Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant

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Abstract

Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant

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Background: In April 2009 a novel influenza A virus (AHINIv) of swine origin (swine flu) emerged, spreading rapidly and achieving pandemic status in June 2009. Pregnant women were identified as being at high risk of severe influenza-related complications and as a priority group for vaccination against AHINIv. Limited information was available about the maternal and fetal risks of AHINIv infection or of antiviral drug or AHINIv vaccine use in pregnancy.

Objectives: To assess rates of and risk factors for adverse outcomes following AHINIv infection in pregnancy and to assess the adverse effects of the antiviral drugs and vaccines used in prevention and management.

Methods: Prospective national cohort studies were conducted to identify pregnant women who were (1) suspected to be infected with AHINIv or being treated with antiviral medication in primary care; (2) vaccinated against AHINIv; and (3) admitted to hospital with confirmed AHINIv. Characteristics of women with influenza-like illness (ILI) in primary care were compared with those of women without symptoms accepting or declining immunisation. Characteristics of women admitted to hospital with confirmed AHINIv infection in pregnancy were compared with a historical cohort of over 1200 women giving birth in the UK who were uninfected with AHINIv. Outcomes examined in hospitalised women included maternal death, admission to an intensive care unit, perinatal mortality and preterm birth. Risk factors for hospital and intensive care unit admission were examined in a full regression model.

Results: The weekly incidence of ILI among pregnant women averaged 51/100,000 over the study period. Antiviral drugs were offered to 4.8% [95% confidence interval (CI) 4.0% to 5.9%] and vaccination to 64.8% (95% CI 64.7% to 68.9%) of registered pregnant women. Ninety pregnant women with ILI presenting in primary care were reported to the research team, 55 of whom were prescribed antiviral drugs and in 42 (76%) cases this was within 2 days of symptom onset. After comparison with 1329 uninfected pregnant women offered vaccination, pre-existing asthma was the only maternal factor identified as increasing risk of ILI presentation [adjusted odds ratio (OR) 2.0, 95% CI 1.0 to 3.9]. Maternal obesity and smoking during pregnancy were also associated with hospital admission with AHINIv infection. Overall, 241 pregnant women were admitted to hospital with laboratory-confirmed AHINIv infection. Eighty-three per cent of these women were treated with antiviral agents, but only 6% received antiviral treatment before hospital admission. Treatment within 2 days of symptom onset was associated with an 84% reduction in the odds of admission to an intensive therapy unit (OR 0.16, 95% CI 0.08 to 0.34). Women admitted to hospital with

AH1N1v infection were more likely to deliver preterm; a three times increased risk was suggested compared with an uninfected population cohort (OR 3.1, 95% CI 2.1 to 4.5).

Conclusions: Earlier treatment with antiviral agents is associated with improved outcomes for pregnant women and further actions are needed in future pandemics to ensure that antiviral agents and vaccines are provided promptly to pregnant women, particularly in the primary care setting. Further research is needed on longer-term outcomes for infants exposed to AH1N1v influenza, antiviral drugs or vaccines during pregnancy.

Contents

List of abbreviations

AH1N1v	influenza A (H1N1) 2009 virus
aOR	adjusted odds ratio
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMACE	Centre for Maternal and Child Enquiries
GP	general practitioner
HCP	health-care professional
HPA	Health Protection Agency
ILI	influenza-like illness
IMD	index of multiple deprivation
ITU	intensive therapy unit
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NPIS	National Poisons Information Service
NTD	neural tube defect
OR	odds ratio
PCRN	Primary Care Research Network
RCOG	Royal College of Obstetricians and Gynaecologists
RM&G	research management and governance
UKOSS	UK Obstetric Surveillance System
UKTIS	United Kingdom Teratology Information Service
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

April 2009 saw the emergence of a novel influenza A virus of swine origin (swine flu), subsequently subtyped (and referred to in this document) as AH1N1v. This spread rapidly, achieving pandemic status in June 2009. Pregnant women were identified as being at high risk of severe influenza-related complications, requiring early assessment and treatment of flu-like symptoms, and as a priority group for vaccination against AH1N1v. There was, however, limited information available about the maternal and fetal risks of AH1N1v infection or of antiviral drug or AH1N1v vaccine use in pregnancy. This study was therefore designed to assess rates of and risk factors for adverse outcomes following AH1N1v infection in pregnancy and to assess the adverse effects of the antiviral drugs and vaccines used in prevention and management.

Objectives

The objectives of this research were to:

1. estimate the incidence of AH1N1v influenza in pregnancy during the 'second wave'
2. determine the effect of AH1N1v infection and/or treatment with neuraminidase antiviral drugs in pregnant women and/or AH1N1v vaccination (timing of use, dose and agent) on pregnancy outcome, including specific adverse or beneficial effects of antiviral treatment or AH1N1v vaccination on eventual maternal and fetal outcome
3. ascertain the influence of demographic or pregnancy characteristics and additional aspects of pregnancy management on outcomes for mother and infant
4. produce guidance on the management of AH1N1v infection in pregnancy: initially following systematic review and updated subsequently by monthly review of emerging data from this study such that outcomes for women and infants could be optimised during the current pandemic.

Methods

Prospective national cohort studies were conducted using different sources to identify women in three specific groups:

1. pregnant women suspected of being infected with AH1N1v or treated with antiviral medication and managed in the community
2. pregnant women vaccinated against AH1N1v
3. pregnant women admitted to hospital with confirmed AH1N1v.

Information about pregnancy management and outcomes was collected directly from health professionals caring for infected women in secondary care settings, and from health professionals as well as women themselves, with consent, where infection was managed in primary care.

Women were identified through the following sources:

1. The UK Teratology Information Service (UKTIS) collected data from general practices within and outside the Primary Care Research Networks (PCRNs), as well as from self-notifications from affected women. Some practices acted as 'sentinel' sites, providing data on all presentations, antiviral prescriptions and vaccinations.
2. The UK Obstetric Surveillance System (UKOSS) collected data through its network of collaborating clinicians in all consultant-led maternity units in the UK.

Characteristics of women with influenza-like illness (ILI) in primary care were compared with those of women without symptoms accepting or declining immunisation. Characteristics of women admitted to hospital with confirmed AH1N1v infection in pregnancy were compared with a historical cohort of over 1200 women giving birth in the UK, identified from the same hospitals as the cohort women and uninfected with AH1N1v.

The incidences of suspected AH1N1v infection, use of antiviral drugs and AH1N1v vaccination were estimated from presentation data provided by sentinel general practices. Characteristics of women with ILI were compared with asymptomatic women who were offered vaccination. Use and timing of antiviral agents and uptake of AH1N1v vaccines were also determined.

The incidence of hospitalisation with confirmed AH1N1v influenza in pregnancy was estimated with 95% confidence intervals (CIs) using the most recently available birth data (2007) as a proxy for September 2009 to January 2010. Outcomes examined in hospitalised women included maternal death, admission to an intensive care unit, perinatal mortality and preterm birth. In addition, risk factors for hospital and intensive care unit admission were examined in a full regression model, which was developed by including both potential explanatory and confounding factors in a core model if there was a pre-existing hypothesis or evidence to suggest that they were causally related to admission with AH1N1v influenza in pregnancy.

Results

The weekly incidence of ILI amongst pregnant women in 24 sentinel practices averaged 51/100,000 over the period of study. In the 23 practices providing these data, antiviral drugs were offered to 4.8% (95% CI 4.0% to 5.9%) and vaccination to 64.8% (95% CI 64.7% to 68.9%) of registered pregnant women.

A total of 90 pregnant women with ILI presenting in primary care were reported to the research team: 55 were prescribed antiviral drugs and in 42 (76%) cases this was within 2 days of symptom onset. After comparison with 1329 uninfected pregnant women who were offered vaccination, the only maternal factor identified as increasing odds of ILI presentation was pre-existing asthma [adjusted odds ratio (aOR) 2.0, 95% CI 1.0 to 3.9]. In this small data set there was no significant effect of other comorbid conditions or of age, racial group, body mass index (BMI), index of multiple deprivation (IMD) or smoking status. The data suggest that vaccination occurred in 56% of pregnant women who were offered it, although information on whether or not vaccination was offered was not always provided.

Overall, 241 pregnant women were admitted to hospital with laboratory-confirmed AH1N1v infection. Eighty-three per cent of women who were hospitalised with AH1N1v influenza were treated with antiviral agents, but only 6% received antiviral treatment before hospital admission.

Women hospitalised with AH1N1v influenza in pregnancy were more likely to be overweight (aOR 1.7, 95% CI 1.2 to 2.4) or obese (aOR 2.0, 95% CI 1.3 to 3.0) than the comparison cohort. They were also more likely to have asthma requiring inhaled or oral steroids (aOR 2.3, 95% CI 1.4 to 3.9), to be multiparous (aOR 1.6, 95% CI 1.1 to 2.2), to have a multiple pregnancy (aOR 5.2, 95% CI 1.9 to 13.8) and to be from a black or other minority ethnic group (aOR 1.6, 95% CI 1.1 to 2.3). Younger smokers had a raised odds of admission with confirmed AH1N1v influenza (aOR 4.2, 95% CI 2.0 to 8.9) when compared with older non-smokers.

Treatment within 2 days of symptom onset was associated with an 84% reduction in the odds of admission to an intensive therapy unit (ITU) (OR 0.16, 95% CI 0.08 to 0.34); women admitted to ITU were more likely to be obese (aOR 3.4, 95% CI 1.2 to 9.2) than women who were not admitted to an ITU.

Sixty-three per cent of hospitalised women had completed their pregnancies at the time of reporting. Women admitted to hospital with AH1N1v infection were more likely to deliver preterm; a conservative estimate accounting for the high proportion of women who are undelivered suggests a three times increased risk compared with an uninfected population cohort (OR 3.1, 95% CI 2.1 to 4.5).

Conclusions

Earlier treatment with antiviral agents is associated with improved outcomes for pregnant women. Further actions are needed in future pandemics to ensure that antiviral agents and vaccines are provided promptly to pregnant women, particularly in the primary care setting.

Maternal obesity during pregnancy is associated with both admission to hospital with confirmed infection and critical illness from AH1N1v infection. This highlights the importance of ongoing work to support obesity prevention at a community level.

Maternal smoking, particularly in younger mothers, is also associated with admission with

AH1N1v infection in pregnancy. Smoking in pregnancy is associated with a number of risks to both mother and fetus and thus prevention programmes continue to be important.

Women with asthma and other comorbidities are more likely to present in primary care or be admitted to hospital with AH1N1v infection in pregnancy. Clinicians should be aware of this association and work to ensure that women with coexisting illnesses in pregnancy are treated appropriately.

Data on outcomes of pregnancy in women admitted to hospital with confirmed AH1N1v influenza are, as yet, incomplete. However, there appears to be a significantly increased risk of preterm delivery, which may impact on service provision in a future pandemic.

Further research is needed on longer-term outcomes for infants exposed to AH1N1v influenza, antiviral drugs or vaccines during pregnancy. This includes studies of the effects of these factors on:

1. fetal development and congenital malformations
2. postnatal development
3. potentially associated conditions, such as childhood leukaemia.

Chapter 1
Background

2009 AH1N1v influenza

April 2009 saw the emergence of a novel influenza A virus of swine origin, subsequently subtyped (and referred to in this report) as AH1N1v. Over the subsequent months, this AH1N1v or swine flu virus spread rapidly among humans, achieving pandemic status on 11 June 2009, as declared by the World Health Organization (WHO). The detection of avian influenza H5N1 in humans less than a year previously had stimulated preparation for a possible influenza pandemic. A document produced in anticipation of such an event by the Centers for Disease Control and Prevention (CDC) in the USA[1] identified pregnant women as being at high risk of severe influenza-related complications. Concerns about the effect of AH1N1v infection in pregnancy were further highlighted following the death of a previously healthy pregnant woman in the USA as the second documented death associated with the 2009 outbreak. In the UK, the Department of Health identified pregnant women as a high-risk group requiring early assessment and treatment of flu-like symptoms at the beginning of the pandemic, and, subsequently, as a priority group for vaccination against AH1N1v.

Influenza in pregnancy

Maternal risks

Reports from previous influenza epidemics, such as the Spanish influenza pandemic of 1918–19, and research on seasonal influenza, have been cited as evidence that pregnant women are at risk of increased maternal mortality and morbidity from influenza infection compared with non-pregnant women.[2]

There are inconsistent data, however, regarding the risk of complications in pregnancy after influenza infection. A hospital database-matched cohort study by Cox *et al.* in the USA[3] identified pregnant women with underlying respiratory conditions as having longer hospital admissions and increased delivery complications during the influenza season than hospitalised pregnant women without comorbid respiratory conditions. An earlier study in the USA by Hartert *et al.*,[4] using a similar design but in which influenza and non-influenza cases were matched for comorbid conditions and trimester of pregnancy, failed to identify a significant difference in mode of delivery, duration of delivery admission, episodes of preterm labour and adverse perinatal outcomes between the two groups. The authors did identify, however, that miscarriages, early neonatal deaths and maternal deaths were not studied, potentially resulting in an underestimate of maternal and perinatal mortality.

Pregnant women, particularly in the third trimester of pregnancy, have been reported as being at a higher risk of developing influenza-associated pneumonia and cardiorespiratory complications.[5,6]

Fetal risks

In addition to the maternal risks, there are concerns about the direct and indirect effects of maternal influenza infection on the fetus. An increased risk of spontaneous abortion[7] and stillbirth[8] have been reported in pregnant women with influenza, and there are inconsistent data to suggest that maternal influenza may be associated with an increased risk of certain congenital malformations, including oesophageal atresia[9] and anophthalmos/microphthalmos.[10] An increased risk of anencephaly was also reported following epidemics of Asian influenza.[11–13]

The Hungarian Case–Control Surveillance of Congenital Abnormalities reported an association between maternal influenza during the second and third month of pregnancy and congenital malformations in the offspring, including cleft lip or palate, neural tube defects (NTDs) and cardiovascular abnormalities.[14] In this study the use of antipyretic drugs reduced the risk of congenital malformations, suggesting that these might be due to fever. Use of folic acid supplements reduced or eliminated the apparent risk associated with influenza during pregnancy.

A further case–control study, involving 363 infants with NTDs and 523 normal newborns, indicated an increased risk of NTDs associated with maternal

influenza. However, in this study, risk was enhanced when antipyretic drugs were used, in contrast with the findings of the Hungarian study described above.[15]

Antiviral therapy during pregnancy

Oseltamivir (Tamiflu®, Roche Products) and zanamivir (Relenza®, GlaxoSmithKline) are neuraminidase inhibitors that are effective in the treatment and prophylaxis of influenza types A and B in adults. AH1N1v has been shown to be susceptible to these agents. These drugs prevent viral release from infected cells and subsequent infection of adjacent cells. The National Institute for Health and Clinical Excellence (NICE) has concluded that both of these agents are clinically effective treatments for influenza in the general population,[16] with no clear distinctions between the two agents on the basis of clinical efficacy, and that both are effective for seasonal or postexposure prophylaxis.[17] Oseltamivir is readily absorbed from the gastrointestinal tract following oral administration, and has significant systemic activity.[18] Zanamivir is administered through inhalation and has lower systemic bioavailability.[19] It may therefore be less suitable for severe systemic illness, but low transplacental bioavailability may reduce risks of adverse fetal effects.

