DOI: 10.7860/NJLM/2023/60007.2718

Original Article

Microbiology Section

Significance of Flu Vaccination against SARS-CoV-2 Infection: A Questionnaire-based Survey

RAJEEV KISHORE SAXENA[1], ANAND MOHAN VERMA[2], SANA NUDRAT[3], SOUMYA PANDEY[4]

(cc) BY-NC-ND

ABSTRACT

Introduction: Before the Coronavirus Disease 2019 (COVID-19) vaccines were developed, there was an intense search for preventive measures and effective treatments of COVID-19, which has led to a recommendation of influenza vaccination as a preventive measure against COVID-19. As of August 2022, there are still many countries where percentage of at least one dose of COVID-19 vaccination is ≤20%. In such a scenario it becomes pertinent for a continuous search of other preventive measures such as significance of flu vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.

Aim: To explore any relation between the flu vaccination and SARS-CoV-2 infection.

Materials and Methods: A retrospective case control study was undertaken through questionnaire-based survey with 200 cases who had taken flu vaccination within one year of COVID-19 testing and 800 as controls. All candidates were consecutively enrolled in this study and informed consent was obtained.

Results: Most common age group among vaccinated candidates was 31-40 years. Among 200 individuals of cases group, 3 (1.5%) were positive for COVID-19 and 197 (98.5%) were negative. Among 3 positive individuals in cases only one required hospitalisation. Among 800 control group, 38 (4.7%) were positive and 762 (95.2%) were negative for SARS-CoV-2 infection. Rate of positivity was 2.3% less among vaccinated group in comparison to non vaccinated group.

Conclusion: In this study it was observed that individuals who had received the flu vaccine there was a significant reduction in odds of testing positive for COVID-19 compared to those who did not received the vaccine.

Keywords: Immunisation, Pandemic, Preventive measures

INTRODUCTION

Influenza (flu) and Coronavirus Disease 2019 (COVID-19) are both contagious respiratory illnesses, caused by different viruses. It's not possible to tell the difference between flu and COVID-19 by the symptoms alone because they have some of the same signs and symptoms. Compared with flu, COVID-19 can cause more severe illness in some people. The new virus and disease which were unknown before the outbreak began in Wuhan, China, in December 2019 soon became a global pandemic and has led to nearly three million deaths globally [1]. So, there was an urgent need to search for preventive measures and effective treatments of COVID-19. Many preventive measures and treatment modalities have been suggested since then. One such preventive measure suggested in literature was: immunity against influenza virus may cause some protection against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has led to a recommendation of influenza vaccination as a preventive measure against COVID-19 [2-4]. COVID-19 and flu share common aspects of transmission, so measures to protect against flu might be effective in reducing the risk of contracting COVID-19 [4]. This idea was also supported by similarities in host immune responses to the two viruses. Few hypothesis or theoretical mechanisms for potential protective effect of influenza vaccine against COVID-19 which includes presence of MF59 adjuvant in influenza vaccine, which was shown to help in potentiating immune response against SARS-CoV variants. Another proposal suggested that vaccine could stimulate enough trained innate immune memory, so that when another respiratory pathogen such as SARS-CoV-2 occurred the local lung immune system would be primed for a rapid response. Another theory is based on the suggestion that influenza and COVID-19 viruses engage with Angiotensin Converting Enzyme-2 (ACE-2) and tetraspanin antibodies, therefore ACE-2 and tetraspanin antibodies might inhibit COVID-19 and low pathogenic influenza A viruses [5,6]. However, there have also been concerns of an interaction between influenza vaccination and the risk of SARS-CoV-2 infection [7,8]. As of august 2022 there are still many countries where percentage of at least one dose of COVID vaccination is ≤20% [9]. In such a scenario it becomes pertinent for a continuous search of other preventive measures such as significance of flu vaccination against SARS-CoV-2 infection. So, this study was done to examine whether influenza vaccination altered the risk and clinical outcomes of SARS-CoV-2 infection.

MATERIALS AND METHODS

The present study was a retrospective case-control study. Data from study population was collected by means of questionnaire from July 2021 to March 2022 and analysed further till June 2022. Study was approved by Institutional Ethical Committee vide letter (Ref. No. MCES/EC/673/2021).

Inclusion criteria: Adult individuals, who had taken flu vaccination within 10-12 months of study period, were considered as cases and non flu vaccinated individuals were considered as controls. 200 cases were selected and informed consent was obtained from them. With a ratio of 4:1, 800 controls were selected and included in the study.

Exclusion criteria: Individuals who had taken flu vaccine >12 months before COVID-19 test and individuals less than 18 years of age were excluded from the study.

