

H1N1 ('SWINE FLU ') VACCINATION FOR PREGNANT WOMEN:

INFORMATION FOR PROFESSIONAL STAFF INCLUDING VACCINATORS, MIDWIVES AND HEALTH VISITORS

The purpose of this document is to provide information for professional staff regarding the benefits and risks of H1N1 influenza ('swine flu') vaccination of pregnant women during the current pandemic. The information is provided to support the process of informed consent for vaccination.

KEY MESSAGES

- **Swine flu vaccine will protect pregnant women against swine flu this autumn/winter and also against future waves of infection, if these are caused by the same virus. A further wave of swine flu is now predicted in the UK in 2010;**
- **Pregnant women are likely to have an above average 'attack rate' i.e. more likely to catch swine flu than the general population;**
- **While most pregnant women who get swine flu will have only mild flu symptoms and recover within 7-10 days, pregnant women are 4 times more likely than the general population to become seriously ill and to die, as a result of swine flu infection. At 20th October 2009, 4 of the 15 people admitted to intensive care units in N Ireland with complications of swine flu infection, have been pregnant women (pregnant women make up around 1% of the population);**
- **The risks of swine flu infection are further increased in pregnant women who have additional risk factors e.g. underlying health problems such as asthma or diabetes. Pregnant women who are obese are also at higher risk of complications, should they contract swine flu;**

- **The most likely risk to the fetus of maternal influenza infection appears to be miscarriage or preterm delivery (and the associated complications of prematurity), which is probably related to the associated pyrexia in the mother. Some studies have also found an association between influenza infection and fetal anomalies such as cleft palate, congenital heart disease and neural tube defects;**
- **Swine flu vaccine is a type of flu vaccine. Seasonal flu vaccine has been used for years in pregnant women in other countries. Millions of pregnant women have received seasonal flu vaccine and it has an excellent safety record with very small numbers of women having any side- effects. These side- effects have been the same as described in the general population, such as pain at the site of injection and mild, short lasting flu-like symptoms in a small number of cases. There is no evidence of any harm to the fetus;**
- **Pregnant women will only need one dose of the main swine flu vaccine produced by GSK:**
- **Vaccine should be offered to all pregnant women, irrespective of duration of pregnancy, unless there is documented evidence of a laboratory diagnosis of swine flu (i.e. positive swab for swine flu). Women who have had a previous clinical diagnosis of swine flu, without a positive swab, should be offered vaccination.**

Questions and Answers

1. What is swine flu?

Swine flu is the common name given to a new strain of influenza (flu). It is called swine flu because it has some similarities to pig influenza viruses. The virus was first identified in Mexico in April 2009. It has since become a pandemic, which means it has spread around the globe. It has spread quickly because it is a new type of flu virus that few, if any, people have full resistance to.

2. How likely is it that pregnant women will catch swine flu?

It is difficult to predict how many people will become infected with the H1N1 virus but a significant increase in cases is expected during this autumn and winter, 2009. Pregnant women are likely to have an above average 'attack rate' i.e. are more likely to have swine flu than the general population, because of their age (attack rates are highest in the young) and their exposure to young children.

3. How does swine flu affect pregnant women?

Most pregnant women will have only mild flu symptoms and recover within a week to ten days. However, some pregnant women develop very severe disease.

Information from the UK and USA during this pandemic shows that pregnant / newly delivered women are 4-5 times more likely to be admitted to ICU or to die from swine flu infection, than the general population. The most common complication of swine flu infection is pneumonia.

At 20th October 2009, 4 of the 15 people admitted to intensive care in N Ireland with complications of swine flu infection were pregnant women.

The risks of swine flu infection are further increased in pregnant women who have additional risk factors e.g. underlying health problems such as asthma or diabetes. Pregnant women who are obese are also at higher risk of developing complications.

4. Why do pregnant women develop more severe disease?

It is thought that pregnant women are more likely to develop severe disease as a result of changes to their physiology that occurs during pregnancy. This includes reduced immune system functioning, an increase in the total body water which results in an increase in the amount of fluid in the lungs and splinting of the diaphragm.

