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Cost-Effectiveness and Public Health Impact of Alternative Influenza Vaccination Strategies in High-Risk Adults

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Abstract

Purpose—High-dose trivalent inactivated influenza vaccine (HD-IIV3) or recombinant trivalent influenza vaccine (RIV) may increase influenza vaccine effectiveness (VE) in adults with conditions that place them at high risk for influenza complications. This analysis models the public health impact and cost-effectiveness (CE) of these vaccines for 50–64 year olds.

Methods—Markov model CE analysis compared 5 strategies in 50–64 year-olds: no vaccination; only standard-dose IIV3 offered (SD-IIV3 only), only quadrivalent influenza vaccine offered (SD-IIV4 only); high-risk patients receiving HD-IIV3, others receiving SD-IIV3 (HD-IIV3 & SD-IIV3); and high-risk patients receiving HD-IIV3, others receiving SD-IIV4 (HD-IIV3 & SD-IIV4). In a secondary analysis, RIV replaced HD-IIV3. Parameters were obtained from U.S. databases, the medical literature and extrapolations from VE estimates. Effectiveness was measured as 3%/year discounted quality adjusted life year (QALY) losses avoided.

Results—The least expensive strategy was SD-IIV3 only, with total costs of \$99.84/person. The SD-IIV4 only strategy cost an additional \$0.91/person, or \$37,700/QALY gained. The HD-IIV3 & SD-IIV4 strategy cost \$1.06 more than SD-IIV4 only, or \$71,500/QALY gained. No vaccination and HD-IIV3 & SD-IIV3 strategies were dominated. Results were sensitive to influenza incidence,

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vaccine cost, standard-dose VE in the entire population and high-dose VE in high-risk patients. The CE of RIV for high-risk patients was dependent on as yet unknown parameter values.

Conclusions—Based on available data, using high-dose influenza vaccine or RIV in middle-aged, high-risk patients may be an economically favorable vaccination strategy with public health benefits. Clinical trials of these vaccines in this population may be warranted.

Keywords

High dose influenza vaccine; cost-effectiveness analysis; influenza vaccination policy

INTRODUCTION

High-risk conditions, such as chronic cardiac or pulmonary disease that increase the risk of influenza complications, are major factors determining morbidity and mortality due to influenza A [1, 2]. Influenza vaccine policy seeks to prevent the substantial morbidity [3] and mortality [4] associated with influenza among high-risk persons through the use of the most effective vaccines. Thus, high-dose inactivated influenza vaccine is currently recommended for individuals over age 65 years because of their age-specific reduction in immunological response and the increasing prevalence of chronic conditions in this age group. High-dose influenza vaccine has been shown to elicit higher immunological response [5] and improve protection against influenza [6], compared with the standard-dose influenza vaccine.

Due to the aging of the baby boomer generation, the US population includes an increasing proportion of middle-aged adults with chronic conditions that place them at high risk for influenza complications. The growth of this high-risk population suggests a need to consider vaccine options that could better prevent influenza. Currently, the standard-dose inactivated influenza vaccine (SD-IIV) is recommended for all adults 50–64 years of age, whether they are high risk or not, but the vaccine's effectiveness in recent years has been modest [7]. Similar to older adults, there is some evidence suggesting that 50–64 year-old adults with conditions that increase influenza risk may produce suboptimal responses to standard-dose influenza vaccine and that these, high risk individuals may benefit from high-dose vaccine [8].

Two influenza vaccine options offer the potential to better protect high-risk, middle-aged adults: (1) high-dose trivalent inactivated influenza vaccine (HD-IIV3); and (2) recombinant trivalent influenza vaccine (RIV). However, studies examining their effectiveness in this age group have not been completed. Cost-effectiveness analyses offer a relatively inexpensive and responsive method of evaluating new vaccination strategies. For example, a cost-effectiveness analysis has demonstrated that high-dose trivalent influenza vaccine is economically reasonable for use in individuals ≥ 65 years of age, given its increased effectiveness [9].

An evaluation of the cost-effectiveness of HD-IIV3 and RIV in high-risk middle-aged adults is warranted to help guide influenza vaccine policy. This study uses a Markov decision analysis to examine several strategies that include HD-IIV3 or RIV for vaccinating high-

risk, 50–64-year-old adults to determine their cost-effectiveness and the public health impact that may be realized through their use.