For comparison, cases were matched with selective controls according to gender and age to avoid confounding bias. A feedback form (questionnaire) from each participant was taken for flu vaccination status, SARS-CoV-2 infection, need for hospitalisation, if hospitalised then duration of stay, need of mechanical ventilation or Intensive Care Unit (ICU), presence of any other co-morbid conditions like diabetes, hypertension, lung disease and age more than 60 years. Age >60

years was included in co-morbid condition as reported earlier by Kaeuffer C et al., they reported advanced age as a risk factor for severe COVID-19 or death in hospitalised patients [10]. Sanyaolu A et al., found older patients, especially those who are 65 years old and above who have co-morbidities and are infected, have an increased admission rate into the ICU and mortality from the COVID-19 disease [11]. Similarly, Centre for Disease Control and Prevention (CDC) also report that age >60 years as a factor for severe COVID-19 [12].

Study Procedure

A questionnaire was prepared and was prevalidated by a subject expert. Its feasibility and reliability was checked by a pilot run. The questionnaire was sent on the mobile phones of respondents to avoid any physical contact. Questionnaire consisted of two parts, in first part candidates were asked for demographic details, flu vaccination history, status of COVID-19 and in second part candidate was asked about hospitalization was required or not, any associated co-morbid condition and other details like travel history, any contact with suspected COVID-19, intake of any preventive medicines. Questions were probing type having dichotomous response.

STATISTICAL ANALYSIS

For evaluation the results obtained from feedback/questionnaire were analysed and subjected to statistical analysis using Statistical Package for the Social Sciences (SPSS) software Vesion 16.0. Descriptive statistics was performed by Chi-square test. Odds Ratio (OR) was calculated to assess odds of infection between vaccinated and non vaccinated candidates. A p-value <0.05 was considered as statistically significant.

RESULTS

In this study most common age group among vaccinated candidates was 31-40 years age group. In this age group 45 (22.5%) candidates were vaccinated out of 200. Males were more among all age groups i.e. in 18-30 year age group males were 22 (11%) and females were 16 (8%). In 31-40 year age group males were 27 (13.5%) and females were 18 (9%). In 41-50, 51-60 and more than 60 year age males were 20 (10%), 29 (14.5%) and 22 (11%), respectively and females were 15 (7.5%), 13 (6.5%) and 18 (9%), respectively. Age and sex wise matched cases and controls were compared but data was found to be statistically insignificant. Age and gender distribution among different groups is shown in [Table/Fig-1]. Data from questionnaire was analysed. Among 200 cases, 3 (1.5%) were positive for COVID-19 and 197 (98.5%) were negative. Among control group, 38 (4.7%) were positive and 762 (95.2%) were negative for SARS-CoV-2 infection [Table/Fig-2]. Rate of positivity was 3.2% less among vaccinated group in comparison to non vaccinated group. In candidates who had received the flu vaccine there was a significant reduction in odds of testing positive for COVID-19 compared to those who did not received the vaccine. OR <1 indicates that odds of exposure among cases are lower than the odds of exposure among controls, which was significant (p-value=0.0381).

In addition data like need of hospitalisation, duration of hospital stay, need of ICU and mechanical ventilation among flu Vaccinated COVID-19 positive (V+C+) patient was collected and compared to those of non flu vaccinated COVID-19 positive (V-C+). Among three vaccinated positive individuals only one required hospitalisation and among 38 non vaccinated candidates six required hospitalisation. Data of COVID-19 positive candidates {confirmed by Reverse Transcription Polymerase Chain Reaction (RT-PCR)} who required hospitalisation vs who did not required hospitalisation is shown in [Table/Fig-3]. {Hospitalisation criteria: SpO_2<95%, pulse rate<15 beats per minute, temperature >102°F, ground glass opacities in chest Computed Tomography (CT) scan}. Further, analysis of hospitalised candidates among vaccinated and non vaccinated candidates showed that one

Age	Flu vaccinated Male (n)	Flu non vaccinated Male (n)	Total (n)	χ^2, df, p-value	Flu vaccinated Female (n)	Flu non vaccinated Female (n)	Total (n)	χ^2, df, p-value
18-30	22	88	110	1.0507, 3, 0.9020	16	64	80	0.09,3,1.01
31-40	27	108	135		18	72	90	
41-50	20	80	100		15	60	75	
51-60	29	116	145		13	52	65	
>60	22	88	110		18	72	94	
Total (n)	120	480	600		80	320	400	

[Table/Fig-1]: Age and gender distribution of candidates in different groups.

