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## Invited Editorial

# Pneumonia, mortality, and vaccines: Piecing together the puzzle

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Influenza and other respiratory infections cause a large burden of illness in the United States each year, with the most severe outcomes in the very young and the very old. From 1979-1980 through 2000-2001, influenza-associated hospitalization rates increased significantly for individuals aged >65 years.<sup>1</sup> Seasons where A(H3N2) viruses were widespread had substantially higher influenza-related hospitalizations compared to seasons where A(H1N1) or B viruses were predominant. The annual number of influenza-associated deaths also increased significantly from the mid-1970s to 1999, and influenza A(H3N2) seasons were again associated with the highest mortality rates.<sup>2</sup> National trends in pneumonia hospitalizations are also worrisome: discharges for pneumonia increased 20% from 1988-1990 through 2000-2002 in patients 65-84 years old.<sup>3</sup> The proportion of elderly pneumonia patients with chronic cardiac or pulmonary disease also increased during this time period.

Do these trends hold true for Wisconsin? The article by Schumann and colleagues<sup>4</sup> (p 40) provides some answers regarding mortality from

pneumonia and influenza (P&I), but also raises additional questions. From 1980-1988, age-adjusted P&I mortality increased in Wisconsin, and then gradually declined through 2003. The most dramatic changes were seen in children 0-4 years old. Mortality in this group doubled from 1980 through 1988, dropped sharply during the next 3 years, and then declined modestly over the subsequent decade. Across all age groups and years, more than 95% of deaths were coded as pneumonia (rather than influenza), but the seasonal peaks for pneumonia and influenza were virtually identical, as shown in Figure 1 of the article. Unfortunately, the analysis of long-term trends was complicated by a major change from ICD-9 to ICD-10 diagnosis codes beginning in 1999, and this had a large impact on death certificate coding for P&I. The authors used a conversion factor to adjust for the coding change, but uncertainty remains in the comparison of the pre-1999 and post-1999 mortality rates. Separate analyses of the ICD-9 period (1980-1998) and the ICD-10 period (1999-2003) indicated that P&I mortality rates were stable from 1989 through 1998, but there was a steep decline in P&I mortality from 1999 through 2003.

The Wisconsin mortality trends suggest 2 immunization success stories that may not be readily apparent to readers. First, the dramatic decline in pediatric mortality after 1988 was

most likely due to the licensure and widespread use of *Haemophilus influenzae* type b (Hib) conjugate vaccines in Wisconsin. Hib causes meningitis, bacteremia, pneumonia, and other invasive diseases with a peak incidence in children <18 months old. The first Hib vaccine was licensed in 1985, but it was poorly immunogenic in young children. It was quickly supplanted by 3 protein conjugate vaccines that were developed and licensed from late 1987 through 1989.<sup>5</sup> Through the use of immunogenic carrier proteins, these vaccines enhanced the immune response in infants and had essentially 100% efficacy for preventing invasive Hib disease in clinical trials. The proportion of pediatric P&I mortality due to invasive Hib disease is unknown, but the reduction in P&I mortality among children 0-4 years old coincided with dramatic reductions in the incidence of invasive *H influenzae* disease in both Wisconsin and Minnesota.<sup>6,7</sup>

The second success story is also based on a new pediatric vaccine, but in this case the benefits have accrued to adults as well as children. The 7-valent pneumococcal conjugate vaccine (PCV-7) was licensed for use in infants and young children in March 2000. In a large phase 3 clinical trial, the vaccine was 89%-97% effective for preventing invasive pneumococcal disease.<sup>8</sup> Because PCV-7 reduces nasopharyngeal carriage of vaccine serotypes, it has the potential to reduce

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pneumococcal transmission in the community. Trends in invasive pneumococcal disease incidence from defined populations in 8 states (including Minnesota) suggest that this is exactly what has happened. In these populations, the incidence of invasive pneumococcal disease declined 28% in older adults ( $\geq 50$  years old) from 1998-1999 through 2002-2003.<sup>9</sup> More importantly, the incidence declined 55% for disease caused by the 7 serotypes in PCV-7, but there was no change in disease caused by the 16 serotypes included in the adult polysaccharide vaccine but not in PCV-7. While we do not have specific data on invasive pneumococcal disease incidence in Wisconsin adults, the notable decline in age-adjusted mortality after 1999 is consistent with population-level effects of increasing PCV-7 use in children.

