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Economic Value of Seasonal and Pandemic Influenza Vaccination During Pregnancy

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Abstract

Background—The cost-effectiveness of maternal influenza immunization against laboratory-confirmed influenza has never been studied. The current 2009 H1N1 influenza pandemic provides a timely opportunity to perform such analyses. The study objective was to evaluate the cost-effectiveness of maternal influenza vaccination using both single and two-dosing strategies against laboratory-confirmed influenza secondary to both seasonal epidemics and pandemic influenza outbreaks.

Methods—A cost-effectiveness decision analytic model construct using epidemic and pandemic influenza characteristics from both the societal and third-party payor perspectives. A comparison was made between vaccinating all pregnant women in the United States versus not vaccinating pregnant women. Probabilistic (Monte Carlo) sensitivity analyses were also performed. The main outcome measures were incremental cost-effectiveness ratios (ICERs).

Results—Maternal influenza vaccination using either the single or two-dose strategy is a cost-effective approach when influenza prevalence greater than or equal to 7.5% and influenza-attributable mortality is greater than or equal to 1.05% (consistent with epidemic strains). As the prevalence of influenza and/or the severity of the outbreak increases the incremental value of vaccination also increases. At a higher prevalence of influenza (≥30%) the single-dose strategy demonstrates cost-savings while the two-dose strategy remains highly cost-effective (ICER ≤ $6,787.77 per quality adjusted life year).

Conclusions—Maternal influenza immunization is a highly cost-effective intervention at disease rates and severity that correspond to both seasonal influenza epidemics and occasional pandemics. These findings justify ongoing efforts to optimize influenza vaccination during pregnancy from an economic perspective.

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Keywords

Influenza; maternal vaccination; epidemic; pandemic; cost-effectiveness

Introduction

The ongoing 2009 pandemic of H1N1 swine-origin influenza A has heightened the world's attention to the inevitability of influenza pandemics [1]. Wide-scale efforts to improve the understanding of the epidemiology of the current outbreak have been undertaken to temper the extent of the current outbreak and mitigate future pandemics. Nonetheless, human cases with this novel pandemic influenza strain have been confirmed in all areas of the world. The critical role in global disease prevention of a strain-specific vaccine is recognized and a vaccine against the current 2009 H1N1 influenza strain is now available and scheduled for use [2]. Uncertainty remains for different patient populations over whether the anticipated vaccine program against 2009 H1N1 will consist of single or multiple successive doses. It is clear, however, that the greatest benefits will be realized through implementation of wide-scale vaccination programs that successfully immunize a critical mass of the population.

Pregnant women and neonates less than 6 months of age represent two unique yet interrelated patient populations that historically have been disproportionately affected by both seasonal and pandemic outbreaks of influenza. Significantly higher morbidity and mortality (compared to the general population) were recorded among both neonates and pregnant women during the twentieth century influenza pandemics [3–7]. These disproportionate rates of morbidity are also repeatedly noted for neonates and pregnant women during seasonal influenza epidemics [4,8–11]. In addition, emerging data also suggests that the current 2009 H1N1 influenza pandemic strain is generating higher morbidity and mortality among pregnant women consistent with previous pandemics [12].

The Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists (ACOG) recommend yearly influenza vaccination for all pregnant women during influenza season [4,13]. Despite these recommendations data from the Centers for Disease Control and Prevention (CDC) highlight poor national rates (13%) of maternal vaccination despite demonstrated safety of the trivalent inactivated influenza vaccine [4,14,15]. In addition, recent data suggest that reluctance exists among pregnant women to accept vaccination using a rapidly developed pandemic avian influenza vaccine [16]. A further barrier to influenza prevention for neonates is their exclusion from vaccination recommendations [4].

The cost-effectiveness of maternal seasonal single-dose influenza vaccination for the prevention of influenza-like illness (ILI) during pregnancy has been previously demonstrated [17]. Although well-performed, this analysis quantified prevention of ILI and did not investigate the direct value of vaccination to prevent laboratory-confirmed influenza. Neither protection conferred to neonates by maternal vaccination nor costs associated with likely increases in preterm birth during influenza pandemics were included. Recent data have confirmed the previously theoretical benefit of neonatal influenza prevention following maternal vaccination, adding greatly to the cumulative benefits of maternal influenza immunization [18].

The goal of the current study was to assess the cost-effectiveness of universal maternal influenza vaccination using both a single and two-dose approach during seasonal and pandemic influenza outbreaks. It is hypothesized that immunization of pregnant women against both

seasonal and novel pandemic influenza strains will be cost-effective regardless of number of doses administered.