5. What are the potential risks of swine flu infection (in the mother) to the unborn baby?

There is not yet enough information to know precisely how likely these risks are. Based on what is known about the effects of seasonal flu and other maternal infections, the most likely risk to the fetus would appear to be miscarriage or preterm delivery (and the complications of prematurity), which is probably related to the associated pyrexia in the mother. Some studies have found an association between influenza infection and fetal anomalies such as cleft palate, congenital heart disease and neural tube defects.

Uncontrolled high temperatures resulting from swine flu infection may cause a miscarriage. It is important that any fever is controlled by taking regular paracetamol and drinking plenty of fluids (to avoid dehydration).

See extract of an article on pandemic influenza and pregnant women, published in the Journal of Emerging Infectious Diseases, in Appendix 1.

6. Is the effect of the swine flu different depending the trimester of a pregnancy?

There is not yet enough information to be certain about the effects of swine flu on the different trimesters of pregnancy. Serious complications appear to be more likely in the second half of pregnancy. In general, pneumonia and chest infection are a little more likely to occur and more difficult to manage in later pregnancy because the large womb can put some pressure on the lungs and make it hard for them to fill and empty as completely as they would normally. Women in the early post-partum period also appear to be at increased risk of complications.

7. If I have been in close contact with someone who has swine flu, should I get vaccinated?

Vaccination for swine flu is recommended for all pregnant women. If there is a case in a household the pregnant woman should be offered vaccination at the next available opportunity. However, the vaccine is unlikely to give enough immunity in time to prevent the development of flu.

The pregnant woman should contact her GP for advice. The GP will consider whether an antiviral medicine is appropriate, as a preventative measure. Even if a pregnant woman does not have any symptoms, antiviral medicine may reduce the risk of infection and the seriousness of infection, if it occurs.

8. If I have already had swine flu before/while I was pregnant, should I still be vaccinated?

Vaccine should be offered to all pregnant women, irrespective of duration of pregnancy, unless there is documented evidence of a confirmed laboratory diagnosis of swine flu (i.e. positive swab for swine flu). Women who have had a previous clinical diagnosis of swine flu, without a positive swab result from a laboratory, should be offered vaccination.

It is quite safe to be vaccinated even if the woman has already had swine flu.

9. If I have had antivirals before/while I was pregnant, should I still be vaccinated?

Antiviral drugs do not produce any immunity.

Vaccine should be offered to all pregnant women, irrespective of duration of pregnancy, unless there is documented evidence of a confirmed laboratory diagnosis of swine flu (i.e. positive swab for swine flu). Women who have had a previous clinical diagnosis of swine flu, without a positive swab result from a laboratory, should be offered vaccination.

10. Can the vaccination be dangerous to my unborn baby/cause miscarriage?

Although pregnant women and their carers are naturally cautious about taking vaccines, very few vaccines cause risks in pregnancy. Vaccines similar to the swine flu vaccine have been regularly used in other countries. Millions of pregnant women have received seasonal flu vaccine in the USA.

11. What is the difference between antiviral and vaccine?

Antiviral drugs are given to pregnant women if the woman has reported symptoms of swine flu or has been in close contact with a case of swine flu. The most important role of vaccination is to protect individuals from potentially serious effects of swine flu. Vaccination may also help reduce the spread of the infection.

12. When is the best time in pregnancy to be vaccinated?

Vaccine should be offered to all pregnant women, irrespective of duration of pregnancy.

13. What are the benefits of having the vaccination?

The vaccine will protect the pregnant woman against swine flu this autumn/winter and also against future waves of infection, should they occur, if these are caused by the same virus. A further wave of swine flu is now predicted in the UK in 2010. It will also reduce the likelihood of infection among the pregnant woman's family and close contacts (although if any of these contacts are in a high risk group, they should also be vaccinated).

Studies suggest that the antibody response to influenza vaccine is similar in pregnant women and non-pregnant women. Therefore it is expected that these vaccines will be adequately immunogenic in pregnant women i.e. will significantly reduce the risk of swine flu infection occurring in a pregnant woman exposed to the swine flu virus.

