Matern Child Health J (2014) 18:1599–1609
DOI 10.1007/s10995-013-1399-2

Efficacy and Effectiveness of Maternal Influenza Vaccination During Pregnancy: A Review of the Evidence

Jill M. Manske

Published online: 24 November 2013

Abstract Influenza vaccine is universally recommended for pregnant women during any trimester of pregnancy. In light of this recommendation, a comprehensive literature review was conducted to examine the available evidence regarding influenza vaccine efficacy and effectiveness during pregnancy. A comprehensive Medline search identified potentially relevant articles published between January 1, 1964 and February 1, 2013. Articles were selected that specifically evaluated the efficacy and effectiveness of maternal influenza vaccine in protecting women and infants from influenza infection. These were reviewed with a particular focus on the methods used to confirm influenza infection. Ten of 476 articles met the inclusion criteria. None of the six studies evaluating maternal outcomes were randomized controlled studies using a laboratory-confirmed influenza diagnosis to measure vaccine efficacy. Two studies included reverse-transcriptase polymerase chain reaction confirmation; four relied solely on clinical outcomes. The reported vaccine effectiveness (VE) ranged from −15 to 70 %. Seven studies examined the potential for maternal vaccination to protect infants. Four of these applied some form of laboratory confirmation, with VE ranging from 41 to 91 %. Vaccination against infectious disease is an unparalleled public health success. However, studies to date demonstrate that influenza vaccine provides only moderate protection from influenza infection in pregnant women. This review found broad heterogeneity among studies, with no uniform outcome measured and little data based on laboratory-confirmed influenza, leading to wide-ranging estimates of effectiveness. Rigorously designed studies assessing clearly defined outcomes are needed to support the development of reasoned public health policy about influenza prevention in this population.

Keywords Influenza vaccine · Pregnancy · Maternal immunization · Efficacy

J. M. Manske (✉)
Department of Biology, University of St. Thomas, St. Paul, MN 55105, USA
e-mail: jmmanske@stthomas.edu

Background

Evidence collected over several decades indicates that pregnant women and young infants are at increased risk for complications from influenza; indeed, vaccination of pregnant women with inactivated TIV began in the mid-1960s. Influenza infections in pregnancy have been associated with adverse maternal and neonatal outcomes, including preterm labor and delivery, respiratory hospitalization, pneumonia, acute respiratory distress syndrome, overwhelming sepsis, and death [1–12].

Control of influenza infection in these populations represents an important public health concern. Although vaccination is the most effective method for preventing influenza virus infection [13], the estimated influenza vaccination coverage for pregnant women is consistently below 50 %. In reports from the 2010–2011 season, vaccination levels ranged from 39 to 49 % [14, 15]. For the two subsequent influenza seasons, 2011–2012 and 2012–2013, self-reported vaccination rates were approximately 47 % among pregnant women [16, 17].

Recommendations for universal vaccination of woman at all stages of pregnancy has been the policy of the Advisory Committee on Immunizations Practices (ACIP) [18] of the Centers for Disease Control (CDC) since 2004 [19–21], followed by the World Health Organization in 2005 [22]. The American College of Obstetrics and

Gynecology (ACOG) issued new guidelines in September 2010 recommending that all pregnant women at any gestational age be vaccinated against influenza [23]. Finally, the latest WHO Strategic Advisory Group of Experts (SAGE) recommendation, published in 2012, urges countries using or considering introducing seasonal influenza vaccination to include all pregnant women as the highest priority group [24].

There has been increased scrutiny of influenza vaccine effectiveness (VE), as well as a developing debate regarding the extent to which vaccination prevents morbidity and mortality across all populations. Despite the often-cited 70–90 % effectiveness rates, actual influenza vaccine protection has been demonstrated to be lower in the general population. For example, a recent meta-analysis of randomized controlled trials (RCTs) observed a more modest overall VE of 59 % [25], and other studies [26–28] have reported similar results.

The recommendation that all US women during *any* trimester of pregnancy receive influenza vaccine is unique. No other US vaccine carries this recommendation [29]. Nonetheless, the supporting evidence has not been adequately reviewed using the same stringent criteria that recent reviews have applied to influenza vaccine efficacy and effectiveness involving other population groups [25–28]. The more recent data on influenza VE [25–28] (i.e., providing evidence of less effectiveness than previously accepted) compels further analysis of efficacy and effectiveness in pregnant women and neonates. To this end, available literature was selected to assess the evidence supporting current recommendations for universal vaccination of pregnant women, and reviewed with a particular focus on identifying studies that employed sensitive and highly specific diagnostic tests to definitively confirm influenza infection in the evaluation of efficacy and effectiveness.

Data and Methods

MEDLINE (PubMed), which includes all supporting studies for vaccine licensure in the United States [25], was searched for articles on maternal influenza vaccine published in English between January 1, 1964 and February 1, 2013. The earliest included publication date reflects the year the CDC established and convened the ACIP. At this first meeting, the ACIP recommended influenza vaccination for certain high-risk segments of the population, including pregnant women [30].

For purposes of this review, influenza vaccine efficacy was defined as the relative reduction in influenza risk following vaccination as determined by a RCT using medically attended, laboratory-confirmed influenza as the primary outcome of interest. Laboratory-confirmed influenza was defined as reverse-transcriptase polymerase chain reaction (RT-PCR) or culture-confirmed influenza. Influenza VE was defined as the relative reduction in risk among vaccinated individuals in observational studies using medically attended influenza, influenza-like illness (ILI), or acute respiratory illness (ARI) as the primary outcome of interest. Reviews of literature, policy studies, and research designed to evaluate immunogenicity without evaluation of clinical endpoints were excluded. The literature review process is illustrated in Fig. 1.

Results

The search strategy identified ten articles that met the inclusion criteria. Three studies focused solely on pregnant women, four examined the effectiveness of maternal vaccine for protecting infants from influenza, and three included both pregnant women and their infants.