COVID-19 status	Status of flu vaccination		Total n (%)	Odds ratio	χ^2, df, p-value
	Vaccinated n (%)	Non vaccinated n (%)			
Positive (exposed)	03 (1.5%)	38 (4.7%)	41 (4.1%)	0.31	4.298, 1, 0.0381*
Negative (non exposed)	197 (98.5%)	762 (95.2%)	959 (95.9%)		
Total	200 (100%)	800 (100%)	1000 (100%)		

[Table/Fig-2]: Cross tabulation showing number of candidates in two groups.
*p-value <0.05 was considered statistically significant.

COVID-19 status	Status of flu vaccination and COVID-19 positivity		Total (n=41) n (%)
	Vaccinated positive n (%)	Non vaccinated positive n (%)	
Hospitalised	1 (2.4)	6 (14.6)	7 (17%)
Not Hospitalised	2 (4.8)	32 (78)	34 (83%)

[Table/Fig-3]: Number of patients required hospitalisation among COVID-19 positive flu vaccinated (n=3) and non vaccinated (n=38) individuals.

Parameter	V+C+(n=1)			V-C+ (n=6)		
Duration of hospital stay	≤7 days	7 to 15 days	≥15 days	≤7 days	7 to 15 days	≥15 days
	1	0	0	4	1	1
Need for ICU	00			02		
Mechanical ventilation required	00			01		

[Table/Fig-4]: Parameters for which data of hospitalised candidates was compared.

vaccinated patient required hospitalization for ≤7 days. While among non vaccinated group four candidates required hospitalisation for ≤7 days, one candidate required 7 to 15 days and one candidate required ≥15 days of hospitalisation [Table/Fig-4].

Data regarding history of co-morbid conditions like diabetes, hypertension, age>60 years, previous lung disease in both vaccinated and non vaccinated positive individuals was taken in questionnaire. Among vaccinated positive group, one candidate reported presence of diabetes, two candidates reported hypertension, no participant had previous lung disease and one patient was above 60 years of age [Table/Fig-5].

Co-morbid conditions present	Groups of study	
	V+C+, (n)	V-C+, (n)
Diabetes	1	9
Hypertension	2	12
Prev. Lung Disease	0	2
Age>60 years	1	6

[Table/Fig-5]: Presence of co-morbid conditions among study groups.

Among group of vaccinated individuals, 24% candidates had history of fever and among group of non vaccinated individuals 16.5% had fever. In vaccinated group 44.5% individuals and 33.5% in non vaccinated group reported that they were taking some preventive medicine. Travel history was present in 83 vaccinated candidates and 398 non vaccinated candidates. Seventeen vaccinated candidates were detected as contact with suspected COVID-19 and 352 non vaccinated candidates had history of contact with suspected COVID-19 [Table/Fig-6].

Parameters	Response	Vaccinated n (%)	Non-vaccinated n (%)
Fever	Present	48 (24)	132 (16.5)
	Absent	152 (76)	668 (83.5)
Preventive medicine	Yes	89 (44.5)	268 (33.5)
	No	111 (55.5)	532 (66.5)
Travel history	Yes	83 (41.5)	398 (49.7)
	No	117 (58.5)	402 (50.2)
Contact with suspected COVID-19 subjects	Yes	17 (8.5)	352 (44)
	No	183 (91.5)	448 (56)

[Table/Fig-6]: Individual question-responses in vaccinated (n=200) and non vaccinated groups (n=800).

DISCUSSION

It has been well-established and recognised that vaccination is one of the most important public health interventions which curbs the spread of viral illness, protects vulnerable populations and the public alike from disease and ultimately saves lives. However, it is also well-known that various levels of hesitancy exist in different populations towards receiving vaccinations for a multitude of reasons [13]. One in five children in the United States have a parent who is vaccine hesitant, and hesitancy is negatively associated with childhood influenza vaccination [14]. It is known that the growth of one virus can be inhibited by the previous infection with another (related or unrelated) virus in the same host through mediators like interferons and others. The phenomenon is called virus interference. The virus interference can occur even when the first virus invader is an inactivated virus, such as in the vaccines. The data suggesting flu vaccination can increase the risk of non influenza respiratory virus infections further intensify the questions about viral interference [15]. The concerns are that the SARS-CoV-2 virus infection in the individuals vaccinated for influenza may trigger a booster response for flu through memory cells. Simultaneously, the memory cells will inhibit the engagement and activation of naive B cells by the SARS-CoV-2 virus leading to an inadequate immune response, explaining the increased incidence of COVID-19 after flu vaccination [15]. Although, before the COVID-19 vaccines were developed; few studies suggested that an influenza vaccine may stimulate non specific immune responses that reduce the risk of COVID-19 infection or the severity of COVID-19 illness after infection [4,5,16]. In this study it was found that COVID-19 positivity rate among influenza vaccinated group was 1.5% and among non flu vaccinated group was 4.7% i.e. difference of 3.2% positivity rate was observed between two groups. Huang K et al., reported 0.9% and 1.2% infectivity rate among flu vaccinated and non vaccinated individuals [17]. Difference in positivity rates was 0.3% whereas, Conlon A et al., reported 0.9% difference of positivity rates among flu vaccinated and non vaccinated groups [2]. Significant difference between positivity rates was observed in studies by Conlon A et al., and Huang K et al., [2,17].