14. What are the side / adverse effects of vaccination?

As with all medicines, some people have experienced side effects following vaccination. The most common side effects are: headache, fever, fatigue, arthralgia, myalgia, induration, swelling, pain and redness at injection site are very common side effects. Other common reactions include lymphadenopathy, increased sweating, shivering, influenza like illness, and injection site reactions such as ecchymosis, warmth, pruritus.

These side- effects are usually much milder than the symptoms of flu and usually resolve within a couple of days. Vaccines may very rarely cause a serious allergic reaction. However, the health professionals who administer vaccines are trained to manage this situation, even though it is very rare.

See extract from a report by the European Medicines Agency, published on 24 September 2009 in Appendix 2.

15. Has the swine flu vaccine been “rushed through” without safety checks?

No. The swine flu vaccine is a new vaccine because the H1N1 “swine flu” influenza virus is a new virus. However, it is based on a vaccine that has been in development for some time as part of the preparations for pandemic influenza. As the strain that will cause a pandemic cannot be predicted, influenza vaccines against a new pandemic virus cannot be produced until the specific virus strain has started to circulate. Prior to this pandemic, however, vaccine manufacturers had developed and tested new types of influenza vaccines that could be adapted when a pandemic arose. The swine flu vaccine has been developed in this way. The development process has included testing the vaccine on over 5,000 non pregnant adults.

16. Why has the vaccine not been tested in pregnant women?

Testing vaccine or any medicines on pregnant women is not allowed.

17. If the vaccine has not been tested on pregnant women, how do we know it is safe?

The vaccine has been tested on non-pregnant adults and has been found to be safe. The vaccine is very similar to seasonal flu vaccine which is routinely given to pregnant women in other countries. Seasonal flu vaccine has been given to millions of pregnant women world- wide. Follow up of pregnant women given seasonal flu vaccine has shown a very low incidence of side-effects, which are mostly local reactions. Influenza vaccine has not been shown to cause adverse pregnancy outcomes.

A study of over 2000 pregnant women who received influenza vaccine demonstrated no associated adverse fetal effects (Heinonen *et al.*, 1973). There is no evidence of risk from vaccinating pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids (Plotkin *et al.*, 2009).

18. Will the vaccine offer any protection to the baby?

We do not know for sure if maternal swine flu vaccination will confer any immunity on the baby. As with other antibodies, those produced by swine flu

vaccination may cross the placenta. However, we do not know if this will confer any protection to the baby.

19. What does the vaccine contain?

The swine flu vaccine contains antigen (parts of the swine flu virus), adjuvant and preservative.

20. What is adjuvant?

Adjuvant is a substance that is added to vaccines to improve the body's immune response to the vaccine. Use of an adjuvant means that the dose of the antigen ('virus parts') used is smaller, the body develops immunity more quickly, the immunity produced lasts longer and the immune response is stronger.

21. What is Thiomersal?

Thiomersal is a compound containing mercury that is used as a preservative in medicines. It is added to prevent bacterial contamination occurring during the preparation and subsequent storage and use of the vaccine.

There is no evidence of risk from thiomersal-containing vaccines to pregnant women, their offspring or young children. In 2003, the Committee on Safety of Medicines concluded that the balance of benefits and risks of thiomersal-containing vaccines remains overwhelmingly positive (CSM, 2003). In 2004, the European Agency for the Evaluation of Medicinal Products concluded that there was no association between vaccination with thiomersal containing vaccines and specific neurodevelopmental disorders (EMA, 2004).

We are all exposed to mercury in the environment and in the food we eat. The type of mercury in Thiomersal is metabolised and excreted very quickly.

22. How many doses of vaccine will I need?

Only one dose is required in pregnant women.

23. Should I breastfeed if I have had the vaccine?

Yes, women should breastfeed as normal after having the vaccine.

REFERENCES/SOURCES OF INFORMATION

APPENDIX 1

<http://www.cdc.gov/eid/content/14/1/95.htm>

Extract of an article on pandemic influenza and pregnant women, published in the Journal of Emerging Infectious Diseases, in 2008.

'Although certain infections are well recognized to increase the risk for adverse pregnancy outcomes, the effects of maternal influenza infection on the fetus are not well understood. Viremia is believed to occur infrequently in influenza, and placental transmission of the virus also appears to be rare. However, even in the absence of fetal viral infection, animal studies suggest that adverse effects can still occur. Prenatal influenza infection in the mouse has been associated with histopathologic changes in the brain and behavioural alterations in offspring.'

