Chapter 36. Pneumococcal Vaccination Prior to Hospital Discharge

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Background

*Streptococcus pneumoniae* (pneumococcus) is a leading cause of serious community-acquired infections, especially pneumonia, the sixth leading cause of death in the United States.\(^1\) It causes over 50,000 cases of bacteremia and at least 500,000 cases of pneumonia annually in the United States.\(^1-3\) Although pneumococcus is an important pathogen in meningitis, bronchitis, and otitis media, these disease processes will not be discussed in this report.

The epidemiologic rationale for targeting pneumococcal vaccination among hospitalized patients derives from research showing that two-thirds of patients hospitalized with serious pneumococcal infections had been hospitalized at least once in the previous 3-5 years.\(^4-6\) One retrospective study showed that about 60% of persons 65 years of age and older hospitalized with pneumonia had been discharged from a hospital at least once in the prior 4 years.\(^4\) A prospective cohort study of patients aged $\geq 65$ discharged from the hospital showed that the 5-year probability for readmission with pneumonia was over 7%.\(^4\) Hospitalization, therefore, is a marker for patients at increased risk of developing subsequent pneumococcal infection. Despite the scope of the problem and the appeals for action from multiple specialty societies and national health care organizations, the vaccine is underutilized in the inpatient setting.\(^5-7\) This underutilization has been attributed to uncertain effectiveness of the vaccine and ineffective methods of vaccine delivery during hospitalization.

Hospital-based vaccination for patients at high risk of contracting pneumococcal infections is part of the action plan for adult immunizations developed by the Federal Centers for Disease Control and Prevention (CDC) and the Health Care Financing Administration (HCFA).\(^6\) It is also endorsed by the CDC’s Advisory Committee on Immunization Practices (ACIP)\(^5,6\) and the National Vaccine Advisory Committee. In addition, most national guidelines for the management of patients hospitalized with community-acquired pneumonia recommend vaccination against pneumococcus at time of discharge.\(^1,8\)

Practice Description

Currently, pneumococcal vaccines contain 23 capsular polysaccharide antigens of *S. pneumoniae* (23-valent vaccines). Over 88% of the serotypes that cause invasive disease in the United States, as well as 88% of serotypes accounting for penicillin-resistant isolates, are included in the 23-valent vaccine.\(^2,9\) Newer conjugate vaccines designed primarily to enhance the immune response in children are not covered in this review.

The practice of hospital-based pneumococcal vaccination is recommended for patients at increased risk for pneumococcal infection or increased risk of experiencing severe disease. Patients $\geq 65$ years of age, or patients with certain chronic illnesses, including chronic cardiovascular disease, chronic pulmonary disease, diabetes, alcoholism, chronic liver disease, and functional or anatomic asplenia, are deemed high-risk.\(^3\) It is also recommended that all immunocompromised patients (due to HIV infection, leukemia, lymphoma, long term steroid use, or organ transplantation, among other causes) and any patient admitted with a diagnosis of community-acquired pneumonia be vaccinated.\(^1,3,8\) Vaccination could occur at any time during the hospitalization, but is often recommended at discharge.
Prevalence and Severity of the Target Safety Problem

The goal of pneumococcal vaccination in hospitalized patients is to reduce the morbidity and mortality associated with pneumococcal infection, namely pneumococcal bacteremia and pneumococcal pneumonia. The CDC estimates the annual incidence of pneumococcal bacteremia at 15-30 cases per 100,000 population and 50-83 cases per 100,000 in persons aged ≥65. A recent study of the epidemiology of invasive \textit{S. pneumoniae} (ie, associated with bacteremia) in the United States found an overall incidence of 23.2 cases per 100,000, corresponding to 62,840 cases annually. The incidence among adults aged 65 and older was 59.7 per 100,000. The overall fatality rate was 10%, but patients aged 18-64 with an ACIP indication for vaccination had a fatality rate of 12.1%. Patients ≥65 years of age accounted for 51.4% of all deaths. These figures result in national estimates of over 6000 deaths in 1998 attributed to invasive pneumococcal disease.

The precise incidence of pneumococcal pneumonia is harder to estimate due to the poor sensitivity and specificity of diagnostic tests for this disease. At least 25-35% of all pneumonias are linked to \textit{S. pneumoniae}, resulting in a minimum of 500,000 cases of pneumococcal pneumonia annually. Bacteremia complicates pneumococcal pneumonia in 10-25% of cases. The mortality rate for all patients hospitalized with community-acquired pneumonia is estimated at between 10-15%.

