

Influenza vaccination in pregnancy: current evidence and selected national policies

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In several countries, pregnant women are recommended seasonal influenza vaccination and identified as a priority group for vaccination in the event of a pandemic. We review the evidence for the risks of influenza and the risks and benefits of seasonal influenza vaccination in pregnancy. Data on influenza vaccine safety in pregnancy are inadequate, but the few published studies report no serious side-effects in women or their infants, including no indication of harm from vaccination in the first trimester. National policies differ widely, mainly because of the limited data available, particularly on vaccination in the first trimester. The evidence of excess morbidity during seasonal influenza supports vaccinating healthy pregnant women in the second or third trimester and those with comorbidities in any trimester. The evidence of excess mortality in two previous influenza pandemics supports vaccinating in any trimester during a pandemic.

Introduction

Certain population groups are known to be at higher risk of morbidity and mortality from influenza infection. Pregnancy is considered to be one of the conditions conferring increased risk; however, several countries, including the UK and Germany, do not routinely vaccinate in pregnancy,^{1,2} whereas others, such as the USA and Canada, recommend vaccinating healthy pregnant women regardless of trimester.^{3,4} In Australia, the vaccine is offered to healthy pregnant women in any trimester who will be in the second or third trimester during the influenza season.⁵ WHO's current position paper recommends that all pregnant women should be immunised during the influenza season.⁶ There has been no indication that inactivated vaccines given during pregnancy harm the fetus; however, safety data are limited.

Information on the burden of disease from seasonal influenza in healthy pregnant women is also limited. This is by contrast with the possible burden that may occur in

an influenza pandemic, which is of international concern.⁷ The 2005 UK Health Departments' Influenza Pandemic Contingency Plan⁸ identified pregnant women in the third trimester as a provisional priority group for immunisation, recognising that morbidity and mortality patterns from a new pandemic strain cannot be predicted.

We examine the risks from both seasonal and pandemic influenza infection together with the benefits and risks of inactivated vaccine to the mother and fetus. The UK Yellow Card data (the UK's passive reporting system on adverse events associated with medicines), current WHO recommendations, and the policies of selected countries are also reviewed. All references to influenza vaccines in this Review refer to inactivated vaccines only. "Comorbidity" is used to describe medical conditions that are associated with increased risk of influenza-related complications.

The risks of influenza viral infection in pregnancy

Risk of seasonal influenza in pregnant women

Women are commonly exposed to influenza (figure) during pregnancy. 11% of 1659 women in the 1993–94 influenza season in the UK had a four-fold rise in antibody titres indicative of new influenza infections.⁹ Following the 1989–90 severe influenza season in the UK, a one in 15 random sample of records of all fatal cases was compared with a "regular" season in 1985–86.¹⁰ Using these methods, eight deaths in pregnant women were counted in the severe season and two in the regular season, suggesting a four times higher risk of death during a severe influenza season. These figures were extrapolated to an excess of 90 deaths in pregnant women out of the 25 185 total excess deaths estimated in the 1989–90 influenza season.¹¹

Although several observational studies using routine hospital admission data have noted a higher risk of hospital admission in pregnancy with influenza-like illness, the precise level of risk and the extent that risk varies by trimester are unclear because of varying outcome definitions and difficulty in controlling for unknown underlying morbidity. In one of the first observational studies, directly standardised rates of acute cardiorespiratory illness in hospitalised pregnant women with no known

