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Cost-Effectiveness and Public Health Impact of Influenza Vaccine Strategies for US Seniors

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Abstract

Objectives—Four influenza vaccines are available in the US for persons aged ≥ 65 years: trivalent inactivated influenza vaccine (IIV3), quadrivalent inactivated influenza vaccine (IIV4), a more expensive high-dose IIV3, and a newly approved adjuvanted IIV3, but their cost-effectiveness when all 4 vaccines are compared is unknown.

Methods—Markov model to estimate the cost-effectiveness and public health benefits of influenza vaccination strategies in US elders.

Results—IIV3 cost \$3690 per quality adjusted life year (QALY) gained compared to no vaccination. Compared to IIV3, IIV4 cost \$20,939/QALY gained and, compared to IIV4, high-dose IIV3 cost \$31,214/QALY. The model projected 83,775 fewer influenza cases and 980 fewer deaths with high-dose IIV3 compared to the next most effective vaccine, IIV4. In a probabilistic sensitivity analysis, high-dose IIV3 is the favored strategy if willingness to pay is ≥ \$25,000/QALY gained. Adjuvanted IIV3 cost-effectiveness depends on its price and effectiveness (both not yet determined in the US), but could be favored if its relative effectiveness is 15% greater than IIV3.

Conclusions—From economic and public health standpoints, high-dose IIV3 for adults ≥ 65 years old is likely to be favored over the other vaccines, based on currently available data. The cost-effectiveness of adjuvanted IIV3 should be reviewed after its effectiveness compared to other vaccines is determined and its US price established.

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For “yes” x mark(s): give brief explanation below:

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Keywords

Influenza vaccination; High dose IIV3; Cost effectiveness

INTRODUCTION

Influenza continues to be a major cause of morbidity and mortality in persons 65 years of age and older in the US. Every year, up to 250,000 hospitalizations due to influenza occur in this age group,(1) with up to 30,000 influenza-related deaths per year.(2) However, protection afforded to older populations through influenza vaccination is unclear and controversial, leading to investigation of vaccination options for this group.(2) At present, 4 influenza vaccines are available in the US for persons aged 65 years: trivalent influenza vaccine (IIV3) which, until relatively recently, was the only option available; quadrivalent influenza vaccine (IIV4), which adds a 2nd influenza B lineage to IIV3; a newer and more expensive high-dose IIV3; and a recent FDA-approved adjuvanted IIV3, whose US price is not yet determined and whose effectiveness compared to high-dose IIV3 is, at present, unknown. A multicenter, randomized, controlled, phase IIIb-IV study found better protection with high-dose IIV3 compared to IIV3, with comparable safety outcomes between vaccines.(3) A trial-based cost effectiveness analysis comparing these 2 vaccines showed high-dose IIV3 be a less costly and more effective than IIV3; (4) other vaccines were not considered in this analysis.

Influenza vaccine choice in elders poses some dilemmas. Head-to-head clinical trial effectiveness comparisons are limited to high-dose IIV3 versus IIV3, without comparisons to IIV4 or adjuvanted IIV3. It is not clear if the benefits of the newer vaccines are worth their added cost. In addition, there is currently only 1 US high-dose IIV3 manufacturer, potentially limiting choice and bringing market forces into play in vaccine choice decisions. Finally, consideration of adjuvanted IIV3 requires ongoing observation to measure population comparative effectiveness and more specific pricing information.(5)

To investigate these issues, we performed a cost-effectiveness analysis comparing, in the main analysis, IIV3, high-dose IIV3, and IIV4 in older individuals, seeking to explore how model parameter variation might affect influenza vaccine decision making in this vulnerable group. In a separate analysis, we also explore the favorability of adjuvanted IIV3 compared to the other vaccines in hypothetical scenarios.

