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Influenza vaccine for community-acquired pneumonia

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Many observational studies suggest that influenza vaccine substantially reduces the risk of hospital admission due to pneumonia in elderly adults.^{1–5} In today's *Lancet*, Michael Jackson and colleagues⁶ challenge these findings with results from a well-designed case-control study about the effectiveness of inactivated influenza vaccine against community-acquired pneumonia in adults aged 65–94 years. This study was done in a US managed-care population over three seasons when the antigenic match between vaccine and circulating influenza strains was good. The investigators identified cases of pneumonia validated by review of medical records, with controls matched by age and sex.

To tease out the effects of bias, the investigators examined the association between vaccination and pneumonia during periods before influenza circulated (ie, preinfluenza periods) when a vaccine effect was not biologically plausible. Influenza vaccination was associated with a 40% reduction in pneumonia during preinfluenza periods—a reduction that was due to confounding. The investigators attempted to reduce this confounding to a minimum by adjusting for measures of disease severity, receipt of medications, and functional status limitations (eg, need for assistance with eating or bathing). After adjustment, essentially no effect of influenza vaccination was noted during preinfluenza periods. Finally, they included these factors in an analysis of vaccination and pneumonia during influenza seasons when a biological effect of vaccination was expected.

The results were not encouraging. Vaccination was associated with an 8% reduction in pneumonia (95% CI –10 to 23%) during broadly defined influenza periods. During peak influenza periods, when influenza-related pneumonia should be most common, vaccine effectiveness was –4%. Why are the results so different from those of previous observational studies, which

found more striking (and statistically significant) reductions in pneumonia incidence in vaccinated elderly patients? At least three factors contributed. First, Jackson and colleagues reviewed medical records to obtain detailed information about illness severity and functional status of participants, and used this information to adjust for confounding. By contrast, most previous studies failed to adjust for disease severity or functional status, and thus did not account for important differences in the health status between vaccinated and unvaccinated individuals. Second, the authors validated all diagnoses of pneumonia. Third, they included both inpatient and outpatient cases, whereas previous studies focused on those admitted to hospital (although a subanalysis for patients with pneumonia admitted to hospital did not find substantial effectiveness, this group represented only 36% of enrolled cases).

Jackson and colleagues mention two possible explanations for their findings. The first is that influenza infections account for only a small fraction of all pneumonia episodes. The second is that vaccination has at best a small effect on prevention of influenza-related pneumonia. Unfortunately, we cannot yet distinguish between these possibilities. Few studies have used sensitive diagnostic tests to prospectively establish the cause of lower respiratory tract infection in hospitalised adults during winter. In four such studies, influenza accounted for 7–53% of episodes.^{7–10} The highest proportion (53%) arose during the peak 4 weeks of an unusually severe influenza season,⁸ and influenza accounted for less than 15% of episodes in two other studies in different winter seasons.^{7,9} Other studies of 12 months or more suggest that 8–19% episodes of patients admitted to hospital with pneumonia are associated with influenza infection, but these studies might underestimate the proportion attributable to

influenza during winter.¹¹⁻¹⁴ Even less is known about the proportion of outpatient pneumonia cases that might be attributable to influenza.

Although the proportion of pneumonia caused by influenza is not known in Jackson and colleagues' study, we can estimate the effectiveness of influenza vaccine to prevent influenza-related pneumonia. We used the 8% effectiveness they found that for prevention all-cause pneumonia and several assumptions (table). Our analysis suggests that vaccine effectiveness against influenza-related pneumonia might be about 70% if no more than 10% of pneumonia episodes were influenza related. On the other hand, vaccine effectiveness against influenza-related pneumonia could be less than 35% if influenza caused 30% or more of all pneumonia episodes during the months included in their analysis.

Where do we go from here? We need additional studies about causes of pneumonia in elderly adults, particularly in highly vaccinated populations. Studies to estimate vaccine effectiveness to prevent illnesses and admissions associated with laboratory-confirmed influenza infections will be important. These studies should enrol and test patients with sensitive and specific diagnostic tests (such as PCR) for influenza. Many patients who are admitted with influenza A do not have infiltrates,^{7,10} and future studies on vaccine effectiveness should include not only pneumonia but also other influenza-confirmed acute illnesses. On the other hand, we see no need for additional effectiveness studies for the influenza vaccine with non-specific outcomes such as pneumonia admissions or influenza-like illness. The potential for overestimation or underestimation of vaccine effectiveness is too great when non-specific outcomes are used.

