Influenza vaccine during the 2019–2020 season and COVID-19 risk: A case-control study in Québec

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Abstract

Background: We carried out a case-control study that examined whether receipt of the inactivated influenza vaccine during the 2019–2020 season impacted on the risk of coronavirus disease 2019 (COVID-19), as there was a concern that the vaccine could be detrimental through viral interference.

Methods: A total of 920 cases with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (diagnosed between March and October 2020) and 2,123 uninfected controls were recruited from those who were born in Québec between 1956 and 1976 and who had received diagnostic services at two hospitals (Montréal and Sherbrooke, Québec). After obtaining consent, a questionnaire was administered by phone. Data were analyzed by logistic regression.

Results: Among healthcare workers, inactivated influenza vaccine received during the previous influenza season was not associated with increased COVID-19 risk (AOR: 0.99, 95% CI: 0.69–1.41). Among participants who were not healthcare workers, influenza vaccination was associated with lower odds of COVID-19 (AOR: 0.73, 95% CI 0.56–0.96).

Conclusion: We found no evidence that seasonal influenza vaccine increased the risk of developing COVID-19.

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Introduction

During the early stage of the coronavirus disease 2019 (COVID-19) pandemic, a hypothesis was raised that inactivated influenza vaccine could paradoxically enhance the risk of developing COVID-19, and this suggestion was picked up by some anti-vaccine advocates on the internet. Such viral interference has been described between the influenza vaccine and coronaviruses (other than severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) although the validity of these findings has been questioned (1,2). This interference was reported more frequently among persons who had received the influenza vaccine during the 2017–2018 season. A further concern was that one sentinel surveillance and three other observational studies showed that receipt of the trivalent influenza vaccine during the 2008–2009 season increased the risk of medically attended pandemic H1N1 illness 1.4-fold to 2.5-fold during the spring-summer 2009. The authors offered several potential mechanisms for their findings (3).

The objective of the present study was to determine whether there was any detrimental viral interference between influenza vaccine and SARS-CoV-2 infection such that the former increased the risk of the latter. If so, this would need to be taken into consideration in the planning of upcoming seasonal influenza vaccine campaigns.

Methods

In mid and late 2020, we carried out a large case-control study to determine whether the Bacillus Calmette-Guérin (BCG) vaccine (against tuberculosis) administered during infancy or childhood, through its non-specific effect on innate immunity, provided long-term protection against infection with SARS-CoV-2 (the results of this study will be published elsewhere). We also included in our questionnaire an exploratory question regarding influenza vaccination in the 2019–2020 season. Such self-reports are thought to be reliable for the most recent season (4). A total of 920 cases with polymerase chain reaction-confirmed SARS-CoV-2 infection (diagnosed between March and October 2020) and 2,123 uninfected controls (individuals who never had a SARS-CoV-2 polymerase chain reaction assay, either positive or negative) were recruited among persons born in Québec between 1956 and 1976. Identification of potential participants was made through the databases of the microbiology laboratories of the Hôpital Maisonneuve-Rosemont (HMR) in Montréal and the Centre Hospitalier Universitaire de Sherbrooke (CHUS). The institutional review boards of these two hospitals authorized this study.

For controls only, exclusion criteria were used to ensure that they were relatively representative of the overall catchment population of the two hospitals rather than its sickest fraction. For this, we excluded as potential controls individuals who had been hospitalized (for any reason) or had attended the emergency room during the study period, as well as those who were attending clinics where immunocompromised patients are often seen (hematology, oncology, rheumatology, HIV, renal transplants, dialysis, etc.). Persons living in long-term care facilities were also excluded as cases or controls, as most would have been unable to give an informed consent. We used frequency matching on sex and year of birth, aiming for two controls per case at HMR and three at CHUS.

Consenting individuals were administered a questionnaire over the phone which, after verifying eligibility, gathered sociodemographic data and information about occupation—healthcare worker (HCW) or not. We also verified the six-digit postal code that was used to obtain a census-based material deprivation index as per an application developed by the Institut national de santé publique du Québec (5). Other collected variables were not germane to the current paper (e.g. self-reported BCG/smallpox scar, age at BCG, etc).

Univariable and multivariable analyses were carried out by unconditional logistic regression, using R version 4.0.2 (6). Potential confounders, which could have been linked to both SARS-CoV-2 and influenza vaccination, included age (as a continuous variable), sex, recruitment hospital, census-based material deprivation quintile and HCW status. We elected to adjust for all these *a priori* confounders regardless of their contribution to the fit of the models. Effect modification by HCW status, sex and age was evaluated by including an interaction term in three separate regression models including all potential confounders (HCW status*influenza vaccination, sex*influenza vaccination, age group*influenza vaccination) to obtain a *p*-value for each interaction term. Stratified analyses according the HCW status, sex and age group were also conducted to estimate odds ratios (OR) and 95% confidence intervals for the association between influenza vaccination and SARS-CoV-2 in these subgroups.