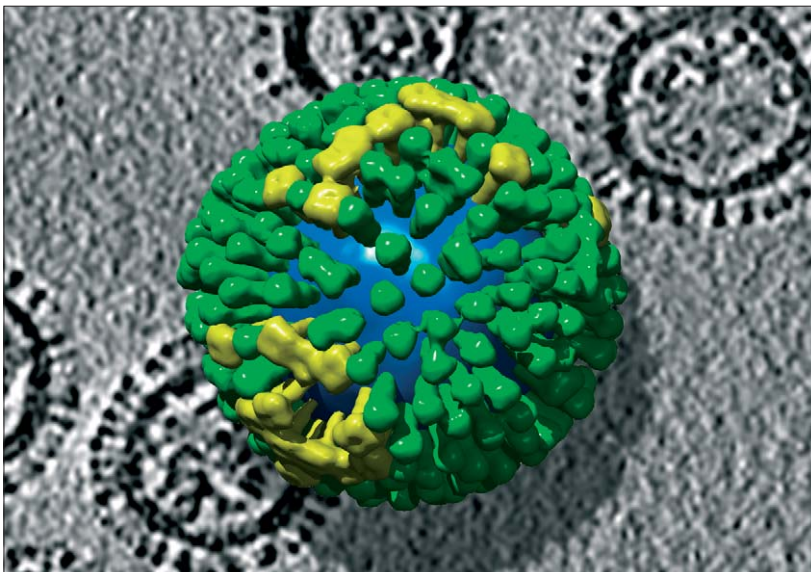


Figure: 3D electron tomography of the influenza virus (120 nm). Haemagglutinin spikes are in green; neuraminidase spikes are in yellow. Reproduced with permission from Alasdair Steven.

comorbidities were compared with those in hospitalised postpartum women in the winter when influenza was not circulating, using Tennessee Medicaid data from 1974–93.¹² Peri-influenza season rates were subtracted from those in the influenza period to obtain excess hospital admission rates attributable to influenza. Women in the second and third trimesters had excess hospital admission rates of 6.32 (95% CI 2.90–9.74) and 10.48 (6.70–14.26) per 10000 woman-months, respectively. Women in the first trimester and women in the postpartum period had excess hospital admission rates of only 3.06 (0.44–5.68) and 1.16 (–0.09 to 2.42) per 10000 woman-months, respectively, similar to the rate in non-pregnant women of 1.91 (1.51–2.31) per 10000 woman-months. The excess hospital admission rate attributable to influenza in healthy women in the last trimester was equivalent to that seen in non-pregnant women with chronic medical conditions.¹³ Medicaid provides health care for those without personal insurance and poorer sociodemographic groups are therefore over-represented in this population. Residual confounding—eg, by tobacco—is likely to bias upwards any effect observed.

Excess hospital admission rates attributable to influenza were calculated by similar methods in a 1990–2002 population-based record linkage study of 134188 pregnant women from Nova Scotia.¹⁴ Rates of hospital admission and medical visits during defined influenza, peri-influenza, and non-influenza seasons were compared per trimester. The influenza-attributable excess rates of hospital admissions because of respiratory illness were 1.1 (–0.1 to 2.3), 0.4 (–1.1 to 1.9), and 2.0 (–0.3 to 4.3) per 10000 healthy woman-months in the first, second, and third trimesters, respectively, after subtracting the background peri-influenza season rates. The results from this study were lower than those from the Tennessee study, which could partly be explained by the conservative definition of hospitalisation (admissions that included delivery were omitted, as were admissions for asthma exacerbation without influenza-related diagnostic codes); adjustments for confounders such as smoking and socioeconomic status made no difference to the risk of hospital admission.

Two other studies examined outpatient medical visits reported in US health maintenance organisation (HMO) databases as opposed to hospital admissions.^{15,16} The first, on a small study population from a Washington HMO, examined rate differences in influenza-like illness diagnosed in an inpatient or outpatient visit, compared with influenza-unexposed weeks in healthy pregnant women during defined weeks when influenza circulated from 1991–97. Excess rates attributable to influenza were 5.8, 9.8, 14.1, and 11.0 per 10000 woman-weeks in the first, second, and third trimesters, and postpartum period, respectively, but with only 5.4% of episodes considered severe—eg, pneumonia or requiring an emergency visit.¹⁵ Low admission rates for influenza and pneumonia in pregnancy were also noted in another HMO dataset.¹⁷

In the second study, Oregon HMO data were used to compare outpatient medical visits for acute respiratory disease in pregnant women with non-pregnant women. Four severe influenza seasons (1975, 1976, 1978, 1979) and one regular season (1977) were included.¹⁶ During the 1978 season, influenza A H1N1 reappeared, a subtype that had not circulated for 20 years. Pregnant women had a significant excess rate of medical visits of 48.1 per 1000 visits categorised as influenza, pneumonia, upper respiratory illness, and respiratory symptoms. By contrast, pregnant women did not have an excess acute respiratory disease rate in the 1975, 1976, and 1979 seasons when predominant circulating strains were all H3N2 variants. This finding suggests that different strains or previous exposure to subtypes could selectively affect the impact of an influenza season. Nearly all acute respiratory disease medical encounters were supernumerary visits and therefore not attributable to increased opportunity to report a respiratory illness during the regular prenatal encounters.

