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Cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women

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Abstract

Objective: To evaluate the cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women using data from three recent influenza seasons in the United States.

Design, setting, and participants: We developed a decision-analytic model following a cohort of 5.2 million pregnant women and their infants aged <6 months to evaluate the cost-effectiveness of vaccinating women against seasonal influenza during pregnancy from a societal perspective. The main outcome measures were quality-adjusted life-year (QALY) gained and cost-effectiveness ratios. Data sources included surveillance data, epidemiological studies, and published vaccine cost data. Sensitivity analyses were also performed. All costs and outcomes were discounted at 3% annually.

Main outcome measures: Total costs (direct and indirect), effects (QALY gains, averted case numbers), and incremental cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women (cost per QALY gained).

Results: Using a recent benchmark of 52.2% vaccination coverage among pregnant women, we studied a hypothetical cohort of 2,753,015 vaccinated pregnant women. With an estimated vaccine effectiveness of 73% among pregnant women and 63% among infants <6 months, QALY gains for each season were 305 (2010–2011), 123 (2011–2012), and 610 (2012–2013). Compared with no vaccination, seasonal influenza vaccination during pregnancy was cost-saving when using data from the 2010–2011 and 2012–2013 influenza seasons. The cost-effectiveness ratio was greater than $100,000/QALY with the 2011–2012 influenza season data, when CDC reported a low attack rate compared to other recent seasons.

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Author contributions: Dr. Xu had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Xu, Zhou, Messonnier. Acquisition, analysis, or interpretation of data: Xu, Zhou, Reed, Chaves, Messonnier, Kim. Drafting of the manuscript: Xu, Zhou, Reed, Chaves, Messonnier, Kim. Critical revision of the manuscript for important intellectual content: Xu, Zhou, Reed, Chaves, Messonnier, Kim. Statistical analysis: Xu, Zhou. Study supervision: Xu, Zhou, Reed, Chaves, Messonnier, Kim.

Conflict of interest: All authors report no conflicts of interest.

Conclusions: Influenza vaccination for pregnant women can reduce morbidity from influenza in both pregnant women and their infants aged <6 months. Seasonal influenza vaccination during pregnancy is cost-saving during moderate to severe influenza seasons.

Keywords

Seasonal influenza vaccination; Cost-effectiveness analysis; Pregnancy

1. Introduction

In the United States, pneumonia and influenza is one of the leading causes of morbidity and mortality each year [1]. In 2012–2013, influenza illness was estimated to be responsible for over 300,000 hospitalizations [2]. Pregnant women are at a higher risk of developing influenza-related complications [3]. Additionally, among children, infants aged <6 months have the highest rates of influenza-attributable hospitalization [3]. Seasonal influenza vaccine is the first line of defense to prevent influenza and influenza-associated complications, but current influenza vaccines are not licensed for children <6 months old [4]. Vaccinating women during their pregnancy can provide protection not only for themselves but also for their infants <6 months [5,6]. Since 2004, the Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists have recommended influenza vaccination for all women who are or will be pregnant during the influenza season, regardless of trimester [4]. In the 2013–2014 influenza season, 52.2% of pregnant women received a seasonal inactivated influenza vaccine, similar to the coverage in the preceding season [7]. However, the coverage is still well below the Healthy People 2020 target of 80% influenza vaccination among pregnant women [8].

The costs of medical care and productivity losses associated with influenza are substantial [9]. Consideration of these costs in relation to vaccination costs can provide valuable information to immunization programs and policy makers in order to make recommendations for seasonal influenza vaccination. Several studies have analyzed the cost-effectiveness of influenza vaccination for pregnant women and they reached different conclusions [10–12]. All previous studies suggested that the cost-effectiveness ratio (CER) was heavily dependent on the influenza incidence rate, although one study also suggested the impact of timing of vaccination relative to gestational age on cost-effectiveness estimates [12]. These studies used influenza incidence data collected during or before the 2009 H1N1 pandemic. Since the 2009 influenza season, the influenza landscape in the US has greatly changed. Influenza morbidity per case has likely declined due to the increased use of antiviral therapy [13,14]. Influenza case ascertainment and, therefore, surveillance data, may have improved due to availability of more sensitive diagnostic techniques [15]. These recent developments make our study, especially because of the inclusion of post-2009 pandemic data, a timely addition to the literature on the cost-effectiveness of influenza vaccination. In this study, we estimated the cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women using data from three recent influenza seasons.

