If You Could Halve the Mortality Rate, Would You Do It?

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(See the article by Hak et al. on pages 370–7)

THE CURRENT STATE OF AFFAIRS

From approximately November through March of each year, a highly transmissible biological agent infects millions of Americans, leading to an estimated 65 million persons who develop symptomatic illness, 30 million who seek medical care, 300,000 who are hospitalized, and 25,000 who die—the vast majority of whom are elderly [1–3]. This scenario is repeated year after year, despite the availability of a safe, effective vaccine and safe, effective antiviral drugs that are capable of both preventing and treating infection. The annual cost associated with these yearly epidemics in the United States is $12 billion. Readers may at first be surprised to learn that this biological agent is the influenza virus. More surprising is the evidence that health care workers often fail to protect patients with the available vaccine and antiviral agents.

It has taken almost 2 decades to move from a 20% influenza-vaccination coverage rate for persons aged ≥65 years to a 60% coverage rate, despite Medicare coverage of influenza vaccination during this period. This slow rate of coverage has occurred even though national recommendations have been in place for the universal use of influenza vaccine in the elderly population since the 1960s. An even higher goal has been set by the US Public Health Service: to increase influenza and pneumococcal vaccination rates among individuals aged ≥65 years to a 90% level.

In this issue of Clinical Infectious Diseases, Hak et al. [4] report the results of a serial cohort study conducted over 2 influenza seasons that assessed the risk of hospitalization or death due to influenza and the effectiveness of influenza vaccine among healthy and high-risk elderly members of 3 managed-care organizations scattered across the United States. A total of 122,974 participants were evaluated during the 1996–1997 influenza season, and 158,454 participants were evaluated during the 1997–1998 season. Influenza vaccination was associated with a 48% reduction in hospitalization or death during the 1996–1997 season and a 31% reduction during the 1997–1998 season. Although these benefits extended to all subgroups of risk, the absolute risk reductions were 2.4–4.7-fold higher among high-risk subjects (including subgroups of patients with heart and lung disease, diabetes, immunosuppression, and other comorbid conditions) than they were among healthy elderly subjects. The 1996–1997 influenza season was characterized by widespread H3N2 influenza A/Wuhan-like virus circulation throughout the United States, which was well matched with the strains of influenza included in the influenza vaccine available that year. In contrast, the 1997–1998 influenza season was characterized by widespread H3N2 influenza A/Sydney virus circulation, which was poorly matched with the available vaccine that year. Although reduced rates of hospitalization and death were seen in 1997–1998, significant protection was still observed. These findings were true despite the fact that vaccinated participants in that study were older and more likely to have high-risk medical conditions than were the unvaccinated cohorts.

CONFIDENCE IN THE FINDINGS

Given the magnitude and importance of these findings, how confident can we be that influenza vaccine really did reduce the mortality rate by 38%–50% during the study period? Replication of data in other settings by other investigators and over a
period of time creates confidence in the results and is among the hallmarks of science. In this regard, it is reassuring that the findings of Hak et al.’s study [4] are not unique, nor do they differ from the results of other similar studies, thereby strengthening the validity of the currently reported findings. In addition, the study was essentially repeated in 2 different influenza seasons, and the similar results found in both studies strengthen confidence in the validity of the findings.

Nichol et al. [5] reported similar results in a series of papers. A 1994 study examined influenza vaccine efficacy during 3 influenza seasons (1990–1991, 1991–1992, and 1992–1993) in a single large managed-care organization. Reductions in the rate of hospitalization and mortality were 48%–57% and 39%–54%, respectively, and the rates were consistent during the 3 years studied. In addition, vaccination was associated with direct mean savings of $117 per person vaccinated. Later, those authors reported the results of a similar serial cohort study that involved all elderly members (age, ≥65 years) of a managed-care organization over 6 influenza seasons, again with similar findings (a 30% decrease in hospitalizations and a 50% decrease in all-cause mortality among those vaccinated) [6]. Essentially identical results were found in a study of a subgroup of elderly persons with chronic lung disease [7]. In a recent study of 3 large health-maintenance organizations (HMOs) over a 2-year period, investigators found that hospitalization rates were reduced by 20% among vaccinated subjects, and the mortality rate decreased from 35% to 61%, depending on the year [8].

