



# HHS Public Access

Author manuscript

*Am J Obstet Gynecol.* Author manuscript; available in PMC 2015 August 28.

Published in final edited form as:

*Am J Obstet Gynecol.* 2012 September ; 207(3 0): S17–S20. doi:10.1016/j.ajog.2012.06.070.

## Benefits of influenza vaccination during pregnancy for pregnant women

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### Abstract

Influenza vaccination is a cornerstone of influenza prevention efforts among pregnant women. Prior to 2005, data from studies conducted on pregnant women were limited, with much of the supporting evidence coming from influenza vaccine studies conducted among nonpregnant, age-matched populations. Since 2005, however, an increasing number of studies have demonstrated the safety and immunogenicity of influenza vaccine for pregnant women, including evidence of maternal transfer of antibody. In addition, the clinical benefit of influenza vaccination, both for the mother and infant, was demonstrated in a landmark randomized clinical trial conducted in Bangladesh. Additional randomized clinical trials with laboratory-confirmed influenza as the primary outcome are underway in countries without a current influenza vaccination program, but such trials are unlikely to be conducted in the United States or other countries that already recommend the vaccination of pregnant women. However, current evidence supports the safety and immunogenicity of inactivated influenza vaccine and its effectiveness in reducing the risk of influenza-related illness among pregnant women.

### Keywords

influenza vaccination; pregnancy

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Pregnancy places women at increased risk for severe complications from influenza virus infection.<sup>1,2</sup> Beginning as early as 1960, influenza vaccination has been recommended for pregnant women to prevent influenza virus infection and its complications.<sup>3</sup> Since 2004, the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, the American College of Obstetricians and Gynecologists, and other professional organizations have recommended that all pregnant women receive the trivalent inactivated vaccine, regardless of pregnancy trimester<sup>4</sup> to avoid missed opportunities for vaccination.

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The authors report no conflict of interest.

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We critically evaluated published literature on the safety, immunogenicity, and clinical benefits to the mother of influenza vaccination during pregnancy. Because only the inactivated vaccine is recommended in pregnancy, this review includes only results from studies evaluating the inactivated influenza vaccine.

We reviewed studies assessing the immunogenicity of influenza vaccine in pregnant women and studies of clinical impact of vaccination on pregnant women. Immunogenicity studies measure the level of influenza-specific antibody elicited after vaccination, with hemagglutination inhibition (HI) testing of pre- and postvaccination serum samples being the most commonly used test for assessing influenza vaccine immune response. Although there is no specific HI titer level above which infection will not occur, higher postvaccination antibody titers correspond with lower risk of influenza illness. And HI titers of 1:40 or greater, or a 4-fold rise in HI titer are often used in clinical trials as benchmarks for defining an acceptable immune response.

Clinical studies, including observational and randomized trials, measure the ability of the vaccine to prevent illness. The primary clinical outcome in vaccine trials may be nonspecific (eg, acute respiratory illness) or specific (eg, laboratory-confirmed influenza illness). Randomized, double-blind, placebo-controlled study designs provide the strongest evidence for benefit. Although observational studies can provide important data, interpretation can be complicated because of the differences among persons who choose or choose not to receive influenza vaccination.

Efficacy refers to the ability of the vaccine to prevent illness in the context of randomized clinical trials, whereas effectiveness refers to the ability of vaccine to prevent illness in vaccinated populations outside a randomized clinical trial. Various factors affect the observed effectiveness and efficacy of the influenza vaccine. Characteristics of the recipient, such as age, immune status, and, potentially, pregnancy status, may influence efficacy and effectiveness. Characteristics of the virus, including the match between the vaccine and the circulating influenza virus and vaccine immunogenicity, which can vary greatly from year to year, can affect vaccine efficacy and effectiveness. In addition, the specific clinical outcome being measured may affect the estimate of efficacy or effectiveness. For example, because acute respiratory illness may be caused by a number of different pathogens that the vaccine would not be expected to prevent, the point estimate of effectiveness is expected to be lower because outcomes other than laboratory-confirmed influenza are used.<sup>4</sup>

