The Global Influenza Initiative recommendations for the vaccination of pregnant women against seasonal influenza

Alejandro E. Macias, Alexander R. Precioso, Ann R. Falsey, on behalf of the Global Influenza Initiative

There is a heavy disease burden due to seasonal influenza in pregnant women, their fetuses, and their newborns. The main aim of this study was to review and analyze current evidence on safety, immunogenicity, and clinical benefits of the inactivated influenza vaccine (IIV) in pregnant women. Current evidence shows that in pregnant women, the seasonal and pandemic IIVs are safe and well tolerated. After vaccination, pregnant women have protective concentrations of anti-influenza antibodies, conferring immunogenicity in newborns. The best evidence, to date, suggests that influenza vaccination confers clinical benefits in both pregnant women and their newborns. Vaccination with either the seasonal or pandemic vaccine has been shown to be cost-effective in pregnancy. There are scarce data from randomized clinical trials; fortunately, new phase 3 clinical trials are under way. In the Northern and Southern Hemispheres, data suggest that the greatest clinical benefit for infants occurs if the IIV is administered within the first weeks of availability of the vaccine, at the beginning of the influenza season, regardless of the pregnancy trimester. The optimal timing to vaccinate pregnant women who live in tropical regions is unclear. Based on evaluation of the evidence, the Global Influenza Initiative (GII) recommends that to prevent seasonal influenza morbidity and mortality in infants and their mothers, all pregnant women, regardless of trimester, should be vaccinated with the IIV. For countries where vaccination against influenza is starting or expanding, the GII recommends that pregnant women have the highest priority.

Keywords: Global Influenza Initiative, influenza, pregnancy, pregnant women, recommendations, vaccination.

Introduction

Influenza is more likely to cause severe illness and has increased risk for hospitalization or death in pregnant women than in non-pregnant women. This predisposition can be explained by changes in the immune system and the pulmonary and cardiovascular physiology of pregnant women. In addition, children of unvaccinated women seem to be more likely to have influenza. Thus, if published and ongoing studies can show that vaccination against seasonal influenza during pregnancy is safe, immunogenic, and clinically beneficial for the mother and her newborn, it would be a highly advisable measure for prevention and control because it would target two high-risk groups with one vaccine dose. As current knowledge tends to support such a view, the Strategic Advisory Group of Experts in Immunization (SAGE) of the World Health Organization (WHO) recently specified that pregnant women are the highest priority group for influenza vaccination. The SAGE also noted that where countries are considering initiating or expanding influenza vaccination programs, pregnant women should be the highest priority group. In the United States, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) similarly recommends now that during the influenza season, all women who are or will be pregnant should be vaccinated against influenza.

The Global Influenza Initiative (GII) has been attentive to these new recommendations. However, evidence regarding influenza vaccination and pregnancy is, overall, of low quality, which makes continuous reviewing a must to support recommendations. The GII, founded in 2012, is an international expert scientific group composed of scientists, researchers, and clinicians with expertise in epidemiology, infectious diseases, immunology, and public health. The aim of the GII is to strengthen and communicate scientific evidence on the epidemiology and burden of disease of influenza, raise the profile of influenza as an important...
vaccine-preventable disease, and outline the strategies for disease prevention, intervention, and management. The GII is funded by Sanofi Pasteur, but the recommendations are made by the group members independently of the funding source. The main objective of the present document was to review and analyze current evidence surrounding the burden of influenza in pregnant women and their newborns, as well as the evidence on safety, immunogenicity, and clinical benefits of vaccination, to develop the GII recommendations regarding seasonal vaccination of pregnant women.

