

**CHAPTER 3**

**A clinical prediction rule for pneumonia and  
influenza hospitalization and death during  
influenza epidemics**

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### A clinical prediction rule for pneumonia and influenza hospitalization and death during influenza epidemics

**Background** Uncertainties among providers and patients about a patient's risk for serious influenza associated complications and the potential benefits from vaccination may contribute to unsatisfactory low influenza vaccination rates. In order to quantify risk for serious outcomes during influenza seasons, we developed a clinical prediction rule for the probability of pneumonia or influenza associated hospitalization or death among seniors.

**Methods** We developed the clinical prediction rule using data from linked, administrative databases on 16,280 non-institutionalized and unvaccinated seniors. Validation of the rule was conducted in five unvaccinated and six vaccinated additional cohorts of more than 11,000 elderly members of three managed care organizations. Using logistic regression analysis, the following predictors were selected: age, gender, presence of pulmonary, cardiac and renal disease, dementia/stroke and cancer, number of outpatient visits and hospitalization for pneumonia and influenza in the previous year.

**Results** Reliability of the regression model was good (goodness-of-fit test,  $p=0.64$ ) and it discriminated well between those with and without the combined end point (area under the receiver-operating curve 0.83, 95% CI 0.81-0.85). Validation revealed moderately lower but acceptable discriminating values between 0.72 and 0.81. The prognostic accuracy of the prediction rule in the derivation cohort was high when a cut-off sum-score  $\geq 50$  points, reflecting a predicted probability  $\geq 1.0\%$ , is chosen (subjects with end point vaccinated: 89%, without end point unvaccinated: 51%) while only 50% of seniors would be selected for vaccination. The influenza vaccine reduced hospitalization or death by 43% (95% CI 39% to 47%) in subjects with a high score ( $\geq 50$  points).

**Conclusions** The prediction rule may be useful to make sure that at risk seniors are vaccinated and to target additional measures for vaccination to those most likely to benefit.

**Key words:** influenza, immunization, elderly, administrative database, epidemiology

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Influenza continues to cause considerable morbidity and mortality worldwide.<sup>1</sup> In the United States, it is estimated that influenza is responsible for hundreds of thousands of hospitalizations,<sup>2</sup> tens of thousands of deaths<sup>3</sup> and billions of dollars in excess costs.<sup>4</sup> Most of the excess morbidity and mortality occurs among the elderly. To reduce these consequences of influenza, recommendations include yearly vaccination of vulnerable patient groups.<sup>5,6</sup>

Although influenza vaccination is effective in reducing morbidity and mortality,<sup>7-10</sup> and cost-saving among the elderly,<sup>11</sup> nearly 40 percent of this

target population fail to receive the vaccine each year.<sup>5</sup> Vaccination rates for high-risk persons under 65 are even lower. Uncertainties among providers and their high risk patients about the risk of serious, influenza related, complications and benefits of vaccination may contribute to these low vaccination rates. Recent data from a survey of Medicare beneficiaries, for example, suggest that lack of awareness of personal risk is among the most common reasons for failing to receive the influenza vaccine.<sup>12</sup>

Another recent issue attracted attention to a higher need for individual risk stratification. In a notice to readers, physicians were urged to identify high-risk persons because a shortfall of the influenza vaccine was expected for the 2000-2001 season.<sup>13</sup> This might happen more often during coming influenza seasons and in case of a pandemic a substantial delay or shortfall of vaccine will likely occur as well in which information on a patient's risk will undoubtedly be of use.<sup>14</sup>

For these reasons a careful risk assessment using an accurate, objective model of prognosis could help physicians assess risks of individual patients and improve the decisions about immunization and additional care. We assessed the prognostic value of clinical information derived from administrative databases of three health plans to develop a prediction rule for the probability of hospitalization for pneumonia and influenza and all-cause death during influenza epidemics among non-institutionalized persons over 65 years of age. We further demonstrated performance of the model when applied to our patients and the consequences of its use in future populations.