Methods

Model Structure

Using TreeAge Pro Suite 2008 (TreeAge Software, Williamstown, MA), a stochastic decision analytic computer simulation model was constructed to simulate the decision of maternal immunization for an influenza epidemic and/or pandemic. The model evaluated outcomes for both mothers and neonates. Figures 1a and 1b show the overall structure of the model. The model was run from both the third-party payor and societal perspectives, as well as with single and two-dose approaches. The two-dose approach was included to simulate potential pandemic vaccination scenarios.

Each pregnant woman entering the model has the option of being vaccinated against influenza (against either seasonal or pandemic strains) during an already scheduled prenatal visit. She then has a probability of experiencing acute side effects from the vaccine, including but not limited to injection site irritation, fever, and myalgias. Based on the predicted efficacy of the vaccine and the predicted prevalence of influenza, each woman has a probability of developing influenza. Women that develop influenza have a probability of home self-treatment, a clinic visit for evaluation and management, and/or being hospitalized for more severe illness. Only hospitalized women have a probability of death. Gestational age at time of maternal influenza infection determines the probability of survival for the fetus if the mother dies after hospitalization. Twenty-four weeks of gestation was chosen as the cut-point for neonatal survival with increasing rates of survival at later gestations consistent with national data on preterm birth [19].

Neonatal probability of influenza was modified by maternal influenza vaccination status. Neonates whose mothers had been vaccinated while pregnant had a decreased probability of influenza [18]. In the baseline seasonal scenario, neonatal risk of influenza was set equal to the estimated background risk of confirmed seasonal influenza of 0.125 (range: 0.05–0.20) [4,20]. Development of influenza infection in the neonate was independent of maternal influenza. Neonates who developed influenza had a chance of hospitalization for severe disease and only hospitalized neonates were at risk for death.

Data Inputs

All cost and probability variables and their respective distributions that were included are shown in Table 1. Triangular distributions were used for all variables except the costs of maternal and neonatal hospitalization, and cost of lost wages, which assumed gamma distributions. For the two-dose strategy against pandemic strains, vaccine cost and probability of side effects were doubled, while all other parameters remained consistent with the single-dose model. All costs were in 2009 U.S. dollars. A discount rate of 3% converted past and future costs into 2009 dollars.

Quality-adjusted life-years (QALYs), an accepted measure of disease burden, were used to quantify the effectiveness of maternal vaccination and clinical outcomes associated with vaccination and influenza in both mother and neonate. A QALY value of 1 was used to represent the best possible health and was attributed to healthy newborns. A QALY value of 0 was ascribed for death, and intermediate decrements were applied for both the natural aging process and disease states. This model assumed that pregnant women in the model had a median age of 27.1 years, consistent with data at the National Vital Statistics System at the Centers for Disease Control and Prevention [28]. The QALY expectancies used for effectiveness

calculations were 43.96 years and 72.64 years for pregnant mothers and neonates, respectively, based on age and clinical condition-specific QALY decrements applied to projected life expectancy estimates from the Human Mortality Database [29]. The baseline utility in QALYs used for a 27.1 year old pregnant woman was 0.92 and 1.0 for a neonate [27,30,31].

Model assumptions were made based on previous published literature and convention for economic analyses of influenza (4,21,32,33). Length of influenza infection (as well as side effects from vaccination) for both mothers and neonates was 7 days (range 3–10 days). The length of hospitalization for those admitted was 4 days. An outpatient visit for influenza resulted in four hours of lost productivity and wages from the societal perspective. No lost productivity and/or wages were attributed to already scheduled visits for prenatal care where the influenza vaccine was administered. The corresponding QALYs attributed for the 7 days of infection were: 0.5 (range: 0.38–0.63) for hospitalization, indicating that that women hospitalized for influenza function at 50% (range: 38–63%) of their maximum expected quality of life compared to healthy non-hospitalized women without influenza. Additional condition-specific QALY values included 0.65 (range: 0.49–0.81) for influenza without hospitalization, and 0.95 (range: 0.71–1.00) for the vaccine side [21,34,35].