Randomized Controlled Clinical Trials of Vaccine Efficacy During Pregnancy

The goal of this review was to identify studies that employed sensitive and highly specific diagnostic tests to confirm influenza infection. None of the studies reviewed used RCT to evaluate vaccine efficacy against laboratory-confirmed influenza.

Vaccine Effectiveness During Pregnancy

This review of nearly 50 years of research identified six studies evaluating VE in pregnant women (Table 1). These studies covered nine different influenza seasons and included 116,570 pregnant women. Four studies used clinical symptoms of influenza as the primary outcome [31–34]. Two employed either laboratory-confirmation by RT-PCR or clinical influenza diagnosis [35, 36].

In the earliest study included in this review, Hulka [32] measured VE in a cohort study of 544 pregnant women during a 1962–1963 outbreak of Asian influenza. Researchers asked immunized and nonimmunized patients if they had experienced influenza symptoms during the influenza season. While fewer immunized patients reported respiratory illness with fever (11 vs. 20 %, respectively), there was no significant difference in reports of respiratory illness between the two patient groups.

A major methodological limitation of this study is that women were asked to recall whether or not they had experienced influenza symptoms with no corresponding laboratory confirmation of infection.

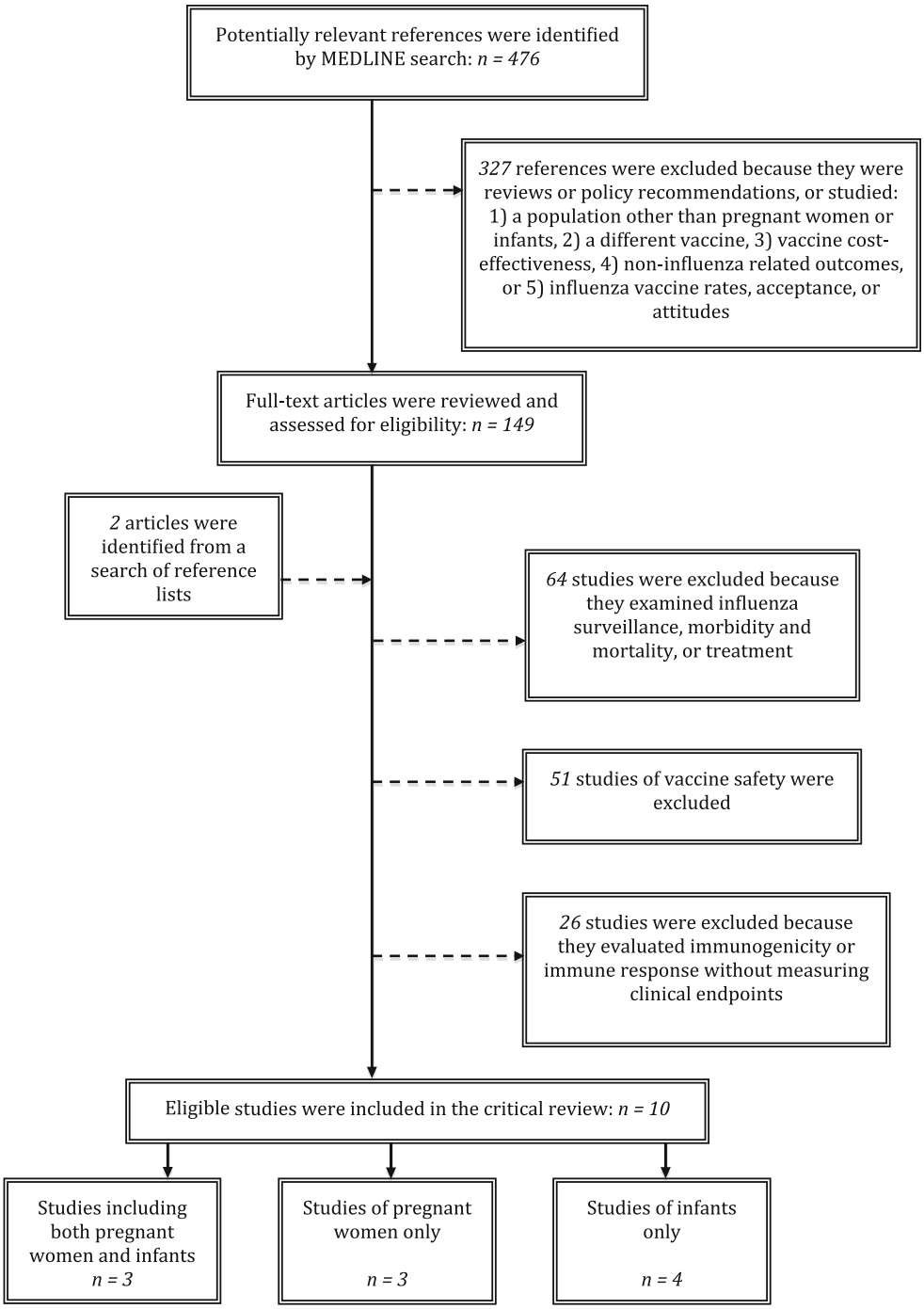

Fig. 1 Flow diagram of study selection process

Black et al. [31] assessed VE in a retrospective cohort study of nearly 50,000 pregnant women across five influenza seasons (1997–2002). VE was determined by the number of outpatient visits for ILI or hospitalization for influenza or pneumonia. The risk of a medical visit for respiratory symptoms was essentially the same for vaccinated and unvaccinated women (adjusted hazard ratio = 1.151; CI 0.979–1.352); VE = −15 % (CI −35 to 2 %).

This study has several limitations. VE was measured by clinical symptoms without laboratory confirmation of influenza. The power of the study was limited because the absolute rate of hospitalization was very low. Results from five influenza seasons were combined without information regarding strain match of vaccine to circulating strain for each influenza season.

