Letters

- Pneumococcal vaccination and myocardial infarction

Pneumococcal vaccination and myocardial infarction

François Lamontagne and colleagues recently reported an association between receipt of pneumococcal vaccination and a lower risk of myocardial infarction with an adjusted odds ratio of 0.53.[1] Paradoxically, they reported greater protection with more remote vaccination. If these results are to be considered an undistorted reflection of the true protection attributable to vaccination, the vaccine's effectiveness against myocardial infarction would be 47%.[1,2] In other words, about half of incident myocardial infarctions would have to be attributed to *Streptococcus pneumoniae* infections, preventable simply through pneumococcal vaccination. Moreover, the authors' finding of an adjusted odds ratio of 0.33 for vaccination given 2 or more years previously means that up to two-thirds of myocardial infarctions should be preventable in just 2 years through universal pneumococcal immunization at middle age. Unfortunately, there is a much more plausible explanation for the authors' results.

Their results are strangely reminiscent of the approximately 50% reductions in all-cause mortality of elderly adults that were previously promulgated for influenza vaccination but more recently questioned under the lens of healthy-user bias and confounding by indication.[3–5] In other words, immunization may be a marker for factors such as diet, lifestyle and exercise that are not documented in administrative databases of the kind used by Lamontagne and colleagues but that are known to be associated over the long term with risk of diseases including atherosclerosis and myocardial infarction.[6] Moreover, the controls chosen by the authors (patients admitted to a surgical department for a reason other than myocardial infarction) are likely to be a healthier group generally than patients admitted to medical wards, as illustrated in their Table 1.[1]

Extreme caution is required when applying observational designs to administrative databases without full control of established but uncaptured covariates. Attributable risk (and its counterpart, vaccine effectiveness) provides a reality check that can help investigators place improbable findings into stark perspective. Consideration of attributable risk as an initial test of logic should be routine lest we draw phenomenal conclusions from controvertible evidence. Magic bullets are, after all, rare.

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Although patients who had previously had a myocardial infarction were excluded from the study by François Lamontagne and colleagues,[1] some patients who had received the pneumococcal vaccine and had had an acute ischemic event were excluded as well. For example, if a vaccinated patient had had a myocardial infarction 1 month before being admitted to 1 of the medical wards of the hospital for another reason, he would not have participated in the study. Thus, the supposed protective effect of the vaccine would not have been measured.

The authors did not report the number of risk factors (hypertension, dyslipidemia and diabetes) for each patient in the study. There is an increase in cardiovascular risk for men and women who have 2 or 3 risk factors.[2,3] The absence of stratification may have impaired the comparison between the groups. Furthermore, there are other relevant factors, such as a positive family history, that were not evaluated in the study.

It is known that antibody levels decrease 5–10 years after receipt of the pneumococcal polysaccharide vaccine, and this occurs more quickly in some groups than others.[4] This does not fit with the authors' finding that pneumococcal vaccination appeared to have a greater protective effect over time. Given these concerns, the relation between the use of pneumococcal vaccine and reduction of myocardial infarction risk appears to be suspect, despite the authors' suggestion of a strong causal association.

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Two of the authors respond

We thank Danuta Skowronski and colleagues for their comments regarding the potential pitfalls of using administrative databases to estimate vaccine efficacy. Unmeasured covariables, such as smoking, diet or exercise, might have confounded the association between pneumoccocal vaccination and risk of myocardial infarction, as we discussed in our report.[1] However, 2 points require clarification. First, if controls were healthier than cases, the results would have been biased toward the null; this cannot explain the protective effects seen. Furthermore, multivariable adjustment did not change the point estimate of efficacy.

Second, we do not attribute the 50% reduction in the rate of myocardial infarction to prevention of pneumococcal infection; that would be improbable. A more likely explanation is an effect of pneumococcal vaccination on oxidized low-density lipoproteins, which has been demonstrated in animal models.[2] It is possible that the reduction we observed in our study may turn out to be greater than would be seen in further studies; however, given the prevalence of heart disease in Canada, even a modest protective effect would translate into considerable benefit at the population level.

Eduardo Rosa and colleagues are correct: we intentionally excluded patients who had already had a myocardial infarction, as our objective was to test the effect of the vaccine in a primary prevention strategy. The impact of the vaccine in patients with established cardiovascular diseases is worth studying separately, but vaccination is already routinely recommended for this population.

We agree that the apparent increased effectiveness of pneumococcal vaccination over time is intriguing. Our study does not supply a mechanistic explanation for this finding. If the vaccine alters atherosclerotic plaque inflammation, the protective effect could well be measured after the immunogenic effect has passed. We reiterate that prospective validation will determine whether the effect we measured is real and better estimate the true protective efficacy. As cardiovascular disease becomes the leading cause of death worldwide, we urgently need further observational studies (and eventually randomized controlled trials) measuring the protective effect of pneumococcal vaccination in populations at risk of cardiovascular disease.

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