Sensitivity Analyses

To examine the impact of altering the values of key variables probabilistic sensitivity analyses were performed for all input parameters over the ranges noted in Table 1. Prevalence of influenza was systematically varied from 0.001 to 0.35 to simulate a wide range of theoretical influenza outbreaks. Maternal mortality from influenza was varied from the seasonal influenza mortality of 0.0105 to four times this value, 0.0420, to simulate more virulent circulating strains of influenza consistent with influenza pandemics [3–7]. Estimates of vaccine efficacy (and ranges) were derived from values in the literature and were triangular distributions. The base case scenario for maternal vaccine efficacy was 73% (range: 50–80%) and for neonatal efficacy an efficacy of 63% (range: 5–85) was employed [4,18]. Vaccine efficacy also varied in both the pregnant woman and neonate together from 25% to 50%. This variation accounted for potential lower vaccine efficacy against novel pandemic strains given potential for less robust immune responses.

Results

Simulation runs were conducted of 1,000 trials of 1,000 pregnant women (or 1,000,000 total pregnant women traveling through the model) from both the societal and third-party payor perspectives for single and two-dose strategies. All simulations used the incremental cost-effectiveness ratio (ICER) of maternal influenza vaccination, calculated as follows:

$$\mathrm{ICER}=\frac{\mathrm{Cost}_{\text{Maternal Influenza Vaccination}}-\mathrm{Cost}_{\text{No Maternal Influenza Vaccination}}}{\mathrm{Effectiveness}_{\text{Maternal Influenza Vaccination}}-\mathrm{Effectiveness}_{\text{No Maternal Influenza Vaccination}}}$$

Table 2 shows how the optimal choice of whether to vaccinate a pregnant woman for influenza varies depending on prevalence of influenza, probability of death from influenza (severity), and the number of doses administered. When vaccination yields cost savings as well as better effectiveness, it “dominates” the no-vaccination option. In addition, when the ICER is ≤ $50,000/QALY (a previously established threshold) an intervention is considered cost-effective.

Simulations run from the societal perspective with a single-dose strategy were performed first. Table 2 lists the respective ICERs using the base-case efficacy of 73% in pregnant women and 63% in neonates and compares single to two-dose strategies. These simulations demonstrate

that when influenza prevalence is ≥30% and the probability of death from influenza is set equal to the expected seasonal influenza mortality, or the prevalence of influenza is ≥25%, and mortality is 2, 3 and 4 times the seasonal rate, vaccination is the dominant strategy. Single-dose maternal immunization was also found to be cost-effective when influenza prevalence was as low as ≥5% and the probability of death from influenza is set equal to the expected seasonal influenza mortality (or higher), or the prevalence of influenza is ≥2.5% and mortality is 2, 3 and 4 times the seasonal mortality rate. Simulations run from the third-party payor perspective (data not shown) likewise demonstrate that single-dose vaccination is the dominant strategy when influenza prevalence is ≥30% and the probability of death from influenza is set equal to the expected seasonal influenza mortality, or higher. Single-dose vaccination remains cost-effective when the prevalence of influenza is ≥2.5% and the probability of influenza-attributable mortality is greater than or equal to the expected seasonal rate.

Simulations using the two-dose strategy from societal perspective were subsequently performed using the same efficacy above (Table 2). A two-dose strategy also demonstrated cost-effectiveness when influenza prevalence is ≥7.5% and the probability of death from influenza is set equal to the expected seasonal influenza mortality and 2 times this rate, and when the prevalence of influenza is ≥5% and influenza-attributable mortality is 3 or 4 times the expected seasonal rate. Compared to the single-dose approach, cost-effectiveness at baseline vaccine efficacy is realized for the two-dose approach at a slightly higher prevalence of influenza (≥5% for 2-dose vs. ≥2.5% for 1-dose). This is noted for all levels of vaccine efficacy and mortality. A two-dose strategy, however, never dominates the no-vaccination approach.

Sensitivity analyses testing lower vaccine efficacies (25% and 50% for both maternal and neonatal efficacy) were performed from the societal perspective using both the single and two-dose strategies At the lowest presumed vaccine efficacy of 25%, vaccination remained cost-effective at influenza prevalence levels ≥ 7.5% for single-dose immunization at all levels of influenza-attributable mortality. Cost-effectiveness was realized for a two-dose immunization strategy when the prevalence of influenza is ≥ 12.5% (expected seasonal value) and the probability of mortality due to influenza is equal to expected seasonal influenza mortality, or when influenza prevalence is ≥ 10% and the probability of influenza-attributable mortality is 2, 3, or 4 times the expected seasonal mortality rate.

