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Influenza vaccination and mortality benefits: New insights, new opportunities

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ABSTRACT

Influenza vaccination control strategies in most countries rely on vaccination of seniors and other high risk groups. Although placebo-controlled randomized trials show influenza vaccine is effective in younger age groups, few seniors >70 years were studied even though they suffer >90% of influenza-related deaths. Excess mortality studies could not confirm a national decline in influenza-related mortality while vaccine coverage quadrupled. Cohort studies have consistently reported that vaccination reduces all-cause winter mortality by ~50%, an astonishing claim given only ~5% of all winter deaths are attributable to influenza. This VE overestimation has now been attributed to profound confounding frailty selection bias. A way forward includes a new generation of unbiased studies with laboratory endpoints, and requires an agreement that the evidence base was flawed. The latter may clear the way for more immunogenic vaccines for seniors and exploration of other influenza control strategies.

1. Background

Influenza vaccine was originally developed in the 1940s to protect young, healthy adults in the military. In 1960, influenza vaccines were recommended for control of severe outcomes in high risk groups and persons >65 years of age [1] who account for ~90% of all influenza-related deaths [2,3]. From the inception of this policy there has been concern about immune senescence – the decline in immune response with advancing age. At the time Alexander Langmuir was chief of the influenza branch at the Centers for Disease Control and Prevention; he co-authored an early evaluation of the vaccine program in a 1964 report, with his colleagues DA Henderson (chief of surveillance) and Robert Serfling (chief, statistics section) [1] that read:

> "An appraisal of experience for the past three and a half years indicates little progress in control of influenza. The basic assumptions of the control program must be reassessed. There is little evidence that recent vaccines have significantly prevented clinical illness, as well as equally little evidence to evaluate effects on mortality. How long such a program should be continued without better scientific evidence is problematic. Sounder bases are needed for an influenza control program."

But decades later this concern had subsided with the accumulation of hundreds of cohort studies of HMO databases that all reported an approximate ~50% reduction in all deaths in vaccinated seniors compared to unvaccinated prior and during the influenza season. On its face, this finding suggests a 50% vaccine effectiveness (VE) against death from any cause sounds too good to be true, if only because influenza is related to an average of only about ~5% of all senior deaths during winter and the observed impact occurring prior to the season [3].

Furthermore, a 2003 study by contemporary CDC epidemiologists [2] found that national influenza-related mortality rates among seniors increased in the 1980s and 1990s as the senior vaccination coverage quadrupled. That apparent lack of effect of increased vaccination could not be explained by adjusting for aging and viral circulation patterns [3], but many simply cited the inherent inferiority of trends studies to brush this observation aside. Although trends studies do have limitations, they are frequently celebrated when they seem to confirm vaccination program benefits for childhood diseases such as measles, Hib, pertussis, varicella and most recently rotavirus.

Such opposing views about the benefits of influenza vaccination in the elderly have been suppressed for quite some time. In fact, immunologists often use influenza vaccination as a model system in experimental studies of immune senescence (see reviews [4,5]). Ironically, a recent NEJM paper recapitulated similar astonishing cohort study findings of 50% VE published many times since the 1980s [6] almost simultaneously with our review of the flaws and how cohort studies could be improved [7]. Yet, unless these con-

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cepts are appreciated by the public health community, there will be no more demand for improved control through alternative policies and improved vaccines. Indeed, at the recent ESWI meeting, this issue was presented as a "controversy". Here, we seek to put this issue to rest to remove any incontrovertible uncertainly.

2. Influenza and the sea of death

How large a proportion of all winter deaths in seniors can reasonably be attributed to influenza? The standard approach to investigating the seasonal burden of influenza involves national vital statistics data and statistical analysis of seasonal death rates. Even in the absence of influenza outbreaks, the winter death rate in temperate climates is elevated so that a graph of death rate versus time shows regular winter waves on top of the sea of deaths. Coinciding with influenza epidemics, excess deaths accumulate on top of those waves (Fig. 1). Analysis of the death rate from all causes in excess of the seasonal baseline yields an estimate of "excess all-cause mortality," an excellent indicator of the total burden of death related to influenza [8]. Researchers at the Centers for Disease Control and Prevention (CDC), among others, estimate that about 30,000 excess all-cause deaths occur every year among seniors in the United States [2], about 5% of the approximately 600,000 senior deaths that occur in winter months (December through March) [3].

