



## Major Article

## Impact of the influenza vaccine on COVID-19 infection rates and severity

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## Key Words:

COVID-19

Influenza vaccination

**Background:** With a unique influenza season occurring in the midst of a pandemic, there is interest in assessing the role of the influenza vaccine in COVID-19 susceptibility and severity.

**Methods:** In this retrospective cohort study, patients receiving a laboratory test for COVID-19 were identified. The primary outcome was comparison of positive COVID-19 testing in those who received the influenza vaccine versus those who did not. Secondary end points in patients testing positive for COVID-19 included mortality, need for hospitalization, length of stay, need for intensive care, and mechanical ventilation.

**Results:** A total of 27,201 patients received laboratory testing for COVID-19. The odds of testing positive for COVID-19 was reduced in patients who received an influenza vaccine compared to those who did not (odds ratio 0.76, 95% CI 0.68–0.86;  $P < .001$ ). Vaccinated patients testing positive for COVID-19 were less likely to require hospitalization (odds ratio, 0.58, 95% CI 0.46–0.73;  $P < .001$ ), or mechanical ventilation (odds ratio, 0.45, 95% CI 0.27–0.78;  $P = .004$ ) and had a shorter hospital length of stay (risk ratio, 0.76, 95% CI 0.65–0.89;  $P < .001$ ).

**Conclusion:** Influenza vaccination is associated with decreased positive COVID-19 testing and improved clinical outcomes and should be promoted to reduce the burden of COVID-19.

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## INTRODUCTION

The novel coronavirus of 2019 (COVID-19) was first identified in Wuhan, China in December 2019, and was declared a public health emergency of international concern within one month. As of February 2021, more than 106 million confirmed cases of COVID-19 and over 2.3 million deaths have been reported globally.<sup>1</sup> The clinical spectrum of illness caused by COVID-19 is broad, with severity of disease ranging from mild symptoms to acute respiratory distress syndrome with rapid deterioration.<sup>2</sup> Pre-existing cerebrovascular, liver, kidney and gastrointestinal diseases, as well as hypertension, diabetes, COPD, and age greater than 60 confer higher susceptibility to infection by COVID-19 and greater risk of mortality with infection.<sup>3,4</sup>

Importantly, patients with pre-existing cardiovascular risk factors are more likely to experience severe disease resulting from both direct and indirect cardiovascular complications of COVID-19, including myocarditis, arrhythmias, and venous thromboembolism.<sup>5</sup>

Clinical trials of dexamethasone<sup>6,7</sup> and Remdesivir<sup>8</sup> have shown a reduction in complications in very ill COVID-19 patients, and while effective vaccines against COVID-19 from both Pfizer-BioNTech and Moderna have been approved for use in the United States, they are not yet broadly available, making it imperative to explore the effects of currently available medical interventions that may lessen the susceptibility to and burden of disease.

With the influenza season upon us, there is interest in exploring the relationship between influenza vaccination and COVID-19 susceptibility and disease severity. Recent studies have suggested that prior vaccination to pathogens such as tuberculosis and influenza may confer some protection against COVID-19.<sup>9–14</sup> An analysis of over 92,000 COVID-19 patients in a nonpeer reviewed study from Brazil found a 17% reduced odds of mortality, 8% lower odds of need for intensive care treatment and 18% lower odds of invasive respiratory support in those who received an influenza vaccine.<sup>12</sup> Separate

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institution would not be captured in our search. However, the purposes of this study was to compare COVID-19 infection rates and clinical outcomes based on influenza vaccination status within a single cohort, and not to report on absolute statistics, which we appreciate may be skewed in our population.

Finally, the search was conducted in the midst of the COVID-19 pandemic, with new cases still being reported daily. We therefore may not have captured the full extent of outcomes for those recently diagnosed with COVID-19 and cannot predict how future case rates will affect our results. However, with the peak of the influenza season encroaching, there is a sense of urgency to help healthcare providers and patients make better informed medical decisions.

## CONCLUSION

In this electronic medical records based retrospective cohort study, we found a significant reduction in the odds of testing positive for COVID-19 in patients who received an influenza vaccine compared to those who did not receive the vaccine. In addition, in patients who tested positive for COVID-19, those who previously received an influenza vaccine had significantly better clinical outcomes. Future prospective studies are needed to establish a causal relationship between the influenza vaccine and COVID-19 susceptibility and severity. Until the COVID-19 vaccine becomes widely available, the influenza vaccine should be promoted to reduce the burden of disease during this pandemic.

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## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.ajic.2021.02.012>.