## Methods

### Setting

This study is part of an ongoing collaborative effort between three large managed care organizations from geographically disparate locations across the US to pool data derived from their linked medical databases in order to provide assessments of impact of influenza and the health and economic benefits of vaccination among members of their health care plans. HealthPartners (HP) is a nonprofit health maintenance organization with about 890,000 members in Minnesota and Wisconsin. It offers coverage for 280,000 members through a staff model HMO, while the other members are covered through a network HMO model. Kaiser Permanente Northwest Division (KPNW) provides medical care for nearly 420,000 persons in the Portland, Oregon-Vancouver and Washington regions. Oxford Health Plans (Oxford) provides health benefit

plans to 1.8 million members in New York, New Jersey, Pennsylvania and Connecticut. In all, over 3 million members receive medical care from these health plans. The health plans used protocols specifying the same definitions of co-morbidity and outcomes and obtained all study data, including baseline information, vaccination status and outcomes from their linked, administrative and clinical databases.

#### Study subjects

All members of the three health plans, aged over 65 years as of October 1, 1996 in the first year and October 1, 1997 for the second year, continuously enrolled for 12 or more months prior to October 1 of each year and non-institutionalized were included. A large enrollment period was chosen to ensure valid prognostic information to derive and validate the regression model.<sup>15</sup> Institutionalized patients were excluded because vaccination status was unknown.

#### Definitions of potential predictors

After an extensive literature search, we selected 15 clinical characteristics that possibly could be related to serious clinical outcomes during influenza epidemics. At baseline, the following potential predictors were included: age, gender, and a hospitalization for influenza and pneumonia and number of outpatient visits in the previous year. Underlying disease of eligible subjects was classified into 11 non-mutually exclusive disease categories according to entries of relevant codes in the *International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM)* in outpatient clinic or hospital databases 12 months prior to October 1 of each year: (1) pulmonary disease (ICD-9-CM codes 011, 460, 462, 465-466, 480-511, 512.8, 513-517, 518.3 518.8, 519.9, 714.81), (2) cardiac disease (093, 112.81, 130.3, 391, 393-398, 402, 404, 410-429, 745-746, 747.1-747.49, 759.82, 785.2, 785.3), (3) diabetes/other endocrine disorders (250-251), (4) renal disease (274.1, 403, 580-591, 593.71-593.73, 593.9), (5) immune-deficiency/organ transplants (042, 079, 279, V08, V42) (6) non-hematological and hematological cancer (140-198, 199.1, 200-208), (7) anemia spleen (280-289, 759.0), (8) cirrhosis (571), (9) nutritional deficiencies (254-255, 259.2, 260-269), (10) dementia/stroke (290-4, 331, 340-1, 348, 438), and (11) vasculitis/ rheumatologic diseases (446, 710, 714-714.4, 714.8, 714.89, 714.9).

#### Influenza seasons and vaccination

During the 1996-97 and 1997-98 epidemic, influenza activity was widespread in most US states, exceeding baseline levels for more than 5 consecutive weeks.<sup>16,17</sup> Influenza periods were defined as follows on the basis of Centers of Disease Control (CDC) surveillance data: Year 1, HealthPartners November

22, 1996 through May 24, 1997, Oxford: October 5, 1996 through May 3, 1997. Kaiser: November 22, 1996 through March 22, 1997. Year 2, HealthPartners: December 7, 1997 through March 28, 1998, Oxford: November 23, 1997 through April 4, 1998, Kaiser: December 21, 1997 through March 7, 1998. Vaccination rates varied from 39% to 71% during the years in the different health plans.

#### **End point**

The combined end point was the occurrence of hospitalization for influenza or, its main complication, pneumonia (ICD-9-CM codes 480-487) or death from all causes during the studied influenza seasons.

