

EDITORIALS



Influenza — The Goal of Control

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Annual administration of inactivated influenza vaccine to older adults has long been recommended by public health authorities.¹ The risks of influenza-related complications, hospitalizations, and deaths increase with age, as does the prevalence of underlying medical conditions. Prospective, randomized, controlled studies have demonstrated that inactivated vaccine is protective against laboratory-confirmed influenza in young adults and, according to much more limited data, in older adults as well.²

Since the vaccine reduces the risk of influenza, it would be reasonable to expect that vaccination would also reduce the risks of influenza-related complications in recipients. Demonstrating this type of effect in a prospective, randomized, placebo-controlled trial in the elderly would be extremely difficult. An alternative approach is to use health care databases in which information about vaccine status can be linked to outcomes such as hospitalizations and death. Such studies have consistently shown that influenza vaccination in the elderly is associated with substantial reductions in the risk of wintertime or seasonal pneumonia-related and influenza-related hospitalizations and deaths. Surprisingly, vaccination is also associated with reductions in deaths from any cause³ and with reductions in the rates of heart attack and stroke.⁴ The implications of these studies are not only that the vaccine is effective in the elderly but also that influenza must account, either directly or indirectly, for a substantial proportion of all the wintertime deaths in the elderly.

From 1988 to 1992, the Health Care Financing Administration performed a demonstration project in which influenza vaccination was provided free in certain communities and not in others, and influenza-related morbidity and mortality were

compared. This project concluded that influenza vaccination was a beneficial and cost-saving intervention in the elderly,⁵ and in 1993, influenza vaccine became a covered benefit under Medicare Part B. Because of improved funding, and also because of the increasing evidence of vaccine effectiveness, the proportion of all persons over 65 years of age in the United States who received influenza vaccine increased between 1986 and 1996 from about 30% to more than 60%.

Given the demonstrated effectiveness of the vaccine, one might have expected that as the rates of vaccination increased, there would be a corresponding decrease in flu-related hospitalizations and deaths. Instead, the opposite has occurred, with winter hospitalizations and deaths increasing during this period.⁶ There are many possible explanations for this phenomenon, but this observation has called into question previous studies showing large effects on the rates of death from any cause. Many of the previous cohort studies have been limited in that they analyzed only one or two seasons or were conducted at a single site, since reported morbidity due to influenza may vary significantly by season and region.⁷ The study reported by Nichol et al. in this issue of the *Journal*⁸ addresses many of these concerns and increases our confidence in the benefits of influenza vaccination for older adults.

The investigators analyzed the effect of influenza vaccination during 10 influenza seasons in three geographically different health maintenance organizations (HMOs). Overall, these HMOs had vaccination rates of about 58%, although whether this rate changed over the course of the seasons analyzed is not reported. After controlling for covariates, Nichol et al. found that vaccination was associated with an average reduction of 27% in

the risk of hospitalization for pneumonia or influenza during influenza seasons, and with a 48% decrease in the risk of death from any cause. Reductions in risk associated with vaccination were observed during multiple influenza seasons, including seasons dominated by influenza H3, H1, or B viruses, and were similar among the three participating HMOs. The only exceptions were slight decreases in the effectiveness against hospitalizations in the 2 years when there was an antigenic mismatch between the vaccine and the predominant circulating virus. These results convincingly dispel concerns that the previous studies were artifacts of a specific influenza season or unique population.

A more difficult issue to deal with is the potential for confounding by factors not included in the database. A major factor would be functional status.⁹ For example, those who were very frail might be less likely to receive vaccine but might also be much more likely to die during the subsequent winter. Or, persons who choose to be vaccinated might also be those who are more compliant with medications, exercise regularly, or are more likely to seek medical care early in an illness. The vaccinated group would then have a lower mortality rate, but it would not specifically be the result of vaccination.

