Table 6. Safety of inactivated influenza vaccine in pregnant women

Is seasonal inactivated influenza vaccine versus non-influenza vaccine in pregnant women safe in regard to health outcomes for the mother and the neonate?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCTs and post-hoc analysis[1, 2, 3, 4, 5]	4
	Factors decreasing confidence	Limitation in study design	Serious[6]	-1
		Inconsistency	None serious	0
		Indirectness	None serious[7]	0
		Imprecision	Serious[8]	-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 safety of influenza vaccination in pregnant women is limited.
	Conclusion			No fetal, perinatal or maternal serious adverse reactions were reported to be related to influenza vaccine given to pregnant women in their third trimester. There was no statistically significant difference between influenza and control vaccine recipients regarding minor local systemic side effects, local pain and fewer as well as regarding the numbers of death or hospitalization.

NOTES

[1] *RCTs:*

RCTs used for grading of safety issues assessed safety of inactivated influenza vaccine in pregnant women since these vaccines are the only influenza vaccines licensed for vaccination of pregnant women whereas live attenuated influenza vaccines are either contraindicated or require a careful assessment of the benefit-risk balance for pregnant women.

Zaman et al. 2008 conducted an RCT in Bangladesh in 2004 to 2005 which included 340 pregnant women in the third trimester that were follow-up until 6 months after delivery together with their newborns. 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. 159 infants that received TIV and 157 infants received pneumococcal polysaccharide vaccine were followed-up.

The initial study purpose was to assess safety and immunogenicity of pneumococcal vaccination as well as effectiveness of influenza vaccine. Safety assessment data are available from the supplementary annex of the study and from the post-hoc analysis (Steinhoff et al. 2012). During the first 7 days after immunization, minor local and systemic reactions and local pain were proportionally less common among women who received influenza vaccine compared to pneumococcal vaccine. However, there was no statistically significant difference between the two groups regarding minor local systemic side effects, local pain and

fewer within 72 hours. Among serious adverse events assessed, three stillbirths occurred during the study period among influenza vaccinated mothers. However, no fetal, perinatal or maternal serious adverse event was reported to be related to vaccine or participation in the study and there were no statistical differences in the numbers of death or hospitalization between the influenza and control vaccine groups.
Additional neonatal outcomes were described in the post-hoc analysis by Steinhoff et al. 2012. The authors stated that no significant differences between influenza and control vaccine recipients were identified for outcomes such as distribution of infant gestational age at birth, APGAR score, parity, height and postpartum weight. Further evaluation of neonatal outcomes stratified by period of influenza virus circulating or non-circulating revealed no significant differences between the periods. Nevertheless, maternal vaccination during virus circulating periods led to a lower proportion of infants being small for gestational age and to an increase in mean birth weight compared to the control group.

From 1991 to 1992 Englund et al. (1993) conducted an RCT in the US enrolling 30 healthy pregnant women in the last trimester of pregnancy that were randomized to receive TIV or tetanus toxoid vaccine. The two groups were similar in terms of mean maternal age at delivery, estimated gestational age at the time of immunization, and regarding the median interval between vaccination and delivery. At time of birth, all babies born (29 and one set of twins) were healthy without any fetal perinatal or infant complication. Of 26 women who had blood specimens drawn at or within 5 days of delivery, 13 were vaccinated with TIV and 13 with tetanus toxoid vaccine and were followed-up between 1 and 3 months after delivery. All infants born to the 26 women were healthy at time of examination during the 1 to 3 months. Safety assessment related to maternal outcomes shows no significant adverse reactions including fever, moderate or severe pain, or need to visit a physician in any recipient following either TIV or tetanus toxoid vaccine.

[2] *Observational data (prospective and retrospective cohort studies):*
Heionen et al. (1973) published one of the first studies on maternal influenza vaccination and assessed malignancies arising after exposure to polio and influenza vaccines in utero. Among approximately 2,300 women vaccinated during pregnancy, there was only one malignancy identified, which was not different from expected background rates. Two further observational studies in women immunized against influenza during or just before pregnancy were conducted during the 1976 swine flu vaccination campaign: Sumaya and Gibbs (1979) found no difference in congenital defects between influenza vaccinated and unvaccinated women and no increased fetal complications associated with the influenza vaccine. Similarly, Deinard and Ogburn (1981) did not detect an association between immunization and maternal complications, pregnancy outcome or postpartum course. There was also no difference between infants born to vaccinated and unvaccinated mothers with regard to teratogenicity, infant birth outcome, or physical or neurological assessment at 8 weeks of life.
In a more recently published analysis Black et al. (2004) reviewed medical claim records over five influenza seasons of 3,719 women vaccinated during pregnancy and of 45,866 pregnant women not vaccinated against influenza. After adjustment for age, there was no significant difference in risk of cesarean section and preterm delivery between vaccinated and unvaccinated pregnant women. Using a similar approach of reviewing medical records, Munoz et al. (2005) found no significant difference in infant pregnancy outcomes such as complicated or cesarean delivery and infant medical complications from births to 6 months of age. In contrary, congenital anomalies were at elevated level among infants born to unvaccinated mothers. There was no difference in serious adverse events including deaths and hospitalization in mothers within 42 days of vaccination.

All observational studies (and database reports, see note 3) are particularly prone to bias arising from lack of causality assessment between intervention and potential safety outcome. Pregnancy outcomes are influenced by multiple factors and even if confounding by, e.g. co-morbidities was adjusted for, other issues such as obstetric complications may have impacted on outcomes, and increase the possibility for residual confounding. In addition, baseline differences between vaccinated and unvaccinated pregnant women may exist and few observational studies account for them.

