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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 pneumococcal vaccination and risk of myocardial infarction, as we discussed in our report.<sup>1</sup> 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, multi-variable 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.<sup>2</sup> 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 vaccina-

tion in populations at risk of cardiovascular disease.

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