### Influenza burden during pregnancy

There is a heavy disease burden due to seasonal and pandemic H1N1 influenza in pregnant women and their newborns, although the evidence comes mainly from retrospective cohorts and from the 2009 pandemic.²,¹³–¹⁸,²⁰ Pregnant women are at an increased risk for influenza-related complications due to changes in their cardiac, respiratory, and immune systems.¹,⁵,¹⁹,²¹,²³ During the 2009 H1N1 pandemic, pregnant women were at higher risk for severe disease, leading to the need for hospitalization or admission to an intensive care unit, as compared to non-pregnant women and the general population.⁷ Five percent of all deaths from pandemic influenza occurred in pregnant women in the United States, although they represented only ~1% of the population;¹⁸,²³ a systematic review found that influenza hospitalization increased in pregnancy but not influenza mortality.²⁰ Studies suggest that maternal risk is the greatest during the third trimester, as compared to women at early pregnancy stages.⁵,¹⁸ Regarding the infant, maternal disease increases the risk for premature labor and delivery, fetal loss, small-for-gestational-age infants, and low birth weight.¹⁵,²⁴,²⁵ Children born to women with pH1N1 illness during pregnancy were at increased risk for low birth weight (OR, 1-8), premature birth (OR, 2-2), and death (OR, 4-5).¹⁵

### Safety of influenza vaccination in pregnancy

Safety is the most important factor to make an unambiguous recommendation to vaccinate all women who are or will be pregnant during the influenza season. During the past few decades, the inactivated influenza vaccine (IIV) has been administered to millions of pregnant women with no serious adverse events for the mother, fetus, or newborn.⁷,²⁶–³² This safety profile remains positive throughout the three trimesters of pregnancy.³⁰ The US-based Vaccine Adverse Event Reporting System has shown no safety concerns over the past 20 years in the vaccination of pregnant women.³³ The Global Advisory Committee on Vaccine Safety reviewed in 2012 the safety data available for influenza vaccines derived from clinical trials, observational studies, and spontaneous reporting, concluding that ‘the data confirm the safety of non-adjuvanted trivalent inactivated seasonal influenza vaccines in pregnancy’.³⁴ A recent randomized trial with IIV in 2310 pregnant women showed that injection-site reactions were more frequent in vaccinated than in placebo recipients (no other significant differences in solicited reactions were found).³⁵ Neither the seasonal nor the pandemic IIV has been associated with teratogenicity when administered during the first trimester,³⁶ although there is still concern because few studies have assessed safety at that stage of pregnancy, and the current ongoing clinical trials also do not do so. Therefore, influenza vaccine safety in the first trimester is an issue requiring more evidence before anybody can ensure that there are no such risks at this pregnancy stage. Moreover, no studies have compared safety and clinical benefit across IIV reformulated from year to year. Importantly, however, no study has ever found an increased risk of either maternal complications or untoward fetal outcomes associated with IIV.³⁷ In addition, no scientific evidence exists that vaccines that still include thimerosal, a mercury-containing compound, increase the number of adverse effects among children born to women who received influenza vaccine during pregnancy.³⁸

### Immunogenicity of the influenza vaccine during pregnancy

Immunization against influenza induces protective antibodies for both mothers and their infants; this is critical as no vaccine is licensed for infants aged <6 months. After vaccination, pregnant women have protective concentrations of anti-influenza antibodies, reaching levels similar to those previously reported in non-pregnant adults.³²,³⁹ Vaccination confers antibodies to newborns,³²,⁴⁰–⁴³ and the passive transfer of the persistent maternal antibodies to infants has been documented.³⁹,⁴⁰,⁴²–⁴⁵ In a recent randomized trial in 376 mothers and their newborns, influenza vaccination during pregnancy was highly immunogenic for both.³⁵ Immunization <15 days before delivery, however, does not increase hemagglutination inhibition antibody titers in newborns.⁴²

