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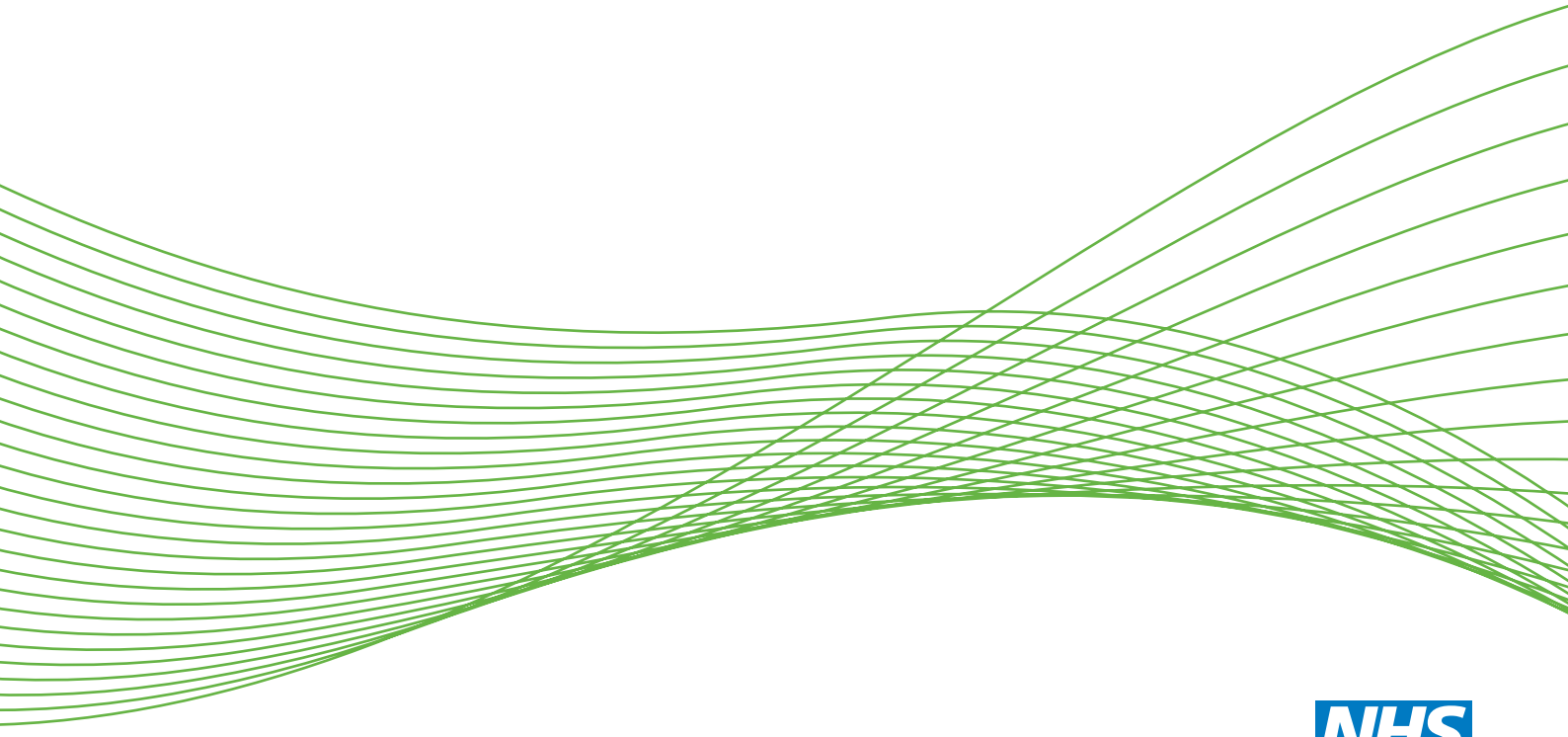

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Planning for a cohort study to investigate the impact and management of influenza in pregnancy in a future pandemic

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Abstract

Planning for a cohort study to investigate the impact and management of influenza in pregnancy in a future pandemic

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Background: Evidence from the 2009 A/H1N1 influenza pandemic demonstrated that pregnant women are particularly vulnerable to infection and at an increased risk of death. Active data collection through the UK Obstetric Surveillance System (UKOSS) about women admitted to hospital during the 2009 A/H1N1 pandemic was used to inform ongoing clinical guidance regarding the use of antiviral treatment for pregnant women and demonstrated that, in addition to an increased risk of maternal morbidity, influenza infection in pregnancy is associated with poor perinatal outcomes, including an increased risk of stillbirth and preterm birth. This evidence influenced the decision to offer routine influenza immunisation to pregnant women. Even in a non-epidemic period, pregnant women continue to die from influenza.

Objective: To establish, and then to put into hibernation, the study mechanisms needed to mount a rapid investigation of the impact of pandemic influenza in pregnancy in the event of a newly emerging pandemic strain.

Design: A new UKOSS cohort study was designed, based on the 2009–10 study, and following consultation with the Pandemic Flu Planning Group at the Royal College of Obstetricians and Gynaecologists and the UKOSS Steering Committee, to identify potential previously unanswered questions.

Setting: UK maternity units.

Participants: All pregnant women admitted to hospital with influenza in a future pandemic.

Main outcome measures: Management of pregnant women with influenza infection, intervention rates, treatment and pregnancy outcome for both the mother and fetus.

Results: The study was designed and approved by the UKOSS Steering Committee and then placed into hibernation for activation in the event of an influenza pandemic.

Conclusions: Pregnant women, as a result of their changed immunological status, appear to be particularly susceptible to infection, including from influenza. The existence of the UKOSS enabled us to rapidly mount a study of pregnant women who were hospitalised with 2009 A/H1N1 influenza. Minor modifications to incorporate previously unanswered questions and our previous study enabled us to design, and then put into hibernation, a new study ready to investigate the impact and management of influenza in pregnancy, which is poised for activation in the event of a newly emerging pandemic strain. This will enable real-time data to be available on which to base rapid changes in clinical management as the as-yet-unforeseen pandemic unfolds. In the event of an influenza pandemic the study will be available to be immediately activated following expedited regulatory approvals.

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List of abbreviations

aOR	adjusted odds ratio
BPSU	British Paediatric Surveillance Unit
CI	confidence interval
CPRD	Clinical Practice Research Datalink
ECMO	extracorporeal membrane oxygenation
UKOSS	UK Obstetric Surveillance System

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Plain English summary

Pregnant women have an increased chance of developing infections and becoming seriously ill; this includes being more likely to catch influenza (flu). During the 'swine flu' pandemic of 2009–10 we carried out a study to investigate the effect of flu on pregnant women using a system called the UK Obstetric Surveillance System (UKOSS). We set up UKOSS in 2005 to study serious rare conditions affecting pregnant women, so, when 'swine flu' was declared as a pandemic, we rapidly set in place a study to look at its effects in pregnancy. We found that pregnant women had an increased risk of becoming severely ill and were also more likely to have a stillborn or premature baby. The results from the study were used to make changes to the treatment offered to pregnant women infected with 'swine flu' and also led to the recommendation that all pregnant women should receive vaccination against seasonal flu routinely – this is the flu that occurs every year in winter time. We know that, even though there is not a flu pandemic currently, a small number of pregnant women have nevertheless died from seasonal flu.

Using our experience from the 'swine flu' pandemic we have set everything in place so that if there is another flu pandemic we can rapidly activate a new UKOSS study to investigate what happens. This will provide the necessary information, once again, to enable treatment and vaccination provided during pregnancy to be tailored to the particular needs of pregnant women.

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Chapter 1 Background

Evidence from the last influenza pandemic (2009 A/H1N1) showed that pregnant women were particularly vulnerable to severe complications of infection,[1–5] resulting in increases in both maternal and perinatal mortality.[5–7] Further investigations, including in the UK,[5] highlighted specific groups of women who were at higher risk of morbidity after 2009 A/H1N1 infection in pregnancy. Factors associated with admission to hospital with 2009 A/H1N1 in pregnancy included maternal obesity, asthma, multiparity, multiple pregnancy, black or other minority group ethnicity, and smoking among women aged < 25 years.[1,3,5] Women have continued to die from influenza associated with pregnancy seasonally since the pandemic.[8]

Active data collection on pregnant women at the time of admission to hospital with confirmed 2009 A/H1N1 influenza, as well as identifying particular subgroups who were at risk of the severest disease and hence a particular target for preventative interventions, also pinpointed aspects of management that resulted in improved outcomes for women, including the importance of early antiviral treatment.[5] In the 2009 pandemic, monthly analysis of emerging data was used to inform ongoing clinical guidance. Admission to an intensive care unit, taken as a proxy for severe morbidity, was also associated with delay in starting treatment with antiviral medication (> 2 days after the onset of symptoms) in other population studies.[1,3,4,9] This has been confirmed in more recent meta-analyses of observational data.[10]

Many studies of 2009 A/H1N1 in pregnancy reported very incomplete outcomes or outcomes for only a subset of severely affected women.[1,3,4,9,11,12] Half of the initial published outcome rates were calculated using subsamples of < 50% of the study cohort. The majority of studies did not follow up women to the end of their pregnancy[3,4,9,11] or, in some cases, the follow-up time was too short to collect outcome information on women infected at all gestations.[3,6] This approach will have biased any results towards reporting preterm births and is likely to have led to overly pessimistic results.