Secondary effects of influenza-like illness or pneumonia in pregnancy on the fetus were examined in 6277508 hospital admissions for pregnant women, representing a 20% sample of US public hospitals from 1998–2002.¹⁸ 2.3% of hospital admissions during influenza seasons included pneumonia or influenza compared with 1.2% during the rest of the year, excluding hospital stays in which a delivery occurred. Hospitalised pregnant women with respiratory illness had higher odds of preterm delivery, fetal distress, and caesarean section (adjusted odds ratios (OR) 4.08 [95% CI 3.57–4.67], 2.48 [1.84–3.35], and 3.91 [3.48–4.39], respectively) compared with hospitalised pregnant women without respiratory illness.

Risk to pregnant women with comorbidities

In the US public hospitals study of admissions for pregnancy and respiratory illness, pregnant women with a comorbid condition were three times more likely to have a respiratory illness compared with healthy pregnant women (OR 3.2 [3.0–3.5]) during defined influenza months (1998–2002).¹⁸ In a separate cohort analysis of 297 pregnant women with respiratory hospitalisation in the Tennessee Medicaid database (1985–93), pregnant women with a history of asthma had the highest rate of respiratory hospital admission at 597 per 10000 (OR 10.63 [8.18–13.83]) compared with pregnant women without comorbidities during defined influenza seasons.¹⁹ Most recently, nearly 13500 pregnant women with one or more comorbidities were reviewed in the Nova Scotia study (1990–2002).¹⁴ Their influenza-attributable rate of hospital admission was 3.9 (–6.4 to 14.2), 6.7 (–4.1 to 17.5), and 35.6 (21.1 to 50.1) per 10000 woman-months for the first, second, and third trimesters, respectively, when comparing influenza and peri-influenza seasons. Based on an average season of 3.4 influenza-exposed months during the study, excess hospital admissions during the

third trimester would occur in 121 per 10 000 pregnant women with comorbidities and in 6·8 per 10 000 healthy pregnant women.

Risk to pregnant women in pandemics

During the influenza pandemic of 1918–19, more than 20 million people died, with pregnant women among those at high risk for complications or death. For example, 1350 pregnant women diagnosed with influenza were ascertained from a mail survey of members of the American obstetrical societies and all physicians in Maryland.²⁰ Overall, the case fatality rate was 27%, but all deaths occurred within the 678 cases complicated by pneumonia. The case fatality rate within the pneumonia subgroup was 54%. A similarly high rate was noted in Chicago (IL, USA) in 101 hospitalised pregnant women with influenza illness complicated by pneumonia compared with a 32% case fatality rate in 2053 non-pregnant patients admitted with pneumonia in the same 7-week period.²¹

Eickhoff and colleagues²² noted in 1961 that “An association of influenza-associated deaths and pregnancy is a common clinical impression”. For instance, of a total of 216 influenza deaths during the 1957–58 pandemic documented in New York City (NY, USA), 22 deaths were in unvaccinated pregnant women, only seven of whom had rheumatic heart disease.²³ Deaths from all causes in pregnant women were double the expected number compared with the number of deaths in pregnant women in the preceding 4 years. A similar doubling of risk of death from all causes in pregnancy compared with previous years was seen in England and Wales in 1957, where 12 of the 103 women aged 15–44 years who died from influenza were pregnant. These 12 deaths were within the 477 deaths reported to the Central Public Health Laboratory Service (now known as the Health Protection Agency), accounting for 3% of all excess deaths.²⁴ In Minnesota, USA, 11 deaths in unvaccinated pregnant women accounted for over half of this state’s deaths in women of child-bearing age during the 1957–58 pandemic.²⁵ All fatal pregnant cases in this last study had fulminant, in most cases haemorrhagic, pulmonary oedema.