Efficacy of inactivated influenza vaccine among adults has been demonstrated in several randomized placebo-controlled trials with the outcome of laboratory-confirmed influenza.<sup>5–12</sup> A recent meta-analysis reported a pooled vaccine efficacy of 59% (95% confidence interval, 51–67%) for the trivalent inactivated influenza vaccine among adults aged 18–64 years.<sup>13</sup> Among studies that enrolled participants with similar age distributions to those of pregnant women, demonstrated vaccine efficacy ranged from 54% to 89%.<sup>9–12</sup> A 2-year study among healthy workers younger than 65 years found no efficacy in year 1 when the vaccine match was poor but found 86% efficacy against influenza-like illnesses (ILI) plus serologically confirmed influenza in year 2. Also, in year 2, vaccinated adults had 34% fewer ILIs, 42% fewer physician visits for ILI, and 32% fewer lost workdays for ILI.<sup>6</sup> Most

recently, a group of investigators in Michigan conducted double-blind, randomized studies comparing placebo, live attenuated vaccine, and inactivated vaccine among healthy adults younger than 50 years of age. Over 3 influenza seasons, inactivated influenza vaccine efficacy ranged from 54% to 77%.<sup>9–11</sup>

Although the efficacy and effectiveness of influenza vaccination in preventing influenza infection and illness has been demonstrated in nonpregnant, healthy adults, the immune response to vaccination might be different in pregnant women for several reasons. During pregnancy, immune alterations that allow the mother to tolerate fetal tissue of paternal origin occur. Although these immune alterations are not well understood, a shift away from cell-mediated immunity and toward humoral immunity is thought to occur.<sup>14</sup> Although these immune changes are not expected to affect the efficacy or effectiveness of vaccines in pregnancy, it is important to carefully review influenza vaccination studies conducted among pregnant women.

Several immunogenicity studies have been conducted in pregnant women dating back to the early 1960s. In 1962–1963, Hulka<sup>15</sup> conducted a nonrandomized cohort study in which 225 pregnant and 44 nonpregnant women received either 2 doses of whole virus-inactivated influenza vaccine or a placebo. The pattern of rise and fall of influenza titer levels was similar in pregnant and nonpregnant women. In 1976–1977, Murray et al<sup>16</sup> conducted a prospective cohort study using monovalent, whole-virus-inactivated vaccine. Using HI antibody testing, the postimmunization geometric mean antibody titers were not significantly different in 26 pregnant and 18 nonpregnant women, with no significant differences in antibody titers by trimesters. Also in 1976–1977, Sumaya and Gibbs<sup>17</sup> identified 40 pregnant women who had been vaccinated with monovalent whole-virus-inactivated vaccine and had available serum samples. Results of HI antibody testing showed antibody response among the pregnant women to be similar to that of nonpregnant adults who participated in a national vaccine trial.

In 1992–1993, Englund et al<sup>18</sup> conducted a prospective cohort study in which 13 pregnant women in the third trimester were vaccinated with trivalent inactivated influenza vaccine. Maternal seroconversion to vaccine antigen was found in all 13 vaccinated pregnant women. As part of a randomized controlled clinical trial in Bangladesh, Steinhoff et al<sup>19</sup> tested samples from 311 pregnant women using an HI assay. Vaccinated pregnant women had higher levels of protective influenza antibodies compared with pregnant women who received the control vaccine. Jackson et al<sup>20</sup> randomly assigned 120 pregnant women to receive either a low or high dose of 2009 H1N1 monovalent inactivated vaccine in a 2 dose series. One dose of either vaccine elicited an antibody response typically associated with protection against influenza infection. Similarly, Tsatsaris et al<sup>21</sup> (n = 102) and Fisher et al<sup>22</sup> (n = 14) found protective levels of antibody in healthy pregnant women who received the 2009 H1N1 monovalent vaccine.

In summary, these studies consistently show that pregnant women administered influenza vaccine develop protective concentrations of antiinfluenza antibodies, similar to nonpregnant women.