Increasing the vaccine efficacy to 50% demonstrates that a single-dose vaccination strategy is cost-effective when influenza prevalence is ≥ 5% and the probability of death from influenza is set equal to the expected seasonal influenza mortality, or higher. Cost-effectiveness is also realized for a two-dose approach when the prevalence of influenza is ≥ 10% and the influenza-attributable mortality rate is equal to the expected seasonal rate or twice that, or when prevalence of influenza is ≥ 7.5% and the probability of death from influenza is 3 or 4 times the expected seasonal mortality rate.

Figure 2(a–c) highlights the findings of a single-dose approach, comparing different vaccine efficacies and influenza prevalence, in addition to increasing levels of mortality (severity of infection). The two key factors noted to impact cost-effectiveness of both dosing strategies to the greatest extent are influenza prevalence and severity of illness.

Figure 3 shows the acceptability curves for different influenza prevalence levels when vaccine efficacy is 73% in the mother and 63% in the neonate and the probability of death from influenza is 1.05%. These curves demonstrate that when influenza prevalence is 12.5% and the maximum willingness-to-pay is $50,000, vaccinating pregnant women for influenza is cost-effective approximately 90% of the time. As the prevalence of influenza increases, the same probability of maternal vaccination yielding cost-effectiveness is achieved at lower

willingness-to-pay thresholds (approximately $30,000 at 15% prevalence, $20,000 at 20%, and $15,000 at 25%).

Discussion

These results demonstrate the clear cost-effectiveness of maternal influenza vaccination at disease prevalence rates consistent with both seasonal influenza epidemics and the occasional influenza pandemic. This comes during an active influenza pandemic when novel vaccine and mass-vaccination protocols are under development and implementation. Importantly, the results of this study remain robust regardless of whether a single or two-dose strategy is adopted. The cost-effectiveness of maternal vaccination also becomes increasingly more pronounced as the clinical severity and prevalence of influenza increase in the population, which is characteristic of influenza pandemics such as 2009 H1N1. It is also important to highlight that even with more mild outbreaks typical of a seasonal influenza (lower prevalence and/or severity of infection), cost-effectiveness of maternal vaccination remains.

While this investigation is timely for 2009 H1N1, it is acknowledged that vaccine acceptance is a key component related to the effectiveness of large immunization programs and maternal seasonal influenza immunization efforts suffer from poor acceptance [14]. Moreover, the recently reported reticence among the obstetric community to accept a rapidly developed pandemic influenza vaccine may pose challenges among this vulnerable population [16]. Strong support for maternal immunization exists when one considers the combination of demonstrated safety in pregnancy, ethical obligations for protecting vulnerable populations, and the favorable economics delineated herein. Although vaccine acceptance has many influential factors, it is hoped that these data strengthen ongoing efforts and improve acceptance overall, particularly against 2009 H1N1.

Previous investigators have demonstrated the cost-effectiveness of seasonal maternal influenza vaccine for the prevention of ILI [17]. The most important difference is that the model presented herein directly assesses the cost-effectiveness of maternal influenza vaccination against rates of laboratory-confirmed cases, not self-reported influenza-like illness. This is a noteworthy difference because the point estimates and prevalence ranges used for ILI represent much higher estimations of influenza-attributable outcomes than those used in the current investigation. Thus, an overestimation of the true level of potential influenza-specific disease prevention is possible when considering ILI. The current model includes conferral of protection from vaccinated mother to fetus, and also acknowledges increased rates of preterm birth and the associated economic burden that have been demonstrated in previous influenza pandemics [5,7,8,18,[19]}. Another important distinction is that the current model simulates both single-dose and two-dose mass vaccination approaches. The current model thus strives to provide wider-ranging influenza scenarios and produce economic projections that approximate the fluctuating characteristics of influenza disease more directly.

Analysis of the cost-effectiveness of influenza immunization for seasonal outbreaks among healthy adult populations has yielded mixed results. Nichol et al. demonstrated many significant clinical benefits of vaccination that translated into an approximate cost-savings of $46.85 per person vaccinated [36]. A subsequent investigation failed to show robust yearly cost savings [37]. These authors attributed their non-robust yearly findings to fluctuations between vaccine and seasonal strain compatibility. The higher rates of untoward influenza-associated outcomes noted among pregnant women and neonates plus the additional measurable neonatal protection from maternal vaccination provides a basis for the robust nature of our findings [3–7,9–11,18].