METHODS

Population and Model Dynamics

The decision analytic Markov model used in this analysis extended the Influenza Decision Analysis (IDA) model, which was developed to evaluate alternative influenza vaccination strategies in the U.S. population, to a high-risk, 50–64 year-old U.S. population [9]. The dynamics of the decision tree, including detailed descriptions of cost and benefit valuations and model assumptions, have been previously reported [9]. The enhanced model used in the present analysis retains the same event logic, where the probabilities of vaccination, illness, complications, treatment, recovery, and death are computed for a hypothetical cohort of individuals for each of 10 monthly cycles corresponding with a single influenza season.

In the Markov state transition model, five strategies for 50–64 year-olds were compared: no vaccination, only standard-dose trivalent influenza vaccine offered (SD-IIV3 only), only standard-dose quadrivalent influenza vaccine offered (SD-IIV4 only), high-risk patients receiving HD-IIV3 and non-high-risk individuals receiving SD-IIV3 (HD-IIV3 & SD-IIV3), and high-risk patients receiving HD-IIV3 and non-high-risk individuals receiving SD-IIV4 (HD-IIV3 & SD-IIV4). The analysis took a societal perspective, following the recently updated recommendations of the Panel on Cost-Effectiveness in Health and Medicine [10].

The present model differs from the original IDA model [9] in the population age cohort and the vaccination strategies recommended for high-risk and non-high-risk 50–64-year-old patients. The model was supplemented with logic to allow the comparison of strategies with unknown vaccine effectiveness, as the comparator strategies are either too new to have generated reliable population data or have not been routinely used in the high-risk middle-aged population. The potential cost-effectiveness of RIV was modeled in a secondary analysis in which RIV was substituted for HD-IIV3 in the HD-IIV3 & SD-IIV3 and the HD-IIV3 & SD-IIV4 strategies. This analysis was conducted as a hypothesis-generating exercise to explore scenarios where inclusion of RIV might alter the favored vaccination strategy.

Measures

Parameters used in the model are shown in Table 1. Whenever possible, costs, utilities, and probabilities were selected from the most current and robust data sources, as noted. Though several values of vaccine efficacy required new estimations based on analogous data in related populations, previously developed peer-reviewed estimates were selected when available.

A systematic review and meta-analysis of all published reports provided a pooled value for SD-IIV3 vaccine effectiveness of 59% in the adult non-elderly population [11]. This was used as the base case vaccine efficacy for the subset of non-high-risk adults 50–64 years old. The efficacy of SD-IIV3 was reduced by 10% for high-risk patients per recent findings among working-age adults [8]. Reliable estimates of the effectiveness of HD-IIV3 in high-risk adults <65 were not available. Therefore, HD-IIV3 effectiveness among high-risk 50–64

year olds was calculated as an increase in relative effectiveness over SD-IIV3. The magnitude of this difference was assumed to be similar to the observed difference (.242) reported in randomized trial data in the 65-year-old population [6]. The relative difference in effectiveness of SD-IIV4 versus SD-IIV3 was calculated by applying the protection offered by SD-IIV3 against influenza A strains to the average likelihood of infection from the influenza B lineage not included in the vaccine from 1999–2000 through 2013–14 [12]. Because VE against influenza B has recently been greater than that of influenza A, this assumption could bias against IIV4. Additionally, no cross-protection against influenza B is assumed to be offered in IIV3 variants. This assumption may bias against IIV3 variants. Similarly, RIV effectiveness was calculated as a relative effectiveness increase over SD-IIV3 from a randomized trial of adults aged 50 years or more [13], converting that study's relative effectiveness compared to SD-IIV4 (= 0.31) to relative effectiveness vs. SD-IIV3, using the average likelihood of IIV3 uncovered influenza B (as above), to facilitate comparisons between HD-IIV3 and RIV.

Adverse event risk was assumed to be the same among all vaccine types [6]. Quality-adjusted life years (QALYs) lost due to influenza-related causes were used to quantify strategy effectiveness and were discounted at 3% per year. All costs, except for RIV which was not available in 2014, were adjusted to 2014 levels based on the U.S. Consumer Price Index [14]. Expected event frequencies for hospitalization and death due to influenza in the modeled cohort were calculated using the base case parameters of the model (Table 1) multiplied by the U.S. Census estimated 2014 50–64-year-old population.