2. Methods

2.1. Decision analysis model

We developed a cohort decision analysis to estimate the cost-effectiveness of vaccinating women during pregnancy against seasonal influenza from a societal perspective (Fig. 1). As the at-risk population and probability of birth are conditional on calendar week and gestational age, we used the Markov state-transition model in Excel software to track weekly changes in delivery patterns and disease incidence. Our model estimated the averted direct medical costs and indirect productivity loss due to influenza-associated illness, quality-adjusted life year (QALY) gains for both mother and their infants aged <6 months due to vaccination, and overall cost-effectiveness of vaccination.

We assumed that sub-types of influenza across seasons are different and there is no cross protection between different sub-types. Based on 2011–2012 National Centers for Health Statistics (NCHS) data, we constructed two hypothetical populations: pregnant women and infants [16]. A hypothetical cohort of 5.2 million pregnant women who experienced defined influenza season during their pregnancy was targeted for influenza vaccination. Following a live birth, we assumed an infant was protected for 6 months [5,6]. Hence, infants aged <6 months were also included in the analysis, as they receive passive immunity through transplacental transfer of antibodies following maternal immunization [17]. We simulated the two interrelated populations from July 1 to June 30 of any 2 consecutive calendar years based on weekly distribution. We also assumed a sufficient vaccine supply would be available one month after the beginning of the study period in the first week of August. Once the seasonal influenza vaccine became available, pregnant women were assumed to receive influenza vaccine during their next scheduled prenatal visit based on influenza vaccination coverage among pregnant women. We assumed an immunogenic response followed two-weeks after receiving the vaccine [18]. The probability of adverse events associated with influenza vaccination was assumed to be the same for pregnant women as for the general population. For pregnant women in the model, the risk of contracting influenza-associated illness was conditional on vaccine effectiveness (VE), weekly incidence rates, and previous infection in the study period. For infants aged <6 months in the model, development of influenza illness was conditional on maternal vaccination status, as well as the seasonal attack rate of influenza-associated diseases among infants. In our model, deaths occurred only among hospitalized women and infants.

2.2. Costs and utilities associated with influenza illness

Influenza illness is responsible for substantial medical costs, as well as productivity losses [9]. We included both direct and indirect costs associated with influenza illness in our analysis. All costs were converted to 2013 dollars using the Consumer Price Index provided by the U.S. Department of Labor Bureau of Labor Statistics [19]. Future costs were adjusted to the current value using a 3% annual discount rate. We summarized the value and range of our model inputs in Table 1.

2.2.1. Direct costs—Direct costs included the medical costs of influenza-associated outpatient visits and the costs of hospitalizations among pregnant women and their infants

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aged <6 months. The length of hospitalization for both mothers and infants aged <6 months was assumed to be seven days, based on previously published studies [10–12,20]. Medical costs for influenza-associated hospitalizations and outpatient visits were obtained from 2010 to 2012 Marketscan data [21]. The cost per case was calculated based on the algorithms described by Molinari et al. [9]. We also included travel costs incurred by those who sought medical care for their influenza-associated illness. However, we did not include additional travel costs for vaccination, as pregnant women are assumed to be vaccinated during a scheduled prenatal visit. Only a portion (42%) of those who developed influenza-associated illness sought medical care [22]. To account for those who did not seek medical care, we used the average cost of over-the-counter (OTC) medication as a proxy for direct medical costs.