Opportunities for Impact

Despite recommendations to routinely vaccinate eligible hospitalized patients, pneumococcal vaccine is underutilized. The high potential impact of vaccination is borne out by recent epidemiologic evidence. Based on 1998 projections, 76% of invasive pneumococcal disease and 87% of deaths occur in patients who are eligible for pneumococcal vaccine. In addition, 88% of penicillin-resistant isolates during the same time period were of serotypes included in the 23-valent vaccine.

The vaccine is currently recommended for over 30 million persons aged ≥65 and over 23 million persons <65 who are at high risk. In 1997 only 45% of persons 65 and over reported ever receiving the vaccine. A 12-State study of Medicare patients hospitalized with pneumonia showed that the opportunity to provide the vaccine was missed in over 80% of patients, and only 0.4% of hospitalized elderly patients were vaccinated prior to discharge. More recent data from 1999 found a hospital vaccination rate in elderly patients screened, and not already vaccinated, of less than 9%. In this same study, vaccination rates were higher for patients with a discharge diagnosis of pneumonia (23.6%), but still far below the Public Health Service goal of 60%. Few data are available on rates of vaccination in patients <65 years of age who are otherwise at risk for pneumococcal infection.

In this chapter we considered two independent, but linked sets of studies: those evaluating the effectiveness of pneumococcal vaccination and those assessing strategies to increase vaccination rates in hospitalized patients. These two areas are reviewed separately below.

36.1. Vaccine Effectiveness

Study Designs and Outcomes

Three meta-analyses (published in 1994, 1999, and 2000) have analyzed the effectiveness of pneumococcal vaccination in adults. The first study by Fine et al included 9
randomized controlled trials (RCTs) of vaccines (valences ranging from 6 to 17) in adults with and without risk factors for pneumococcal infection. Results were pooled and analyzed for effects in various subgroups with careful attention to study heterogeneity (rate differences (RD) were reported when significant heterogeneity existed). The second study included 13 randomized and quasi-randomized studies of vaccines with valences ≥2. Consequently, this study included 2 quasi-randomized studies with vaccine valences <6 that were excluded by Fine, but included a study by Austrian et al that was only partially included in the Fine meta-analysis. Results of this second meta-analysis were reported as pooled odds ratios; when significant heterogeneity existed, ranges were presented instead of pooled results.

The most recent meta-analysis identified 12 reports of 13 randomized controlled trials. The authors excluded 3 prior trial reports based on a predetermined decision to exclude quasi-randomized trials. Of these 3 quasi-randomized studies, the 2 older studies (26,000 patients) reported efficacy for the vaccine, while the more recent study (27,000 Finnish patients over aged 65) found no efficacy for pneumococcal vaccination. The 13 trials included 3 reports published after 1996 that were not included in either of the prior meta-analyses.

Despite the volume of RCTs that have been published, controversy still exists as to vaccine effectiveness in certain patient populations (high-risk, elderly), as well as to the vaccine’s effectiveness in reducing certain outcomes (pneumonia generally, and pneumococcal pneumonia). Consequently, we reviewed the 1997 summary report and recommendations of the Advisory Committee on Immunization Practices, which synthesizes multiple case-control and cohort studies of vaccine effectiveness in high-risk patients. As an additional means to evaluate effectiveness, researchers from the CDC reported results of an indirect cohort analysis using a national database of pneumococcal bacteremia that compared distribution of pneumococcal serotypes causing infection in vaccinated and unvaccinated patients.

The 3 meta-analyses reported Level 1 outcomes, including systemic pneumococcal infection and pneumococcal pneumonia. Two of these studies report infection rates with vaccine-type and non-vaccine-type organisms, and 2 of the 3 meta-analyses additionally report on all-cause pneumonia, bronchitis and mortality. All studies analyze data separately for elderly patients and high-risk patients, but the study by Hutchison et al differs from the other two with respect to this part of the analysis. In this study, vaccine efficacy in elderly and high-risk patients is assessed with logistic regression analysis after pooled odds ratios were determined, in contrast to the 2 other groups who report pooled odds ratios and relative risk separately for elderly, high-risk patients. The definition of pneumococcal pneumonia varied in many studies included in the pooled results, and in subsequent studies looking at the 23-valent vaccine.

The indirect cohort analysis by Butler et al reported presumptive measures of effectiveness based on differing rates of isolation for certain serotypes of pneumococcus in vaccinated and unvaccinated patients (Level 2 outcome).