There has been substantial confusion of "*excess* all-cause deaths" with "all-cause deaths" over winter. The first term is the proportion of deaths that CDC's and our statistical models attribute to influenza. The second is just the total of all winter deaths due to any cause. It is, of course, only excess all-cause mortality—the whitecaps—that influenza vaccines can be expected to prevent. These are the deaths that would be prevented if influenza viruses stopped circulating altogether, or if everyone received a 100% effective vaccine. Nevertheless, the cohort study findings imply that 50% of the seasonal all-cause deaths – effectively half of the ocean of deaths – could be prevented with influenza vaccine (Fig. 1).

3. The lack of evidence from clinical trials

In a recent review [7], we examined evidence from all types of studies that address influenza vaccination and mortality prevention among seniors. "Gold standard" evidence from randomized clinical trials was scarce and no study was statistically powered to study mortality outcomes. A single placebo-controlled trial in Dutch seniors concluded that vaccination prevents 50% of *laboratory-confirmed* influenza infections among healthy people age 60 and over [9]. The authors expressed concerns that the benefit seemed to drop substantially with advancing age for 4 of 5 endpoints studied. Although the number of older trial participants was too small to resolve the uncomfortable possibility that the vaccine was not effective in seniors over 70—none of the VE estimates in this age group were significantly different from 0%—a result that is consistent with the concept of immune senescence. The lack of "gold standard" data for older seniors is unfortunate because about three-quarters of all influenza-related deaths occurs in people 70 years and older [2,7]. We conclude that there is no "gold-standard" randomized clinical trials to document influenza vaccine benefits in seniors aged 70 and older, and what the Dutch study suggested in underpowered analyses was not encouraging (Table 1).

4. Cohort studies – a flawed evidence base

Because of the lack of clinical trials data to inform the immune senescence question, the mainstay of the evidence is a large number of cohort studies set in electronic HMO databases [7]. These non-randomized studies compared differences in rates of death among people who were vaccinated to those who were not. Control for confounding differences between vaccinated and unvaccinated seniors was accomplished analytically, often by adjusting for diagnosis codes recording co-morbid conditions. Recent meta-analyses of such studies [10–12] concluded that winter death rates in

