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Letters to the Editor

RE: "DELIVERING INFLUENZA VACCINE TO PREGNANT WOMEN"

In the last issue of *Epidemiologic Reviews*, Naleway et al. (1) failed to cite relevant studies that justify influenza vaccination during pregnancy and, more importantly, ignored potential, serious risks.

Neuzil et al.'s study (2) was limited to a Medicaid population and was based on only hospital admission rates, not clinical outcomes. Among low-risk women, hospitalizations attributed to influenza were only 3–10 per 10,000 women-months. More importantly, the study failed to uncover any significant mortalities or morbidities associated with influenza other than the event of a hospital admission. A study by Black et al. (3) describing an influenza-related hospitalization rate of only 1.8 per 10,000 in a large, non-Medicaid population was never cited.

Cited studies from the 1918 and 1957 epidemics are irrelevant now that pneumonia can be easily diagnosed and treated with modern technology. The study by Harris (4) did not actually conclude that pregnancy is a high-risk condition, even in 1918. Greenberg et al. (5) reported during the 1957 epidemic that about one third of the fatal outcomes during pregnancy occurred in women who also had rheumatic heart disease. Freeman and Barno (6) described 11 deaths among pregnant women throughout Minnesota, but all were due to pneumonia and pulmonary edema.

Mullooly et al. (7) found no maternal mortality and a hospitalization rate of only 2 per 1,000 during the 1975–1979 flu seasons. In a Hungarian population of more than 38,000 pregnancies from 1980 to 1996, *influenza-like illnesses* occurred in only 4.6 percent of women and without any difference in maternal, neonatal, or pregnancy outcomes (8).

Naleway et al. state that "vaccination seems to be the best way to decrease a woman's risk of influenza and complications during pregnancy" (1, p. 48), but these citations do not support this conclusion. Two studies actually reported a greater risk of influenza-like illness among vaccinated women (2, 9).

Benefit to the newborn via passive immunization also appears unproven, as reported by Sumaya and Gibbs (10). The only study that evaluated neonatal outcomes failed to detect clinical benefit following maternal immunization (3), yet Naleway et al. (1) once again seem to be comfortable overstating this benefit of immunizing the mother.

Finally, all seven references cited in support of vaccination safety have significant limitations. Englund et al. (11) and Yeager et al. (12) reported only immediate maternal vaccine reactions. Black et al. (3) examined rates of cesarean section and preterm delivery only. None examined fetal development or viability. Munoz et al. (9) could not have reported fetal deaths because they included only those cases that resulted in infants seen at a well-baby clinic. Heinonen et al. (13, 14) recorded birth defects, but not fetal viability, and actually reported an *increased* risk of several specific birth defects (cleft palate, microcephaly, pyloric stenosis) associated with prenatal influenza vaccine exposure as well as increases in malformations following exposures to the vaccine preservative thimerosal. Because of small size, the study by Deinard and Ogburn (15) was limited in detecting less frequent, adverse outcomes.

Because of the recent expanded recommendations, it is imperative that safety studies are adequately designed. To date, no such study is known to exist. This is critical; the majority of injectable flu vaccines contain thimerosal, and several studies have reported dose-dependent fetal deaths in various animal models exposed to thimerosal or its by-product, ethyl mercury (16). Even thimerosal's Manufacturing Safety Data Sheet discloses teratogenic and reproductive toxicity. A recent review of the Vaccine Adverse Event Reporting System showed a temporal-geographic cluster of late-trimester fetal deaths following flu vaccination, some with shared vaccine lots (17).

In light of all these shortcomings, Naleway et al.'s (1) eagerness to promote an untimely vaccination without adequate safety testing and of unproven effectiveness to prevent a disease rarely significant to the uncomplicated pregnancy is perplexing.

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References

1. Naleway AL, Smith WJ, Mullooly JP. Delivering influenza vaccine to pregnant women. Epidemiol Rev 2006;28:47–53. (DOI: 10.1093/epirev/mxj002).
2. Neuzil KM, Reed GW, Mitchel EF, et al. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148:1094–102.
3. 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;21:333–9.
4. Harris JW. Influenza occurring in pregnant women: a statistical study of thirteen hundred and fifty cases. JAMA 1919;72:978–80.
5. Greenberg M, Jacobziner H, Pakter J, et al. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. Am J Obstet Gynecol 1958;76:897–902.
6. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. Am J Obstet Gynecol 1959;78:1172–5.
7. Mullooly JP, Barker WH, Nolan TF. Risk of acute respiratory disease among pregnant women during influenza A epidemics. Public Health Rep 1986;101:205–11.

8. Acs N, Banhidy F, Puho E, et al. Pregnancy complications and delivery outcomes of pregnant women with influenza. J Matern Fetal Neonatal Med 2006;19:135–40.
9. Munoz FM, Greisinger AJ, Wehmanen OA, et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2005;192:1098–106.
10. 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.
11. Englund JA, Mbawuike IN, Hammill H, et al. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. J Infect Dis 1993;168:647–56.
12. Yeager DP, Toy EC, Baker B. Influenza vaccination in pregnancy. Am J Perinatol 1999;16:283–6.
13. Heinonen OP, Shapiro S, Monson RR, et al. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. Int J Epidemiol 1973;2: 229–35.
14. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Boston, MA: Publishing Sciences Group, 1976.
15. Deinard AS, Ogburn P. A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. Am J Obstet Gynecol 1981;140:240–5.
16. Ayoub DM, Yazbak FE. Influenza vaccination during pregnancy: a critical assessment of the recommendations of the advisory committee on immunization practice (ACIP). J Am Physicians Surg 2006;11:41–7.
17. Yazbak FE. Influenza vaccine during pregnancy: a very bad idea. Red Flags online health journal. June 2, 2006. (http://www.redflagsdaily.com/yazbak/2006_jun02).

David M. Ayoub[1] and F. Edward Yazbak[2] (e-mail: raypoke@mac.com)
[1] *Prairie Collaborative, Springfield, IL 62704*
[2] *TL Autism Research, Falmouth, MA 02540*

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