Published in final edited form as:

Vaccine. 2009 April 6; 27(16): 2251–2257. doi:10.1016/j.vaccine.2009.02.024.

A Predictive Model of the Economic Effects of an Influenza Vaccine Adjuvant for the Older Adult (Age 65 and Over) Population

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Abstract

Immunosenescence decreases influenza vaccine efficacy in older adults (age 65 and over). Strategies such as vaccine adjuvants are being developed to overcome immunosenescence. Our computer simulation model represented the decision to give an older adult either standard influenza vaccine or adjuvanted influenza vaccine and found the adjuvanted vaccine to be dominant in many scenarios, resulting in lowered cost and greater effectiveness. An adjuvanted vaccine that is 100% effective in overcoming immunosenescence remained dominant until its cost exceeded the standard vaccine cost by \$65. In a single influenza season, the adjuvant would prevent 496,533 influenza cases, 171,981 hospitalizations, and 70,429 deaths.

Keywords

Influenza Vaccine Adjuvant; Computer Simulation; Older Adults

INTRODUCTION

Influenza is a significant problem in the older adult (age 65 and over) population. Although influenza affects all age groups, the rates of serious illness and death are highest among persons aged 65 years and greater.[1] Influenza vaccination is the primary method for preventing influenza and its severe complications.[2,3] Studies have clearly demonstrated the clinical and cost-effectiveness of vaccinating older individuals.[1,2,4–7]

However, influenza vaccine efficacy appears to be significantly lower in older adults than in younger adults, even when the vaccine strains match the circulating influenza virus strains. [8] This “vaccine efficacy deficit” among older adults may be the result of immunosenescence, i.e., the aging immune system.[9,10] An older and weaker immune system may not generate an adequate response to the influenza vaccine. The “vaccine efficacy deficit” leaves older adults more susceptible to influenza and related complications such as pneumonia, hospitalization, and death.

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Vaccine adjuvants are one possible solution to this “vaccine efficacy deficit” among the older adult population. Adjuvants are vaccine components that enhance, accelerate, and/or prolong a body’s immune response to the vaccine and, in turn, may overcome immunosenescence. Various influenza vaccine adjuvants are currently under development. We developed a computer simulation model to predict the potential morbidity and mortality benefits as well as the economic impact of introducing adjuvanted influenza vaccine to the older adult population in the United States (U.S.). The aim of our model was to quantify the impact of immunosenescence, better understand the potential added value of an influenza vaccine adjuvant, and provide information that may help price this technology once it reaches the market. Since the ability of adjuvants to overcome immunosenescence has not been clearly quantified, we explored the hypothetical range of adjuvant effectiveness rather than base our model on results from any specific clinical study of influenza vaccine adjuvants.

METHODS

Cohort Model

Using TreeAge Pro 2005 (TreeAge Software, Williamstown, Massachusetts), we developed a decision analytic computer simulation model, with probabilistic sensitivity analyses, comparing the use of regular (standard) influenza vaccine with the use of an adjuvanted influenza vaccine in the U. S. older adult population. The model aimed to quantify the incremental morbidity, mortality, and cost-effectiveness associated with introducing the vaccine adjuvant to this population. The base case scenario assumed the societal perspective and accounted for direct and indirect costs of illness. An additional scenario took the third-party payer perspective and considered only the direct costs of illness.

Figures 1a and 1b depict the general structure of the decision model. The time frame for the model was one year, i.e., a single influenza season. The model represented the decision to give a patient over 65 years of age either standard influenza vaccine or an influenza vaccine with adjuvant. Our model divided the older adults into two populations (those living in the general community and those residing in nursing homes), based on studies that these two populations may have different influenza incidences and outcomes.[11]

After a person receives the vaccine, he or she could have a variety of different possible outcomes. This person may develop local side effects, which would require one day of ibuprofen treatment or systemic side effects, which would require 3 days of ibuprofen treatment. The patient may contract influenza during the subsequent year, depending on the effectiveness of the vaccine. Of the patients who develop influenza, a certain percentage requires hospitalization. Those who do not require hospitalization either just treat themselves with over-the-counter medications or visit an outpatient medical clinic. A subset of patients requiring hospitalization develops pneumonia, necessitating treatment. A subset of hospitalized patients does not survive.

Since we obtained distributions for most of our data inputs, we performed a probabilistic (Monte Carlo) sensitivity analysis, allowing us to simultaneously vary all parameters for cohorts who received either adjuvanted or non-adjuvanted influenza vaccine and accounting for the natural stochasticity of the subsequent outcomes.