The UK study[13] followed up 94% of the original study cohort ($n = 256$) and demonstrated that poor perinatal outcomes, in addition to poor maternal outcomes, were associated with 2009 A/H1N1 influenza infection in pregnancy. The risks of poor outcomes persisted after adjustment for maternal and pregnancy characteristics that were known to be associated with poor perinatal outcomes. The study[13] suggested an increased risk of perinatal mortality in women infected with 2009 A/H1N1 compared with the general population {perinatal mortality rate 39 per 1000 total births [95% confidence interval (CI) 19 to 71 per 1000 total births] compared with 7 per 1000 total births (95% CI 3 to 13 per 1000 total births), adjusted odds ratio (aOR) = 5.7; 95% CI 2.2 to 15.1}. This was explained largely by an increased risk of stillbirth, although the neonatal death rate was also significantly higher than the national rate (odds ratio 3.8, 95% CI 1.2 to 11.8). The study strengthened the evidence for offering routine immunisation to pregnant women and informed subsequent guidance in Europe.[14] More recent cohort studies using routinely collected data have identified similar findings.[15]

In addition to the mortality risk, infants were at greater risk of preterm birth (aOR 4.0, 95% CI 2.7 to 5.9);[13] this was a mixture of both iatrogenic and spontaneous preterm delivery. The data suggest that women with 2009 A/H1N1 infection who gave birth preterm were more likely to have been infected in their third trimester. Secondary infection with bacterial pneumonia played an important role in preterm delivery in this 2009–10 cohort; secondary pneumonia was also associated with preterm birth in women with pandemic influenza in 1919.[16] In the UK data, the risk of preterm birth associated with 2009 A/H1N1 infection persisted even after accounting for the role of secondary pneumonia, which suggested that the excess risk could not be explained by this factor alone.[13]

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Almost half of the infants delivered preterm were delivered early because of maternal compromise. Women are typically delivered during the third trimester in order to aid mechanical ventilation. However, emerging evidence suggests that when women are referred for management with extracorporeal membrane oxygenation (ECMO), in the absence of fetal compromise there may not be an indication to deliver the fetus early.[17] This is noted particularly at gestations of < 30–32 weeks, when the size of the uterus is unlikely to affect mechanical ventilation. Increased availability and use of ECMO may therefore have the potential to impact positively on infant outcomes, even in the presence of maternal critical illness, including not only mortality, but also long-term morbidity, care costs and emotional stress for parents.

Overall, these studies show a clear increase in risk of poor maternal and pregnancy outcomes in women infected with 2009 A/H1N1 influenza. Importantly, immunisation against 2009 A/H1N1 influenza for pregnant women was shown to have a significant impact on health outcomes for both mother and baby.[14] Almost half of the preterm births were due to early delivery for maternal compromise, indicating that the health of pregnant women, which is improved with rapid treatment with antiviral agents, is an important public health priority in future waves of this and other influenza pandemics.

In a future pandemic, however, these observed patterns may differ, and a rapid study of this susceptible group will be important to inform both ongoing preventative and management policies. In the early period of the 2009 A/H1N1 pandemic, agencies took time to co-ordinate and agree guidance. There was thus a delay before any guidance on the care of pregnant or postpartum women with A/H1N1 was issued, and delays in updating this guidance. A rapid study would minimise these delays, and allow prompt dissemination of new learning. In particular, a number of clinical questions remain unresolved, which would be informed by a future study. Of note, it is important to establish whether or not pregnancy can be successfully continued in women managed with ECMO. Limited evidence currently exists as to whether or not pregnancy can be continued during and after ECMO treatment,[17] but further data are needed to fully inform management guidance and also service planning. Additionally, it will be important to investigate whether or not the seasonal influenza immunisation current at the time of the pandemic protects women against pandemic influenza. Immunisation policy changed subsequent to the most recent pandemic, such that pregnant women are now offered seasonal influenza immunisation as part of a routine programme.[18] However, uptake in pregnancy remains relatively low; at the time of writing, vaccine coverage is about 25% in pregnant women with no other complications.[19] In a new pandemic situation, establishing whether or not pregnant women have any protection from existing vaccines, as well as establishing reasons for non-immunisation, will inform immediate public health actions.

Chapter 2 Study objective

The objective of the project reported here was to establish, and then to put into hibernation, the study mechanisms and materials needed to mount a rapid investigation of the impact of pandemic influenza in pregnancy in the event of a newly emerging pandemic strain. This report thus describes the study planning and set-up phase but, as a further pandemic has not yet occurred, the study does not include any new data on influenza in pregnancy.

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Chapter 3 Methods and results

The UK Obstetric Surveillance System (UKOSS) is a research platform to enable the study of rare or severe complications in pregnancy.[20] Reporting clinicians, who include midwives, anaesthetists and obstetricians, are located in all 211 consultant-led maternity units in the UK. The conditions studied using the system change over time; cases that are currently under study are reported monthly on a report card, which is returned to the central UKOSS administration team in Oxford. The monthly card is also used to update contact details when reporting staff change, so that the list of reporters is kept continually up to date. When the reporting clinician indicates on the monthly card that they have a new case to report, the UKOSS administration team will then mail out a specific data collection form. The data collection forms, which are individually designed for each condition-specific study, contain information about a woman's sociodemographic, medical and pregnancy characteristics, together with information about the management of her condition and the outcomes of pregnancy for both her and her baby. All of the information collected is anonymous and thus can be collected without requiring women's consent.

The UKOSS was used to conduct the UK study of pregnant women who were hospitalised with 2009 A/H1N1 influenza in the second wave of the pandemic in late 2009.[13] The normal processes of UKOSS were adapted to allow online reporting of cases and rapid return of electronic data collection forms. Data were analysed monthly and used to inform ongoing clinical guidance.

In order to prepare a new study for a potential future pandemic of influenza, the data from the previous study were examined, and the lead for the Pandemic Flu Planning Group at the Royal College of Obstetricians and Gynaecologists, together with the UKOSS Steering Committee, which includes both public and professional members, was consulted about potential unanswered questions or issues that might be pertinent to pregnant women in future pandemics. On the basis of this consultation, the data collection form that had been used to collect information in the 2009 pandemic was modified. New questions were added, particularly on the use of respiratory support, including ECMO and the timing of delivery in relation to the use of respiratory support. The data collection forms for the Influenza A/H1N1 Pandemic Study and the new study are included in *Appendix 1*.

The relevant regulatory approvals were obtained, a database was programmed together with a web portal for reporting cases, and the study was hibernated pending activation in the event of a pandemic. The authors were provided with a key contact at the funding body, who would advise activation in the event of a pandemic.

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Chapter 4 Discussion

The UKOSS is a research platform that allows for rapid activation of studies of pregnancy complications. The set-up of this new study required very minor modifications to the data collection system that had been set up in 2009. If regulatory approvals are facilitated, the UKOSS could be mobilised rapidly to study pregnancy outcomes of any new emerging infection;[13] we estimate that a study could be implemented within 2–4 weeks of approvals being obtained. Advance approval, prior to any new infection emerging, would clearly allow for even more rapid activation.

It is important to note that the UKOSS is a maternity hospital-based system; therefore, it is likely to capture only severe pregnancy complications and outcomes, or those complications and outcomes that occur during the same hospital admission as delivery. It will not, for example, necessarily identify women who have had an early pregnancy loss or termination as a result of influenza or other emerging infection, as, even if they were hospitalised, they would not necessarily be brought to the attention of maternity services. In the event of future infections, it would therefore be beneficial also to collect information in general practice. This was undertaken in the UK to a limited extent during the 2009 A/H1N1 influenza pandemic;[5] however, it proved much more difficult to obtain information from the community than from hospital owing to the large number of individual reporting organisations involved. Other health systems have used routine data to identify early pregnancy complications of 2009 A/H1N1 infection; it would be beneficial in the UK if routine systems, such as the Clinical Practice Research Datalink (CPRD), could be used on a rapid basis to identify such complications in the future. Additional data to be identified from general practice data could include these early pregnancy complications, as well as hospitalisations in settings other than maternity. Although the CPRD currently covers only a small proportion of UK general practices, if coverage is expanded, a comprehensive future study could include both a UKOSS study and a linked study using the CPRD to collect additional information about complications of influenza in pregnancy presenting in other settings.