In a retrospective case–control study of five influenza seasons (1995–2003), Munoz et al. [33] estimated the potential protective effect of vaccination by recording the occurrence of acute respiratory infection (ARI) in 252 vaccinated versus 826 unvaccinated pregnant women. The

Table 1 Effectiveness of maternal influenza vaccine

Study	Study period	Study location	Study design	Population	Outcomes measured	Influenza vaccine protection
Hulka [32]	1962–1963	Allegheny County, Pennsylvania, USA	Retrospective and prospective cohort	544 pregnant women 363 immunized 181 non-immunized 176 non-pregnant women 138 immunized 38 non-immunized	Incidence of ILI	Non-significant reduction in incidence of ILI (20 vs. 11 %)
Black et al. [31]	1997–2002	Northern California, USA	Retrospective cohort	49,585 pregnant women 3,707 immunized 45,878 non-immunized	Medical visit for respiratory symptoms	No difference in medical visits ($p = 0.088$) Adjusted hazard ratio = 1.151 (CI 0.979–1.352) Clinical effectiveness: −15 % Excluding medical visits for asthma, no difference ($p = 0.988$) Adjusted hazard ratio = 1.001 (CI 0.838–1.196) Clinical effectiveness: 0 %
Munoz et al. [33]	1998–2003	Houston, Texas, USA	Retrospective cohort	Pregnant women 252 immunized 826 non-immunized	Medically attended ARI	Non-significant trend towards lower incidence of ARI (18.9 vs. 22.6 %; $p = 0.24$) Clinical effectiveness: −20 % (CI −59.5 to 9) any time during pregnancy 39 % (CI −56 to 76) during peak of influenza season
Zaman et al. [34]	2004–2005	Bangladesh	Randomized, double-blind controlled trial	340 pregnant women 172 immunized with TIV 168 immunized with pneumococcal vaccine	Respiratory illness with fever	Significant reduction of respiratory illness with any fever: Risk difference: −14.2 (CI −25.5 to 2.9) Clinical effectiveness: 35.8 % (CI 3.7–57.2) Reduction in respiratory disease with fever over 38 °C: Risk difference: −7.3 % (CI −14.5 to 0.1) Clinical effectiveness: 43.1 % (CI −9.0 to 70.3)
Haberg et al. [35]	2009	Norway	Retrospective cohort	113,331 pregnant women 59,266 vaccinated 54,065 non-vaccinated	RT-PCR or physician contact with ICPC R80 diagnostic code for influenza	Reduced risk of influenza diagnosis Adjusted hazard ratio = 0.30 (CI 0.25–0.34) Clinical effectiveness: 70 %

Table 1 continued

Study	Study period	Study location	Study design	Population	Outcomes measured	Influenza vaccine protection
Richards et al. [36]	2009	Georgia, Maryland, Virginia, District of Columbia, USA	Retrospective cohort	3,236 mothers who gave birth between May 25, 2009 and April 17, 2010	RT-PCR or medical visit during pregnancy with influenza-related ICD-9 diagnosis code during the period of A(H1N1)pdm09 virus circulation	Clinical effectiveness: 61 % (CI 15.5–82.5 %)

researchers reported a nonsignificant ($p = 0.24$) trend toward lower incidence of medically attended ARI in the vaccinated cohort than in unvaccinated women (18.9 and 22.6 %, respectively) [33]. In this study, only three women were diagnosed with ILI, all during the peak influenza seasons of 1999–2000 and 2000–2001; one was vaccinated and two were not. Using the relative risks reported in the study, VE was −20 % for ARI any time during pregnancy (CI −59 to 9 %); and 39 % (CI −56 to 76 %) during the peak of the influenza season [33].

The low rates of ILI as well as the small number of vaccinated women in the study population (vaccination rate was 3.5 % of the 7,183 mothers who met the inclusion criteria) are major limitations of this study's findings.

Zaman et al. [34] published the only RCT of influenza VE in pregnant women, in which 340 women were randomized to receive either TIV or pneumococcal polysaccharide vaccine during the third trimester of pregnancy. Nonspecific respiratory illness with fever was recorded. Respiratory illness was significantly less frequent among women who received TIV, compared to pneumococcal vaccination. Clinical effectiveness of 35.8 % (CI 3.7–57.2 %) was reported for respiratory illness with any fever, and 43.1 % for fever over 38 °C (CI −9.0 to 70.3 %). A limitation is the use of nonspecific respiratory illness as the outcome for this study, with no laboratory confirmation of influenza infection.

The 2009 H1N1 pandemic provided an opportunity to evaluate the effectiveness of maternal vaccination during an influenza season in which there was a high rate of viral circulation, as well as a close match between the vaccine strain and the circulating viral strain. Haberg et al. [35] used data from National Health Registries in Norway to focus on the safety of A(H1N1)pdm09 adjuvanted vaccine (Pandemrix, GlaxoSmithKline) in a retrospective cohort study of 113,331 pregnancies. VE was reported as a secondary outcome in this study. A clinical diagnosis of influenza during the pandemic wave was recorded for 2,278 women in the study. Cases were diagnosed either by RT-PCR (n = 516) or physician contact resulting in an ICPC R80 diagnostic code for influenza (n = 1,762) [35]. Vaccination was correlated with a reduced risk of influenza diagnosis (adjusted hazard ratio = 0.30; CI 0.25–0.34; VE = 70 %; CI 66–75 %).

A limitation of this study is that data resulted from physician contacts leading to diagnosis of influenza. The authors acknowledge that women with more severe symptoms would be more likely than those with milder symptoms to contact a physician. Therefore, it is possible that mild cases were missed, which may influence estimates of VE.

In a retrospective cohort study focusing on birth outcomes during the 2009 H1N1 pandemic, Richards et al. [36] analyzed Kaiser Permanente medical records of 3,236

mothers in Georgia and Mid-Atlantic states. This study reported a VE in pregnant women of 61 % (CI 15.5–82.5 %) against the circulating H1N1 infection, diagnosed by RT-PCR or a medical visit during pregnancy with an influenza-related ICD-9 diagnosis code.

A limitation of this study is that the effectiveness of vaccination was not assessed during any trimester of pregnancy. The primary focus of this study was birth and infant outcomes; therefore, the study population was restricted to women who had started their third trimester of pregnancy at or after the start date of the study.