In addition to the immunogenicity studies, several clinical trials have evaluated the ability of influenza vaccine to prevent illness in pregnant women. However, until 2008 when the Mother's Gift Project,<sup>23</sup> a randomized trial, was published, much of the information about the clinical benefits of vaccinating pregnant women came from observational studies that used nonspecific, non-laboratory-confirmed outcomes and failed to demonstrate a benefit of vaccination.

The cohort study by Hulka<sup>15</sup> in 1962–1963 included both prospective and retrospective components. For the prospective portion of the study, he vaccinated pregnant and nonpregnant women with whole-virus–inactivated vaccine and also vaccinated pregnant and nonpregnant women with placebo. His study also included a retrospective component in which all women attending the prenatal clinic in April 1963 who were not part of the prospective component were asked whether they had been vaccinated against influenza the preceding winter. Participating nonvaccinated women were added to the prospective control group and were asked whether they had experienced influenza-like illness defined as flu with fever. Eleven percent of the vaccinated pregnant women compared with 20% of the nonvaccinated pregnant women reported influenza-like illness; this difference was not statistically significant.

Black et al<sup>24</sup> conducted a retrospective analysis of outpatient visits and hospitalizations at Kaiser Permanente spanning 5 influenza seasons using an administrative database (1997–2002). They found a low burden of medical care for influenza-like illness (defined based on *International Classification of Diseases* (ninth revision)-coded medical visits) with no pregnant women hospitalized with a diagnosis of influenza during the study period and only 9 of 49,585 pregnant women hospitalized with a diagnosis of pneumonia during influenza season. Furthermore, women who received influenza vaccination had the same risk for outpatient visits for influenza-like illness compared with unvaccinated pregnant women (hazard ratio, 1.15;  $P = .088$ ).

The main limitation of this study is that this type of administrative data does not accurately distinguish influenza from other respiratory illness, thereby including nonspecific endpoints, and therefore, any effect of influenza vaccine would likely be substantially underestimated. Munoz et al<sup>25</sup> conducted a retrospective review of 5 influenza seasons (1998–2003) at a large, multidisciplinary clinic in Houston, TX, and compared 225 vaccinated pregnant women with 826 nonvaccinated pregnant women, matched by age, month of delivery, and type of medical insurance. There were no significant differences in medical visits for acute respiratory infections between vaccinated and unvaccinated women, with 23% (51 of 225) of vaccinated women compared with 19% (156 of 826) of unvaccinated women seeking medical care for an acute respiratory infection ( $P = .24$ ). This is another example of a study that used a very nonspecific outcome.

The landmark randomized clinical study among pregnant women was conducted in 2004–2005 in Bangladesh. In the Mother's Gift Project,<sup>23</sup> pregnant women were randomized to receive either inactivated influenza vaccine ( $n = 172$ ) or pneumococcal vaccine ( $n = 168$ ). Pregnant women who received influenza vaccine were 36% (95% confidence interval 4–57%) less likely to have respiratory illness with fever compared with those who received

pneumococcal vaccine; the study did not include an influenza laboratory-confirmed outcome for the mothers. Because of its randomized design and use of a control vaccine, this study provides the strongest evidence of maternal benefit of influenza vaccine. Although laboratory-confirmed influenza was not included as an outcome in the mothers, it was included as an outcome in the infants. Infants younger than 6 months of age were found to have a 63% lower risk of laboratory-confirmed influenza. The less specific outcome used for the mothers would have underestimated the point estimate of efficacy for influenza vaccine.

The Mother's Gift Project, because of its large size and randomized design, provides the most direct and compelling evidence of the maternal benefits of influenza vaccination in pregnancy. Additional information regarding the maternal benefits of influenza vaccination in different settings is needed, and several randomized trials on the efficacy of influenza in pregnant women are currently underway (Clinicaltrials.gov, #NCT01430689 and #NCT01034254).