### Clinical benefit of the influenza vaccination during pregnancy

Clinical efficacy of the IIV and the size of its effect remain subjects of debate due to the scarcity of randomized trials; the interpretation of results of other trials can be complicated by the fact that observational studies are prone to biases. Most data from non-randomized trials suggest that vaccination during pregnancy confers clinical benefits in both the pregnant woman and her newborn.⁶,³⁰,⁴⁶–⁴⁹ For example, respiratory illness with fever has been shown to be reduced in
pregnant women, while in infants, findings include a reduction in laboratory-confirmed influenza (ILI) and number of small-for-gestational-age babies, along with higher birth weights.\textsuperscript{6,47} A case-controlled study found that 42\% of pregnant women with confirmed influenza had been vaccinated during the study season compared to 58\% and 63\% among influenza-negative controls and matched acute respiratory infection-negative controls, respectively, for a vaccine efficacy of 44–53\%.\textsuperscript{50} In a non-randomized prospective cohort study, maternal influenza vaccination during pregnancy was associated with a reduced risk for influenza infection [relative risk (RR) 0.59\] and hospitalization for influenza-like illness (ILI) (RR 0.61) among infants aged <6 months; increased antibody titers were also noted in infants at birth and up to 2–3 months of age.\textsuperscript{51} Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), there are four completed clinical trials assessing seasonal and A(H1N1) 2009 vaccines in pregnant women; the primary objective was to evaluate safety and immunogenicity (Table 1). Immunogenicity appears to be strong, and in the studies comparing immunogenicity in pregnant versus non-pregnant women, the response is similar; it is not possible, however, to obtain systematized information from these studies due to their small sample size and non-uniform design, as reported already by Adegbola et al.\textsuperscript{7} On the other hand, a retrospective study, using data from clinical records, found no reduction in ILI among vaccinated pregnant women or their children.\textsuperscript{31} In another big retrospective cohort study in 41 129 infants, consultations for respiratory diseases among children of vaccinated mothers were not significantly reduced.\textsuperscript{52} To date, the evidence of highest quality on vaccine efficacy comes from two randomized controlled trials. In a small study with 340 mothers in Bangladesh, Zaman et al.\textsuperscript{6} provided trivalent IIV vaccination during the third pregnancy trimester with a follow-up until 24 weeks after birth. There were fewer cases of LCI in children from vaccinated mothers than among infants in the control group, with a significant vaccine effectiveness of 63\%; among the vaccinated mothers, there was a significant reduction of 36\% in the rate of respiratory illness with fever. In the second trial, a large double-blind, placebo-controlled study in South Africa, Madhi et al. studied 2116 women who were not infected with HIV and 194 women who were infected with HIV.\textsuperscript{35} They followed mothers and their children until 24 weeks after birth, finding a significant drop of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza from 3-6\% to 1.8\% for mothers and from 3-6\% to 1.9\% for their children, for a significant vaccine-efficacy rate of 50-4\% and 48-8\%, respectively [number needed to treat (NNT), 56

### Table 1. Clinical trials of seasonal and A(H1N1) 2009 vaccines evaluating safety and immunogenicity in pregnant women

| Identifier, Clinicaltrials.gov | Year       | Vaccine                                | Comparisons                                                                 | Pregnant women, n | Design, results                                                                 |
|------------------------------|------------|----------------------------------------|-----------------------------------------------------------------------------|-------------------|--------------------------------------------------------------------------------|
| NCT00905125                  | 2008–2009  | Trivalent IIV, seasonal                | Compared influenza virus vaccines Fluzone\textsuperscript{6} (Sanofi Pasteur, Swiftwater, PA, USA) versus Fluarix\textsuperscript{6} (GlaxoSmithKline, Dresden, Germany). 0.5 ml IM | 102               | Randomized. No safety problems detected. Immunogenicity at 28 days post-vaccination similar for both vaccines |
| NCT01173211                  | 2010–2011  | Trivalent IIV, seasonal                | Compared influenza virus vaccines Fluzone\textsuperscript{6}, Fluarix\textsuperscript{6}, and Agrifu\textsuperscript{6} (Novartis Vaccines and Diagnostics Inc., Cambridge, MA, USA). 0.5 ml IM | 139 (44 non-pregnant women) | Randomized, pregnant women and non-pregnant controls. No safety problems detected. Immunogenicity not reported yet |
| NCT00963430                  | 2009       | Unadjuvanted, inactive H1N1 pandemic   | Compared two 25 μg versus two 49 μg of hemagglutinin doses (Sanofi Pasteur), administered 21 days apart | 120               | Randomized, pregnant women. No safety problems detected. Immunogenicity similar for both doses. Published\textsuperscript{32} |
| NCT00992719                  | 2009       | Unadjuvanted, inactive H1N1 pandemic   | Compared 15 versus 30 μg of hemagglutinin doses (Novartis Vaccines and Diagnostics Inc.) administered 21 days apart | 56 (28 non-pregnant women) | Randomized, pregnant women and non-pregnant controls. No safety problems detected. Immunogenicity not reported yet |

IIV, inactivated influenza vaccine.
and 59, respectively]. The drop for the HIV-infected cohort was from 17% to 7% for vaccinated mothers, with a significant vaccine efficacy of 57.7% (NNT, 10) and from 6-8% to 5% for their children, for a non-significant vaccine efficacy of 26-7%. Unlike the study in Bangladesh, this South Africa study did not show reduction in the overall outcomes of clinical respiratory illness in either mothers or infants.