#### **Model development**

To develop the model, we used the data on all eligible study subjects from the HealthPartners database that were enrolled in the first season and who were not vaccinated against influenza ( $n=16,280$ ). Absence of a characteristic in the medical database was assumed to indicate no presence of the characteristic under study and therefore missing values were absent. Age was classified into the following 5 categories according to exponential increase in risk of outcomes: 65-69, 70-74, 75-79, 80-89,  $\geq 90$ . Similarly, the number of outpatient visits during the prior 12 months was classified into 4 categories: 0, 1-6, 7-12,  $\geq 13$ . Descriptive statistics as proportions and means (SD) using SPSS for Windows, version 9.0, (SPSS Inc., Chicago, Illinois, USA) were calculated to describe baseline characteristics in the two comparison groups (with or without end point). The construction of the prognostic model started with a univariate assessment of the prognostic effect of each characteristic separately as given in terms of odds ratio's (OR) and their 95% confidence intervals (95% CI) using logistic regression analysis. In the next stage we used multivariate logistic regression modeling with a backward elimination procedure to select those variables that were related to the outcome with a p-value  $< 0.15$  as a criterion for selection. We first used the continuous variables age and number of outpatient visits to ensure that the selection of the corresponding classified variables was independent of the choice of the cut-off values. Forward selection was additionally performed to verify whether any previously deleted potentially relevant characteristic was incorrectly eliminated from the model. Interaction between variables included in the model was assessed to determine deviations from the additivity assumption by including first-order interaction terms in the final model. For each patient we calculated the individual probability of the outcome from the final model (predicted probability).

### Model evaluation

The reliability of the multivariate logistic regression model derived from the derivation set was determined by the Hosmer-Lemeshow goodness-of-fit statistic.<sup>18</sup> The area under the receiver-operating-curve (ROC) was used to assess the model's discriminative ability.<sup>19</sup> The ROC is a plot of the true-positive rate (sensitivity) and false-positive rate (1-specificity) which is evaluated for each cut-off point of the predicted probability. The area under the ROC can be explained as the probability that the logistic regression model will assign a higher probability of the outcome to a randomly chosen patient with an outcome (hospitalization/death) than to a randomly chosen patient without outcome. An area under the curve (AUC) estimate of 0.5 indicates no discrimination whereas an estimate of 1.0 indicates perfect discrimination. External validation of the model was performed by comparing the AUC values across the other 11 cohorts stratified by immunization status (no/yes), site (1,2,3) and year (1,2).

### Development and applicability of the prediction rule

The regression coefficients of the derived multivariate model were used to construct the prediction rule.<sup>20,21</sup> The predicted probability of outcome equals  $1 / (1 + e^{-LP})$  where the linear predictor (LP) =  $-6.0906 + 0.4681 \times \text{age-category} + 0.2939 \times \text{gender} + 2.0872 \times \text{previous P\&I hospitalization} + 0.3794 \times \text{outpatient visits-category} + 0.6012 \times \text{lung disease} + 0.1952 \times \text{heart disease} + 0.4135 \times \text{renal disease/transplant} + 0.7273 \times \text{dementia/stroke} + 1.5887 \times \text{cancer}$ . For practical interpretation we have chosen to multiply the regression coefficients by 30 and round them to form the score. All scores indicating the relative influence of the variable on the occurrence of the combined endpoint were added to form a sum-score and classified. For sum-score cut-off points the following test characteristics were calculated: positive predictive value, sensitivity, specificity, proportion of outcomes missed (1.0-sensitivity) and proportion of persons selected.

### Vaccine effectiveness

To assess whether patients with high or low risk score could benefit from the influenza vaccine, we calculated the vaccine effectiveness for the seniors in both risk groups using logistic regression. In this analysis, the association of vaccination status as main explanatory variable with the dichotomous end point was assessed, independent of other predictors, site and year. Vaccine effectiveness (VE) was determined as  $1 - \text{OR}$  times 100 percent.<sup>11</sup> Absolute reduction (AR) per 1,000 vaccinees was calculated as the vaccine effectiveness (VE) times the incidence of the end point in non-vaccinees.

## Results

Of the 16,280 study subjects of the derivation cohort, 399 were hospitalized or died during that season (2.5%); 122 (0.7%) were hospitalized for pneumonia or influenza and 287 (1.8%) died from all causes.