2.2.2. Indirect costs—For infants who developed influenza illness, we included the productivity loss of caregivers. To calculate the value of lost productivity, we multiplied the estimated number of hours of missed work due to caring for sick infants by the median hourly wage [23]. In lieu of actual data for caregiver work days missed due to infant illness, we assumed each visit resulted in a productivity loss of 4 h based on previously published literature [11]. We also assumed the productivity loss for those who do not seek medical care were a half-day [24]. Travel cost to a caregiver per clinic/hospital visit was $23.07 [25].

2.2.3. Program costs—The total annual program costs included the costs of vaccine, vaccine administration, and vaccine-associated adverse events. The private sector vaccine prices were obtained from the 2013 CDC vaccine price lists [26]. The vaccine administration cost per dose at a private clinic was assumed to be $15.78 [27].

2.2.4. Year-specific rate of influenza illness—We calculated influenza incidence rates for three recent influenza seasons (2010–2011, 2011–2012, and 2012–2013) based on the methodology described by Kostova et al. [28], using the existing national Influenza Hospitalization Surveillance Network (FluSurv-NET) data. We used the data to construct examples of “moderate” (2010–2011), “mild” (2011–2012), and “moderately severe” (2012–2013) influenza seasons as described in CDC’s influenza activity report in our model [29–31]. The severity of an influenza season was determined based on several factors that included the number of influenza-associated illnesses, hospitalizations, and deaths.

The model compared the costs and outcomes associated with partial vaccine coverage (~52%) of all pregnant women to the costs and outcomes associated with no vaccination of pregnant women. In the base case, we used incidence rates estimated from three recent seasons of varying intensity to represent what could happen in seasons of similar influenza activity. Estimates of the incidence of influenza illness by month of each included season for pregnant women were assumed to be similar to the incidence of influenza in the general population, using methods described by Reed et al. [32] and Kostova et al. [28]. Finally, we fit monthly incidence data into the weekly time step of our model, by assuming cases were uniformly distributed throughout each day in a given month.

2.2.5. Influenza vaccine effectiveness—Estimates of seasonal influenza VE found by clinical trial and observational studies range from 47–85% for pregnant women and

5–85% for infants [10,17,33]. We followed previous studies and assumed a base case vaccination effectiveness of 73% for pregnant women and 63% for infants aged <6 months [11,12]. To reflect the uncertainty of this assumption, we performed sensitivity analyses on this parameter.

2.2.6. Cost-effectiveness (CE)—We used QALYs gained as one of our primary outcome measurements. One QALY indicates one year of perfect health. QALY losses associated with influenza illness were based on the days associated with QALY losses and health utility index obtained from previous literature (Table 1). Because a pregnant woman's overall health and quality-of-life is different from that of a healthy woman who is not pregnant, we followed the literature and attributed 0.92 QALYs to the year that an otherwise healthy woman is pregnant [11]. We assumed a healthy infant had a baseline QALY value of 1.

We measured the CE of vaccination using CER, defined as cost in US dollars per QALY gained. We assumed the median age of the pregnant women cohort in our model is 25.8 years old based on the U.S. birth and natality data. The life expectancies of pregnant women and infants were 54 years and 78 years, respectively [34]. Table 1 presents the health utility indexes associated with different health conditions. For example, the QALY multiplier associated with an outpatient visit was 0.65 among pregnant women. In other words, we assumed that pregnant women who had an outpatient visit due to influenza experienced a quality-of-life equal to 65% of their expected quality-of-life compared to women (both pregnant and non-pregnant) who did not contract influenza.

2.3. Sensitivity analyses

To investigate the effect of changes in our assumptions and key model inputs on our calculated CERs, one-way sensitivity analyses were performed. Specifically, we assessed the effect of changes in the following parameters: (1) the starting time of vaccine availability, (2) duration of vaccination program, (3) vaccination cost (4) vaccination coverage, (5) productivity loss of a caregiver, (6) VE against influenza-associated illness for pregnant women and their infants aged <6 months, and (7) medical costs of influenza-associated illness.