Sensitivity analysis

One-way and multi-way sensitivity analyses were conducted to test the stability of model results under varying parameter values as shown in Table 1. One-way comparisons demonstrate the effect of individual parameters; multi-way analyses plot model results when selected parameters are varied simultaneously across their plausible ranges.

RESULTS

In the primary analysis comparing alternative influenza vaccination strategies in middle-aged, high-risk adults, no vaccination and the HD-IIV3 & SD-IIV3 strategy were more costly and less effective than other strategies and thus were dominated. SD-IIV3 only was the least expensive strategy, with total influenza vaccination and illness cost of \$99.84 per person. SD-IIV4 only cost \$0.91 more, and prevented the loss of 0.000024 QALY compared to SD-IIV3 only, thus costing \$37,700/QALY gained. HD-IIV3 in high-risk patients and SD-IIV4 in others cost \$1.06 more and prevented the loss of 0.000015 QALY than SD-IIV4 only, or \$71,500/QALY gained.

The public health impact of the modeled strategies indicated that, when applied to the 2014 50–64-year-old U.S. population (n=62.6 million persons) and using base case model parameter values, the SD-IIV3 only strategy averted 830,000 cases, 16,000 hospitalizations, and 1,110 deaths compared to no vaccine. Using HD-IIV3 in high-risk patients and SD-IIV4 in the remainder averted an additional 100,000 cases, 1,900 hospitalizations and 130 deaths.

Results were sensitive to variation of three uncertain parameters: the absolute decrease in SD-IIV3 effectiveness in high-risk patients, the relative increase in vaccine effectiveness of HD-IIV3 in high-risk patients, and SD-IIV3 vaccine effectiveness in the entire population. Three-way sensitivity analyses using a \$100,000/QALY acceptability threshold (Figure 1) showed that if the relative increase in effectiveness associated with HD-IIV3 in high-risk patients were 0.18 or less (base case value = 0.242), then high-dose vaccine would not be favored, regardless of SD-IIV3 effectiveness, varied over plausible ranges, in high-risk patients or in the general population. Results were also sensitive to variation of influenza incidence parameters and vaccine costs.

Substituting RIV for HD-IIV3 in all relevant strategies, the alternative vaccination strategy using RIV in high-risk patients would cost more than \$100,000/QALY gained unless its relative effectiveness increase compared to SD-IIV3 were 0.23 or greater (base case value = 0.41). Supplemental Figure 1 pictures these results in a three-way sensitivity analysis.

DISCUSSION

This cost-effectiveness assessment of vaccination strategies for middle-aged, high-risk patients suggests that under the right conditions, administration of HD-IIV3 in high-risk patients 50–64 years old and SD-IIV4 to the remaining 50–64 year-olds can have substantial public health impact. However, the strength of this conclusion is tempered by a lack of consistent vaccine effectiveness over the past few years, due in part, to mismatch between the vaccine and circulating viruses in the 2014–15 season [15]. The seasonal variability in the effectiveness of SD-IIV3 and the lack of risk group-specific SD-IIV3 and HD-IIV3 effectiveness estimates increase the importance of sensitivity analyses where the economically favorable strategy can shift in response to model inputs. While the NIH's INVESTED trial seeks to provide data comparing HD-IIV3 and IIV4 in this population [16], in the absence of more consistent population estimates of pivotal model parameters, no changes to the present immunization administration recommendations are currently warranted.

The other new vaccine option, RIV, has also shown greater effectiveness in adults than standard dose quadrivalent inactivated influenza vaccine [13]. Similar studies have not been completed specifically among high-risk, middle-aged adults. Thus, given the same unknown factors (i.e., SD-IIV3 effectiveness in high-risk, middle-aged adults and in the general population) and unclear added benefit of RIV in high-risk groups, further research may be needed before changes to present influenza vaccination recommendations regarding RIV can be made.

Strengths and Limitations

This analysis has some notable strengths and limitations. It was based on the previously reported IDA model using robust population and cost-effectiveness parameters. Sensitivity analyses performed in the current study reveal that the uncertainty of vaccine efficacy parameters results in changes to strategy favorability within plausible parameter ranges. Continued surveillance and additional clinical trials are needed to strengthen the conclusions suggested from this model.