There is an absence of evidence of an increased risk of influenza-associated morbidity or mortality in pregnant women in the 1968–69 pandemic that had variable global impact. Previous immunity against the influenza A N2 neuraminidase of the 1968–69 pandemic strain possibly had a role in the different risk patterns observed.²⁶

Risk to the fetus from maternal infection

In general, the viral risk to the fetus from maternal influenza infection is low, since transplacental transmission of influenza infection is rare. Although there have been one or two case reports of in-utero infection confirmed by viral culture at fetal autopsy,²⁷ a seroepidemiological study in Nottingham, UK, found no IgM anti-influenza antibodies or autoantibodies in the

cord sera of 138 infants whose mothers had acute influenza infection confirmed by serology.⁹ By contrast, a cluster of 12 fetal deaths within 3 weeks (eight spontaneous abortions and four stillbirths) was reported in one UK general practice where an average of 84 births and hence 12–14 fetal losses are expected per year. Serological evidence of exposure to influenza A during pregnancy was seen in all the 12 mothers, compared with none in nine randomly selected postpartum mothers of live babies born in the same time period and registered with the same practice.²⁸

There is a lack of clear evidence for an association between maternal influenza infection or influenza-induced maternal high fever and congenital abnormalities in human beings. Influenza infection induces pyrexia greater than 37·8°C in 50–100% of cases, usually persisting for 3 days (up to 5 days) with a range between 38°C and 40°C.¹¹ Suggestions of a teratogenic link with pyrexia are difficult to discern in the presence of important causes such as genetic disease or drugs. There are few studies²⁹ assessing the risk to the fetus using serological confirmation of maternal influenza infection, which is a major limitation when up to half of influenza infections are mild or subclinical.

Risk to the neonate from maternal infection

Infants are at high risk of morbidity from influenza. In a prospective cohort study in three American counties, 160 (5·7%) of 2797 children under the age of 5 years presenting to selected clinics and hospitals with respiratory illness in 2000–04 had positive nasal or throat viral swabs for influenza.³⁰ Hospital admission rates for laboratory-confirmed influenza in children aged 0–5 months, 6–23 months, and 24–59 months were 4·5 (3·4–5·5), 0·9 (0·7–1·2), and 0·3 (0·2–0·5), respectively, per 1000 children. The rates of influenza in non-hospitalised young children revealed a different trend. Children aged 0–5 months had the lowest annual rates of outpatient clinic visits and laboratory-confirmed influenza, whereas those aged 6–23 months had the highest. Other cohort studies of hospital admissions with laboratory-confirmed diagnoses suggest a rate of about 2 per 1000 children under 12 months of age; however, with only 60–70% of admissions being laboratory investigated, there is scope for biased ascertainment of virologically proven cases and overestimation of the rates.^{31,32} The differences in infant hospital admission rates in seasons with circulating influenza compared with no circulating influenza in the USA were of similar magnitude.³³

The benefits and risks of influenza vaccination in pregnancy

The potential benefits of protecting against the increased risk from influenza in pregnancy need to be balanced against any actual or theoretical concerns of vaccination during pregnancy.

Evidence for influenza vaccine immunogenicity in pregnancy

The few serological studies on pregnant women suggest that antibody response to influenza vaccine is similar in pregnant and non-pregnant women.^{34,35} Antibody response measured in 15 pregnant women 4–6 weeks following vaccination in the second or third trimester was similar to titres in non-pregnant vaccinated adults.³⁶ In a small randomised trial, maternal seroconversion to one or more antigens was seen in all 13 women given influenza vaccine in the last trimester of pregnancy and in none of 13 women who received tetanus toxoid in the control arm.³⁴

Evidence for influenza vaccine efficacy and effectiveness in pregnancy

Based on evidence of higher risk of mortality in pregnant women from two previous influenza pandemics, it is assumed that vaccinating this population against a pandemic influenza strain will prevent a substantial number of deaths. The assumed benefits of vaccinating pregnant women against seasonal influenza include reduced maternal morbidity and the possibility of reduced mortality in a severe influenza season. An additional benefit of vaccinating a pregnant woman may be the reduced risk of clinically significant influenza illness in the young infant.