3. Results

3.1. Base case

Under our base case assumptions, vaccinating a cohort of pregnant women with influenza vaccine cost $77,600,368, annually. The projected average numbers of averted influenza-associated hospitalizations among pregnant women and infants aged <6 months were 2636 and 1512, respectively (Table 2). The annual hospitalizations among infants aged <6 months range from 1440 to 3939. From a societal perspective, influenza vaccination during pregnancy can save, on average, $107,742,336 in medical costs and $111,593,174 in total societal costs. Compared with the no-vaccination scenario, the estimated QALYs saved with pregnancy vaccination ranged from a low of 123 in a mild influenza season (2011–2012) to a high of 610 in a moderately severe influenza season (2012–2013).

Table 2 presents the CERs of vaccination among pregnant women using the incidence data from different seasons. Using our base case values, seasonal influenza vaccination during pregnancy was cost-saving in a moderately severe influenza season. We found similar results using data from a moderate influenza season. However, the cost per QALY gained was $250,689 using 2011–2012 data. This relatively high CER indicates that fewer cases were prevented when the underlying incidence rate was relatively low. According to the CDC Fluview report, the 2011–2012 season started late and was considered mild compared to previous seasons [30].

3.2. Sensitivity analyses results

We performed several one-way sensitivity analyses to assess the impact of changes in our model inputs. Table 3 lists the new CER after sensitivity analysis and Fig. 2 shows the related tornado graph using 2011–2012 data where seasonal influenza vaccination during pregnancy is not cost-saving. We first changed vaccine availability start date from August to September. The results showed that a delay in vaccine availability decreased the number of desirable health outcomes and thereby decreased the cost-effectiveness (i.e., generated higher CERs) of immunization. The change in the CER was around 2% in a mild influenza season to 12% in a moderately severe influenza season. We also examined the impact of the length of the vaccination program on the CER. The CER decreased as expected in all three scenarios if no vaccination would deliver beyond December. The decreases in CER might be due to the fact that infants born to women received vaccines at the end of a calendar year are more likely to be delivered after the peak of influenza season. We also analyzed the effect of increased vaccination coverage on CER. The universal vaccination program would save, on average, $206,498,862 in medical costs and $213,885,584 in total societal costs. However, the improved vaccination coverage would have little impact (<1%) on the CER. There is a debate in the literature whether or not to include productivity losses for a caregiver in infants, as infants need care regardless of their medical condition. If we exclude the productivity loss of care givers, then the CER would increase 6% in a mild influenza season. Vaccination strategy would be still cost-saving in a moderate or moderately severe influenza season. To account for the variability in VE for both pregnant women and their infants aged <6 months, we compared the CER using different values of VE. Given infants obtain protection from maternal antibodies, we proportionally changed the VE for both pregnant women and infants. As expected, cost-effectiveness was improved with higher VE. With lower VE, fewer cases were prevented and the cost per QALY gained was higher. To assess the impact of vaccination cost on the CER, we used the lowest possible vaccination cost, based on CDC contract vaccine prices and the vaccine administration fee at a public-sector health care provider [26]. We found that lower vaccination cost improved the CER. We also tested the influence of medical costs on the CER by increasing and decreasing the base values by 10%. With lower medical costs per case, vaccination was still cost-saving in a moderate or moderately severe influenza season. The cost-effectiveness per QALY increased from $250,689 to $286,529 in a mild influenza season (2011–2012). In the high medical cost scenario, the cost-effectiveness per QALY decreased from a $250,689 to $214,850, a 14% reduction. The CER increased as the medical-cost per case decreased.

4. Discussion

We found that vaccinating women during their pregnancy reduced influenza-associated outpatient visits and hospitalizations in both pregnant women and their infants. Using data from three recent influenza seasons in the post-pandemic period, we found that vaccinating pregnant women against seasonal influenza saved 123–610 QALYs at a program cost of $77,600,368 per season. Cost-effectiveness ranged from cost-saving to $250,689 per QALY saved. Compared with a no-vaccination strategy, vaccinating pregnant women against influenza was cost-saving in moderate or severe influenza seasons. However, even with a low incidence rate such as in the 2011–2012 season, cost per QALY was lower or comparable to other vaccines recommended during pregnancy [35].

