Bias and Problems with Adjustment for Bias in Database Studies of Influenza Vaccine Effectiveness in Seniors

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Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly

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Annual Influenza Vaccination in Community-Dwelling Elderly Individuals and the Risk of Lower Respiratory Tract Infections or Pneumonia

Betty C. G. Voordouw, MD, PhD, MPH; Miriam C. J. M. Steenhouw, PharmD, PhD; Jeanne P. Dieleman, PhD; Theo Stijen, PhD; Johan van der Lei, MD, PhD; Bruno H. C. Stricker, MD, PhD

Influenza Vaccination in Community-Dwelling Elderly: Impact on Mortality and Influenza-Associated Morbidity

Betty C. G. Voordouw, MD, MPH; Paul D. van der Linden, PharmD, PhD; Simon Simon, PhD; Johan van der Lei, MD, PhD; Miriam C. J. M. Steenhouw, PharmD, PhD; Bruno H. C. Stricker, MD, PhD

Benefits of Influenza Vaccination for Low-, Intermediate-, and High-Risk Senior Citizens

Kristin L. Nichol, MD, MPH; J. Wicorema, RN, BSN, T. von Sternberg, MD

Influenza Vaccine Effectiveness in Preventing Hospitalizations and Deaths in Persons 65 Years or Older in Minnesota, New York, and Oregon: Data from 3 Health Plans


A Cohort Study of the Effectiveness of Influenza Vaccine in Older People, Performed Using the United Kingdom General Practice Research Database

Penrose M. Morgan, P. Phillipson, P. C. B. Rogerson, Jennifer A. Roberts, Felicity T. Gutt, and Andrew J. Hall

Relation between Influenza Vaccination and Outpatient Visits, Hospitalization, and Mortality in Elderly Persons with Chronic Lung Disease

Kristin L. Nichol, MD, MPH; Leslie Baken, MD; and Andrew Nelson, MPH

Additive preventive effect of Influenza and Pneumococcal Vaccines in Elderly Persons

B. Childers, J. Hagedon, P. Lueder, A. Orlicat

Influenza Vaccination and Reduction in Hospitalizations for Cardiac Disease and Stroke among the Elderly

Kristin L. Nichol, MD, MPH; David B. Nelson, PhD; John P. Mullolly, PhD; and Erick J. Hisk, MD

Influenza Vaccination and Risk of Mortality Among Adults Hospitalized With Community-Acquired Pneumonia

Kimberly A. Spadone, MPH; Elias A. Stroyn, MD; Cheryl Kirchner, RN, MS; Alex Kim, MS; and Kristin L. Nichol

Annual Revaccination Against Influenza and Mortality Risk in Community-Dwelling Elderly Persons

Kristin L. Nichol, MD, MPH; David B. Nelson, PhD; John P. Mullolly, PhD; and Erick J. Hisk, MD
In industrialized countries, influenza vaccines offer approximately 70–90% protection against clinical disease in healthy adults, provided there is a good match between the vaccine antigens and circulating virus(es). Among elderly people not living in institutions, vaccination may reduce the number of hospitalizations by 25–39% and has also been shown to reduce overall mortality by 39–75% during influenza seasons.
Influenza Virus Isolates, 2001-2002 influenza season

Number of isolates

1-Aug 1-Sep 1-Oct 1-Nov 1-Dec 1-Jan 1-Feb 1-Mar 1-Apr 1-May 1-Jun 1-Jul

Pre-influenza period
Influenza season
Post-influenza period

Influenza vaccine first available

Source: MMWR 2002; 51(23):503-6
Association of flu vaccine and risk of all cause mortality, adjusted for age and sex, by time interval

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-flu</td>
<td>0.56</td>
</tr>
<tr>
<td>Flu</td>
<td></td>
</tr>
<tr>
<td>Post-flu</td>
<td></td>
</tr>
</tbody>
</table>
Association of flu vaccine and risk of all-cause mortality, by time interval

- Pre-flu: RR = 0.39
- Flu: RR = 0.56
- Post-flu: RR = 0.74
Association of flu vaccine and risk of all cause mortality, by time interval

- Pre-flu: RR 0.39
- Flu: RR 0.56
- Post-flu: RR 0.74

Bias
Association of flu vaccine and risk of pneumonia hospitalization, by time interval

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-flu</td>
<td>0.72</td>
</tr>
<tr>
<td>Flu</td>
<td>0.82</td>
</tr>
<tr>
<td>Post</td>
<td>0.95</td>
</tr>
</tbody>
</table>
Association of flu vaccine and risk of injury or trauma hospitalization, by time interval

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-flu</td>
<td>0.67</td>
</tr>
<tr>
<td>Flu</td>
<td>0.88</td>
</tr>
<tr>
<td>Post</td>
<td>0.85</td>
</tr>
</tbody>
</table>
What about adjustment?
### Covariates defined by ICD9 codes

<table>
<thead>
<tr>
<th>Covariate</th>
<th>ICD9 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>093, 112.81, 130.3, 391, 393-398, 402, 404, 410-429, 745, 746, 747.1, 747.49, 759.82, 785.2, and 785.3</td>
</tr>
<tr>
<td>Lung disease</td>
<td>011, 460, 462, 465, 466, 480-511, 512.8, 513-517, 518.3, 518.8, 519.9, and 714.81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250, 251</td>
</tr>
<tr>
<td>Renal disease</td>
<td>274.1, 408, 580-591, 593.71-593.73, and 593.9</td>
</tr>
<tr>
<td>Cancer</td>
<td>200-208, 140-198, and 199.1</td>
</tr>
<tr>
<td>Others…</td>
<td></td>
</tr>
</tbody>
</table>
Association of flu vaccine and risk of all cause mortality, by time interval, unadjusted and adjusted analyses

- Pre-flu: Unadjusted (0.39), Adjusted for age and sex (0.56)
- Flu: Adjusted for age and sex (0.51)
- Post-flu: Adjusted for age, sex, and diagnosis code covariates (0.74, 0.66)
Effect of adjustment for disease covariates on the estimate of the association of influenza vaccine and risk of all cause mortality during influenza season in published studies
Functional status
Functional status as ascertained by medical record review

- Requires asst ambulation: OR 5.45
- Requires asst bathing: OR 13.43
- Dementia: OR 2.81

Legend:
- Blue: Likelihood of vaccination
- Red: Risk of death
Association of flu vaccine and risk of all cause mortality during flu season, 1997/1998 case control study

Adjusted for functional status covariates: 0.71
Unadjusted: 0.59
Adjusted for ICD9 covariates: 0.45
Among women randomized to placebo, comparison of risk of health outcomes in high adherers vs low adherers
Placebo adherence and risk of outcomes in the WHI

HR, high placebo adherence compared to low placebo adherence

Adjusted for age and sex
Placebo adherence and risk of outcomes in the WHI

HR, high placebo adherence compared to low placebo adherence

Adjusted for prospectively identified factors such as education, smoking, alcohol, fruit/vegetable intake, red meat intake, BMI, physical activity, colonoscopy ever, depression, number of medications taken, type of medications taken.
Conclusions

• The “healthy adherer” effect can be very strong

• Traditional methods of adjustment for health status may be ineffective in reducing the influence of this bias

• Even detailed, prospectively collected markers of health status may be ineffective

• Observational studies should, whenever possible, incorporate methods, such as the use of control time period, exposures, or outcomes, to evaluate the possible influence of bias on the association of interest