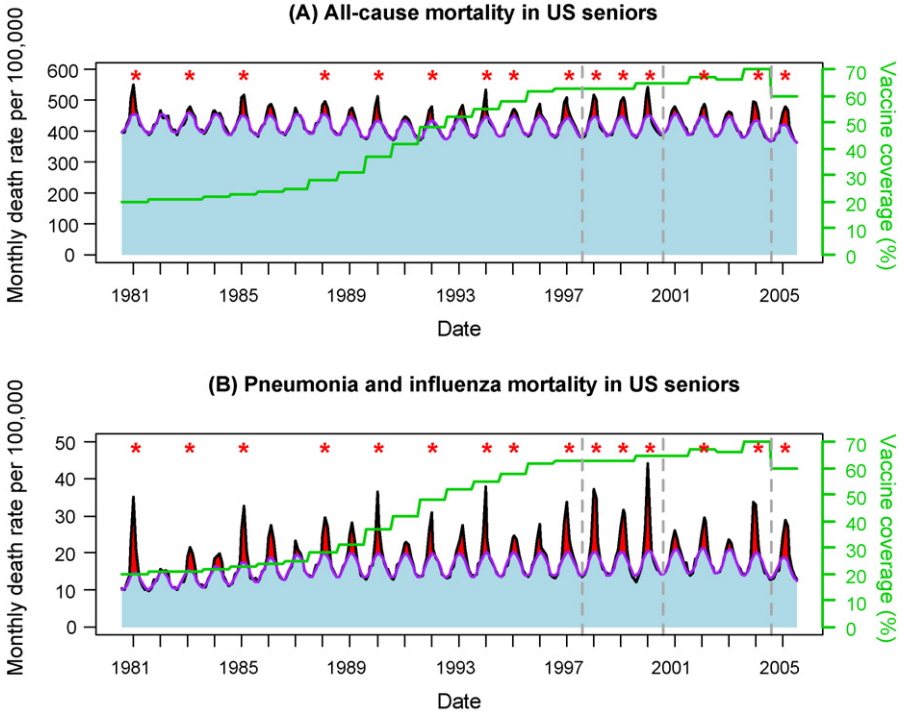

Fig. 1. Monthly numbers of all-cause deaths in US seniors during 1980–2005 and seasonal vaccination coverage in seniors. The red foam on top of the waves illustrates the influenza-related deaths, which contribute ~5% (~30,000) of all winter deaths in seniors in an average season [2,3]. These national figures demonstrate the influenza burden is far lower than the implied proportion of 50% preventable winter deaths by cohort studies. Asterisks indicate H3N2-dominated seasons.

Table 1
Gold standard evidence for influenza vaccination in seniors is scarce. All vaccine efficacy comparisons for senior age groups available from the Dutch randomized clinical from 1994 [9]. Most participants were healthy seniors in their 60s, and consequently none of the VE estimates for seniors >70 are significant.

Influenza-related outcome (from higher to lower specificity)	Vaccine efficacy 60–69 years of age [95% CI]**	Vaccine efficacy ≥70 years of age [95% CI]
Sero-conversion in persons with diagnosed influenza-like illness*	59% (20–79%)	57% (−36% to +87%)
Serology fourfold titer rise	57% (33–72%	23% (−51% to +61%)
Influenza-like illness according to Family practitioner	59% (12–81%)	15% (−117% to +67%)
Clinical illness according to Sentinel Stations	36% (9–55%)	10% (−79% to +54%)
Clinical illness ICHPPS-2-Defined	20% (−4% to +39%)	4% (−66% to +44%)

* An additional study outcome contributed recently by the authors [24] based on data not previously published from the original 1994 trial [9].
** Note that the 95% CI ranges for all five VE estimates for the older senior age group include 0% (not significant).

vaccinated seniors was about half of that of their unvaccinated peers. Furthermore, that astonishing mortality benefit appeared regardless of the severity of the seasons, and was greatest in the oldest and sickest seniors, in some cases surprisingly showing no VE in young healthy seniors. In one study a 2% VE reduction in all-cause mortality was found for younger seniors aged 65–74, compared to 31% for seniors aged 80 years and older [13].

5. Demonstration of overwhelming selection bias in cohort studies

Two recent findings deliver what should be the *coupe de grace* to the cohort study literature. The greatest difference in mortality rates among vaccinated and unvaccinated seniors in the HMO database studies turned out to occur in the months *before* the influenza epidemic period [14], and strategies commonly used for adjustment of bias in cohort studies were counter-productive [15]. Jackson et al. first applied the standard cohort study methods to repeat the finding of an apparent 50% VE for all-cause mortality over the entire winter. But when the authors subsequently stratified the data by calendar month, they found that the differences in all-cause mortality rates between vaccinated and unvaccinated seniors was at its highest in the period immediately after the vaccination season in autumn – months before the influenza epidemic period. In terms of the relative risk (RR), the estimates were lowest in the autumn and early winter, then increasing towards the null the winter and into next spring. Because these studies estimate the VE as 1-RR, the apparent vaccine effectiveness would steadily decline over winter. In other words, there was no evidence that the vaccine prevented more deaths in the influenza period than in surrounding time periods. The fact that vaccination apparently prevented mortality more effectively before the influenza season than during influenza season unambiguously demonstrates vaccination selection bias.

The systematic and serious mis-measurements and overestimation in the observational studies were not picked up by meta-analyses [10,11], although the published Cochrane review commented that there were systematic inconsistencies [12]. What has become clear, however, is that the many cohort studies that have for decades formed the evidence base for vaccination in seniors, did in fact *not* measure vaccine benefits at all. Strong evidence for this position is that (1) the vaccine was purported to reduce 50% of all deaths, despite findings from national vital statistics studies that found ~5% of winter deaths were related to influenza in an average season, and (2) largest differences in mortality rates between vaccinated and unvaccinated persons are observed before influenza season, when the vaccine cannot be producing a true benefit [14]. The main source of bias is likely the presence a small subset of frail and terminally ill seniors who are less likely to become vaccinated during the preceding autumn months because of their deteriorating health – a classic recipe for confounding. The mis-measurement was magnified by the use of non-specific endpoints such as all-cause mortality in winter.