Standard methods to compare vaccine effectiveness across different seasons and in different populations are needed. Effectiveness varies across seasons because of variation in antigenic match, and it might differ across regions on the basis of geographic patterns of influenza virus circulation. Vaccine effectiveness is also affected by age and immunocompetence of the recipient, and by the outcome studied (eg, illness, medically attended illness, or admission). The study by Jackson and colleagues has confirmed that indicators of functional status can confound the relation between influenza vaccination and diagnosis of

Proportion of pneumonia cases that are influenza-related during influenza season	Percentage vaccinated	Estimated vaccine effectiveness for influenza pneumonia, with 8% effectiveness for all pneumonia
10%	60%	74%
	70%	72%
	80%	69%
20%	60%	49%
	70%	46%
	80%	43%
30%	60%	34%
	70%	33%
	80%	33%

Estimates derived from probability model that assumes proportion of pneumonia related to influenza infection and proportion of elderly patients vaccinated are in ranges in table. Consistent with results from reference 6.

Table: Estimates of effectiveness of influenza vaccine for prevention of influenza-confirmed community-acquired pneumonia

community-acquired pneumonia. Their study suggests that the confounding introduced by differences in functional status can be substantially reduced. More studies that use laboratory-confirmed outcomes and adjust for a broad range of confounding variables will provide valuable information about the effects of antigenic match and other factors that affect vaccine effectiveness in elderly adults. However, interpretation of the results of vaccine effectiveness might be difficult (despite optimum study design) in observational studies of elderly populations in which vaccine coverage is high. Residual confounding can never be ruled out when a small proportion of the population chooses to remain unvaccinated.

*Edward A Belongia, David K Shay

Marshfield Clinic Research Foundation, Marshfield, WI 54449, USA (EAB); and Influenza Division, US Centers for Disease Control and Prevention, Atlanta, GA, USA (DKS)
 belongia.edward@marshfieldclinic.org

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Supervised injecting facilities: time for scale-up?

The spread of infectious diseases and overdoses among injection drug users remain major public-health challenges globally. In response to these concerns, an increasing number of countries have implemented supervised injection facilities where drug users can inject pre-obtained illicit drugs under the supervision of health-care professionals.¹ Despite a growing body of evidence which suggests that such facilities are effective in addressing various harms, few interventions have been as vigorously contested and difficult to implement.

Supervised injection facilities first appeared in the 1980s as a pragmatic response to public injecting, overdoses, and syringe sharing.² The first modest programmes opened in a few European cities, and included facilities that operated out of church basements.¹ Since then, the facilities have become increasingly specialised, with newer ones offering a range of inhouse services, including care by physicians, addiction counselling, and detoxification. There are about 65 supervised injection facilities in eight countries, with Norway and Luxembourg being the latest to open facilities.^{1,3} However, proposals to establish facilities have been hotly debated and eventually dismissed in Austria, France, Portugal, Ireland, Denmark, and the Czech Republic.^{1,3}

More recently, pilot supervised injection facilities were started in Sydney, Australia, and Vancouver, Canada, two cities that had historically favoured strict law enforcement over health-focused responses to injection drug use. Both small pilot programmes were allowed to proceed under intense public scrutiny and

were contingent on rigorous scientific evaluation.^{4,5} The evaluations showed that the facilities met their primary objectives of reducing public injecting, syringe sharing, and overdose risks, and increasing access to addiction treatment. The evaluations also revealed that the facilities were not encouraging drug use or increasing crime, and high levels of public support and cost-effectiveness were also documented.^{5,6}

The favourable evaluations of the Australian and Canadian facilities led to renewed interest in such centres. Recently, in England and Scotland, government-sponsored reports have called for pilot supervised injection facilities.^{7,8} Perhaps most surprising, however, were recent discussions among public-health officials and legal experts focused on the feasibility of establishing facilities in the USA.⁹ Despite the growing body of evidence that supports the effectiveness of these facilities, proposals to establish centres in these settings have been blocked by conservative forces. UK officials have gone as far as declaring supervised injection facilities unlawful,⁸ and a US Senator introduced a federal bill amendment, later defeated, that would have allowed for cuts to federal health funds for any locality that opened a facility.¹⁰

Much ideologically driven opposition to supervised injection facilities has been fuelled by well-orchestrated efforts by international organisations, including the UN's International Narcotics Control Board (INCB) and the Drug Free America Foundation. In its 2007 annual report, the INCB stated that supervised injection facilities “contravene the most fundamental principle of the international drug control conventions” and