Cost-Effectiveness of Pneumococcal Polysaccharide Vaccine Among Healthcare Workers During an Influenza Pandemic

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Objective: To assess the usefulness and cost-effectiveness of pneumococcal polysaccharide vaccine (PPV) among healthcare workers compared with nonuse of PPV during an influenza pandemic.

Study Design: Markov modeling was used to estimate the cost-effectiveness of PPV in previously unvaccinated healthcare workers during an influenza pandemic.

Methods: Invasive pneumococcal disease (IPD) incidence rates were incorporated into the model, which assumed that IPD events occurred at twice the usual rate during a year of pandemic influenza. Societal and hospital perspectives were examined. Assumptions were that pneumococcal disease transmission from healthcare worker to patient did not occur, heightened IPD risk occurred for only 1 year, and PPV did not prevent noninvasive pneumonia, all of which potentially bias against vaccination.

Results: From a societal standpoint, PPV of healthcare workers during an influenza pandemic is economically reasonable, costing $2935 per quality-adjusted life-year gained; results were robust to variation in multiple sensitivity analyses. However, from the hospital perspective, vaccinating healthcare workers was expensive, costing $1676 per employee absence day avoided, given an IPD risk that (although increased) would remain less than 1%.

Conclusions: Vaccinating all healthcare workers to protect against pneumococcal disease during a pandemic influenza outbreak is likely to be economically reasonable from the societal standpoint. However, PPV is expensive from the hospital perspective, which might prevent implementation of a PPV program unless it is externally subsidized.

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For author information and disclosures, see end of text.

As governmental, scientific, medical, and public health communities responded to the 2009 influenza pandemic, many strategies were considered to reduce the possibility of widespread morbidity and mortality. Primary, secondary, and tertiary prevention measures were devised, including the development of priority groups for pandemic influenza immunization.[1] In a pandemic, during which demand for healthcare would inevitably increase, the stability of healthcare systems would be threatened if healthcare workers became ill in sufficient numbers, a possible scenario given their heightened exposure to a highly infectious illness. Therefore, the Centers for Disease Control and Prevention (CDC)[1] listed healthcare workers among tier 1 groups for priority influenza vaccination.

Secondary pneumococcal infections caused as much as 20% of mortality during the 1918-1919 pandemic, as demonstrated in a review of autopsy series showing that 27% of blood cultures were positive for *Streptococcus pneumoniae*.[2] This led to recommendations that pandemic preparedness plans comprise more than just influenza vaccination and include, for example, vaccination against pneumococcal disease.[2,3]

Vaccinating healthcare workers against pneumococcal disease is a strategy with significant potential, but it is not without countervailing arguments. For example, based on what is known about the efficacy of pneumococcal polysaccharide vaccine (PPV) against invasive pneumococcal disease (IPD), is this a cost-effective solution? Given the worldwide nature of a pandemic, potential costs associated with prevention measures must be considered. Furthermore, concerns about hyporesponsiveness (ie, immunologic interference from the first dose, limiting gains from a subsequent dose)[4] raise the question whether vaccination of healthy healthcare workers during a pandemic merely shifts the burden of pneumococcal disease to later years, without changing the cumulative incidence of disease. The objective of this study was to use Markov modeling to assess the cost-effectiveness of PPV among healthcare workers compared with nonuse of PPV during an influenza pandemic. The results of these analyses will help health systems to anticipate needs and costs in their pandemic preparedness planning.

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METHODS

The cost-effectiveness of 23-valent PPV use among healthcare workers was compared with nonuse of PPV

Take-Away Points

A cause of extended morbidity and mortality in previous influenza pandemics has been invasive pneumococcal disease.