Evidence for Effectiveness of the Practice

The meta-analyses by Fine et al and Hutchison et al showed a protective effect of vaccination for systemic pneumococcal disease (66% effective overall, 83% effective against vaccine-types in the former; 73% effective overall, 83% effective against vaccine-types in the latter). Fine et al found the vaccine 53% effective for presumptive pneumococcal pneumonia, but analysis for heterogeneity showed that the rate difference was not statistically significant. The summary odds ratios for all other outcomes did not achieve statistical significance, either
overall or in high-risk patients (ie, patients age • 55 years, patients with one or more chronic medical problems, and immunocompromised patients). Results for pneumococcal infection-related outcomes did achieve significance in low-risk patients. Hutchison et al found effectiveness against pneumococcal pneumonia ranging from 31% to 76% (results were significant in 3 trials), but study heterogeneity prevented a pooled estimate. Regression analysis suggested similar benefits for systemic pneumococcal infection in elderly patients, but were inconclusive for systemic infection in chronically ill patients. For elderly patients, the authors estimated a number needed to treat (NNT) of 2520 to prevent a single case of pneumococcal bacteremia per year.11

The most recent meta-analysis12 reported that in 3 comparisons involving approximately 21,100 immunocompetent subjects, pneumococcal vaccination was associated with significant reductions in the incidence of all-cause pneumonia (relative risk 0.56, 95% CI: 0.47-0.66), pneumococcal pneumonia (relative risk 0.16, 95% CI: 0.11-0.23), pneumonia deaths (relative risk 0.70, 95% CI: 0.50-0.96) and bacteremia (relative risk 0.18, 95% CI: 0.09-0.34). However, in 10 comparisons involving over 24,000 subjects who were elderly or likely to have impaired immune systems, the authors found no benefit to pneumococcal vaccination in terms of any clinical outcome of interest.12 While the relative risk for pneumococcal bacteremia in elderly or high-risk patients showed a trend towards benefit, the results were not statistically significant (relative risk 0.53, 95% CI: 0.14-1.94).

One additional publication21 has appeared since the search period covered by this most recent meta-analysis. This publication represents a 6-month preliminary report from a prospective comparison between 2 large cohorts (>100,000 subjects each) of Swedish patients age • 65 years. Patients in one group received pneumococcal vaccine, influenza vaccine, or both. The other cohort consisted of all patients from the same region and age group who chose not to receive either of the vaccines. Among all vaccinated patients (results are pooled for pneumococcal and influenza vaccines), hospital admission for pneumonia (including all-cause pneumonia, pneumococcal pneumonia and invasive pneumococcal pneumonia) was significantly reduced, and overall mortality was reduced by 57% (95% CI: 55-60%). This study design has significant potential for bias, in that people who elect to participate in clinical studies tend to have better outcomes independent of the treatments they receive. Nonetheless, it seems unlikely that the results observed in this study, including a 57% reduction in all-cause mortality over a 6-month period, could be attributable solely to a selection effect tied to patients’ decision to participate in the study.

36.2. Vaccine Delivery Methods

Study Designs and Outcomes

Multiple studies have evaluated the effectiveness of various methods of increasing rates of vaccination among eligible patients in both the inpatient and outpatient settings. We focused our review on interventions relating to inpatient settings (ie, hospitals and nursing homes). Two systematic reviews published in 1994 and 1999 evaluate multiple strategies. The first review identified 3 studies in hospitalized patients and one in institutionalized patients. The second review includes studies identified in the first, and comments on several additional studies. Both reviews grade the included studies and report pooled estimates of effectiveness. The 2 reviews use slightly different definitions of the types of interventions, but are internally consistent with respect to the most effective strategy, namely standing orders.
All studies of the effectiveness of vaccine delivery methods reported vaccination rates. The results of several heterogeneous studies were pooled. There are few RCTs included in the summary estimates, and most interventions were studied with a before-after analysis of vaccination rates. Where possible, we report pooled estimates for given methods of improving vaccine delivery, and then comment on individual studies with the most promise for improving vaccination rates. No study of delivery methods looked at clinical outcomes.