Early studies on healthy military recruits provide clear evidence of influenza vaccine efficacy and reduced morbidity in (non-pregnant) young adults.³⁷ A Cochrane systematic review concluded that inactivated influenza vaccines prevented 67% (51–78%) of serologically confirmed and 25% (13–35%) of clinically apparent cases in non-pregnant healthy adults.³⁸ Limitations of summarising across studies from 1966–2003 were acknowledged. For example, vaccine standardisation and composition changed in the same period. A separate systematic review found influenza vaccine efficacy to be even higher if summarised across more recent studies.³⁹

In pregnant women, a recent randomised trial in Bangladesh found that influenza vaccine effectiveness against febrile respiratory illness in women immunised in the third trimester was 28% (4–46%).⁴⁰ Vaccine efficacy based on laboratory-confirmed influenza illness is awaited.⁴⁰

Two studies have shown transplacental influenza-specific antibodies and some protection to infants from naturally acquired maternal influenza infection.^{41,42} The first study, from Texas, USA (1975–78), found that where cord blood influenza IgG titres were 1/8 or more, infants did not have laboratory-confirmed, clinically apparent acute influenza before 8 weeks of age.⁴¹ The second study, from Florida, USA, followed 39 mother-infant pairs in the 1978–79 influenza season. Although no reduction in the rate of clinically apparent, serologically proven acute infection occurred in infants born to infected mothers, there was evidence to suggest that their respiratory illness was milder and with delayed onset.⁴²

In 13 immunised pregnant women, vaccine-acquired influenza-specific maternal antibodies had high transplacental transfer ranging from 87% to 99%, depending on the IgG antibody.³⁴ The half-life of antibodies in the babies was 43–53 days, similar to the half-life of transplacental antibodies from naturally acquired maternal influenza infection.³⁴ The cord titres in 26 maternal-newborn serum pairs did not differ significantly if maternal vaccination occurred in the second or third trimester.³⁶

Results from the small Bangladesh randomised trial in immunised pregnant women indicate protection against laboratory-confirmed febrile illness caused by influenza in the infants (vaccine efficacy 61% [9–84%]).⁴⁰ A 2003–05 database review from Texas found that infants under 6 months of age born to immunised pregnant women were less likely to have a medically attended acute respiratory illness (not laboratory confirmed) during the peak of the 2004/05 influenza season, when compared with those infants born to non-immunised pregnant women matched by age and date of delivery (10.9% vs 31%, $p < 0.001$).⁴³ Two retrospective reviews (1997–2002¹⁷ and 1995–2001⁴⁴) from the USA using managed care databases did not find a reduction in the incidence of medically attended acute respiratory illness (not laboratory confirmed) in immunised mothers¹⁷ or their infants.^{17,44} Both studies were, however, based on easily measured but, by their nature, non-specific outcomes and they were also underpowered because of lower outcome rates or lower maternal vaccine coverage than expected.

Evidence for influenza vaccine safety in pregnancy

There are only a handful of studies on the safety of influenza immunisation in human pregnancy. Two studies have provided long-term data after first trimester vaccinations. The largest, from the USA, analysed 650 mother-child pairs registered within the US Collaborative Perinatal Project (1959–65) who had received influenza vaccine in the first trimester. The project followed 50897 pregnant women at more than 20 weeks' gestation attending antenatal clinics in several US hospitals. The main aim was to examine factors in pregnancy related to cerebral palsy and other damage to the central nervous system.⁴⁵ The immunised cohort was exposed to some or all of these immunisations: trivalent inactivated influenza, oral polio, inactivated polio, tetanus toxoid, and diphtheria toxoid vaccines. In the first week of life and at 12 months of age the children were assessed by a paediatrician and at 4, 8, 12, and 24 months of age their mothers were interviewed. Thereafter, the children were followed for deaths up to the age of 4 years (autopsy data were available on just over 80% of deaths) and followed up to the age of 7 years for hearing impairment, learning disabilities, and malformations. Influenza vaccination was not associated with any excess minor or major malformations.⁴⁶ Based on a total of 2291 pregnant women vaccinated in all trimesters in the same study, there was no evidence for an excess

incidence of childhood malignancies up to 1 year of age and cancer mortality up to 4 years of age.⁴⁷

A smaller study (1976–77) found no difference between 41 mothers vaccinated in the first trimester and 517 non-vaccinees followed up at 8 weeks for physical and neurological development or maternal, perinatal, or infant complications.⁴⁸ Similarly, no differences were noted in 58 women vaccinated in the second and 77 women vaccinated in the third trimester.⁴⁸ There were no serious adverse events in the vaccinated group with an incidence of side-effects (eg, fever, headache, myalgias) under 3%.