Results were robust to changes in selected variables, including vaccination availability, exclusion of productivity loss of a caregiver, vaccination coverage, and medical cost per case, but were sensitive to changes in VE, duration of vaccination program, and vaccination cost. Previous studies that focus on the cost-effectiveness of influenza vaccines among pregnant women in the U.S. reached different conclusions. Only Myers et al. [12] accounted for the interaction of variation in the population at risk of developing influenza and seasonal variation in incidence rates. They found that vaccinating pregnant women with seasonal influenza vaccination was not cost-saving under any scenario, while we found it was cost-saving when the influenza activity is at least moderate. These differing conclusions may be due to the different incidence data we used. Meyer et al. [12] used lower incidence rates than we found in the three recent seasons using influenza surveillance data. When we modeled a mild influenza season, our results corresponded much more closely to those of Myer et al. [12].

Our study is the first to assess cost-effectiveness of vaccinating pregnant women against seasonal influenza illness in the seasons following the 2009 H1N1 pandemic. Previous US cost-effectiveness studies of seasonal influenza vaccination among pregnant women were based on the incidence rates in the pre-pandemic period or based on projected incidence rates [10–12]. We acknowledge the changes in influenza landscape in the US in recent years and, more importantly, derive weekly incidence information of influenza-associated illness among pregnant women as well as infants from CDC surveillance data. Another advantage of our analysis is our explicit calculation of medical costs associated with influenza-associated illness among pregnant women rather than among the general population. Providing updated cost-effectiveness estimates of vaccinating pregnant women with seasonal influenza can improve our understanding of the influenza burden and further support current maternal influenza vaccination recommendations.

Vaccinating pregnant women is the best strategy for protecting pregnant women and their infants aged <6 months against influenza-associated complications. Despite the empirical evidence on the effectiveness and safety of vaccinating pregnant women with influenza vaccine, vaccination coverage is still not at the optimal level. Although vaccine coverage has been increasing over time, some obstetrician/gynecologist offices still do not provide influenza vaccination due to inadequate reimbursement and insufficient training on vaccine administration [36]. Strengthening partnerships with health care providers and other public health programs will be essential to increasing vaccine coverage in pregnant women.

This study is subject to a number of limitations. First, our model did not include the effects of herd immunity. Therefore, we may underestimate the cost-effectiveness of vaccinating pregnant women. However, pregnant women are a small portion of the population and unlikely to alter the overall transmission in the community. Another limitation arises from an incomplete estimate of influenza activity during the 2011–2012 season. There is evidence suggesting that the 2011–2012 season had an unusual late peak in influenza activity. The CDC FluSurv-NET system only collects data from October to April. As a result, the incidence rates used may not have captured the complete magnitude of influenza activity for the 2011–2012 season. Therefore, the results using 2011–2012 data may underestimate the cost-effectiveness for that scenario and should be interpreted with caution. Due to the lack of pre-pregnancy data, we assumed that all pregnant women who received seasonal influenza vaccine were vaccinated after they became pregnant, during their first prenatal visit. However, it is possible that some pregnant women received influenza vaccine before pregnancy, and their infants may not fully obtain passive influenza immunity. To that extent, we may overestimate the benefits of the program to infants. While a large portion of pregnant women received influenza vaccines through obstetricians/gynecologists, it is possible for pregnant women to receive influenza vaccines in other facilities. To that extent, our cost estimates on the administration fee may be biased although we do not know in which direction testing biases may go. Finally, there is empirical evidence that receipt of inactivated influenza vaccine during pregnancy is associated with reduced likelihood of prematurity during at least widespread influenza activity periods [37]. We did not include the costs associated with preterm birth because of seasonal influenza as there is a lack of population-based data. Nevertheless, the inclusion of preterm birth costs would increase the incremental value of vaccination and make vaccination more cost-effective.

