospital system for the entire study period, ensuring consistent access to occupational health records and vaccination programs.

In addition, participants were required to have a documented SARS-CoV-2 PCR test result in the hospital's laboratory information system during the study timeframe, as this record was essential for accurately ascertaining the primary outcome of COVID-19 infection.

Participants were excluded from the analysis if their employment records indicated a service lapse or if they were hired after the study period began. We also excluded individuals with missing or indeterminate influenza vaccination status for the season, as this was the primary exposure variable. Additionally, any HCW with a documented positive SARS-CoV-2 test result before the start of the study period was excluded to ensure we captured incident (new) COVID-19 cases. Finally, individuals under 18 were excluded from this analysis.

### Sample size calculation

We calculated the sample size using the standard  $\alpha = 0.05$  (two-tailed) value of 1.96, the conventional power of 80 % (0.84), and the power of 90 % (1.28). These numbers were utilized to ascertain the sample size. The analysis indicates that at least 199 individuals are required in each cohort (vaccinated and unvaccinated)

to achieve an 80 % probability of detecting a 50 % reduction in influenza risk (from 20 % to 10 %) with 95 % confidence. Finally, we selected 252 subjects.

### Study population and data collection

This historical cohort study utilized the occupational health and medical records of HCWs at Golestan Hospital in Ahvaz. The exposed group consisted of HCWs who received the influenza vaccine during the hospital's organized vaccination campaign in October and November 2021. A comparable control group was formed from HCWs within the same facility who did not receive the vaccine during that campaign. To establish a baseline cohort free of current infection, the study included only HCWs who had a clinical evaluation documented by a pulmonary specialist before the start of the follow-up period, confirming they were not actively infected with COVID-19. Data on demographic characteristics, influenza vaccination status, and documented history of previous COVID-19 infection were systematically extracted from the hospital's electronic medical records and occupational health databases. The EQUATOR reporting guideline was selected based on the Equator Network guideline.<sup>(13)</sup>

### Follow-up and outcome measurement

The 3-month observation period used in this study was selected based on established evidence regarding the peak and subsequent waning of immunogenicity of seasonal influenza vaccines, a critical window for evaluating vaccine-induced protection. According to some research,<sup>(14,15,16)</sup> vaccine responses remain equally protective for both previously vaccinated individuals and first-time recipients after 3 months. This study used the medical and occupational health records of HCWs at Golestan Hospital in Ahvaz. The primary outcome was a confirmed COVID-19 diagnosis within 3 months of the influenza vaccination campaign. A case was defined by a positive RT-PCR test or, for symptomatic individuals with a negative PCR, a confirmed diagnosis by an experienced pulmonary specialist based on clinical assessment and computed tomography (CT) scan findings. From the records, we extracted data on age, gender, influenza vaccination status, history of prior COVID-19 infection, and, for confirmed cases, disease severity, infection duration, and hospitalization details.

### Statistical analysis

Descriptive statistics were presented as frequency (percentage) and mean  $\pm$  standard deviation (SD) for normally distributed continuous variables, and frequency (percentage) for categorical variables. Group comparisons between the vaccinated (Group 1) and unvaccinated (Group 2) cohorts were performed using the independent t-test for normally distributed continuous variables, the Chi-square ( $\chi^2$ ) test for categorical variables, or Fisher's Exact test where cell counts were low (<5). The primary measure of effect was vaccine effectiveness (VE), calculated as  $(1 - \text{Risk Ratio}) \times 100\%$ . The risk of developing COVID-19 in the vaccinated group was compared with that in the unvaccinated group by calculating the relative risk (RR) with a 95 % confidence interval (CI). Adjusted analyses were conducted using a modified Poisson regression with robust error variances to directly estimate RR while controlling for a priori-identified confounders, including age, gender, and prior COVID-19 infection. A two-sided  $p < 0.05$  was regarded as a significant statistical difference. Data analysis was done using SPSS version 21.0 (SPSS Inc., Chicago, Ill., USA).