Limited information was available on the safety of neuraminidase inhibitor use during pregnancy prior to the AH1N1v pandemic. A review article cited a total of 61 cases of oseltamivir exposure in pregnancy, collected during postmarketing surveillance.[20] Although complete details of these cases were not provided, the majority of pregnancies were reported to result in a normal baby. Ten abortions (of which six were therapeutic – no further details provided) were reported. There were also single cases of trisomy 21 and anencephaly; in both cases causality was considered as not related to treatment with oseltamivir.

There were no epidemiological studies regarding exposure to zanamivir during human pregnancy. Three pregnancies were reported during preclinical marketing studies carried out by the manufacturer; of these pregnancies, one resulted in the birth of a normal healthy baby, one pregnancy was terminated electively and one resulted in a spontaneous abortion. No other details were available.[21]

Influenza vaccination during pregnancy

Published outcome data on the use of seasonal influenza vaccines during pregnancy have not indicated an association with an increased incidence of congenital malformations.[22–30] However, the majority of reports focused on use during the second and third trimesters of pregnancy, after organogenesis has taken place.

In a prospective cohort study comparing 189 women who were vaccinated with the influenza A vaccine during pregnancy (41 of whom were vaccinated in the first trimester) with a control group of 517 non-vaccinated women, the rate of congenital malformations was within the expected range in both groups.[24] In addition, no increase in perinatal or infant complications was observed following maternal vaccination. A prospective longitudinal, population-based study by the Collaborative Perinatal Project published findings from 650 pregnant women who were given seasonal influenza vaccinations in the first 4 months of pregnancy.[23] After follow-up from birth to 7 years of age, there was no observed increase in risk of stillbirth, congenital malformation, childhood cancer or neurocognitive disability in the offspring.

Other prospectively and retrospectively gathered data have not indicated an increased incidence of adverse pregnancy outcomes in over 4000 pregnant women who received the influenza vaccine during the second or third trimesters of pregnancy.[23–29]

A recent randomised controlled trial found that immunisation of pregnant women against influenza in the third trimester ($n = 172$) reduced the rate of influenza-like illness (ILI) in the mothers and children by 29% and reduced laboratory-proven influenza infections in 0- to 6-month-olds by 63% (95% CI 5% to 85%).[27] The authors did not report any congenital malformations or adverse fetal effects that were attributable to vaccination in the influenza vaccine-exposed infants. The rates of maternal, neonatal and infant mortality were all within the expected ranges.

Review of published and unpublished data from the first AH1N1v influenza wave up to September 2009

Prior to commencing recruitment for this study, a systematic search for information about AH1N1v influenza and its treatment in pregnancy was performed by the research team and has been reported separately.[31] In addition to reviewing data published in the scientific literature, this also considered evidence provided by antiviral manufacturers, teratology information services and drug regulatory bodies. Interpretation of data identified in this systematic review was difficult because important information was often missing or incomplete, and there was overlap of data collected from different sources, the extent of which was uncertain. Pooling of published data from different sources identified reports involving 135 pregnant women with AH1N1v infection.

Mortality

Mortality in this group of 135 women was high, with death occurring in at least 26 of the women involved. However, these reports addressed the characteristics of patients with AH1N1v influenza who were admitted to hospital and/or who died. It is thus likely that this published literature is heavily biased towards reporting of severe or fatal cases. Estimation of mortality from these data is likely to be very misleading.

Comorbidity

Comorbidity was also common amongst these published cases. At least 26 (19.4%) of the 135 pregnant women with swine flu were reported to have coexisting medical conditions. These included asthma, tuberculosis, heart disease, diabetes, hypertension and hyperthyroidism, obesity and Factor V Leiden deficiency. It should be noted that three (50%) out of the six women reported by Jamieson *et al*.[2] to have died had underlying health conditions, as did 8 out of the 16 fatal cases reported by Vaillant *et al*.[32] Although comorbidity is reported in other case series, it is not clear from the data presented whether this correlates with a higher risk of hospital admission or of death. Asthma was the most frequently reported associated chronic illness in these women, in keeping with experience from the study of Hartert *et al*.[4] on seasonal influenza, in which pregnant women with asthma accounted for one-half of all respiratory admissions during influenza seasons.

Trimester of illness

It has been widely quoted that women in the third trimester of pregnancy are at increased risk of hospitalisation due to respiratory illness during the influenza season.[6] With respect to the published literature on the 2009 AH1N1v pandemic, most papers do not report on pregnancy trimester for the women admitted to hospital or who die. Although the numbers are too small to identify a statistically significant difference between hospitalisation rate and case fatality rate by trimester of pregnancy for the cases reported by Jain *et al*.[33] and Jamieson *et al*.,[2] respectively, the absolute number and percentage of women affected in the third trimester is greater than the percentage of women in the first and second trimesters. This may reflect a trend of increased risk to women in the third trimester of pregnancy. It should be emphasised, however, that none of the 16 deaths from AH1N1v infection in pregnancy reported by Vaillant *et al*.[32] was categorised by trimester.

Timing of antiviral treatment

Only two articles provided details of the interval between onset of symptoms and initiation of antiviral treatment.[2,34] Of the 34 women described in the study of Jamieson *et al*.,[2] 17 received treatment with oseltamivir and eight were treated within 2 days of symptom onset. The six women who died received antiviral drugs, a median of 9 days (range 6–15) after symptom onset. No details of antiviral treatment were provided in any of the other studies.

Fetal risks

From the data available thus far, no clear pattern of congenital abnormalities suggestive of teratogenicity due to oseltamivir or zanamivir exposure has emerged. Information on fetal outcome is not available for the majority of AH1N1v infection in pregnancy cases referred to in the published literature, as many of these women were still pregnant at the time of publication. This is in keeping with the lack of outcome data available from the UK and other teratology information services. Interestingly, live born infants were delivered by caesarean section to five of the six fatal cases described by Jamieson

et al.[2] and were doing well with no evidence of influenza infection. The sixth case was associated with a miscarriage at 11 weeks' gestation at the time of maternal death. At the time of writing, it was too early in the pandemic to expect sufficient information regarding congenital malformation rates in babies born to mothers infected with AH1N1v in the first trimester.

Preparation for the AH1N1v (2009) influenza 'second wave'

As the initial peak of the 2009 AH1N1v pandemic subsided in the summer, predictions were made about a second, potentially more virulent, wave of AH1N1v influenza emerging in the autumn of 2009. In anticipation of a second peak, expedited AH1N1v research was identified as a government priority, and the need for evidence-based guidance of the management of AH1N1v (2009) influenza in pregnancy during the second wave was evident. In particular, there was a need to better characterise the adverse maternal and fetal effects of influenza infection involving this new pandemic strain, and to obtain more data on the safety of antiviral therapy during pregnancy. Subsequently, following the licensing of vaccines for AH1N1v, there was a need to collect information on the safety of these vaccines when used in pregnancy.

This study, one of several commissioned by the National Institute for Health Research (NIHR), aimed to collect information on pregnant women during the second wave of the pandemic, with a view to providing interim analyses of the data to inform guidance on the management of AH1N1v infection in pregnancy.

Study objectives

The objectives of this research were to:

1. estimate the incidence of AH1N1v influenza in pregnancy during the second wave
2. determine the effect of AH1N1v influenza infection and/or treatment with neuraminidase antiviral drugs in pregnant women and/or AH1N1v vaccination (timing of use, dose and agent) on pregnancy outcome, including specific adverse or beneficial effects of antiviral treatment or AH1N1v vaccination on eventual maternal and fetal outcome
3. ascertain the influence of demographic or pregnancy characteristics and additional aspects of pregnancy management on outcomes for mother and infant
4. produce guidance on the management of AH1N1v infection in pregnancy: initially following systematic review, updated subsequently by monthly review of emerging data from this study such that outcomes for women and infants could be optimised during the current pandemic.

This report describes study results for the period September 2009 to January 2010, concentrating on clinical outcomes of episodes of influenza in pregnant women. Data collection is continuing and further information on pregnancy and fetal outcomes will be published when this is available.

Chapter 2
Methods

The research described in this report comprises two separate prospective observational cohort studies. In one, information was collected with consent from pregnant women who were recruited in the primary care setting and met the study inclusion criteria. This research was lead by the UK Teratology Information Service (UKTIS). The second study, performed in a secondary care setting, used anonymised data collected by the UK Obstetric Surveillance System (UKOSS) on pregnant women with confirmed influenza who were admitted to hospital. These two studies were intended to provide data on the full spectrum of AH1N1v infection and its management during pregnancy. Information on participants was collected directly from heath professionals caring for these women in secondary care settings, and from health professionals, as well as the women themselves, for women recruited in primary care.

Health professionals were made aware of the study via information on the National Poisons Information Service (NPIS) online database TOXBASE® and websites of the UKTIS, UKOSS, Royal College of Obstetricians and Gynaecologists (RCOG) and Medicines and Healthcare Products Regulatory Agency (MHRA), and via advice provided on AH1N1v influenza by the Health Protection Agency (HPA). Recruitment in primary care was encouraged across the UK and was supported by the Primary Care Research Networks (PCRNs).

Women with suspected AH1N1v infection or antiviral exposure managed in primary care

Case definition

Initially, pregnant women in the UK with confirmed or suspected AH1N1v influenza, or, who were offered antiviral medication for treatment or prophylaxis, were eligible for inclusion in the study. The study protocol was subsequently amended in November 2009 (see details for assessing the full study protocol at the end of the paragraph), following licensing of AH1N1v vaccines, to allow in addition the recruitment of pregnant women offered immunisation against AH1N1v influenza (full study protocol available at www.uktis.org).

Influenza cases were defined as pregnant women with suspected or confirmed AH1N1v influenza. Antiviral exposure cases included women exposed to antiviral medication in pregnancy, either for treatment of suspected swine flu or as prophylaxis. AH1N1v vaccination cases were defined as pregnant women vaccinated with the AH1N1v vaccine. Data were also sought from pregnant women who were offered, but were not subsequently undergoing, vaccination. Data provided in this report include women who had suspected AH1N1v infection or antiviral treatment or were offered immunisation between 7 September 2009 and 29 January 2010.

Data collection

Women presenting in primary care with suspected AH1N1v infection were notified to UKTIS by health professionals when clinical advice was sought from the service, by means of a dedicated UKTIS swine flu reporting line or by reporting form available for download from the UKTIS website. In addition, the MHRA and HPA Regional Microbiology Laboratory Network alerted clinicians to the study when they reported adverse events or sent specimens. Clinicians were then asked to seek consent from patients for their details to be provided to UKTIS. Women were also invited to self-report to UKTIS via the dedicated swine flu reporting telephone line referred to above.

Brief clinical details of women identified by their health professionals or identifying themselves to the research team were collected. Health professionals sought verbal consent from eligible women for the provision of this personally identifiable information to UKTIS, to allow an approach for written consent to participate from the research team.

Potential participants were then sent a participant information sheet and consent documentation, together with an initial data collection sheet that they were asked to complete if they wished to take part. Only women providing written consent were asked to provide further health information.

The reporting health professional was asked to alert the research team should the status of the patient change after initial notification, to avoid the small risk of contacting individuals who might have died or experienced a distressing or adverse pregnancy outcome. In these cases, information was collected from the health professional only when consent to do so had been granted. For cases where women were notified with suspected swine flu, further information on the illness was sought from the participant and health professional 4 weeks after initial contact. Patients who remained unwell from influenza continued to be followed up at 4-weekly intervals until recovery. If the patient had recovered, the next follow-up was planned for approximately 2 weeks after the expected date of delivery, in order to obtain maternal and pregnancy outcome information, again collected from the woman and her health professional. If a completed data collection form was not received back by UKTIS after 3 weeks, a further reminder was sent. Anonymised details of patients declining participation were also notified to UKTIS.

Participants and health professionals were offered the opportunity to report any additional information of relevance to the study (e.g. illnesses, exposures or pregnancy complications) at any point during the study in addition to the planned follow-up intervals.

Virological testing of women with suspected AH1N1v infection

Virological confirmation of infection was not a requirement for participation in the primary care element of the study, but details of those who had not been tested for AH1N1v in a diagnostic setting were forwarded to the HPA North East virology laboratory, with their consent. A self-administered swabbing kit was provided to the participant by post from the UKTIS research team, enclosed with the initial participant information sheet, and consent forms as detailed below. The kit comprised two viral swabs, an instruction leaflet and a prepaid envelope with the necessary transport tubes for return of the sample to the virology laboratory. Given the known difficulties of obtaining informative throat swabs by self-testing, a nasal swab from each nostril was requested. This is thought to achieve an equivalent diagnostic yield. Swabs returned through research testing were processed immediately by the HPA North East virology laboratory to extract and store total nucleic acids and tested for AH1N1v. Testing including extraction, amplification and detection was performed in accordance with the national standard operating procedures for detection of AH1N1v. Samples needing additional testing to clarify status were referred to the HPA Centre for Infections, Colindale, London.

Assessment of incidence in primary care

The incidence of presentation in primary care with ILI and of use of antiviral therapy and vaccination was estimated by collecting all cases from selected general practives agreeing to act as 'sentinel' sites. These practices were asked to submit weekly anonymised data, with null reporting, of all pregnant women consulting with suspected swine flu, prescribed antiviral drugs, offered AH1N1v vaccination and receiving the AH1N1v vaccine over the period of study. Details were also provided of practice list sizes and the numbers of women aged 15–45 years, as well as the numbers of women in the practices who were recorded as being pregnant on 1 December 2009.

Comparison groups

The characteristics of pregnant women with suspected or confirmed AH1N1v influenza were compared with those of pregnant women who did not report influenza-like symptoms and who were not treated with antiviral drugs, but who qualified for inclusion in the study because they were offered vaccination and consented to provide their details to the research team. Information from women receiving AH1N1v vaccination in pregnancy was compared with that collected from participants who were offered vaccination but not vaccinated.

Sample size

The available sample size was dependent on rates of infection, antiviral use or vaccination among pregnant women, the list sizes of participating general practices, the proportion of potential participants who provided consent for data handling and subsequent follow-up, and the UK maternity rate (around 760,000 maternities per year at the outset of the study). With the limited available data from the first wave of AH1N1v influenza and assuming similar rates of presentation, we anticipated identifying 500–1000 affected pregnancies, using the combined UKTIS and UKOSS approach, over the 6-month initial study period.

Statistical analyses

Index of multiple deprivation (IMD) scores were obtained by linking patients' postcodes to small geographical areas referred to as Super Output Areas (SOAs). IMD scores[35] are publicly available continuous measures of compound social and material deprivation, and are calculated using a variety of data including current income, employment, health, education and housing. As the IMD score increases, the level of deprivation increases.

Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) for women displaying swine flu symptoms compared with women not displaying symptoms nor taking antiviral drugs were estimated for potential risk factors, using unconditional logistic regression and adjusted for putative confounding factors. A full regression model was developed by including both potential explanatory and confounding factors in a core model if there was a pre-existing hypothesis or evidence to suggest that they were causally related to AH1N1v influenza in pregnancy, for example asthma. Potential interactions were tested by the addition of interaction terms between all variables in the model and subsequent likelihood ratio testing on removal. Data for case and comparison women were compared using the chi-squared test – $p < 0.05$ was considered evidence for a significant interaction.

Secondary care hospital admission with confirmed AH1N1v infection in pregnancy

Case definition

Cases were defined as any pregnant women admitted to hospital in the UK with confirmed AH1N1v infection between 1 September 2009 and 31 January 2010. Women with AH1N1v infection in pregnancy who were not admitted to hospital and women with AH1N1v infection diagnosed post partum were excluded from this arm of the study.

