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Commentary: Benefits of influenza vaccine in US elderly—new studies raise questions
W Paul Glezen1* and Lone Simonsen2

During the period from 1989 to 1997 the vaccination rate for elderly persons >65 years of age in the US increased from 30 to 67%.
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at greater risk for complications of influenza than their unvaccinated cohorts. The apparent 50% reduction in mortality is remarkable because the wintertime excess all-cause mortality that might be attributed to influenza was found to be <10% of total wintertime deaths.1,3 The finding that influenza vaccine protection in these observational studies exceeded any possible expectation requires some explanation.

A partial explanation for this paradox is provided by the studies reported in this issue of the Journal by Jackson and her colleagues who have examined the bias that may occur from evaluations of influenza vaccine effectiveness in large HMO populations of persons >65 years of age who elect to receive or not receive the influenza vaccine. They conclude that elderly who choose to take the vaccine are, contrary to the cohort studies cited above, in better health than those who fail to get the vaccine.5,6 The first study compared total wintertime mortality and pneumonia hospitalization rates in the pre-epidemic period (September 1 to the beginning of the epidemic), the epidemic period defined by virus surveillance, and the post-epidemic period for both vaccinated and unvaccinated elderly patients enrolled in a large managed care programme.5 The relative risk (RR) of death for vaccinated compared with unvaccinated patients was 0.39 before the influenza epidemic, 0.56 during the epidemic, and 0.74 after the epidemic. Adjustment for co-morbidities listed on the administrative data file, as usually done by authors of cohort studies, did not substantially change the RRs. Therefore, persons who were unvaccinated had a pre-existing higher risk for death and hospitalization before the influenza epidemic that essentially nullifies the apparent protection (RR = 0.56) during the influenza epidemic.

The explanation for the overall higher mortality and morbidity (not just during the influenza epidemic) for the unvaccinated
patients is presented in the second report that describes a nested case–control study of 252 patients who died during the 1997–98 influenza season. Medical records were examined for evidence of functional limitations, such as needing assistance for bathing. These indicators of frailty were highly prevalent among cases and were associated with a decreased likelihood of vaccination among the controls. Adjustment for functional limitations resulted in an estimate of the RR of death in vaccinated patients, compared with unvaccinated patients, that was closer to the null (RR = 0.71) compared with the unadjusted estimate (RR = 0.56). In contrast, adjustment for co-morbidities listed on the administrative data file moved the estimate farther from the null (RR = 0.45). The studies showed that the unvaccinated patients were frailer and more often had limited mobility. These limitations made health care less accessible and reduced opportunities for vaccination. The bias introduced by these factors leads to substantial overestimation of vaccine benefits.

The reports from Jackson et al. imply that even within a large managed care organization, some patients may not access care optimally as evidenced by fewer co-morbidities noted on administrative data files and failure to receive influenza vaccine. This difference in delivery of care can occur within a large HMO, the discrepancies in access to health care would be expected to be more pronounced in the general population. This, in fact, is the case. In Harris County, Texas, the hospitalization rates for acute respiratory conditions were ten times higher for uninsured patients compared with those with health insurance. Influenza infection was the most common respiratory virus infection associated with these hospitalizations. Furthermore, the reports of Jackson et al. dictate that better studies of the benefits of influenza vaccine in elderly and other high-risk groups are necessary to guide strategies for influenza control. Clinical endpoints tend to be non-specific and attenuate estimates of effectiveness. Laboratory confirmation of influenza virus infection for at least a sample of the two comparison groups would improve the ability to detect true protection. For example, the recent study by Falsey et al. determined viral aetiologies for elderly patients hospitalized with pneumonia. By comparing vaccine status of subjects with proven influenza virus infections to a group with respiratory syncytial virus infection it was possible to estimate that vaccine provided ~30% protection against influenza-associated hospitalization. With new technologies available, studies such as this could be expanded to demonstrate efficacy of the influenza vaccine for prevention of both hospitalizations and death in the elderly.

The unfolding picture of increasing influenza mortality and hospitalization rates and this new demonstration of serious bias and overestimated vaccine benefits in cohort studies clearly show that better vaccines are needed to protect elderly patients who are particularly vulnerable to complications of influenza. In the meantime, recognition that protection in the vulnerable groups may only be marginal with currently available vaccines, other strategies should be considered. Many studies have shown that school children have the highest rates of infection with influenza each year and that they are the major spreaders of influenza in the community and introducers into the household. Immunization of school children, therefore, will reduce exposure of vulnerable patients to influenza. This concept is imbedded into current recommendations that include vaccination of household contacts and caretakers of high-risk patients, and health care workers. With these recommendations already in place, it is not a major extension to move towards a universal recommendation that would include all school children. One of the problems with the current risk-based recommendations is that high-risk persons are relatively inaccessible; no improvement in vaccine coverage has occurred since 1997. School children could be accessible through school-based vaccine clinics allowing rapid administration of vaccine to large numbers representing all socioeconomic groups within a short period of time. Competition for vaccine doses with high-risk and elderly patients does not need to be an issue, because the available live, attenuated influenza vaccine has been licensed for healthy children and adults, 5–49 years of age. This allows for the continued use of inactivated vaccine for the prioritized high-risk groups whose protection can be enhanced by immunization of the major transmitters of the virus with the live, attenuated vaccine.

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