Ongoing clinical trials in pregnant women

As already discussed, there are scarce data from randomized clinical trials of IIVs in pregnancy. It is therefore encouraging that, in addition to the South Africa study,35 two more late-phase clinical trials sponsored by the Bill and Melinda Gates Foundation are under way.

NCT01034254 This phase 3 study in Nepal has an estimated enrollment of 3000 pregnant women. Primary outcomes in pregnant women and their infants aged ≤6 months include incidence of ILI or LCI episodes; distribution of causes of febrile illness and the incidence of clinic visits and hospitalizations; incidence of low birth weight; the distribution of birth weight; and gestational age and growth of the infants.

NCT01430689 The number of enrolled women in this phase 4 study in Mali is not yet reported; the study compares pregnant women randomized to receive IIV or meningococcal conjugate vaccine during the third trimester of pregnancy. Primary outcomes are the number of infants with influenza (across 2 years) and incidence of LCI in infants aged ≤6 months. It is anticipated that when the results of these trials become available, more gaps in the knowledge of influenza vaccination during pregnancy will be closed.

Cost-effectiveness and timing of the influenza vaccination during pregnancy

There is limited health economics evidence on influenza vaccination in pregnant women, but vaccination with either the seasonal or pandemic vaccine has been shown to be cost-effective,53 with most benefit arising from prevention of symptomatic episodes.54 During pandemic and seasonal influenza seasons, vaccination of pregnant women becomes most cost-effective when the prevalence and severity of influenza increase.55,56 The timing of influenza vaccination of pregnant women within the influenza season is important for cost-effectiveness – the greatest benefit to infants occurred when their pregnant mothers were vaccinated within the first 4 weeks of vaccine availability.54,57 Furthermore, when all women who were pregnant at the time of vaccine availability were vaccinated, vaccination of newly pregnant women seemed to provide benefits for mothers but not for infants.57 Unfortunately, although the first priority is to protect the mother, if vaccination is not given in the third trimester of pregnancy, the newborn is unlikely to derive much benefit. In this regard, there is some evidence from the TDaP vaccine suggesting that newborns benefit more if the vaccine is given in the third trimester.59 Thus, factors influencing cost-effectiveness include attack and death rate, at what stage of pregnancy vaccination occurs, potential vaccine protection for infants, potential persistence of vaccine protection, when during the influenza season vaccination occurs; cost of vaccine delivery; and vaccine efficacy.

Table 2. Global Influenza Initiative (GII) recommendations regarding influenza vaccination during pregnancy

| Recommendation                                                                 | Comment |
|--------------------------------------------------------------------------------|---------|
| 1. To prevent seasonal influenza morbidity and mortality in infants and their mothers, pregnant women, regardless of trimester, should be vaccinated with the inactivated influenza vaccine (IIV) |
| 2. Pregnant women should not receive the live attenuated influenza vaccine (LAIV) |
| 3. Postpartum women, even if they are breastfeeding, can receive either the IIV or LAIV |
| 4. Because it is difficult to predict the onset of the influenza season, routine influenza vaccination is recommended for pregnant women and those who expect to be pregnant during the influenza season. The duration of each geographic region’s influenza season should be an important consideration because in some countries, influenza is seasonal, whereas in others it occurs year-round. In regions with defined influenza seasons, the GII recommends the vaccination of pregnant women as a priority group immediately after the vaccine becomes available, regardless of the pregnancy trimester |
| 5. For countries where vaccination of influenza is starting or expanding, the GII recommends that pregnant women have a high priority |
| 6. For countries with programs of immunization against influenza, where pregnant women are not considered as a priority for vaccination, a policy change is required to consider them as such |
| 7. Vaccination coverage of pregnant women is low worldwide; therefore, there is a need to encourage education of all healthcare providers (not solely obstetricians) that a pregnant woman is likely to see that maternal immunization is effective, well tolerated, and safe. If the healthcare professional does not recommend the vaccine, even highly educated women are unlikely to receive it |
| 8. Wherever possible, influenza vaccination during pregnancy must be administered at least 15 days before delivery |
| 9. Where quadrivalent IIV is available, it can be administered in pregnant women instead of the trivalent one |
| 10. Influenza vaccination should become standard in women’s health care |
mended across all trimesters by the WHO, the CDC, and the Canadian Guideline Committee. To achieve this goal, healthcare providers’ recommendations are key to vaccine uptake.