Data Inputs

Table 1 lists the various data inputs for our model, dividing them into probabilities, costs, and utilities. The table also shows the distribution parameters used and the data sources for each variable. We used beta distributions for all of our utility variables and normal distributions for all other variables. Where possible, data inputs came from published meta-analyses.

Our base case scenario assumed that the adjuvant completely overcame immunosenescence. In other words, the adjuvant increased the effectiveness of standard influenza vaccine to the levels seen in the younger adult (ages 20–64) population: (as listed in Table 1) the probability of a community-dwelling older adult developing influenza decreased from 0.04 to 0.02 and developing pneumonia from 0.21 to 0.11 while the probability of a nursing home resident developing influenza decreased from 0.10 to 0.04 and developing pneumonia 0.43 to 0.21. Subsequent sensitivity analyses varied the effectiveness of the vaccine adjuvant. In our model, the vaccine adjuvant not only lowered the patient's probability of developing influenza but also lowered the chance of requiring hospitalization, developing pneumonia, and not surviving and raised the probability of local and systemic side effects. For example, the probability of a community dwelling older adult developing influenza when receiving vaccine with adjuvant is:

$$\text{Probability of Community Dwelling Adult Developing Influenza}_{\text{vaccine without Adjuvant}} + [\text{Adjuvant Potency} \times (\text{Probability of Young Adult Developing Influenza}_{\text{Standard Vaccine}} - \text{Probability of Community Dwelling Adult Developing Influenza}_{\text{vaccine without Adjuvant}})]$$

All costs were in 2007 U.S. dollars. Our base case assumed that an adjuvanted vaccine would cost the same as standard vaccine. Additional analyses looked at the effects of increasing the cost of the adjuvanted vaccine.

Our model measured effectiveness in quality adjusted life-years (QALY). Patients who did not develop vaccine side effects or influenza throughout our model time frame accrued 0.84 QALYs, based on the quality of life utility obtained by Gold *et al* for persons aged 65 years or greater with no health conditions.[12] Vaccine side effects, influenza, hospitalization, and pneumonia each resulted in different decrements in QALY. We used the following formula to calculate the loss of QALYs from death:

$$\text{Loss of QALYs from Death} = (\text{Age of Patient}) \times (\text{Life Expectancy of Patient at that Age})$$

Table 2 shows the age distribution and corresponding life expectancy of persons age 65 and greater in the U.S. This table helped us develop the distribution of QALY loss from death.

United States (U.S.) Model

Our U. S. model extended the Cohort model to the entire U. S. population to predict the national morbidity, mortality, and economic effects of the influenza vaccine adjuvant. The U.S. model used the data from Table 2.

Sensitivity Analyses

We examined the effects of varying different parameter values individually throughout the ranges listed in Table 1. Multi-dimensional sensitivity analyses were performed on selected parameters. In addition, we conducted probabilistic (Monte Carlo) sensitivity analyses.

RESULTS

Cohort Model

In the base case scenario in which both the adjuvanted and non-adjuvanted vaccines cost the same, employing the adjuvant was the dominant strategy. From the societal perspective, the adjuvant in one year per person resulted in lower costs and greater effectiveness (Table 3). The adjuvanted vaccine remained the dominant strategy even when the adjuvanted vaccine cost was increased to \$10, \$20, and \$30 more than the standard vaccine.

The adjuvanted vaccine remained dominant in similar scenarios from the third party perspective. In the base case scenario with adjuvanted vaccine costing the same as the standard

vaccine, the vaccine with adjuvant was dominant and resulted in lower costs (Adjuvanted Vaccine, $\$38.47 \pm 5.53$; Standard Vaccine, $\$75.77 \pm \12.45) and greater effectiveness (Adjuvanted Vaccine, 0.81 ± 0.1 ; Standard Vaccine, 0.78 ± 0.1). The adjuvanted vaccine remained the dominant strategy even when the adjuvanted vaccine cost was increased to \$10 more than the standard vaccine (Adjuvanted Vaccine, $\$48.35 \pm \5.58 ; Standard Vaccine, $\$75.57 \pm \12.69), \$20 more (Adjuvanted Vaccine, $\$58.45 \pm \5.61 ; Standard Vaccine, $\$75.90 \pm \12.63), and \$30 more (Adjuvanted Vaccine, $\$68.51 \pm \5.87 ; Standard Vaccine, $\$75.93 \pm \12.73).