These studies are heterogeneous, did not measure any uniform outcome, and provide very little effectiveness data based on laboratory-confirmed influenza. Consequently, wide-ranging estimates of VE in pregnant women are reported, from −15 to 70 % effectiveness.

The cumulative evidence to date reporting significant clinical effectiveness of influenza vaccine during pregnancy is provided by three studies: one randomized study of women who received TIV, demonstrating 35.8 % VE against respiratory disease with any fever and 43.1 % for fever over 38 °C [34]; one study of adjuvanted A(H1N1)pdm09 vaccine reporting 70 % effectiveness against laboratory-confirmed (23 % of cases) or clinical diagnosed H1N1 influenza; and one study of nonadjuvanted A(H1N1)pdm09 vaccine reporting 61 % effectiveness in pregnant women.

Maternal Vaccination to Protect Infants

An important secondary—or "two-for-one"—benefit of maternal vaccination could be the protection from influenza afforded to infants during the first months of life. Over the past 8 years, seven studies have evaluated the effect of maternal immunization on influenza in 94,119 infants over ten influenza seasons. Four of these studies showed protection; the first three studies discussed below did not (Table 2).

In their retrospective cohort study, Black et al. [31] found that infants born to vaccinated women had the same risk of hospitalization for influenza or pneumonia as infants born to unvaccinated women (CI 0.889–1.029). They also reported that maternal vaccination was not a significant determinant of risk for ILI or otitis media.

This large study (48,639 infants) is limited by its design, which combines the results from five influenza seasons without providing information regarding strain match of vaccine to circulating strain for each influenza season. Additionally, the rates of hospitalization for infants were very low, limiting the statistical power of the study.

France et al. [37] included 3,160 infants of immunized mothers and 37,969 infants of nonimmunized mothers, followed up from 1995 to 2001 and during four specific periods: peak influenza, respiratory syncytial virus predominance, periseasonal, and summer season. No difference in medically attended ARI [incident rate ratio for peak influenza season (IRR) 0.96, CI 0.86–1.07] was found during any of the four specific periods.

Limitations of this study include the use of clinical ARI evidence rather than laboratory confirmation of influenza infection, the combination of heterogeneous influenza data from six different years, and low statistical power due to the small sample size of infants born to immunized mothers. The low maternal vaccination rate ranged from 0.7 to 20.8 % across the 6-year study period.

In a study that examined data across five influenza seasons (1995–2003), Munoz et al. [33] reported no difference between infants of vaccinated versus nonvaccinated mothers in the rate of hospitalizations for respiratory illness with fever during the peak of influenza season.

The limitations of this study include the combination of data across five seasons and the use of a clinical outcome rather than laboratory confirmation of infection to analyze VE.

In contrast, a more recent (2000–2009) matched case–control study by Benowitz et al. [38] reported maternal influenza vaccination to be 91.5 % effective (CI 61.7–98.1 %, $p = 0.001$) in preventing hospitalization of infants younger than 6 months of age for seasonal influenza. Their study included 305 infants younger than 12 months. Influenza cases were identified by a positive influenza direct fluorescent antibody (DFA) test.

A limitation to this study is the combination of nine influenza seasons, with no information regarding the strain match of vaccine to circulating strain for each season.

Eick et al. [39] conducted a prospective cohort study in the White Mountain and Navajo reservations over three influenza seasons. The authors analyzed 83 cases of laboratory-confirmed influenza infection in infants under 6 months of age. Of these cases, 71 (86 %) were confirmed by serology, 10 (12 %) by viral culture, and two (2 %) by rapid influenza testing. Using these three measures of influenza infection, the authors reported a 41 % reduction in the risk of laboratory-confirmed influenza for infants born to vaccinated women (RR 0.59; CI 0.37–0.93) and a 39 % reduction in the risk of ILI hospitalization (RR 0.61; CI 0.45–0.84).

Despite the use of laboratory confirmation of infection, this study has methodological limitations. Results were pooled from three different assay methods, each with different sensitivities, to document influenza infection. Pooling assays with differing diagnostics is a limitation. Using serology to document influenza in young infants is problematic and its use in 86 % of the cases is a major weakness of the study. The immune systems of infants younger than 6 months are immature and immunologically inexperienced. The ability to produce antibodies in response to infection is

Table 2 Effectiveness of maternal vaccination for protection of infants

Study	Study period	Study location	Study design	Population	Outcomes measured	Protection by maternal vaccination
Black et al. [31]	1997–2002	Northern California, USA	Retrospective cohort	3,652 infants of immunized mothers 44,987 infants of non-immunized mothers	Hospitalization for pneumonia and influenza	No difference in risk for hospitalization ($p = 0.235$) Adjusted hazard ratio: 0.956 (CI 0.889–1.029) Clinical effectiveness: 4 % (CI −3 to 11 %) No difference in risk including otitis media visit ($p = 0.506$) Adjusted hazard ratio: 0.938 (CI 0.777–1.132) Clinical effectiveness: 6 % (CI −13 to 22 %)
Munoz et al. [33]	1998–2003	Houston, Texas, USA	Retrospective cohort	225 infants of immunized mothers 826 infants of non-immunized mothers	Hospitalization or clinic visits for respiratory conditions	No difference in hospitalization During 1st month, infants of immunized mothers had more clinic visits for bronchitis ($p = 0.04$); fewer for respiratory distress ($p = 0.04$) No other differences
France et al. [37]	1995–2001	Colorado, Northern California, Oregon, and Washington, USA	Retrospective matched cohort	3,160 infants of immunized mothers 37,969 infants of non-immunized women	Medically attended ARI	No reduction in clinic visit rates Incident rate ratio: 0.96 (CI 0.86–1.07)
Zaman et al. [34]	2004–2005	Bangladesh	Randomized, double-blind controlled trial	316 infant mother pairs followed for 24 weeks	Clinic visits for respiratory illness Laboratory-confirmed influenza before 24 weeks of age (confirmation by rapid test)	63 % effective at preventing laboratory-confirmed influenza in infants up to 6 months old (CI 5–85 %) 29 % effective in preventing febrile illness (CI 6.9–45.7 %) 42 % effective in preventing clinic visit (CI 18.2–58.8 %)
Benowitz et al. [38]	2000–2009	New Haven, Connecticut, USA	Matched case–control	Infants less than 12 months old 113 cases 192 matched controls	Laboratory-confirmed influenza (confirmation by DFA test)	91.5 % effective at preventing hospitalization of infants less than 6 months of age ($p = 0.001$; CI 61.7–98.1 %) No significant effect on infants older than 6 months
Eick et al. [39]	2002–2005	Navajo and White Mountain Indian Reservation, Arizona, USA	Prospective cohort	1,169 infant mother pairs	Laboratory-confirmed influenza (confirmation by viral culture, fourfold rise in HI antibody in cord serum, or rapid test)	Laboratory-confirmed influenza decreased among infants born to vaccinated women compared to controls Risk ratio 0.59 (CI 0.37–0.93) Clinical effectiveness: 41 % Hospitalization Risk ratio 0.61 (CI 0.45–0.84) Clinical effectiveness: 39 %