Systems such as UKOSS now exist in several specialties. UKOSS was based on the model developed by the British Paediatric Surveillance Unit (BPSU),[21] and the BPSU has been successfully used to conduct studies of emerging infections in the paediatric population, an example being new variant Creutzfeldt–Jakob disease.[22] A new system has recently been set up, covering early pregnancy units – the UK Early Pregnancy Surveillance Service[23] – and this would be a possible route to obtaining information about severe pregnancy complications as a result of infection in the first trimester. Other systems exist in other specialty areas, for example ophthalmology,[24] paediatric surgery[25] and neurology,[26] all of which could be used to investigate emerging public health threats on a rapid basis.

Robust identification of rare, but extremely severe, pregnancy complications in association with emerging infections such as pandemic influenza can be a challenge even on a national basis, as studies will have limited statistical power to identify such complications. The International Network of Obstetric Survey Systems[27] includes member countries across Europe and Australasia, all of whom operate systems that are similar to UKOSS. Rapid activation of a study across the entire network in a future pandemic would allow for rapid collection and collation of information on a large number of pregnancies, thus providing information to guide both prevention and management of infected pregnant women with the most efficiency.

It is important to note that information about the implications and outcomes of seasonal influenza in pregnancy is incomplete. The European Centre for Disease Prevention and Control technical report summarising the scientific advice on seasonal influenza vaccination of children and pregnant women[14] identified significant gaps in the data from Europe on the burden of seasonal influenza in pregnant women, as well as data on vaccine effectiveness and safety. The majority of the limited data available comes from North America. The question therefore arises as to whether or not this study should be activated in the absence of a pandemic in order to provide those data on seasonal influenza in pregnancy for the UK. Robust UK data may further help to counsel women about the risks and benefits of influenza vaccination, as well as aiding economic evaluation.

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Chapter 5 Conclusions

Pregnant women, as a result of their altered immune system and physiology, may be uniquely susceptible to not only influenza, but also other emerging infections. We were able to use the UKOSS to conduct a rapid study of pregnant women who were hospitalised with 2009 influenza A/H1N1. Only minor modifications were required to develop a study to investigate the impact and management of influenza in pregnancy ready for activation in the event of a future pandemic. The UKOSS may be used for rapid studies of any emerging infections in pregnancy; the conduct of studies across an international network may allow for even more rapid information to guide advice and management in pregnancy.

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Contribution of authors

Marian Knight (Professor of Maternal and Child Population Health) designed the study and wrote the first draft of the manuscript.

Peter Brocklehurst (Professor of Women's Health) assisted with the design of the study and revised the manuscript.

Pat O'Brien (Consultant Obstetrician) assisted with the design of the study and revised the manuscript.

Maria A Quigley (Professor of Statistical Epidemiology) assisted with the design of the study and revised the manuscript.

Jennifer J Kurinczuk (Professor of Perinatal Epidemiology) assisted with the design of the study and revised the manuscript.

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Appendix 1 Data collection forms

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Appendix 1.1 UKOSS 2009 A/H1N1 Pandemic Influenza Study data collection form

ID Number:

UKOSS

UK Obstetric Surveillance System

Influenza Study 04/09

Data Collection Form - CASE

Please report all pregnant women admitted on or after 1st September 2009

and before 1st February 2010

Case Definition:

Any woman admitted to hospital with confirmed H1N1v influenza infection in pregnancy.

SAMPLE CASE

Please return the completed form to:

UKOSS
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford
OX3 7LF
Fax: 01865 289701
Phone: 01865 289714

Case reported in: _____

Royal College of Obstetricians and Gynaecologists

npeu National Perinatal Epidemiology Unit

Instructions

1. Please do not enter any personally identifiable information (e.g. name, address or hospital number) on this form.
2. Please record the ID number from the front of this form against the woman's name on the Clinician's Section of the blue card retained in the UKOSS folder.
3. Fill in the form using the information available in the woman's case notes.
4. Tick the boxes as appropriate. If you require any additional space to answer a question please use the space provided in section 7.
5. Please complete all dates in the format DD/MM/YY, and all times using the 24hr clock e.g. 18.37
6. If codes or examples are required, some lists (not exhaustive) are included on the back page of the form.
7. If the woman has not yet delivered, please complete the form as far as you are able, excluding delivery and outcome information, and return to the UKOSS Administrator. We will send these sections again for you to complete two weeks after the woman's expected date of delivery.
8. If you do not know the answers to some questions, please indicate this in section 7.
9. If you encounter any problems with completing the form please contact the UKOSS Administrator or use the space in section 7 to describe the problem.

Section 1: Woman's details

1.1 Year of birth Y Y Y Y

1.2 Ethnic group[1]* *(enter code, please see back cover for guidance)* ☐☐

1.3 Marital status single ☐ married ☐ cohabiting ☐

1.4 Was the woman in paid employment at booking? Yes ☐ No ☐

If Yes, what is her occupation

_____

If No, what is her partner's (if any) occupation

_____

1.5 Height at booking ☐☐☐ cm

1.6 Weight at booking ☐☐☐.☐ kg

1.7 Smoking status never ☐ gave up prior to pregnancy ☐ current ☐ gave up during pregnancy ☐

Section 2: Previous Obstetric History

2.1 Gravidity

Number of previous completed pregnancies beyond 24 weeks ☐☐

Number of previous pregnancies less than 24 weeks ☐☐

If no previous pregnancies, *please go to section 3*

*For guidance please see back cover

SAMPLE CASE

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2.2 **Did the woman have any previous pregnancy problems?[2]*** Yes ☐ No ☐

If Yes, please specify _____

Section 3: Previous Medical History

3.1 **Does the woman have asthma requiring regular inhaled or oral steroids?** Yes ☐ No ☐

3.2 **Has the woman had any other previous or pre-existing medical problems?[3]*** Yes ☐ No ☐

If Yes, please specify _____

3.3 **Has the woman been immunised against H1N1v?** Yes ☐ No ☐

If Yes, please give dates immunised D D / M M / Y Y

D D / M M / Y Y

Section 4: This Pregnancy

4.1 **Final Estimated Date of Delivery (EDD)[4]*** D D / M M / Y Y

4.2 **Was this pregnancy a multiple pregnancy?** Yes ☐ No ☐

If Yes, specify number of fetuses ☐

4.3 **Were there problems in this pregnancy?[2]*** Yes ☐ No ☐

If Yes, please specify _____

4.4 **Was the woman admitted to hospital?** Yes ☐ No ☐

If Yes, please give date of admission D D / M M / Y Y

Diagnosis of Influenza A H1N1v

4.5 **Please indicate presenting symptoms and date of onset in the table below**

Symptom	Tick if Yes	If Yes, give date of onset
Fever	☐	D D / M M / Y Y
Cough	☐	D D / M M / Y Y
Sore throat	☐	D D / M M / Y Y
Headache	☐	D D / M M / Y Y
Tiredness/lethargy	☐	D D / M M / Y Y
Limb or joint pain	☐	D D / M M / Y Y
Diarrhoea	☐	D D / M M / Y Y
Breathlessness	☐	D D / M M / Y Y
Vomiting	☐	D D / M M / Y Y
Rhinorrhoea	☐	D D / M M / Y Y

*For guidance please see back cover

SAMPLE CASE

4.6 **Has virological testing for H1N1v been carried out?** Yes ☐ No ☐

If Yes, did this confirm the diagnosis? Yes ☐ No ☐

If Yes, please specify

Type identified _____

Sample source _____

Date of first positive test D D / M M / Y Y

If No, what was the final diagnosis? _____

4.7 **Was this a clinical diagnosis only?** Yes ☐ No ☐

Therapy

4.8 **Were anti-viral drugs used for H1N1v infection?** Yes ☐ No ☐

If Yes, please specify

	First Agent	Second Agent
Agent used		
Date treatment started	D D / M M / Y Y	D D / M M / Y Y
Date treatment stopped	D D / M M / Y Y	D D / M M / Y Y
Dose		
Route		
Schedule *(e.g. bd)*		
Adverse effects		

4.9 **Were other drugs used during pregnancy?** Yes ☐ No ☐

If Yes, please specify _____

4.10 **Were steroids given to enhance fetal lung maturation?** Yes ☐ No ☐

If Yes, please specify

	First Agent	Second Agent
Agent used		
Date given	D D / M M / Y Y	D D / M M / Y Y
Dose		

4.11 **Did this woman receive ECMO?** Yes ☐ No ☐

4.12 **Was this woman transferred to another hospital?** Yes ☐ No ☐

If Yes, please indicate name of hospital _____

*For guidance please see back cover

SAMPLE CASE

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Section 5: Delivery

5.1 **Did this woman have a miscarriage?** Yes ☐ No ☐

If Yes, please specify date D D / M M / Y Y

5.2 **Did this woman have a termination of pregnancy?** Yes ☐ No ☐

If Yes, please specify date D D / M M / Y Y

Was the pregnancy terminated due to a congenital malformation? Yes ☐ No ☐

If Yes, please specify _____

5.3 **Is this woman still undelivered?** Yes ☐ No ☐

If Yes, Will she be receiving the rest of her antenatal care from your hospital? Yes ☐ No ☐

If No, please indicate name of hospital providing future care

_____

If still undelivered, please complete section 6a and then go to section 7.