What about the impact of immunizing adults in Wisconsin, particularly against influenza? Influenza vaccine coverage in Wisconsin adults  $\geq 65$  years old increased from 50% in 1993 to 72% in 2003, an impressive accomplishment given the difficulty of reaching adult populations for vaccination. Has this contributed to declining mortality from P&I? Perhaps, but the evidence to date is not very convincing. A meta-analysis of 20 observational studies concluded that influenza vaccination reduced mortality due to P&I by 47%, and all-cause mortality by an astounding 50%.<sup>10</sup> If this is true, the 22% increase in vaccination of older adults in Wisconsin from 1993 to 2003 might be expected to yield about a 10% reduction in mortality. Excess influenza-related mortality was not calculated by Schumann and colleagues, but total P&I mortality rates declined only slightly from 1993 to 2002 in Wisconsin adults 65-74 years old, a group targeted for influenza vaccination. Models of excess influenza mortality in the elderly in the United

States from 1968 to 2001 suggest that previous observational studies have overestimated the benefits of influenza vaccination.<sup>11</sup> For each of the 33 seasons studied, influenza-related excess mortality accounted for less than 10% of the total number of winter deaths in the elderly. There were simply not enough influenza-related deaths to support the conclusion that influenza vaccination can reduce total winter mortality in the elderly by anything close to 50%. There was also no downward trend in age-adjusted excess mortality from 1980 to 2001 in the United States, a period of increasing influenza vaccine coverage in the elderly.

The discrepancy between observational studies and the results of time-series analyses may be explained by bias due to preferential receipt of influenza vaccine by healthy seniors. In particular, elderly people with end-stage disease may be less likely to receive influenza vaccine if they are not expected to survive through the influenza season, causing mortality rates to be inflated in the unvaccinated population. This would have the effect of overestimating influenza vaccine effectiveness. A recent study in a large elderly HMO population confirmed this type of bias and found that the magnitude of bias was sufficient to explain the association between seasonal mortality and vaccination.<sup>12</sup>

We should not infer that influenza vaccination is ineffective despite the inability to clearly demonstrate a vaccine-associated reduction in nonspecific mortality in large populations. Most observational studies of influenza trends and influenza vaccination do not specifically identify deaths or hospitalizations from laboratory-confirmed influenza infection, and it is difficult to distinguish influenza from the myriad other causes of respiratory illness and death using

administrative databases. Multiple clinical trials have proven the benefit of influenza vaccination for reducing morbidity, particularly when there is a good match between the vaccine strain and circulating viruses.<sup>13-16</sup> However, these findings do highlight the urgent need for better ways to evaluate the public health impact of influenza vaccination, accounting for year-to-year variability in vaccine effectiveness.

Despite some uncertainties regarding the population-level effects of influenza vaccination on mortality, the proven impact on morbidity justifies ongoing efforts to immunize the elderly and other high-risk individuals. Clinicians should continue to promote and encourage influenza (and pneumococcal) vaccination in older adults based on current guidelines from the CDC Advisory Committee on Immunization Practices ([www.cdc.gov/nip/publications/acip-list.htm](http://www.cdc.gov/nip/publications/acip-list.htm)). Vaccination of young children with influenza vaccine and PCV-7 is critical not only for their own protection, but also to reduce the risk of transmission to susceptible adults. Strategies to reduce comorbid conditions and susceptibility to serious infection are harder to implement, but aggressive efforts to deal with obesity and smoking are straightforward and likely to yield long-term benefits. For researchers, there is an urgent need to develop more potent and immunogenic vaccines for older adults. Finally, we need more studies like the one reported by Schumann et al to better understand the epidemiology of influenza and pneumonia in Wisconsin.

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