- In an influenza pandemic, healthcare resources will be strained as increased numbers of patients seek care and healthcare workers fall ill and cannot work.
- A potential means of preventing healthcare worker illness and absence from work is to vaccinate them with pneumococcal polysaccharide vaccine.
- From a societal perspective, this strategy is cost-effective, costing $3.14 per healthcare worker and $2935 per quality-adjusted life-year gained.
- From the hospital perspective, vaccinating healthcare workers was expensive, costing $1676 per employee absence day avoided.

during an influenza pandemic using a Markov model, shown schematically in **eAppendix A** (available at **www.ajmc.com**). The model was programmed using available software (TreeAge Pro Suite; TreeAge Software Inc, Williamstown, MA). In the model, identical hypothetical cohorts of previously unvaccinated healthcare workers can remain well or develop IPD. Those developing IPD can recover completely, become disabled, or die of IPD. Risks of death from other causes for individuals in any health state can be determined from US life table data.[5] Patients with disabilities due to IPD will die at higher rates. We model increases in IPD rates that might occur as a result of influenza but do not model influenza itself.

Three model assumptions were made that potentially bias it against PPV use in healthcare workers. The first assumption is that pneumococcal disease transmission from healthcare worker to patient does not occur. This assumption is based on pneumococcal disease resulting as an influenza complication in an individual already colonized with pneumococci and the unlikely possibility of simultaneous transmission of influenza and pneumococcus.[6] The second assumption is that heightened IPD risk due to pandemic influenza occurs for only 1 year, as the duration of any influenza pandemic is unknown. The third assumption is that PPV does not prevent noninvasive pneumonia, as PPV protection against noninvasive pneumonia is unclear and controversial.[6]

Analyses were performed from societal and hospital perspectives. In the societal perspective analysis, the time horizon was 15 years with costs and benefits discounted at 3% per year, following the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine.[7] Effectiveness was valued in quality-adjusted life-years (QALYs) to account for changes in life span and quality of life due to PPV. Quality-adjusted life-years are the product of the time spent in a health state and the quality-of-life utility associated with that state summed over time; utilities are a measure of preference for a health state, ranging from 0 (death) to 1 (perfect health). In all analyses, costs were estimated in 2006 US dollars. In the hospital perspective analysis, the effectiveness term was employee absence day avoided over a 5-year time horizon, and the following 3 additional assumptions were made: (1) all direct medical costs are covered by insurance, (2) all healthcare workers with IPD miss work for 10 days, and (3) 2 months are required to replace healthcare workers who are disabled due to IPD or who die of IPD.

Age-specific IPD incidence data in **eAppendix B** (available at **www.ajmc.com**) were incorporated into the model.[8] In the base-case analysis, we assumed that IPD cases and deaths occurred at twice the usual rate during the year of pandemic influenza in healthcare workers with a mean age of 45 years. This age was derived using US Bureau of Health Professions data for registered nurses and licensed practical nurses, who comprise the bulk of healthcare workers.[9,10] We averaged the published age distributions of these workers to calculate the usual IPD rate for this cohort, 13.7 cases per 100,000, using CDC Active Bacterial Core surveillance data (**eAppendix C** available at **www.ajmc.com**).[8] Using similar methods, we aged the cohort 15 years and calculated an IPD risk of 24.4 cases per 100,000 and then used linear interpolation to estimate IPD risk between years 1 and 15. We used the general population risk because there are no specific data on IPD risk in healthcare workers. Therefore, IPD rates were varied from 50% to 150% of their base-case levels in a separate sensitivity analysis.

The concept of increased pneumococcal disease rates is based on autopsy studies[2,11] demonstrating pneumococcal bacteremia and empyema in the 1918-1919 pandemic and bacterial lung infection in the 2009 pandemic. Because the specific effect of influenza on IPD is unknown, we arbitrarily set IPD rates at twice the usual rate and varied the relative risk of IPD from 1 (no change in IPD rates) to 6 (6 times the usual IPD rates) in sensitivity analyses. The probability that IPD was caused by a pneumococcal serotype contained in the PPV was derived from CDC Active Bacterial Core surveillance data[12] in **eAppendix C**. Costs related to vaccination and vaccination adverse events were also obtained from the literature,[13-16] and age-specific IPD costs were obtained from the 2006 National Inpatient Sample (**Table 1**).[17-21] A panel of pneumococcal disease experts estimated duration-specific protection from PPV for susceptible pneumococcal serotypes,[12] basing their estimates on data by Shapiro et al[22] (**Table 2**). Invasive pneumococcal disease–related meningitis incidence was used as a proxy for the probability of IPD-related disability.[12]

For all variables, the base-case value and range of values examined in 1-way sensitivity analyses are given in Table 1.