If the woman has delivered, please continue.

5.4 **Was delivery induced?** Yes ☐ No ☐

If Yes, please state indication _____

Was vaginal prostaglandin used? Yes ☐ No ☐

5.5 **Did the woman labour?** Yes ☐ No ☐

If Yes, please give date and time of onset of labour D D / M M / Y Y h h : m m (24hr)

5.6 **Was delivery by caesarean section?** Yes ☐ No ☐

If Yes, please state:

Grade of urgency[5]* ☐

Indication for caesarean section _____

Method of anaesthesia: Regional ☐ General anaesthetic ☐

SAMPLE CASE

*For guidance please see back cover

Section 6: Outcomes

Section 6a: Woman

6a.1 Was the woman admitted to ITU? Yes ☐ No ☐

If Yes, please specify

Duration of stay ☐☐ days

Or Tick if woman is still in ITU ☐

Or Tick if woman was transferred to another hospital ☐

6a.2 Did any other major maternal morbidity occur?[6]* Yes ☐ No ☐

If Yes, please specify _____

6a.3 What was the woman's date of discharge after her admission for flu? D D / M M / Y Y

6a.4 Did the woman die? Yes ☐ No ☐

If Yes, please specify date and time of death D D / M M / Y Y h h : m m (24hr)

What was the primary cause of death as stated on the death certificate?

(Please state if not known.) _____

Section 6b: Section 6b: Infant 1

NB: If more than one infant, for each additional infant, please photocopy the infant section of the form **(before filling it in)** and attach extra sheet(s) or download additional forms from the website: www.npeu.ox.ac.uk/ukoss

6b.1 Date and time of delivery D D / M M / Y Y h h : m m (24hr)

6b.2 Mode of delivery

Spontaneous vaginal ☐ Ventouse ☐ Lift-out forceps ☐ Rotational forceps ☐

Breech ☐ Pre-labour caesarean section ☐ Caesarean section after onset of labour ☐

6b.3 Birthweight ☐☐☐☐ g

6b.4 Was the infant stillborn? Yes ☐ No ☐

If Yes, *please go to section 7.*

6b.5 5 min Apgar ☐☐

6b.6 Was the infant admitted to the neonatal unit? Yes ☐ No ☐

If Yes, please specify

Duration of stay ☐☐ days

Or Tick if infant is still in neonatal unit ☐

Or Tick if infant was transferred to another hospital ☐

6b.7 Did any other major infant complications occur?[7]* Yes ☐ No ☐

If Yes, please specify _____

*For guidance please see back cover

SAMPLE CASE

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6b.8 Did the infant have a congenital anomaly? Yes ☐ No ☐

If Yes, please specify _____

6b.9 Did this infant die? Yes ☐ No ☐

If Yes, please specify date of death D D / M M / Y Y

What was the primary cause of death as stated on the death certificate?

(Please state if not known.) _____

Section 7:

Please use this space to enter any other information you feel may be important

Section 8:

Name of person completing the form _____

Designation _____

Today's date D D / M M / Y Y

You may find it useful in the case of queries to keep a copy of this form.

*For guidance please see back cover

SAMPLE CASE

Definitions

1. UK Census Coding for ethnic group

WHITE
- 01. British
- 02. Irish
- 03. Any other white background

MIXED
- 04. White and black Caribbean
- 05. White and black African
- 06. White and Asian
- 07. Any other mixed background

ASIAN OR ASIAN BRITISH
- 08. Indian
- 09. Pakistani
- 10. Bangladeshi
- 11. Any other Asian background

BLACK OR BLACK BRITISH
- 12. Caribbean
- 13. African
- 14. Any other black background

CHINESE OR OTHER ETHNIC GROUP
- 15. Chinese
- 16. Any other ethnic group

2. Previous or current pregnancy problems, including:

Thrombotic event
Amniotic fluid embolism
Eclampsia
3 or more miscarriages
Preterm birth or mid trimester loss
Neonatal death
Stillbirth
Baby with a major congenital abnormality
Small for gestational age (SGA) infant
Large for gestational age (LGA) infant
Infant requiring intensive care
Puerperal psychosis
Placenta praevia
Gestational diabetes
Significant placental abruption
Post-partum haemorrhage requiring transfusion
Surgical procedure in pregnancy
Hyperemesis requiring admission
Dehydration requiring admission
Ovarian hyperstimulation syndrome
Severe infection e.g. pyelonephritis

3. Previous or pre-existing maternal medical problems, including:

Cardiac disease (congenital or acquired)
Renal disease
Endocrine disorders e.g. hypo or hyperthyroidism
Psychiatric disorders
Haematological disorders e.g. sickle cell disease, diagnosed thrombophilia
Inflammatory disorders e.g. inflammatory bowel disease
Autoimmune diseases
Cancer
HIV

4. Estimated date of delivery (EDD):

Use the best estimate (ultrasound scan or date of last menstrual period) based on a 40 week gestation

5. RCA/RCOG/CEMACH/CNST Classification for urgency of caesarean section:

1. Immediate threat to life of woman or fetus
2. Maternal or fetal compromise which is not immediately life-threatening
3. Needing early delivery but no maternal or fetal compromise
4. At a time to suit the woman and maternity team

6. Major maternal medical complications, including:

Persistent vegetative state
Cardiac arrest
Cerebrovascular accident
Adult respiratory distress syndrome
Disseminated intravascular coagulopathy
HELLP
Pulmonary oedema
Secondary infection e.g.pneumonia
Renal failure
Thrombotic event
Septicaemia
Required ventilation

7. Fetal/infant complications, including:

Respiratory distress syndrome
Intraventricular haemorrhage
Necrotising enterocolitis
Neonatal encephalopathy
Chronic lung disease
Severe jaundice requiring phototherapy
Major congenital anomaly
Severe infection e.g. septicaemia, meningitis
Exchange transfusion

SAMPLE CASE

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UKOSS

UK Obstetric Surveillance System

H1N1v ("swine flu") in Pregnancy

Case ID:

Thank you for reporting the above case to UKOSS.

Now please make a note of the following details to keep in the UKOSS folder in case of future queries.

Patient's name: _____

Patient's Hospital number: _____

Patient's year of birth: _____

EDD: _____

Case reported by:

Date reported:

Please keep this sheet with these identifying details,
do not send them to UKOSS.

Return the rest of the form to the address given on the front.

SAMPLE CASE

Appendix 1.2 UKOSS new planned Pandemic Influenza Study data collection form

ID Number:

UKOSS

UK Obstetric Surveillance System

Influenza
Study XX/XX

Data Collection Form - CASE

Please report all pregnant women admitted on or after 1st Xxxx XXXX

and before 1st Xxxx XXXX

Case Definition:

Any woman admitted to hospital with confirmed pandemic influenza infection in pregnancy.

CASE

Royal College of Obstetricians and Gynaecologists

Bringing to life the best in women's health care

Please return the completed form to:

UKOSS
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford
OX3 7LF
Fax: 01865 617775
Phone: 01865 289714

Case reported in: _____

npeu National Perinatal Epidemiology Unit

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Instructions

1. Please do not enter any personally identifiable information (e.g. name, address or hospital number) on this form.
2. Please record the ID number from the front of this form against the woman's name on the Clinician's Section of the blue card retained in the UKOSS folder.
3. Fill in the form using the information available in the woman's case notes.
4. Tick the boxes as appropriate. If you require any additional space to answer a question please use the space provided in section 7.
5. Please complete all dates in the format DD/MM/YY, and all times using the 24hr clock e.g. 18.37
6. If codes or examples are required, some lists (not exhaustive) are included on the back page of the form.
7. If the woman has not yet delivered, please complete the form as far as you are able, excluding delivery and outcome information, and return to the UKOSS Administrator. We will send these sections again for you to complete two weeks after the woman's expected date of delivery.
8. If you do not know the answers to some questions, please indicate this in section 7.
9. If you encounter any problems with completing the form please contact the UKOSS Administrator or use the space in section 7 to describe the problem.