Figure 2 shows the effects of varying the cost and potency of the adjuvant and the cost-potency combinations that resulted in the adjuvant being the dominant strategy. The gains in cost savings and effectiveness increased as the potency of the adjuvant increased. The cost advantage decreased as the cost of the adjuvant increased. If the adjuvant were 100% effective in overcoming immunosenescence, then the adjuvant ceased to be the dominant strategy when priced \$65 over the cost of standard influenza vaccine.

United States (U.S.) Model

The base case U.S. model suggested that the adjuvant would result in considerable savings and health benefits. In one year, employing the adjuvant prevented 496,533 influenza cases, 171,981 hospitalizations, and 70,429 deaths. Employing the adjuvant would save society \$824 million if the adjuvanted vaccine were to cost the same as standard vaccine, \$595 million if it were to cost an extra \$10, \$369 million if it were to cost an additional \$20, and \$167 million if it were to cost an additional \$30. Using the adjuvant would save third party payors \$842 million if the adjuvanted vaccine were to cost the same as standard vaccine, \$614 million if it were to cost an extra \$10, \$394 million if it were to cost an additional \$20, and \$167 million if it were to cost an additional \$30.

Sensitivity Analyses

Figure 3 illustrate acceptability curves at different vaccine adjuvant costs. As long as the difference between the costs of the adjuvanted vaccine and standard vaccine is less than \$20, the adjuvanted vaccine was always the dominant strategy regardless of the one's willingness to pay. When the adjuvanted vaccine is \$40 more than the standard vaccine, it ceases to be the favorable strategy when willingness to pay is less than \$750 per QALY saved. When the adjuvanted vaccine is \$60 more than the standard vaccine, the willingness-to-pay threshold is \$1,500 per QALY saved. This threshold moves up to \$2,250/QALY saved when the adjuvanted vaccine is \$80 more and \$3,000/QALY saved when the adjuvanted vaccine is \$100 more.

Some may speculate that increasing the conventional vaccine dose could increase its effectiveness, and hence blunt the advantage of an adjuvanted vaccine. A separate sensitivity analysis examined this possibility, postulating a doubled dose conventional influenza vaccination and assuming it has the same side effects profile as standard vaccination and half the potency of the adjuvanted vaccine in overcoming immunosenescence. If the adjuvanted vaccine has 25% potency in overcoming immunosenescence, it dominates the double dose vaccine if it costs < \$18 more than the double dose; if 50% potent, it dominates if a cost difference of < \$31 is present; and if 75% potent, adjuvanted vaccine dominates if it costs < \$42 more than the doubled dose vaccine.

DISCUSSION

Our results suggest that introducing an adjuvanted influenza vaccine to the older adult (age 65 and over) population could save significant morbidity, mortality, and costs. Employing the adjuvant remained a dominant strategy (i.e., results in both cost and health savings) throughout

a variety of adjuvant cost and potency scenarios. The magnitude of the health benefits depended heavily on how well the adjuvant overcame immunosenescence, while the magnitude of the cost savings depends largely on the cost of the adjuvanted vaccine. Our analyses suggested that pricing the adjuvanted vaccine at less than 533% of the standard influenza vaccine will result in net cost savings. This information may be useful when it is time to establish the price and reimbursement for adjuvanted vaccines should they reach the market.

Our analyses highlight the significant annual burden of immunosenescence in the U.S. This problem will continue to grow as the life expectancy and number of older individuals continues to increase.[13,14] In fact, our model may have underestimated influenza incidence and consequently the burden of immunosenescence. Many influenza cases may go unreported, and influenza may be the underlying cause behind many exacerbations of chronic pulmonary, cardiac, or diabetic conditions.[15,16] As a result, existing data may underreport hospitalizations and deaths due to influenza in the older adult population. Moreover, immunosenescence may play a large but underappreciated factor in influenza pandemic planning. The older adult population may continue to contract and spread the pandemic virus despite being vaccinated against the pandemic strain. Ignoring this potential problem could represent a gaping hole in our public health preparedness.