**Table 1.** Association of clinical characteristics with hospitalization and death in derivation set (n= 16,280). Percentages are given, unless stated otherwise

Characteristic	Patients with outcome (n=399)	Patient without outcome (n=15,881)	Univariate Odds ratio (95% CI)	Multivariate Odds ratio* (95% CI)	P-value
<i>Demographics</i>					
Mean age (SD), y	81 (8)	75 (8)	1.8 (1.6-1.9) <sup>†</sup>	1.6 (1.4-1.8) <sup>†</sup>	<0.001
Female	41	38	1.2 (1.0-1.4)	1.3 (1.1-1.7)	0.008
<i>Prior health care use</i>					
Previous P&I hospitalization	16	1	22.4 (16.3-30.6)	8.1 (5.7-11.5)	< 0.001
Mean (SD) no. outpatient visits	26 (27)	11 (14)	2.4 (2.1-2.7) <sup>†</sup>	1.5 (1.3-1.8) <sup>†</sup>	< 0.001
<i>Co-morbidity‡</i>					
Heart disease	50	24	3.2 (2.6-3.8)	1.2 (1.0-1.5)	0.10
Lung disease	40	14	4.1 (3.3-5.0)	1.8 (1.4-2.3)	<0.001
Dementia/stroke	31	9	4.6 (3.7-5.8)	2.1 (1.6-2.7)	<0.001
Renal disease	13	4	4.0 (2.9-5.4)	1.5 (1.1-2.1)	0.02
Cancer	12	2	6.8 (4.9-9.4)	4.9 (3.4-7.0)	<0.001
Diabetes	19	12	1.8 (1.4-2.3)	-	
Anemia	24	8	3.7 (2.9-4.7)	-	
Nutritional def.	5	2	3.7 (2.4-5.9)	-	
Vasculitis/rheum	3	2	1.3 (0.7-1.3)	-	
Immunodeficiency	2	1	2.0 (1.0-4.0)	-	
Cirrhosis	1	0.3	3.1 (1.1-8.7)	-	

-: p-value >0.15

\* Likelihood ratio test (LR): p<.001; Hosmer-Lemeshow Goodness-of-fit test: p=0.65

<sup>†</sup> odds ratio's for the corresponding classified variable are given

<sup>‡</sup> see methods section for corresponding ICD-9-CM codes

Mean age was 75 years (SD 8, range 65 to 110 years) and 38% were male. High-risk co-morbid conditions, e.g. cardiopulmonary disease, were present in 47% of subjects.

**Table 2.** Area under the receiver-operating-curve (AUC) and 95% confidence intervals (95% CI) of the clinical prediction rule in validation cohorts by year, immune status and region

Population	Year 1			Year 2		
	N	AUC	95% CI	N	AUC	95% CI
<i>Non-immunized</i>						
Region A	16,280	0.83	0.81-0.85	15,492	0.72	0.69-0.75
Region B	23,914	0.81	0.79-0.84	39,641	0.77	0.76-0.79
Region C	11,775	0.80	0.77-0.82	11,320	0.76	0.73-0.80
Overall	51,969	0.81	0.80-0.82	66,453	0.76	0.75-0.78
<i>Immunized</i>						
Region A	24,478	0.79	0.76-0.82	25,019	0.73	0.70-0.76
Region B	15,193	0.73	0.68-0.78	34,846	0.74	0.72-0.76
Region C	31,334	0.80	0.77-0.82	32,136	0.75	0.73-0.77
Overall	71,005	0.78	0.76-0.79	92,001	0.74	0.73-0.76

In gray-shade is the derivation cohort (n=16,280).

In univariate analysis, all potential predictors appeared more prevalent in subjects who were hospitalized or died and statistically significant associated with the combined end point, except for a history of immune-deficiency (see Table 1). In seniors with the end point, markedly higher prevalence of previous P&I hospitalization (16% versus 1%), pulmonary disease (40% versus 14%), dementia/stroke (31% versus 9%) and cancer (12% versus 2%) as compared to controls was observed.