We found that vaccination of women during pregnancy against seasonal influenza provides substantial public health benefits to both pregnant women and their infants aged <6 months. We also demonstrate that influenza vaccination is cost-saving during moderate or severe influenza seasons. We are often unable to determine the length and severity of an influenza season early in the season, however delaying vaccination until the point that is known is not a reasonable option and would greatly diminish the value of the vaccine. Future research should go beyond the current study, exploring better incidence data that captures the delay of peak influenza activity, and provide a more complete estimate of the cost effectiveness ratio of influenza vaccination among women during their pregnancy. Better estimates of VE for both pregnant women and their infants could also refine model assumptions and facilitate future cost-effectiveness studies.

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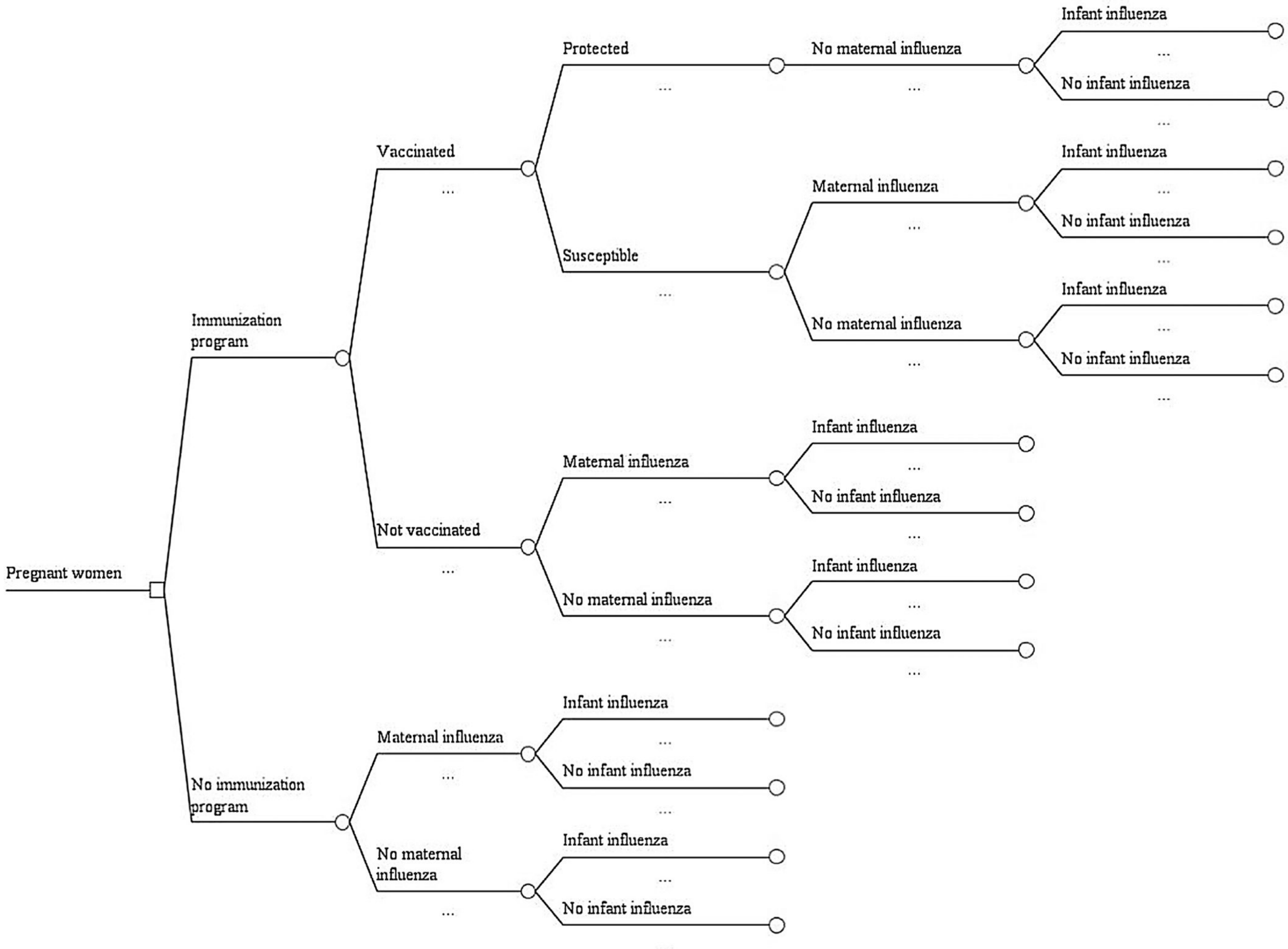

Fig. 1.
Simplified decision tree.