In summary, because pregnant women are at increased risk for influenza-associated complications,<sup>26</sup> it is important to reduce the risk of influenza infection among pregnant women. Influenza vaccination is an important component of prevention efforts among pregnant women. Although few data on clinical efficacy are available from randomized trials in pregnant women, immunogenicity studies in pregnant women, results from clinical effectiveness studies in similarly aged nonpregnant adults, and studies demonstrating the clinical benefits to infants all support efforts to vaccinate pregnant women.

## Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Vaccine Program Office, the Centers for Disease Control and Prevention, or the Food and Drug Administration.

## References

1. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. *Am J Obstet Gynecol.* 2011; 205:10–8. [PubMed: 21345415]
2. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. *Emerg Infect Dis.* 2008; 14:95–100. [PubMed: 18258087]
3. Burney LE. Influenza immunization: statement. *Public Health Rep.* 1960; 75:944. [PubMed: 19316369]
4. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep.* 2010; 59:1–62. [PubMed: 20689501]
5. Beran J, Vesikari T, Wertzova V, et al. Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: a prospective, randomized, placebo-controlled trial. *J Infect Dis.* 2009; 200:1861–9. [PubMed: 19909082]
6. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA.* 2000; 284:1655–63. [PubMed: 11015795]
7. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis.* 1994; 169:68–76. [PubMed: 8277200]

8. Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine*. 1997; 15:1114–22. [PubMed: 9269055]
9. Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med*. 2009; 361:1260–7. [PubMed: 19776407]
10. Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med*. 2006; 355:2513–22. [PubMed: 17167134]
11. Ohmit SE, Victor JC, Teich ER, et al. Prevention of symptomatic seasonal influenza in 2005–2006 by inactivated and live attenuated vaccines. *J Infect Dis*. 2008; 198:312–7. [PubMed: 18522501]
12. Wilde JA, McMillan JA, Serwint J, Butta J, O’Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA*. 1999; 281:908–13. [PubMed: 10078487]
13. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012; 12:36–44. [PubMed: 22032844]
14. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerg Infect Dis*. 2006; 12:1638–43. [PubMed: 17283611]
15. Hulka JF. Effectiveness of polyvalent influenza vaccine in pregnancy. Report of a controlled study during an outbreak of Asian influenza. *Obstet Gynecol*. 1964; 23:830–7. [PubMed: 14168242]
16. Murray DL, Imagawa DT, Okada DM, St Geme JWJ. Antibody response to monovalent A/New Jersey/8/76 influenza vaccine in pregnant women. *J Clin Microbiol*. 1979; 10:184–7. [PubMed: 583151]
17. 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; 140:141–6. [PubMed: 479636]
18. Englund JA, Mbawuike IN, Hammill H, Holleman MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *J Infect Dis*. 1993; 168:647–56. [PubMed: 8354906]
19. Steinhoff MC, Omer SB, Roy E, et al. Influenza immunization in pregnancy—antibody responses in mothers and infants. *N Engl J Med*. 2010; 362:1644–6. [PubMed: 20427817]
20. Jackson LA, Patel SM, Swamy GK, et al. Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. *J Infect Dis*. 2011; 204:854–63. [PubMed: 21849282]
21. Tsatsaris V, Capitán C, Schmitz T, et al. Maternal immune response and neonatal seroprotection from a single dose of a monovalent nonadjuvanted 2009 influenza A(H1N1) vaccine: a single-group trial. *Ann Intern Med*. 2011; 155:733–41. [PubMed: 22147712]
22. Fisher BM, Van BJ, Hart J, et al. Pandemic influenza A H1N1 2009 infection versus vaccination: a cohort study comparing immune responses in pregnancy. *PLoS One*. 2012; 7:e33048. [PubMed: 22457731]
23. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008; 359:1555–64. [PubMed: 18799552]
24. Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D. 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; 21:333–9. [PubMed: 15311370]
25. Munoz FM, Greisinger AJ, Wehmanen OA, et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol*. 2005; 192:1098–106. [PubMed: 15846187]
26. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. *Am J Obstet Gynecol*. 2012; 207:S3–8. [PubMed: 22920056]