Except for the co-morbid conditions diabetes, anemia, nutritional deficiencies, vasculitis/ rheumatological disorders, immune-deficiency and cirrhosis, all other variables independently contributed to the multivariable logistic regression model (table 1). In the modeling procedure, the presence of non-related diseases did not add to the limited prediction model including age, gender, previous P&I hospitalization and number of outpatient visits or predictive value was unacceptably low in the validation cohorts ( $p > 0.15$ ). After



**Table 3.** Prediction rule for estimating the probability of hospitalization for pneumonia and influenza and all-cause death

Characteristic	Score*
Age <70	0
70-74	+14
75-79	+28
80-89	+42
>=90	+56
Female	+9
Outpatient visits in last year	
0 visits	0
1-6 visits	+11
7-12 visits	+22
>=13 visits	+33
Previous hospitalization for influenza or pneumonia	+63
Co-morbidity:	
Lung disease	+18
Heart disease	+6
Renal disease or transplantation	+12
Dementia or stroke	+22
(Non-)haematological cancer	+48

\* The sum-score for a given persons can be obtained by summing the scores for each applicable characteristic. The sum-score correlates with the predicted probability through the formula (see methods section).

including first-order interaction terms in the final model, six terms were statistically significant: gender×dementia/stroke, heart disease×cancer, age×heart disease, age×hospitalization, lung disease×hospitalization, dementia/stroke×hospitalization. Although it may be clinically plausible that risks of these combinations is more than the additive risks of each separate variable, we decided not to include them in the final prognostic model for three reasons: (1) these interactions were not observed in earlier studies, (2) they were not statistically significant in the other external cohorts and (3) they did not materially contribute to the discriminative value of the model. Performance of the final model was good (Goodness-of-fit test  $p=0.65$ ). The model discriminated well between those with outcome (predicted probability  $10\% \pm 1\%$ ) and those without outcome ( $0.2\% \pm 0.4\%$ ). The AUC was 0.83 (95%

**Table 4.** Test characteristics of sum-score cut-off points in derivation cohort (n=16,280)

Sum-score Category	No. (%)	OP (%)	RR	Cut-off point	PPV (%)	SE (%)	SP (%)	OM (%)	Selection (%)
≥0-<10	519 (3.2)	0.2	1.0	0	2.5	100	0	0	100
≥10-<20	1153 (7.1)	0.4	2.0	10	2.5	99.7	3.3	0.3	96.8
≥20-<30	2552 (15.7)	0.2	1.0	20	2.7	98.4	10.5	1.6	89.7
≥30-<40	2371 (14.6)	0.5	2.5	30	3.2	96.9	26.5	3.1	74.0
≥40-<50	1579 (9.7)	1.1	5.5	40	3.9	93.6	41.3	6.3	59.4
≥50-<60	2128 (13.1)	1.2	6.0	50	4.4	89.2	51.1	10.8	49.7
≥60-<70	1787 (11.0)	2.0	10.0	60	5.5	82.8	64.3	17.0	36.6
≥70-<80	1329 (8.2)	2.5	12.5	70	7.1	74.0	75.3	25.8	25.6
≥80-<90	938 (5.8)	4.2	21.0	80	9.2	65.7	83.5	34.1	17.4
≥90-<100	700 (4.3)	5.1	25.5	90	11.6	44.1	89.2	43.9	11.6
≥100	1224 (7.4)	15.4	77.0	100	15.4	46.9	93.4	52.9	7.4

OP: observed probability of outcome, RR: relative risk (<10 points is reference), PPV: positive predictive value, SE: sensitivity, SP: specificity, OM: outcomes missed

CI 0.81-0.85). AUC estimates were moderately lower, but acceptable across the validation cohorts (see table 2, range 0.72 to 0.81). The average discriminative power was approximately 0.05 points lower in the second as compared to the first season and 0.03 points lower in the immunized as compared to the non-immunized persons.

The prediction rule was derived from the final multivariate model in which a score was assigned to the presence or level of each variable (table 3). A sum-score for each patient, reflecting the probability of reaching an end point, was calculated by adding the scores of relevant characteristics. For instance, the sum-score for a 66-year old female patient with Hodgkin's disease who visited the outpatient clinic 7 times in the previous year and is recently diagnosed with asthma is 97 (9 + 48 + 22 + 18) which is a 25.5 times higher risk than the lowest risk category (see also table 4).