Further evidence of vaccine safety in the second and third trimesters is available from a third more recent, historical cohort database study of five influenza seasons in Texas (1998–2003). No serious adverse events were noted up to 42 days post-vaccination in 252 pregnant women immunised in the second or third trimester, and there were no differences in outcomes of pregnancy or infant hospital admissions up to 6 months of age compared with matched, unvaccinated healthy controls.⁴⁹ Information on two further years (2004–05) were recently reported with similar follow-up of infants to 6 months of age.⁴³ In this larger study no serious adverse events in pregnancy were detected in 1006 vaccinated pregnant women compared with 1495 matched unvaccinated pregnant controls.

Other studies have only looked at immediate post-vaccine adverse events. Some safety studies followed the US experience of mass immunisation with swine influenza vaccine in 1976. One study followed 11 pregnant women vaccinated in the second trimester and 45 women vaccinated in the third trimester.³⁶ 40 of the 56 women were followed for 24 h after immunisation. Seven vaccinated pregnant women had side-effects, of whom three reported mild fever. Other side-effects included coryza, influenza-like symptoms, headache, and dizziness. The type and number of vaccine reactions were described as similar to other clinical trials, and pregnancy outcomes as identical to controls.

Finally, in the randomised immunogenicity trial during the 1988–89 season, 30 healthy women in the third trimester received either trivalent influenza or tetanus toxoid vaccine. No significant reactogenicity was noted in any recipient, including fever, pain, or health-care seeking.³⁴

Other potential risks from influenza vaccination in pregnancy

By contrast with the risk of fever from naturally acquired maternal infection, a low-grade fever rarely occurs in response to influenza vaccination. In one study, 1.3% of 189 vaccinated pregnant women had a temperature of more than 37.8°C, which lasted between 1 and 2 days.⁴⁸ In view of the possible teratogenic effect of hyperthermia in pregnancy based on observations from animal models,⁵⁰ there may be a theoretical risk of teratogenicity from maternal pyrexia secondary to vaccination.⁵ In trials of influenza vaccine in other, older populations, however,

no difference in fever was noted in 904 patients in the active arm compared with 902 patients in the placebo control arm (1.3% vs 0.7%, $p=0.15$).⁵¹ There is also the possibility of fetal hypoxia associated with maternal anaphylaxis, for example in reaction to the vaccine's egg protein or other constituents.

Other adverse events associated with influenza vaccine in the general population should also apply to pregnant women and include local reaction, headaches, and malaise. Antigenic determinants can change annually and manufacturers' formulations of influenza vaccines can also change and vary in safety profile, as seen with the 1976 swine influenza vaccine.

Finally, thiomersal, an organic mercury compound, has been used since the 1930s as a preservative in some vaccines, including influenza, to prevent contamination during the production process. Neither a UK retrospective cohort of more than 100 000 children⁵² nor a UK prospective study of more than 14 000 children⁵³ followed from birth to more than 7 years of age found any causal association between thiomersal-containing vaccines and neurodevelopmental disorders. In 2001, the US Institute of Medicine (IOM) reviewed fetal exposure to mercury and found insufficient evidence to suggest a causal relation between vaccines containing thiomersal and neurodevelopmental disorders; however, the IOM considered the risk to be biologically plausible.⁵⁴ In 2004, the IOM reviewed cumulative paediatric exposure to thiomersal-containing vaccines (including data from new population-based epidemiology studies), which led them to reject the hypothesis of a causal link between infants exposed to thiomersal-containing vaccines or the measles, mumps, and rubella vaccine and autism.⁵⁵ The European Medicines Agency also concluded there was no evidence of a risk of autism or speech disorders associated with the use of thiomersal-containing vaccines.⁵⁶ The Global Advisory Committee on Vaccine Safety (GACVS), an advisory body to WHO, concluded that there is currently no evidence of mercury toxicity from thiomersal in vaccines and no reason to change current immunisation practices on the grounds of safety, but noted the paucity of safety data for malnourished or preterm infants.⁵⁷