Vaccine safety is always an important consideration when contemplating widespread use. The safety profile used for the current investigation was modeled with the same high level of safety noted in pregnancy using the seasonal trivalent inactivated influenza vaccine given identical manufacturing technology (4,15). It is acknowledged that safety of future vaccines are never known until widespread use. Thus, any arising safety concerns noted with a pandemic influenza vaccine could impact these results in an economically disadvantageous manner. Likewise, the decision not to include Guillain-Barré Syndrome (GBS) as a side-effect of influenza vaccination may have underestimated the overall costs associated with vaccination. The decision to omit GBS as a clinical outcome was made given the paucity of data clearly linking GBS and current influenza vaccination and the fact that most cases of Guillain-Barré appear to come from natural infections, including influenza. Thus, GBS could also occur in increased frequency (thus generating costs) if the vaccine was not administered [38,39].

It is also important to consider that all computer simulation models are simplifications of real life and cannot represent every possible event that may result from influenza infection or vaccination. For example, mass vaccination “clinics” (and any associated costs) were not factored into this model given regional variability in immunization methods. The data inputs for this model also come from studies of varying quality, and computer models are subject to their respective assumptions. However, frequently referenced sources were used and thus represent the current best approximations of these values.

Nonetheless, clear cost-effectiveness against influenza prevalence rates noted during yearly epidemics and during pandemic outbreaks is demonstrated. Maternal immunization becomes increasingly cost-effective (generating actual cost-savings) as the prevalence and/or severity of influenza increases. These findings economically justify ongoing efforts to maximize maternal influenza immunization under all disease scenarios.

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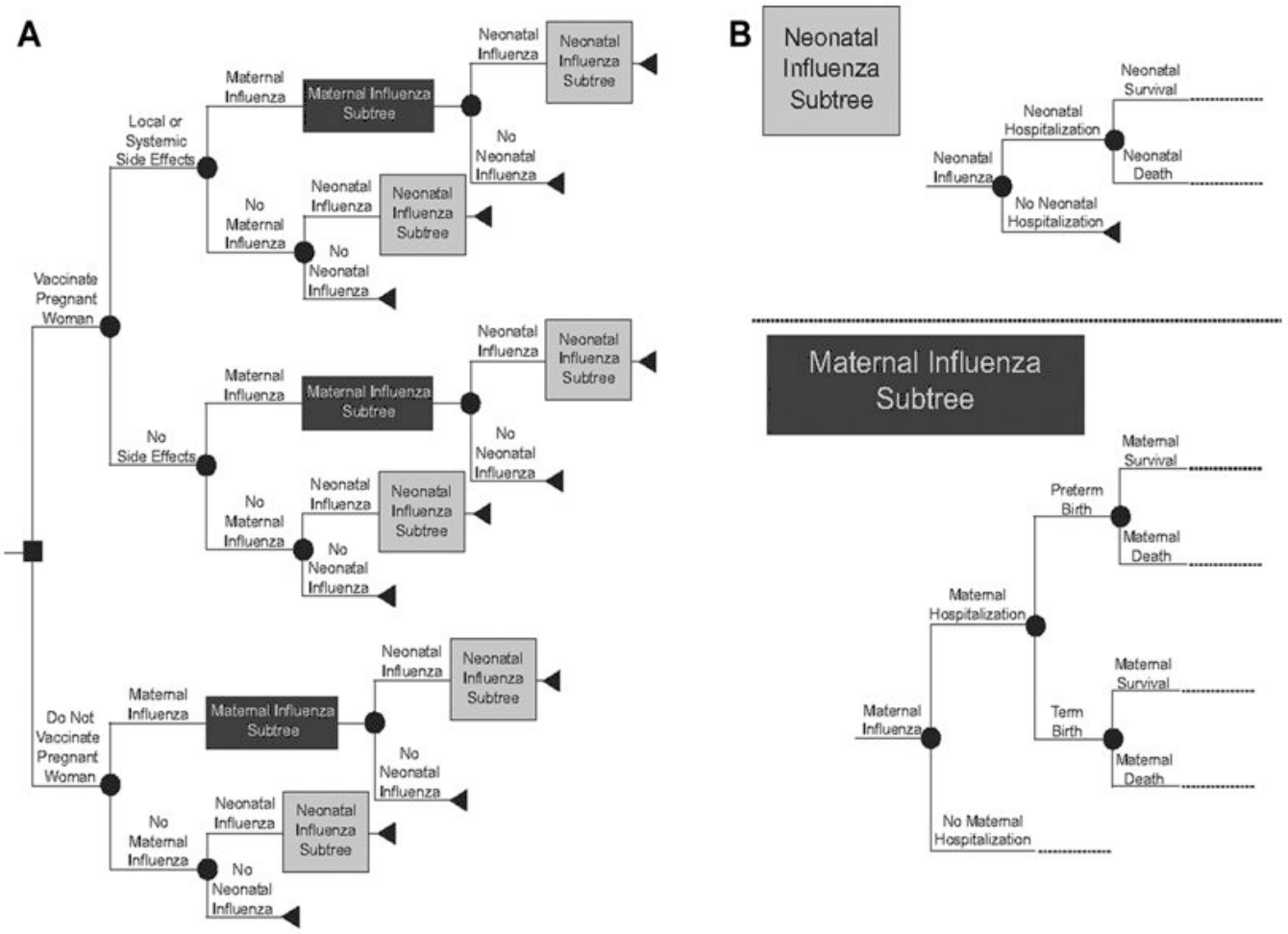

