

Table 1a: Pregnant women, maternal outcomes

Is inactivated influenza vaccine versus no intervention or non-influenza vaccine in pregnant women effective to prevent influenza infection and severe outcomes of infection in pregnant women?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1 RCT and post-hoc analysis ^{1, 2, 3}	4
	Factors decreasing confidence	Limitation in study design	None serious ⁴	0
		Inconsistency	None serious	0
		Indirectness	Serious ⁵	-1
		Imprecision	Serious ⁶	-1
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			2
Summary of Findings	Statement on quality of evidence		Our confidence in the estimate of effect of maternal influenza vaccine in pregnant women is limited.	
	Conclusion		Effectiveness against respiratory illness with fever was 35.8% (95% CI: 3.7 to 57.2) implying a significant reduction achieved by influenza vaccination of pregnant women . No information on vaccine efficacy in pregnant women and the impact on laboratory- confirmed influenza were available. No significant difference in effectiveness of influenza vaccine versus other vaccine against clinical visits for respiratory illness with fever was observed.	

NOTES

¹ Zaman et al. 2008, RCT conducted in Bangladesh in 2004-05, included 340 pregnant women in the 3rd trimester that were follow-up until 6 months after delivery. The intervention group consisted of 172 pregnant women that received TIV and the control arm consisted of 168 pregnant women that received pneumococcal polysaccharide vaccine.

² In addition to immunogenicity data provided by Zaman et al. (2008), there was another RCT assessing immunogenicity and safety of TIV in pregnant women (Englund et al. 1993). Significantly higher GMT of antibodies against influenza vaccine strains were demonstrated among TIV vaccinated pregnant women compared to controls (tetanus toxoid vaccine recipients) as well as among infants of TIV vaccine recipients versus control group infants, which suggests an active transport of influenza-specific maternal IgG across the placenta during pregnancy. Safety assessment by Englund et al. (1993) revealed no observed significant adverse reactions in the vaccine versus control group. No fetal, perinatal or infant complications among the offspring of vaccinated women were observed.

³ There was one relevant observational study identified that assessed vaccine effectiveness against the number of episodes of febrile upper respiratory tract infections (Hulka et al. 1964) in pregnant women which showed lower illness rates among pregnant women vaccinated against influenza versus those vaccinated with placebo. Other observational studies, some with serious methodological limitations, reported on safety of TIV in pregnant women (Black et al. 2004, Deinard et al. 1981, Hulka et al. 1964, Munoz et al. 2005, Tavares et al. 2011) and found no major differences between vaccinated and unvaccinated/placebo vaccinated pregnant women (or compared to rates in the general population) for several outcomes including serious adverse events, cesarean section/delivery, preterm delivery maternal, fetal, perinatal or infant complications, congenital abnormality, and miscarriage.

Murray et al. (1979) compared vaccinated pregnant women to vaccinated non-pregnant women and did not find any significant adverse reaction or complications among pregnant women. Sumaya et al. (1979) assessed the safety of inactivated influenza vaccine in 56 women and did not find significant adverse events associated with the vaccination. However, no comparison group was used in this study. Another observational study compared adverse reactions among pregnant women receiving either a single or two doses of pandemic H1N1 vaccine and found no difference between the two groups (Horiya et al. 2011). Further post-marketing surveillance reports published as peer-reviewed manuscripts and subject to bias are available suggesting positive benefit-risk balances for pregnant women (e.g. Tsai et al. 2010).

⁴ Adequate blinding, masking, and allocation sequence concealment. Small loss to follow-up (93% followed up until week 24).

⁵ Maternal outcome reported was respiratory illness and no information on vaccine efficacy in pregnant women is available. Regarding the immunogenicity data, which were not graded here, there were no virological data but an accepted surrogate measure was used.

⁶ Shortage and insufficient sensitivity of rapid tests for detection of episodes of respiratory illness with fever may have affected the vaccine effectiveness outcome considered for pregnant women. It is not clear why laboratory-confirmed influenza was only reported for the infants.

No downgrading for the fact that control group is not placebo but another active non-influenza vaccine since this may lead to potential underestimation of the true effect of maternal influenza vaccination (see table 1b for infant outcome).

References

Black, S.B., et al., *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, 2004. **21**:333-9.

Deinard, A.S. and P. Ogburn, Jr., *A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome*. American Journal of Obstetrics and Gynecology, 1981. **140**:240-5.

Englund, J.A., et al., *Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants*. The Journal of Infectious Diseases, 1993. **168**:647-56.

Horiya M, Hisano M, Iwasaki Y, Hanaoka M, Watanabe N, Ito Y, Kojima J, Sago H, Murashima A, Kato T, Yamaguchi K. Efficacy of double vaccination with the 2009 pandemic influenza A (H1N1) vaccine during pregnancy. Obstetrics and Gynecology, 2011. **118**:887-94.

Hulka, J.F., *Effectiveness of Polyvalent Influenza Vaccine in Pregnancy. Report of a Controlled Study during an Outbreak of Asian Influenza*. Obstetrics and Gynecology, 1964. **23**:830-7.

Munoz, F.M., et al., *Safety of influenza vaccination during pregnancy*. American Journal of Obstetrics and Gynecology, 2005. **192**:1098-106.

Murray, D.L., et al., *Antibody response to monovalent A/New Jersey/8/76 influenza vaccine in pregnant women*. Journal of Clinical Microbiology, 1979. **10**:184-7

Sumaya, C.V. and R.S. Gibbs, *Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant*. The Journal of Infectious Diseases, 1979. **140**:141-6.

Tavares, F., et al., *Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: a prospective cohort study*. Vaccine, 2011. **29**:6358-65

Tsai, T., et al., *Exposure to MF59-adjuvanted influenza vaccines during pregnancy--a retrospective analysis*. Vaccine, 2010. **28**:1877-80.

Zaman, K., et al., *Effectiveness of maternal influenza immunization in mothers and infants*. The New England Journal of Medicine, 2008. **359**:1555-64.