Data collection

Cases were identified through the UKOSS network of collaborating clinicians.[36] In view of the need for rapid and ongoing data analysis, clinicians were asked to report, using a web-based rapid reporting system, all pregnant women with confirmed AH1N1v infection who were admitted to their unit, as soon as possible after the woman's admission. In response to a report of a case, clinicians were able to download a data collection form with a unique UKOSS identification number, asking for further detailed information about diagnosis, management and outcomes. If a completed data collection form was not received back by the central team after 3 weeks, a reminder letter was sent. A further reminder was sent 6 weeks after the initial case report, and, if the completed form had not been received after 9 weeks, a further prompt was sent with a new copy of the form to complete.

In addition, every 2 weeks nominated UKOSS reporting clinicians were sent a summary detailing the cases that had been reported from their unit and were asked to confirm that there were no additional cases to report. Clinicians were also asked to return a 'nil report' indicating that there had been no women admitted so that participation could be monitored and the denominator population for the study could be confirmed. The cases included in this report include all data returned up to, and including, 23 February 2010.

All data were double-entered into a customised database. Cases were checked to confirm that they met the case definition and to exclude duplicate reports. Where data were missing or the response invalid, the reporting clinician was contacted by e-mail and asked for the correct information. If the woman was undelivered at the time of discharge following her AH1N1v infection, a further copy of the data collection form was sent to the reporting clinician 2 weeks after the expected date of delivery in order to obtain details of the outcome of pregnancy.

All information collected was anonymous.

Additional case ascertainment

At the end of the data collection period, the Centre for Maternal and Child Enquiries (CMACE) was contacted and provided with information on cases of maternal death in association with AH1N1v infection in pregnancy reported through UKOSS, identifying the hospital and date of death. They were asked to compare the cases they had identified with the cases reported to UKOSS.

Comparison group

Information about comparison women delivering in UK hospitals was obtained from previously collected UKOSS data. The comparison women

were identified by UKOSS reporters as the two women delivering in the same hospital immediately before other UKOSS cases.[37] This cohort was chosen for pragmatic reasons to facilitate rapid comparisons during the epidemic, and, as a historical cohort, to ensure that none of the women could have been infected with AH1N1v.

Statistical analyses

The incidence of hospitalisation with confirmed AH1N1v influenza in pregnancy was estimated with 95% CIs using the most recently available birth data (2007) as a proxy for September 2009 to January 2010.[38]

Data for case and comparison women were compared using the chi-squared test or the Wilcoxon rank-sum test, as appropriate. Figures presented show the percentages of those with data. Unadjusted ORs with 95% CIs were estimated for potential risk and confounding factors using unconditional logistic regression. A full regression model was developed by including both potential explanatory and confounding factors in a core model if there was a pre-existing hypothesis or evidence to suggest that they were causally related to admission with AH1N1v influenza in pregnancy, for example asthma. Continuous variables were tested for departure from linearity, and potential interactions were tested by the addition of interaction terms between all variables in the model and subsequent likelihood ratio testing on removal – $p < 0.05$ was considered evidence for a significant interaction or departure from linearity.

The risk factors for admission to an intensive care unit were examined in a regression model including only women admitted to hospital with confirmed AH1N1v infection. This analysis had 80% power at the 5% level of statistical significance to detect an OR for obesity [body mass index (BMI) of 30 kg/m^2 or greater] in pregnancy of 3.0 or greater.

Interim reporting

During the pandemic, clinical guidance was produced by the Department of Health and RCOG. Rather than issuing potentially confusing additional guidance, the team informed the development of management guidelines through a series of reports to the organisations developing guidance. The data were analysed on an approximately monthly basis from November 2009. Interim reports were produced and made available to the Department of Health, the Influenza Clinical Information Network and the RCOG pandemic influenza working group, as well as to collaborating clinicians, in order to inform development of ongoing clinical guidance during the course of the pandemic. Interim reports were also publicly available on the UKOSS website.[39–41]

Research approvals

This study, and the subsequent protocol amendment allowing the inclusion of pregnant women undergoing vaccination, was approved by the County Durham & Tees Valley 1 Research Ethics Committee (study reference 09/H0905/66). The UKOSS general methodology has previously been approved by the London Research Ethics Committee (study reference 04/MRE02/45).

For the primary care element, research management and governance (RM&G) approval was required from all UK NHS organisations acting as participant identification sites for the original study and, subsequently, for the protocol amendment. This entailed applications to 319 NHS organisations for the original study and 192 organisations for the amendment.

Chapter 3
Results

Women identified in primary care

Incidence of AH1N1v influenza in pregnancy in primary care

Twenty-four general practices, including some linked to the PCRNs in England, Wales, Scotland and Northern Ireland, as well as some non-PCRN practices, provided complete weekly figures to UKTIS, with null reporting, of numbers of pregnant women consulting with suspected swine flu during the study period from 7 September 2009 to 29 January 2010 by the cut-off date of 8 March 2010. These sentinel practices had a combined list size of 216,193 women, including 45,647 who were aged 15–45 and 2431 (1.1%) who were recorded as pregnant as of 1 December 2009. These practices reported 26 consultations involving ILI in pregnant women over the 21 study weeks, giving a mean weekly consultation rate of 51/100,000 amongst pregnant women. As a proportion of all pregnant women, 1.1% (95% CI 0.7% to 1.6%) were reported to have presented with suspected influenza at some point during the study period.

Twenty-three of the practices (combined list size 189,245, with 2061 pregnant women and 40,555 women aged 15–45 years) also provided weekly data on prescribing of antiviral drugs and use of AH1N1v vaccination in pregnant women over the 21-week study period. Antiviral drugs were offered to 100 pregnant women (4.85%, 95% CI 3.98% to 5.89%) and vaccination to 1378 (64.8%, 95% CI 64.7% to 68.9%). Of the pregnant women who were offered vaccination, 520 were reported to have been vaccinated, representing 25.2% (95% CI 23.4% to 27.7%) of all pregnant women and 37.7% (95% CI 35.2% to 40.4%) of those reported to have been offered vaccination.

Recruitment of participants

In total, 159 general practices across the UK forwarded details of at least one pregnant woman who met UKTIS study inclusion criteria and who gave verbal consent for her/their details to be forwarded to the research team. The number of women notified per practice ranged from 1 to 69.

A total of 1587 women were notified to the research team for the period of study. Of these, 1565 were notified with their verbal consent by health professionals and 22 self-reported to the study team. Thirteen notifications from secondary care and 122 retrospective reports (121 health professionals and one self-report) were excluded because pregnancy outcome or an abnormal antenatal result was already known at the time of reporting. There were 1432 health-care reports that met the study inclusion criteria and were included in the current analysis (*Figure 1*).

The health professional reports comprised 90 patients with ILI, 55 of whom were treated with antiviral drugs; 13 patients without symptoms who received antiviral drugs; and 1329 women who were not reported to have influenza symptoms or to have received antiviral therapy but who met the study inclusion criteria because they were pregnant and were offered vaccination.

Of the 13 women reported via secondary care, nine were also included in the UKOSS data set described below, while three cases did not meet the UKOSS inclusion criteria for this study. One case had not been reported to UKOSS, but the information available for this woman was insufficient to determine whether or not she would have met the UKOSS case definition for inclusion in the hospital cohort. None of these women was included in the primary care analysis.

Of the 1565 women consenting verbally to their details being passed to the study team, 234 had provided written consent by the end of the data collection period to allow the study team to collect further information on their pregnancy outcome and infant's health at 6 months. In total, 263 women meeting the study inclusion criteria had completed the initial participant questionnaire; 26 women withdrew from the study during the period of this analysis.

Of the 90 women reported with influenza symptoms, 23 had been tested for AH1N1v at the time of reporting by a health professional. Of these, two swabs were AH1N1v positive, six were

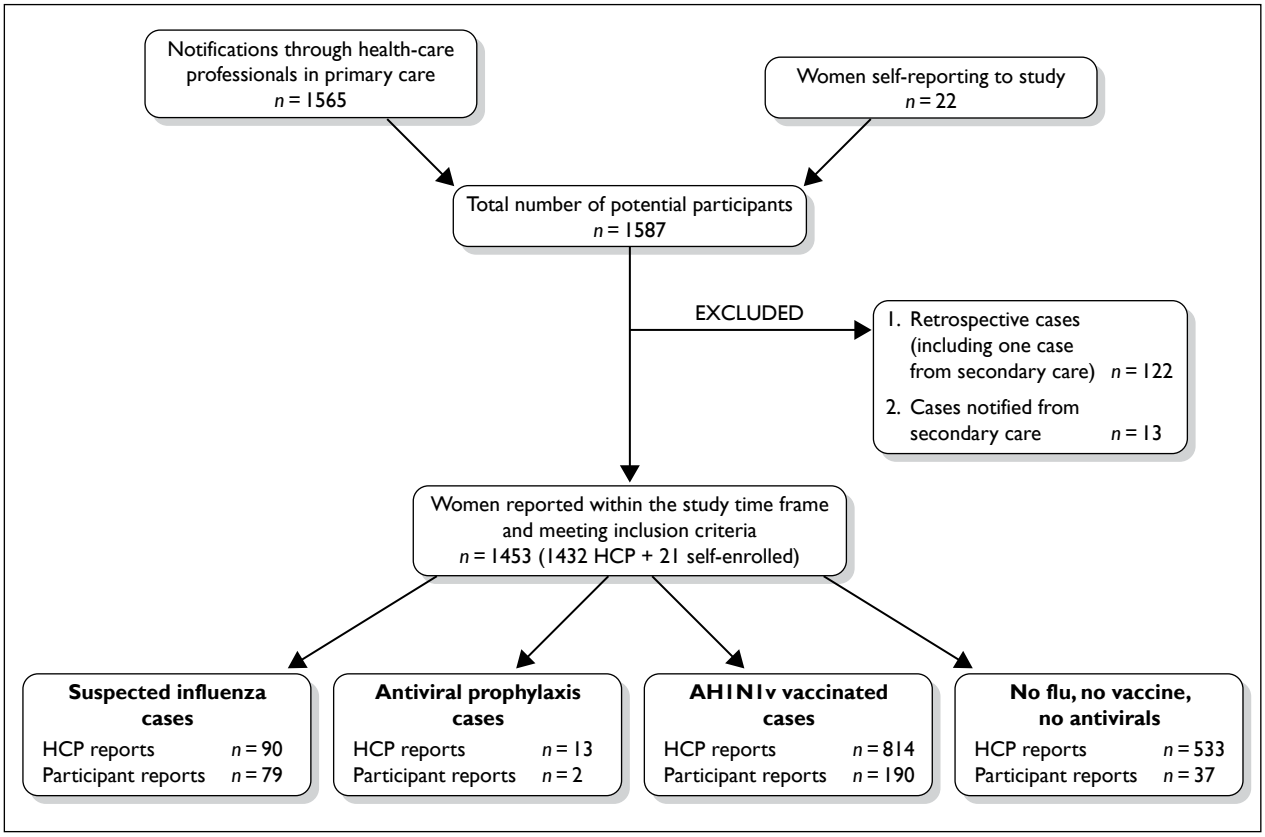

FIGURE 1 *Recruitment in primary care. HCP, health-care professional.*

AH1N1v negative and results were pending for 16 (one women whose initial swab was negative was swabbed again). The study team posted virology swabs to 25 women with suspected AH1N1v influenza or influenza symptoms who had not been tested as part of their routine health care. Of the 25 swabs sent, eight swabs were returned to the virology laboratory: two of these were positive and six were negative for AH1Nv and 17 swabs were not returned. Swabs were not sent to the remaining 42 participants as notification occurred outside the period of illness.

Characteristics of women with ILI

Characteristics of the 90 women reported from primary care with suspected or confirmed AH1N1v infection and those of the comparison cohort are detailed in *Table 1*. Of these, 14 (15.6%) were in their first trimester, 25 (27.8%) in their second trimester and 43 (47.8%) in their third trimester. The trimester was not specified on eight (8.9%) reports.

Factors associated with increased risk of presenting with ILI were assessed by comparing suspected influenza cases with a comparison group of 1329 women without reported symptoms or antiviral treatment offered vaccination. The characteristics of this control group of women are shown in *Table 2*.

The low number of cases limits the power of this analysis to compare the characteristics of pregnant women, described in *Tables 1* and *2*, with an ILI and those who were not ill. Nevertheless, we found a significant association between presentation with an ILI and asthma [adjusted OR (aOR) 2.0, 95% CI 1.0 to 3.9]; there were no statistically significant associations with other comorbid conditions or age (including as a continuous variable), racial group, BMI, IMD score or smoking status (*Table 3*).

Presenting symptoms of pregnant women with an ILI, as reported by their general practitioner (GP) or midwife, are shown in *Table 4*; fever ($n = 64$, 71%), cough ($n = 61$, 68%) and sore throat ($n = 54$, 60%) were the most frequent.

TABLE 1 *Characteristics of women notified with suspected AH1N1v infection in primary care (n = 90)*

			Trimester			
			I	II	III	Unknown
Cases	**All**	**(%)**	**14**	**25**	**43**	**8**
Age						
Unknown	9	(10)	0	5	3	1
< 20	2	(2)	0	2	0	0
20–34	71	(79)	13	16	36	6
≥ 35	8	(9)	1	2	4	1
Ethnicity						
British or white background	48	(53)	6	11	30	1
Black or other ethnic minority	11	(12)	4	0	6	1
Unknown	31	(34)				
Smoking behaviour						
Never smoked	34	(38)	8	7	16	3
Gave up	15	(17)	2	3	10	0
Current smoker	12	(13)	0	2	9	1
Unknown	29	(32)				
Comorbidity						
Asthma	14	(16)	3	3	6	2
Psychiatric illness	3	(3)	0	1	2	0
Diabetes	2	(2)	0	2	0	0
Obesity	4	(4)	1	1	2	0

Note: (a) some women fall into more than one group and (b) reporting forms were not always received from the health-care professional when women self-reported.

The information provided by health professionals indicated that 55 (61%) of women with influenza symptoms were prescribed zanamivir or oseltamivir. In 42 cases (76%) these were prescribed within 2 days of symptom onset (*Table 5*).

Thirty-five (39%) of the symptomatic women did not receive antiviral treatment. In 28 cases reasons were not provided; in the remaining cases reasons were: the antiviral drugs were offered but refused, the GP wanted to see the participant before prescribing treatment, the participant was worried about the effects of the antiviral drugs, symptoms were mild, the symptoms had resolved by the time the participant presented themselves at the surgery, and in two cases participants were prescribed antibiotics instead of antiviral drugs.

The only reported adverse effects attributed to antiviral use were vomiting in one woman taking zanamivir, and nausea and vomiting in one woman who was prescribed oseltamivir.

AH1N1v vaccination in pregnancy

Of the 1432 pregnant women reported to us for this study, 194 (13.5%) were not offered vaccination, often because the report predated availability of the vaccines. A further 406 declined vaccination and 814 women (56.8%) were reported as vaccinated. Other than injection site reactions, health professionals reported adverse effects infrequently (*Table 6*).