Figure 1.
A General model structure *B* Maternal and neonatal influenza subtrees.

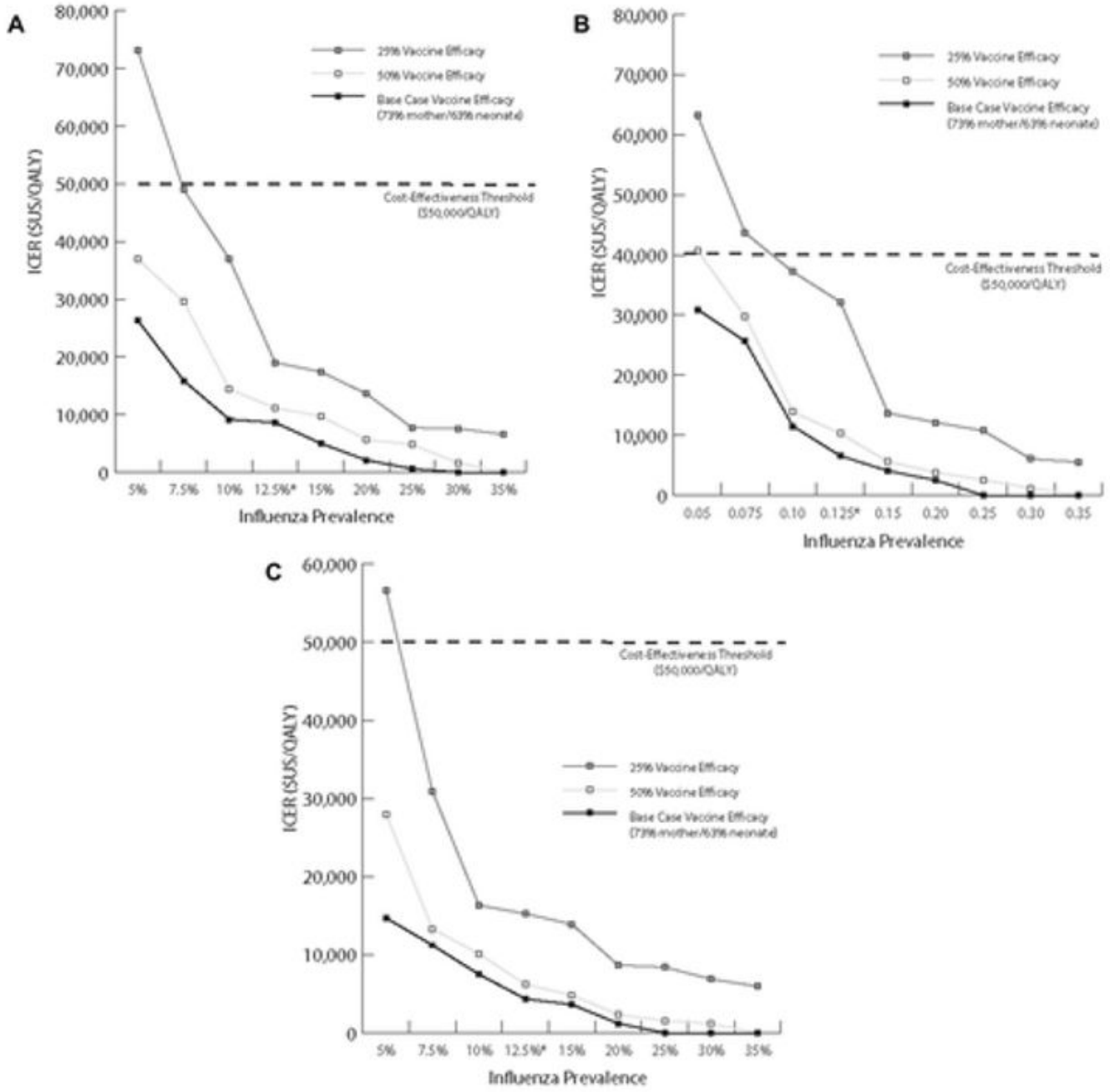

Figure 2.