Section 1: Woman's details

1.1 Year of birth Y Y Y Y

1.2 Ethnic group[1]* *(enter code, please see back cover for guidance)* ☐☐

1.3 Marital status single ☐ married ☐ cohabiting ☐

1.4 Was the woman in paid employment at booking? Yes ☐ No ☐

If Yes, what is her occupation

_____

If No, what is her partner's (if any) occupation

_____

1.5 Height at booking ☐☐☐ cm

1.6 Weight at booking ☐☐☐.☐ kg

1.7 Smoking status never ☐ gave up prior to pregnancy ☐ current ☐ gave up during pregnancy ☐

Section 2: Previous Obstetric History

2.1 Gravidity

Number of previous completed pregnancies beyond 24 weeks ☐☐

Number of previous pregnancies less than 24 weeks ☐☐

If no previous pregnancies, *please go to section 3*

2.2 Did the woman have any previous pregnancy problems?[2]* Yes ☐ No ☐

If Yes, please specify _____

*For guidance please see back cover

CASE

Section 3: Previous Medical History

3.1 **Does the woman have asthma requiring regular inhaled or oral steroids?** Yes ☐ No ☐

3.2 **Has the woman had any other previous or pre-existing medical problems?[3]*** Yes ☐ No ☐

If Yes, please specify _____

3.3 **Has the woman been immunised against pandemic influenza?** Yes ☐ No ☐

If Yes, please give:

Dates immunised	Was this seasonal influenza vaccine or pandemic-type vaccine?	
D D / M M / Y Y	Seasonal ☐	Pandemic ☐
D D / M M / Y Y	Seasonal ☐	Pandemic ☐
D D / M M / Y Y	Seasonal ☐	Pandemic ☐
D D / M M / Y Y	Seasonal ☐	Pandemic ☐

If No, please state reasons for non-immunisation *(tick all that apply)* Not offered ☐ Not available ☐ Contraindicated ☐ Safety concerns ☐ Woman's preference ☐ Not known ☐

Section 4: This Pregnancy

4.1 **Final Estimated Date of Delivery (EDD)[4]*** D D / M M / Y Y

4.2 **Was this pregnancy a multiple pregnancy?** Yes ☐ No ☐

If Yes, specify number of fetuses ☐

4.3 **Were there problems in this pregnancy?[2]*** Yes ☐ No ☐

If Yes, please specify _____

4.4 **Was the woman admitted to hospital?** Yes ☐ No ☐

If Yes, please give date of admission D D / M M / Y Y

Diagnosis of Pandemic Influenza

4.5 **Please indicate presenting symptoms and date of onset in the table below**

Symptom	Tick if Yes	If Yes, give date of onset
Fever	☐	D D / M M / Y Y
Cough	☐	D D / M M / Y Y
Sore throat	☐	D D / M M / Y Y
Headache	☐	D D / M M / Y Y
Tiredness/lethargy	☐	D D / M M / Y Y
Limb or joint pain	☐	D D / M M / Y Y
Diarrhoea	☐	D D / M M / Y Y
Breathlessness	☐	D D / M M / Y Y
Vomiting	☐	D D / M M / Y Y
Rhinorrhoea	☐	D D / M M / Y Y
Flu-like symptoms	☐	D D / M M / Y Y

*For guidance please see back cover

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4.6 Has virological testing for influenza been carried out? Yes ☐ No ☐

If Yes, did this confirm the diagnosis? Yes ☐ No ☐

If Yes, please specify

Type identified _____

Sample source _____

Date of first positive test D D / M M / Y Y

Were there any subsequent positive tests? Yes ☐ No ☐

If Yes, please give date(s) of subsequent positive tests 1: D D / M M / Y Y

2: D D / M M / Y Y

If No, what was the final diagnosis? _____

4.7 Was this a clinical diagnosis only? Yes ☐ No ☐

Therapy

4.8 Were anti-viral drugs used for influenza infection? Yes ☐ No ☐

If Yes, please specify	First Agent	Second Agent
Agent used		
Date treatment started	D D / M M / Y Y	D D / M M / Y Y
Date treatment stopped	D D / M M / Y Y	D D / M M / Y Y
Dose		
Route		
Schedule *(e.g. bd)*		
Adverse effects		

4.9 Were other drugs used during pregnancy? Yes ☐ No ☐

If Yes, please specify _____

4.10 Were steroids given to enhance fetal lung maturation? Yes ☐ No ☐

If Yes, please specify

	First Agent	Second Agent
Agent used		
Date given	D D / M M / Y Y	D D / M M / Y Y
Dose		

4.11 Was this woman managed with extracorporeal membrane oxygenation (ECMO)? Yes ☐ No ☐

If Yes, please indicate:

Date ECMO commenced D D / M M / Y Y

Name of ECMO centre _____

Was this woman delivered during her ECMO treatment? Yes ☐ No ☐

If Yes, please give reason for delivery _____

*For guidance please see back cover

Section 5: Delivery

5.1 Did this woman have a miscarriage? Yes ☐ No ☐

If Yes, please specify date D D / M M / Y Y

5.2 Did this woman have a termination of pregnancy? Yes ☐ No ☐

If Yes, please specify date D D / M M / Y Y

Was the pregnancy terminated due to a congenital malformation? Yes ☐ No ☐

If Yes, please specify _____

5.3 Is this woman still undelivered? Yes ☐ No ☐

If Yes, Will she be receiving the rest of her antenatal care from your hospital? Yes ☐ No ☐

If No, please indicate name of hospital providing future care

_____

If still undelivered, please complete section 6a and then go to section 7.

If the woman has delivered, please continue.

5.4 Was delivery induced? Yes ☐ No ☐

If Yes, please state indication _____

Was vaginal prostaglandin used? Yes ☐ No ☐

5.5 Did the woman labour? Yes ☐ No ☐

If Yes, please give date and time of onset of labour D D / M M / Y Y h h : m m (24hr)

5.6 Was delivery by caesarean section? Yes ☐ No ☐

If Yes, please state:

Grade of urgency[5]* ☐

Indication for caesarean section _____

Method of anaesthesia: Regional ☐ General anaesthetic ☐

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Section 6: Outcomes

Section 6a: Woman

6a.1 Was the woman admitted to Level 3 critical care? Yes ☐ No ☐

If Yes, please specify

Duration of stay ☐☐ days

Or Tick if woman is still in Level 3 critical care ☐

Or Tick if woman was transferred to another hospital ☐

6a.2 Did any other major maternal morbidity occur?[6]* Yes ☐ No ☐

If Yes, please specify _____

6a.3 What was the woman's date of discharge after her admission for flu? D D / M M / Y Y

6a.4 Did the woman die? Yes ☐ No ☐

If Yes, please specify date and time of death D D / M M / Y Y h h : m m (24hr)

What was the primary cause of death as stated on the death certificate?

(Please state if not known.) _____

Section 6b: Section 6b: Infant 1

NB: If more than one infant, for each additional infant, please photocopy the infant section of the form **(before filling it in)** and attach extra sheet(s) or download additional forms from the website: www.npeu.ox.ac.uk/ukoss

6b.1 Date and time of delivery D D / M M / Y Y h h : m m (24hr)

6b.2 Mode of delivery

Spontaneous vaginal ☐ Ventouse ☐ Lift-out forceps ☐ Rotational forceps ☐

Breech ☐ Pre-labour caesarean section ☐ Caesarean section after onset of labour ☐

6b.3 Birthweight ☐☐☐☐ g

6b.4 Sex of infant: Male ☐ Female ☐ Indeterminate ☐

6b.5 Was the infant stillborn? Yes ☐ No ☐

If Yes, *please go to section 7.*

6b.6 5 min Apgar ☐☐

6b.7 Was the infant admitted to the neonatal unit? Yes ☐ No ☐

If Yes, please specify

Duration of stay ☐☐ days

Or Tick if infant is still in neonatal unit ☐

Or Tick if infant was transferred to another hospital ☐

6b.8 Did any other major infant complications occur?[7]* Yes ☐ No ☐

If Yes, please specify _____

*For guidance please see back cover

CASE

6b.9 Did the infant have a congenital anomaly? Yes ☐ No ☐

If Yes, please specify _____

6b.10 Did this infant die? Yes ☐ No ☐

If Yes, please specify date of death D D / M M / Y Y

What was the primary cause of death as stated on the death certificate?

(Please state if not known.) _____

Section 7:

Please use this space to enter any other information you feel may be important

Section 8:

Name of person completing the form _____

Designation _____

Today's date D D / M M / Y Y

You may find it useful in the case of queries to keep a copy of this form.

