

# Influenza Immunization in Pregnancy

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Among healthy persons, two groups are notable for increased risk of serious illness and hospitalization with influenza infection: healthy women in pregnancy and their healthy infants (aged 0 to 6 months). Inactivated influenza vaccine has been used in pregnant women since the 1960s in both the United States and Canada; however, currently, only 15% of pregnant women receive the vaccine. A randomized, controlled trial has shown influenza immunization of pregnant women reduced influenza-like illness by more than 30% in both the mothers and the infants and reduced laboratory-proven influenza infections in 0- to 6-month-old infants by 63%. Physicians caring for pregnant women should be aware of the risks of influenza and of the availability of an effective and cost-saving intervention.

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Among healthy persons without chronic illness or other risk factors, two groups are notable for having increased risk of serious illness and hospitalization with influenza: Healthy women in pregnancy and healthy infants 0–6 months of age. This commentary outlines the influenza risks for these two groups and updates information on strategies for influenza prevention in the mother–infant dyad.

During pregnancy, healthy women have a fourfold to fivefold increased rate of serious illness and hospitalization with influenza.<sup>1</sup> Influenza-related hos-

pitalization of healthy pregnant women occurs at the rate of 1–2 per 1,000 or 0.1%.<sup>1</sup>

Trivalent inactivated influenza vaccine has been used in pregnant women since the 1960s in the United States and in Canada; however, currently, only 15% of pregnant women receive the vaccine. Both the Advisory Committee on Immunization Practices in the United States and the National Advisory Committee on Immunization in Canada recommend the trivalent inactivated influenza vaccine in pregnancy. These recommendations were based on studies showing increased risk of respiratory-related hospitalization in pregnancy, the immunogenicity of the vaccine in pregnancy, and the data on safety in pregnancy in prospective studies of more than 10,000 pregnant women<sup>2,3,4</sup> (Appendix 1).

Newborns and young infants aged 0–6 months are also at high risk of symptomatic influenza infection. National surveys in the United States show annual deaths in children associated with influenza to number from 40 to 150 per year with a high proportion of these deaths in healthy infants aged 0–6 months.<sup>5</sup> Furthermore, recent studies of influenza in infants have shown an increased risk of postinfluenza secondary bacterial pneumonia with pneumococcus<sup>6</sup> and with *Staphylococcus aureus*.<sup>7</sup> Influenza virus leads to increased healthcare consultations and increased hospitalizations in North America (Fig. 1).<sup>2,5</sup> The rates for laboratory-confirmed influenza hospitalization for young infants aged less than 6 months are estimated to be up to 12 per 1,000, and in some years nearly 10% of infants aged less than 6 months have serious illness with laboratory-proven influenza infection.<sup>5</sup>

While there is increasing recognition that 0- to 6-month-old infants are a high-risk group for serious infection with influenza, prevention has been problematic, as neither vaccine nor antiviral drugs are licensed for use in this age group. Studies have shown that influenza vaccine has limited immunogenicity before 6 months of age.<sup>8</sup> While it is possible that new vaccines or dose formats will eventually prove immunogenic in young infants, prevention in this age group will be a challenge, given the already complex early-infant immunization schedules and the need to com-

See related editorial on page 206.

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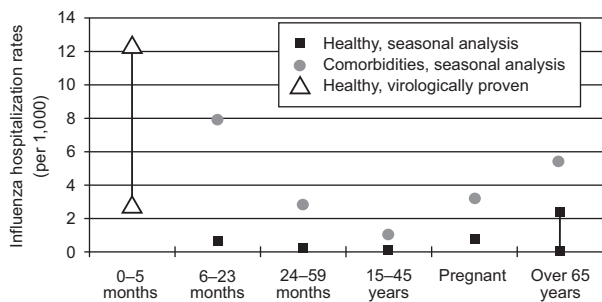
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**Fig. 1.** Seasonal analysis of flu-related hospitalization rates in North America (per 1,000) by age group, estimated by comparing respiratory admissions during flu season to summer. “Healthy, virologically proven” shows data from a separate population-based surveillance. The vertical line connecting points shows the range of data.

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plete two-dose influenza immunization in the limited time window before the influenza season begins.

A cost-effectiveness analysis of influenza immunization in U.S. pregnant women suggests that, compared with supportive treatment of influenza illnesses in pregnancy, the use of influenza vaccine reduces costs overall, resulting in an estimated savings of approximately \$50 per immunized woman.<sup>10</sup> The cost savings from prevention of infant influenza hospitalization are likely to be many-fold greater.

A report of data from the U.S. Vaccine Adverse Event Reporting System has shown that in recent years there have been eight to nine reports per year of adverse events associated with influenza vaccine administered in pregnancy. Of 26 reports from 2000 to 2003, most were of vaccine administered inadvertently without adverse events, of self-limiting local or systemic events, and three miscarriages. Since an estimated 2 million pregnant women received influenza vaccine during the years reported, these voluntary reports suggest a very low rate of severe events in the U.S. Vaccine Adverse Event Reporting System data base.<sup>10</sup>

### NEW DATA ABOUT MATERNAL IMMUNIZATION: BENEFIT FOR BOTH THE PREGNANT WOMAN AND HER BABY

Until recently, there had been no prospective randomized controlled trials to assess the effectiveness of influenza vaccine in pregnant women or their infants. Zaman and colleagues<sup>11</sup> (including one of the present authors) have recently reported a randomized, controlled prospective study in Bangladesh that showed that immunizing pregnant women not only benefits the women but also to their young

infants aged less than 6 months.<sup>11</sup> Influenza immunization of pregnant women reduced febrile influenza-like illness by more than 30% in both the mothers and their young infants and reduced laboratory-proven influenza infections in the 0- to 6-month-old infants by 63%.<sup>11</sup> This study substantively expands the concept raised two decades ago that natural maternal influenza antibodies passed to the infant before birth or via breast milk could offer young infants protection against serious illness from influenza.