The UK Health Departments, while noting the lack of evidence of toxicity, currently recommend use of the thiomersal-free vaccine in pregnant women, where this is available, based on the precautionary principle. If only thiomersal-containing vaccine is available, however, the benefit of vaccination is felt to outweigh any theoretical risk and the vaccine is not considered contraindicated in pregnant women.¹

UK data: Yellow Card reporting 1994–2004

For this Review, the Post Licensing Division of the UK Medicines and Healthcare products Regulatory Agency (MHRA) searched the Yellow Card database from June 1, 1994 to June 22, 2004. A causal link between influenza vaccination and adverse events cannot be formed from

these case reports and, as with other passive reporting schemes, inherent limitations in these systems include lack of information on the denominator, under-reporting, and incomplete information on confounders. Among 1366 reports of adverse reactions to influenza vaccine in 10 years, eight occurred in pregnancy. Seven of these eight cases were vaccinated in the first trimester. Six of the pregnant women were documented as having a medical history of asthma (four women), pleurisy (one), or diabetes (one). Four women received other medications, of whom two were exposed to other vaccines; the remaining four cases did not provide medication history. The adverse outcomes reported were one stillbirth, three spontaneous abortions, and three cases of fetal growth retardation, of which two delivered prematurely. The eighth case was a congenital urinary tract anomaly at an 18-week ultrasound scan that resolved or was artifactual, since the outcome was a healthy delivery and normal postnatal renal scan. In view of the reporting and denominator limitations to these data, firm conclusions cannot be made from these eight case reports.

Recommendations from WHO and selected countries

In 2004 and 2006, the GACVS recommended that authorities reconsider their national policies and review the risk-benefit of influenza vaccination in pregnancy, “given the high risk to the mother—and thus to the fetus—of the disease itself and the likely small risk to mother and fetus of the inactivated influenza vaccine”.^{58,59} The 2005 WHO position paper contains a stronger statement that “influenza vaccination in pregnancy is considered safe and is recommended for all pregnant women during the influenza season” and it specifies that this recommendation aims to protect the mother as well as the infant in the first months of life.⁶

In the USA, influenza vaccine in pregnancy was considered safe and practised in the 1950s and 1960s. Official recommendation was provided in 1997 by the Advisory Committee on Immunization Practices (ACIP) for routine immunisation in the second or third trimester. The ACIP now recommends (since 2004) routine influenza vaccination in all trimesters for healthy pregnant women during the influenza season.³ Canada’s national advisory committee has expanded its recommendations to vaccinate women in all trimesters for the 2007–08 season.⁴ In previous years, this practice was “encouraged” for any healthy pregnant Canadian woman wishing to avoid influenza morbidity, and explicitly recommended for women in the third trimester expecting to deliver during the influenza season, with the rationale that they were household contacts to their infants.⁶⁰ In Australia, vaccination is recommended for healthy women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination.⁵ In the UK, vaccination is recommended for pregnant women with any condition listed as a high-risk comorbidity regardless of

trimester, but no routine recommendation for healthy pregnant women has been made;¹ this policy is currently under review. Many countries, however, provide no routine recommendation to vaccinate in pregnancy. For example, Germany’s Standing Commission on Vaccination (STIKO) does not routinely recommend influenza vaccine in pregnancy.^{2,61} STIKO notes the safety evidence is incomplete but no teratogenic effect has been clearly identified. Although pregnancy is not considered as a contraindication, STIKO recommends individual risk-benefit assessment and avoiding first trimester vaccination if there is no urgent indication.

Discussion

In two previous influenza pandemics (1918–19 and 1957–58), pregnant women were at higher risk of morbidity and mortality from influenza-related complications compared with non-pandemic years. In seasonal influenza, pregnant women are at increased risk of influenza-related hospital admission compared with non-pregnant or postpartum women during influenza-exposed periods and occasionally increased mortality in a severe season. This risk rises with increasing length of gestation, and even more strongly with comorbidity.