If this type of bias regarding healthy vaccinees were present, then the relative protection should persist in the summer months, when influenza is not present. A previous study using a managed-care database showed such an effect, suggesting that a healthy-vaccinee bias does affect the estimates of the efficacy of influenza vaccine.¹⁰ However, in the current study there was no difference in summertime hospitalizations. This is consistent with a study that used the instrumental variable method to control for self-selection and also showed significant benefit of influenza vaccine against influenza-related hospitalization.¹¹ Another feature that suggests that the protective effect is real is that it varies by the degree to which the vaccine and epidemic strain match.

Nichol et al. have also determined that if an undetected confounder were present, it would have to be very prevalent and have a large effect to account for the effectiveness demonstrated in the study. Using a sensitivity analysis, they showed that even if a factor present in 60% of the population had the effect of decreasing the rate of vaccination by 50%, while also increasing the risk

of influenza outcomes by a factor of 3, vaccination would still have a relative effectiveness of at least 7% for hospitalization and 33% for death.

Overall, this study provides additional support for the current strategy to vaccinate elderly adults. The methodologic issues are important to debate, and doubt about the precise magnitude of the benefit of vaccination in this age group remains. However, there is no doubt that influenza is harmful and that the vaccine is beneficial and should be used widely. At the same time, it is clear that inactivated influenza vaccine is not a perfect solution to the problem. About half of the wintertime hospitalizations and deaths observed in this study occurred in the vaccinated population. Some of these deaths were probably due to other viruses, such as respiratory syncytial virus, that can mimic influenza,¹² but many probably represent vaccine failures. Influenza vaccine is less immunogenic, and probably less effective, in older persons than in young healthy adults, and the development of safe but more immunogenic and effective vaccines for the elderly is an important goal.

In the meantime, influenza cannot develop in elderly persons if they are not exposed to influenza virus from others. Elderly persons have frequent contact with health care workers and others in the health care system. Those people often report to work even when they are not feeling well and can easily serve as vehicles of doom for their unsuspecting patients. This is why the extraordinarily low rates of vaccination of health care workers in the United States are so appalling.¹³ The implementation of programs that bring the vaccine directly to the workplace, as well as of policies that require mandatory vaccination (with informed declination), can markedly increase vaccination rates¹⁴ and should be considered by all health care institutions.

The most intriguing possibility is that high vaccination rates among the general population, particularly among children, might interrupt transmission and provide secondary protection to those who cannot be protected directly by vaccination. A similar phenomenon has been observed for pneumococcal disease.¹⁵ It has been suggested that vaccination of children results in reduced rates of influenza in the elderly.¹⁶ Although these studies are not definitive, they may be pointing toward a more effective strategy.¹⁷ Ultimately, the key to optimal control of the devastating effects of influenza in elderly persons may be found in

our ability to effectively vaccinate the youngest members of the population.

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Treatment of Neuropsychiatric Symptoms in Patients with Dementia

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Although cognitive deficits are the clinical hallmark of dementia syndromes, noncognitive symptoms are common and can dominate the disease course. These include a range of neuropsychiatric symptoms, such as agitation, delusions, hallucinations, repetitive vocalizations, and wandering. Neuropsychiatric symptoms develop in as many as 60% of community-dwelling patients with dementia¹ and in more than 80% of patients living in nursing homes. These symptoms are associated with greater morbidity, higher costs of care, and reduced quality of life for the patient as well as increased burden and depression for the caregiver. Indeed, neuropsychiatric symptoms are a primary predictor of nursing home placement.² Thus, interventions aimed at treating these symptoms could have a tremendous effect on patients, caregivers, and society.

The Food and Drug Administration (FDA) has not approved any medication for the treatment of neuropsychiatric symptoms in patients with dementia. However, off-label use of medications, especially antipsychotics, is common practice. Several studies have suggested that cholinesterase inhibitors may reduce the severity of neuropsychiatric symptoms among patients with dementia. Although some placebo-controlled trials and a meta-analysis of many cholinesterase inhibitors³ have shown statistically significant differences favoring their use, the magnitude of effect has been small and of questionable clinical significance.

In this issue of the *Journal*, Howard and colleagues present the findings of an ambitious randomized, controlled trial intended to determine whether treatment with donepezil (an FDA-approved and commonly prescribed cholinesterase