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BRIEF REPORT

Influenza Vaccine Does Not Increase the Risk of Coronavirus or Other Noninfluenza Respiratory Viruses: Retrospective Analysis From Canada, 2010–2011 to 2016–2017

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(See the Editorial Commentary by Sullivan on pages 2289–90.)

Influenza vaccine effectiveness against influenza and noninfluenza respiratory viruses (NIRVs) was assessed by test-negative design using historic datasets of the community-based Canadian Sentinel Practitioner Surveillance Network, spanning 2010–2011 to 2016–2017. Vaccine significantly reduced the risk of influenza illness by >40% with no effect on coronaviruses or other NIRV risk.

Keywords. influenza; coronavirus; respiratory viruses; vaccine effectiveness; nonspecific immunity.

Influenza vaccine effectiveness (VE) is commonly estimated through the test-negative design (TND), an observational method that compares the odds of vaccination among influenza test-positive cases to influenza test-negative controls through the odds ratio (OR), with adjustment for confounders and VE derived as (1 – OR) × 100%. The core prerequisite for valid VE estimation by TND is that vaccine has no effect on alternate etiologies of the same clinical syndrome included in the control group. Comparison of per-protocol and TND analyses of several large randomized controlled trial (RCT) datasets involving more than 6000 participants has verified this prerequisite for influenza VE estimation, with the OR for influenza vaccine effect against noninfluenza causes of influenza-like illness (ILI) approximating 1.0 (VE approximating zero) [1].

If, however, influenza infection induces immunity that is cross-protective against noninfluenza respiratory viruses (NIRVs; eg, through nonspecific innate immunity), then vaccination that effectively prevents influenza may indirectly result in greater NIRV risk among vaccinated compared with unvaccinated individuals. Cowling et al [2] hypothesized such vaccine interference with infection-induced immunity to explain a significant 4-fold increased NIRV risk among 69 children randomized to receive the 2008–2009 influenza vaccine compared with 46 children receiving placebo. That small RCT, however, included just 23 NIRV cases in total and was underpowered to show VE against influenza, as required by the interference hypothesis [2]. Conversely, in TND analysis of 6 study seasons (2004–2005 to 2009–2010), Sundaram et al [3] reported that influenza vaccine significantly halved the risk of acute respiratory illness due to influenza virus, but on univariate analysis showed no vaccine effect on NIRV risk, with comparable rates of vaccination among 641 NIRV-positive versus 754 NIRV-negative controls.

More recently, Wolff [4] used TND analysis to explore the influenza vaccine interference hypothesis among US Department of Defense beneficiaries during the 2017–2018 season. Wolff showed significant vaccine protection against influenza with an adjusted OR of 0.48 (95% confidence interval [CI], .43–.52), corresponding to a VE of 52% (95% CI, 48–57%), but no vaccine effect against NIRVs with an adjusted OR of .97 (95% CI, .86–1.09). In separate univariate analysis of individual NIRVs, however, Wolff showed that receipt of influenza vaccine was associated with greater risk of coronavirus (OR, 1.36; 95% CI, 1.14–1.63) and human metapneumovirus (HMPV) (OR, 1.51; 95% CI, 1.20–1.90) infection.

Four seasonal coronaviruses (229E, NL63, OC43, HKU1) are established causes of the common cold, with NL63 and OC43 being most frequently identified [5, 6]. Three other coronaviruses have been associated with more severe illness, including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and more recently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the latter emerging in late 2019 and responsible for the ongoing pandemic of coronavirus disease 2019 (COVID-19) [5, 6]. Wolff's findings for seasonal coronaviruses, coincidentally published in January 2020, have triggered concern that influenza vaccination may detrimentally affect COVID-19 risk [4]. Here, we use historic datasets of the community-based Canadian Sentinel Practitioner Surveillance Network (SPSN) to assess the association between influenza vaccine and NIRV risk—notably, seasonal coronaviruses.

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METHODS

We retrospectively applied TND analysis to Canadian SPSN influenza VE study specimens collected during the 2010–2011 to 2016–2017 seasons [7], when specimens were tested for both influenza and NIRVs. Specimens were included if collected November–April from consenting patients aged 1 year or older who presented within 7 days of ILI onset to a sentinel practitioner in the provinces of Alberta, British Columbia, Ontario, or Quebec. Influenza-like illness was defined by fever and cough plus 1 or more of arthralgia, myalgia, prostration, or sore throat. Fever was not required for adults aged 65 years and older after 2010–2011.