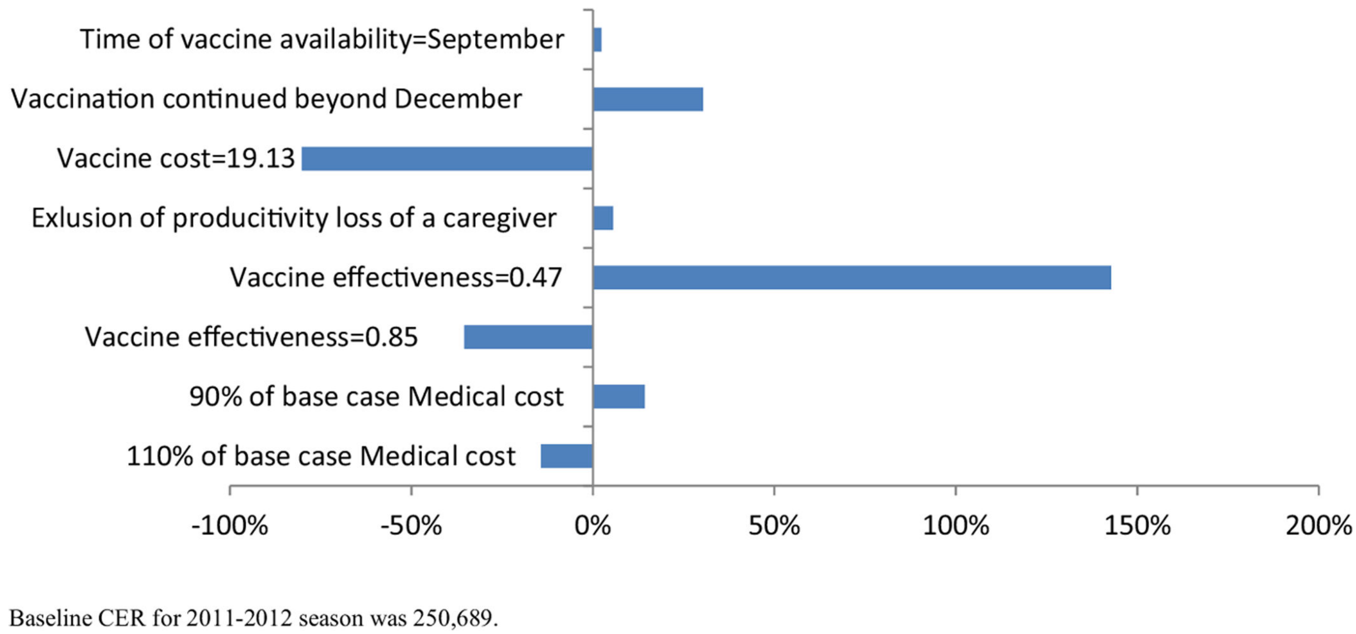

Fig. 2.

Sensitivity analysis: change in cost-effectiveness ratio. Baseline CER for 2011–2012 season was 250,689.

Table 1

Probabilities and cost inputs used in the model.