Data reported by participants

Data were received directly from 263 participants, 79 of whom had symptoms of ILI. Of these, eight had been tested for AH1N1v, with one positive and one negative result available and the remainder

TABLE 2 *Characteristics of comparison group of women with no influenza symptoms and no antiviral drug exposure (n = 1329)*

			Trimester			
			I	II	III	Unknown
Controls	**All**	**(%)**	**131**	**507**	**576**	**115**
Age						
Unknown	114	(9)	16	40	42	16
< 20	47	(4)	3	21	20	3
20–34	932	(70)	95	340	418	79
≥ 35	236	(18)	17	106	96	17
Ethnicity						
British or white background	743	(56)	78	290	334	41
Black or other ethnic minority	105	(8)	10	43	49	3
Unknown	481	(36)				
Smoking behaviour						
Never smoked	533	(40)	45	209	241	38
Gave up	243	(18)	25	89	119	10
Current	106	(8)	14	39	48	5
Unknown	447	(34)				
Comorbidity						
Asthma	95	(7)	5	36	48	6
Chronic kidney disease	1	(0)	0	1	0	0
Chronic lung disease	1	(0)	0	0	1	0
Chronic liver disease	1	(0)	0	1	0	0
Chronic heart disease	1	(0)	1	0	0	0
Chronic neurological disease	9	(1)	0	4	4	1
Obesity	68	(5)	5	30	33	0
Psychiatric illness	3	(0)	0	0	3	0
Epilepsy	3	(0)	0	2	1	0
Immunosuppression	1	(0)	0	0	1	0
Diabetes	5	(0)	0	2	3	0
Hypertension	4	(0)	0	1	2	1

pending or unreported. The most common reported symptoms were rhinorrhoea ($n = 57$, 72%), sore throat ($n = 56$, 71%), and cough and tiredness (each $n = 57$, 66%). Eighteen women (23%) had been prescribed antiviral drugs, in 16 cases (89%) zanamivir and in two cases (11%) oseltamivir. In five cases (28%) antiviral drugs were prescribed within 2 days of symptom onset. Two women reported adverse effects with zanamivir (nausea, headaches and dizziness, worsening of asthma) and one reported adverse effects with oseltamivir (nausea and nightmares).

Comparison of the characteristics of the 79 women with symptoms with 182 women without symptoms did not identify significant associations with age, BMI, IMD score, black or ethnic minority group, asthma or trimester of pregnancy, although the conclusions that can be drawn are limited by the very small sample size involved.

Of the asymptomatic participants, two had received antiviral drugs and 212 had been offered vaccination. Of the latter group, 190 (89.6%) had been vaccinated. Adverse effects reported by participants being vaccinated included injection site reactions ($n = 97$, 51%), myalgia ($n = 54$, 28%), fever ($n = 25$, 13%), headache ($n = 19$, 10%) and arthralgia ($n = 8$, 4.2%).

TABLE 3 *Analysis of characteristics of women with suspected AH1N1v influenza in pregnancy and comparison women in primary care*

Characteristic	Case frequency (%[a]), *n* = 90	Comparison group frequency (%), *n* = 1329	Analysis			
			Univariate		Multivariate	
			OR [95% CI]	*p*-value	aOR [95% CI]	*p*-value
Age						
< 20	2 (2)	47 (4)	0.6 [0.1 to1.9]	0.05	0.6 [0.1 to 2.1]	0.08[b]
20–34	71 (88)	932 (77)	1[c]		1[c]	
≥ 35	8 (10)	236 (19)	0.4 [0.2 to 0.8]		0.5 [0.2 to 1.0]	
BMI						
Normal	15 (54)	225 (56)	1[c]	0.84	–[d]	
Overweight	9 (32)	109 (27)	1.2 [0.5 to 2.9]			
Obese	4 (14)	67 (17)	1.9 [0.2 to 2.6]			
IMD score						
IMD < 20	50 (61)	844 (67)	1[c]	0.56	1[c]	0.73[b]
IMD 20–40	23 (29)	311 (25)	1.2 [0.7 to 2.0]		1.2 [0.5 to 2.5]	
IMD > 40	8 (10)	97 (8)	1.4 [0.6 to 2.9]		1.2 [0.7 to 2.1]	
Black or other minority ethnic group						
Yes	11 (19)	105 (12)	1.6 [0.8 to3.1]	0.16	–[d]	
No	48 (81)	743 (88)	1[c]			
Current smoking						
Yes	12 (13)	106 (12)	1.8 [0.9 to 3.2]	0.08	1.3 [0.6 to 2.7]	0.33
No	78 (87)	1223 (88)	1[c]			
Asthma						
Yes	14 (16)	95 (7)	2.4 [1.3 to 4.3]	0.005	2.0 [1.0 to 3.9]	0.04
No	76 (84)	1234 (93)	1[c]			
Trimester						
I	14 (17)	131 (11)	2.2 [1.1 to 4.2]	0.07	–[d]	
II	25 (31)	507 (42)	1[c]			
III	43 (52)	576 (47)	1.5 [0.9 to 2.5]			

a Percentage of those with data.
b *p*-value for the total effect of the variable, not the individual categories.
c Reference group.
d Omitted from multivariable model owing to missing data.

Maternal and fetal outcomes

No maternal deaths of pregnant women with suspected swine flu or cases requiring hospitalisation have been reported in the primary care cohort for this study period. However, the amount of follow-up information available from consenting women is currently very limited.

Further follow-up of women included in the study will take place until 6 months after the latest expected dates of delivery and these data, including maternal and fetal outcomes, will be reported when available.

TABLE 4 *Symptoms reported in pregnant women with suspected AH1N1v infection notified to the research team by primary care health professionals (n = 90)*

			Trimester			
			I	II	III	Unknown
Symptom	**All**	**(%)**	**14**	**25**	**43**	**8**
Aching muscles	22	(24)	4	11	3	4
Breathlessness	24	(27)	3	8	12	1
Chills	31	(34)	6	7	16	2
Cough	61	(68)	12	16	27	6
Diarrhoea	13	(14)	0	5	8	0
Fever (> 38°C)	64	(71)	10	16	31	7
Headache	47	(52)	6	16	23	2
Limb or joint pain	30	(33)	6	8	16	0
Loss of appetite	26	(29)	5	6	14	1
Rhinorrhoea	32	(36)	1	13	14	4
Sneezing	12	(13)	0	7	4	1
Sore throat	54	(60)	3	14	31	6
Tiredness	41	(46)	8	10	20	3
Vomiting	23	(26)	6	8	9	0
Other	17	(19)	3	5	9	0

TABLE 5 *Use of antiviral agents in pregnant women with suspected AH1N1v infection in primary care who were notified to the research team (n = 90)*

			Antiviral agents administered for		Trimester			
	All	**%**	**Treatment**	**Not reported**	**Unknown**	**I**	**II**	**III**
Antiviral agents prescribed								
Zanamivir	50	(56)	30	20	2	10	14	24
Oseltamivir	5	(6)	3	2	1	2	0	2
Both	0		0	0	0	0	0	0
None	35	(39)						
Intervals between first symptoms and prescription								
0–2 days	42	(76)	26	16	2	9	11	20
3–5 days	8	(15)	3	5	0	1	2	5
> 5	1	(2)	1	0	1	0	0	0
Unknown	4	(7)	3	1	0	2	1	1

TABLE 6 *AH1N1v vaccination in pregnant women notified to the research team (n = 1432)*

			Trimester			
Study patients	**All**	**%**	**III**	**I**	**II**	**Unknown**
Immunised (n = 1432)						
Yes	814	(57)	369	70	308	67
No	470	(33)	205	63	164	38
Not offered	194	(14)	86	14	77	17
Refused	406	(28)	172	58	142	34
Not known/reported	98	(10)	5	14	66	13
Reported adverse effects (n = 814)						
Headache	15	(2)	4	2	5	4
Arthralgia	6	(1)	2	2	2	0
Myalgia	26	(3)	10	1	12	3
Reaction at injection site	127	(16)	66	8	48	5
Fever	22	(3)	5	3	9	5

Women admitted to secondary care with confirmed AH1N1v infection in pregnancy

Cases reported

Reports were received from 221 of the 223 hospitals with consultant-led maternity units in the UK (99%). Using the most recently available birth data from the Office for National Statistics (2007), there were an estimated 314,135 maternities (women delivering) during the study period. Thirty-five per cent of hospitals returned negative reports, i.e. hospitals indicated that there had not been any pregnant women admitted with confirmed AH1N1v influenza during the study period. Hospitals reporting cases recorded between 1 and 18 cases, with a median of two cases reported per hospital.

A total of 427 cases were reported, with complete data received for 349 cases (82%) (*Figure 2*). Thirty-four cases were subsequently reported by clinicians as not cases and there were 11 duplicate reports. Data collection forms were received for 304 women. A further 63 women were excluded because on further examination they did not meet the case definition: 48 women were not confirmed to have had AH1N1v influenza on testing, seven were never admitted to hospital, seven contracted AH1N1v, or were admitted to hospital, after delivery; for one woman, dates of symptoms and admission were missing and thus we were unable to confirm that she met the case definition. There was thus a total of 241 women admitted to hospital in the UK with confirmed AH1N1v influenza in an estimated 314,135 maternities, representing an estimated incidence of 7.7 hospitalised cases per 10,000 maternities (95% CI 6.7 to 8.7 per 10,000 maternities).

The women who were not confirmed to have AH1N1v infection had a range of final diagnoses: 14 had an unspecified viral respiratory infection, four had a bacterial chest infection, three had a urinary tract infection and seven had a variety of other diagnoses. The final diagnosis was unknown for 20 women.

Figure 3 shows the distribution of cases by week of hospital admission or start of symptoms if the date of admission was unknown. The peak number of admissions occurred in week 42, the week commencing 12 October 2009. The epidemic was largely over by the end of 2009, with only four reported admissions during January 2010.

Characteristics of cases and risk factors

Of the 241 women admitted with confirmed AH1N1v, 15 (6%) were in their first trimester, 32 (13%) were in their second trimester and 193 (80%) were in their third trimester. For one woman, the

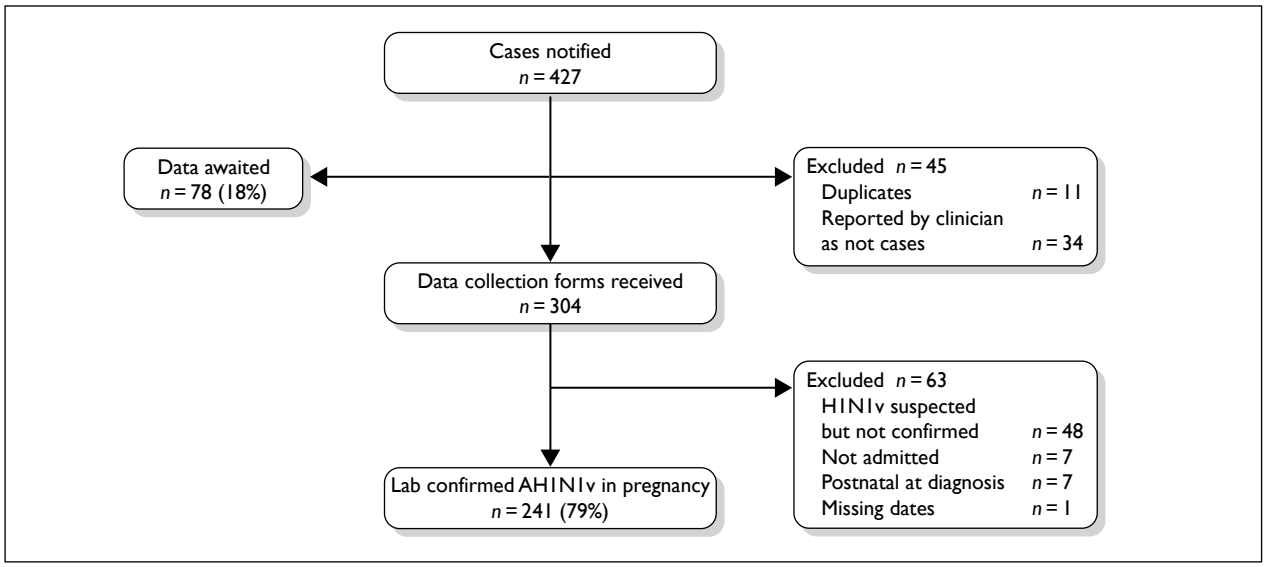

FIGURE 2 *Case reporting and completeness of data collection for women hospitalised with AH1N1v influenza in pregnancy.*

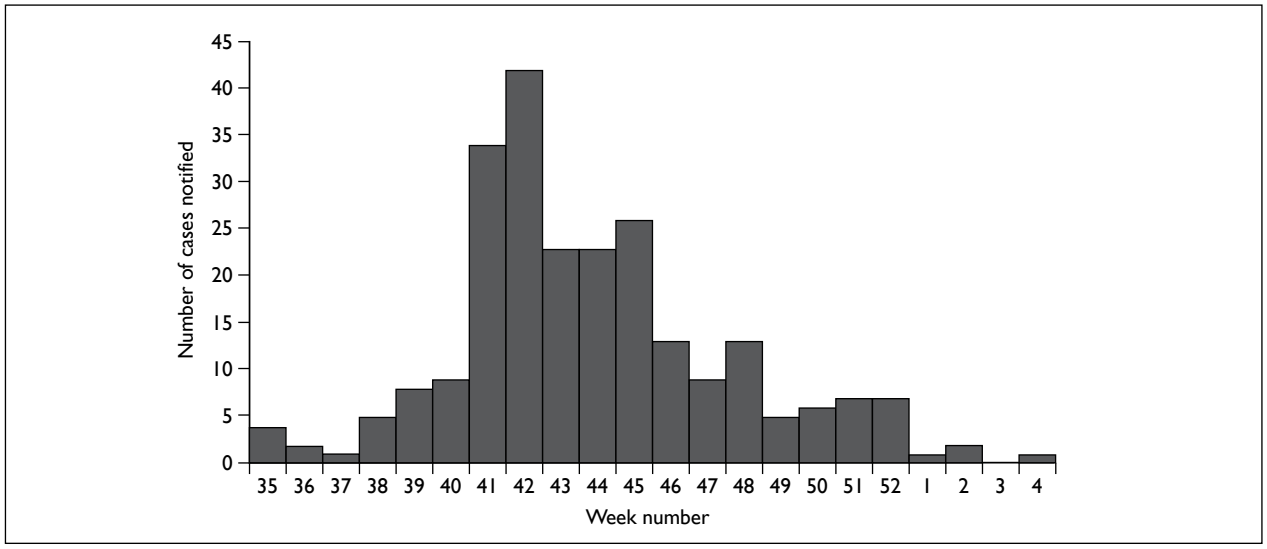

FIGURE 3 *Hospital admissions of pregnant women with AH1N1v by week of hospital admission or start of symptoms (2009–10).*

trimester of admission was unknown. *Table 7* shows the characteristics of women who were admitted with AH1N1v and the comparison cohort. A one unit increase in BMI was associated with a 5% increase in the odds of admission with AH1N1v in pregnancy (95% CI 2% to 8%) after adjusting for potential confounders, thus women admitted with AH1N1v influenza were significantly more likely to be overweight (aOR 1.7, 95% CI 1.2 to 2.4) or obese (aOR 2.0, 95% CI 1.3 to 3.0) than the comparison cohort. They were also more likely to have asthma requiring inhaled or oral steroids (aOR 2.3, 95% CI 1.4 to 3.9), to be multiparous (aOR 1.6, 95% CI 1.1 to 2.2), to have a multiple pregnancy (aOR 5.2, 95% CI 1.9 to 13.8) and to be from a black or other minority ethnic group (aOR 1.6, 95% CI 1.1 to 2.3), although this last association was of borderline statistical significance ($p = 0.03$).