### Results

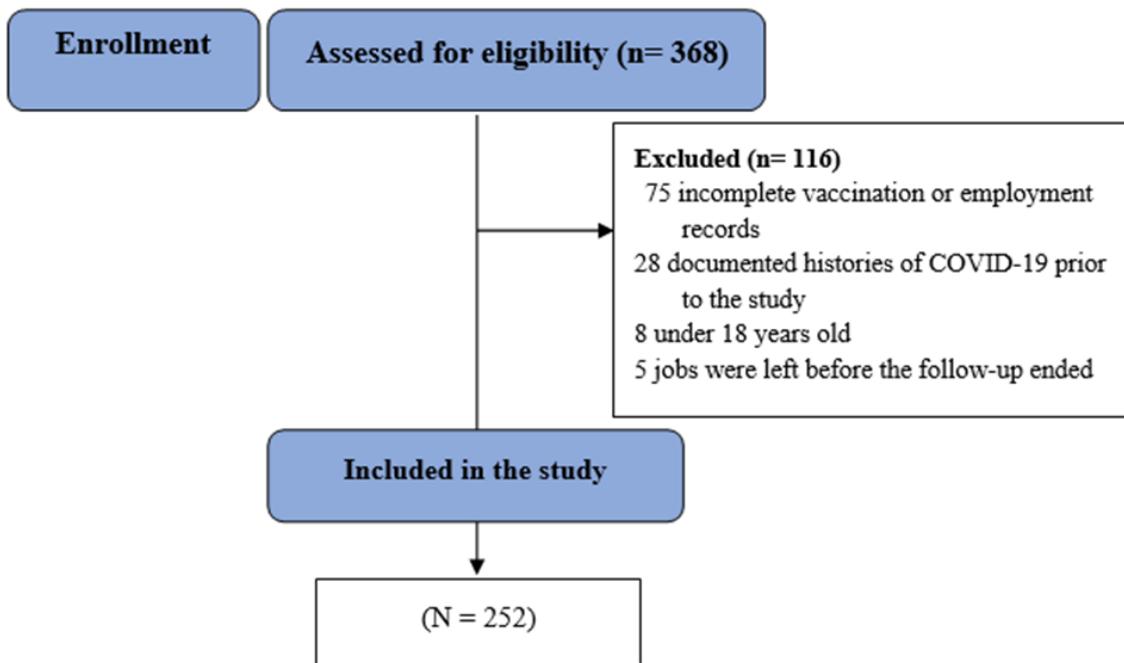
The initial pool of potential participants included all 420 HCWs employed at Golestan Hospital during the October-November 2021 vaccination campaign. From this group, 368 individuals were assessed for eligibility based on their employment and medical records. A total of 116 individuals were excluded for the following reasons: 75 had incomplete vaccination or employment records, 28 had a documented history of COVID-19 before the study period, eight were under 18 years old, and five had left employment before the start of the follow-up period. Consequently, 252 subjects were confirmed eligible and included in the study cohort. All 252 participants completed the 3-month follow-up, and their data were analyzed. The flow of participants is summarized in Figure 1.

The descriptive statistics of the participants' characteristics are shown in Table 1.

The associations between the qualitative independent variables and influenza vaccination status are displayed

**Table 1.** Descriptive statistics of characteristics of study subjects.

	Variables	Frequency	Percentage (%)
Marital status	Single	83	32.94
	Married	169	67.06
	Under diploma	8	3.17
Education level	Diploma	30	11.90
	Associate Degree	27	10.71
	Bachelor	122	48.41
	Master	21	8.33
	Ph.D.	44	17.46
	Physician	45	17.86
	Nurse	88	34.92
	Health care assistant	13	5.16
	Associate health care assistant	20	7.94
Job position in the hospital	Worker	32	12.70
	Office	36	14.29
	Other	18	7.14
	Emergency	53	21.03
	Special places of corona patients	18	7.14
Place of service in the hospital	Operating rooms	23	9.13
	Other	158	62.70
	Yes	111	44.05
COVID-19	No	141	55.95
	< 3 months before flu vaccination	29	11.51
COVID-19 history	> 3 months before flu vaccination	42	16.67
	< 3 months after flu vaccination	15	5.95
	> 3 months after flu vaccination	24	9.13
	No COVID-19	143	56.75
	PCR	86	34.13
Diagnosis method	CT scan	23	9.13
	No COVID-19	143	56.75
	< two weeks	66	26.19
Duration of COVID-19	> two weeks	43	17.06
	No COVID-19	143	56.75
	Outpatient	105	41.67
Hospitalization	Inpatient	4	1.59
	No COVID-19	143	56.75
Influenza	Yes	163	64.68
	No	89	35.32

**Fig. 1.** CONSORT flow diagram of participant enrollment and exclusions.**Table 2.** The associations between qualitative independent variables and influenza vaccination status.

Variables	Influenza vaccinations status		Statistics	P-value*
	No (%)	Yes (%)		
COVID-19 infection	No	28 (19.9)	=33(49. $X^2$ )1	< 0.001*
	Yes	61 (55)		
Duration of COVID-19 infection	< 2 weeks	29 (26.6)	=14(92. $X^2$ )1	< 0.001†
	> 2 weeks	29 (26.6)		
Need for hospitalization	No	57 (54.3)	=27.68( $X^2$ )1	0.2
	Yes	1 (25)		

\*: Chi-square test. †: Trend chi-square test.