Variable	Base case	Range	Source
Vaccine coverage	0.522		[7]
Vaccine efficacy			
Mother	0.73	0.47–0.85	[4,10–12,38]
Infant	0.63	0.05–0.85	[11,12,17,33]
Outpatient visit given influenza infection			
Mother	0.559	0.313–0.625	[9]
Infant	0.547	0.455–0.551	[9]
Hospitalization given influenza infection			
Mother	0.024	0.004–0.036	[9,12]
Infant	0.028	0.014–0.031	[9,12]
Death per 1000 infection			
Mother	0.09	0.06–0.12	[9]
Infant	0.04	0.03–0.05	[9]
Vaccination cost (US$)			
Vaccine price	12.34	8.92–12.34	[26]
Vaccine administration fee	15.78	8.09–15.78	[25,27]
Disease cost (US$)			
Hospitalization			
Mother	14,839.96	5472–21889	[9,12,21]
Infant	15,462.25	3283–16417	[9,12,21]
Outpatient visit (US$)			
Mother	488.57	54.72–793.50	[9,12]
Infant	503.06	54.72–628.23	[9,12,39,40]
Over-the-counter medications (US$)	4.53		[9]
Guillain-Barré syndrome (US$)	46,165	39,586–393,523	[10,12]
Adverse effects Medications (US$)	0.89	0.79–4.45	[10–12]
Transportation cost (US$)	23.07		[27]
Productivity/QALY lost (days)			

Variable	Base case	Range	Source
Not seeking medical attention	0.5		[9,11]
Outpatient	0.5		[9,11,12]
Hospitalization	7		[9,11,12]
Health utility index			
Outpatient visit			
Mother	0.65	0.49–0.81	[10–12]
Infant	0.99	0.97–1.0	[12,41,44]
Hospitalization			
Mother	0.5	0.38–0.63	[10,12,45]
Infant	0.95	0.74–1.0	[12,41–44]
Adverse effects			
Minor	0.99	0.71–1.0	[10–12]
Guillain-Barré syndrome	0.5	0.25–0.75	[12]

Cost values are given in 2013 US dollars.

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Table 2

Base case results for vaccination strategy among pregnant women in the United States.

	Moderate (2010–2011)	**Mild (2011–2012)**	**Moderately severe (2012–2013)**
Mother			
Averted hospitalization	3100	1181	3626
Averted outpatient visits	46,668	20,528	114,217
Infants			
Averted hospitalization	1925	704	1909
Averted outpatient visits	33,972	12,929	41,769
Total			
Direct medical cost saved (US$)	116,018,240	45,002,614	162,206,155
Indirect cost saved (US$)	4,622,804	1,724,501	5,205,207
Societal cost saved (US$)	120,641,044	46,727,115	167,411,362
Program cost (US$)	77,600,368	77,600,368	77,600,368
Net savings/costs (US$)	43,040,676	(30,873,253)	89,810,994
QALY saved	305	123	610
Cost per QALY saved	Cost-saving	250,689	Cost-saving

Cost values are given in 2013 dollars.

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Table 3

One-way sensitivity analyses.

Variable	Cost-effectiveness ratio		
	Moderate (2010–2011)	**Mild (2011–2012)**	**Moderately severe (2012–2013)**
Base case[a]	Cost-saving	250,689	Cost-saving
Time of vaccine availability			
September	Cost-saving	256,666	Cost-saving
Duration of vaccination program			
August to December	Cost-saving	326,764	Cost-saving
Vaccination cost[b] (US$)			
19.13 (CDC contract price)	Cost-saving	49,724	Cost-saving
Vaccination coverage			
100%	Cost-saving	250,447	Cost-saving
Productivity loss of a caregiver			
Exclusion of productivity of a caregiver	Cost-saving	264,692	Cost-saving
Vaccine effectiveness (%)			
Low: 47	Cost-saving	608,641	Cost-saving
High: 85	Cost-saving	161,777	Cost-saving
Medical cost			
90% of base case cost	Cost-saving	286,529	Cost-saving
110% of base case cost	Cost-saving	214,850	Cost-saving

Cost values in 2013 dollars.

[a]Under base case scenario, vaccine is available at the beginning of August; vaccination cost in private sector is 27.4. Vaccine effectiveness for mothers and infants are 73 and 63, respectively.

[b]Vaccination cost include vaccine cost and administration fee.