6. A SIR model to explore the hypothesis of frailty selection bias

What should be expected in terms of the seasonal pattern in mortality savings attributed to the vaccine?

We explored the hypothesis that the presence of a small subset of under-vaccinated frail and terminally ill seniors could explain the cohort study results. We generated a simple SIR model, and assumed that 5% of the population was frail and at 20-fold higher risk of dying in any month starting in the autumn, and that frail seniors were vaccinated at half the rate of non-frail seniors (Fig. 2). Using this model, which assumes *no* vaccine benefits, we were able to fit the "VE" point estimates by Jackson et al. from the HMO study remarkably well (Fig. 3). The fitted line illustrates how Jackson's observed declining "VE" estimates are in fact not vaccine benefits but rather the result of unrealized heterogeneity in the study population; the frail and under-vaccinated sub-population of seniors were dying off gradually starting in the vaccination period and made a substantial contribution to all deaths in the total unvaccinated study group.

We took these model simulation findings to mean that frailty selection bias is a satisfying explanation for the mis-measurement and profound overestimation of vaccine benefits in the "electronic" cohort studies evidence base.

7. A way forward

Because there is only a single large clinical trial available that studied VE in young, healthy seniors [9] and no such gold standard studies of VE for seniors over 70 years of age – and because such studies are expensive and ethically problematic for an age group for which the vaccine is already recommended – the evidence base currently relies on observational studies.

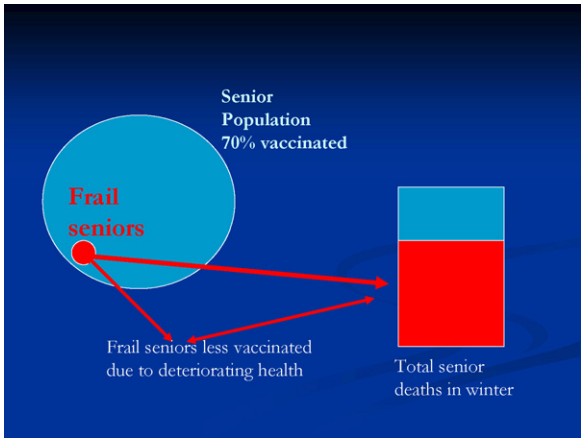

Fig. 2. Diagram illustrating the frailty bias hypothesis explaining the profound confounding bias in most cohort studies.

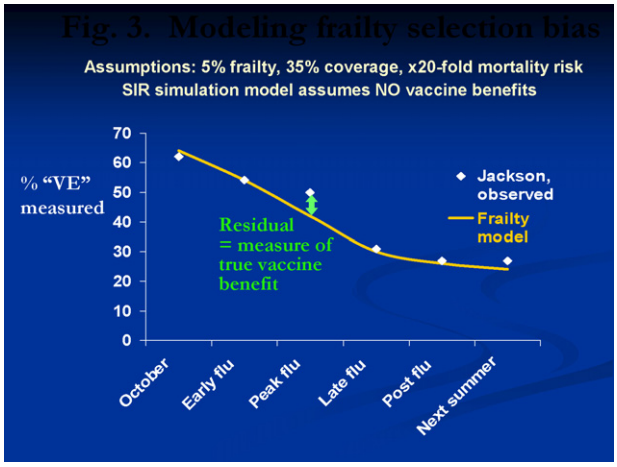

Fig. 3. A SIR model simulation used to test the frailty selection bias hypothesis. The model assumes a 5% subset of frail seniors who are 20-fold more likely to die each month and half as likely to get influenza vaccinated in autumn.

But much of the evidence for vaccine effectiveness from observational studies in seniors over 70 years of age is unreliable, and the remaining evidence suggests that vaccination is far less effective than previously thought [7,14]. Nevertheless, influential journals continued to publish papers with profound selection bias that conclude influenza vaccination prevents almost 50% of *all deaths* that happen during influenza seasons [6]. Such a reduction would correspond to about one life saved for every 200 vaccine doses given to seniors – a proposition that suggests that inexpensive influenza vaccine is enormously cost-effective.

