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## Correspondence

# Ecological fallacy in COVID-19 epidemiological inference: Influenza vaccination rate as an example

To the Editor,

While the effective vaccines against COVID-19 are not yet broadly available, recent studies have suggested that prior vaccination to tuberculosis and influenza would confer some protection against COVID-19.<sup>1,2</sup> We conducted an ecological study to evaluate the association between the influenza vaccine coverage percentage and cumulative incidence rate, cumulative mortality rate, and case fatality risk in the United States of America (USA).

The data of the cumulative number of COVID-19 cases and deaths in each state from Feb 1st to Apr 30th was obtained from the Centers for Disease Control and Prevention (CDC) of the USA. The total population, population density, average temperature and humidity, and the influenza vaccine coverage percentage of each state were collected from the USA Census Bureau, the National Climatic Data Center and the USA CDC, respectively.

The cumulative incidence and mortality of COVID-19 of each state were identified as the numbers of cumulative cases and deaths divided by the population. The case fatality risk was calculated as the ratio of the cumulative number of deaths to the cumulative number of confirmed COVID-19 cases. All the variables were categorized into categorical variables.

Poisson regression analysis was used to assess the adjusted rate ratio (RR) and 95% confidence intervals (CIs) on the cumulative incidence and the mortality rate. Logistic regression analysis was used to evaluate the adjusted odds ratio (OR) and 95% CIs for the case-fatality risk. Statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC,

USA). A *p*-value of less than 0.05 was considered statistically significant.

After adjusting for the weather parameters and population density, the RRs of influenza vaccine coverage percentages over 40% were 0.48 (95% CIs, 0.47–0.48) and 0.43 (95% CIs, 0.42–0.44) on the cumulative incidences and mortality rates, respectively. The adjusted OR was 0.89 (95% CIs, 0.87–0.91) on the case fatality risk of the COVID-19 (Table 1).

The results showed that the influenza vaccine coverage percentage over 40% had a potential protective effect against the COVID-19 pandemic in the USA. However, a fallacy in COVID-19 epidemiological inference may arise from an ecological study such as this. The data in this study is at the population level that the aggregate-level correlation and the individual-level correlation may differ greatly or even in opposite signs.<sup>1,3</sup> Also, receiving the influenza vaccine would be a surrogate for race disparities or socioeconomic status. For example, underserved African-Americans had a lower rate of influenza vaccination.<sup>4</sup> Asians had a relatively higher rate of vaccination<sup>5</sup> and were more likely to wear masks than non-Asians. The ecological study aimed to generate a hypothesis that it should be validated by future large-scale, individual-level studies. Adjusting for potential confounders is mandatory for any legitimate causal inference. Current evidence regarding the protective effect of the influenza vaccine against the COVID-19 was still conflicting.<sup>1–3</sup> The information provided in this study should be interpreted with caution for the containment of COVID-19 outbreaks in the unavailability of COVID-19 vaccines.

<https://doi.org/10.1016/j.jfma.2021.03.011>

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**Table 1** The adjusted effects of variables on the COVID-19 outbreaks in the United States of America.

Variables	Cumulative incidence rate <sup>a</sup> RR* <sub>adjusted</sub> (95% CIs)	Cumulative mortality rate <sup>a</sup> RR <sub>adjusted</sub> (95% CIs)	Case fatality risk <sup>a</sup> OR* <sub>adjusted</sub> (95% CIs)
Average temperature <sup>b</sup>			
≤50°F	1	1	1
>50°F	0.24 (0.24–0.24)	0.16 (0.16–0.17)	0.69 (0.68–0.71)
Relative humidity <sup>b</sup>			
<40%	1	1	1
40% to 60%	0.51 (0.50–0.52)	0.446 (0.40–0.50)	0.82 (0.73–0.91)
≥60%	0.26 (0.25–0.27)	0.20 (0.16–0.25)	1.01 (0.92–1.12)
Population density <sup>c</sup>			
>120 persons/mile <sup>2</sup>	1	1	1
≤120 persons/mile <sup>2</sup>	0.38 (0.38–0.39)	0.31 (0.30–0.32)	0.88 (0.86–0.91)
Influenza vaccine coverage <sup>d</sup>			
≤40%	1	1	1
>40%	0.48 (0.47–0.48)	0.43 (0.42–0.44)	0.89 (0.87–0.91)

Abbreviations: RR: risk ratio, CI: confidence interval, OR: odds ratio.