■ **Table 1.** Base-Case Values and Ranges Examined in Sensitivity Analyses for Societal Perspective and Hospital Perspective

Variable	Base Case	Range		Source
		Low	High	
Age of cohort, mean, y	45	20	59	Assumed
PPV efficacy	Table 2	—	—	Smith et al,[12] 2008
IPD incidence, nonpandemic	eAppendix B	—	—	Centers for Disease Control and Prevention,[8] 2008
IPD relative risk, pandemic[a]	2	1	6	Assumed
IPD-related disability, %				
Probability	5.9	0	10.0	Centers for Disease Control and Prevention,[8] 2008
Yearly mortality excess	10.0	0	50.0	Estimate, Smith et al,[12] 2008
Vaccine adverse effects				
Probability, %	3.2	2.2	4.6	Jackson et al,[18] 1999
Duration, d	3	1	8	Jackson et al,[18] 1999
Societal Perspective Costs, $				
IPD, per episode				National Inpatient Sample data
Discharged alive, age range, y				
20-29	25,008	Base	Base	
30-39	20,758	Base	Base	
40-49	22,870	Base	Base	
50-64	24,519	Base	Base	
65-74	20,416	Base	Base	
Died during hospitalization, age range, y				
20-29	36,518	Base	Base	
30-39	41,468	Base	Base	
40-49	34,043	Base	Base	
50-64	33,778	Base	Base	
65-74	29,263	Base	Base	
Vaccination	30	10	50	Messonnier et al,[17] 2009
Disability per year	10,000	0	20,000	Estimated
Hospital Perspective Costs, $				
Temporary replacement per worker with IPD[b]	2676	Base	Base	US Bureau of Labor Statistics,[19] 2008
Disability per worker disabled with IPD	32,000	16,000	48,000	Kamal-Bahl et al,[20] 2006
Death per worker dying of IPD	55,000	27,500	82,500	Kamal-Bahl et al,[20] 2006
Permanent replacement, recruitment, training	28,000	14,000	42,000	Kamal-Bahl et al,[20] 2006
Utilities				
Healthy, age range, y				
18-54	0.92	0.84	1.00	Gold et al,[21] 1998
55-64	0.88	0.80	0.96	Gold et al,[21] 1998
64-74	0.84	0.77	0.91	Gold et al,[21] 1998
IPD	0.2	0.1	0.60	Sisk et al,[13] 2003
Disabled	0.4	0.2	0.60	Estimate, Gold et al,[21] 1998
Vaccine adverse effects	0.9	0.8	0.99	Estimate, Gold et al,[21] 1998

IPD indicates invasive pneumococcal disease; PPV, pneumococcal polysaccharide vaccine.
[a]Base case assumes that IPD incidence during an influenza pandemic is twice the usual age-specific IPD incidence.
[b]Assumes each healthcare worker with IPD misses 10 days of work, and a 50% premium for temporary healthcare workers is assessed.

Two-way sensitivity analyses were conducted to examine the combined effect of age and IPD rate variation on model results. To test the robustness of model results, parameter values were varied simultaneously in a probabilistic sensitivity analysis in which variables were assigned distributions and values were chosen from each distribution 5000 times. Uniform distributions were used for utility values, triangular distributions were used for hospital perspective costs, and clinical trial data and CDC data were assigned distributions based on data characteristics and skewness. Triangular distributions were also used to model estimates of PPV efficacy using the time-specific base-case estimates given in Table 2 as the most common value and the low-range and high-range efficacy estimates as the lower and upper bounds of these distributions.