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Definitions

1. UK Census Coding for ethnic group

WHITE
- 01. British
- 02. Irish
- 03. Any other white background

MIXED
- 04. White and black Caribbean
- 05. White and black African
- 06. White and Asian
- 07. Any other mixed background

ASIAN OR ASIAN BRITISH
- 08. Indian
- 09. Pakistani
- 10. Bangladeshi
- 11. Any other Asian background

BLACK OR BLACK BRITISH
- 12. Caribbean
- 13. African
- 14. Any other black background

CHINESE OR OTHER ETHNIC GROUP
- 15. Chinese
- 16. Any other ethnic group

2. Previous or current pregnancy problems, including:

Thrombotic event
Amniotic fluid embolism
Eclampsia
3 or more miscarriages
Preterm birth or mid trimester loss
Neonatal death
Stillbirth
Baby with a major congenital abnormality
Small for gestational age (SGA) infant
Large for gestational age (LGA) infant
Infant requiring intensive care
Puerperal psychosis
Placenta praevia
Gestational diabetes
Significant placental abruption
Post-partum haemorrhage requiring transfusion
Surgical procedure in pregnancy
Hyperemesis requiring admission
Dehydration requiring admission
Ovarian hyperstimulation syndrome
Severe infection e.g. pyelonephritis

3. Previous or pre-existing maternal medical problems, including:

Cardiac disease (congenital or acquired)
Renal disease
Endocrine disorders e.g. hypo or hyperthyroidism
Psychiatric disorders
Haematological disorders e.g. sickle cell disease, diagnosed thrombophilia
Inflammatory disorders e.g. inflammatory bowel disease
Autoimmune diseases
Cancer
HIV

4. Estimated date of delivery (EDD):

Use the best estimate (ultrasound scan or date of last menstrual period) based on a 40 week gestation

5. RCA/RCOG/CEMACH/CNST Classification for urgency of caesarean section:

1. Immediate threat to life of woman or fetus
2. Maternal or fetal compromise which is not immediately life-threatening
3. Needing early delivery but no maternal or fetal compromise
4. At a time to suit the woman and maternity team

6. Major maternal medical complications, including:

Persistent vegetative state
Cardiac arrest
Cerebrovascular accident
Adult respiratory distress syndrome
Disseminated intravascular coagulopathy
HELLP
Pulmonary oedema
Secondary infection e.g.pneumonia
Renal failure
Thrombotic event
Septicaemia
Required ventilation

7. Fetal/infant complications, including:

Respiratory distress syndrome
Intraventricular haemorrhage
Necrotising enterocolitis
Neonatal encephalopathy
Chronic lung disease
Severe jaundice requiring phototherapy
Major congenital anomaly
Severe infection e.g. septicaemia, meningitis
Exchange transfusion

UKOSS

UK Obstetric Surveillance System

Pandemic Influenza in Pregnancy

Case ID:

Thank you for reporting the above case to UKOSS.

Now please make a note of the following details to keep in the UKOSS folder in case of future queries.

Patient's name: _____

Patient's Hospital number: _____

Patient's year of birth: _____

EDD: _____

Case reported by:

Date reported:

Please keep this sheet with these identifying details,
do not send them to UKOSS.

Return the rest of the form to the address given on the front.

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Appendix 2 Study protocol

Project reference 11/46/12 version 3 12/09/12

Project Protocol

1 Project title

Maternal and perinatal outcomes of pandemic influenza in pregnancy.

Project reference 11/46/12.

2 Planned investigation

2.1 Research objectives

a) To determine:
   i) The incidence of hospitalisation with pandemic-type influenza in pregnancy.
   ii) The outcomes of pandemic-type influenza in pregnancy for mother and infant.

b) To investigate:
   i) The influence of demographic or pregnancy characteristics on outcomes for mother and infant.
   ii) The influence of prior immunisation with seasonal influenza vaccine or specific influenza vaccine on outcomes for mother and infant, including an assessment of reasons for non-immunisation.
   iii) The influence of timing of delivery, particularly in relation to the use of extracorporeal membrane oxygenation on outcomes for mother and infant.
   iv) The influence of other variations in management on outcomes for mother and infant.

b) To produce guidance on the management of pandemic-type influenza infection in pregnancy by monthly review of emerging data from this study such that outcomes for women and infants are optimised during the pandemic.

2.2 Existing research

Evidence from the last influenza pandemic (2009/H1N1) showed that pregnant women were particularly vulnerable to severe infection (1-5), resulting in increases in both maternal and perinatal mortality (5-7). Further investigations, including through the UK Obstetric Surveillance System (UKOSS) (5), highlighted specific groups of women who were at higher risk of morbidity after 2009/H1N1 infection in pregnancy. Factors associated with admission to hospital with 2009/H1N1 in pregnancy included maternal obesity, asthma, multiparity, multiple pregnancy, black or other minority group ethnicity and smoking among women younger than 25 years (1, 3, 5).

Active data collection on pregnant women admitted to hospital with confirmed AH1N1 influenza, conducted using the UKOSS, as well as identifying particular subgroups of pregnant women who were at risk of the severest disease and hence a particular target for preventive interventions, also

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pinpointed important aspects of management which resulted in improved outcomes for women, including the importance of early antiviral treatment (5). Monthly analysis of emerging data was used to inform ongoing clinical guidance during the pandemic. Admission to an intensive care unit, taken as a proxy for severe morbidity, was also associated with delay in starting treatment with antiviral medication (more than two days after the onset of symptoms) in other population studies (1, 3, 4, 8).

Most studies of 2009/H1N1 in pregnancy reported very incomplete outcomes or outcomes for only a subset of severely affected women (table 1) (1, 3, 4, 8-10). Half of outcome rates were calculated using subsamples of less than fifty per cent of the study cohort. The majority of studies did not follow up women to the end of their pregnancy (3, 4, 8, 10) or in some cases the follow up time was too short to collect outcome information on women infected at all gestations (8, 9). This approach will bias any results towards reporting preterm births which is likely to lead to overly pessimistic results.

The UKOSS study (6) followed up 94% of the original study cohort (n=256) and demonstrated that poor perinatal outcomes, in addition to poor maternal outcomes, were associated with 2009/H1N1 influenza infection in pregnancy. The risks of poor outcomes persisted after adjustment for maternal and pregnancy characteristics known to be associated with poor perinatal outcomes. The study suggested an increased risk of perinatal mortality in women infected with 2009/H1N1 compared with the general population (perinatal mortality rate 39 per 1,000 total births (95%CI 19 to 71) compared to 7 per 1,000 total births (95%CI 3 to 13), aOR: 5.7; 95%CI 2.2 to 15.1), which was explained almost entirely by an increased risk of stillbirth. The study was cited by the European Center for Disease as an important European advance, strengthening the evidence for offering routine immunisation to pregnant women in Europe (11).

Table 1: Studies of pregnancy outcomes among 2009/H1N1 infected women

Study	Study period	Study population	Number of pregnant women reported	Number of women with outcome data (%)	Pregnancy outcome	Number affected (%)
Siston 2010 (4)	14/04/2009 – 21/08/2009	Pregnant women with 2009/H1N1 influenza, USA	788[a]	169 (21)	Preterm delivery	51 (30)
				200 (25)	Spontaneous Abortion	8 (4)
Louie 2010 (3)	23/04/2009 – 11/08/2009	Women with confirmed 2009/H1N1 requiring intensive care, California, USA	18	12 (67)	Preterm delivery	10 (83)
		Hospitalised (>24 hrs) or dead women with confirmed 2009/H1N1, California, USA	94	37 (39)	Spontaneous Abortion	2 (5)
Creanga 2010 (8)	01/05/2009 – 30/06/2009[b]	Hospitilised women with H1N1v infection, New York, USA	62	40 (65)	Preterm delivery	6 (15)
					Neonatal death	2 (5)
Hewagama 2010 (10)	20/05/2009 – 31/07/2009	Hospitalised pregnant women with 2009/H1N1 infection, Victoria, Australia	43	15 (35)	Preterm delivery	6 (40)
				24 (55)	Stillbirth[d]/ Neonatal death	3 (13)
ANZIC 2010 (1)	01/06/2009 – 31/08/2009	Pregnant or recently postpartum women admitted to intensive care unit with 2009/H1N1, Australia and New Zealand	64	61 (95)	Miscarriage[c]	2 (3)
					Stillbirth[d]	4 (7)
					Preterm delivery	22 (37)
					Low birth weight	18 (31)
Dubar 2010 (9)	01/08/2009 - 31/12/2009 [e]	Pregnant women admitted to hospital with confirmed 2009/H1N1, France	314	146 (46)	Stillbirth	2 (1)
					Loss of pregnancy prior to 24 weeks	4 (2)
					Low birth weight	22 (16)
					Preterm birth	26 (19)
Pierce (UKOSS) 2011 (6)	01/09/2009 - 31/01/2010	Pregnant women admitted to hospital with confirmed 2009/H1N1, UK	272	256 (94)	Loss of pregnancy prior to 24 weeks	5 (2)
					Stillbirth	7 (3)
					Neonatal death	3 (1)
					Preterm birth	59 (24)

[a] Including 509 hospitalised women.
[b] Followed up until 18/09/2009
[c] Defined as in utero death <20 weeks gestation
[d] Defined as in utero death ≥20 weeks gestation
[e] Followed up until 31/04/2010

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In addition to the mortality risk, infants were at greater risk of preterm birth (aOR 4.0, 95%CI 2.7 to 5.9). The data suggest that women with 2009/H1N1 infection who gave birth preterm were more likely to have been infected in their third trimester. Secondary infection with pneumonia played an important role in preterm delivery in this 2009-10 cohort; secondary pneumonia was also associated with preterm birth in women with pandemic influenza in 1919 (12). In the UK data, the risk of preterm birth associated with 2009/H1N1 infection persisted even after accounting for the role of secondary pneumonia which suggests that the excess risk cannot be explained by this factor alone.