METHODS

We estimated the cost effectiveness and expected population outcomes of influenza vaccination strategies for US adults 65 years of age using a Markov state transition model. The model simulated identical hypothetical cohorts moving through influenza vaccination and infection health states over the course of a single influenza season. In the primary analysis, we compared four strategies: 1) no vaccine, 2) IIV3, 3) IIV4, or 4) high-dose IIV3. We used quality adjusted life years (QALYs) to measure the duration and quality of life in cost effectiveness comparisons. The analysis took a societal perspective, following reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine.(6) In a

secondary analysis, we add consideration of the adjuvanted IIV3 in hypothetical scenarios, due to uncertainties regarding its comparative effectiveness and its ultimate US price.(5)

The Markov model began with all individuals unvaccinated in August and terminated in May after 10 monthly iterations over a single influenza season. Vaccination likelihood by month was derived from the observed US monthly influenza vaccination average frequencies(7) was 0 for all 10 months, and was the same for each vaccine type. The monthly likelihood of influenza infection was computed from the reported incidence from the 2009–2010 through 2013–2014 influenza seasons to approximate influenza frequency in the unvaccinated. Both vaccinated and unvaccinated individuals were susceptible to influenza infection. For those who were vaccinated, influenza likelihood was adjusted by each vaccine's effectiveness.(7) Increased IIV4 effectiveness compared to IIV3 was modeled as a relative increase in effectiveness, based on the average likelihood of uncovered influenza B from 1999–2000 through 2013–2014.(8) Increased high-dose IIV3 effectiveness compared to IIV3 was calculated as an increase in relative effectiveness (0.242), based on randomized trial data.(3) We assumed that vaccine-related adverse event risk was the same for all vaccine types, using available data for IIV3 adverse event incidence due to sparse data on the other vaccines.(3) We modeled three outcomes from influenza infection: recovery, hospitalization and recovery, or death. The model excluded all other causes of death, assuming mortality from other causes is unaffected by vaccination strategy, perhaps biasing against vaccination. Recovered individuals remained immune through the remainder of the influenza season.

Modeling identical cohorts assumes that all noninfluenza events will occur identically between modeled strategies, cancelling out between strategies in incremental analyses, and that risk is homogenous within the cohort. Differences in vaccine effectiveness that might occur due to comorbidities or immunosuppressive treatment within portions of the cohort were examined through varying vaccine effectiveness for the entire cohort over plausible ranges in sensitivity analyses.

Model parameters are shown in Table 1. When possible, we selected costs, utilities, and probabilities from the most current and robust data sources, as noted. We estimated vaccination coverage and influenza incidence as cumulative monthly likelihoods. These values were calculated by first computing the average monthly proportions of vaccine uptake and influenza incidence across the prior five influenza seasons and then by defining a function to output a standardized cumulative monthly value for these parameters. (7) These functions were applied to the overall seasonal probabilities of vaccine receipt and of contracting influenza to produce values for each monthly Markov cycle. The model assumed that only one vaccine type was available in each strategy, which excludes patient or physician preference as a factor, and used identical values for vaccination uptake for all strategies. The model did not account for possible indirect (herd immunity) effects, which are expected to be low when elders are vaccinated but, if present, could bias the analysis against vaccination strategies.

We derived influenza illness event probabilities from estimates of US influenza complications and mortality.(9, 10) Additionally, we computed a probability of seeking

outpatient care among non-hospitalized influenza cases as a function of published age-specific influenza complication rates (10) For those seeking outpatient care, we assumed 100% would receive antivirals and varied this value widely in sensitivity analyses.(11) Age-specific influenza complication rates informed the estimation of time spent seeking or receiving care.(10) Among those who sought outpatient care and were not hospitalized, we assumed one physician visit.

Hospitalization due to influenza was modeled as a case-hospitalization rate, identical for all vaccines, which assumes that hospitalization rates are affected only by vaccination effects on influenza case rates, and not by any vaccination-specific effects on influenza hospitalization. This assumption is consistent with clinical trial and epidemiologic data.(3, 12) We tested these influenza case-hospitalization assumptions in sensitivity analyses both by varying case-hospitalization rates simultaneously for all vaccines over broad ranges to include rates from recent data (3, 12) and by examining differential vaccine protection from hospitalization.