It is clear that a new generation of adequately adjusted observational studies is needed to build a reliable evidence base on which to gauge the VE and cost-effectiveness of influenza vaccination in seniors. Researchers may have to abandon the convenient "electronic cohort study" approach in favor of primary observational studies with more laboratory-confirmed endpoints and/or a careful eye towards effective control for confounding bias by manual chart review. We would like to point to two different observational study designs that carry little risk of bias. First, a carefully controlled in-patient study of RSV hospitalizations in seniors had also studied laboratory confirmation of influenza and influenza vaccination rates [16]. Thus, using RSV-confirmed hospitalization events as "controls" it was possible to estimate a VE against laboratory-confirmed pneumonia hospitalizations at 23% [17]. Second, the recent publication of a carefully conducted cohort study by Jackson et al. [18] that used manual chart review (a relatively specific endpoint of X-ray confirmed pneumonia hospitalisations), and controlled for bias by adjusting the RR to 1 in pre-influenza periods generated a non-significant VE point estimate of 8% against pneumonia during the influenza period, and −4% during the peak influenza period. In conclusion, there was no evidence of the vaccine preventing pneumonia after careful adjustment for bias [18].

Taken together, there are only a few well-controlled (and likely bias-free) observational studies at this point; these studies suggest low vaccine benefits for seniors, with point estimates ranging from 0% [18] to 29% VE for laboratory-confirmed influenza [16,17]. Of course, new randomized, placebo-controlled trial powered to estimate VE for severe outcomes would be better, but that is an expensive and ethically complex proposition. It should be possible, however, to compare new and improved senior formulations with the current flushot formulations in head-to-head clinical trials.

From the point of view of methology in public health research, the emerging insight into the profound consequences of confounding bias in cohort studies evaluating benefits of the influenza vaccine efforts is a powerful lesson. While it is well known that this observal study type is prone to bias, it is not often we get a chance to objectively measure the magnitude of the mis-measurement. But the unique winter-spiked influenza epidemics, combined with the well-defined timing of the autumn vaccination season, were factors that allowed a rare "gold standard" window in the pre-influenza period in which the bias could be documented. Also, the insight that unrealized hetergenecity in a study population can result in severe mis-measurement when outcomes are non-specific is a valuable example to epidemiologists [19]. This does not mean that observational studies must be abandoned; rather it calls for more prudent strategies to investigate and control for bias – and healthy skepticism of public health benefits that seem beyond what is reasonable.

Finally, the realization for public health that it is difficult to protect seniors with a single dose of influenza vaccine is discouraging, but there are opportunities for improvement. We are coming to a more realistic view of what vacciatino can and cannot do; in order to fix a problem, one must first accept that there *is* a problem. The changing tides in the evidence base have given vaccine developers powerful incentives to invest in new vaccine preparations, as well as encouragement that clinically testing new candidate against the current formulations will perhaps pay dividends. Adjuvanted vaccines may enhance effectiveness; indeed, an adjuvanted vaccine formulation for seniors from Chiron (now Novartis) has already been widely used in Europe for years, and GSK has just announced a very large Phase III randomized clinical trial to test its new adjuvanted vaccine formulation in seniors head-to-head with the current flushot formulation [20]. Furthermore, increasing antigen dosing has already been shown to be more immunogenic in seniors [21]. Finally, more aggressive use of antivirals could augment the partial protection afforded by the current vaccine formulation in outbreak settings.

People at highest risk for severe influenza outcomes may fuel a change in influenza control philosophy, moving the strategy towards interrupting transmission as an additional goal. Indeed, several studies have demonstrated that vaccinating more schoolchildren might substantially reduce viral transmission, and thereby protect seniors indirectly [22–24].

We do not suggest that seniors should not be vaccinated. Although one well-controlled observational studies found no vaccine benefits in seniors in terms of reducing X-ray confirmed pneumonia [25], another suggested a significant albeit low (29%) VE against laboratory-confirmed influenza-pneumonia hospitalisations [16,17]. More large, well-controlled observational studies, at best with laboratory-confirmed outcomes, set in seniors >70 are needed to get more confidence in the true VE estimate. But the idea that influenza vaccine can prevent up to 50% of ALL winter deaths is preposterous. The time to consider more immunogenic vaccines for seniors and other strategies for enhancing protection of this high risk age group has come.

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