All of this supports the value of investing time, effort, and resources into developing influenza vaccine adjuvants and other ways of overcoming immunosenescence. Although most influenza vaccines currently do not contain any adjuvants, adding adjuvants to influenza vaccines may be on the horizon.[17] The U.S. Food and Drug Administration (FDA) has approved the use of alum as an adjuvant for several vaccines. MF59 has been used as an influenza vaccine adjuvant outside the U.S., and its use in the U.S. is currently under evaluation.[18–21] Several other naturally-occurring and synthetic compounds are in various stages of development.[22–24]

Our study is not limited to influenza vaccine adjuvants. Any intervention that overcomes immunosenescence could easily replace the adjuvant in our analysis. Evidence suggests that improving diet, increasing exercise, providing social support, decreasing stress, and limiting alcohol intake may help enhance the immune response in older individuals.[25] Other potential strategies include using higher doses of influenza vaccine or other medications in conjunction with influenza vaccination.[26,27]

The problem of immunosenescence extends beyond influenza and influenza vaccination. The aging immune system and its attenuated response make older individuals more susceptible to a wide variety of infectious diseases, including infections of the respiratory tract, gastrointestinal tract, and central nervous system.[28–30] It also may decrease the response or the persistence of an immune response to other vaccines.

However, as we demonstrate in our consideration of a hypothetical doubled dose influenza vaccine, effectiveness comparisons between these interventions and an adjuvanted vaccination strategy would be a key feature in determining the relative cost-effectiveness of these differing strategies.

Limitations

Every computer model is a simplification of real life. No model can fully represent every single event and outcome that may ensue in the year after an influenza vaccination. For example, in our model, no individuals sought complementary and alternative therapies or visited the emergency room without being hospitalized. Moreover, our model did not account for the significant co-morbidities that exist in many of the older population. Such co-morbidities may increase a person's risk of influenza and influenza-related complications and even change the

type of complications that may occur. For example, a patient with severe chronic obstructive pulmonary disease (COPD) may require intubation and mechanical ventilation.

Additionally, such computer models usually do not fully represent the heterogeneity of the population. Considerable diversity exists within the older adult population. Community-dwelling older adults range from those with full-time jobs to those who spend considerable time in health care and nursing facilities. Nursing home residents range from individuals requiring round-the-clock medical care to those in very low acuity settings. Our model does not look at how potential differences in race, ethnicity, and socioeconomic status may affect probability of hospitalization, complications, and death and ultimately the cost and effectiveness of the adjuvant.

Finally, based on convention, we arbitrarily chose 65 years as the lower age limit for our older adult population. There is no evidence that immune systems change overnight between 64 and 65 years of age. Immunosenescence is more likely a gradual process that depending on the individual may start well before or after age 65 and proceed at different rates.

Conclusions and Future Directions

Our study quantified the burden of immunosenescence to society and third party payors and suggested that effective influenza vaccine adjuvants could save considerable money, morbidity, and mortality. As long as the adjuvanted vaccine costs less than 533% of the standard vaccine, employing the adjuvanted vaccine would dominate employing the standard vaccine in the older adult population. Our findings portray the significant problem posed by immunosenescence and the importance of finding ways to overcome this problem. Future studies will take a closer look at using the adjuvant in different subpopulations, such as patients on immunosuppressive therapy, patients with immunological diseases, younger adults with chronic disease, and subpopulations of the older adult population (e.g., diabetics, age 90 and over).

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Figure 1a

FIGURE 1.
1a and 1b: Structure of Model

FIGURE 2.
Dominant Strategy at Different Vaccine Adjuvant Potency and Cost Combinations

FIGURE 3.
Acceptability Curves at Different Vaccine Adjuvant Costs

TABLE 1

Data Inputs for Model Variables

Description (units)	Mean	95% Range		Source
		Lower Limit	Upper Limit	
COSTS				
Standard Influenza Vaccine (\$US)	15.75	11.81	19.69	[31]
Influenza Vaccine Adjuvant (\$US)	0	0	100.00	
Influenza Treatment				
Over the Counter Medications (\$US)	14.71	11.03	18.39	[31,32]
Outpatient Visit (\$US)	95.88	71.91	119.85	[33]
Productivity Loss for Outpatient Visit (\$US)	32.78	24.59	40.98	[34]
Hospitalization (\$US)	5,402.73	4,052.05	6,753.41	[35]
Death in Hospital (\$US)	5,000.00	3,750.00	6,250.00	[36]
Treatment of Vaccine Side Effects				
Local Vaccine Side Effects (\$US)	0.72	0.54	0.90	[31]
Systemic Vaccine Side Effects (\$US)	2.88	2.16	3.60	[31]
DURATIONS				
Influenza (days)	7.00	5.25	8.75	[37–42]
Local Vaccine Side Effects (days)	1.00	0.75	1.25	Estimate
Systemic Vaccine Side Effects (days)	2.00	1.50	2.50	Estimate
Pneumonia (days)	10.00	7.50	12.50	[36]
UTILITIES				
One Year of Life for Older Adult (QALY)	0.84	0.63	1.00	[12]
<i>Loss of Utility/Day</i>				
Influenza (QALY)	0.65	0.49	0.81	[43]
Pneumonia (QALY)	0.50	0.38	0.63	[36]
Systemic Vaccine Side Effects (QALY)	0.80	0.60	1.00	Estimate
Local Vaccine Side Effects (QALY)	0.95	0.71	1.00	Estimate
PROBABILITIES				
<i>General</i>				
Older Adult Living in a Nursing Home	0.05	0.03	0.06	[44]
Outpatient Visit if Develop Influenza	0.50	0	1.00	Estimate
<i>Community Dwelling Older Adults</i>				
Death from Influenza-related Pneumonia	0.38	0.28	0.47	[11]
<i>Nursing Home Residents</i>				
Death from Influenza-related Pneumonia	0.51	0.42	0.61	[11]
<i>Standard Influenza Vaccine</i>				
Systemic Vaccine Side Effects	0.11	0.08	0.14	[11]
Local Vaccine Side Effects	0.18	0.13	0.22	[11]
<i>Community Dwelling Older Adults</i>				