In the cost-effectiveness calculation, effectiveness was tracked as a disutility value, representing the lost quality and duration of life from influenza vaccination and illness events.(10) QALYs lost due to influenza mortality were discounted at 3% per year. All vaccine-related adverse events were assumed to be minor and to result in a maximum of one day of lost quality of life.

Costs were obtained from relevant medical economic databases and scientific literature sources as noted in Table 1. Vaccine prices were determined by the private sector costs of the 2014 CDC Adult Influenza Price List(13) except for high-dose IIV3, which was estimated using its average wholesale price.(14) Oseltamivir was the selected antiviral treatment for individuals seeking medical treatment(11) and the cost of a 40 count bottle of 200 mg ibuprofen tablets was assessed for each non-hospitalized vaccine adverse event.(15) Additionally, all costs were inflated to 2014 levels based on the US Consumer Price Index.

We computed the expected population outcomes of each immunization strategy for influenza cases, influenza-related deaths, and influenza-related hospitalizations, as calculated by the decision model, based on event frequency in the modeled cohort when base case parameter values (Table 1) were used. These cohort-based per-person event probabilities were then multiplied by the US Census estimated 2013 US population 65 years or older(16) to obtain event frequency values.

In sensitivity analyses, each parameter was individually varied (i.e., a 1-way sensitivity analysis) across its listed range (Table 1). Then all parameters were simultaneously varied in a probabilistic sensitivity analysis, where values were randomly sampled, once per model iteration, from parameter-specific distributions for 5,000 iterations. Distributions were assigned to parameters based on data characteristics, parameter uncertainty and methodologic standards.(17) Probabilities, utilities, and vaccine effectiveness values were assigned beta distributions, costs assigned gamma distributions, and counts used Poisson distributions. Exceptions include QALYs lost due to influenza death and days of influenza-related hospitalization, which used gamma distributions. Probabilistic sensitivity analysis

results are presented using the commonly cited benchmark of \$100,000 per QALY gained. (18, 19)

RESULTS

Table 2 shows the base case results. Per person influenza vaccination and illness costs were \$4.13 higher with IIV3 compared to no vaccination while gaining 0.00112 QALYs (or about 10 hours) at a value of \$3693 per QALY gained. Compared to IIV3, IIV4 cost \$2.02 more and gained 0.0001 QALYs, or \$20,939/QALY gained. High-dose IIV3, compared to QID, cost \$31,214 per QALY gained.

From a public health standpoint, when model-based influenza outcome probabilities for the modeled cohort were applied to the 2013 US population aged 65 or older (44,704,074), IIV3 prevented 510,643 influenza cases, 21,498 hospitalizations, and 5975 deaths compared to no vaccination. IIV4, compared to IIV3, prevented an additional 39,136 cases, 1,648 hospitalizations, and 458 deaths. Compared to IIV4, high-dose IIV3 averted 83,775 additional cases, 3537 hospitalizations, and 980 deaths. When considering total population influenza vaccination and illness costs, IIV3 cost about \$185 million more than no vaccination, while IIV4 cost \$90 million more than IIV3 and high-dose IIV3 cost \$289 million more than IIV4.

One-way sensitivity analyses showed that, under most circumstances, high-dose IIV3 cost less than \$100,000/QALY gained compared to IIV3 or IIV4. However, variation of 4 parameters: IIV3 effectiveness, the relative increase in high-dose IIV3 effectiveness compared to IIV3, the proportion of influenza caused by influenza B that was not a IIV3 component, and influenza likelihood in the unvaccinated, caused high-dose IIV3 to cost > \$100,000/QALY gained. Vaccination strategy favorability was most sensitive to variation of IIV3 effectiveness (base case estimate 39%): if it was <10%, no vaccination was favored; if between 10% and 12.1%, IIV3 was favored; if between 12.1% and 15.5%, IIV4 was favored; and if >15.5%, high-dose IIV3 was favored. Also, high-dose IIV3 cost > \$100,000/QALY gained (and IIV4 favored) if the relative increase in high-dose IIV3 effectiveness was <0.143 (base case 0.242), the proportion of influenza due to uncovered influenza B was >17.6% (base case 7.7%), or influenza likelihood was <2.4% (base case 5.9%). Individual variation of all other probability, cost, and utility parameters over their listed ranges in Table 1 and of the likelihood of receiving antiviral therapy did not affect the favorability of high-dose IIV3. Thus, results were sensitive to potential fluctuations in yearly influenza attack rates, virus variability, and vaccine effectiveness, but not to other model parameters, including vaccination cost.