Evidence for Effectiveness of the Practice

The systematic reviews of vaccine delivery methods with provider reminders in the inpatient setting were associated with absolute increases in vaccination rates that ranged from 7.5%-17% (Table 36.2.1).26,27 One subsequent before-after study of chart reminders in hospitalized patients showed that vaccination rates in eligible patients increased from 0% to 28.8%.28 The most impressive effects were seen for system-related changes, which increased vaccination rates by 45-51%. The most effective system-related change was the implementation of standing orders, which produced increases of 69-81% over usual care.27 Studies of pneumonia clinical pathways (Chapter 52) have shown no effect on pneumococcal vaccination rates despite improvements in other pathway processes.7

Potential for Harm (from pneumococcal vaccination)

Three of the studies analyzed by Fine et al10 reported data on adverse effects. Erythema ranged from 30.6-35.1% in the vaccine group compared with 1.7-3.5% in the control group. Fever developed in 2.0% of vaccinated patients compared with 1.2% of controls. No fatal or life-threatening adverse events occurred. Moore et al12 report that in one study, in addition to increased rates of fever, vaccine recipients were more likely to experience a swollen or sore arm. There is the theoretical concern that patients vaccinated in the hospital may have an increased chance of being inappropriately revaccinated if they are unaware of their prior vaccination status (due to illness, etc.) or are being cared for by a physician other than their primary care doctor. A recent study compared the safety of the vaccine in patients receiving a first vaccination and patients receiving re-vaccination 5 years after their prior dose. There was an increase in self-limited local reactions with re-vaccination (RR 3.3, 95% CI: 2.1-5.1), but no serious adverse reactions were reported.29 Few data address rates of adverse reactions in hospitalized patients vaccinated at discharge who receive re-vaccination earlier than 5 years after their prior dose.

Finally, the recent study in Ugandan HIV-infected adults showed trends toward increased rates of invasive pneumococcal disease, all pneumococcal events, and a statistically significant increase in all-cause pneumonia (hazard ratio 1.89, 95% CI: 1.1-3.2) among vaccine recipients.19 This study calls into question the utility of giving pneumococcal vaccine to HIV-infected individuals.

Costs and Implementation

The cost-effectiveness of hospital-based pneumococcal vaccination is difficult to determine in light of the debate over how effective the vaccine is in reducing pneumococcal outcomes in at-risk populations. A cost-effectiveness analysis of vaccination for all elderly patients in the United States recently demonstrated a wide range of possible outcomes that depended on assumptions of vaccine effectiveness and duration of protection.30 Base-case estimates showed that vaccination was cost saving at $8.27, and gained 1.21 quality-adjusted days of life per person vaccinated. Factoring in the future medical costs of survivors, vaccinating all patients ≥ 65 years of age would cost $9600 per quality-adjusted life year under the most
optimistic assumptions about vaccine effectiveness, and $51,661 per quality-adjusted life-year under worst-case assumptions. A recent systematic review of pneumococcal vaccine cost-effectiveness by authors from the Cochrane Vaccines Field concluded that there is too much variability in assessments of cost-effectiveness (largely attributed to uncertainty over vaccine effectiveness) to reach any firm conclusions. The authors called for a moratorium on all economic modeling until completion of a Cochrane review of pneumococcal vaccine effectiveness.

Comment

Pneumococcal vaccine is effective in reducing invasive disease in low-risk patients. It appears effective in reducing invasive disease in the elderly and high-risk patients based on results of one meta-analysis, multiple case-control studies, and a CDC serotype prevalence study. Importantly however, 2 meta-analyses failed to demonstrate a significant benefit of the vaccine for any outcomes in elderly or other high-risk patients. The vaccine appears efficacious in non-bacteremic disease (pneumococcal pneumonia) in low-risk patients, and one meta-analysis suggests a protective effect against pneumococcal pneumonia in the elderly, but the others do not. No study has demonstrated reductions in mortality. Thus, in the population most likely to be targeted by hospital-based immunization programs (elderly, high-risk) vaccine efficacy remains inconclusive. If it is assumed to be effective in reducing the incidence of the most serious outcome in this population (pneumococcal bacteremia), best estimates suggest a very large NNT (>2500).