In the present study, duration of hospital stay in vaccinated candidates was reported ≤7 days in one patient and non vaccinated patient's hospital stay of ≤7 days, 7 to 15 days and ≥15 days was reported in 4, 1 and 1 patient respectively. Susan M et al., reported in their study 3.31% rate of hospital stay in non vaccinated patient and 2.19% among vaccinated patients [18]. In another study done by Bujani MZ et al., reported 25% reduction rate in influenza vaccinated candidates for hospitalisation [19]. Soha H et al., found that 5-7 days hospital stay was reported for vaccinated candidates and more than two weeks hospital stay was reported in non vaccinated candidates, those were infected with COVID-19 [20].

In this study, it was observed that among vaccinated group 8.5% candidates gave history of contact with suspected COVID-19 individuals, 41.5% gave history of travel and 44.5% were taking some preventive medicine whereas, among non vaccinated group 44% candidates gave history of contact with suspected COVID-19 individuals, 49.7% gave history of travel and only 33.5% were taking some preventive medicine. In a previous study by Saxena RK et al., they reported that 43%, candidate had history of travel, 56% gave positive history of contact and 66% were taking some preventive medicine for COVID-19 among case group whereas 74%, 65.7%, 54.3% had history of travel, history of contact and were taking some preventive medicine for COVID-19, respectively among control group [21]. A newspaper article also reported that 60% new cases in 2021 have travel history from Jamshedpur, Jharkhand, India [22]. This shows that candidates among case group were not only vaccinated but also more aware and were following COVID-19 appropriate behaviour, which could possibly be also the reason of lower positivity rate among the vaccinated group.

Limitation(s)

This was a retrospective case control study in which data was collected by means of questionnaire and thus was reliable on data provided by candidates, in future a cross-sectional study can be planned in which data can be collected at time of vaccination so that more details like type of vaccination can also be collected. Paediatrics age group was also not included in this study, which can be included in further studies.

CONCLUSION(S)

In the present study, it was observed that individuals who had received the flu vaccine, a significant reduction in odds of testing positive for COVID-19 compared to those who did not received the vaccine. So, in context of findings it can be said influenza vaccination can be considered as a part of management of COVID-19 pandemic where percentage of at least one dose of COVID vaccination is still ≤ 20% and, at such places flu vaccination may play a important preventive role in spread of disease.

REFERENCES

[1] Centre for Disease Control and Prevention. Similarities and Differences between Flu and COVID-19. 2022. Available from: https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm.