As in any modeling exercise, some simplifying assumptions were made, such as, the exclusion of lost productivity from influenza-related costs. These assumptions may have limited model realism but, whenever possible, assumptions that bias the model against alternative vaccination strategies were selected. Thus, the alternative vaccination strategies' cost-effectiveness values are likely to be somewhat more pessimistic than they would have been otherwise. Likewise, any cross-protection against influenza B lineages offered by IIV3 variants[17] was not included in relative effectiveness ratios including IIV4. Including this additional source of protection will more strongly favor the tri-valent vaccines over IIV4. Another potential limitation to the analysis is the exclusion of herd immunity and differential epidemic dynamics. In addition, HD-IIV3 vaccine effectiveness was extrapolated from individuals 65 years to persons with chronic conditions aged 50–64 years; anticipated data from the ongoing INVESTED trial can clarify this value. Because RIV was only recently approved by the FDA for use in patients >49 years [5], the available published data were not robust enough to support direct comparison with the incumbent vaccination options. Consequently, the secondary analysis was conducted as a hypothesis-generating exercise to explore the conditions where inclusion of RIV might alter the favored vaccination strategy.

Conclusions

Based on available data, the use of high-dose influenza vaccine in middle-aged, high-risk patients may be an economically favorable vaccination strategy with public health benefits. To better estimate the cost-effectiveness of the available vaccine options in this population, future research will need to provide robust estimates of SD-IIV4 and HD-IIV3 vaccine effectiveness in high-risk patients 50–64 years old, and seasonally consistent SD-IIV4 vaccine effectiveness in the entire population. Similarly, recommendations for future RIV use will require robust vaccine effectiveness estimates in high-risk, middle-aged adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SD-IIV	Standard-dose inactivated influenza vaccine
HD-IIV	High-dose trivalent inactivated influenza vaccine

RIV	Recombinant trivalent influenza vaccine
IDA	Influenza Decision Analysis
SD-IV4	standard-dose quadrivalent influenza vaccine offered
QALY	Quality-adjusted life year

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Highlights

- Use of HD-IIV3 or RIV may increase vaccine effectiveness in high-risk adults
- Use of HD-IIV3 and RIV to middle-aged, high-risk patients may increase public health benefits
- Clinical trials of these vaccines in the adult, high-risk population may be warranted

Figure 1.

Three-way sensitivity analysis. Colored areas depict where influenza vaccination strategies are favored, at \$100,000 per quality adjusted life year, when varying increased relative effectiveness of the high-dose vaccine (different panels), population effectiveness of the standard-dose vaccine (x-axis), and absolute decreases in standard-dose vaccine effectiveness in high-risk patients (y-axis). If the increase in relative effectiveness associated with the high-dose vaccine is 0.18 or less (left panel), then the high-dose vaccine strategy (the black area in the other panels) is not favored regardless of standard-dose vaccine effectiveness in general or high-risk populations. IIV3 = trivalent inactivated influenza vaccine, IIV4 = quadrivalent inactivated influenza vaccine, HD-IIV3 = high-dose trivalent inactivated influenza vaccine