Recent studies have highlighted influenza vaccination effects on hospitalization(3, 12), where high-dose IIV3 decreased both influenza case rates and hospitalization rates relative to IIV3, with case and hospitalization rates moving similarly. These findings suggest that vaccination affects hospitalization rates though effects on influenza case rates, and not by any vaccination-specific effects on hospitalization. However, in sensitivity analyses, we specifically examined influenza hospitalization rates by varying case-hospitalization rates for all vaccines and by exploring possible differential protection from hospitalization

between vaccines. When case-hospitalization was decreased from 4.21% (base case) to 2.2%, the lowest value observed in a recent clinical trial(3), high-dose IIV3 cost \$32,766/QALY gained (compared to \$31,214/QALY in the base case analysis) and \$19,462/QALY when case-hospitalization was 20%. When examining differential hospitalization protection between vaccines, if the IIV3 case-hospitalization rate was 5.7%, then IIV3 was dominated (more costly, less effective) by other strategies. Conversely, if high-dose IIV3 case-hospitalization is halved (to 2.1%), high-dose IIV3 was favored, costing \$19,440/QALY gained.

A cost-effectiveness acceptability curve (Figure 1) depicts the probabilistic sensitivity analysis results showing, for each x-axis willingness-to-pay value, the probability that each strategy would be acceptable at that value over 5000 model iterations. In this analysis, high-dose IIV3 was favored in 49.3% of iterations if willingness-to-pay is \$50,000/QALY gained and in 68.5% of iterations at \$100,000/QALY gained. If willingness-to-pay is \$25,000/QALY gained or more, high-dose IIV3 was the most likely strategy to be favored.

In a secondary analysis, adding consideration of the newly licensed but as yet unavailable adjuvanted IIV3(20) we examined scenarios varying its effectiveness compared to the other vaccines and its cost, given unresolved uncertainty in these areas.(5, 20) These analyses assumed equal adverse event frequency between adjuvanted IIV3 and high-dose IIV3. Adjuvanted IIV3 was compared to the other strategies in a 2-way sensitivity analysis, simultaneously varying adjuvanted IIV3 effectiveness relative to IIV3 (range 0 to 0.5 increased) and its price (\$10–\$50). Over the entire price range and assuming willingness to pay of \$100,000/QALY gained, adjuvanted IIV3 was not favored if its relative effectiveness increase was <0.15, but was favored if its relative effectiveness was 0.32. If its relative effectiveness increase equals that of high-dose IIV3(0.242), it would be favored if its cost was less than high-dose IIV3's cost, \$31.20.

DISCUSSION

A newer, more expensive high-dose influenza vaccine is available for use in US elders. Our analysis suggests that, even with its substantially higher per-dose cost (\$21.51 more), high-dose IIV3 is an economically favorable strategy in for US adults 65 years of age, costing \$31,214 per QALY gained compared to other available vaccines. Model projections of added public health benefit due to high-dose IIV3 use found substantial decreases in influenza cases, hospitalization, and deaths compared to other vaccine options in US elders. Results were robust in sensitivity analyses, but were sensitive to variation of vaccine effectiveness and influenza likelihood parameters. Most importantly, if the relative effectiveness of high-dose IIV3 compared to IIV3 is much lower than that observed in clinical trials, then high-dose IIV3 will no longer be the favored strategy. The newer adjuvanted IIV3 could be favored, but further consideration of this vaccine awaits comparative effectiveness data and pricing information.