Research on influenza vaccines is limited in pregnant women. This population is excluded from controlled randomised trials and reproductive toxicity testing until now has not been a regulatory requirement for existing vaccines.⁶² The few prospective studies of women immunised in the second or third trimester suggest the vaccine is safe.

Safety data for the use of any inactivated vaccine in pregnancy, particularly in the first trimester, are limited but have not clearly identified any risk to the fetus. Some reassurance is provided by the inactivated tetanus toxoid vaccines, for which there is more evidence for safety in pregnancy; these vaccines are widely used in all trimesters to prevent neonatal tetanus.^{46,63}

There is less evidence about harmful effects of seasonal influenza infection in healthy women in the first trimester compared with the second and third trimesters. A recommendation to routinely immunise healthy women in the first trimester remains determined more by theoretical risks and benefits than by available current evidence. A practical concern is spontaneous abortion, which occurs more often in early pregnancy and could be misattributed to the vaccine.

Vaccination of women before knowledge of a first trimester pregnancy does occur—perhaps more frequently in countries that recommend influenza vaccine for their health-care workforce—and there is no current evidence to suggest harm to the fetus. A recommendation to offer first trimester immunisation routinely would be strengthened if future studies demonstrate adverse effects from early maternal influenza exposure. One seroepidemiological study

provided evidence suggestive of a higher risk to the fetus of adult schizophrenia if maternal influenza exposure occurred in the first half of pregnancy.²⁹

The USA reached just 16% influenza vaccination coverage of pregnant women in 2005.³ Improvements in vaccine uptake will require practical efforts to reduce barriers and address any concerns of pregnant women and their health providers.⁶⁴

Since the current evidence base to fully assess the risk-benefit of influenza immunisation in pregnancy is incomplete, countries have produced different recommendations. These guidelines do not apply to pandemic influenza, where pregnant women are expected to be at much higher risk of infection, disease, and mortality.

Conclusions

There is evidence to support seasonal influenza vaccination in pregnancy in two groups: healthy pregnant women in the second or third trimester and pregnant women with comorbidities in any trimester. There is also good evidence that pregnant women are more vulnerable during pandemic influenza. Further evaluation of the assumed benefits from maternal immunisation is needed. It is encouraging that the first randomised effectiveness trial of maternal influenza immunisation in the third trimester found significant protection to the mother from febrile respiratory illnesses and indirect protection to their young infants against clinically apparent and influenza-proven febrile respiratory illness.⁴⁰

No serious adverse effects of influenza immunisation in pregnancy have been reported in the few published

studies on vaccine safety. There are, however, limited data on safety in the first trimester. Furthermore, the risk from infection and hence the assumed benefit of vaccination in the first trimester are unclear. Influenza vaccines containing thiomersal are not contraindicated in pregnant women. Preference for the use of thiomersal-free influenza vaccines in pregnancy is a precautionary measure only. Further research on the risk of influenza in pregnancy and longer term safety data on influenza immunisation are needed. Consideration should be given to developing mechanisms for following up pregnancy outcomes after maternal immunisation to augment passive surveillance, particularly if national recommendations are broadened for this group.

Conflicts of interest

We declare that we have no conflicts of interest.

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Search strategy and selection criteria

Data for this Review were identified by searches of the PubMed database without date restriction up to August, 2007, for relevant articles in English, with the following medical subject headings: (1) "influenza, human" OR "influenza A virus", (2) "influenza vaccine", (3) "pregnancy", "pregnancy trimesters", OR "pregnancy outcome", OR "pregnancy maintenance", OR "pregnancy complications", alone and in combination with major topic subheadings: "administration and dosage", "adverse effects", "contraindications", "epidemiology", "immunology", "mortality", "pathology", "prevention and control", "therapeutic use", "therapy", or "toxicity". The Cochrane Library and System for Information on Grey Literature in Europe (SIGLE) and selected countries' influenza vaccination policies were also searched. Bibliographies of key articles and the authors' own extensive files were reviewed. Citation hits were found through the Web of Science. This study obtained permission from the UK Medicines and Healthcare products Regulatory Agency to review a summary of Yellow Card reports from June, 1994, to June, 2004.

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