In the Northern and Southern Hemispheres, data suggest that the greatest clinical benefit for infants occurs if the IIV is administered within the first weeks of availability of the vaccine, at the beginning of the influenza season, regardless of the pregnancy trimester. This strategy confers maximum protection in the mother and fetus (administering vaccine long before the start of the season is unlikely to have any benefit). It is unclear when it is optimal to vaccinate pregnant women who live in tropical regions, where influenza tends to occur year-round; ongoing clinical trials are not assessing this. Because inactivated trivalent influenza vaccine (TIV) contains only one B strain, there is a new inactivated quadrivalent influenza vaccine containing both circulating B lineages, which has been used in healthy adults, resulting in superior immunogenicity for the added B strain, without affecting the antibody response to the TIV strains, and without compromising safety.

There is still a lot we do not know about the timing of influenza vaccinations in pregnancy, including (i) the optimal vaccination strategies for pregnant women with comorbidities; (ii) the impact that breastfeeding has on protection duration, the effect that breastfeeding has on vaccination strategies; and (iii) the vaccination strategies for developing countries.

GII recommendations for influenza vaccination during pregnancy

Based on our review, the GII recommends the vaccination of women during pregnancy because evidence of high and moderate quality suggests that internationally available IIVs reduce the risk of ILI in mothers and infants as well as the risk of LCI in infants. In addition, the GII recommendation considers that the IIVs lack teratogenicity, induce an immunogenic response of the mothers and newborns, and are contraindicated in children younger than 6 months. Postpartum women can receive either the IIV or the live attenuated influenza vaccine. In addition, the GII proposes several other recommendations regarding vaccination during pregnancy (Table 2). We require future research on specific knowledge gaps on vaccine efficacy and its duration, and we expect the studies in progress to yield new data, which we will incorporate in future recommendations.

Acknowledgements

The GII is supported by a grant from Sanofi Pasteur and managed by PAREXEL, the scientific secretariat for this program. We acknowledge the editorial assistance of PAREXEL, which was supported by Sanofi Pasteur. We are also most grateful to the GII members.

Conflict of interests

AEM, ARP, and ARF are members of the GII. AEM and ARP have no other financial, funding, or employment interests to declare. ARF has received research grants from Sanofi Pasteur, GlaxoSmithKline, ADMA Biologics, Inc., and AstraZeneca, and consulting fees from Regeneron and Novavax.