Table 2 continued

Study	Study period	Study location	Study design	Population	Outcomes measured	Protection by maternal vaccination
Poehling et al. [43]	2002–2009	Davidson County, Tennessee, Hamilton County, Ohio, Monroe County, New York, USA	Case–control	Infants less than 6 months old hospitalized with fever or respiratory symptoms 151 cases 1,359 controls	Laboratory-confirmed influenza (confirmation by viral culture or PCR)	Hospitalized infants whose mothers were immunized were 45–48 % less likely to have laboratory-confirmed influenza Adjusted odds ratio (OR) 0.52 (CI 0.30–0.91)

often absent or delayed during the child's first 18 months, even when virus can be isolated [40]; therefore, most of the available serum antibodies are maternally derived.

In the only randomized, blinded clinical study to assess infant protection, Zaman et al. [34] reported a VE of 63 % (CI 5–85 %) against laboratory-confirmed influenza in infants up to 6 months of age. Influenza was confirmed by rapid test (Z Stat Flu). When respiratory illness and fever were used as a measure of disease, the reported effectiveness was 29 % (CI 7–46 %).

This frequently cited study of maternal vaccination [41] has limitations that raise some concern. First, of the 146 infants who visited clinics, 120 were tested for influenza, with 18 % testing positive; notably, influenza tests were ordered for 85 % of the infants in the control group, while only 75 % of the infants of TIV-vaccinated women were tested for influenza. Because this was a randomized, blinded study, the proportion of missed cases due to this inequality in testing rates should be similar between the groups, and the inequality should have minimal influence on the VE estimation. However, during the first 3 months of rapid testing there were *more* cases of influenza in infants of vaccinated mothers than in infants of nonvaccinated women. This is biologically and immunologically implausible, suggesting that unrecognized confounders may have influenced the outcome or interpretation of the study.

Secondly, this study did not assess the role of breastfeeding. However, a subsequent study performed a secondary analysis on data from this study population. This later study examined the role of exclusive breastfeeding in preventing respiratory illness in the infants. Although the researchers in the second study did not directly assess influenza infection, when adjusted for exclusive breastfeeding, maternal influenza vaccination was significantly associated with lower risk of respiratory illness with fever in infants (OR = 0.72; CI 0.55–0.77). Maternal vaccination had an independent effect of 28 % reduction of infant respiratory illness [42].

A 2011 study by Poehling et al. [43] sought to determine whether maternal vaccination during pregnancy was associated with a reduced risk of laboratory-confirmed influenza hospitalizations in 1,510 infants over seven consecutive influenza seasons (2002–2003 through 2008–2009), and across three diverse US geographic regions. Of the 1,510 infants hospitalized with fever or respiratory symptoms, 151 (10 %) had laboratory-confirmed influenza. To avoid bias associated with clinician-ordered testing, all infants in this study were tested by viral culture or RT-PCR for influenza.

In the analysis across all study years, 12 % of mothers of influenza-positive infants reported being vaccinated during pregnancy and 20 % of mothers of influenza-negative infants reported the vaccination [43], yielding an adjusted odds ratio of 0.52 (CI 0.30–0.91). This suggests that infants born to mothers who received influenza vaccines during pregnancy were 48 % less likely to have laboratory-confirmed influenza than infants of unvaccinated women.

A limitation of this study was that neither confirmed influenza vaccination status nor documented influenza illness was available for the mothers. Furthermore, no serological assays were performed to confirm maternal immunity.

Discussion and Conclusion

The negative impact of influenza infection in pregnant women and newborns is well documented. The increased risk for morbidity and mortality resulted in the universal recommendation that pregnant women be vaccinated for influenza at any stage of pregnancy. Although this recommendation has been in place since 2004, there is a paucity of well-designed epidemiological studies on vaccine efficacy and effectiveness in pregnant women, with few studies using sensitive and specific laboratory-confirmed influenza as the primary outcome.

Over the past 49 years, six studies have evaluated VE in pregnant women. Of the four studies examining effectiveness during nonpandemic years, only one showed significant protection against respiratory disease, reporting a

clinical effectiveness of 36 % [34]. All four of these studies used clinical symptoms, rather than laboratory-confirmed influenza, as the primary outcome. Clinical symptoms of influenza without laboratory confirmation are nonspecific outcomes. Many respiratory pathogens cause symptoms similar to influenza, but influenza vaccines are specifically targeted to influenza viruses and are not designed to prevent other causes of influenza-like respiratory illness.

Simply stated, interpretation and quantification of a vaccine's true effectiveness using only clinical outcomes can lead to inaccurate VE estimates. Laboratory confirmation, either by RT-PCR or viral culture, remains the best diagnostic tool for confirming influenza and truly evaluating vaccine efficacy and effectiveness.