[3] *Postmarketing surveillance and reporting system data:*
In addition to observational studies, post-marketing surveillance and influenza vaccine pregnancy registries as part of pharmacovigilance programs are available data sources. Since they are based on passive surveillance, they are prone to bias such as underestimation, lack of confirmed or definitive diagnosis of reported events, missing denominator definitions of administered doses and lack of established causality. As observational data, they are not used for grading of evidence but main findings are highlighted in the following.
A database of reports of influenza vaccination during pregnancy is part of the Vaccine Adverse Event Reporting System (VAERS) and data from 2000 to 2003 suggest a low rate of adverse events associated with administration of inactivated influenza vaccine during pregnancy and showed no unexpected vaccine adverse event detected (Pool, Iskander 2006). Similarly, between 1990 and 2009 (11.8 million pregnant women vaccinated with influenza vaccine, 148 reports after inactivated vaccine received), VAERS reports found no specific adverse event associated to inactivated vaccine and no maternal deaths. The conclusion drawn was that reported influenza vaccine associated health complications among pregnant women are exceedingly rare and vaccination did not result in an increased risk of adverse pregnancy outcomes compared to background rates and there was no evidence of increased or unexpected patterns of adverse neonatal outcomes (Moro et al. 2011a).

[4] *Studies on 2009 H1N1 influenza pandemic vaccine:*
Available studies on influenza pandemic vaccine in pregnant women found a mild and self-limiting reactogenicity and no evidence of teratogenicity or adverse impact on pregnancy outcomes including stillbirth, congenital anomaly, and preterm delivery (e.g. Folkenberg et al. 2011, Lim et al. 2010, Tsai et al. 2010, Tavares et al. 2011). The post-authorization safety study of adjuvanted monovalent H1N1 influenza vaccine by Tavares et al. (2011) did not observe higher prevalence of spontaneous abortions and stillbirths compared to those in the general pregnant population. There was no increased risk among those vaccinated and no neonatal adverse outcomes were recorded or monitored after delivery (Tavares et al. 2011). However, as true for some other observational studies, there was possibly insufficient power to detect adverse outcomes related to exposure, particularly in the first trimester. In Murray et al. (1979) the intervention group of 59 influenza vaccinated pregnant women was compared to non-pregnant influenza vaccinated women and no significant adverse reaction, fetal, perinatal or infant complications was detected among offspring of vaccinated women.
An evaluation through a database for adverse events in pregnant women that received MF59-adjuvanted or unadjuvanted vaccine at any time in pregnancy did not show a difference in distribution of pregnancy outcomes (normal, abnormal and terminated in abortion) between the two interventions (Tsai et al. 2010). However, only a relatively small number of pregnant women were included which does not allow drawing a definitive conclusion, particularly on the risk associated with exposure to adjuvanted TIV.
In another study without control group, Zuccotti et al. (2010) assessed infant outcomes of pandemic influenza A H1N1 vaccine up to 5 months after delivery and detected no serious adverse event in mothers and infants. Horiya et al. 2011 studied safety issues among pregnant women who received one dose compared to those receiving two doses of 2009 H1N1 influenza vaccine and reported five infants born with congenital anomalies in the two dose group. However, none of these infants were born to mothers who had been vaccinated in the first trimester, which makes it less likely that the outcome is related to the vaccine. Overall, no significant difference in adverse reactions was reported between single and two dose vaccination group.
A report based on review of the VAERS database for 2009 H1N1 influenza pandemic vaccines similarly concluded that from October 2009 through February 2010 (2.4 million pregnant women received the vaccine, 294 reports were submitted), no concerning patterns of abnormal maternal or fetal outcomes were observed (Moro et al. 2011b) and outcomes were not higher than in the general population. In a recently published Danish cohort study among over 7,000 women vaccinated against influenza A/H1N1 2009 (adjuvanted) during pregnancy, there was no association between vaccination and increased risk of fetal death, or its components stillbirth and spontaneous abortion (Pasternak et al. 2012).

[5] In addition to the references listed above, reviews covering studies on safety outcomes of influenza vaccination during pregnancy have been published (Bednarczyk et al. 2012, Ortiz et al. 2011, Tamma et al. 2009). They conclude that influenza vaccination in pregnancy has a good safety record and that there are no harmful effects of influenza vaccine to pregnant recipients. Overall, the reviews provide supportive statements for inactivated influenza vaccination of pregnant women and suggest, based on available data, a positive benefit-risk balance for pregnant women.

[6] Adequate blinding, masking, and allocation sequence concealment, small loss to follow-up (93% followed up until week 24) in Zaman et al. 2008, few details on study design issues available from Englund et al. 1993 since the main objective was the evaluation of transfer of vaccine-specific antibodies. Given the main study focuses of the trials, there was no power analysis performed or statistical power to detect rare but severe adverse events or to estimate minimal detectable risks and ratios between influenza vaccinated women and controls.

[7] The primary study purpose of the RCTs was not (only) the assessment of safety but rather immunogenicity and transfer of vaccine-specific antibodies. Therefore, no clear safety outcome definitions and definitions for relatedness and severity of adverse events were provided by the trials. No downgrading was applied since safety was not stated to be the primary objectives of the studies.

[8] In both trials, the control group is not placebo but another non-influenza vaccine. Of higher importance is the fact that in both trials the vaccines were given in the third and last trimester, after a period when most malformations and other adverse fetal outcomes would be most likely to occur. Given the high vulnerability for the developing fetus during the first trimester of pregnancy, it is particularly crucial to have safety data on maternal influenza immunization in early pregnancy. Based on that and provided a low number of study participants, stratification of outcomes by trimester of influenza vaccination was not possible in the studies evaluated.

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