References

1 Jamieson DJ, Honein MA, Rasmussen SA et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009; 374:451–458.
2 Louie JK, Acosta M, Jamieson DJ, Honein MA, California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2010; 362:27–35.
3 Steinhoff MC, MacDonald N, Pfeifer D, Muglia LJ. Influenza vaccine in pregnancy: policy and research strategies. Lancet 2014; 383:1611–1613.
4 Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions. Vaccine 2011; 29:4439–4452.
5 Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998; 148:1094–1102.
6 Zaman K, Roy E, Arifeen SE et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008; 359:1555–1564.
7 Adegbola R, Nesin M, Wairagkar N. Immunogenicity and efficacy of influenza immunization during pregnancy: recent and ongoing studies. Am J Obstet Gynecol 2012; 207(3 Suppl):S28–S32.
8 World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, April 2012 – conclusions and recommendations (seasonal influenza vaccine). Wkly Epidemiol Rec 2012; 87:201–216.
9 World Health Organization. Vaccines against influenza WHO position paper – November 2012. Wkly Epidemiol Rec 2012; 87:461–476.
10 World Health Organization. Influenza vaccines: WHO position paper. Wkly Epidemiol Rec 2005; 80:277–288.
11 Centers for Disease Control and Prevention (CDC). Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices – United States, 2013–2014. MMWR Recomm Rep 2013; 62:1–42.
12 Galvao TF, Silva MT, Zimmermann IR, Lopes LAB, Bernardo EF, Pereira MG. Influenza vaccination in pregnant women: a systematic review. ISRN Prev Med 2013; 2013:879493. doi: 10.5402/2013/879493.
13 Brown CM. Severe influenza A virus (H1N1) infection in pregnancy. Obstet Gynecol 2010; 115:412–414.
14 Creanga AA, Kamimoto L, Newsome K et al. Seasonal and 2009 pandemic influenza A (H1N1) virus infection during pregnancy: a population-based study of hospitalized cases. Am J Obstet Gynecol 2011; 204(6 Suppl 1):S38–S45.
15 Doyle TJ, Goodin K, Hamilton JJ. Maternal and neonatal outcomes among pregnant women with 2009 pandemic influenza A(H1N1) illness in Florida, 2009–2010: a population-based cohort study. PLoS ONE 2013; 8:e79040.
16 Ersbøll AS, Hesselvig AB, Hedegaard M, Krebs L. [Pregnant women are known to be at increased risk of severe illness when exposed to influenza A (H1N1)]. Ugeskr Laeger 2012; 174:2920–2921.

17 Jamieson DJ, Rasmussen SA, Uyeki TM, Weinbaum C. Pandemic influenza and pregnancy revisited: lessons learned from 2009 pandemic influenza A (H1N1). Am J Obstet Gynecol 2011; 204(6 Suppl 1):S1–S3.

18 Siston AM, Rasmussen SA, Honein MA et al. Pandemic 2009 influenza A/H1N1 virus illness among pregnant women in the United States. JAMA 2010; 303:1517–1525.

19 Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis 2006 Nov; 12:1638–1643.

20 Mertz D, Kim TH, Johnstone J et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ 2013; 347:f5061.

21 Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med 2005; 33(10 Suppl):S390–S397.

22 Mosby LG, Rasmussen SA,Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol 2011; 205:10–18.

23 Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med 2004; 350:1283–1293.

24 Centers for Disease Control and Prevention (CDC). Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1) – United States, April 2009–August 2010. MMWR Morb Mortal Wkly Rep 2011; 60:1193–1196.

25 Legge A, Dodds L, MacDonald NE, Scott J, McNeil S, Rates and determinants of seasonal influenza vaccination in pregnancy and association with neonatal outcomes. CMAJ 2014; 186:E157–E164.

26 Kharbanda EO, Vazquez-Benitez G, Lipkind H et al. Inactivated influenza vaccine during pregnancy and risks for adverse obstetric events. Obstet Gynecol 2013; 122:659–667.

27 Lin SY, Wu ET, Lin CH, Shyu MK, Lee CN. The safety and immunogenicity of trivalent inactivated influenza vaccination: a study of maternal-cord blood pairs in Taiwan. PLoS ONE 2013; 8:e62983.

28 Munoz FM, Greisinger AJ, Wehmanen OA et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2005; 192:1098–1106.

29 Nordin JD, Kharbanda EO, Benitez GV et al. Maternal safety of trivalent inactivated influenza vaccine in pregnant women. Obstet Gynecol 2013; 121:519–525.

30 Sheffield JS, Greer LG, Rogers VL et al. Effect of influenza vaccination in the first trimester of pregnancy. Obstet Gynecol 2012; 120:532–537.

31 Black SB, Shinefield HR, France EK et al. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol 2004; 21:333–339.

32 Jackson LA, Patel SM, Swamy GK et al. Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. J Infect Dis 2011; 204:854–863.

33 Moro PL, Broder K, Zheteyeva Y et al. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990–2009. Am J Obstet Gynecol 2011; 204:146.e1–e7.

34 World Health Organization. Global Advisory Committee on Vaccine Safety. June 2012. Wkly Epidemiol Rec 2012; 87:277–288.