Incremental cost - effectiveness ratio (ICERs) for vaccinating pregnant women for influenza at different vaccine efficacies and influenza prevalence (single vaccine dose). Probabilities of mortality were 1.05%, 2.10%, and 4.20% for panels *A–C*, respectively. *12.5% is the most likely value from the Centers for Disease Control and Prevention annual influenza prevalence estimate. QALY, quality - adjusted life year.

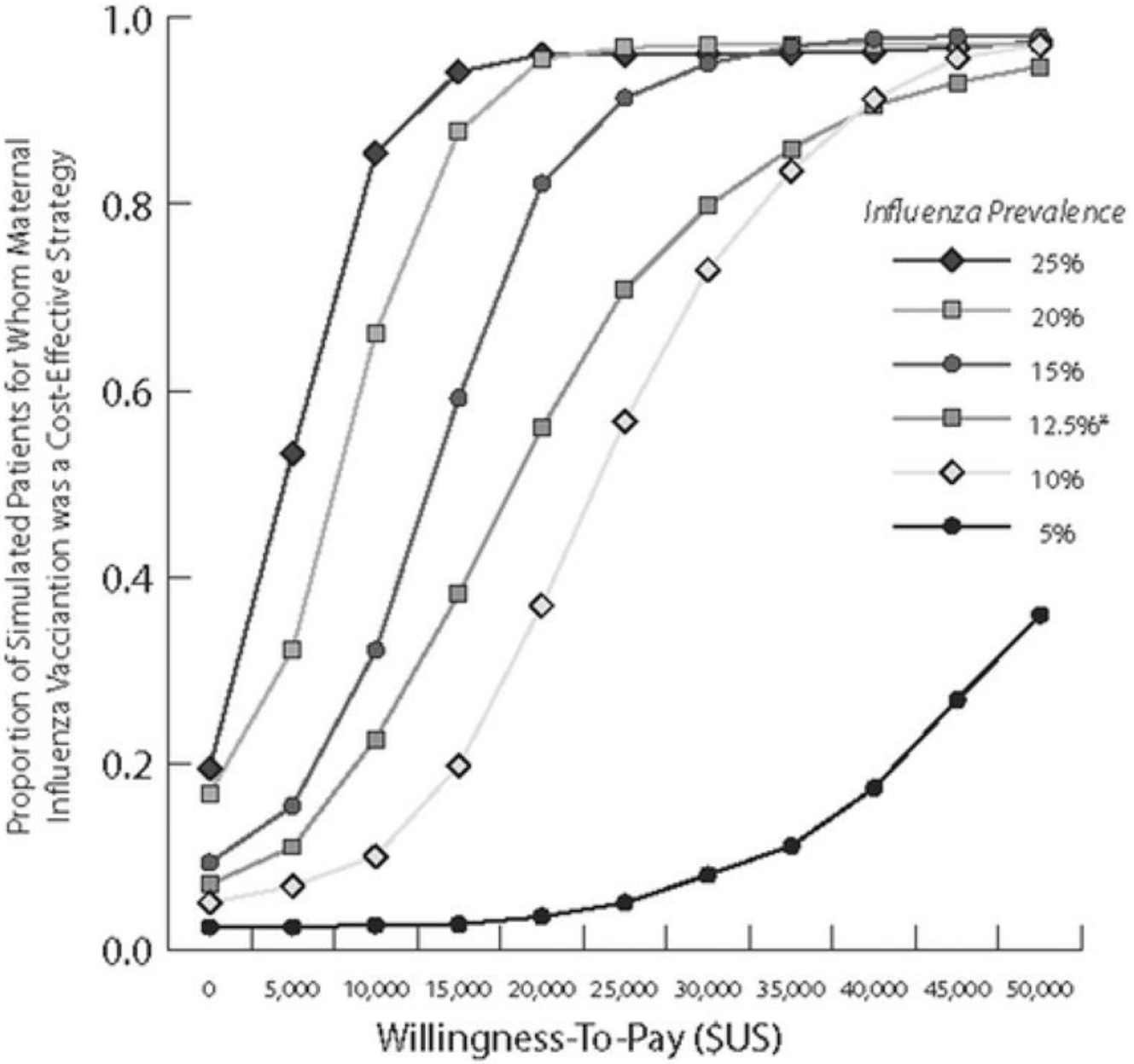

Figure 3.