Data on influenza vaccination was missing for 42 cases and 16 controls. The analytical sample thus consisted in 878 cases and 2,107 controls for whom this information was available.

There were some missing data for the deprivation index (unavailable for recent residential developments and postal codes where more than 15% of the population lived in an institution) for 6.3% of the participants (56 cases and 132 controls). To address this issue and to avoid excluding subjects with known influenza vaccination status, multiple imputation by chained equations was performed for this variable (20 imputed datasets).

Results

Characteristics of cases and controls are shown in **Table 1**. As expected, given that the study was carried out before the availability of SARS-CoV-2 vaccines, there were more HCW among cases than controls.

Table 1: Characteristics of cases and controls

Characteristics	Cases n=878		Controls n=2,107	
	n	%	n	%
Sex				
Men	333	37.9	814	38.6
Women	545	62.1	1,293	61.4
Age (years)				
44–49	213	24.3	525	24.9
50–54	213	24.3	465	22.1
55–59	250	28.5	579	27.5
60–64	202	23.0	538	25.5
Hospital				
Maisonneuve-Rosemont	591	67.3	1,226	58.2
CHUS	287	32.7	881	41.8
Material deprivation				
Lowest	149	17.0	292	13.9
Low	159	18.1	386	18.3
Middle	163	18.6	442	21.0
High	202	23.0	460	21.8

Table 1: Characteristics of cases and controls (*continued*)

Characteristics	Cases n=878		Controls n=2,107	
	n	%	n	%
Material deprivation (*continued*)				
Highest	149	17.0	395	18.7
Missing	56	6.4	132	6.3
Work				
Healthcare settings	425	48.4	231	11.0
All others	453	51.6	1,876	89.0

Abbreviation: CHUS, Centre hospitalier universitaire de Sherbrooke

One third of healthcare workers and one fifth of other workers had been vaccinated against influenza. Results of univariable and multivariable logistic regression are shown in **Table 2**.

Inactivated influenza vaccine during the 2019–2020 season was not associated with COVID-19 among HCW. Among participants who were not HCW, it was associated with lower odds of COVID-19. However, there was no indication of interaction when considering the interaction term. The association between influenza vaccination and COVID-19 did not differ by sex or age group based on the estimates of association or the *p*-values or interaction terms (Table 2).

Discussion

We found that in non-HCW, seasonal influenza vaccine was associated with lower odds of SARS-CoV-2 infection and not with an enhanced risk as initially hypothesized. No effect of seasonal influenza vaccine on odds of SARS-CoV-2 infection was seen among HCW. There is no reason to believe that influenza vaccine could offer cross-protection against SARS-CoV-2 through adaptive immune mechanisms, given the dissimilarity in the surface proteins of these two viruses. A possible hypothesis to explain this apparent protective effect in non-HCW is that vaccine-derived protection against influenza during the 2020 spring (its efficacy in Canada was estimated at 58%) (7) may have lowered the chances of consulting for influenza-related upper

Table 2: Influenza vaccine during the 2019–2020 season among cases of COVID-19 and uninfected controls

Characteristics	Cases n=878		Controls n=2,107		Crude		Adjusted		*p*-value for interaction[a]
	N	%	N	%	OR	95% CI	OR	95% CI	
All participants									
Not vaccinated	649	73.9	1,626	77.2	1.00	N/A	1.00	N/A	N/A
Vaccinated	229	26.1	481	22.8	1.19	0.99–1.43	0.81	0.66–1.00[b]	
Healthcare workers									
Not vaccinated	273	64.2	149	64.5	1.00	N/A	1.00	N/A	0.14
Vaccinated	152	35.8	82	35.5	1.01	0.72–1.42	0.99	0.69–1.41[c]	
Not healthcare workers									
Not vaccinated	376	83.0	1,477	78.7	1.00	N/A	1.00	N/A	0.14
Vaccinated	77	17.0	399	21.3	0.76[c]	0.58–0.99[c]	0.73	0.56–0.96[c,d]	
Men									
Not vaccinated	252	75.7	645	79.2	1.00	N/A	1.00	N/A	0.73
Vaccinated	81	24.3	169	20.8	1.23	0.90–1.66	0.87	0.62–1.23[e]	
Women									
Not vaccinated	397	72.8	981	75.9	1.00	N/A	1.00	N/A	0.73
Vaccinated	148	27.2	312	24.1	1.17	0.93–1.47	0.78	0.60–1.01[e]	
Age 44–54 years									
Not vaccinated	321	75.4	812	82.0	1.00	N/A	1.00	N/A	0.86
Vaccinated	105	24.6	178	18.0	1.49[c]	1.13–1.96[c]	0.85	0.62–1.17[f]	
Age 55–64 year									
Not vaccinated	328	72.6	814	72.9	1.00	N/A	1.00	N/A	0.86
Vaccinated	124	27.4	303	27.1	1.02	0.79–1.30	0.82	0.62–1.08[f]	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N/A, not applicable; OR, odds ratio

