

Subject: Forthcoming review in Lancet Infectious Diseases “Mortality benefits of influenza vaccination in elderly people: an ongoing controversy”

9/18/07 DRAFT

Background

Influenza vaccination policy aims not to reduce transmission, but to limit death and hospitalization following influenza infection by targeting people at high risk for such severe outcomes, including anyone with chronic health problems and seniors.

Influenza causes an average of 36,000 deaths each winter. During seasonal epidemics, 80-90% of influenza-related deaths occur among elderly people. Influenza-related deaths make up an average of only 5% of all deaths that occur among seniors each winter.

Data from randomized, placebo-controlled clinical trials of influenza vaccine in seniors are few. They indicate that vaccination is reasonably effective at preventing influenza illness in younger seniors (age 60-69) but effectiveness may decline substantially with increasing age after 70.

Many cohort and other observational studies have consistently reported that influenza vaccination reduces the total risk of winter death from any cause among seniors by a whopping 50%—an odd result that is fully 10 times the seasonal mortality burden as measured by CDC.

Key findings: The review by Simonsen et al discusses several types of studies that bear on the question of how well vaccination can prevent influenza-related mortality in seniors, including clinical trials, observational studies and excess mortality trends studies.

The authors resolve the paradoxical findings from the various study types. They explore recent evidence that cohort studies have grossly overestimated the ability of influenza vaccination to cut mortality among seniors by failing to adequately control for selection bias. They hypothesize that a small subset of frail seniors who are far more likely than other seniors to die in the coming winter are also more likely to end up in the “unvaccinated” cohort, and that this imbalance led to the exaggerated claims of vaccine benefits. Their hypothesis is supported by recent reports that the highest measures of vaccine benefits in cohort studies occur before influenza epidemics begin.

The authors demonstrate that, once the flawed cohort studies are set aside, the remaining evidence supporting vaccination of seniors at risk is limited to a handful of studies, and that these found limited vaccine benefits. None were designed or statistically powered to provide evidence for seniors aged 70 years and older—precisely the group that suffers most influenza-related deaths.

The authors propose a framework for identifying unadjusted bias in cohort studies. This framework is intended as a way forward in terms of improving the accuracy of vaccine effectiveness estimates from cohort studies. It can be used to guide design more appropriate future observational studies, and to re-examine bias in published studies..

Talking Points

- **The authors DO point out that little is known about influenza vaccine benefits in seniors aged 70 years and older – the group that suffers the lion’s share of influenza related deaths.**
 - The evidence base of cohort studies had systematically and greatly overestimated vaccine benefits. The remaining studies are not conclusive but suggest there is ample room for improvement.
- **The authors DO NOT suggest that elderly people forgo their annual influenza vaccination.**
 - Influenza is a serious disease that causes substantial mortality among the elderly. Even a partially effective vaccine is better than none at all.
- **The authors point to the need for better flu vaccines for seniors, and other strategies for reducing severe influenza outcome among this group.**
 - Improved vaccines may include adjuvanted preparations, higher vaccine doses, and other kinds of vaccines (e.g. live-attenuated).
 - Other strategies include:
 - *Universal immunization*: protect elderly indirectly through herd immunity; perhaps focus on children
 - *Better targeting*: identify and vaccinate frail elderly people at highest risk of severe influenza outcomes
 - *Use Influenza Antivirals*: use antivirals more aggressively for treatment and prophylaxis in seniors and their contacts.
- **NIH already funds research aimed at improving vaccines for seniors**
 - Immune senescence—reduction in response to vaccines with increasing age—is a well established phenomenon.
 - NIH funds several projects on immune senescence and influenza vaccine, including an NIAID grant on stimulating a more vigorous Th1 response in the elderly with novel booster strategy and several NIA grants studying cellular immune response to influenza in seniors
- **Please note that influenza-related (*excess*) all-cause mortality is very different from all-cause mortality; this is often misunderstood**
 - Excess all-cause mortality is a measure of the winter-seasonal *deaths* above a seasonally adjusted baseline and a measure of deaths specifically attributable to influenza. Excess deaths (~32,000 annually in seniors according to CDC) contributes only ~5% of all winter deaths in seniors
 - All-cause mortality is just that—death from any and all causes.
 - The cohort studies report that flu vaccine reduces the risk of all-cause mortality over the winter by 50%. That claim simply doesn’t stand up.