'Adverse pregnancy outcomes have been reported following previous influenza pandemics. During the influenza pandemic of 1918, remarkably high rates of spontaneous abortion and preterm birth were reported, especially among women with pneumonia (for example, in 1 study, >50% of pregnancies in which the pregnant woman had influenza and accompanying pneumonia were not carried successfully to term). During the Asian influenza pandemic of 1957, studies suggested a possible increase in defects of the central nervous system and several other adverse outcomes, including birth defects, spontaneous pregnancy loss, fetal death, and preterm delivery.'

'Studies of the effects of seasonal influenza infection on the fetus have been contradictory. A small increased risk for birth defects in general and for specific birth defects have been observed in some but not all studies. Using data from a recent case-control study, investigators showed that mothers of infants with any type of birth defect were slightly more likely to report influenza during early pregnancy than mothers of control infants (adjusted odds ratio 1.4; 95% confidence intervals 1.3 –1.6), with statistically significant associations for cleft lip with or without cleft palate, and neural tube and congenital heart defects. The risk associated with influenza was reduced for women who received treatment with antifever medications and for those who had taken folic acid before and during early pregnancy.'

'Even if the influenza virus does not have a direct effect on the fetus, fever that often accompanies influenza infection could have adverse effects. Both

animal and human epidemiologic studies suggest that hyperthermia is associated with an increased risk for adverse outcomes, especially neural tube defects.'

APPENDIX 2

<http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/60825909en.pdf>

Extract from a report by the European Medicines Agency, published on 24 September 2009.

'Experience with non-adjuvanted influenza vaccines

The benefit of influenza vaccines has rarely been assessed specifically in this population, and there are few data from clinical trials in pregnant women. Most knowledge comes from seasonal influenza inactivated vaccines utilised in the general population.

The benefit for the newborn of vaccination with seasonal inactivated influenza vaccines during pregnancy relies on the placental transfer of maternal antibodies. Although this transfer has been demonstrated, rendering possible an indirect protection of the newborn, there is limited evidence available.

Safety data of inactivated (non-adjuvanted) seasonal influenza vaccines in pregnant women that has been collected within clinical trials is very limited. However, these data on pregnant women vaccinated with different inactivated, non-adjuvanted seasonal vaccines indicate no malformative or foetal/ neonatal toxicity. Moreover, there is extensive experience from seasonal influenza vaccination in all trimesters of pregnancy, since such vaccination has been recommended for several years in some countries. For instance, from the years 2000-2003, two million pregnant women were vaccinated in the USA, and available safety data from passive surveillance and epidemiological studies have not raised concerns. The adverse events profile from vaccinated pregnant women is similar to that for vaccinated adults.

Experience with pandemic vaccines

For the three pandemic vaccines (Celvapan, Focetria and Pandemrix), no clinical data are available in pregnant women. Clinical trials with the mock-up vaccines and to some extent the A (H1N1) v strain provide immunogenicity

results in women of childbearing age. Based on experience from other influenza vaccines, it is assumed that immunogenic responses in non-pregnant women can be extrapolated to pregnant women.

Celvapan

Reproductive and developmental animal toxicity studies have been performed. The serological responses to the vaccine and exposure of foetuses to specific antibodies were demonstrated. According to the data presented, no vaccine-related harmful effects were seen on mating performance or female fertility, embryo-foetal survival or development, or on pre- and post-natal development. Clinical experience with whole-virion vaccines does not suggest any harmful effects for the foetus.

Pandemrix

Non-clinical studies with regard to female fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period) were conducted in rats with the Pandemrix mock-up vaccine containing the AS03 adjuvant. There was no cause for concern identified in this study. No data are available on administration around the implantation phase of the embryos. There are no data in pregnant women with a vaccine that contains the AS03 adjuvant.

There is no indication at the present time that inclusion of adjuvants in vaccines is associated with adverse outcomes on pregnancy.