Specimens were tested for influenza and NIRV at provincial public health reference laboratories by reverse transcriptase polymerase chain reaction (RT-PCR) and/or commercial multiplex RT-PCR assays (Supplementary Material 1). Ontario panels did not include the HKU1 coronavirus. During seasons for which Ontario (2015–2016) and Alberta (2015–2016/2016–2017) did not perform multiplex testing they were excluded from influenza and NIRV analyses.

Participants who self-reported influenza vaccination 2 weeks or more before ILI onset were considered vaccinated. Participants with unknown timing or self-reporting vaccination less than 2 weeks before ILI onset were excluded; the latter were also explored as unvaccinated (as per Wolff) [4]. Odds ratios compared influenza vaccination rates among influenza and NIRV test-positive cases relative to test-negative, pan-negative, and NIRV-positive controls. Influenza test-positive specimens were excluded from NIRV analyses. The NIRV cases were assessed in combination and separately grouped as coronaviruses, entero-/rhinoviruses (EV/RV), HMPV, parainfluenza, and respiratory syncytial virus (RSV). Coxsackie-/echovirus, adenovirus, and bocavirus estimates are not presented due to limited detection but are included in combined NIRV analyses. Coinfections across NIRV groupings were included among controls but not cases; in sensitivity analyses, cases also included coinfections. All models adjusted for age, province, specimen collection interval, calendar time, and season; participants missing information for any of these covariates were excluded. Comorbidity and sex were also assessed in sensitivity analyses but had no confounding effect.

RESULTS

The study included 4281 influenza, 2565 NIRV, and 3841 pan-negative specimens; in sensitivity analyses, 175 coinfections were included. The NIRV detections included the following: EV/RV (645; 25%), coronavirus (570; 22%), RSV (524; 20%), HMPV (390; 15%), parainfluenza (316; 12%), adenovirus (114; 4%), and bocavirus (6; <1%). Coronavirus detections included OC43 (230; 40%), NL63 (112; 20%), 229E (88; 15%), 229E/NL63 combined targets (81; 14%), HKU1 (53; 9%), and 6 coronavirus coinfections. Median ages of influenza (35 years), coronavirus (37 years), and combined NIRV cases (34 years) and their respective test-negative controls (36–37 years) were similar. Among cases of influenza, coronavirus, and combined NIRV outcomes, 27% (1165/4281), 20% (113/570), and 29% (751/2565), respectively, were children younger than 20 years old.

The adjusted OR for influenza vaccination among influenza cases versus influenza test-negative controls was .55 (95% CI, .50–.61), corresponding to a VE of 45% (95% CI, 39–50%). The ORs were similar when pan-negative (.58; 95% CI, .52–.65) or NIRV-positive (.51; 95% CI, .45–.58) controls were instead used and also similar when participants vaccinated less than 2 weeks before ILI onset were considered unvaccinated as per Wolff [4] (.56; 95% CI, .51–.62) (Table 1). Conversely, influenza vaccine had no significant effect on any NIRV explored, separately or in combination (Table 1), including sensitivity analyses (Supplementary Material 2). In particular, the adjusted OR for influenza vaccination among coronavirus cases versus coronavirus test-negative controls was 1.04 (95% CI, .85–1.28), and also similar using pan-negative (1.09; 95% CI, .89–1.34) or NIRV-positive (.98; 95% CI, .79–1.22) controls or when participants vaccinated less than 2 weeks prior to ILI onset were considered unvaccinated (1.04; 95% CI: .85–1.27). The ORs for vaccine effect against influenza did not differ between children aged less than 20 years and adults 20 years and older (.56 [95% CI, .44–.70] and .55 [95% CI, .49–.61]), and in neither of the age groups did vaccine significantly affect coronavirus risk (.74 [95% CI, .42–1.32] and 1.11 [95% CI, .89–1.38]).

DISCUSSION

In this 7-season analysis by the Canadian SPSN, influenza vaccine was protective against medically attended ILI due to influenza viruses, significantly reducing the risk by more than 40%. Conversely, influenza vaccine had no effect on noninfluenza causes of ILI, with the likelihood of vaccination among NIRV cases relative to test-negative controls approaching unity. In particular, influenza vaccine did not affect seasonal coronavirus risk. Our findings provide reassurance against the speculation that influenza vaccine may negatively affect COVID-19 risk. Addressing such speculation is important to maintain influenza vaccine coverage through the ongoing COVID-19 pandemic.