Table 2. Estimates of Pneumococcal Polysaccharide Vaccine Efficacy for Susceptible Serotypes Over Time by Expert Panel[12,22]

Time After Vaccination, y	Base Case, %	Range, %	
		Low	High
1	93	80	95
3	89	74	94.5
5	85	66	90
7	60	40	75
10	20	0	30
15	0	0	20

RESULTS

Societal Perspective

Base-case results are summarized in Table 3. For healthcare workers with a mean age of 45 years and twice the usual IPD incidence and mortality rates during the pandemic influenza year, the per-patient total cost (including vaccination and IPD costs) for the PPV strategy was $3.14 greater than no vaccination, while gaining 0.00107 QALY (about 0.4 day). Therefore, the incremental cost-effectiveness ratio of vaccination compared with no vaccination was $2935 per QALY gained.

We estimated that 284 cases and 32 deaths per 100,000 healthcare workers would occur without PPV and that 171 cases and 19 deaths per 100,000 healthcare workers would occur with PPV. Therefore, a PPV strategy prevented about 40% of IPD cases and deaths in healthcare workers.

In 1-way sensitivity analyses in which parameter values were individually varied, results were most sensitive to healthcare worker age, with incremental cost-effectiveness ratios exceeding $100,000 per QALY for healthcare workers 29 years or younger (Figure 1). Conversely, pandemic-based PPV was cost saving for healthcare workers 49 years or older under base-case assumptions. Results were less sensitive to variation of IPD relative risk (eAppendix D available at **www.ajmc.com**). In a 2-way sensitivity analysis, we varied the healthcare worker age and the relative risk of IPD during an influenza pandemic year (Figure 2). Using an acceptability threshold of $100,000 per QALY gained, PPV would be favored for workers 29 years or older when the relative IPD risk is 1 or higher or for all workers (regardless of age) when the relative risk is 3.4 or higher.

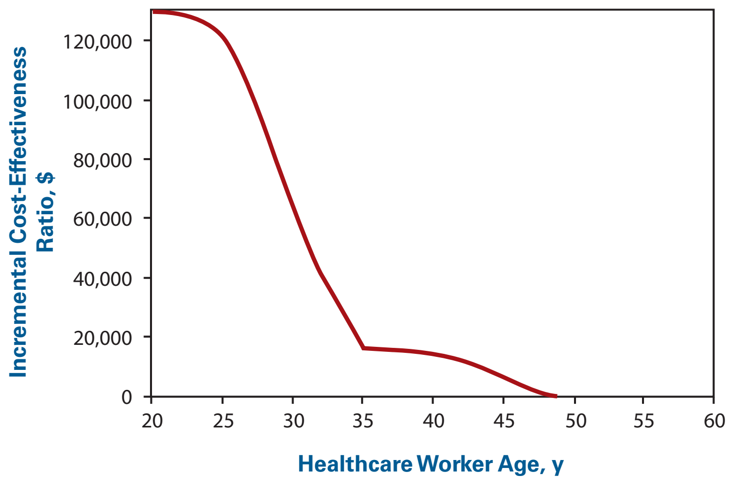
When the base-case variables were used with a heightened IPD risk related to pandemic influenza lasting 2 years instead of 1 year, PPV costs $398 per QALY gained. If no increase in IPD rates occur with an influenza pandemic or if a pandemic occurs after PPV loses effectiveness (ie, after 15 years), PPV costs $6199 per QALY. While there is no standard criterion for cost-effectiveness, interventions that cost less than $100,000 per QALY gained are generally acceptable and are comparable to other commonly used interventions.[23] Interventions that

Table 3. Cost-Effectiveness of Pneumococcal Polysaccharide Vaccine (PPV) Among Healthcare Workers in the Base-Case Analysis