The randomized, controlled trial by Zaman et al<sup>11</sup> thus highlights the importance of ensuring that pregnant women receive influenza vaccination as recommended, especially those who will be in their third trimester during influenza season, and for mothers whose infants will be under the age of 6 months during the influenza season.

Both seasonal influenza epidemics and previous pandemics cause increased morbidity and mortality in pregnant women compared with women who are not pregnant.<sup>12</sup> A novel influenza A (H1N1) virus has been reported to cause illness in three pregnant women in the United States, one of whom did not survive.<sup>13</sup> See the accompanying commentary<sup>14</sup> for further information regarding these novel viruses in 2009.

### INCREASING INFLUENZA IMMUNIZATION UPTAKE BY PREGNANT WOMEN

Surveys suggest that few pregnant women, even those with comorbidities, receive influenza vaccine.<sup>15</sup> Several reasons have been put forward, including the lack of availability of influenza vaccine in obstetric practices, unawareness that healthy pregnant women are at increased risk of hospitalization in influenza season, and ongoing concerns about vaccine safety for the mother and her fetus (Halperin BA, MacKinnon-Cameron D, McNeil S. Survey of knowledge, attitudes, and behaviour regarding influenza vaccination in pregnancy and childhood [abstract]. Presented at the International Conference on Women and Infectious Diseases. Atlanta, GA, March 17–19, 2006).<sup>15,16</sup> The substantial protection shown in the study by Zaman et al<sup>11</sup> may well increase the interest of pregnant women in receiving influenza immunization. Public “Baby on Board” messages directed to pregnant women noting the benefit for the baby as well as for themselves should be developed. To provide the same protections to infants as to the mothers and other immunized groups, consideration should be given in the United States to adding infant outcomes after maternal influenza immunization to the National Vaccine Compensation Program.



## FUTURE RESEARCH DIRECTIONS

More data collected and reported in a systematic way regarding the safety of contemporary influenza vaccine products is needed and could be captured from well-designed, prospective case-control studies. These studies could also add information on the effectiveness of influenza immunization in both the mothers and the infants. Prospective studies to assess the effectiveness of postpartum immunization of mothers and the role of breastfeeding to reduce illness in their neonates are also critical. Although postpartum influenza vaccine is recommended for mothers, studies are needed to assess the degree of protection of infants either through reduction of viral transmission from the mothers or through passive protection through breast milk antibody.

We also need studies to assess the best approaches to increase immunization coverage of pregnant women, to determine the ideal venues for immunization of this high-risk group, and to test strategies that promote postpartum immunization of mothers and families of neonates.

In summary, influenza vaccination is low-cost intervention with the potential for substantial benefit for mother and baby. As we plan for each year's influenza season, we must make every effort to increase influenza immunization among pregnant women. This includes more work to expand the vaccine strategies, as well as their reach, and the vaccine uptake. Pregnant women and their young infants are at risk, and we have a vaccine and the robust evidence that it works to protect both of these high-risk groups.

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## Appendix 1. Summary of Data on Adverse Events Reported in Studies of Influenza Vaccine Given to Pregnant Women

| First Author          | Year | Influenza Immunized | Controls               | Design                       | Results   |
|-----------------------|------|---------------------|------------------------|------------------------------|---|
| Heinonen <sup>1</sup> | 1973 | 2,291               |                        | Cohort                       | No differences in malformations   |
| Sumaya <sup>2*</sup>  | 1979 | 56                  | 0                      | Cohort                       | No differences in AEs   |
| Murray <sup>3*</sup>  | 1979 | 59                  | 27 (NP)                | Cohort                       | No differences in AEs   |
| Deinard <sup>4*</sup> | 1981 | 176                 | 517                    | Cohort                       | No differences in AEs   |
| Englund <sup>5</sup>  | 1993 | 13                  | 13                     | Cohort                       | No differences in AEs   |
| Black <sup>6</sup>    | 2004 | 3,707               | 49,585 (W), 48,639 (I) | Case-control                 | No differences in cesarean delivery, premature delivery, or infant outcomes |
| Munoz <sup>7</sup>    | 2005 | 252                 | 826                    | Retrospective                | No differences in AEs   |
| France <sup>8</sup>   | 2006 | 3,160               | 37,969 (I)             | Case-control                 | No differences in infant outcomes   |
| Munoz <sup>9</sup>    | 2007 | 1,006               | 1,495                  | Cohort                       | No differences in AEs   |
| Zaman <sup>10</sup>   | 2008 | 170                 | 170                    | Randomized, controlled trial | No significant differences in mothers or infants                            |
| Totals                |      | 10,885              | 52,628 (W)             |                              |   |

AE, adverse event; NP, nonpregnant; W, women; I, infants.

\* "Swine flu," 1976.

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