Women hospitalised with AH1N1v influenza in pregnancy were younger than comparison women (unadjusted OR for age less than 20 years = 1.9, 95% CI 1.2 to 3.1; OR associated with a 1-year increase in age OR = 0.94, 95% CI 0.92 to 0.96). After testing for all possible two-way interactions in the adjusted model, there was a statistically significant interaction found between age and smoking ($p = 0.01$, *Table 8*). Amongst non-smokers, a 1-year increase in age was associated with a 6%

TABLE 7 *Characteristics of women hospitalised with AH1N1v influenza in pregnancy and comparison women*

	Characteristic case frequency (%), *n* = 241	Comparison group frequency (%), *n* = 1223	Analysis			
			Univariate		Multivariate	
			OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Age						
< 20	25 (10)	62 (5)	1.9 [1.2 to 3.1]	< 0.001[a]	–[c]	
20–34	188 (78)	897 (73)	1[b]			
≥ 35	28 (12)	264 (22)	0.5 [0.3 to 0.8]			
BMI						
Normal	84 (40)	563 (53)	1[b]	0.001[a]	1[b]	0.0014[a]
Overweight	70 (33)	306 (29)	1.5 [1.1 to 2.2]		1.7 [1.2 to 2.4]	
Obese	58 (27)	202 (19)	1.9 [1.3 to 2.8]		2.0 [1.3 to 3.0]	
Managerial or professional occupation						
Yes	44 (28)	766 (70)	0.9 [0.6 to 1.3]	0.58	–[d]	
No	112 (72)	334 (30)	1[b]			
Black or other minority ethnic group						
Yes	54 (23)	220 (18)	1.3 [0.9 to 1.8]	0.13	1.6 [1.1 to 2.3]	0.03
No	184 (77)	974 (82)	1[b]		1[b]	
Current smoking						
Yes	55 (23)	258 (22)	1.1 [0.8 to 1.6]	0.53	[c]	
No	180 (77)	940 (78)	1[b]			
Multiparous						
Yes	148 (62)	696 (57)	1.3 [0.9 to 1.7]	0.12	1.6 [1.1 to 2.2]	0.01
No	89 (38)	525 (43)	1[b]		1[b]	
Asthma						
Yes	32 (13)	66 (5)	2.7 [1.7 to 4.2]	< 0.001	2.3 [1.4 to 3.9]	0.001
No	206 (87)	1154 (95)	1[b]		1[b]	
Multiple pregnancy						
Yes	8 (3)	13 (1)	3.3 [1.3 to 8.0]	0.006	5.2 [1.9 to 13.8]	0.001
No	228 (97)	8 (3)	1[b]		1[b]	

a *p*-value for the total effect of the variable, not the individual categories.
b Reference group.
c Entered multivariate model as an interaction term – see *Table 8*.
d Omitted from multivariate model owing to missing data.

decrease in the odds of admission with AH1N1v in pregnancy (95% CI 3% to 9%), among smokers, a 1-year increase in age was associated with a 15% decrease in the odds of admission with AH1N1v in pregnancy (95% CI 8% to 20%). Thus, younger smokers had the highest odds of admission with confirmed AH1N1v influenza (aOR 4.2, 95% CI 2.0 to 8.9) when compared with older non-smokers (*Table 8*).

Women hospitalised with AH1N1v influenza in pregnancy also had a number of other medical problems, although owing to differences in data collection we were unable to compare these formally with the frequency in comparison women in the multivariate model. Forty-two women had other medical problems, but these disorders were very heterogeneous: 10 women had a metabolic disease, 10 women a haematological

TABLE 8 *ORs for admission to hospital with confirmed AH1N1v influenza in pregnancy in different age and smoking groups after adjusting for potential confounders*

Exposure	*n* cases (%)	*n* comparison group (%)	Adjusted OR [95% CI][a]
Age under 20, smoking	13 (6)	25 (2)	4.2 [2.0 to 8.9]
Age under 20, non-smoking	11 (5)	35 (3)	1.8 [0.8 to 4.1]
Age 20 or over, smoking	42 (18)	233 (19)	1.0 [0.7 to 1.5]
Age 20 or over, non-smoking	169 (72)	905 (76)	1[b]

a Adjusted for factors included in multivariate analysis in *Table 7*.
b Reference group.

disorder, five women had chronic lung disease (excluding asthma), four women had cardiac disease, four women had neurological disease, four women had gastrointestinal disease, three women had endocrine disorders, two women had essential hypertension, and nine women had other problems. Seven women had two or more additional medical problems.

Presenting symptoms and prior immunisation

The most frequent presenting symptoms of AH1N1v infection in pregnancy were fever (206 women, 88%) and cough (201 women, 86%) (*Figure 4*). Almost one-half of all women also reported a sore throat, vomiting, headache, lethargy and joint pain. The median number of symptoms experienced was five (interquartile range 3–6). Four women had fever as their sole symptom.

Six women (2%) had been vaccinated before their admission for AH1N1v influenza in pregnancy. These women had been vaccinated a median of 3 days before the onset of symptoms (range 0–9 days) and a median of 7.5 days before the diagnosis of AH1N1v infection was confirmed (range 3–16 days).

Inpatient management

Eighty-three per cent of women hospitalised with AH1N1v were treated with antiviral agents (197 of 237 with known treatment status). The most common first-line antiviral treatment was zanamivir (139 of 196 women where the agent was known, 71%). The route of administration was known for 129 women treated with zanamivir, with 99% (128 women) inhaled (two women, 2% by nebuliser) and 1% (1 woman) intravenous. The remaining 28% of women were given oseltamivir as first line treatment (57 of 196 women), all receiving it orally or by nasogastric tube. Eighteen women who were initially given zanamivir were subsequently switched to oseltamivir. One woman treated initially with oseltamivir was subsequently switched to intravenous zanamivir. Overall, 60% of women received an antiviral agent within the

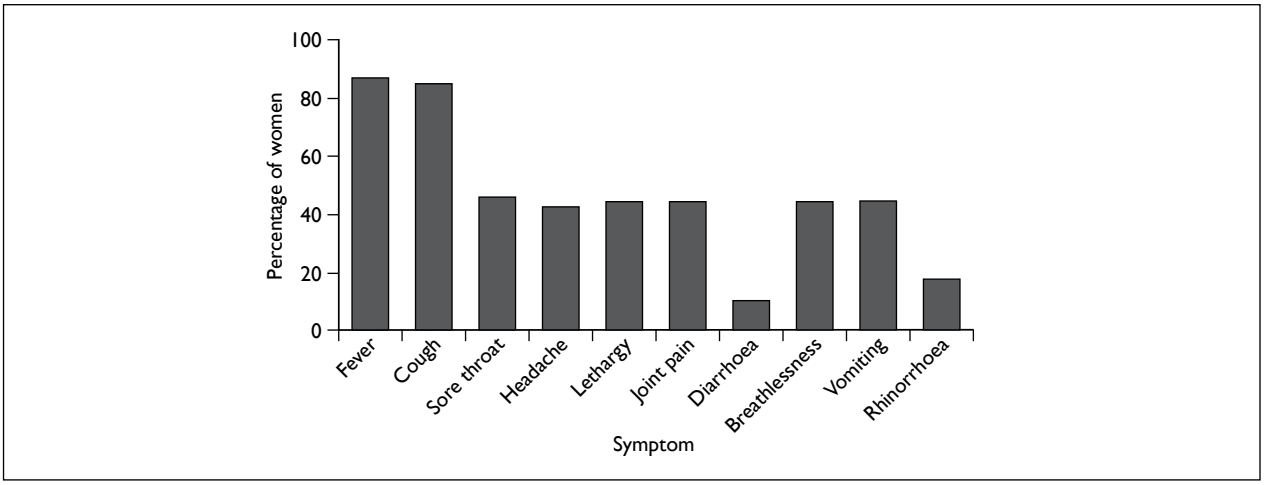

FIGURE 4 *Presenting symptoms of AH1N1v influenza in hospitalised pregnant women.*

recommended 2 days from symptom onset (134 of 224), but only 6% (14 of 224) received antiviral treatment before admission to hospital (a median of 2 days before admission, range 1–5).

In addition, 34 women (14%) were managed with corticosteroids to enhance fetal lung maturation.

Women were admitted for a median of 3 days with 50% of cases in the range 2–6 days. The longest length of stay was 76 days. Twenty-two per cent of women were admitted to an intensive therapy unit (ITU) (51 of 234 women) and eight women (3%) were reported to have received extracorporeal membrane oxygenation. This represents an estimated incidence of 1.6 pregnant women admitted to ITU with confirmed AH1N1v infection per 10,000 maternities (95% CI 1.2 to 2.1 per 10,000 maternities). Forty-four of the women admitted to ITU (86%) were in their third trimester of pregnancy (*Figure 5*). Women admitted to ITU were more likely to report breathlessness as a symptom of AH1N1v infection than those not admitted to ITU ($n = 31$, 62% versus $n = 74$, 41%; $p = 0.01$), but were less likely to report sore throat ($n = 17$, 34% versus $n = 91$, 51%; $p = 0.04$) or joint pain ($n = 14$, 28% versus $n = 89$, 50%; $p = 0.006$). *Table 9* shows the characteristics of women admitted to ITU and those who were admitted to hospital but not to an ITU. Treatment within 2 days of symptom onset was associated with an 84% reduction in the odds of admission to ITU (OR 0.16, 95% CI 0.08 to 0.34); 26% of women (12 of 46) admitted to ITU were treated within 2 days of symptom onset compared with 68% of women who were not admitted to ITU (119 of 174). After adjustment, the only other factor statistically significantly associated with ITU admission was BMI; women admitted to ITU were more likely to be obese (aOR 3.4, 95% CI 1.2 to 9.2) than women not admitted to an ITU; a one-unit increase in BMI was associated with a 9% increase in odds of ITU admission (95% CI 2% to 17%) (*Table 9*).

Maternal outcomes

Four women reported to UKOSS, who met the case definition, died, representing a case fatality of 1.7% of women admitted to hospital with confirmed AH1N1v influenza in pregnancy (95% CI 0.5% to 4.2%). Note that an additional two women who died were reported to UKOSS but did not meet the case definition; one woman did not have virological confirmation of AH1N1v infection and the second had symptom onset after delivery. Maternal deaths were cross-checked with those reported to the Centre for Maternal and Child Enquiries (CMACE); four cases meeting the case criteria had been reported to CMACE. Three of these cases had also been reported to UKOSS; one case was identified uniquely through UKOSS and one uniquely through CMACE, representing a total of five deaths in women hospitalised with confirmed AH1N1v infection in pregnancy in an estimated 314,135 maternities, an estimated 1.6 deaths per 100,000 maternities (95% CI 0.5 to 3.7). Note that this figure does not include deaths in women with a symptom onset in the postpartum period.

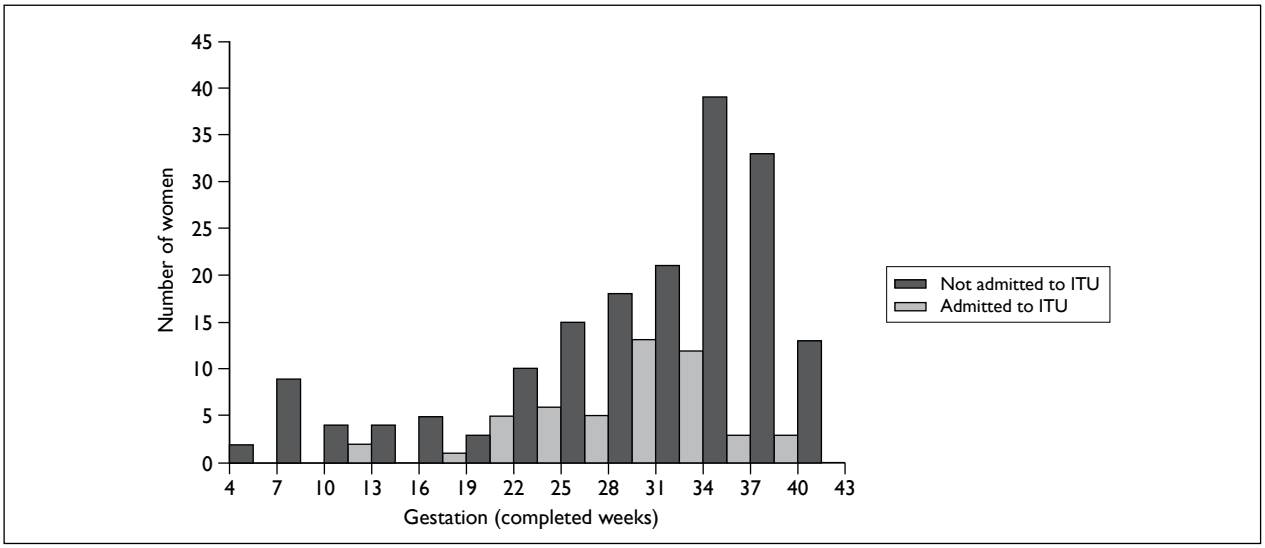

FIGURE 5 *Gestation at admission for pregnant women with confirmed AH1N1v influenza admitted to an ITU and those admitted to hospital but not to an ITU.*

TABLE 9 *Characteristics of women hospitalised with AH1N1v influenza in pregnancy admitted to ITU*

Characteristic	ITU frequency (%), *n* = 51	Non-ITU frequency (%), *n* = 183	Analysis			
			Univariate		Multivariate	
			OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Age				0.44[a]		0.81[a]
< 20	2 (4)	22 (12)	0.3 [0.1 to 1.3]		0.3 [0.1 to 2.1]	
20–34	44 (86)	139 (76)	1[b]		1[b]	
≥ 35	5 (10)	22 (12)	0.7 [0.3 to 2.0]		0.4 [0.1 to 2.0]	
BMI				0.01[a]		0.008[a]
Normal	11 (25)	71 (44)	1[b]		1[b]	
Overweight	14 (32)	56 (34)	1.6 [0.7 to 3.8]		1.3 [0.5 to 3.5]	
Obese	19 (43)	36 (22)	3.4 [1.5 to 7.9]		3.4 [1.2 to 9.2]	
Managerial or professional occupation						
Yes	9 (29)	35 (28)	1.0 [0.4 to 2.5]	0.95	–[c]	
No	22 (71)	88 (72)	1[b]			
Black or other minority ethnic group						
Yes	7 (14)	47 (26)	0.5 [0.2 to 1.1]	0.08	0.6 [0.2 to 1.8]	0.37
No	43 (86)	134 (74)	1[b]		1[b]	
Current smoking						
Yes	15 (30)	39 (22)	1.5 [0.8 to 3.1]	0.23	2.1 [0.8 to 5.5]	0.14
No	35 (70)	140 (78)	1[b]		1[b]	
Multiparous						
Yes	35 (70)	110 (61)	1.5 [0.8 to 2.9]	0.25	0.8 [0.3 to 1.8]	0.55
No	15 (30)	70 (39)	1[b]		1[b]	
Asthma						
Yes	4 (8)	28 (15)	0.5 [0.2 to 1.4]	0.18	2.2 [0.6 to 9.0]	0.26
No	46 (92)	154 (85)	1[b]		1[b]	
Multiple pregnancy						
Yes	0	8 (4)	–[d]		–[d]	
No	51 (100)	172 (96)				
Treated within 2 days						
Yes	12 (26)	119 (68)	0.2 [0.1 to 0.3]	<0.001	0.1 [0.1 to 0.3]	<0.001
No	34 (74)	55 (32)	1		1	

a *p*-value for the total effect of the variable, not the individual categories.
b Reference group.
c Omitted from multivariate model due to missing data.
d Not calculable due to zero cells.