The prediction rule can be used to identify those at highest risk for serious influenza associated complications and those therefore most likely to benefit from vaccination. Using the derivation cohort, for each cut-off level of the

**Table 5.** Practical implication of using a cut-off score ( $\geq 50$ ) in validation cohorts by year, immunization status, and region. Percentages are given

Cohorts	Year 1					Year 2				
	OP	SE	OM	SP	RE	OP	SE	OM	SP	RE
<i>Non-immunized</i>										
Region A*	4.4	89	11	51	50	2.3	81	19	50	50
Region B	3.7	81	19	65	64	3.9	83	17	54	53
Region C	5.5	72	28	70	69	3.0	83	17	56	56
Overall	4.3	82	18	62	61	3.3	83	17	54	53
<i>Immunized</i>										
Region A	2.0	87	13	47	46	1.7	83	17	43	43
Region B	1.4	80	20	49	48	2.3	90	10	36	35
Region C	3.1	78	22	64	64	2.0	87	13	44	44
Overall	2.2	81	19	55	54	2.1	88	12	41	40

OP: observed probability, SE: sensitivity, OM: outcomes missed, SP: specificity, RE: reduction of the target population

\* In gray-shade is the derivation cohort (n=16,280).

sum-score we calculated test characteristics (see table 4). A cut-off score of  $\geq 50$  had a sensitivity of 89% (1 out of 10 outcomes is missed) while the number of seniors selected would be halved. Patients with low risk assignment (score  $< 50$ ) had an observed average probability of 0.5%, those with high risk ( $\geq 50$ ) had an average probability of 4.0%. With increasing cut-off level, the proportion of non-selected persons would increase, but the proportion of outcomes missed increases accordingly. Since the benefits of the cut-off value of  $\geq 50$  outweighed the risk of missing disease in the derivation cohort, we showed the practical consequences of this cut-off value in the different validation cohorts (table 5). On average, the sensitivity was high (82% to 83% in the non-immunized, 81% to 88% in the immunized) whereas the reductions of selected persons would range from 40% to 61%. When analyzing the test characteristics for both subsidiary end points separately, results were similar (not in table). Finally, influenza vaccination reduced any hospitalization or death by 43% (95% CI 39% to 47%) in persons with a score  $\geq 50$  and 33% (95% CI 24% to 45%) in those  $< 50$  points. The absolute reduction resulting from the vaccine in the high-risk segment of the population would be 16 per 1,000 vaccinated persons. In other words, only 67 persons have to be vaccinated to save one end point from happening.

## Discussion

This study is unique in that we were able to derive and validate a prediction rule with acceptable reliability, discriminating ability and generalizability using data on large-sized cohorts of seniors from three geographically disparate located health plans across the US. In comparison with previous prognostic studies,<sup>7-10,22-26</sup> our prediction rule has distinctive strengths. First, we developed a 9-factor prognostic scoring system in non-selected persons using information on predictors that can be readily assessed by both patients and health care providers at any time. Second, patients can be easily assigned to high or low risk category enabling providers to balance costs and benefits of health care. Third, the reliability, accuracy and generalizability of the rule are supported by derivation in 16,280 seniors and validation in 11 large-sized external cohorts representing other areas across the United States, different epidemic season and immunization status.

The predictors incorporated in our prediction rule have been established in earlier epidemiological studies.<sup>7-10,22-26</sup> Age is a strong predictor for both respiratory infections, its main complication pneumonia and associated death.<sup>27</sup> Males also have been found to be at higher risk than females for influenza infections.<sup>27</sup> Patients with cardiac disease, especially congestive heart failure, are prone to exacerbations of underlying systemic disorders.<sup>28</sup> In addition, the disseminating potential of influenza infection in the lungs of patients with chronic respiratory disease is well known.<sup>29</sup> Patients with renal transplants<sup>30</sup> and cancer patients receive immune-suppressive medication which put them at risk for infections.<sup>31</sup> Also, previous hospitalization for pneumonia or influenza has been reported previously as a risk factor.<sup>32</sup> Relatively little is known, however, about the risk of elderly with dementia or stroke. Our results indicate that there is substantial risk for these persons of dying or being hospitalized during an influenza epidemic.