By way of example, in a study examining ILI in pregnant women, researchers described the clinical characteristics, prognosis, and etiology. Influenza was defined as a fever of 37.8 °C or greater and at least two of the following symptoms: cough, sore throat, headache, rhinorrhea, myalgia, or shortness of breath, with laboratory confirmation using real-time PCR or viral culture [44]. Of 45 women who presented with ILI, only 31 % had confirmed influenza (H1N1) infection, 24.4 % were infected with other viruses, and no etiological agent was identified in the remaining 44 % [44]. Although the sample size was small, well over half of the women (64.5 %) who presented with clinical symptoms were not actually infected with influenza, leading to the conclusion that "we have not seen even a trend suggesting that A(H1N1)pdm09 infection can be clinically distinguished from other respiratory infections" [44].

Nonetheless, all of the published studies on seasonal influenza VE in pregnant women included in the present review used clinical symptoms as the primary outcome. The more recent studies during the 2009 H1N1pandemic report higher VEs of 61 and 70 % for nonadjuvanted and adjuvanted vaccines, respectively. In addition to clinical diagnosis, these studies employed more sensitive diagnostic tools not available for use during most of the earlier studies. It remains to be determined whether these higher VEs are the result of more accurate methods used to document influenza, to differences in vaccine-induced immune responses to the novel influenza strain in a naïve population, or perhaps a combination of factors.

While the VEs reported in these two studies are fairly similar, the higher VE was reported in a study of adjuvanted vaccine. No adjuvanted influenza vaccines are currently licensed in the US, nor are adjuvanted vaccines recommended for pregnant women in the US. In addition, the impact of adjuvants on immunologically-primed human populations to date has been marginal [45, 46], suggesting that adjuvants may be most beneficial in pandemic situations [47]. More studies will be necessary to evaluate the efficacy and effectiveness of adjuvanted influenza vaccines in pregnant women.

Even if influenza vaccination provides sub-optimal protection in pregnant women, its potential to provide protection to young infants remains a separate and important justification for the vaccine recommendation. Infants younger than 6 months of age are at particular risk for serious illness from influenza, exhibiting the highest rates of severe influenza compared to other pediatric populations [41]. However, currently available influenza vaccines are not licensed for use in infants under the age of 6 months due to their modest immunogenicity and low efficacy [48].

Several studies have demonstrated transplacentally acquired antibodies after natural influenza infection or vaccination of the mother [49–57]. However, beyond immunogenicity studies, epidemiological studies examining maternal vaccination for protection of newborns are limited.

Of the seven studies in which protection of infants via maternal vaccination was examined, only one used viral culture or RT-PCR to confirm influenza infection. This study reported 45–48 % VE in infants hospitalized with respiratory disease [43]. The other six studies reported highly varied effectiveness, ranging from no effect to 91.5 % effective. Combining these studies in an attempt to provide conclusions regarding the effectiveness of maternal immunization in preventing newborn disease is problematic. The studies measured different outcomes of disease, used different means of determining infection rates, and all but one combined data across multiple influenza seasons, often without reporting how well the vaccine matched the circulating influenza strain.

Finally, several recent studies have suggested that maternal influenza vaccination is associated with improved pregnancy outcomes such as birth weight and preterm birth [36, 58–60]. While studies examining birth outcomes are beyond the scope of this review, these reports suggest that an additional infant health benefit may be derived from maternal vaccination that warrants further attention and examination.

Conclusion

The universal recommendation for influenza vaccine in pregnant women is driven by the increased risk for morbidity and mortality in this population [1], a long track record of vaccine safety, and an expectation of effectiveness. A review of VE studies in pregnant women suggests that the foundation for recommending TIV for seasonal influenza is somewhat weak. There are only four studies of VE in pregnant women, with only one of these showing significant protection. The two studies of the effectiveness of pandemic A(H1N1)pdm09 vaccination do suggest higher VE against novel pandemic strains.

The evidence for newborn protection through maternal vaccination is encouraging, but mixed. The results of studies measuring rates of ARI, clinic visits, or hospitalization range from no vaccine effect to 42 % effectiveness [31, 33, 37]. The four studies that used some form of laboratory-confirmed influenza as the primary outcome are more encouraging, reporting VEs ranging from 41 to 91.5 % [34, 38, 39, 43]. While outcomes and study designs differ, these studies do suggest that maternal vaccination may have potential to decrease influenza illness in newborns. However, more studies with confirmed viral infection as the endpoint and adequate numbers of mother/infant pairs are needed to ascertain the extent to which maternal vaccination can protect infants from influenza.

In summary, data in support of the current seasonal influenza vaccine recommendations are limited and mixed. There is little evidence that the current seasonal vaccine is more than moderately effective in protecting pregnant women from influenza. The data may be more encouraging during pandemics and for neonatal protection, with some studies demonstrating that maternal vaccination protects infants from illness and may have additional secondary benefits. However, rigorous, well-designed studies are needed to confirm these observations.

In recent years, the science required to study influenza vaccine efficacy and effectiveness has improved. The use of RT/PCR and/or culture-confirmed outcomes and rigorous study designs are now more readily available to provide VE evidence. As we recalibrate our assumptions and conclusions regarding influenza vaccine, it is imperative that the relevant policies and recommendations be based on the results of such studies. Without such initiatives, pregnant women and newborns will be underserved and vulnerable to serious influenza illness.

Acknowledgments The author thanks Nicholas S. Kelley, Ph.D. for his helpful suggestions and assistance with the literature review, and Elaine Lilly, Ph.D., for her expert editorial assistance.