In assessing Wolff's paper we identified a major methodological problem to account for his unexpected findings [4]. In combined NIRV analysis, relative to pan-negative controls, Wolff adjusted for age and excluded specimens that tested influenza positive. In that analysis, shown in his Table 3, the OR approached unity, indicating no vaccine effect as expected. Conversely, in univariate (unadjusted) analysis of individual NIRV outcomes (eg, coronaviruses), Wolff retained influenza test-positive specimens in NIRV test-negative control groups, thereby violating the core

Table 1. Odds Ratios for Influenza Vaccination Comparing Influenza and Noninfluenza Respiratory Virus Cases With Various Control Groups: Canadian Sentinel Practitioner Surveillance Network, 2010–2011 to 2016–2017

Target Pathogen[a]	Test-positive Cases[b]	Test-negative Controls[c]	Unadjusted OR (95% CI)	Adjusted[d] OR (95% CI)	Pan-negative Controls[e]	Unadjusted OR (95% CI)	Adjusted[d] OR (95% CI)	NIRV-Positive Controls[f]	Unadjusted OR (95% CI)	Adjusted[d] OR (95% CI)
Influenza										
Vaccinated	843	1963	.58 (.53, .63)	.55 (.50, .61)	1101	.61 (.55, .68)	.58 (.52, .65)	862	.53 (.48, .60)	.51 (.45, .58)
Unvaccinated	3438	4618	Reference	Reference	2740	Reference	Reference	1878	Reference	Reference
NIRV combined										
Vaccinated	817	NA	NA	NA	1101	1.16 (1.04, 1.30)	1.11 (.99, 1.26)	NA	NA	NA
Unvaccinated	1748	NA	NA	NA	2740	Reference	Reference	NA	NA	NA
Coronavirus										
Vaccinated	187	1756	1.17 (.97, 1.40)	1.04 (.85, 1.28)	1101	1.22 (1.01, 1.47)	1.09 (.89, 1.34)	655	1.08 (.89, 1.32)	.98 (.79, 1.22)
Unvaccinated	383	4191	Reference	Reference	2740	Reference	Reference	1451	Reference	Reference
EV/RV										
Vaccinated	179	1758	.89 (.74,1.07)	.99 (.82, 1.21)	1101	.96 (.79, 1.15)	1.06 (.86, 1.30)	657	.79 (.65, .96)	.92 (.73, 1.14)
Unvaccinated	466	4084	Reference	Reference	2740	Reference	Reference	1344	Reference	Reference
HMPV										
Vaccinated	146	1808	1.44 (1.16, 1.78)	1.19 (.95, 1.51)	1101	1.49 (1.20, 1.85)	1.23 (.97, 1.58)	707	1.36 (1.09, 1.70)	1.15 (.90, 1.47)
Unvaccinated	244	4349	Reference	Reference	2740	Reference	Reference	1609	Reference	Reference
PIV										
Vaccinated	92	1862	.96 (.75, 1.24)	.96 (.73, 1.26)	1101	1.02 (.79, 1.32)	1.02 (.78, 1.35)	761	.88 (.68, 1.14)	.89 (.67, 1.19)
Unvaccinated	224	4366	Reference	Reference	2740	Reference	Reference	1626	Reference	Reference
RSV										
Vaccinated	184	1759	1.30 (1.08, 1.57)	1.11 (.89, 1.37)	1101	1.35 (1.11, 1.63)	1.18 (.95, 1.48)	658	1.22 (.99, 1.49)	1.03 (.82, 1.30)
Unvaccinated	340	4219	Reference	Reference	2740	Reference	Reference	1479	Reference	Reference

Abbreviations: CI, confidence interval; EV/RV, entero-/rhinovirus; HMPV, human metapneumovirus; NA, not applicable; NIRV, noninfluenza respiratory virus; OR, odds ratio; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

[a]Specimens that test positive for influenza virus were excluded from all analyses for which NIRVs were the target pathogen. Vaccinated participants who received vaccine <2 weeks prior to onset of influenza-like illness were excluded.

[b]Single detections, excluding coinfections across NIRV groupings from cases (coinfections within NIRV groupings retained; eg, multiple coronavirus infections).

[c]Test-negative for the target pathogen; coinfections allowed among controls.