Increasing antibiotic resistance, the aging of the US population and the major burden of pneumococcal disease among adults and elderly patients make increasing vaccination rates an obvious goal if, in fact, the vaccine is effective. The evidence supports system changes (in particular, the use of standing orders) as the best method of increasing vaccine rates in eligible, hospitalized patients. Though such rates can be increased, available data regarding vaccine efficacy raise doubts about the overall utility of both local and national initiatives aimed at increasing the rates of pneumococcal vaccination at hospital discharge. Early enthusiasm explains the large number of national pneumococcal vaccine initiatives, however available data on effectiveness provide only modest support for these initiatives.
### Table 36.1. Pneumococcal vaccine efficacy*

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Study Design, Outcomes</th>
<th>Results (95% Confidence Interval)</th>
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</table>
| Meta-analysis of 9 RCTs. Vaccine valences 6-17, included international studies, high- and low-risk patients.\(^{10}\) | Level 1A, Level 1 | Definitive pneumococcal pneumonia:  
OR 0.34 (0.24-0.48), RD 4/1000 (0-7)  
Definitive pneumococcal pneumonia, vaccine types:  
OR 0.17 (0.09-0.33), RD 8/1000 (1-16)  
Presumptive pneumococcal pneumonia:  
OR 0.47 (0.35-0.63), RD 13/1000 (-21 to 47)  
All cause pneumonia: OR 0.90 (0.77-1.04)  
Mortality: OR 1.02 (0.90-1.14)  
Stratified results show no benefit in any outcome for high-risk patients. |
| Meta-analysis of 13 RCTs and “quasi-randomized” trials. Vaccine valences 2-17, includes international trials, high and low-risk patients.\(^{11}\) | Level 1A, Level 1 | Systemic infection, vaccine type: OR 0.17 (0.09-0.31)  
Systemic infection all types: OR 0.27 (0.13-0.49)  
All cause pneumococcal pneumonia: OR range 0.24-0.69, results significant in 3 studies  
Pneumococcal pneumonia, vaccine types:  
OR range 0.08-0.85, 8 of 9 studies showed reduced risk, results significant in 6 studies.  
Stratified results show benefit in elderly, mixed results in chronically ill. |
| Meta-analysis of 13 RCTs including three recent trials published after the last meta-analysis.\(^{12}\) | Level 1A, Level 1 | All pneumonias:  
Healthy (H), RR 0.56 (0.47-0.66), NNT 29 (24-36);  
Elderly, High Risk (E) RR 1.08 (0.92-1.27)  
Pneumococcal pneumonias:  
H, RR 0.16 (0.11-0.23), NNT 38 (33-45);  
E, RR 0.88 (0.72-1.07)  
Pneumococcal bacteremia:  
H, RR 0.18 (0.09-0.34), NNT 32 (26-44);  
E, (3 trials and only 927 pts), RR 0.53 (0.14-1.94)  
Pneumonia-related death:  
H, RR 0.70 (0.50-0.96), NNT 213 (114-1660);  
E, RR 0.93 (0.72-1.20) |
| Six-month preliminary results report from prospective comparison between cohort of 100,242 Swedish patients age • 65 years who received pneumovax, influenza vaccine, or both, and patients from the same region and age group who chose not to participate in the study.\(^{21}\) | Level 2, Level 1 | Results pool all vaccinated patients.  
Hospital admission for all cause pneumonia reduced by 29% (24-34), for pneumococcal pneumonia 36% (3-58), invasive pneumococcal pneumonia 52% (1-77).  
Overall mortality reduced by 57% (55-60) |

* OR indicates odds ratio; RD, risk difference; and RR, relative risk.
### Table 36.2.1. Vaccine delivery

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Study Design, Outcomes</th>
<th>Results</th>
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<tbody>
<tr>
<td>Systematic review of studies from 1980-1997 of methods to increase vaccination rates. Multiple vaccines (eg, pneumococcal, influenza, hepatitis) delivered in multiple inpatient and ambulatory settings were reviewed, but this summary focuses on pneumococcal vaccine in hospitalized patients</td>
<td>Level 2A-3A Vaccination rates (Level 2)</td>
<td>Provider reminders increased vaccination rates by 17% (pooled absolute increases for all vaccines in all settings, with a range of 1-67%). Standing orders achieved a 51% mean absolute increase in vaccination rates (range 30-81%) for all vaccine types; pneumococcal vaccination in particular the increases ranged from 69% to 81% (in hospital setting and long-term care facility).</td>
</tr>
<tr>
<td>Systematic review of studies from 1979-1992. Multiple vaccine types in multiple settings.</td>
<td>Level 2A-3A Vaccination rates (Level 2)</td>
<td>Provider-oriented interventions resulted in a 7.5% increase in vaccination coverage (3.4-11.6%) System-oriented interventions resulted in a 45.5% increase in vaccination coverage (95% CI: 37.2-53.7%).</td>
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### References