The favorability of high-dose IIV3 over other vaccines in US elders largely hinges on the reproducibility of heightened high-dose IIV3 effectiveness, as seen in clinical trials, in population-based settings. Whether this is the case is unclear at this point. An industry-

sponsored trial provides evidence for greater high-dose vaccine effectiveness,(3, 20) and similar results were found in an FDA-sponsored retrospective cohort study using US Medicare claims data during the 2012–2013 influenza season, with the high-dose influenza vaccine 22% more effective in preventing influenza infections and hospitalizations than the standard-dose vaccine.(12) Future verification of heightened effectiveness will be required.

CDC and its Advisory Committee on Immunization Practices (ACIP) have not yet expressed any preference regarding the influenza vaccines available for individuals aged 65 years or older.(21) In making their recommendations, ACIP uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to provide an evidence base for their deliberations,(22) where evidence is graded based on type (e.g., randomized trials, observational studies) and strength .(22) Changes in CDC recommendations regarding high-dose IIV3 use in older individuals will likely depend on further confirmation of industry-supported clinical trial findings. In any case, influenza morbidity and mortality in older Americans suggests the need for better protection than that afforded by IIV3. This analysis supports use of high-dose IIV3 to reduce influenza impact in the elderly.

This analysis has some notable strengths and limitations. It was based on randomized controlled trial data that suggested significantly improved effectiveness with high-dose IIV3 use in elders,(3) with those findings subsequently supported by a retrospective study.(12) A prior trial-based cost-effectiveness analysis compared IIV3 and high-dose IIV3, but did not include the other vaccines.(4) We performed extensive sensitivity analyses and found our results robust to simultaneous variation of all model parameters in a probabilistic sensitivity analysis, but sensitive to individual variation of some vaccine effectiveness and influenza likelihood parameters, pointing out areas where continued surveillance is needed. As in any modeling exercise, some simplifying assumptions were made, perhaps limiting model realism. However, whenever possible, our assumptions consistently biased the model against vaccination strategies, for example, assuming that influenza vaccination affected only deaths due to influenza and not those due to other causes, and that vaccinating elders had no herd immunity effects. Thus, our vaccination strategy cost-effectiveness values are likely somewhat more pessimistic than they would be if assumptions without this consistent bias were made. However, we did not consider the possibility of differential availability/affordability of higher cost vaccines or how vaccine manufacturers might adjust prices based on the availability and market share of newer vaccines which are potential limitations to the analysis. In addition, we used published sources for influenza-related health care utilization and costs, not Medicare claims data, and thus could have underestimated the benefits of vaccination; if this is the case, then vaccination would be even more favorable.

We anticipate development of a high-dose quadrivalent influenza vaccine. When that occurs, the cost-effectiveness of this new vaccine will need to be compared to the existing vaccines. The development of new influenza vaccines will continue, highlighting the importance of continuing evaluation of what might be gained through the use of new vaccines compared to their added cost, and whether gains are worth those costs.

CONCLUSION

Based on available data and robust analyses, high-dose IIV3 for adults ≥ 65 is likely to be an economically favorable influenza vaccination strategy with a clear, moderate public health impact. A revision of CDC influenza vaccination recommendations for elders may be warranted, pending confirmation of heightened effectiveness of high-dose IIV3 and further investigation of adjuvanted IIV3 effectiveness in the general population of individuals aged 65 years and older.

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Figure 1. Cost effectiveness acceptability curve

Plot of the results of a probabilistic sensitivity analysis. Each increment on the x axis of willingness-to-pay represents 5000 complete model iterations where the values for every variable are randomly selected from an appropriately parameterized distribution. The plotted values on the y axis represent the percentage of iterations where each strategy was cost-effective at the given willingness-to-pay. High-dose trivalent influenza vaccine strategy was favored if the willingness-to-pay was $\leq \$25,000/\text{quality adjusted life year gained}$