Acceptability curves at different influenza prevalence levels for base case vaccine efficacy and influenza - attributable mortality from a societal perspective (single vaccine dose). *12.5% is the most likely value from the Centers for Disease Control and Prevention annual influenza prevalence estimate. Base case vaccine efficacy, 73% for mothers and 63% for neonates; base case influenza - attributable mortality, 1.05%.

Table 1

Cost and Probability Inputs

Description	Value	Reference(s)
Cost, US$		
Death		
Mother	5000.00	[21]
Neonate	5000.00	[21]
Home treatment of influenza		
Mother	15.61 (11.70–19.51)	[22]
Neonate	15.61 (11.70–19.51)	[22]
Home treatment of vaccine - related adverse effects	0.76 (0.68–3.82)	[22]
Hospitalization for influenza		
Mother	3526 ± 302.10	[23]
Neonate	2323.84 ± 262.38	[23]
Influenza vaccine, per dose	15.00 (10.00–20.00)	[22]
Preterm birth		
Third - party payor perspective	37,366.89	[19]
Societal perspective	58,076.25	[19]
Productivity loss for outpatient visit for illness[a]	64.08 ± 5.04	[24]
Probabilities		
Death due to influenza		
Hospitalized mother	0.0105	[20]
Neonate	0.0000088 (0.0000052–0.0000139)	[4,25]
Preterm neonate	0.02 (0.0088–0.151)	[4]
Hospitalization		
Mother	0.004 (0.001–0.007)	[20]
Neonate	0.0048 (0.0024–0.0072)	[20]
Influenza		
Mother	0.125 (0.05–0.20)	[20]
Neonate	0.125 (0.05–0.20)	[20]
Preterm birth	0.12 ± 0.1	[19,26]
Adverse effects of vaccination, per dose	0.05	[27]
Vaccine efficacy		
Mother	0.73 (0.50–0.80)	[20]
Neonate	0.63 (0.05–0.85)	[18]

NOTE. Data are mean ± standard deviation or mean (95% confidence interval).

[a] Only applied for societal perspective simulations; assumes 4 h of lost wages.

Table 2

Incremental Cost - Effectiveness Ratios (ICERs) for Single - and 2 - Dose Maternal Influenza Vaccination using 73% and 63% Efficacy for Mothers and Neonates, Respectively (Societal Perspective)

	Probability of death (severity of influenza strain)[a]							
	Single - dose option				**Two - dose option**			
Prevalence of influenza	**0.0105**	**0.021 (2×)**	**0.0315 (3×)**	**0.042 (4×)**	**0.0105**	**0.021 (2×)**	**0.0315 (3×)**	**0.042 (4×)**
0.025	76,835.47	**35,049.72**	**31,080.77**	**30,929.89**	138,012.76	101,747.98	236,745.07	122,145.75
0.05	**26,307.67**	**30,903.57**	**30,591.51**	**14,708.87**	71,032.61	77,562.47	**47,330.25**	**43,318.68**
0.1	**9165.78**	**11,506.89**	**7061.17**	**9933.36**	**27,079.08**	**31,931.70**	**22,240.58**	**21,130.45**
0.125[b]	**7718.32**	**6543.38**	**6090.59**	**4350.15**	**19,527.97**	**26,221.96**	**17,400.19**	**10,148.43**
0.15	**5019.41**	**4059.41**	**3721.89**	**3634.95**	**18,068.06**	**15,808.83**	**14,158.94**	**8899.62**
0.25	**603.42**	**Vaccinate**	**Vaccinate**	**Vaccinate**	**9284.22**	**6490.86**	**5394.14**	**4581.31**
0.3	**Vaccinate**	**Vaccinate**	**Vaccinate**	**Vaccinate**	**6787.77**	**4223.76**	**3057.21**	**2597.23**
0.35	**Vaccinate**	**Vaccinate**	**Vaccinate**	**Vaccinate**	**4499.38**	**2387.32**	**2516.00**	**1657.27**

NOTE. Data are ICERs in US$ per quality - adjusted life year. Boldface font indicates scenarios that were cost - effective (ICER, ≤ $50,000 per quality - adjusted life year). Underlined entries in boldface font are scenarios in which vaccination was the dominant strategy (ie, maternal vaccination was less costly and more effective than no maternal vaccination).

[a] Represents base case probability of maternal death from influenza strain among hospitalized women.

[b] Represents base case influenza prevalence