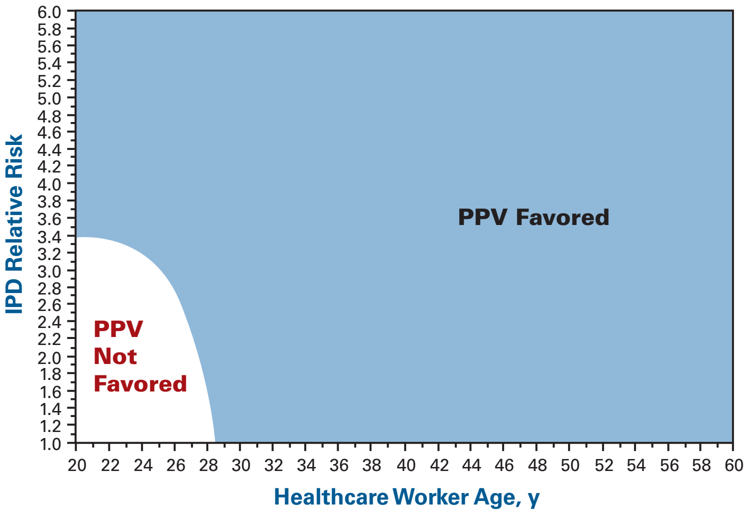
Vaccination Strategy	Cost, $	Incremental Cost, $	Effectiveness[a]	Incremental Effectiveness[a]	Cost-Effectiveness Ratio, $
Societal Perspective					
No PPV	60.01	—	10.70071	—	—
PPV	63.16	3.14	10.70178	0.00107	2935
Hospital Perspective					
No PPV	13.23	—	0.01759	—	—
PPV	33.94	20.71	0.00523	0.01236	1676

[a]Effectiveness and incremental effectiveness are quality-adjusted life-years for societal perspective and employee absence days avoided for hospital perspective.

■ **Figure 1.** One-Way Sensitivity Analysis Showing the Effects of Age Variation on Cost-Effectiveness Results



■ **Figure 2.** Two-Way Sensitivity Analysis Showing the Effects of Simultaneous Variation



Using an acceptability threshold of $100,000 per quality-adjusted life-year gained shows the effects of simultaneous variation of age and the invasive pneumococcal disease (IPD) multiplier (the relative risk of IPD) during a pandemic influenza year compared with a usual year.
PPV indicates pneumococcal polysaccharide vaccine.

cost less than $20,000 per QALY gained are typically thought to be a "good buy" and to represent strong evidence for adoption.[24] Evidence suggests higher acceptability thresholds for interventions related to occupational health,[25] making our results even more favorable from that standpoint. The CDC Active Bacterial Core surveillance IPD risk data are risks for the general population; it is unclear if this risk applies to healthcare workers. Using 50% to 150% of the general public's risk as a way to assess varying risk for healthcare workers, PPV in healthcare workers costs $31,600 per QALY if their IPD risk is 50% of the general population risk, and PPV is cost saving if healthcare worker risk is 150% of the general population risk.

In a probabilistic sensitivity analysis, all variable values listed in Table 1 were simultaneously varied. Vaccinating all healthcare workers was favored more than 91% of the time using an acceptability threshold of $20,000 per QALY and more than 99% of the time using an acceptability threshold of $100,000 per QALY.

Hospital Perspective

From a hospital perspective, the PPV strategy had a total cost per vaccinated worker that was $20.71 greater than no vaccination, while avoiding 0.01236 absence day per worker, for a cost-effectiveness ratio of $1676 per employee absence day avoided (Table 3). This figure could be an overestimate given the assumption of no vaccine efficacy for noninvasive pneumonia, and that does not account for lost revenue due to reduced hospital manpower and capacity, as well as the intangible costs of negative public perception if hospital services were to be curtailed. Pneumococcal polysaccharide vaccination in healthcare workers costs $4103 per employee absence day avoided if their IPD risk is 50% of the general population risk and costs $867 per employee absence day avoided if their IPD risk is 150% of the general population risk. In a probabilistic sensitivity analysis, the 95% probability range for vaccination compared with no vaccination was $20 to $10,800 per employee absence day avoided.

DISCUSSION

In this analysis, PPV is an economically reasonable strategy to be considered for healthcare workers during an influenza pandemic from a societal perspective, with robust results in 1-way sensitivity analyses and a high likelihood of cost-effectiveness in a probabilistic sensitivity analysis. Our results are comparable to findings of a recent analysis by the CDC examining PPV use in critical infrastructure personnel (eg, healthcare workers and utility workers).[17,26] The investigators estimated 35,000 invasive and non-IPD cases in a population of 20 million, or an attack rate of 175 per 100,000. Using their age-specific hospitalization rates and assuming that 25% of workers are 50 years or older, the pneumococcal disease hospitalization rate was about 25.8 per 100,000. If half of those hospitalized had IPD, then the IPD rate was 12.9 cases per 100,000, slightly less than our calculated IPD rate in healthcare workers, 13.7 cases per 100,000. Using 0.942 (ie, 12.9 of 13.7), the IPD relative risk derived from their study, in our analysis produces an incremental cost-effectiveness ratio of $6419 per QALY gained. This value falls within the range of their discounted life-years saved result of $37,320 (95% confidence interval, $5865-$80,359). Unlike our analysis, the CDC study did not use utilities or account for disability or PPV effects beyond the pandemic year.[17]