References

1. Tamma, P. D., Steinhoff, M. C., & Omer, S. B. (2010). Influenza infection and vaccination in pregnant women. *Expert Review of Respiratory Medicine, 4*(3), 321–328.
2. Schanzer, D. L., Langley, J. M., & Tam, T. W. (2007). Influenza-attributed hospitalization rates among pregnant women in Canada 1994–2000. *Journal of Obstetrics and Gynaecology Canada, 29*(8), 622–629.
3. Jamieson, D. J., Theiler, R. N., & Rasmussen, S. A. (2006). Emerging infections and pregnancy. *Emerging Infectious Diseases, 12*(11), 1638–1643.
4. Laibl, V. R., & Sheffield, J. S. (2005). Influenza and pneumonia in pregnancy. *Clinics in Perinatology, 32*(3), 727–738.
5. Griffiths, P. D., Ronalds, C. J., & Heath, R. B. (1980). A prospective study of influenza infections during pregnancy. *Journal of Epidemiology and Community Health, 34*(2), 124–128.
6. Lindsay, L., Jackson, L. A., Savitz, D. A., et al. (2006). Community influenza activity and risk of acute influenza-like illness episodes among healthy unvaccinated pregnant and postpartum women. *American Journal of Epidemiology, 163*(9), 838–848.
7. Dodds, L., McNeil, S. A., Fell, D. B., et al. (2007). Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ, 176*(4), 463–468.
8. Cox, S., Posner, S. F., McPheeters, M., Jamieson, D. J., Kourtis, A. P., & Meikle, S. (2006). Hospitalizations with respiratory illness among pregnant women during influenza season. *Obstetrics and Gynecology, 107*(6), 1315–1322.
9. Hartert, T. V., Neuzil, K. M., Shintani, A. K., et al. (2003). Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *American Journal of Obstetrics and Gynecology, 189*(6), 1705–1712.
10. Kort, B. A., Cefalo, R. C., & Baker, V. V. (1986). Fatal influenza A pneumonia in pregnancy. *American Journal of Perinatology, 3*(3), 179–182.
11. Panda, B., Panda, A., & Riley, L. E. (2010). Selected viral infections in pregnancy. *Obstetrics and Gynecology Clinics of North America, 37*(2), 321–331.
12. Mosby, L. G., Rasmussen, S. A., & Jamieson, D. J. (2011). 2009 Pandemic influenza A (H1N1) in pregnancy: A systematic review of the literature. *American Journal of Obstetrics and Gynecology, 205*(1), 10–18.
13. Cox, N. J., & Subbarao, K. (1999). Influenza. *Lancet, 354*(9186), 1277–1282.
14. CDC. (2012). Influenza vaccination coverage among pregnant women—2010–11 influenza season. *Morbidity and Mortality Weekly Report, 60*(32), 1078–1082.
15. Kennedy, E. D., Ahluwalia, I. B., Ding, H., Lu, P. J., Singleton, J. A., & Bridges, C. B. (2012). Monitoring seasonal influenza vaccination coverage among pregnant women in the United States. *American Journal of Obstetrics and Gynecology, 207*(3 Suppl), S9–S16.
16. CDC. (2012). Influenza vaccination coverage among pregnant women—2011–12 influenza season, United States. *Morbidity and Mortality Weekly Report, 61*, 758–763.
17. CDC. (2012). Pregnant women and flu shots.
18. CDC. (2004). Updated interim influenza vaccination recommendations–2004–05 influenza season. *Morbidity and Mortality Weekly Report (MMWR), 53*(50), 1183–1184.
19. Fiore, A. E., Shay, D. K., Broder, K., et al. (2009). Prevention, control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Recommendations and Reports, 58*(RR-8), 1–52.
20. Harper, S. A., Fukuda, K., Uyeki, T. M., Cox, N. J., & Bridges, C. B. (2004). Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Recommendations and Reports, 53*(RR-6), 1–40.
21. Fiore, A. E., Uyeki, T. M., Broder, K., et al. (2010). Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Recommendations and Reports, 59*(RR-8), 1–62.
22. WHO. (2005). WHO position paper on influenza vaccine.
23. CDC. (2009). Updated interim recommendations for obstetric health care providers related to the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season.
24. Reingold, A. L. (2012). Proposed revisions to the 2005 WHO position paper on influenza vaccines, 2012.
25. Osterholm, M. T., Kelley, N. S., Sommer, A., & Belongia, E. A. (2012). Efficacy and effectiveness of influenza vaccines: A