Serological studies exploring the immunogenicity suggest that antibody response to influenza vaccine is similar in pregnant women and non-pregnant women. Therefore it is expected that these vaccines will be adequately immunogenic in pregnant women. Although currently available safety data are very limited, non-clinical data with the current vaccines/adjuvants and experience from other types of vaccines (both non-adjuvanted and adjuvanted) do not raise concerns with respect to use during pregnancy.

Furthermore, vaccine safety in pregnant women and effectiveness will be closely monitored, as part of the RMP. Observational studies using established pregnancy registries are planned. ‘

‘Coadministration with other vaccines

For the mock-up vaccines with H5N1 strains there are data on co-administration of non-adjuvanted subunit influenza seasonal and Focetria (H5N1) in adults. These data did not reveal any immune interference between the seasonal and the H5N1 strains. There were no differences in serious

adverse events (SAEs) between groups, and all SAEs were unrelated. There are no such data for Pandemrix (H5N1) or Celvapan (H5N1).

There are no data on co-administration of Celvapan, Pandemrix and Focetria A (H1N1) v vaccines with seasonal influenza vaccines, or other vaccines. Ongoing studies will examine whether giving a pandemic A (H1N1) v vaccine and seasonal influenza vaccine simultaneously or sequentially will affect the immune response to either vaccine. However, if co-administration with another vaccine is indicated, immunisation should be carried out in separate limbs. It should be noted that the adverse reactions may be intensified.

Thiomersal

Thiomersal is a compound containing mercury that is used as a preservative in medicines. Thiomersal is metabolised into ethylmercury and thiosalicylate, and contains 49.6% mercury by weight. It is often used in vaccines, to comply with the requirements in the European Pharmacopeia for multi-dose containers, where it helps to prevent bacterial or fungal contamination.

The multi-dose presentations of Pandemrix and Focetria contain thiomersal. These vaccines have been authorised with a two-dose vaccination schedule separated by at least a three-week interval. The maximal exposure to thiomersal is two administrations of 50 micrograms per dose (corresponding to 25 micrograms mercury) separated by at least three weeks.

Concerns have been raised in the past because chronic exposure of infants to high doses of methylmercury (a similar compound present in food) may induce neurological adverse events. However, studies have shown that ethylmercury is eliminated faster from the body. In animals its administration is less neurotoxic than that of methylmercury.

Based on a large amount of scientific data, the WHO, the United States Institute of Medicine and the European Medicines Agency have concluded that the evidence favours the rejection of a causal relationship between thiomersal-containing vaccines and autism. Additional publications have underscored the lack of an association between thiomersal and neurodevelopmental disorders.

Most of the knowledge on the exposure of pregnant women to organic mercury is derived from food consumption. Pregnant women (as well as the fetuses they are bearing) are known to be more sensitive to organic mercury than the normal population. Everybody in the population (including pregnant women) is expected to be exposed to small amounts of methylmercury via

food, especially fish. The Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives established a provisional tolerable weekly intake of 1.6 microgram per kg for organic mercury from fish (equivalent to 96 micrograms in a 60-kg woman).

These data suggest that vaccination with two doses of Pandemrix or Focetria separated by at least three weeks are considered safe in pregnant women.

Thiomersal is a contact allergen to which approximately 1-5 % of adolescents and adults in Europe are allergic, having the potential to develop skin reactions. There have been case reports in the literature of occurrences of generalised allergic skin reactions to thiomersal after vaccination. However, over 90% of patients who have a contact allergy to thiomersal do not have an allergic reaction after intramuscular vaccination with a thiomersal-containing vaccine. Therefore, these reactions occur very rarely and an existing thiomersal contact allergy is not a contraindication to the use of a thiomersal-containing vaccine.

The CHMP acknowledges that the presence of thiomersal in some vaccines is necessary, either as a preservative in multidose vials of vaccines or due to the use of organic mercury compounds during the vaccine's manufacture. After evaluation of the scientific evidence, the CHMP has concluded that immunisation with vaccines containing thiomersal continues to offer benefits to the general population.'

DEVELOPED BY THE N IRELAND H1N1 VACCINATION PROGRAMME
AS A RESOURCE FOR PROFESSIONAL STAFF

OCTOBER 2009