

CORRESPONDENCE



Effectiveness of Influenza Vaccination

TO THE EDITOR: In their article about the effectiveness of influenza vaccination in the community-dwelling elderly (Oct. 4 issue),¹ Nichol and colleagues define the influenza season as the time from the reporting of the first isolate to the reporting of the last isolate, for each region and season. We are concerned that their analysis included deaths early and late in the season that were almost certainly unrelated to influenza and that could not have been prevented by vaccination. The actual period of elevated risk for influenza-related death is substantially shorter than the interval between the reporting of the first isolate and that of the last isolate. In two West Coast cities, the period of predominant influenzavirus transmission accounted for less than half of the total time between the reporting of the first and last seasonal isolates.² The same is true in Wisconsin, where we have prospectively tested patients in a population-based cohort over three seasons. Nichol et al. should consider additional analyses to determine whether the benefit of vaccination with respect to mortality varies over time within each influenza season. If the effect is real, the benefit should be greatest during the 4-to-8-week period of maximum virus circulation and should

be much lower at the beginning and end of the season.

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TO THE EDITOR: Nichol et al. report that elderly persons receiving influenza vaccine have lower risks of death and hospitalization for pneumonia or influenza than nonvaccinated elderly persons during the influenza season. In an 8-year study of a similar population of members of a health maintenance organization, we found risk reductions among vaccinated elderly persons during the influenza season to be essentially identical to those reported by Nichol et al. (Table 1).¹ However, we also found even greater reductions before the influenza season. During that period, vaccination is not expected to have an effect, so any apparent vaccine benefit represents bias due to the preferential use of vaccine by healthier elderly persons. Instead of using a hypothetical-unmeasured-confounder model, which in their study included restricted and weak assumptions about the strength of confounding^{2,3} and did not consider multiple confounders,⁴ Nichol et al. should have evaluated the actual influence of bias in their study by calculating the relative risks during all the noninfluenza control periods, thus filling in the blanks in Table 1. In the absence of

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Table 1. Relative Risk of Death or Hospitalization among Vaccinated Elderly Persons vs. Unvaccinated Elderly Persons in the Studies by Nichol et al. and Jackson et al., According to Period.

| Outcome | Relative Risk (95% CI)* | |
|--|-------------------------|------------------|
| | Nichol et al. | Jackson et al. |
| Death from any cause | | |
| Before influenza season | Not reported | 0.36 (0.30–0.44) |
| During influenza season | 0.52 (0.50–0.55) | 0.51 (0.47–0.55) |
| After influenza season | Not reported | 0.66 (0.61–0.72) |
| Hospitalization for pneumonia or influenza | | |
| Before influenza season | Not reported | 0.65 (0.53–0.80) |
| During influenza season | 0.73 (0.68–0.77) | 0.71 (0.65–0.78) |
| After influenza season | 0.94 (0.74–1.19) | 0.82 (0.73–0.92) |

* Relative risks were adjusted for age, sex, and disease covariates. CI denotes confidence interval.

such analyses, and given the existing evidence of extensive bias,¹ the results reported by Nichol et al. should be interpreted cautiously.

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TO THE EDITOR: Nichol et al. did not succeed in eliminating frailty bias in their observational studies. As argued previously,^{1,2} given that only approximately 5% of all wintertime deaths among elderly persons are attributable to influenza, the conclusion that influenza vaccination can prevent half of all wintertime deaths is simply not plausible. Frailty bias is the most likely explanation of this result.

Application of four criteria from our recently published bias-detection framework² (vaccine match, season severity, age, and outcome specificity) indicates profound bias in the data presented by Nichol et al. (Table 1). The authors do not present the data needed to apply our crucial fifth criterion, seasonality.^{2,4} If vaccination is found to be effective in the weeks before each influenza epidemic starts, bias must be present.^{2,4} The au-

Table 1. Application of a Bias-Detection Framework to Estimates of Vaccine Effectiveness Presented by Nichol et al.*

| Criterion | Setting in Which Higher Effectiveness Is Expected | Effectiveness Estimate | Setting in Which Lower Effectiveness Is Expected | Effectiveness Estimate | Evidence of Overwhelming Bias |
|---------------------------------|---|------------------------|--|------------------------|-------------------------------|
| | | % | | % | |
| Seasonality | Peak influenza season | Not given | Period before influenza season | Not given | Cannot resolve |
| Vaccine match (AH3N2 component) | Well-matched seasons (all except 1992–1993 and 1997–1998) | 27 | Mismatched seasons (1992–1993 and 1997–1998) | 22–38 | Yes |
| Season severity† | Severe season (1998–1999) | 28–36 | Mild season (1991–1992) | 38 | Yes |
| Age | Healthy people 65–70 yr | 20 | Healthy people >80 yr | 40–50 | Yes |
| Outcome specificity‡ | Hospitalization for pneumonia or influenza | 27 | Deaths from any cause | 48 | Yes |

* The bias-detection framework is described by Simonsen et al.² The estimates of vaccine effectiveness listed are for effectiveness against hospitalization for pneumonia or influenza.

† Severe and mild seasons were those with high and low excess mortality, respectively, according to the Centers for Disease Control and Prevention.³

‡ Hospitalization for pneumonia or influenza is an outcome of moderate specificity, whereas death from any cause has a low specificity (approximately 5%, since 95% of deaths are unrelated to influenza).

thors' postepidemic analysis is inadequate, because the bias decreases over time. We urge the authors to report vaccine-effectiveness estimates for the period before the influenza season or for the very beginning of the season, which would clarify the level of bias in their studies.