systematic review and meta-analysis. *The Lancet Infectious Diseases, 12*(1), 36–44.
26. Osterholm, M. T., Kelley, N. S., Manske, J. M., Ballering, K. S., Leighton, T. R., Moore, K. A. (2012). The compelling need for game-changing influenza vaccines: An analysis of the influenza vaccine enterprise and recommendations for the future. CIDRAP. http://www.cidrap.umn.edu/sites/default/files/public/downloads/ccivi_report.pdf.
27. CDC. (2013). Early estimates of seasonal influenza vaccine effectiveness—United States, January 2013. *MMWR Morbidity and Mortality Weekly Report*, *62*, 32–35.
28. CDC. (2013). Interim adjusted estimates of seasonal influenza vaccine effectiveness—United States, February 2013. *Morbidity and Mortality Weekly Report, 62*(07), 119–123.
29. Skowronski, D. M., & De Serres, G. (2009). Is routine influenza immunization warranted in early pregnancy? *Vaccine, 27*(35), 4754–4770.
30. Long, P. H. (1964). Recommendations for influenza immunization and control: 1964–1965. *Medical Times, 92*, 1203–1205.
31. Black, S. B., Shinefield, H. R., France, E. K., Fireman, B. H., Platt, S. T., & Shay, D. (2004). Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. *American Journal of Perinatology, 21*(6), 333–339.
32. Hulka, J. F. (1964). Effectiveness of polyvalent influenza vaccine in pregnancy. Report of a Controlled Study during an Outbreak of Asian Influenza. *Obstetrics and Gynecology, 23*, 830–837.
33. Munoz, F. M., Greisinger, A. J., Wehmanen, O. A., et al. (2005). Safety of influenza vaccination during pregnancy. *American Journal of Obstetrics and Gynecology, 192*(4), 1098–1106.
34. Zaman, K., Roy, E., Arifeen, S. E., et al. (2008). Effectiveness of maternal influenza immunization in mothers and infants. *New England Journal of Medicine, 359*(15), 1555–1564.
35. Haberg, S. E., Trogstad, L., Gunnes, N., et al. (2013). Risk of fetal death after pandemic influenza virus infection or vaccination. *The New England Journal of Medicine, 368*(4), 333–340.
36. Richards, J. L., Hansen, C., & Bredfeldt, C., et al. (2013). Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: Impact on preterm birth, birth weight, and small for gestational age birth. *Clinical Infectious Diseases*, *56*(9), 1216–1222.
37. France, E. K., Smith-Ray, R., McClure, D., et al. (2006). Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. *Archives of Pediatrics and Adolescent Medicine, 160*(12), 1277–1283.
38. Benowitz, I., Esposito, D. B., Gracey, K. D., Shapiro, E. D., & Vazquez, M. (2010). Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clinical Infectious Diseases, 51*(12), 1355–1361.
39. Eick, A. A., Uyeki, T. M., Klimov, A., et al. (2011). Maternal influenza vaccination and effect on influenza virus infection in young infants. *Archives of Pediatrics and Adolescent Medicine, 165*(2), 104–111.
40. Anderson, S. G., Donnelley, M., French, E. L., Kalra, S. L., & White, J. (1953). Influenza in Victoria, 1950 and 1951. *The Medical Journal of Australia, 2*(2), 44–47.
41. Ortiz, J. R., Englund, J. A., & Neuzil, K. M. (2011). Influenza vaccine for pregnant women in resource-constrained countries: A review of the evidence to inform policy decisions. *Vaccine, 29*(27), 4439–4452.
42. Henkle, E., Steinhoff, M. C., & Omer, S. B., et al. (2013). The effect of exclusive breastfeeding on respiratory illness in young infants in a maternal immunization trial in Bangladesh. *The Pediatric Infectious Disease Journal*, *32*(5), 431–435.
43. Poehling, K. A., Szilagyi, P. G., Staat, M. A., et al. (2011). Impact of maternal immunization on influenza hospitalizations in infants. *American Journal of Obstetrics and Gynecology, 204*(6 Suppl 1), S141–S148.
44. Pano-Pardo, J. R., Martinez-Sanchez, N., & Martin-Quiros, A., et al. (2011). Influenza-like illness in pregnant women during summertime: Clinical, epidemiological and microbiological features. *European Journal of Clinical Microbiology Infectious Diseases*, *30*(12), 1497–1502.
45. Potter, C. W., & Jennings, R. (2003). Effect of priming on subsequent response to inactivated influenza vaccine. *Vaccine, 21*(9–10), 940–945.
46. Couch, R. B., Keitel, W. A., & Cate, T. R. (1997). Improvement of inactivated influenza virus vaccines. *The Journal of Infectious Diseases, 176*(Suppl 1), S38–S44.
47. Epstein, S. L. (2006). Prior H1N1 influenza infection and susceptibility of Cleveland Family Study participants during the H2N2 pandemic of 1957: An experiment of nature. *The Journal of Infectious Diseases, 193*(1), 49–53.
48. Blanchard-Rohner, G., & Siegrist, C. A. (2011). Vaccination during pregnancy to protect infants against influenza: Why and why not? *Vaccine, 29*(43), 7542–7550.
49. Englund, J. A., Mbawuike, I. N., Hammill, H., Holleman, M. C., Baxter, B. D., & Glezen, W. P. (1993). Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *Journal of Infectious Diseases, 168*(3), 647–656.
50. Zuccotti, G., Pogliani, L., Pariani, E., Amendola, A., & Zanetti, A. (2010). Transplacental antibody transfer following maternal immunization with a pandemic 2009 influenza A(H1N1) MF59-adjuvanted vaccine. *JAMA, 304*(21), 2360–2361.
51. Puleston, R. L., Bugg, G., Hoschler, K., et al. (2010). Observational study to investigate vertically acquired passive immunity in babies of mothers vaccinated against H1N1v during pregnancy. *Health Technology Assessment, 14*(55), 1–82.
52. Fisher, B. M., Van Bockern, J., Hart, J., et al. (2012). Pandemic influenza A H1N1 2009 infection versus vaccination: A cohort study comparing immune responses in pregnancy. *PLoS One, 7*(3), e33048.
53. Tsatsaris, V., Capitant, C., Schmitz, T., et al. (2011). Maternal immune response and neonatal seroprotection from a single dose of a monovalent nonadjuvanted 2009 influenza A(H1N1) vaccine: A single-group trial. *Annals of Internal Medicine, 155*(11), 733–741.
54. Jackson, L. A., Patel, S. M., Swamy, G. K., et al. (2011). Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. *The Journal of Infectious Diseases, 204*(6), 854–863.
55. Puck, J. M., Glezen, W. P., Frank, A. L., & Six, H. R. (1980). Protection of infants from infection with influenza A virus by transplacentally acquired antibody. *Journal of Infectious Diseases, 142*(6), 844–849.
56. Reuman, P. D., Ayoub, E. M., & Small, P. A. (1987). Effect of passive maternal antibody on influenza illness in children: A prospective study of influenza A in mother-infant pairs. *The Pediatric Infectious Disease Journal, 6*(4), 398–403.
57. Steinhoff, M. C., Omer, S. B., Roy, E., et al. (2010). Influenza immunization in pregnancy—Antibody responses in mothers and infants. *New England Journal of Medicine, 362*(17), 1644–1646.
58. Steinhoff, M. C., Omer, S. B., Roy, E., et al. (2012). Neonatal outcomes after influenza immunization during pregnancy: A randomized controlled trial. *Canadian Medical Association Journal (CMAJ), 184*(6), 645–653.
59. Fell, D. B., Sprague, A. E., Liu, N., et al. (2012). H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. *American Journal of Public Health*, *102*(6), e33–e40.
60. Omer, S. B., Goodman, D., Steinhoff, M. C., et al. (2011). Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: A retrospective cohort study. *PLoS Medicine, 8*(5), e1000441.