**Table 3.** Incidence of COVID-19 and association with influenza vaccination status and severity of COVID-19 outcomes among infected participants (n=111).

Outcome	1 <sup>st</sup> group (n=163)	2 <sup>nd</sup> group (n=89)	RR (95 % CI)	P-value
COVID-19 infection, n (%)	50 (30.7 %)	61 (68.5 %)	0.45 (0.34, 0.59)	<0.001
Vaccine effectiveness (VE), % <sup>†</sup>	----	----	55% (41%, 66 %)	----
Outcome	1 <sup>st</sup> group (n=50)	2 <sup>nd</sup> group (n=61)	RR (95 % CI)	P-value
Hospitalization, n (%)	1 (2 %)	2 (4.9 %)	0.41 (0.04, 3.83)	0.62*
Prolonged illness (>2 weeks), n (%)	14 (28 %)	29 (47.5 %)	0.59 (0.35, 1.00)	0.03

1<sup>st</sup> group: vaccinated group. 2<sup>nd</sup> group: unvaccinated group. RR: Risk Ratio. 95 % CI: 95 % confidence interval. \*: p-value from Fisher's Exact test due to low cell count. CI: Confidence Interval. <sup>†</sup>Vaccine effectiveness (VE) calculated as  $(1 - \text{Risk Ratio}) \times 100\%$ ; derived from RR of COVID-19 infection and not shown as a separate value.

in Table 2. Our results have demonstrated that the COVID-19 infection rate in medical staff who received influenza vaccination was significantly lower (80.1 % vs 45.0 %) ( $P < 0.001$ ). Additionally, it was found that the duration of COVID-19 was significantly lower than 2 weeks compared with those who lacked vaccine recipients (72.5 % vs 26.6 %) ( $P < 0.001$ ). Further analysis indicated that in severe COVID-19 cases requiring hospitalization, there was no difference between vaccinated and non-vaccinated patients ( $P=0.2$ ).

The analyses show that the risk in the vaccinated group compared to the unvaccinated group was 30.7 % (50/163) and 68.5 % (61/89), respectively (Table 3). Additionally, the vaccinated group had a 55 % lower risk of getting COVID-19 (RR: 0.45, 95 % CI: 0.34, 0.59) compared with the unvaccinated group (Table 3). The analysis of severity in the subgroup that became infected (n = 111) shows that among those who contracted COVID-19, the vaccinated group had less severe outcomes than the unvaccinated group (Table 3).

## Discussion

This study aimed to evaluate the potential protective effect of influenza vaccination against COVID-19 infection among HCWs, a high-risk group due to their ongoing exposure to SARS-CoV-2. Our findings demonstrated a significant association between influenza vaccination and a reduced risk of COVID-19 infection, as well as a lower likelihood of prolonged

illness among vaccinated healthcare professionals. The data suggest that influenza vaccination may offer partial cross-protection or enhance the immune response to SARS-CoV-2, thereby decreasing both the likelihood of infection and the severity of illness in this population. Several studies have examined the relationship between influenza vaccination and COVID-19 outcomes, yielding varied conclusions.<sup>(11,12)</sup> Ragni et al.<sup>(17)</sup> demonstrated that influenza vaccination reduced the likelihood of testing positive for COVID-19, particularly among the elderly. Similarly, Massoudi et al.<sup>(18)</sup> found that individuals vaccinated against influenza had a reduced likelihood of developing symptomatic COVID-19, suggesting a possible indirect protective effect. Conversely, many studies have not supported these associations, highlighting the need for further research to clarify this connection.<sup>(10)</sup> Our findings align with previous research suggesting that influenza immunization may reduce the frequency and severity of COVID-19.

This association's scientific plausibility may be attributed to the immunomodulatory effects of the influenza vaccine. Some people believe that getting the influenza shot boosts innate immune memory, known as "trained immunity." This enhances the body's response to other viruses, including SARS-CoV-2, upon future exposure.<sup>(19)</sup> In vaccinated individuals, increased T-cell diversity and a balanced activation of natural killer (NK) cells and cytokines may help clear viruses more efficiently and reduce excessive inflammation.<sup>(20)</sup> This could explain why vaccinated

healthcare workers in our study had a lower infection rate and shorter illness duration. From a public health standpoint, these findings are especially important in hospital settings, as even small reductions in illness length could help keep staff stable during pandemic peaks.