<sup>a</sup> Coronavirus Disease 2019: Cases in the U.S. Vol 2020: Centers for Disease Control and Prevention 2020. Available from <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>. Accessed May 01, 2020.

<sup>b</sup> National Climatic Data. Vol 2020: National Climatic Data Center; 2020. <https://www.ncdc.noaa.gov/dataaccess>. Accessed May 01, 2020.

<sup>c</sup> State Population Totals and Components of Change: 2010–2019. Vol 2020: US Census Bureau 2020. Available from <https://www.census.gov/data/tables/time-series/demo/popest/2010s-state-total.html>. Accessed May 01, 2020.

<sup>d</sup> Flu Vaccination Coverage, United States, 2018–19 Influenza Season. Vol 2020: Centers for Disease Control and Prevention 2020. <https://www.cdc.gov/flu/fluview/coverage-1819estimates.htm>. Accessed May 01, 2020.

## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

## References

- Rivas MN, Ebinger JE, Wu M, Sun N, Braun J, Sobhani K, et al. BCG vaccination history associates with decreased SARS-CoV-2 seroprevalence across a diverse cohort of health care workers. *J Clin Invest* 2021;131:e145157.
- Jehi L, Ji X, Milinovich A, Erzurum S, Rubin BP, Gordon S, et al. Individualizing risk prediction for positive coronavirus Disease 2019 testing results from 11,672 patients. *Chest* 2020;158:1364–75.
- Riccio MD, 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 Environ Res Publ Health* 2020;17:7870.
- Bazargan M, Wisseh C, Adinkrah E, Ameli H, Santana D, Cobb S, et al. Influenza vaccination among underserved African-American older adults. *BioMed Res Int* 2020;2020:2160894.
- Tse SC, Wyatt LC, Trinh-Shevrin C, Kwon SC. Racial/ethnic differences in influenza and pneumococcal vaccination rates among older adults in New York City and Los Angeles and Orange Counties. *Prev Chronic Dis* 2018;15:E159.

Yi-Chu Chen  
Institute of Epidemiology and Preventive Medicine, College  
of Public Health, National Taiwan University, Taipei,  
Taiwan

Department of Nursing, Fu-Jen Catholic University, New  
Taipei City, Taiwan

Patrick Chow-In Ko  
Department of Emergency Medicine, National Taiwan  
University Hospital, Taipei, Taiwan  
Department of Emergency Medicine, College of Medicine,  
National Taiwan University, Taipei, Taiwan

Wen-Chung Lee  
Institute of Epidemiology and Preventive Medicine, College  
of Public Health, National Taiwan University, Taipei,  
Taiwan  
Innovation and Policy Center for Population Health and  
Sustainable Environment, College of Public Health,  
National Taiwan University, Taipei, Taiwan

Wan-Ching Lien\*  
Department of Emergency Medicine, National Taiwan  
University Hospital, Taipei, Taiwan  
Department of Emergency Medicine, College of Medicine,  
National Taiwan University, Taipei, Taiwan

\*Corresponding author. Department of Emergency Medi-  
cine, National Taiwan University Hospital and National  
Taiwan University, No.7, Chung-Shan South Road, Taipei  
100, Taiwan. Fax: +886 2 23223150.  
E-mail address: [wanchinglien@ntu.edu.tw](mailto:wanchinglien@ntu.edu.tw) (W.-C. Lien)

25 February 2021