Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 (eg, BCG, MMR) in studies that were also subject to selection bias and confounding (see, eg, Pawlowski et al, which showed strong protective effects for pneumococcal and hepatitis vaccines[13]) and/or other obvious methodological shortcomings (eg, the ecological study by Klingen et al[14]) suggests that the common thread across this body of research may be methodological shortcomings and not a plausible causative mechanism. Indeed, the strength of the associations reported in Conlon et al. (ranging from 24% to 55% reduction in the odds of COVID-19-related outcomes) suggest that there might be extraneous factors biasing the observed relationships.

Therefore, given the potential for misinterpretation of scientific findings and substantial vaccine hesitancy, it is prudent to be extremely cautious in interpreting findings such as Conlon et al's. For the reasons outlined above, while this study does warrant further research on the effects of non-COVID-19 vaccination on COVID-19 outcomes, it does not provide enough grounds for suggesting a causal association between influenza vaccination and protection against COVID-19 infection.

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Response to "Potential for bias in assessing risk and protective factors for COVID-19: Commentary on Conlon et al.'s 'Impact of the influenza vaccination on COVID-19 infection rates and Severity'"

In the commentary on our manuscript "Impact of the influenza vaccination on COVID-19 infection rates and Severity", Valente points out that a causal association cannot be drawn between influenza vaccination and COVID-19 testing and clinical outcomes. Valente brings up valid concerns about drawing causal inference from an observational study, however this was not an assertion that was made in our manuscript. Rather, we discuss at length the potential sources of bias in using observational data, and the potential confounding factors that could have influenced the associations that were found.[1(p.4-5)] Our data come from the very beginning stages of the COVID-19 epidemic in the United States, when we were still gathering information to learn about this novel virus, including its risk factors and consequences. The gold standard for establishing causal associations, randomized clinical trials, were not yet in process, thus making observational data pivotal in informing our knowledge on COVID-19. Yusuf and Maiwald point out the advanced planning, approval processes, and funding necessary to carry out rigorous clinical trials, and the need for rapid information to aid in determining how best to treat patients and curb infections during the time of a pandemic.[2]

As an observational study, regardless of the statistical method used, there is always the potential for bias introduced by unobserved confounding, and these studies can never replace prospective randomized trials to prove causality. As we point out in our discussion, people who seek out the influenza vaccine are likely to be more health conscious than those who do not, and may be more apt to follow CDC guidelines, such as masking and social distancing.[1(p.5)] While also observational in nature, a number of other studies have attempted to account for various potential sources of bias in the relationship between the influenza vaccine and COVID-19 infection, and have also found a negative association between vaccination and COVID-19 susceptibility and severity.[3-5] Recently, Zanettini et al. found a potential protective effect of the influenza vaccine on COVID-19 mortality in the elderly population at the county level that remained significant after controlling for a set of 40 potential confounding factors and was robust to the use of several analytic methods. Their main models found that a 10% increase in vaccination coverage among the elderly was associated with a 5% reduction in the number of deaths from COVID-19.[6]

We agree that the best way to mitigate these biases is at the design stage of the study. To this end, prospective studies using random samples from the population are necessary to further elucidate the observed association between influenza vaccination and COVID-19. Currently, the longitudinal Household Influenza Vaccine Evaluation (HIVE) study is an ongoing CDC and NIH funded prospective cohort study that began in 2010 looking at the effectiveness of the influenza vaccine in over 300 households in southeastern Michigan with year-round surveillance of respiratory

infections and severity. This study will be evaluating the incidence of COVID-19 and transmission using RT-PCR and serology testing, especially among people with mild illnesses that may not seek medical care.[7] This and future prospective trials will provide more insight into the potential relationship between the influenza vaccine and COVID-19.

Valente points out the relatively large amounts of missing data in two of our variables, BMI and smoking. Our data were drawn from electronic medical records, in which information on these two variables were often missing, while data on other medical comorbidities such as chronic pulmonary disease, congestive heart failure, diabetes, and hypertension were nearly complete (0.9% missing). We felt it important to include the available information on these variables, as BMI has been found to be an important risk factor for severe COVID-19 infection,[8,9] and smoking is a known risk factor for viral respiratory infections. Rather than lose the information from these patients completely in our analysis, we included them with an indicator variable for missing data so as not to introduce additional selection bias. Valente comments that our finding of never or former smokers being at higher risk for COVID-19 compared to current smokers in multivariable regression raises concern for confounding, however other studies have found the relationship between smoking and COVID-19 to be complex and incompletely understood.[10] Additionally, the associations that we found between higher rates of COVID-19 in older patients and in those with preexisting comorbidities was consistent with associations demonstrated in prior studies.[11,12]

In conclusion, we agree with the primary concern raised by Valente on the need for caution in attributing a causal association to findings from observational studies. Our paper does not claim to establish causality, but rather attempts to explore a potential association between the influenza vaccine and COVID-19 susceptibility and severity. Additionally, these types of observational studies serve an important role in initial investigations of novel associations. These relationships need to be further investigated with prospective and randomized trials.

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