Description (units)	Mean	95% Range		Source
		Lower Limit	Upper Limit	
Influenza	0.04	0.03	0.05	[2]
Pneumonia	0.21	0.15	0.26	[11]
<i>Nursing Home Residents</i>				
Influenza	0.10	0.08	0.12	[11]
Pneumonia	0.43	0.33	0.52	[11]
<i>Influenza Vaccine with Adjuvant</i>				
Adjuvant Potency	0.50	-	1.00	
Systemic Vaccine Side Effects	0.25	0.23	0.28	[45]
Local Vaccine Side Effects	0.56	0.54	0.57	[45]
<i>Community Dwelling Older Adults</i>				
Influenza	0.02	0.01	0.02	[46]
Pneumonia	0.11	0.08	0.13	[46]
<i>Nursing Home Residents</i>				
Influenza	0.04	0.03	0.05	[46]
Pneumonia	0.21	0.16	0.27	[46]

TABLE 2

Characteristics of Older Adult Population

Age Group	% of Older Adults	Population Number in US 2000	Life Expectancy	% Vaccinated		Estimated Number Vaccinated
				Community	Nursing Home	
65–69	27.2%	9,533,545	18.77	64%	74%	6,149,137
70–74	25.3%	8,857,441	15.27	64%	74%	5,713,049
75–79	21.2%	7,415,813	11.98	64%	74%	4,783,199
80–84	14.1%	4,945,367	9.14	64%	74%	3,189,762
85–89	8.0%	2,789,818	6.78	64%	74%	1,799,433
90–94	3.2%	1,112,531	4.79	64%	74%	717,582
95+	1.0%	337,238	3.35	64%	74%	217,519
Total	100.0%	34,991,753	13.53			22,569,681
Source	[47]	[47]	[48]	[49]	[50]	

TABLE 3

Results from Cohort Model

		Societal Perspective			
		Vaccine No Adjuvant		Vaccine with Adjuvant	
Adjuvant Cost		Cost	Effectiveness	Cost	Effectiveness
\$	0	\$76.13 +/- \$12.48	0.79 +/- 0.10	\$39.26 +/- \$5.51	0.81 +/- 0.10
\$	10.00	\$76.11 +/- \$12.58	0.79 +/- 0.10	\$49.22 +/- \$5.55	0.81 +/- 0.10
\$	20.00	\$76.13 +/- \$12.58	0.78 +/- 0.10	\$59.24 +/- \$5.50	0.81 +/- 0.10
\$	30.00	\$77.18 +/- \$12.66	0.79 +/- 0.10	\$69.78 +/- \$5.62	0.81 +/- 0.10
		Third Party Perspective			
		Vaccine No Adjuvant		Vaccine with Adjuvant	
Adjuvant Cost		Cost	Effectiveness	Cost	Effectiveness
\$	0	\$75.77 +/- \$12.45	0.78 +/- 0.10	\$38.47 +/- \$5.53	0.81 +/- 0.10
\$	10.00	\$75.57 +/- \$12.69	0.78 +/- 0.10	\$48.35 +/- \$5.58	0.81 +/- 0.10
\$	20.00	\$75.90 +/- \$12.63	0.78 +/- 0.10	\$58.45 +/- \$5.61	0.81 +/- 0.10
\$	30.00	\$75.93 +/- \$12.73	0.78 +/- 0.10	\$68.51 +/- \$5.87	0.81 +/- 0.10