[2] Conlon A, Ashur C, Washer L, Eagle KA, Hofmann MA. Impact of the influenza vaccine on Covid-19 infection rates and severity. AJIC Am J Infect Control. 2021;49(6):694-700.
[3] Salem ML, El-Hennawy D. The possible beneficial adjuvant effect of influenza vaccine to minimize the severity of COVID-19. Med Hypotheses. 2020;140. Doi: 10.1016/j.mehy.2020.109752.
[4] Alos F, Zaldua CY, Rodriguez VM, Del Val Garcia JL, Sánchez-Callejas A, Colomer MÀ. Does influenza vaccination reduce the risk of contracting COVID-19. J Clin Med. 2022;11(18):5297.
[5] Almadhoon HW, Hamdallah A, Elsayad MS, Hagrass AI, Hasan MT, Fayoud AM. et al. The effect of influenza vaccine in reducing the severity of clinical outcomes in candidates with Covid-19: a systematic review and meta analysis. Sci Rep. 2022;12(1):14266.
[6] 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.
[7] Kristensen JH, Hasselbalac RB, Pries-heje M, Nielsen PB, Dehlbæk Knudsen A, Fogh K, et al. Effect of influenza vaccination on risk of Corona virus disease 2019. A prospective cohort study of 46000 healthcare worker. J Infect Dis. 2022;226(1):06-10.
[8] Depoux A, Martin S, Karafillakis E, Preet R, Wilder-Smith A, Larson H. The pandemic of social media panic travels faster than the COVID-19 outbreak. J Travel Med. 2020;27(3):taaa031.
[9] Holder J. Tracking Coronavirus vaccination around the world. The New-York Times. 2022;08:15
[10] Kaeuffer C, Hyaric CL, Fabacher T, Mootien J, Dervieux B, Ruch Y, et al. Clinical characteristics and risk factors associated with severe COVID-19: Prospective analysis of 1,045 hospitalised cases in North-Eastern France, March 2020. Euro Surveill. 2020;25(48):2000895. Available from: https://doi.10.2807/1560-7917.ES.2020.25.48.2000895.
[11] Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069-76. Available from: https://doi.org/10.1007/s42399-020-00363-4.
[12] CDC. Risk factor for severe Covid-19 disease. Provincial Health Services Authority. Available from: https://bccdc.ca/health-professionals/clinical-resources/covid19-care/clinical-care/risk-factors-severe-covid19-disease.
[13] Ruggiero KM, Wong J, Sweeney CF, Avola A, Auger A, Macaluso M et al. Parents' intentions to vaccinate their children against COVID-19. J Pediatr Health Care. 2021;35(5):509-17.
[14] Santibanej TA, Nguyen KH, Greby SM, Fisher A, Scanlon P, Bhatt A, et al. Parental vaccine hesitancy and childhood influenza vaccination. Pediatrics. 2020;146(6):e2020007609.
[15] Patwardhan A, Ohler A. The flu vaccination may have a protective effect on the course of COVID-19 in the pediatric population: When does Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) meet influenza? Cureus. 2021;13(1):e12533.
[16] Riccio DM, Lorini C, Bonaccorsi G, Paget J, Caini S. The Association between Influenza Vaccination and the Risk of SARS-CoV-2 Infection, Severe Illness, and Death: A Systematic Review of the Literature. Int J Envoirn Res Public health 2020;17(21):7859-70.
[17] Huang K, Lin SW, Sheng WH, Wang CC. Influenza Vaccination and the risk of Covid-19 infection and severe illness in older adults in the United States. Sci Rep. 2021;11(1):01-06. Doi: https://doi.org/10.1038/s41598-021-90068-y.
[18] Susan M, Taghioff, Benjamin R. Examining the potential benefits of the influenza vaccine against SARS-COV-2: A retrospective cohort analysis of 74754 patient. PLoS One. 2021;16(8):e0255541. Doi: https://doi.org/10.1371/journal.pone.0255541.
[19] Bujani MZ, Behnampour M, Ranimi N, Safari T, Khazaei Feizabad A, Hossein Sarbazi A, et al. The effect of influenza vaccination on covid 19 morbidity, severity and mortality: Systematic review and meta analysis Malaya J Med Sci. 2021;28(6):20-31.
[20] Soha H, Dana I, Ghatam R. Dose Influenza vaccination help reduce incidence of Covid 19 infection among hospital employees. Medicine 2022;101(2):e28479. Doi: https://doi.org10.1097/MD.0000000000028479.
[21] Saxena RK, Samad AA, Khan UR, Vinay V, Choure AC, Wankhede SV, et al. Assessment of prevalence of SARS-Co-2 infection in patients on anti HBV treatment: A questionnaire based survey. IP Int J Med Microbiol Trop Dis. 2021;7(1):17-23.
[22] News desk. 60% new Covid-19 cases in Jamshedpur have travel history. The Avenue Mall. 2021 Nov. 25. Available from: https:// https://avenuemail.in/60-percent-new-covid-19-cases-in-jamshedpur-have-travel-history/.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor and Head, Department of Microbiology, MDB Autonomous State Medical College, Deoria, Uttar Pradesh, India.
2. Associate Professor and Chief Medical Superintendent, Department of Medicine, MDB Autonomous State Medical College, Deoria, Uttar Pradesh, India.
3. Demonstrator, Department of Microbiology, MDB Autonomous State Medical College, Deoria, Uttar Pradesh, India.
4. Non Medical Scientist, Department of Microbiology, Babu Mohan Singh District Hospital, Deoria, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sana Nudrat,
Demonstrator, Department of Microbiology, MDB Autonomous State Medical College, Deoria, Uttar Pradesh, India.
E-mail: nudratsana1@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 08, 2022
- Manual Googling: Sep 28, 2022
- iThenticate Software: Nov 05, 2023 (11%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 03, 2022**
Date of Peer Review: **Sep 28, 2022**
Date of Acceptance: **Nov 08, 2022**
Date of Publishing: **Apr 01, 2023**