Diabetes was not independently associated with a higher risk of P&I hospitalization or death in both derivation and validation cohorts. In the modeling procedure, similar information needed for risk assessment was acquired through other predictors as age, gender and previous health care use. It appeared that two-thirds of diabetics had a score  $\geq 50$  points and therefore the disease may be seen as an indicator for high influenza risk which is in accordance with other studies.<sup>33</sup>

To our knowledge, this is the first study to demonstrate that risks are not materially modified by changing epidemics or immunization status. We believe

therefore that results are applicable to future epidemic seasons. Furthermore, our prediction rule may be used in non-vaccinated persons, especially those who have high scores, to efficiently target them for influenza vaccination and other appropriate medical care whereas in vaccinated persons with high scores, risk assignment based on the rule help practitioners direct medical care and for those with low scores avoid unnecessary additional diagnostic, therapeutic or preventive measures.

A score  $\geq 50$  points represented a high risk with an average expecting occurrence rate of P&I hospitalization or mortality of 4%. In the derivation cohort, relatively lower numbers of persons were observed with higher cut-off values while the numbers of outcomes missed increased substantially. Although we acknowledge that the proportion of outcomes missed decreases with a lower cut-off score, we feel that using the cut-off level of 50 points was acceptable in all validation cohorts whereas the numbers to select for care were reduced to between 40% and 60% on average. From the scoring formula some patient profiles with high risk can easily be identified on the basis of routine clinical information: e.g. everyone who has had a previous hospitalization for pneumonia or influenza or a history of cancer and who is aged over 90 years, and all elderly aged over 80 years with at least one of the high-risk co-morbid conditions. Since we demonstrated that influenza vaccination reduced P&I hospitalization or death by 43 percent in persons with a score  $\geq 50$  points, no opportunities should be missed to vaccinate these persons against influenza and pneumonia.

For the development of the clinical prediction rule, we studied only persons aged 65 years and older. The majority of excess deaths and many, if not most, of the excess hospitalizations for influenza associated complications occur in this group. However, for many years, persons with high-risk conditions under age 65 have also been included among the high risk groups targeted for vaccination, and for the 2000-2001 season, the ACIP lowered its age-based recommendations for annual vaccination down to 50 years.<sup>34</sup> How our prediction rule might apply to these other high-risk groups remains to be seen.

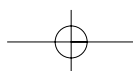
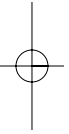
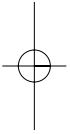
We used pneumonia and influenza hospitalizations and deaths from all causes as the end points for the prediction rule. These outcomes are highly correlated and have traditionally been among the main measures used to assess and define the magnitude and impact of influenza epidemics.<sup>1</sup> However, influenza may also be responsible for a wide range of other complications including exacerbations of underlying medical conditions leading to increased outpatient and inpatient health care use.<sup>11</sup> It is not clear how the results of our model might apply to these other outcomes.



In conclusion, we derived and validated a prediction rule for quantifying the probability of P&I hospitalization or death with acceptable reliability, discriminating ability and generalizability. In addition to the recommendation to routinely immunize all persons over 50 years of age against influenza, our prediction rule may help practitioners to target efficiently additional efforts to those who need preventive and therapeutic measures most.

