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Ischaemic heart disease, influenza and influenza vaccination: a prospective case control study

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Dear Editor

Influenza vaccination is critical to public health, and vaccine uptake should be widely encouraged. The effects of vaccination on non-influenza-specific outcomes - for example, on risk of acute myocardial infarction (AMI) - nonetheless remain controversial. Several studies reported no difference in either initial myocardial infarction¹ or recurrent coronary events among individuals who received influenza vaccination relative to those who did not.² However, a recent meta-analysis of randomized control trials suggests that influenza vaccination may offer additional benefit by preventing cardiac events among high-risk patients.³

The recent observational study of ischemic heart disease and influenza by MacIntyre et al.⁴ also suggests a substantial benefit of vaccination on AMI in a more general population. The critical result of this study is that influenza vaccination dramatically reduces risk of AMI, reported as an odds ratio (OR) of 0.55 in Table 3.⁴ This Table also reports that influenza infection itself is not associated with AMI. The contrast of these results, derived from a single multivariate regression model, raises several methodological concerns.

The obvious mechanism by which influenza vaccine might prevent AMI is by preventing influenza infection; that is, infection is part of the hypothesized causal pathway between vaccination and AMI. However, because the authors control for infection in the regression model that includes vaccination, they report an effect of vaccination *independent of influenza infection*.⁵ Therefore, the estimated vaccine effect is *not mediated by influenza*. If the authors' implicitly causal interpretation of the vaccine effect (e.g., "influenza vaccination in the study year was significantly protective against AMI") is correct, then the vaccine must operate through another pathway.⁵ What is the proposed, biologically plausible mechanism by which influenza vaccination substantially lowers AMI risk independently of influenza infection itself?

We suggest that uncontrolled confounding is a more plausible interpretation of the strong negative association between vaccination and AMI. Specifically, confounding due to the healthy-user bias (well-documented in studies of influenza vaccines⁶ and other preventive medications⁷) may be responsible for the observed association, leading to exaggerated

estimates of vaccine effectiveness. This is because people who choose to be vaccinated may on average be healthier and have healthier behaviors compared to people who do not get vaccinated, which makes them less likely to have an AMI regardless of receiving the vaccine.

Many of these issues can be clarified using simple causal directed acyclic graphs (DAGs).⁸ In Figure 1(A), we show a proposed DAG relating influenza vaccine status to influenza infection and AMI. In the authors' multivariate model, they controlled for infection and possible confounders of the infection-AMI relationship (Z_1 , indicated by boxes around those variables). In this analysis, the pathway from vaccination to AMI through infection is blocked. Thus, assuming Figure 1(A), the authors are attempting to assess only the effect of vaccination on AMI *that is not mediated by influenza infection itself*. This undefined causal pathway is indicated by the arrow with the question mark. While controlling for Z_1 may have been sufficient to eliminate confounding of the infection-AMI relationship, there are likely *additional* confounders of the vaccination-AMI relationship that are distinct from Z_1 and which are not considered by the authors. These additional confounders are represented by Z_2 , and likely include indicators of "healthy users." Thus, the odds ratio for vaccination reported by the authors, derived from a beta coefficient from a model controlling for infection and Z_1 in Figure 1(A), might be best interpreted as a potentially-biased *direct effect* of vaccination on AMI not mediated by influenza infection.⁵ In contrast, if we were interested in estimating a *total effect* of vaccination on AMI risk (that is, the effect by all pathways, including the direct pathway marked with the question mark and the pathway mediated by infection), we would not control for either infection or Z_1 , but rather only on Z_2 , as shown in Figure 1(B).⁵

We note that these interpretations are necessarily conditional on the hypothesized DAG. If the true causal relationships diverge from what is represented by the DAG, then our interpretations might be in error. However, the underlying point will hold regardless. In general, each research question (in this case the separate effects of influenza infection and vaccination on AMI risk) requires a separate causal model and control of a separate (though likely overlapping) set of variables.⁵

Control selection from outpatient ophthalmology and orthopedic clinics may have also contributed to the healthy-user bias. Controls from outpatient clinics may not represent the exposure distribution of the population from which cases arose. In particular, people attending outpatient clinics may have healthier behaviors compared to the general population and if so, might have had both a higher vaccination rate and a lower risk of AMI. Berkson described a similar case of problematic control selection in the comparison of hospitalized cases to controls with outpatient ophthalmologic refractive errors.⁹

The article by MacIntyre et al. highlights several pervasive challenges in estimating the effectiveness of vaccines and other drugs in studies in which the intervention has not been randomly assigned. While we reemphasize our full support of the authors' conclusion that influenza vaccination is vital to public health, we do not find this evidence concerning the impact of vaccines on AMI risk to be convincing.

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Figure 1.

Causal diagrams showing the confounding control strategy used by the authors (**A**) and the appropriate control strategy for estimating an unbiased total effect of influenza vaccination on AMI (**B**). Boxes around variables indicate inclusion in the multivariate regression model (“control” of the variable).