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3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179-86.
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TO THE EDITOR: Influenza vaccination has been found to reduce the risk of influenza in the elderly.¹ Nichol et al. report that influenza vaccination was associated with a 48% reduction in the risk of death from any cause among community-dwelling elderly persons. However, seasonal influenza has been reported to result in a substantially smaller percentage of deaths from any cause among the elderly.²⁻⁴ How can influenza vaccine prevent a much larger percentage of deaths than are caused by the disease that the vaccine is supposed to prevent?

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THE AUTHORS REPLY: Belongia et al. recommend analysis of peripeak influenza data. Such analyses, even if possible, might be misleading for bias detection. We primarily relied not on community-specific surveillance but on regional surveillance that was passive with uneven coverage. Within regions, peaks vary widely. Also, severe complications can occur weeks after the peak. Peak analyses exclude some outcomes and will result in lower absolute risk reductions but not always higher relative risk reductions, as compared with other periods. In a study of healthy adults, the effectiveness of influenza vaccine, measured as the relative risk reduction, for absenteeism due to respiratory illness was nearly identical for the peak influenza period, the total influenza period, and the total outcome period.¹

Nelson et al. and Simonsen et al. suggest the analysis of data from the preinfluenza season. However, analyses of mortality before the influenza season can introduce biases.² To minimize bias, our subjects had to be alive on day 1 of the influenza season. A 2-year longitudinal analysis of more than 120,000 subjects showed significant vaccine effectiveness against hospitalization for pneumonia or influenza during the 1998–1999 and 1999–2000 influenza seasons but not the 1999 and 2000 summer seasons (unpublished data), findings that confirm the implications of our original summer analyses and argue against bias.

In their table, Simonsen et al. report the results of the application of their bias-detection framework³ to our data. The source of the effectiveness estimates for hospitalization for pneumonia or influenza for good-match influenza vaccine as compared with poor-match vaccine that they ascribe to our study is unclear. The actual vaccine-effectiveness estimate for good-match vaccine as compared with poor-match vaccine (29% [95% confidence interval, 24 to 34] vs. 25% [15 to 34]) does not support their conclusion. In addition, our summer analyses (relevant

Table 1. Limitations of the Bias-Detection Framework.

| Criterion | Assumption | Limitations of Assumption |
|---------------------|--|--|
| Vaccine match | Vaccine effectiveness with good match greater than effectiveness with poor match | Effectiveness of poor-match vaccine depends on many factors and may often, but not always, be lower than that of good-match vaccine. In a study of healthy adults, the effectiveness of poor-match vaccine was 77%, ⁴ whereas that of good-match vaccine is typically 70 to 90%. |
| Season severity | Effectiveness during severe season greater than effectiveness during mild season | Absolute risk reductions during severe seasons may be greater than those in mild seasons. However, observed relative risk reductions (measured in terms of vaccine effectiveness) depend on the percentages of outcomes caused by influenza, the degree of vaccine-circulating virus match, and other factors; vaccine effectiveness during a mild season could be greater than that during a severe season. |
| Age | Effectiveness in younger persons greater than effectiveness in older persons | Vaccine nonresponse is incompletely understood; studies looking at age have had conflicting results. ⁵ Other factors, such as nutritional status or frailty, may be more important. |
| Outcome specificity | Effectiveness against more-specific outcome greater than effectiveness against less-specific outcome | Vaccination may be more efficacious against more-severe outcomes. If clinical case definitions are less specific for more-severe outcomes than for less-severe outcomes, then observed vaccine effectiveness could be greater for those more-severe but less-specific outcomes. |

to their seasonality criterion) do not support the claim of bias. Finally, limitations in the assumptions restrict their framework's usefulness (Table 1).

Braun et al. ask about reconciling our vaccine-effectiveness estimates with excess-death estimates. Excess-death estimates depend on the models used. These estimates are imprecise and indirectly measured and may exclude deaths from influenza that contribute to the "baseline" death rates. The total number of influenza-associated deaths is unknown. In addition, excess-death estimates apply to the entire U.S. population. Our results may not be generalizable to all elderly. For instance, nursing-home residents, who make up less than 5% of the elderly in the United States but who account for more than 30% of the deaths, were not included in our study.

Concerns about residual confounding are important. Our sensitivity analyses modeled a prevalent confounder associated with an increased risk of an outcome that is at least as high as that seen with high-risk status or previous hospitalization. As expected, the resulting vaccine-effectiveness estimates were lower than in the overall analysis, but they were still significant. An additional multiple-confounder sensitivity analysis confirmed that only a large and unlikely combination of effects would eliminate vaccine effectiveness with respect to death: multiple independent confounders, combined to create a single normal confounder moderately associated with vaccination ($1/2$ SD between the vaccinated and

unvaccinated groups), would have to have an association with death that was more than 2.35 times that with age for vaccine effectiveness to be reduced to 0%. Since age is generally the strongest predictor of death, together with the other predictors already included in our models, this is a large association to be required for missing confounders. Despite uncertainties about precise levels of benefit, our conclusions are robust: influenza vaccination in community-dwelling elderly persons can prevent hospitalization and death.

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