Table 1

Parameter Values, Ranges, and Distributions Examined in Sensitivity Analyses

	Range for sensitivity analysis				Distribution	Reference
	Base case	Low	High			
Probabilities						
Influenza illness						
Influenza	0.0590	0.0200	0.1000	Beta	(23)	
High risk patient	0.5120	0.2350	0.7850	Beta	(10)	
High risk patient seeking office visit	0.8200	0.5870	0.9630	Beta	(10)	
Non high risk patient seeking office visit	0.6200	0.5660	0.6700	Beta	(10)	
Hospitalization	0.0421	0.0190	0.0730	Beta	(9)	
Influenza mortality	0.0117	0.0059	0.0208	Beta	(9)	
Vaccination						
Vaccinated	0.6470	0.6410	0.6530	Beta	(23)	
Adverse event	0.0830	0.0780	0.0870	Beta	(3)	
Proportion uncovered Influenza B	0.0770	0.0385	0.2000	Beta	(8)	
Efficacy						
All vaccine efficacy	0.390	0.000	0.6500	Beta	(10)	
High-dose IIV3 / increased relative efficacy	0.242	0.097	0.3650	Beta	(3)	
Costs and resource utilization						
Vaccination						
IIV4 ²	\$16.15	\$8.08	\$24.23	Gamma	(13)	
IIV3	\$10.69	\$5.35	\$16.04	Gamma	(13)	
High-dose IIV3 ³	\$31.20	\$15.60	\$46.80	Gamma	(24)	
Vaccine administration cost	\$25.08	\$12.54	\$37.62	Gamma	(25)	
Adverse event	\$2.80	\$1.40	\$4.20	Gamma	(15)	
Influenza illness						
Fatal						
Total cost (high risk patient)	\$42,472.00	\$0.00	\$441,381.00	Gamma	(10)	

	Range for sensitivity analysis				Distribution	Reference
	Base case	Low	High			
Total cost (non-high risk patient)	\$53,971.00	\$0.00	\$418,783.00		Gamma	(10)
Recovered						
Outpatient						
Office visit cost (per visit)	\$73.08	\$60.22	\$92.78		Gamma	(26)
Antiviral medication cost (Oseltamivir)	\$120.60	\$60.00	\$182.00		Gamma	(11)
Non-medical direct costs (per day)	\$162.00	\$81.00	\$243.00		Gamma	(27)
Hospitalized						
Hospitalization cost (per day)	\$1,765.88	\$676.00	\$3,547.00		Gamma	(26)
Days of hospitalization	4.1	1	7		Gamma	(26)
Utility Values						
Utility of 65+	0.840	0.710	0.940		Beta	(28)
Influenza utility	0.558	0.300	0.800		Beta	(29)
Disutility Values						
Vaccination						
Adverse event	0.0027	0	0.005		Beta	Assumed
Influenza illness						
Death (quality adjusted years lost)	9.02	5	16		Gamma	(30)
Recovered						
Non-medically attended						
Days of lost productivity	1.0	0.5	1.5		Poisson	(10)
Outpatient						
Days of lost productivity (high risk patient)	7.0	3.5	10.5		Poisson	(10)
Days of lost productivity (non-high risk patient)	3.0	1.5	4.5		Poisson	(10)
Hospitalized						
Days of lost productivity (high risk patient)	18	10	27		Poisson	(10)
Days of lost productivity (non-high risk patient)	13	6	20		Poisson	(10)

¹ Trivalent influenza vaccine

² Quadrivalent influenza vaccine

High-dose trivalent influenza vaccine

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Cost-Effectiveness Analysis Results for Influenza Vaccination Strategies in US Adults 65*

Table 2

Strategy	Cost	Incremental Cost	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER
No vaccine	\$96.49	–	–0.00652	–	–
IIV3	\$100.62	\$4.13	–0.0054	0.00112	\$3693
IIV4	\$102.64	\$2.02	–0.0053	0.00010	\$20,939
High-dose IIV3	\$109.10	\$6.46	–0.0051	0.00021	\$31,214

* Per person costs and effectiveness

QALY = quality adjusted life year. IIV3 = trivalent inactivated influenza vaccine, IIV4 = quadrivalent inactivated influenza vaccine