## References

- Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20:533–534.
- Goh KJ, Choong MC, Cheong EH, et al. Rapid progression to acute respiratory distress syndrome: review of current understanding of critical illness from COVID-19 infection. *Ann Acad Med Singapore*. 2020;49:108–118.
- Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *Jama*. 2020;323:1612–1614.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
- Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol*. 2020;75:2352–2371.
- Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. *Nature*. 2020;582:469.
- The WHOECAT-TWG. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324:1330–1341.
- Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. *New Engl J Med*. 2020;383:1813–1826.
- O'Connor E, Teh J, Kamat AM, Lawrentschuk N. Bacillus Calmette Guérin (BCG) vaccination use in the fight against COVID-19 - what's old is new again? *Future Oncol*. 2020;16:1323–1325.
- Salem ML, El-Hennawy D. The possible beneficial adjuvant effect of influenza vaccine to minimize the severity of COVID-19. *Med Hypotheses*. 2020;140: 109752.
- 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;93:64–65.
- Fink G, Orlova-Fink N, Schindler T, et al. Inactivated trivalent influenza vaccine is associated with lower mortality among Covid-19 patients in Brazil [e-pub ahead of print]. *BMJ Evid Based Med*. <https://doi.org/10.1136/bmjebm-2020-111549>, Accessed February 26, 2021.
- Zanettini C, Omar M, Dinalankara W, et al. Influenza vaccination and COVID19 mortality in the USA. *medRxiv*; 2020.
- Ragni P, Marino M, Formisano D, et al. Association between exposure to influenza vaccination and COVID-19 diagnosis and outcomes. *Vaccines*. 2020;8:675.
- Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
- Kuitunen I, Artama M, Mäkelä L, Backman K, Heiskanen-Kosma T, Renko M. Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. *Pediatr Infect Dis J*. 2020;39:423–427.
- Tan JY, Conceicao EP, Sim XYJ, Wee LEI, Aung MK, Venkatachalam I. Public health measures during COVID-19 pandemic reduced hospital admissions for community respiratory viral infection. *J Hosp Infect*. 2020;106:387–389.
- Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol*. 2006;35:337–344.
- Jackson ML, Nelson JC, Weiss NS, Neuzil KM, Barlow W, Jackson LA. Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: a population-based, nested case-control study. *Lancet*. 2008;372:398–405.
- Lee CH, Pinho MP, Buckley P, et al. CD8+ T cell cross-reactivity against SARS-CoV-2 conferred by other coronavirus strains and influenza virus. *Med Lett CDC & FDA*. 7 June 2020. 204 Business Insights: Essentials Web 2 Aug 2020.
- Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol*. 2013;34:431–439.
- Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020;20:375–388.
- Debisarun PA, Struycken P, Domínguez-Andrés J, et al. The effect of influenza vaccination on trained immunity: impact on COVID-19. *medRxiv*; 2020. 2020.2010.2014.20212498.
- Donzelli A, Schivalocchi A, Giudicatti G. Non-specific effects of vaccinations in high-income settings: How to address the issue? *Hum Vaccin Immunother*. 2018;14:2904–2910.
- Klinger D, Blass I, Rappoport N, Linial M. Significantly improved COVID-19 outcomes in countries with higher BCG vaccination coverage: a multivariable analysis. *Vaccines (Basel)*. 2020;8:378.
- Pawlowski C, Puranik A, Bandi H, et al. Exploratory analysis of immunization records highlights decreased SARS-CoV-2 rates in individuals with recent non-COVID-19 vaccinations. *medRxiv*. 2020:2020.2007.2027.20161976.
- Antony SJ, Almaghouth NK, Heydemann EL. Are coinfections with COVID-19 and influenza low or underreported? An observational study examining current published literature including three new unpublished cases. *J Med Virol*. 2020;92:2489–2497.
- Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12:36–44.
- Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices - United States, 2019–20 influenza season. *MMWR Recomm Rep*. 2019;68:1–21.
- Cheney MK, John R. Underutilization of influenza vaccine: a test of the health belief model. *SAGE Open*. 2013;3: 2158244013484732.
- Grandhi GR, Mszar R, Vahidy F, et al. Sociodemographic disparities in influenza vaccination among adults with atherosclerotic cardiovascular disease in the United States. *JAMA Cardiol*. 2021;6:87–91.
- Wolff GG. Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017–2018 influenza season. *Vaccine*. 2020;38:350–354.
- Keilman LJ. Seasonal Influenza (Flu). *Nurs Clin North Am*. 2019;54:227–243.
- Kodama M. Influenza myocarditis. *Circ J*. 2010;74:2060–2061.
- Ashur C, Norton E, Farhat L, et al. Higher admission rates and in-hospital mortality for acute type A aortic dissection during influenza season: a single center experience. *Sci Rep*. 2020;10:4723.
- Madjid M, Naghavi M, Litovsky S, Casscells SW. Influenza and cardiovascular disease: a new opportunity for prevention and the need for further studies. *Circulation*. 2003;108:2730–2736.
- Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *Jama*. 2013;310:1711–1720.
- Smith Jr. SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363–2372.