effectiveness against influenzalike illness in people 65 years and older was 35% (19%-47%). Influenzalike illness is relatively nonspecific and includes diseases caused by other respiratory viruses. In the only randomized controlled trial of influenza vaccine in people 60 years and older, the point estimate of influenza vaccine effectiveness against laboratory confirmed disease was higher at 58% (26%-77%).

What the authors have addressed is the effectiveness of influenza vaccination campaigns, rather than influenza vaccines. The previous meta-analysis of influenza vaccine effectiveness and the observational study by Simonsen and colleagues on attributable influenza deaths may both be valid. We agree it is important for this to be sorted out because this argument has a direct impact on assessing influenza vaccine cost-effectiveness.

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Influenza Vaccination Among the Elderly in the United States

Simonsen and colleagues question the effectiveness of influenza vaccination in the elderly because their ecologic analysis found that increases in national influenza vaccine coverage among the elderly beginning in the late 1980s were not associated with decreases in influenza-related death rate estimates. Meta-analyses of studies with data on individual vaccine status have estimated that vaccination is from 27% to 50% effective in reducing influenza-associated deaths. Estimates from meta-analyses are limited by potential selection biases in the observational studies they are based on. Yet conclusions based only on ecologic data are even less robust because no individual-level data are available concerning vaccination status or probable confounders such as the underlying health status of individuals.

We agree with Simonsen and colleagues that influenza-associated deaths substantially increased during the 1990s but think that their conclusions about vaccine effectiveness are not adequately supported. Moreover, one of their key assumptions is incorrect. Simonsen et al reported that the influenza seasons grew shorter during the study period, based on the use of International Classification of Diseases, Ninth Revision code 487. This code for influenza is rarely noted on death certificates and by itself is a poor measure of influenza-associated activity. By con-
In reply

We disagree with Thompson and colleagues’ assertion that our trends study\(^5\) is less robust compared with cohort studies. The strength of our approach is that, unlike cohort studies, we analyzed all deaths in the total elderly US population and are free of the biases to which cohort studies are subject. The comments by Thompson et al are surprising given that they used a similar study design and also found an increase in influenza-related mortality in recent years, which they suggested could be partially explained by aging of the population.\(^2\) Nevertheless, the critique by Thompson et al centers on our modeling assumptions, most of which were addressed in our article, including the duration of epidemic periods. We have provided age-adjusted excess mortality estimates, which addressed the paradoxical observation that mortality rates increased concomitant with a quadrupling in elderly vaccination coverage.\(^1\) If Thompson et al would also adjust their excess mortality estimates, they could test the robustness of our finding that increasing influenza vaccination coverage was associated with less mortality reduction than expected.

Thompson et al next take issue with our conclusion that cohort studies must have overestimated vaccine mortality benefits. But in their numerical example they misinterpret the claims of the cohort studies, which state that influenza vaccination prevents an astonishing 50% of all-winter mortality\(^3,4\) rather than 50% of just the influenza-related (excess) mortality. If we apply the 50% vaccine effectiveness figure from cohort studies to the observation that about 670 000 elderly die during winter months in the United States in recent years,\(^1,2\) we estimate that at 65% vaccination coverage about 323 000 deaths in the elderly are prevented each winter. It should have been easy to spot such a huge mortality decline as vaccine coverage increased from 15% to 65%—but it was not there. We thus maintain our conclusion that there is a huge disconnect between the numbers of influenza-related (excess) deaths and those projected from cohort studies’ estimates of vaccine effectiveness.

Kelly and colleagues, on the other hand, acknowledge this discrepancy and propose that it may be because their cohort study meta-analysis\(^4\) excluded vaccine mismatched seasons such as 1997-1998, when the vaccine probably provided little or no protection.\(^3\) However, influenza-related mortality in that season was not appreciably higher than in surrounding seasons as one would have expected\(^1,2,6,7\); influenza-related mortality still accounted for less than 10% of all winter deaths. Kelly et al also point out that we may be underestimating optimal vaccine benefits owing to a programmatic failure to immunize frail elderly patients at highest mortality risk. We agree, and that is why we put the “disparity hypothesis” forward in our article to explain the observed trends, while also pointing out that this phenomenon could bias cohort studies toward overestimation of vaccine effectiveness.

Ross notes that the elderly can be protected indirectly by vaccinating schoolchildren.\(^8\) He also points out that the elderly pose a particularly difficult challenge for immunization because they may not respond as well as others to the influenza vaccine. Indeed, research is ongoing to elucidate immune senescence with the stated purpose of identifying better strategies and vaccine formulations for successfully immunizing the elderly against influenza. Other possible strategies to reduce influenza-related mortality include indirect protection by...
vaccination of people with frequent and close contact with the elderly and the wider use of influenza antiviral agents.

Ross is not the first to suggest that we should have made policy recommendations according to our findings; however, we do not think that our study alone should form the basis of policy decisions. In particular, we could not rule out a modest mortality benefit, and we did not address the impact of the vaccine on other outcomes such as hospitalization. We want to emphasize that elderly people should continue to receive influenza vaccine. However, given that current vaccination efforts have not substantially reduced influenza-related mortality among the US elderly population as expected, the underlying evidence from cohort studies should be examined more closely for residual self-selection bias while trends studies such as ours should be repeated in other countries.

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Error in Author’s Name. In the article by Chan et al, titled “Risk of Stroke in Women Exposed to Low-Dose Oral Contraceptives: A Critical Evaluation of the Evidence” (2004;164:741-747), one of the authors’ names was spelled incorrectly. Shiphira Ginsburg, MD, MEd, FRCPC, should have been spelled Shiphra Ginsburg, MD, MEd, FRCPC.