[d]All analyses adjusted for age group (1–8, 9–19, 20–49, 50–64, ≥65 years), province (Alberta, British Columbia, Ontario, Quebec), specimen collection interval (≤4, 5–7 days), calendar time (based on week of specimen collection modelled as natural cubic spline functions with 3 equally spaced knots), and season (2010–2011, 2011–2012, 2012–2013, 2013–2014, 2014–2015, 2015–2016, 2016–2017).

[e]Test-negative for influenza and all NIRVs included on the multiplex panel.

[f]Test-positive for at least 1 NIRV included on the multiplex panel, excluding the target pathogen of interest.

prerequisite for valid TND analysis. In the context of effective influenza vaccine, influenza cases would have a lower likelihood of vaccination; as such, their inclusion would systematically reduce the proportion vaccinated in the control group and thereby inflate ORs comparing vaccine exposure between NIRV cases and controls. We illustrate the impact of this bias in Supplementary Material 3, where we have reanalyzed Wolff's data as well as our own, comparing influenza vaccine effect against NIRV when influenza test-positive specimens are properly excluded (as per TND prerequisite) or improperly included (as per Wolff [4]) within the control group. In both datasets and for all NIRVs, ORs for influenza vaccination are biased higher when influenza cases are erroneously included in the control group.

As for any observational design, random variation, bias, and confounding may influence TND findings. Our 7-season analysis was based on a substantial sample size, standardized ILI testing indication, and multivariate analysis to address those concerns, whereas Wolff relied upon a single season, general laboratory submissions, and univariate analysis, despite evidence in his dataset for confounding by age. The importance of adjustment for age and other potential confounders is reinforced by our analyses in which several unadjusted but no adjusted ORs significantly differed from 1 (Table 1, Supplementary Table 2a). Vaccine status was self-reported in our study but recorded before specimen testing, minimizing differential misclassification. Assays varied by province and season. Two SPSN provinces did not conduct NIRV testing during 1–2 of the study seasons, and HKU1 was omitted from the coronavirus panel of 1 province during all seasons. However, HKU1 comprised a small proportion of coronavirus detections in other SPSN provinces (15%; 53/349) and findings were robust across NIRV outcomes and in sensitivity analyses addressing variation in provincial contribution (data not shown). Finally, although we did not find evidence for vaccine interference, population surveillance signals elsewhere suggesting cross-pathogen immunological interactions still warrant immuno-epidemiological investigation [8, 9].

In conclusion, our findings provide reassurance that protective influenza vaccination does not negatively affect NIRV risk, including coronaviruses. Valid TND estimates require that etiologies against which vaccine is effective are specifically excluded from the test-negative control group, and this also applies when exploring vaccine effects on nonvaccine target pathogens. These methodological insights have important implications for other TND applications, including future evaluations of influenza vaccine effects against COVID-19, and vice-versa when SARS-CoV-2 vaccines become available.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Euro Surveill **2013**; 18:1–9. pii: 20585. doi:10.2807/1560-7917.es2013.18.37.20585
2. Cowling BJ, Fang VJ, Nishiura H, et al. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. Clin Infect Dis **2012**; 54:1778–83.
3. Sundaram ME, McClure DL, VanWormer JJ, Friedrich TC, Meece JK, Belongia EA. Influenza vaccination is not associated with detection of noninfluenza respiratory viruses in seasonal studies of influenza vaccine effectiveness. Clin Infect Dis **2013**; 57:789–93.
4. Wolff GG. Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017-2018 influenza season. Vaccine **2020**; 38:350–4.
5. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J **2020**; 39:355–68.
6. Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection and association of antibody responses with severity of disease. medRxiv [Preprint] **2020**. Available at: https://doi.org/10.1101/2020.04.14.20065771. Accessed 2 June 2020.
7. Canadian Sentinel Practitioner Surveillance Network (SPSN). Influenza vaccine effectiveness estimates. Available at: http://www.bccdc.ca/health-info/diseases-conditions/influenza/sentinel-network-spsn. Accessed 2 June 2020.
8. Linde A, Rotzén-Östlund M, Zweygberg-Wirgart B, Rubinova S, Brytting M. Does viral interference affect spread of influenza? Euro Surveill **2009**; 14: pii: 19354. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19354. Accessed 2 June 2020.
9. Anestad G. Interference between outbreaks of respiratory syncytial virus and influenza virus infection. Lancet **1982**; 1:502.