35 Madhi SA, Cutland CL, Kuvwanda L et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014; 371:918–931.

36 Pasternak B, Svanström H, Melgaard-Nielsen D et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A (H1N1) vaccine during pregnancy. JAMA 2012; 308:165–174.

37 Tamma PD, Ault KA, del Rio C, Steinhoff MC, Halsey NA, Omer SB. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2009; 201:547–552.

38 Thompson WW, Price C, Goodson B et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med 2007; 357:1281–1292.

39 Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. J Infect Dis 1979; 140:141–146.

40 Steinhoff MC, Omer SB, Roy E et al. Influenza immunization in pregnancy – antibody responses in mothers and infants. N Engl J Med 2010; 362:1644–1646.

41 Speirling RS, Engel SM, Wallenstein S et al. Immunogenicity of trivalent inactivated influenza vaccine vaccination received during pregnancy or postpartum. Obstet Gynecol 2012; 119:631–639.

42 Blanchard-Rohner G, Meier S, Bel M et al. Influenza vaccination given at least 2 weeks before delivery to pregnant women facilitates transmission of seroprotective influenza-specific antibodies to the newborn. Pediatr Infect Dis J 2013; 32:1374–1380.

43 Englund JA, Mbawuike IN, Hammill H, Hollemann MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. J Infect Dis 1993; 168:647–656.

44 Puck JM, Glezen WP, Frank AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. J Infect Dis 1980; 142:844–849.

45 Reuman PD, Ayoub EM, Small PA. Effect of passive maternal antibody on influenza illness in children: a prospective study of influenza A in mother-infant pairs. Pediatr Infect Dis J 1987; 6:398–403.

46 Steinhoff MC, Omer SB. A review of fetal and infant protection associated with antenatal influenza immunization. Am J Obstet Gynecol 2012; 207(3 Suppl):S21–S27.

47 Steinhoff MC, Omer SB, Roy E et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ 2012; 184:645–653.

48 Steinhoff MC, MacDonald NE. Influenza pandemics – pregnancy, pathogenesis, and perinatal outcomes. JAMA 2012; 308:184–185.

49 Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis 2010; 51:1355–1361.

50 Thompson MG, Li DK, Shifflett P et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010–2011 and 2011–2012 influenza seasons. Clin Infect Dis 2014; 58:449–457.

51 Eick AA, Uyeki TM, Klivom A et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. Arch Pediatr Adolesc Med 2011; 165:104–111.

52 France EK, Smith-Ray R, McClure D, France EK. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. Arch Pediatr Adolesc Med 2006; 160:1277–1283.

53 Roberts S, Hollier LM, Sheffield J, Laibl V, Wendel GD Jr. Cost-effectiveness of universal influenza vaccination in a pregnant population. Obstet Gynecol 2006; 107:1323–1329.

54 Lit M, Cromer D, Baguelin M, Stowe J, Andrews N, Miller E. The cost-effectiveness of vaccinating pregnant women against seasonal influenza in England and Wales. Vaccine 2010; 29:115–122.
55 Chocontá-Piraquive LA, Alvis Guzmán N, De la Hoz Restrepo F. [Cost-effectiveness of vaccinating pregnant women against pandemic influenza in Colombia]. Rev Panam Salud Publica 2012; 31:447–453.
56 Beigi RH, Wiringa AE, Bailey RR, Assi TM, Lee BY. Economic value of seasonal and pandemic influenza vaccination during pregnancy. Clin Infect Dis 2009; 49:1784–1792.
57 Myers ER, Misurski DA, Swamy GK. Influence of timing of seasonal influenza vaccination on effectiveness and cost-effectiveness in pregnancy. Am J Obstet Gynecol 2011; 204(6 Suppl 1):S128–S140.
58 Public Health Agency of Canada. Statement on seasonal influenza vaccine for 2013–2014. Can Commun Dis Rep 2013; 39:ACS-4.
59 Abu Raya B, Srugo I, Kessel A et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – a prospective study. Vaccine 2014; 32:5787–5793.
60 Tinoco JC, Pavia-Ruz N, Cruz-Valdez A et al. Immunogenicity, reactogenicity, and safety of inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine in healthy adults aged ≥18 years: a phase III, randomized trial. Vaccine 2014; 32:1480–1487.