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## References

1. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. *J Infect Dis* 2000;181:831-7
2. Barker WH. Excess pneumonia and influenza associated hospitalization during influenza epidemics in the United States, 1970-78. *Am J Public Health* 1986;76:761-5
3. Glezen WP. Serious morbidity and mortality associated with influenza epidemics. *Epidemiol Rev* 1982;4:25-44
4. McBean AM, Babish JD, Warren JL. The impact and cost of influenza in the elderly. *Arch Intern Med* 1993;153:2105-11
5. Centers for Disease Control and Prevention. Influenza and pneumococcal vaccination levels among adults > or = 65 years--United States, 1997. *JAMA* 1998;280:1818-9
6. Fedson DS, Hirota Y, Shin HK, et al. Influenza vaccination in 22 developed countries: an update to 1995. *Vaccine* 1997;14:1506-11
7. Ahmed AH, Nicholson KG, Nguyen-Van-tam JS. Reduction in mortality associated with influenza vaccine during 1989-90 epidemic. *Lancet* 1995;346:591-5
8. Fedson DS, Wadja A, Nicol JP, et al. Clinical effectiveness of influenza vaccination in Manitoba. *JAMA* 1993;270:1956-61
9. Ohmit SE, Monto AS. Influenza vaccine effectiveness in preventing hospitalization for pneumonia among the elderly during influenza A and type B seasons. *Int J Epidemiol* 1995;24:1240-8
10. Flemming DM, Watson JM, Nicholas S, et al. Study on the effectiveness of influenza vaccination in the elderly in the epidemic of 1989-90 using a general practice database. *Epidemiol Infect* 1995;115:581-9
11. Nichol KL, Margolis KL, Wuorenma J, et al. The efficacy and cost-effectiveness of vaccination against influenza among elderly persons in the community. *N Engl J Med* 1994;331:778-84
12. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System, nationwide online prevalence data, 1999. <http://www.cdc.gov/nccdphp/brfss> (accessed 11/5/2000)
13. Anonymous. Notice to readers: delayed supply of influenza vaccine and adjunct ACIP influenza vaccine recommendations for the 2000-01 influenza season. *MMWR Morb Mortal Wkly Rep* 2000;49:619-22
14. Meltzer MI, Cox NJ, Fukuda K. The economic impact of pandemic influenza in the United States: priorities for intervention. *Emerg Infect Dis* 1999;5:659-71
15. Hasenclever D, Diehl V. A prognostic score for advanced hodgkin's disease. *N Engl J Med* 1998;339:1506-14
16. Centers for Disease Control. Update: influenza activity--United States and worldwide, 1996-97 season, and composition of the 1997-98 influenza vaccine. *MMWR Morb Mortal Wkly Rep* 1997;46:325-30

17. Centers for Disease Control. Update: influenza activity—United States and worldwide, 1996–97 season, and composition of the 1998–99 influenza vaccine. *MMWR Morb Mortal Wkly Rep* 1998;**47**:280–4
18. Hosmer DW, Lemeshow S. Assessing the fit of the model: In: *Applied logistic regression*. New York: *J. Wiley*; 1989:135–75
19. Hanley JA, McNeill BJ. The meaning and use of the area under a receiver operating characteristic curve (ROC) curve. *Radiology* 1982;**143**:29–36
20. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Application and methodological standards. *N Engl J Med* 1985;**313**:793–9
21. A clinical prediction rule for renal artery stenosis. *Ann Intern Med* 1998; **129**: 705–11
22. Barker WH, Mullooly JP. Pneumonia and influenza deaths during epidemics: implications for prevention. *Arch Intern Med* 1982;**142**:85–9
23. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978–81. *Am Rev Respir Dis* 1987;**136**:550–555
24. Paul WS, Cowan J, Jackson GG. Acute respiratory illness among immunized and non-immunized patients with high-risk factors during a split season of influenza A and B. *J Infect Dis* 1988;**157**:633–9
25. Lui KJ, Kendal AP. Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. *Am J Public Health* 1987;**77**:712–6
26. Foster DA, Talsma A, Furumoto–Dawson A, et al. Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. *Am J Epidemiol* 1992;**136**: 296–307
27. Loeb M, McGeer A, McArthur M, Walker S, Simor AE. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med* 1999;**159**:2058–64
28. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;**336**:243–50
29. Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* 1999;**130**:397–403
30. Versluis DJ, Beyer WEP, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporin A, but not by azathioprine. *Transplantation* 1986;**42**:376–9
31. Yousu HM, Englund J, Couch R, et al. Influenza among hospitalized adults with leukemia. *Clin Infect Dis* 1997;**24**:1095–9
32. Hedlund JU, Ortqvist AB, Kalin M, et al. Risk of pneumonia in patients previously treated in hospital for pneumonia. *Lancet* 1992;**340**:396–7
33. Valdez R, Narayan KM, Geiss LS, Engelgau MM. Impact of diabetes mellitus on mortality associated with pneumonia and influenza among non-Hispanic black and white US adults. *Am J Public Health* 1999;**89**:1715–21
34. Anonymous. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Report* 2000;**49**:1–38