Almost half of the infants delivered preterm were delivered early because of maternal compromise. Women are typically delivered during the third trimester in order to aid mechanical ventilation. However, emerging evidence suggests that when women are referred for management with extracorporeal membrane oxygenation (ECMO), in the absence of fetal compromise there may not be an indication to deliver the fetus early (13). This is noted particularly at gestations below 30 to 32 weeks, when the size of the uterus is unlikely to affect mechanical ventilation. Increased availability and use of ECMO may therefore have the potential to impact positively on infant outcomes even in the presence of maternal critical illness.

Overall, these studies show a clear increase in risk of poor maternal and pregnancy outcomes in women infected with AH1N1v influenza. Importantly, immunisation against AH1N1v influenza for pregnant women is thus likely to have a significant impact on health outcomes for both mother and baby. Almost half of the preterm deliveries were due to early delivery for maternal compromise, indicating that the health of pregnant women, which is improved with rapid treatment with antiviral agents, is an important public health priority in future waves of this and other influenza pandemics.

In a future pandemic, however, these observed patterns may differ, and a rapid study of this susceptible group will be important to inform both ongoing preventive and management policies. In particular, a number of clinical questions remain unresolved, which would be informed by the proposed study. In particular, it is important to establish whether pregnancy can be successfully continued in women managed with extracorporeal membrane oxygenation (ECMO). Anecdotal evidence currently exists that pregnancy can be continued during and after ECMO treatment, but further data are needed to fully inform management guidance and also service planning. Additionally it will be important to investigate whether the current seasonal influenza immunisation at the time of the pandemic protects women against pandemic influenza. Immunisation policy changed subsequent to the most recent pandemic, such that pregnant women are now offered seasonal influenza immunisation as part of a routine programme. However, uptake remains relatively low. In a new pandemic situation, establishing whether pregnant women have any protection from existing

vaccines, as well as establishing reasons for non-immunisation, will inform immediate public health actions.

2.3 Research methods

2.3.1 Research Design

This will be a national prospective observational cohort study using the UK Obstetric Surveillance System (UKOSS). UKOSS is a well-established national system to collect information about severe maternal morbidity through more than 700 collaborating clinicians in all 222 hospitals with consultant-led maternity units throughout the UK (see www.npeu.ox.ac.uk/ukoss for further information). All hospitals in the UK with a consultant-led maternity unit collaborate in UKOSS, and thus it is an ideal mechanism to collect comprehensive information about women hospitalised with pandemic influenza in pregnancy, their management and outcomes. In view of the ethical and other difficulties of conducting clinical trials in pregnant women, the collection of national observational data in this way provides the best rapidly available quality evidence to inform ongoing clinical and public health policy and management guidance. This system has been demonstrated to be able to be used to rapidly collect information to inform policy and guidance in a previous pandemic (5, 6).

2.3.2 Cohort Identification

Cases will be identified through the UKOSS network of nominated reporting clinicians in each consultant-led maternity unit in the UK. Nominated reporting clinicians will be asked to report all pregnant women with confirmed pandemic influenza admitted to their unit. In view of the need for rapid and ongoing data analysis and production of guidance, we will use a specific web-based rapid reporting and data collection system for this study to enable UKOSS nominated clinicians to report cases as they occur. In addition, nominated clinicians will be sent a standard UKOSS reporting card each month to further enhance case ascertainment.

Information about comparison women will be obtained from previously collected UKOSS data. The UKOSS database currently contains detailed demographic, pregnancy and delivery information about a cohort of over 1500 women giving birth in the UK identified from the same hospitals as cohort women and data collection is ongoing. Data from comparison women giving birth in the UK in the two years prior to any future pandemic, and not reported to have been infected with influenza, will be used to minimise any potential bias introduced by service changes, which might be possible if an older historical comparison cohort were used.

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2.3.3 Data Gathering

On receiving a case report, the central team will ask the clinician to complete an electronic data collection form (see appendix for draft), asking for further detailed information about women's characteristics, diagnosis, management and outcomes. All data collected will be anonymous; no names, addresses, postcodes, hospital or NHS numbers will be collected. Patients will be identified using a unique UKOSS number supplied by the central team. If a completed data collection form is not received back by the central team after three weeks, a further reminder will be sent out. If there is still no response after a further three weeks, the clinician will be contacted by telephone.

2.3.4 Monitoring Data Collection

Information concerning pandemic influenza in pregnancy will be compared with information from the Health Protection Agency and from the Intensive Care National Audit and Research Centre (ICNARC) database. In addition, adult ECMO centres functioning at the time of the pandemic will be contacted directly to identify cases. The organisation responsible for monitoring perinatal and maternal deaths (currently under review) will also be contacted and asked to provide information on fatal cases of pandemic influenza in pregnancy, or consequent stillbirths or neonatal deaths. If any cases are identified through these sources which have not been identified through UKOSS, the nominated UKOSS clinician in the relevant hospital will be contacted and asked to provide further information on management and outcomes.

2.3.5 Study activation

UKOSS is an ongoing research system with a rolling programme of studies. Preparation of the relevant paperwork (study protocol and data collection form) and programming, together with obtaining UKOSS Steering Committee, ethics committee and NHS management approval in advance (as appropriate) would allow the study to be activated very rapidly (within two weeks) in the event of a future pandemic.

2.4 Planned inclusion/exclusion criteria

The cohort will be all pregnant women in the UK admitted to hospital with confirmed pandemic influenza. Women not meeting the inclusion criteria will be excluded.

In order to facilitate a rapid study without placing an additional data collection burden on clinicians in the context of an influenza pandemic, information about comparison women will be obtained from previously collected UKOSS data. This approach was successfully used in the most recent 2009-10 influenza pandemic (5, 6). The UKOSS database currently contains detailed demographic, pregnancy and delivery information about a cohort of over 1500 women giving birth

in the UK identified from the same hospitals as cohort women and data collection is ongoing. Data from comparison women giving birth in the UK in the two years prior to any future pandemic, and not reported to have been infected with influenza, will be used to minimise any potential bias introduced by service changes, which might be possible if an older historical comparison cohort were used.

The denominator population will be all women giving birth in the UK.

2.5 Ethical arrangements

This study seeks to collect anonymous information only about women who have pandemic influenza during pregnancy. This information is key to identifying evidence to inform ongoing policy and guidance in the context of a pandemic. The collection of information about individuals in this way raises these main ethical issues:

1. Consent. It will not be practicable to obtain consent for data collection from individual women, as this would prevent the achievement of the primary objective of the study, namely to document the numbers of women who are affected in the UK. Accurate measurement of incidence requires documentation about ALL cases occurring in the UK. The National Information Governance Board (NIGB) Ethics and Confidentiality Committee considers that organisations seeking to use NHS information for research purposes without consent should seek anonymised or pseudonymised data only and not any personally identifiable information (14). Accordingly, this study will not collect names, addresses, postcodes, dates of birth, NHS or hospital numbers. Collection of anonymised data in this way in the absence of consent is unlikely to cause significant harm. This UKOSS methodology has received the approval of the London Multi−centre Research Ethics Committee (study reference 04/MRE02/45).
2. Confidentiality and data security. In order to maintain patient confidentiality, no names, addresses, postcodes, dates of birth, hospital or NHS numbers will be collected as outlined above. The security of all data will be maintained by storage on a secure University network, accessible only by the key researchers and responsible members of the University of Oxford who may require access to data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study will only be allowed after review by the UK Obstetric Surveillance System Steering Committee and further reference to a Research Ethics Committee. Prof Jenny Kurinczuk, Director of the National Perinatal Epidemiology Unit, University of Oxford will act as custodian of the data.