[a] *p*-value for the interaction term between influenza vaccination status and each of the three stratification variable (healthcare worker status, sex or age group) obtained from models including the stratification variable, influenza vaccination status, the interaction term and potential confounders

[b] Adjusted for age as a continuous variable, sex, recruitment hospital, census-based material deprivation quintile and healthcare worker status

[c] $p<0.05$

[d] Adjusted for age as a continuous variable, sex, recruitment hospital and census-based material deprivation quintile

[e] Adjusted for age as a continuous variable, recruitment hospital, census-based material deprivation quintile and healthcare worker status

[f] Adjusted for sex, recruitment hospital, census-based material deprivation quintile and healthcare worker status

respiratory tract symptoms when a concomitant SARS-CoV-2 infection could be diagnosed or may have reduced the risk of a more severe (thus better detected) SARS-CoV-2 episode in the presence of a dual infection. Such co-infections are, however, quite uncommon. In the United Kingdom during the first wave of COVID-19 (January–April 2020), out of 19,256 individuals tested, only 58 had a dual infection, while 992 had only an influenza and 4,442 had only a SARS-CoV-2 infection (8). Similar finding were reported from California (9). Furthermore, in Canada, circulation of the influenza virus came to an end in March 2020, and the overwhelming majority of our COVID-19 cases were reported after this date (10).

It is more plausible that non-HCW individuals who get the seasonal influenza vaccine, some of whom have chronic diseases, were more concerned with their health in general such that they may have been more compliant with social distancing and the use of masks, or reduced their potential exposures by staying at home. These public health measures would have reduced their risk of SARS-CoV-2 infection; a variation of the phenomenon known as the healthy vaccinee bias (11). This may not have been the case in HCW, who knew they were at high-risk for occupational COVID-19, and thus may have been consistently very prudent in decreasing exposure to SARS-CoV2.

In a systematic review dating back to October 2020, Del Riccio identified seven methodologically sound studies that had examined this association, and individuals vaccinated against influenza were less likely to have COVID-19 in five (12). More recent publications have also shown influenza vaccine associated with lower odds of SARS-CoV-2 infection in the United States (13–15) and Israel (16), while a smaller American study failed to document any effect (17). The largest study, comprising 137,037 individuals from the Mayo Clinic electronic health record database, showed a lower likelihood of developing COVID-19 not only among individuals vaccinated against influenza, but also in those who had received polio, *Haemophilus influenzae* type B, measles-mumps-rubella, varicella, hepatitis B, hepatitis A or pneumococcal conjugate vaccines (15). Such associations with multiple and unrelated vaccine products suggests a "healthy user" or "healthy vaccinee" effect.

A study limitation was that we did not collect data on co-morbidities since this could not confound the association between BCG and COVID-19, the primary objective of this study (this would have required these diseases to be associated with the administration of BCG four to six decades earlier—a very unlikely scenario). However, among participants who were not HCW, indications for the influenza vaccine include some conditions (diabetes, obesity, cardiac or pulmonary diseases, etc.) that are themselves associated with severe forms of COVID-19, and thus with the likelihood of getting tested. Adjustment for these unmeasured confounders could have slightly altered the measure of association between influenza vaccine and COVID-19 towards the null value if risk mitigation among vaccinees was more marked in patients with co-morbidities.

Another limitation of our study is that we studied individuals aged 44–64 years, whilst the main target of seasonal influenza vaccination is the age group 65 years or older. It seems unlikely, however, that a viral interference between SARS-CoV-2 and the seasonal influenza vaccine would vary with age.

Finally, compared to the controls, a much higher proportion of cases (48%) were HCWs. This reflected the overall epidemiological portrait of COVID-19 in Québec during the first wave, when HCW were at great risk of occupational infection and represented 41% of cases among persons aged 18–59 (18). In this context, a selection bias seems unlikely, but we cannot rule out the possibility that HCWs differed from the other participants in their recollection of influenza vaccination during the previous season due to a social desirability bias. However, such a bias seems unlikely given that only 36% of HCW alleged to have been vaccinated, which is comparable to routine surveillance data of influenza vaccination in healthcare institutions of Québec.

Conclusion

We found no evidence that seasonal influenza vaccine increased the risk of developing COVID-19 and the usual vaccination strategy does not need to be altered for the 2021–2022 season.

Authors' statement

ACL, JP, PDW, MCR, MEP — Conceived the study, analyzed and interpreted the data, drafted and edited the manuscript
MCR, JY — Data analysis
AC, LV — Contributed to data interpretation and writing the manuscript
All authors approved the final version of the manuscript.

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Competing interests

None.

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