## Limitations

Despite the interesting nature of these results, our study has certain limitations. As an observational study, it cannot establish a causal link between influenza vaccination and reduced COVID-19 risk. Factors such as prior exposure, behavioral differences, and health-seeking behaviors may have influenced the results. Additionally, potential recall bias and incomplete vaccination records could have affected data accuracy. Moreover, since the study was conducted within a single cohort of healthcare professionals, the findings may not be generalizable to other populations. Lastly, unmeasured variables—such as comorbidities, concurrent vaccines, or disparities in testing access—may have introduced further bias imprecision.

The influenza vaccine not only protects against influenza, but may also offer a crucial layer of heterologous protection against SARS-CoV-2, helping to safeguard the health of the workforce and maintain the resilience of healthcare systems during future outbreaks. Future research should prospectively validate these findings and clarify the specific immunological mechanisms behind this cross-protective effect.

## Conclusion

This study shows that influenza vaccination is linked to a significantly lower risk of COVID-19 infection and a shorter illness duration among healthcare workers. While it is not a substitute for specific COVID-19 vaccines, the annual influenza shot should be strongly encouraged as an additional public health measure in healthcare settings. Our results indicate a possible protective effect of influenza vaccination against COVID-19 in healthcare professionals, reducing infection risk and lessening disease severity. These findings highlight the importance of annual influenza vaccination for healthcare workers, especially during concurrent viral outbreaks. More comprehensive,

prospective studies are needed to confirm these findings and to explore the immunological mechanisms behind the connection between influenza vaccination and better COVID-19 outcomes.

## Conflict of interest

The authors declare that there is no conflict of interest.

## Author's contributions

Fakher Rahim: designed the study, analyzed the original survey data, and prepared the first draft of the manuscript.

Sorur Souris: designed the study, analyzed the original survey data, and prepared the first draft of the manuscript.

Meissam Moezzi: reviewed the data interpretation from the original studies and contributed to manuscript revisions.

Alireza Rafatei Navaei: designed the study, analyzed the original survey data, and prepared the first draft of the manuscript.

Elham Farhadi: reviewed the data interpretation from the original studies and contributed to manuscript revisions.

All authors have read and agreed to the published version of the manuscript.

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## **Evaluación de la efectividad de las vacunas contra la gripe en la reducción del riesgo de COVID-19 en trabajadores de la salud: estudio de cohorte histórico**

### **Resumen**

La COVID-19 continuará presente, por lo que se requerirán estrategias específicas de prevención, diagnóstico y tratamiento similares a las utilizadas para otras enfermedades. Continúan las preocupaciones sobre el SARS-CoV-2 debido a las mutaciones y la aparición de nuevas cepas. El objetivo de este estudio fue evaluar la efectividad de la vacuna contra la gripe para reducir la incidencia de la COVID-19 entre los trabajadores sanitarios. Los participantes se dividieron en dos grupos: los que habían recibido la vacuna contra la gripe y los que no. Se evaluó la efectividad de la vacuna contra la gripe frente a la COVID-19 durante 3 meses en todos los sujetos. El diagnóstico de COVID-19 se estableció mediante una tomografía computarizada y pruebas de RT-PCR. En este estudio participaron un total de 252 personas, con una edad media de  $33,90 \pm 7,58$  años (rango: 20-59). Del total, 101 (40,08 %) eran hombres y 151 (59,92 %), mujeres. Nuestros hallazgos demuestran que la prevalencia de la infección por COVID-19 entre el personal médico que recibió la vacuna contra la gripe fue significativamente menor (80,1 % frente a 45,0 %) ( $P < 0,001$ ). La duración de la COVID-19 fue significativamente más corta para los receptores de la vacuna en comparación con los no receptores, con 2 semanas o menos (72,5 % frente a 26,6 %) ( $P < 0,001$ ). La cohorte vacunada tenía un 55 % menos de probabilidades de contraer COVID-19 que la cohorte no vacunada (riesgo relativo, RR: 0,45; intervalo de confianza del 95 %, IC: 0,34-0,59). Un análisis más detallado reveló que, en los casos graves de COVID-19 que requirieron hospitalización, no hay diferencias sustanciales entre los pacientes vacunados y los no vacunados ( $P = 0,2$ ). Una encuesta reciente sugirió que la vacuna contra la gripe podría ayudar a mejorar el tratamiento de la COVID-19. El perfil de citocinas del paciente examinado antes de la vacuna contra la gripe es la selección ideal.

**Palabras clave:** COVID-19; SARS-CoV-2; vacunación; influenza.

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