Pregnancy outcomes

One hundred and fifty-three women (63%) had completed their pregnancy at the time of reporting; the remainder currently have ongoing pregnancies. Among those who have delivered, three pregnancies were miscarried or terminated. There were six stillbirths and 147 live births, representing a perinatal mortality of 39 per 1000 total births (95% CI 15 to 83 per 1000 total births). Forty-five women of the 152 with a known gestation at delivery (30%) delivered preterm at less than 37 weeks' completed gestation, taking into account three women who were admitted after 37 weeks' gestation but for whom we do not have other outcome information. Comparison with the uninfected cohort shows that women admitted to hospital with AH1N1v infection were more likely to deliver preterm (OR 5.5, 95% CI 3.7 to 8.3). Note that, owing due to the large number of ongoing pregnancies, these outcome figures are likely to represent a significant overestimate of the proportion of pregnancies with poor outcomes. If we assume, in order to obtain an estimate not biased by lack of outcome data, that all women who are not yet delivered go on to deliver at term, there is still a significant increase in the odds of preterm delivery associated with admission with AH1N1v infection in pregnancy (OR 3.1, 95% CI 2.1 to 4.5).

These figures are very similar when we consider preterm delivery at less than 32 weeks' completed gestation; 12 women of the 164 with a known gestation at delivery (7%) delivered preterm at less than 32 weeks' completed gestation, taking into account 11 women who were admitted while still pregnant after 32 weeks' gestation, who can be assumed to have delivered after 32 weeks' gestation. Comparison with the uninfected cohort shows that women admitted to hospital with AH1N1v infection are also more likely to deliver very preterm at less than 32 weeks (OR 4.3, 95% CI 2.1 to 8.9). If we assume, in order to obtain an estimate not biased by lack of outcome data, that all women who are not yet delivered go on to deliver at greater than 32 weeks' gestation, there is still a significant increase in the odds of very preterm delivery associated with admission with AH1N1v infection in pregnancy (OR 2.9, 95% CI 1.4 to 6.0).

Chapter 4
Discussion

Management of AH1N1v (2009) influenza in primary care

ILI in primary care

Population data from primary care on the effects of influenza, and, more specifically, AH1N1v (2009) influenza, in pregnancy are lacking. Reports published thus far have focused on cases managed in secondary care and are thus likely to be biased towards the severe end of the spectrum. The primary care element of this study aimed to capture information on the incidence and characteristics of pregnant women with suspected AH1N1v influenza presenting in the community, with a view to identifying factors contributing to adverse maternal and fetal outcomes.

The UKTIS is a service commissioned by the HPA to provide advice on drug and chemical exposures during pregnancy. Details of women on whom we provide advice are held to enable follow-up of pregnancy outcome. During the first wave of the 2009 AH1N1v pandemic we collected details of 259 women with suspected AH1N1v influenza or who had been prescribed antiviral medication during pregnancy as part of our routine surveillance activities. Given these figures, the predicted incidence of AH1N1v infection in the second wave, the adoption of our study as NIHR portfolio research and the support of PCRNs across the UK, we had anticipated that we would recruit around 500 pregnant women with suspected AH1N1v influenza presenting in primary care during this 6-month study period. However, recruitment to the study was significantly less than expected for several reasons. First, the incidence of AH1N1v infection circulating in the community during the study period was not as high as anticipated. Second, fewer GP practices than expected were willing to act as participant identification centres for the study. Concern about high influenza consultation rates and staffing during the pandemic was the most frequently expressed reason for non-participation. Compounding this, data that were provided were often incomplete. Third, while ethical approval was provided within a few days of application, there were delays in obtaining the RM&G approvals required before this expedited research could start locally, especially in some parts of the UK. For individual NHS organisations, intervals to approval ranged from 0 to 141 days, with 55% and 19% providing approval for the original application and amendment, respectively, within 2 days. Fourth, although participants had provided verbal permission for their details to be passed to the research team, the numbers of women eventually providing written consent for active follow-up was lower than anticipated.

The move from laboratory-based AH1N1v diagnosis to the treatment phase of the pandemic on 2 July 2009 meant that virological confirmation of AH1N1v in pregnant women presenting in primary care with ILI was no longer performed as a matter of routine. Although AH1N1v rapidly became the dominant circulating strain in certain regions, this was not true in all regions of the UK. In order to characterise accurately the features of AH1N1v infection in pregnancy in primary care and to compare these with those of seasonal influenza, virological confirmation of influenza cases was sought by the study team. The significant delay in launching this study, as described above, resulted in many cases being reported to the study team several weeks after their acute illness. The situation was further exacerbated by the low return rate of consent for follow-up and of self-swabbing kits by consenting participants (8 out of 25).

Interpretation of the AH1N1v influenza infection data collected in primary care is thus limited by the relatively small sample size ($n = 90$) and low rates of virological confirmation. Nevertheless, the study provides some valuable information about the epidemiology of ILI, although not necessarily AH1N1v influenza, during pregnancy in primary care during the second wave of AH1N1v infection. To put this in context, surveillance data during the same period (weeks 37–53 of 2009) identified that between 15% and 50% of GP consultations for respiratory viral infection in England, and 10% and 34.1% in Scotland, were due to AH1N1v.[42,43]

Data collected from the sentinel sites suggests a mean weekly consultation rate for ILI of 51/100,000 pregnant women over the study period. Although it is not possible to undertake a direct comparison with the non-pregnant female

population, these figures are within the range reported by the RCGP Research & Surveillance Centre[44] for the non-pregnant population over the study period. It should be noted that the National Pandemic Flu Service was in operation throughout the study period. This service, consisting of a website and a network of call centres, was able to assess symptoms and provide antiviral drugs for collection without the need for a GP consultation. Policy, however, was for this service to direct pregnant women to their GP for provision of antiviral therapy, so this was not expected to have a major effect on GP consultation rates for pregnant women.

Comparison of data provided about women presenting with suspected AH1N1v infection with that of pregnant women without features of infection who were being offered vaccination allows assessment of factors that may be associated with infection. The limited numbers of women with suspected infection restrict the power of this comparison. The only factor showing a statistically significant association with an increased risk of AH1N1v influenza in pregnancy in this analysis was maternal asthma. This finding is consistent with reports following the first AH1N1v influenza wave and with data collected in the secondary care arm of this study (see below). Although not statistically significant, our data suggest a similarity in characteristics between women with influenza managed in primary care and the more serious cases requiring hospital admission, with a trend towards women who smoke or who have an IMD score of greater than 20 being at increased risk of influenza when compared with pregnant women who did not report influenza symptoms during the second AH1N1v influenza wave.

Use of antiviral drugs

The proportion of pregnant women with ILI who were prescribed antiviral drugs was 61%, with 76% of these treated within 2 days of symptom onset, when reported by health professionals. In contrast, when reported by participants, 23% were treated with antiviral drugs and only 20% received these within 2 days of symptom onset. The differences may be due to women not taking prescribed antiviral drugs, symptoms being of longer duration than recorded by health professionals or women not seeking antiviral therapy when they develop symptoms. The impact of antiviral therapy on outcomes of influenza during a pandemic would be enhanced by encouraging pregnant women to seek medical advice as soon as possible during their illness and to have facilities for this group to be provided with antiviral drugs at an early stage.

Use of AH1N1v vaccines

The majority of pregnant women were offered vaccination during the study period, with the precise proportion depending on the method of data collection. In the sentinel practices, the data indicate that only 65% of pregnant women were offered vaccination; however, it should be recognised that the vaccines were not available for the initial part of data collection. Much higher proportions were reported by health professionals (86.5%) and by participants (88.5%), although these figures may be inflated by under-reporting of women offered but declining vaccination. Uptake of vaccination was lower, with 37% (sentinel practices), 57% (health professional reports) and 79% (participant reports) of those offered vaccination receiving it. Considering that the vaccines became available only during the study period, the levels of vaccination reported in these cohorts are a considerable achievement by the practices involved. It should be recognised, however, that the UK Chief Medical Officer has reported that as of 3 March 2010 148,000 pregnant women had been vaccinated, which is less than one-quarter of the total.[45] It is important to ensure that all pregnant women without contraindications are offered vaccination and that these women have adequate information available about safety and efficacy of vaccines in pregnancy to make an informed choice.

Pregnancy outcomes

Consenting women will undergo follow-up until 6 months after their expected dates of delivery. Because of the very limited number of women with ILI who have provided consent, it is unlikely that this cohort will provide robust information on adverse maternal effects of influenza in pregnancy or the adverse effects of the use of antiviral drugs. In contrast, the number of women available for follow-up following vaccination is substantially larger, and useful information on the safety of vaccine use in pregnancy will become available in due course. Recruitment into the study is continuing and this will increase the amount of follow-up information eventually available.

Hospitalised women with confirmed AH1N1v influenza in pregnancy

This study has shown that the UKOSS can be used effectively in response to a public health emergency to rapidly collect data on disease incidence, management and outcomes in pregnant women. The UKOSS network of collaborating clinicians is based in all UK hospital consultant-led maternity units, allowing comprehensive surveillance of women admitted to hospital with confirmed AH1N1v influenza in pregnancy. This approach, effectively collecting information on the severe end of the disease spectrum, has been recommended as an appropriate method in the pandemic situation, when surveillance of all cases becomes impractical.[46] The availability of the established UKOSS infrastructure allowed for commencement of surveillance within 4 weeks of the study receiving funding and highlights the importance of maintaining such unique national collaborations, especially in the perinatal field where pregnancy exposures, both infective and pharmaceutical, may have major and long-lasting impacts.

We estimate from this study that eight women were hospitalised with AH1N1v influenza for every 10,000 women delivering in the UK. Other national figures for admission with confirmed AH1N1v influenza in pregnancy have been estimated but use both different numerator and denominator figures. The risk of admission to an ITU with AH1N1v influenza in Australia and New Zealand has been estimated as 1 in 14,600 in women with a gestation of less than 20 weeks and 1 in 2700 for women of 20 weeks' or greater gestation.[47] The authors do not report figures for women hospitalised with AH1N1v influenza in pregnancy. They record 59 women who were pregnant at the time of symptoms of influenza who were subsequently admitted to an ITU during the 3 months of 1 June to 31 August 2009, which we calculate to represent an estimated 6.6 women admitted to ITUs in Australia and New Zealand per 10,000 maternities, based on 2008 birth figures[48,49] (95% CI 5.1 to 8.6). This clearly represents a significantly higher rate of admission to an ITU with confirmed AH1N1v influenza in pregnancy than the 1.6 women per 10,000 maternities we estimate in the UK. These differences may reflect an underascertainment of cases admitted to ITUs in the UK, which we hope to investigate further through collaboration with the Intensive Care National Audit and Research Centre, or it may represent a difference in hospital practice or health-care systems between the three countries, for example in access to health care and hence delay in treatment resulting in greater disease severity. It may also reflect a difference in population characteristics between the countries; for example, indigenous ethnicity was an important factor associated with critical illness due to AH1N1v influenza in pregnancy in Australia and New Zealand, clearly not a factor that would impact on illness in the UK. In addition, the Australian and New Zealand data were collected during the peak 3 months of the first wave of the epidemic, whereas our data were collected over 5 months during the second wave; averaging of admissions over a longer period of time may also lead to an apparently lower admission rate, and also there is a possibility that the properties of the circulating virus may have changed over time.

Comprehensive data have recently been reported from the US state of California,[50] documenting 94 pregnant women who were admitted to hospital with confirmed AH1N1v between 3 April and 5 August 2009, a period with an estimated 188,383 live births. This represents an estimated 5.0 admissions per 10,000 live births (95% CI 4.0 to 6.1). The UK data expressed with the same denominator represent an estimated 7.5 admissions per 10,000 live births (95% CI 6.6 to 8.5).[38] This observed difference is likely to be explained entirely by differential case ascertainment in areas with different epidemic characteristics. Disease incidence is known to vary widely across regions;[51] the US study obtained case reports for pregnant cases from jurisdictions representing only 79% of the population, whereas this UK study covered 98.6% of the population of women giving birth.

The date of the peak of admissions with AH1N1v influenza in pregnancy corresponds directly with the peak of infections reported in the UK by the HPA.[52] Only six women hospitalised with AH1N1v influenza in pregnancy had received specific immunisation against the infection; all of these women were infected well within the 3 weeks following vaccination, which it is suggested is required to achieve 98% seroconversion.[53] Note that the main vaccination programme in the UK was rolled out after the peak of hospital admission in this series and these secondary care data are not therefore useful to assess the efficacy of the vaccine.

Risk factors for hospitalisation with AH1N1v influenza in pregnancy

This study has identified a number of factors associated with admission with confirmed AH1N1v infection in pregnancy. The comparison group we used was a historical cohort of women delivering in UK hospitals, and thus the risks documented may represent a raised risk of infection with AH1N1v or a raised risk of hospitalisation following infection, or a combination of both. In order to obtain estimates of the risk factors associated with hospitalisation, we had planned to compare the hospitalised cohort with a cohort of pregnant women with confirmed AH1N1v infection who were not admitted to hospital. Unfortunately, because of difficulties encountered in collecting information about this community cohort, we have not been able to undertake this comparison. Retrospective case identification of community cases is ongoing, and we may be able to undertake this comparison in the future.

We identified that younger maternal age was associated with an increase in the odds of admission with AH1N1v infection in pregnancy; this is likely to reflect a higher infection rate in this group, as national data on AH1N1v infection has demonstrated higher rates of infection amongst younger (aged 16–24) than older adults (aged 25–44).[54] Similarly, parity as a factor is unlikely to be related to an increased severity of illness, but may be a reflection of an increased infection rate among multiparous women who are more likely to have increased exposure to infection through contact with children than nulliparous women. Children have been shown to have the highest rates of infection with AH1N1v.[54] In contrast, obesity has been noted to be a risk factor for severe illness with AH1N1v in both the pregnant[47] and non-pregnant populations.[55] We found a linear increase in risk of hospital admission with AH1N1v in pregnancy with increasing BMI, as well as a linear increase in the risk of admission to an ITU once hospitalised. This increase in risk of admission may be associated with co-existing medical conditions that are known to be more frequent in the obese population;[56] owing to data collection differences we were not able to account for these in our multivariate model. However, there was no difference in the proportion of women with co-existing medical conditions admitted to ITUs when compared with those admitted to hospital but not to an ITU, thus it would appear that obesity per se may be causally related to disease severity.

In common with other studies,[50] we identified asthma – treated with regular inhaled or oral steroids – as a risk factor for admission to hospital with AH1N1v influenza in pregnancy; the proportion of women with asthma among those admitted with AH1N1v influenza in pregnancy was more than double that in the comparison group. Furthermore, this is likely to be an underestimate of the risk of hospitalisation associated with asthma, as the condition was defined differently in each group; in the AH1N1v group, we collected data on all women with asthma treated with regular inhaled or oral steroids, whereas in the comparison group we had collected data on all women with a diagnosis of asthma irrespective of their current treatment. This will therefore be an overestimate of the proportion of comparison women using regular steroid treatment. It has been suggested in other studies that other co-existing illnesses are also over-represented amongst those admitted with AH1N1v infection, whether pregnant or not.[2,47,50,54,55] Our data support these observations; excluding asthma, 17% of women admitted had other co-existing illnesses.