On the other hand, from the hospital perspective, PPV of healthcare workers costs $1676 per employee absence day avoided, which most hospitals would consider a steep premium to pay for a small expected return. Our analysis highlights the dilemma many hospital systems face in trying to do the right thing from a societal standpoint, while at the same time attempting to remain fiscally sound. Managed care faces this tension of hospital versus societal perspectives as it seeks to maximize health in a cost-effective way. Even with a heightened risk of pneumococcal disease during an influenza pandemic, the risk of IPD would probably remain less than 1% for healthcare workers, and this fact might lead hospital systems to defer PPV for their workers unless some subsidy to defray vaccination costs was available. We did not include the possibility that healthcare workers would infect other workers or patients or that hospitals would be unable to meet staffing needs due to absenteeism; therefore, our estimates are conservative. Maintenance of appropriate staffing levels is a priority in managed care. Although expensive from the hospital perspective, vaccination may lead workers to perceive themselves as better protected and to be more willing to work in the face of a pandemic. Given that PPV is less expensive than many other occupationally indicated vaccines, it may be reasonable to consider PPV as a means to allay worker concerns about complications of pandemic influenza.

From a societal standpoint, PPV administration to healthy healthcare workers at the onset of a pandemic has pros and cons. Vaccination is likely to reduce IPD[27-30] and in healthy workers may reduce pneumococcal pneumonia.[31] However, concerns exist about vaccine efficacy against noninvasive pneumonia and about hyporesponsiveness to subsequent vaccination, also known as tolerance.[4] If hyporesponsiveness occurs following PPV, it might simply shift the burden of pneumococcal disease from the time of the pandemic to later in the life of the healthcare worker, without changing the cumulative incidence. Repeat doses of PPV later in life are generally safe[18]; therefore, the concern is not safety at the time of vaccination or of repeat vaccination years later but of potential hyporesponsiveness. Another potential limitation of our analysis is that recent PPV recommendations[32] have added smoking and asthma to the list of comorbid conditions for which vaccination before age 65 years is recommended and could further lessen the effect of healthcare worker vaccination given the considerable proportion of workers falling into these categories.

Because of the current absence of clinical trial data and for the foreseeable future, we used a Markov model to synthesize available data. We also used a series of conservative estimates and assumptions, including PPV effectiveness against IPD, not pneumococcal pneumonia, although some data suggest that PPV may have effectiveness against pneumonia in healthy adults.[31] Despite these assumptions, vaccination of healthcare workers with PPV was cost-effective from the societal perspective. Limitations include the unknown increased IPD risk in a pandemic and the inability to address PPV effect on hyporesponsiveness to future pneumococcal vaccines, either polysaccharide or conjugate, the latter of which may be licensed for adults in the future. We used longer time horizons than prior analyses; this has the advantage of not being limited to pandemic effects but has the disadvantage of not accounting for future new vaccines and changes in epidemiology. Because we used a 15-year time frame and a single PPV in those who were previously unvaccinated and because current CDC recommendations only call for PPV revaccination at age 65 years for those vaccinated before that age, we did not include revaccination as part of our analyses of current workers. If a longer time horizon was examined or if hyporesponsiveness occurred, greater costs per QALY gained would result.

In conclusion, vaccinating all healthcare workers to protect against pneumococcal disease during a pandemic influenza outbreak is likely to be economically reasonable according to a societal perspective in an analysis biased against vaccination. However, when analyzed from a hospital perspective, PPV is expensive, and the small risk of illness might prevent hospital implementation unless vaccination is externally subsidized.

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