Table 1

Parameter Values, Ranges, and Distributions Examined in Sensitivity Analyses

	Range for Sensitivity Analysis			Reference
	Base Case	Low	High	
Probabilities				
Influenza illness				
Influenza	6.60%	2.0%	10.0%	[18]
High-risk adult	30.6%	23.5%	78.5%	[19]
High-risk adult seeking office visit	62.5%	58.7%	96.3%	[19]
Non-high-risk adult seeking office visit	31.3%	28.5%	33.1%	[19]
Hospitalization	1.9%	0.6%	3.2%	[20]
Influenza mortality	0.13%	0.04%	2.08%	[20]
Vaccination				
Vaccinated	46.8%	30.0%	60.0%	[18]
Adverse event [†]	8.3%	7.8%	8.7%	[6]
Proportion uncovered influenza B	7.7%	3.9%	20.0%	[12]
Effectiveness				
SD-IIV3	59%	20%	70%	[11]
Absolute decrease in effectiveness from SD-IIV3 in high-risk adults	10%	0%	25%	[8]
HD-IIV3				
Relative increase in effectiveness over SD-IIV3	0.242	0.097	0.3650	[6]
SD-IIV4 in high-risk adults	52.8%	20.7%	84.0%	Calculated [*]
SD-IIV4 in non-high-risk adults	63.5%	20.7%	84.0%	Calculated [*]
RIV				
Relative increase in effectiveness over SD-IIV3	0.41	0.0	0.5	[21]
Costs and resource use				
Vaccination, \$				
SD-IIV3	\$10.69	\$5.35	\$16.04	[22]
HD-IIV3	\$31.20	\$20.00	\$40.00	[23]
SD-IIV4	\$16.15	\$8.08	\$24.23	[22]
RIV	\$37.19	\$30.00	\$50.00	[14]
Vaccine administration cost	\$25.08	\$12.54	\$37.62	[24]
Adverse event [†]	\$2.80	\$1.40	\$4.20	[25]
Influenza illness				
Fatal, \$				
Total cost high-risk adult	\$152,903	\$76,452	\$229,355	[19]
Total cost non-high-risk adult	\$152,560	\$76,280	\$228,840	[19]
Lost productivity cost from mortality	\$670,430	\$335,215	\$1,005,645	[19]
Recovered				
Outpatient, \$				
Office visit cost per visit	\$73.08	\$60.22	\$92.78	[26]

	Range for Sensitivity Analysis			Reference
	Base Case	Low	High	
Antiviral medication cost (oseltamivir)	\$120.60	\$60.00	\$182.00	[27]
Nonmedical direct costs per day	\$162.00	\$81.00	\$243.00	[28]
Hospitalized				
Hospitalization cost per day, \$	\$1,765.88	\$676.00	\$3,547.00	[26]
Days of hospitalization	4.1	1	7	[26]
Utilities				
Base, age 50–64 years	0.880	0.710	0.940	[29]
Influenza	0.558	0.300	0.800	[30]
Disutilities				
Vaccination				
Adverse event [†]	0.0027	0	0.005	Assumed
Influenza illness				
Death (discounted quality adjusted years lost)	18.65	15	21	[31]
Recovered				
Non-medically attended				
Days of lost productivity	0.50	0.5	1.5	[19]
Outpatient				
Days of lost productivity high-risk adult	4.0	3.5	10.5	[19]
Days of lost productivity non-high-risk adult	2.0	1.5	4.5	[19]
Hospitalized				
Days of lost productivity high-risk adult	24	10	27	[19]
Days of lost productivity non-high-risk adult	13	6	20	[19]

* Calculated from SD-IIV3 and proportion uncovered influenza B

[†] Serious adverse events attributable to influenza vaccination are rare.[6] The most common adverse events are localized soreness and mild flulike symptoms which are rarely reported as adverse events. Thus, the prevalence of these minor events is estimated as the value of all SAE reported in clinical trials.

SD-IIV3 = Standard-dose trivalent inactivated influenza vaccine; SD-IIV4 = standard-dose quadrivalent inactivated influenza vaccine; HD-IIV3 = high-dose trivalent inactivated influenza vaccine; RIV = recombinant hemagglutinin influenza vaccine.

Cost-Effectiveness Analysis Results for Influenza Vaccination Strategies in in High-risk Middle-aged U.S. Adults (Per-Person Costs and Effectiveness)

Table 2

Strategy	Cost	Increased Cost	Effectiveness (QALY)	Incremental Effectiveness (QALY)	Incremental Cost-Effectiveness Ratio
SD-IIV3 only	\$99.84	--	-0.001373	-	-
SD-IIV4 only	\$100.75	\$0.91	-0.001349	0.000024	\$37,700
HD-IIV3 in high-risk, SD-IIV3 in others	\$101.17	\$0.42	-0.001351	-0.000002	Dominated
HD-IIV3 in high-risk, SD-IIV4 in others	\$101.81	\$1.06	-0.001334	0.000015	\$71,500
No vaccine	\$104.07	\$2.26	-0.001586	-0.000252	Dominated

SD-IIV3 = Standard-dose trivalent inactivated influenza vaccine; SD-IIV4 = standard-dose quadrivalent inactivated influenza vaccine; HD-IIV3 = high-dose trivalent inactivated influenza vaccine; RIV = recombinant hemagglutinin influenza vaccine.