We observed that admission to hospital with AH1N1v infection in pregnancy in the UK was associated with black or other minority ethnicity, although this was of borderline statistical significance. Indigenous women were over-represented amongst those admitted to ITUs in Australia and New Zealand, and pregnant women admitted with AH1N1v infection in pregnancy in California were more likely to be Hispanic than non-pregnant women with AH1N1v infection.[47,50] Ethnic minority women in the UK have been shown to be at risk of other severe illness in pregnancy,[37] hypothesised to be due to pre-existing medical factors or to differences in access to care. Both of these explanations may account for the observed increase in the risk of admission with AH1N1v in pregnancy. Pre-existing illness has been shown to be associated as noted above; in addition, delayed access to care, and particularly to antiviral treatment, whether through a language or other barrier, may increase the risk of hospitalisation with AH1N1v in pregnancy among ethnic minority women. Similar factors have been linked to a higher attack rate of AH1N1v influenza amongst indigenous populations in general.[57]

Smoking has not been reported in the US and Australasian series as associated with hospitalisation or ITU admission with AH1N1v influenza in pregnancy,[47,50] although it was not specifically

examined as a factor in either of these studies. We noted an interaction between smoking and age, such that younger smokers were over-represented amongst women hospitalised with AH1N1v. Again, it may be hypothesised that this represents an increased risk of infection in association with smoking or an increased risk of hospitalisation, both of which are biologically plausible. Why this effect varies with age is less clear, perhaps the most likely explanation is that the lack of an observed association in older women is a reflection of low study power to detect this, owing to the smaller number of older women admitted. It is also possible that smoking in younger women is associated with other unmeasured risk behaviours and lifestyle factors not seen in older women and is therefore acting as a proxy measure for a different factor.

Four-fifths of women admitted with AH1N1v influenza in pregnancy were in their third trimester of pregnancy. The trimester of pregnancy clearly represents a risk factor for hospital admission with confirmed AH1N1v influenza in pregnancy, as less than one-third of pregnant women at any one time would be expected to be in the third trimester. This may not necessarily reflect an increased risk of disease severity amongst women in the third trimester, but may reflect admission for fetal considerations in association, for example, with an increased risk of preterm labour in conjunction with maternal fever. However, were this the case, we would expect a lower proportion of women who were admitted in their third trimester to be admitted to an ITU than the proportion of women admitted in the first and second trimester. We did not observe this to be the case; the proportions of women admitted in each trimester who were subsequently admitted to ITUs were very similar. We also noted an association between admission with AH1N1v infection and multiple pregnancy, which may also reflect either fetal or maternal considerations. None of the women admitted with AH1N1v who had a multiple pregnancy were subsequently admitted to ITU, which could be interpreted to mean that this association does reflect pregnancy concerns rather than an increased severity of maternal illness, although this observation should be treated with caution due to the small numbers involved.

Factors associated with admission to an ITU

For every one unit increase in BMI, there was a 9% increase in the odds of admission to an ITU with confirmed AH1N1v infection in pregnancy, independent of age, ethnicity, smoking, parity, asthma or early treatment. Obese women are known to be at risk of a number of complications of pregnancy;[56] this study has identified a further risk of both hospital admission and critical illness associated with AH1N1v influenza, highlighting the importance of public health actions to address obesity prevention. Treatment with antiviral agents within 2 days of symptom onset was associated with an 84% decrease in the odds of admission to an ITU; the association between a delay in treatment and severe disease or death in pregnancy has also been suggested by other studies.[2,47,50] This observation is particularly important given our observation that only 60% of women were treated within 2 days of symptom onset, and, perhaps more importantly, only 6% of women had received antiviral treatment prior to hospital admission. This suggests that further actions may be needed in future pandemics to ensure that antiviral agents are provided promptly to pregnant women, particularly in the primary care setting.

In this analysis, obesity and delayed antiviral treatment were the only factors statistically significantly associated with ITU admission. However, even although this is a national study covering more than 300,000 women giving birth, the power of this analysis is limited due to the rarity of ITU admission. A raised odds of both smoking and asthma treated with inhaled or oral steroids was observed amongst women admitted to ITUs; although this was not statistically significant, it is possible that this also represents a clinically important association.

Maternal outcomes

The number of reported deaths in this series is very small and consequently the conclusions that can be drawn are limited. Maternal death with confirmed AH1N1v influenza is clearly rare, and the estimated maternal death rate from confirmed AH1N1v in pregnancy of 1.6 per 100,000 maternities needs to be seen in the context of the most recent estimated all-cause maternal mortality rate in the UK of 14 per 100,000 maternities.[58] The outcomes of infection for most women are good. There were, however, no reported maternal deaths from influenza between 1997 and 2005 in the UK,[58–60] suggesting that pandemic AH1N1v influenza has had a significant impact on maternal death in the UK in comparison with seasonal influenza.

Pregnancy outcomes

Fewer than two-thirds of women hospitalised with AH1N1v influenza in pregnancy between September 2009 and January 2010 in the UK have completed their pregnancies. Pregnancy outcome data are therefore at this point incomplete and it is thus difficult to draw definitive conclusions as the women for whom we have outcome data undoubtedly represent a biased subset. Hence our figure for perinatal mortality is likely to represent an overestimate. Similarly, using current figures, the risk of preterm delivery and very preterm delivery we estimate is high. However, by assuming that all women not yet delivered deliver at term, we can estimate the lowest likely risk of preterm delivery associated with hospitalisation with AH1N1v infection in pregnancy. Using even this conservative estimate suggests at least a threefold increase in risk; the true risk is likely to lie between this figure and the fivefold increase suggested from our current data. The conservative estimate for very preterm birth suggests a similar estimated threefold increase in risk. These estimates show that AH1N1v infection in pregnancy has an important fetal as well as maternal impact.

We have followed up infants only as far as the mother's hospital discharge. Exposures during the perinatal period are known to be associated with both short- and long-term impacts into childhood and beyond. Maternal history of influenza or pneumonia has been associated with the occurrence of childhood leukaemia,[61] and maternal influenza infection has been hypothesised to be associated with schizophrenia in later life, although a recent meta-analysis of data following the 1957 pandemic does not support this hypothesis.[62] As perhaps one of the most comprehensive cohorts of women hospitalised with AH1N1v infection in pregnancy, it is important to consider whether the infants of these women should be followed up over a prolonged period in order to investigate further some of these longer-term impacts.

Comparison of primary and secondary care data

Incidence

By extrapolating from the data obtained from primary care sentinel practices and UK population data,[38] we can estimate that there were approximately 650,000 pregnant women in the UK at the time the study was conducted. Assuming that the pattern of presentation with ILI in pregnant women in these practices was similar to that in the UK as a whole, this suggests that nationally approximately 7000 pregnant women (1.1%) presented with illness. The secondary care data indicate that 241 women were admitted to hospital with confirmed AH1N1v influenza, an estimated 3.5% or 1 in 29 of those presenting to the GP with ILI.

Risk factors

Although the risk factor data are limited by the low number of cases identified from primary care, there are several points worth noting. The only factor noted to be both a risk factor for presentation with ILI in primary care in pregnancy and admission to hospital with confirmed AH1N1v influenza was asthma. This emphasises the importance of influenza vaccination in this subgroup of pregnant women. Given the high proportion of pregnant women reported to have declined immunisation, almost one-third, it is important that these risks are highlighted by clinicians when counselling pregnant women with asthma about influenza vaccination.

Obesity was noted to be a factor significantly associated with both hospital admission with confirmed AH1N1v influenza in pregnancy and with subsequent admission to intensive care. We were, however, unable to investigate this as a factor associated with ILI presenting in primary care due to the large amount of missing data; BMI data were available for fewer than one-third of the women reported. A number of other risks, maternal and fetal, and both short- and long-term, associated with obesity in pregnancy have been reported.[63] Recording of BMI early in pregnancy is important to allow tailored care for women who are at increased risk of pregnancy complications. In many cases, BMI information and other information was not provided. This may be because women were not present with their hand-held notes when reporting forms were completed, but further investigation is needed to assess whether the poor recording of BMI in the reports from primary care reflects that it is not being routinely recorded as part of pregnancy care.

Several elements of this study suggest that inequalities in health, documented across many disease spectra in the UK[64] may also be evident when considering ILI and AH1N1v infection in pregnancy. Although there was no statistically significant association between deprivation and presentation with ILI in pregnancy in primary care, the observed trend towards women who

present with ILI being more likely to come from deprived areas is worthy of further exploration to see whether this is also observed in other population groups with AH1N1v influenza. The observed increased odds of hospitalisation with AH1N1v infection in young pregnant smokers may contribute to an inequality between different socioeconomic groups, as smoking rates and socioeconomic status are known to be associated.[65] Additionally, we observed an association between admission to hospital with confirmed AH1N1v and black or other minority ethnicity, which needs to be further investigated in the context of addressing health inequalities.

Chapter 5

Further and ongoing research

There is a need to obtain better data on longer-term pregnancy outcomes following AH1N1v infection, treatment with antiviral drugs and vaccination. Although limited numbers of women with AH1N1v infection or treated with antiviral drugs were identified in primary care, as of 9 March 2010 the research team has been provided with details of over 1200 women who have undergone vaccination against AH1N1v, and almost 700 women who have declined vaccination. Over 400 of these women have consented to detailed follow-up of pregnancy outcome and this information will be collected over the next few months. Data collection is continuing and the research infrastructure is in place to collect information during a third wave of infection, should that occur.

UKTIS also received notification of over 300 women with suspected AH1N1v infection during the first wave and efforts will be made to obtain pregnancy outcome information for these women as part of the routine surveillance activity of the service.

The remainder of the hospitalised cohort will also be followed up through UKOSS to ensure that we have a complete picture of the pregnancy outcomes for these women.

Chapter 6
Conclusions

The data currently available, including the research reported here, suggest that pregnant women with AH1N1v infection appear to have worse clinical outcomes than the non-pregnant population. This is evidenced by the higher than expected proportion of pregnant women who are admitted to hospital or require admission to an ITU. Interpretation of published data is difficult because there is limited information available on the numbers of pregnant women who have been infected compared with the non-pregnant population, and the likely under-reporting of women who are pregnant and have had favourable outcomes. There is also evidence that AH1N1v infection has been more severe in younger adults than in older people[66,67] and this may also contribute to the apparently higher proportion of pregnant women with adverse outcomes following infection. Risks of adverse outcomes appear to be increased in pregnant women who have comorbidities, especially asthma and obesity.

The evidence from this report, together with other published data, strongly supports early treatment with antiviral drugs for all pregnant women with influenza symptoms, ideally within 48 hours of onset of symptoms, particularly for those in the third trimester of pregnancy and those with comorbidities. There is, however, currently insufficient evidence, either published or unpublished, to justify a change in the current UK recommendations on choice of antiviral drug. There are limited data available on the safety of antiviral medication use in pregnancy; existing data do not provide strong evidence of a teratogenic risk, but further data collection will be important.

The higher rate of adverse clinical outcomes in pregnant women with AH1N1v infection emphasises the importance of vaccination in this group. According to the limited information collected as part of this research, only a minority of women who were pregnant during the study period were vaccinated and more women will have become pregnant since the previous intensive efforts were made to vaccinate pregnant women. In view of the risk of a third wave of infection, efforts should be made to increase the proportion of pregnant women who have been vaccinated.

Chapter 7

Key points

- Earlier treatment with antiviral agents is associated with improved outcomes for women, yet few women were treated with antiviral drugs prior to admission to hospital. Further actions may be needed in future pandemics to ensure that antiviral agents are provided promptly to pregnant women, particularly in the primary care setting.
- Maternal obesity is associated with both admission to hospital with confirmed AH1N1v infection in pregnancy and critical illness from AH1N1v in pregnancy. This highlights the importance of ongoing work to support obesity prevention at a community level.
- Maternal smoking, particularly in younger mothers, is also associated with admission with AH1N1v infection in pregnancy. Smoking in pregnancy is associated with a number of risks to both mother and fetus and thus prevention programmes continue to be important.
- Women with asthma and other comorbidities are more likely to be admitted to hospital with AH1N1v infection in pregnancy. Clinicians should be aware of this association and work to ensure that women with co-existing illnesses in pregnancy are treated appropriately.
- Data on outcomes of pregnancy in women admitted to hospital with confirmed AH1N1v influenza are, as yet, incomplete. However, there appears to be a significantly increased risk of preterm delivery which may impact on service provision in a future pandemic. Further research on longer-term outcomes for infants exposed to AH1N1v influenza in the perinatal period may be warranted.
- AH1N1v vaccination should continue to be offered to pregnant women in light of the probability that AH1N1v will remain the predominant circulating influenza strain in autumn/winter 2010–11.

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Laura Yates (Consultant Clinical Geneticist and Head of Teratology, UKTIS) contributed to the design, management, data collection and data analysis, and the wrote the first draft of the report relating to the primary care element of the study.

Matthias Pierce (Statistician and Epidemiologist, National Perinatal Epidemiology Unit, University of Oxford) assisted with data coding, conducted the analysis, and contributed to writing and editing the report of the secondary care element of the study.

Sally Stephens (Assistant Head of Teratology, UKTIS) contributed to the management, data collection and data analysis of the primary care element of the study, and assisted with editing of this part of the report.

Aileen Mill (Research Associate and Mathematical Modeller, Institute of Research on the Environment and Sustainability, Newcastle University) performed the statistical analysis of the primary care element of the study and contributed to the writing and editing of this part of the report.

Patsy Spark (Programmer, National Perinatal Epidemiology Unit, University of Oxford), assisted with data coding, conducted validation of the data and some analysis, and contributed to writing and editing the report of the secondary care element of the study.

Jannifer Kurinczuk (Deputy Director and Reader in Perinatal Epidemiology, National Perinatal Epidemiology Unit, University of Oxford) provided advice at every stage of the secondary care study and contributed to the writing and editing of the report of the secondary care element of the study.

Manoj Valappil (Consultant Virologist) coordinated the design and distribution of virological kits and the analysis of submitted samples, and assisted with the editing of the virological primary care sections of this report.

Peter Brocklehurst (Director and Professor of Perinatal Epidemiology, National Perinatal Epidemiology Unit, University of Oxford) provided advice at every stage of the secondary care study, and contributed to the writing and editing of the report of the secondary care element of the study.

Simon Thomas (Professor of Clinical Pharmacology and Therapeutics, Newcastle University) acted as Principal Investigator and contributed to the design, management, data collection and data analysis, and the writing and editing of the report relating to the primary care element of the study.

Marian Knight (Head of UKOSS and Honorary Consultant in Public Health, National Perinatal Epidemiology Unit) designed the secondary care study, co-ordinated data collection, coded data, supervised the analysis and wrote the first draft of the report of the secondary care element of the study.

All authors contributed to and approved this report.

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Appendix 1
Study protocol

Study Protocol

Influenza A/H1N1v in pregnancy: An investigation of the characteristics and management of affected women, A/H1N1v vaccination in pregnancy and the relationship to pregnancy outcomes for mother and infant

1 Research Objectives

a) To conduct a systematic review to summarise existing evidence on the effects of influenza and its treatment, demographic and pregnancy characteristics and additional pregnancy management strategies on pregnancy outcomes.

b) To determine:

i) the incidence of influenza A/H1N1v in pregnancy

ii) the effect of H1N1 Influenza infection and/or treatment with neuraminidase antiviral drugs in pregnant women and /or H1N1 vaccination (timing of use, dose and agent) on pregnancy outcome, including specific adverse or beneficial effects of antiviral treatment or H1N1 vaccination on eventual maternal and fetal outcome

iii) the influence of demographic or pregnancy characteristics and additional aspects of pregnancy management on outcomes for mother and infant

c) To produce guidance on the management of H1N1v infection in pregnancy initially following systematic review updated subsequently by monthly review of emerging data from this study such that outcomes for women and infants are optimised during the current pandemic.