Other researchers have also used similar study designs with nearly identical results. The first study [9] that examined the effect of influenza vaccine on hospitalization and mortality rates in the elderly population was published in 1980 and used a methodology similar to that of Hak and colleagues. In that first study, influenza vaccine was associated with a mean reduction in the rate of hospitalization of 72% (range, 31%–100%) and a reduction in the mortality rate of 87% (range, 52%–100%) [9]. Mullooly et al. [10] studied elderly members of an HMO using a population-based, case-control design over 9 influenza seasons and found nearly identical rates of reduction in hospitalization among vaccinated subjects. Many other studies have demonstrated the safety, efficacy, and cost-effectiveness of influenza vaccine in elderly individuals and in healthy working adults [5, 11–18].

ARE THERE ANY SIGNIFICANT LIMITATIONS TO THE STUDY?

Hak et al. [4] used a serial cohort design, and, although this is the strongest observational study design available, it has biases that would be obviated by the use of a randomized design. However, a randomized study design would be difficult and expensive to perform, making an observational study design the only feasible method when one includes such large numbers of subjects (>150,000 in the current study) observed over a multiyear timeframe. Nonetheless, the nature of this design precludes blinded subject randomization; therefore, it is always possible that biases, although unintended, may significantly influence the study results. However, biases such as vaccine status misclassification, other important clinical outcomes or comorbidities, and concomitant pneumococcal vaccine status would likely slant the study toward finding lower benefits than reported, unless there was a systematic failure to vaccinate sicker subjects. In fact, the vaccinated cohorts had a statistically significant higher prevalence of high-risk conditions, which further strengthens the clinical importance of the findings.

WHAT ARE THE IMPLICATIONS OF THESE FINDINGS TO THE CLINICAL CARE OF PATIENTS?

The magnitude and importance of the results of Hak et al.’s study [4] and those of the other studies briefly reviewed above can no longer be ignored by individual physicians or by the health care institutions that care for elderly patients. Studies performed over 2 decades, across multiple geographic settings, and involving common high-risk medical subgroups have consistently identified highly significant health and economic benefits to influenza vaccination of elderly persons. The data are clear: vaccination of elderly persons, whether they are healthy or have high-risk, chronic medical conditions, saves lives and decreases hospitalization rates. In turn, this reduces suffering and health care costs. We must engage in the hard work of teaching all members of the health care team and all elderly and high-risk patients the personal and societal importance of annual influenza vaccination.

PHYSICIANS AND THE HEALTH CARE SYSTEM AS A BARRIER TO SAVING LIVES

It is clear that an important responsibility rests with physicians and health care systems in achieving high influenza vaccine coverage rates in the elderly population. Sadly, health care providers as a whole may actually be a barrier to preventing death and hospitalization resulting from complications of influenza. As provocative as this may sound, no other conclusion can be discerned from the data at hand. Physicians and health care systems have long been aware of the benefits of the influenza vaccine, because the advantages have been repeatedly demonstrated in high-quality clinical and population-based studies for ≥2 decades. Despite long-standing national recommendations that make influenza vaccination the standard of care, progress in improving influenza coverage rates has been unacceptably slow at best, taking decades to achieve coverage rates of 60%. If an equally safe and effective vaccine to prevent HIV infection were available next month, would it take us decades to offer it to 60% of the at-risk population?
NEXT STEPS: HOW MIGHT WE ACHIEVE UNIVERSAL INFLUENZA VACCINATION OF THE ELDERLY POPULATION?

Multiple studies have demonstrated that achieving high rates of influenza coverage are possible both in ambulatory and hospital settings. Hospitals can initiate standing order programs and allow nurses to screen and vaccinate patients against influenza and pneumococcal disease without a physician’s order. Clinic-based physicians can do the same and can develop workable office systems designed to increase vaccination coverage rates. Such strategies have been reviewed in the literature and include reminder systems, influenza clinics, standing order programs, and others [19–24]. Of importance, achieving influenza vaccination rates of ≥90% will require Medicare and other third parties to reimburse physicians fairly for the cost of the vaccine and its administration—a particular divisive issue, in view of the currently insufficient reimbursement rates and preliminary information that reimbursement may be further decreased. It will be difficult to enlist physicians in a major effort to increase vaccination rates if they must bear the actual cost of doing so themselves. In addition, manufacturers, federal agencies (such as the US Food and Drug Administration and the National Institutes of Health), and academic investigators will need to ensure adequate influenza vaccine availability and the development of new vaccine products. A safe and effective nasal spray vaccine, for example—particularly if it is available over the counter—is very likely to increase vaccination rates by reducing inconvenience barriers. Finally, we must devise and learn how to achieve high influenza vaccination rates for the eventualty of the next influenza pandemic and for the possibility of use of bioengineered influenza as a bioweapon of mass destruction. Now is the time to “get it right” and to begin the process of saving thousands of lives.

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References