2.6 Proposed sample size

As the study we propose is a national observational study, the study sample size will be governed by the disease incidence. As an estimate, based on our experience in the 2009-10 pandemic, we anticipate identifying 300-500 infected pregnant women admitted to hospital. Information on up to

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1500 comparison women is available from existing UKOSS data. We have estimated the study size based on estimated incidence and not any specific outcomes. However, as a guide, the table below indicates the odds ratios detectable by a study of this size, assuming 80% power and a 5% level of significance with a 3:1 ratio of unexposed to exposed:

Frequency of outcome in comparison cohort	Odds ratio detectable by the study
1%	2.8
5%	1.8
10%	1.6
20%	1.4

2.7 Statistical analysis

The following analyses will be conducted:

a) Estimation of the incidence of hospitalisation with pandemic influenza amongst pregnant women with 95% confidence intervals, using the denominator of total maternities in the UK over the relevant time period.

b) Comparison of the rates of individual adverse outcomes (maternal death, level 3 critical care unit admission, other major complication, preterm birth, congenital anomaly, stillbirth, early neonatal death, perinatal death) between women infected with pandemic influenza admitted to hospital and the comparison cohort. Adjustment for potential confounders will be undertaken using Poisson regression (for rare events) or logistic regression (if the outcomes are more frequent). Confounders included in the model will be those known to be associated with the relevant outcomes (age, parity, marital status, ethnicity, smoking status, socioeconomic status, previous preterm delivery, previous perinatal death).

c) The management of pregnant women hospitalised with confirmed pandemic influenza will be described. Differences in outcomes will be explored in different subgroups according to management. The initial subgroups examined will be as follows (although note that these may be revised as more becomes known about the patterns of disease during the pandemic):

   Antiviral treatment received within 48hr of symptom onset (Yes/No)

   Type of antiviral received

   Dose of antiviral received

   Use of ECMO during pregnancy

   Delivery prior to institution of respiratory support (Yes/No)

   Mode of delivery

Guidance on the management of pregnant women with pandemic influenza in pregnancy, informed by ongoing data analysis, will be produced and reviewed monthly with the relevant organisations, for example, the Department of Health, Royal College of Obstetricians and Gynaecologists, Royal

College of Midwives and Royal College of General Practitioners, in order to improve outcomes for women and infants based on the available evidence.

2.8 Proposed outcome measures

The following outcomes will be compared between women with influenza and comparison women, and explored in different subgroups according to management variations:

Maternal death
Maternal level 3 critical care unit admission
Other major maternal complication
Preterm birth
Congenital anomaly
Perinatal death

2.9 Research governance

Research Ethics Committee and NHS management approval will be obtained as appropriate prior to the start of the study. The University of Oxford will act as sponsor of the study.

The overall conduct of the study will be monitored by a Management Group consisting of the Co-Applicants, Information Scientist, Researcher, Project Programmer, Statistician and other external members as considered necessary for the project.

3 Project timetable and milestones

3.1 Timetable

Pre-activation phase (provisional start date 1 June 2012)

June 2012	Apply for necessary approvals, develop web-based reporting systems, finalise and format data collection form and clinician information.

Activation phase

Week 1	Study information mailed/emailed to clinicians
Week 3	Data collection commenced
Months 2-6	Ongoing reporting of new cases, data analysis, production of management guidance and dissemination.
Months 7-10	Collection of remaining pregnancy outcome data
Month 12	Final pregnancy outcome analysis, production of guidance and dissemination

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3.2 Milestones

Pre-activation phase

July 2012	Web-based reporting system in place, data collection form finalised and formatted
August 2012	Approvals completed (assuming no expedited process)

Activation phase

Month 2	First data analysis, first guidance issued
Months 3-5	Ongoing monthly data analysis, revised guidance issued
Month 6	Final report on immediate maternal and pregnancy outcomes, revised guidance
Month 12	Final report on complete pregnancy outcomes, including data on pregnancy outcomes of women undelivered at the time of interim reports

4 Expertise

The research team has the necessary expertise to carry out this comprehensive national study, including public health (MK, JK), congenital malformations (JK), perinatal epidemiology and statistics (MQ, MK, JK, PB), obstetric surveillance (MK), guideline development (JK, PB), and obstetrics (PO'B, PB).

The National Perinatal Epidemiology Unit (NPEU) has a national and international reputation for conducting studies which change policy, influence practice and improve the care of women and their babies. MK developed and launched UKOSS and led the initiative from its inception; since its establishment in 2005, UKOSS has generated evidence to improve prevention and management of a range of severe pregnancy complications in the UK involving a network of over 700 collaborating clinicians at all 222 hospitals with consultant maternity units throughout the UK. The infrastructure is thus in place to allow rapid identification of women hospitalized with pandemic influenza infection in pregnancy through an established active surveillance system.

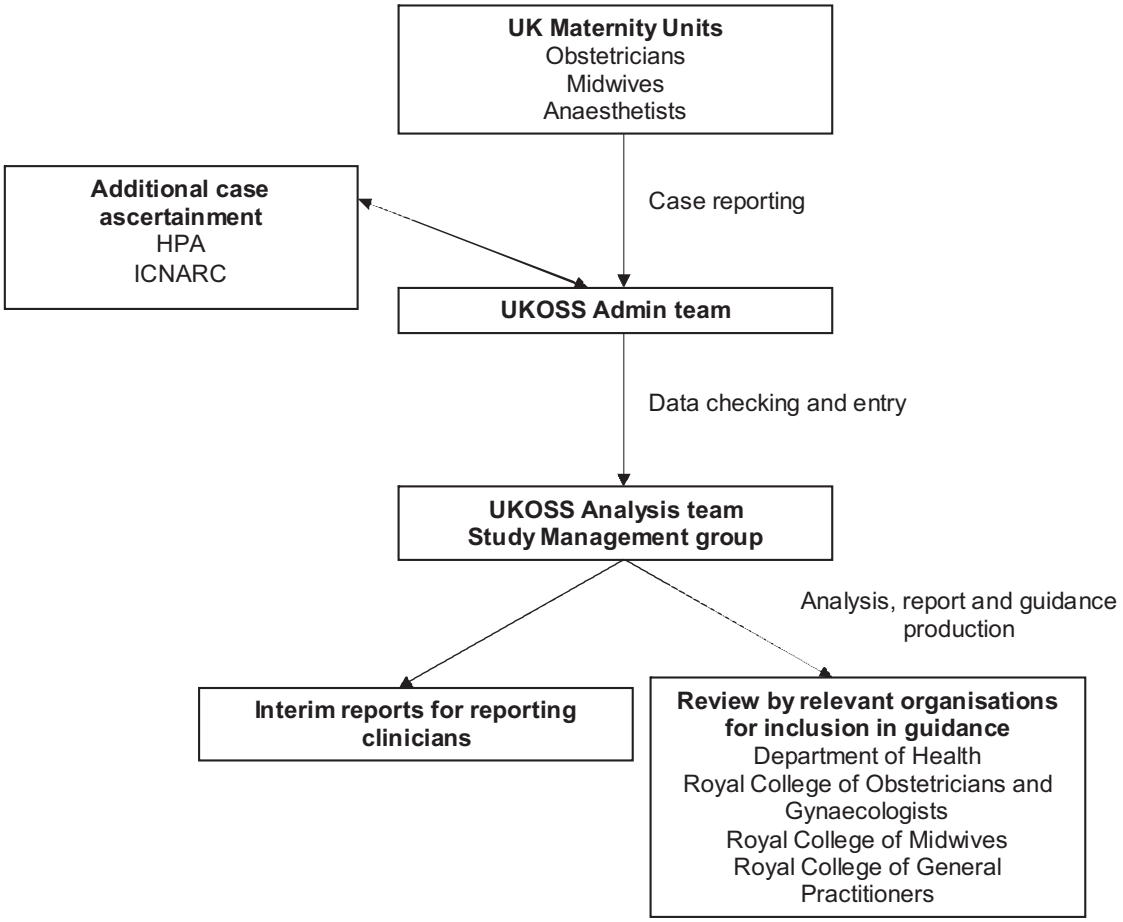
PO'B is the Royal College of Obstetricians and Gynaecologists lead for pandemic influenza planning and will provide a direct link to produce ongoing updated guidance through the RCOG pandemic influenza planning group.

5 Service Users

Lay representatives from the UKOSS Steering Committee and Sands, the stillbirth and neonatal death charity, have been consulted about the development and acceptability of the study protocol, data collection form, information and other materials.

As all data collected will be anonymous, we cannot feedback results directly to women whose data are included in the study. The research team will therefore work directly with Sands, the stillbirth and neonatal death charity, and the NCT (formerly National Childbirth Trust), as well as available net fora such as Mumsnet, to ensure that results and advice are disseminated widely to pregnant women and their partners. The NPEU has an active user and voluntary organisations advisory group through whom dissemination will also be undertaken.

6 Flow diagram



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