2 Existing Research

Influenza infection during pregnancy is associated with adverse maternal and fetal outcomes, including probable increases in the risk of maternal pneumonia and possible increases in risks of certain congenital malformations[1-6]. Recent US H1N1 pandemic experience as well as data from previous influenza pandemics indicates higher morbidity and mortality among pregnant women[7, 8], however, detailed epidemiological studies investigating risks in subgroups of pregnant women and the impact of pregnancy management strategies on outcomes are currently lacking

The neuraminidase inhibitors oseltamivir and zanamivir are effective for prophylaxis and treatment of H1N1 influenza. Neither is licensed for use in pregnancy, but current UK guidance recommends use in pregnancy when indicated. Oseltamivir is an oral treatment *with* limited transplacental bioavailability. Approximately 150 outcomes have been reported following oseltamivir exposure during pregnancy and provide no evidence of specific harms.[9, 10] Because of this, in the USA and Canada, oseltamivir is recommended as first line treatment in women with established H1N1 infection and for prophylaxis. Zanamivir is an inhaled treatment and the amount crossing the placenta is therefore small. For this reason it is preferred in the UK as the first line option in pregnancy, although experience of use in pregnancy is

limited, with only 4 cases published and a further 50 reported to regulatory authorities.[10-12] UK guidance also acknowledges that the benefits of oseltamivir outweigh potential risks during pregnancy.

This inconsistency in guidance between the UK and USA/Canada arises from the paucity of data on the safety of these antiviral drugs during pregnancy, especially relating to zanamivir. The data available are inadequate to exclude a clinically important increase in risk of congenital malformation or neonatal problems. This research is therefore designed to collect further experience of neuraminidase use in human pregnancy on which to base future guidance. The anticipated increase in numbers of cases of H1N1 in the second half of 2009 offers a unique opportunity to collect these data.

H1N1 influenza vaccination

There are currently two vaccines for H1N1 influenza available in the UK; Pandemrix® and Celvapan®. Pandemrix® is adjuvanted with AS03 (squalene, DL α tocopherol, polysorbate 80) and contains thiomersal (a mercury containing compound) as a preservative. Celvapan® is unadjuvanted and does not contain thiomersal. There are no specific safety data on the use of adjuvanted vaccines in pregnancy.

A study from 1973 of over 2000 pregnant women who received influenza vaccine demonstrated no associated adverse fetal effects.[13] There is no evidence of risk from vaccinating pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids.[14] Expert scientific advice is clear that thiomersal-containing vaccines do not present a risk to pregnant women or their offspring, however published studies on the use of thiomersal containing vaccines in pregnancy are limited.

The Department of Health, UK has recommended that all pregnant women should be vaccinated as they are at increased risk of complications from swine flu. JCVI recommended that pregnant women should be given Pandemrix since a one-dose schedule with this vaccine appears to generate adequate levels of antibodies and thereby confer more rapid protection than would be afforded by a two-dose schedule. Once again, however, guidance as to which vaccine to recommend in pregnancy differs between countries, highlighting the lack of data regarding efficacy and safety of these vaccines in pregnant women.

2.1 Justification for research proposal

Preliminary data, particularly from the United States and Mexico, suggest that pregnant women are more susceptible to complications of influenza A/H1N1v infection[15, 16], and worldwide data suggest that younger people, including women of reproductive age are at increased risk of infection. This research will identify, through two existing reporting systems, the UK Teratology Information Service (UKTIS) and the UK Obstetric Surveillance System (UKOSS), all pregnant women hospitalised with confirmed influenza A/H1N1v in the UK, as well as pregnant women with the illness or requiring prophylactic antiviral therapy in the community. We will collect information on their demographic and pregnancy

characteristics as well as management, including use, mode and timing of any antiviral therapy. In addition, we will collect data on the incidence of complications of both influenza and pregnancy, and the outcomes for both women and their infants. We will investigate the relationship between demographic, pregnancy characteristics, management and outcomes in order to generate immediate recommendations for changes in practice to improve outcomes for this vulnerable group.

Data on pregnant women exposed to neuraminidase inhibitors is currently being collected by UKTIS as part of a routine surveillance program commissioned by the Health Protection Agency. Voluntary reporting is, however, known to under ascertain cases. Ascertainment of such cases is reliant on ad hoc reporting by busy health professionals who are primarily requesting advice. Studies using these data are therefore subject to case selection bias and are insufficient to enable scientifically valid conclusions to be drawn regarding the effects of H1N1 infection and/or neuraminidase inhibitor treatment in pregnancy on maternal and fetal outcome. At present, follow up of selected cases only is possible.

UKOSS is an existing network of collaborating obstetricians, midwives and obstetric anaesthetists in all 226 hospitals with consultant-led maternity units in the UK, through which selected studies of severe complications of pregnancy can be conducted[17]. The system has been used to conduct a number of studies of severe morbidities, resulting in improvements in the care of pregnant women throughout the UK[18-23]. The current paper-based system, however, does not allow a sufficiently rapid response to collect data for rapid analysis and production of guidance for clinical management of H1N1v infected women in the current pandemic.

We propose to extend these systems to allow rapid web-based reporting and analysis, together with conducting follow-up and testing of women with suspected influenza infection in pregnancy, to allow us to develop guidance on the management of H1N1v infection in pregnancy and hence improve outcomes for women and their infants.

Vaccination of pregnant women may significantly alter the impact of AH1N1v infection during pregnancy for the remainder of this pandemic, and hence our study period. Information about the AH1N1v and seasonal influenza vaccination status of pregnant women is thus paramount to interpreting the data collected on AH1N1v Influenza and antiviral use during this study. Furthermore, GSK and Baxter (manufacturers of the AH1N1v vaccines available in the UK) are under obligation to the EMEA (European Medicines Agency) to collect data on the effects of AH1N1v vaccination in pregnancy and have approached UKTIS to establish a registry of AH1N1v vaccination in pregnancy in order to collect this data. Given that we are already collecting information on swine flu and its treatment

in pregnancy, and that vaccination against swine flu may impact on the findings of our research, extension of the study to include collection of data on AH1N1v vaccination in pregnancy will enhance our study.

3 Methods – Systematic review

3.1 Research question

How is influenza H1N1v managed in pregnancy and what factors influence disease outcome for mother and infant?

3.2 Search strategy

A literature search will be performed to identify reports of influenza infection and/or treatment with the neuraminidase inhibitors oseltamivir or zanamavir during pregnancy using MEDLINE and EMBASE databases, as well as web search engines. Search terms will include pregnancy, influenza, neuraminidase inhibitors, oseltamivir and zanamavir in various permutations. Further data on H1N1 and neuraminidase inhibitor exposure in pregnancy will be ascertained by personal communication with manufacturers and non-UK teratology organisations including the European Network of Teratology Information Services (ENTIS), European Teratology Society (ETS), Organization of Teratology Information Specialists (OTIS, USA), and Motherisk (Canada).

Studies will be included if these include cases or case series of influenza or antiviral exposure in pregnancy and where data on maternal or fetal outcome has been collected prospectively.

3.3 Outputs

Included studies will be reviewed to identify factors influencing the outcomes of H1N1v infection in pregnancy for mother and infant. The results will be used to develop guidance for clinicians to improve the management and outcomes of infected pregnant women.

4 Methods – cohort study

4.1 Research design

This will be a prospective observational cohort study using several different sources to identify women in order to conduct a comprehensive national study. Information about pregnancy management and outcomes will be collected directly from heath professionals caring for infected women in secondary care settings and from health professionals as well as women themselves, with consent, where infection is managed in a primary care setting.

4.2 Identification of infected women

The cohort will be all pregnant women in the UK identified with confirmed or suspected influenza H1N1v , who have been offered treatment with antiviral medication (e.g. as prophylaxis) or who are offered immunisation against AH1N1v. The denominator population will be all women giving birth in the UK. The cohort will be identified through the following sources:

i. The UK Teratology Information Service (UKTIS). Women will be notified by health professionals when clinical advice is sought from the service, by means of a dedicated Swine Flu reporting line (0191 2606197) and also through a reporting form available for download from the UKTIS website (Appendix 1). Women will be asked for verbal consent for their contact details and initial clinical information to be provided to the research team. This information will then be passed to the research team by telephone, secure fax or where neither of these options is possible by post.

ii. Active notification with null reporting to UKTIS by research midwives through the Reproductive Medicine and Childbirth Research Network and a cohort of GP practices that have agreed to undertake pandemic flu research at short notice through the primary care network. It is anticipated that these practices will provide complete case ascertainment for the accurate estimation of incidence in their practice populations.

iii. The HPA Regional Microbiology Laboratory Network will alert clinicians who have sent specimens to the fact that the study is taking place and will ask them to seek consent for patient details to be provided to the research team

iv. Self reporting by patients to UKTIS via a dedicated patient reporting telephone line and a novel secure website that allows women to enter their details directly onto an online form designed to facilitate easy, rapid and accurate input of data into a database, hence reducing research staffing demands.

v. Active negative surveillance through the UKOSS collaboration of over 700 reporting obstetricians, midwives and anaesthetists in all 226 consultant-led maternity units in the UK through a new web-based reporting system.

Health professionals will be made aware of the study through the research networks, via information on the NPIS on-line database TOXBASE® and the UKTIS website and via advice provided on H1N1 influenza by the HPA. Eligible women will be made aware by information in antiviral distribution centres and via the UKTIS website.

4.3 Virological confirmation of H1N1

Details of pregnant women who have not been tested for H1N1v in a diagnostic setting will, with their consent, be forwarded to the HPA virology laboratory North East. Women recruited to the study who have not already had this will undergo H1N1 testing. This will be arranged by provision of a self administered swabbing kit by post from the UKTIS research team. This will be enclosed with the initial participant information sheet and consent forms. The self swabbing kit for H1N1v testing is already validated and is currently used by NHS Direct in conjunction with the HPA Centre for Infections (CFI). The kit comprises of 2 viral swabs, an instruction leaflet for patients explaining how to obtain optimal samples and a prepaid

envelope with the necessary transport tubes for return of the sample to the virology laboratory. This method of approach is important because reliability of identification of influenza viruses from nasal swabs is highest within 3 days of symptoms. Current routine practice in the UK entails collecting both a nasal and nasopharyngeal throat swab to optimise H1N1 diagnosis. Given the known difficulties of obtaining informative throat swabs by self testing, a nasal swab from each nostril will be requested instead. This is thought to achieve an equivalent diagnostic yield. Swabs returned through research testing will be processed immediately by the HPA virology lab in Newcastle to extract and store total nucleic acids. H1N1 testing will then be carried out at a later date in batched runs to minimise staffing and consumable costs. Testing including extraction, amplification and detection will be performed in accordance with the national standard operating procedures (SOP) for detection of H1N1v. Samples needing additional testing to clarify status will be referred to CFI, Colindale London.

It will be made clear to the patient that not all viral samples collected as part of this research will be analysed for H1N1 and that where testing is performed there is no guarantee that these results will be fed back to the patient or their referrer.

4.4 Data collection

1. Women identified by their health professionals or identifying themselves to the research team will be sent the participant information sheet and consent documentation, together with an initial data collection sheet that they are asked to complete if they agree to take part (Appendix 2). The GP/midwife reporting will be asked to alert the research team should the status of the patient change after initial notification, to avoid the small risk of contacting individuals who may have died. Four weeks after initial contact further information is sought from the participant (Appendix 3) and health professional (Appendix 4). If the patient has recovered, the next follow up will be of maternal and pregnancy outcome two weeks after birth, again collected from patient (Appendix 5) and health professional (Appendix 6). The final follow up questionnaire will be to request information on the baby's health at six months of age (Appendix 8). Patients who remain unwell from influenza will be followed up at four weekly intervals (using the forms in Appendices 3 and 4) until recovery and as above, four weeks after the estimated delivery date. The final follow up questionnaire will be to request information on the baby's health at six months of age (Appendix 8).

For practices that are not associated with a research network, the GP or midwife will identify participants and provide follow up information available from the medical records on two occasions (four weeks after the initial illness/exposure and after delivery). Consent and recruitment will be performed by the research team at UKTIS. For patients identified by the Primary Care Research Network or the Reproductive Medicine and Childbirth Research Networks, identification, recruitment, consent and follow-up may be delivered through GPs or research midwives. Anonymised details of patients declining participation will also be notified to UKTIS (Appendix 6) to allow accurate estimation of incidence. The details of research network involvement are currently being finalised.

Patients will be offered the opportunity to report additional illnesses, exposures or complications during their pregnancy at any point as well as at the planned follow up intervals through the a novel web-based reporting system, or by telephone. If a completed data collection form is not received back by UKTIS after three weeks, a further reminder will be sent out.

2. Nominated UKOSS reporting clinicians will be asked to report all pregnant women with confirmed or suspected H1N1v infection admitted to their unit. In view of the need for rapid and ongoing data analysis and production of guidance, we will set up 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. On receiving a case report, the central team will ask the clinician to complete an electronic data collection form, asking for further detailed information about diagnosis, management and outcomes. Women 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.

4.5 Identification of comparison women

Information about comparison women managed in hospitals will be obtained from previously collected UKOSS data. The UKOSS database contains detailed demographic, pregnancy and delivery information about a cohort of over 1200 women giving birth in the UK identified from the same hospitals as cohort women. Comparative information on several thousand women exposed to other medicines during pregnancy is available from the UKTIS pregnancy outcome register.

4.6 Monitoring ascertainment

The Confidential Enquiry into Maternal and Child Health (CEMACH) will be contacted at the end of the study and provided with information on cases of maternal or perinatal death in association with influenza in pregnancy, identifying the hospital and date of death. They will be asked to compare the cases they have identified with cases reported through UKTIS and UKOSS.

Ascertainment in primary care will be studied by comparing recruitment nationally with that achieved by network-associated practices reporting intensively.

4.7 Study Size

The primary objective of this study is to determine the incidence of H1N1v infection in pregnancy. The study size will therefore be dependent on the infection rate among pregnant women, together with the UK maternity rate (currently 760,000 maternities per year). With the limited available data, we anticipate

identifying 500-1000 affected pregnancies during the 6 month initial study period. Information on 1200 comparison women is available from existing UKOSS data. A study of this size will have 80% power at the 5% level to detect a doubling of the risk of any adverse outcome (severe maternal morbidity or mortality, preterm delivery, congenital malformation or perinatal death) in women with influenza or treated for influenza compared with comparison women.

4.8 Statistical Analysis

Incidence rates with 95% confidence intervals will be calculated and outcomes (maternal death, other major complication, preterm birth, congenital anomaly, perinatal death) compared between women with influenza and comparison women. Odds ratios with confidence intervals will be calculated and adjusted for confounders (age, parity, marital status, ethnicity, smoking status, socioeconomic status, previous preterm delivery, previous perinatal death) using logistic regression. In addition, outcomes will be explored in different subgroups according to demographic and pregnancy characteristics, timing, agent and dose of antiviral treatment, the use of additional treatments in pregnancy, timing and mode of delivery.

4.9 Outputs

The study data will be analysed on an ongoing basis in order to update guidance for management of women with H1N1v in pregnancy on a monthly basis.

4.10 Consent

4.10.1 UKTIS/UKOSS data collection from health professionals

All data collection will either involve anonymised information or will be performed with patient consent. In order to describe the incidence of H1N1v in pregnancy, some data must be collected on ALL cases occurring in the populations in which an accurate estimate of incidence is being made. These are (a) hospital inpatients and (b) people with swine flu infection or exposure identified in the community via specific research network practices. It is not practicable to obtain individual patient consent for all patients. Some potential participants will decline to participate, which may lead to a biased estimate of incidence. Therefore there is a need to pass some anonymised information to the research teams without consent.

Recruitment in the community (UKTIS):
For patients identified in the community, verbal consent will be sought by the responsible health professional for the provision of personal identifiable information to UKTIS, to allow an approach for written consent to participation. In practices where incidence is being measured (i.e. Sentinel Practices), anonymised information will be provided about patient characteristics for women who decline to give verbal consent. These practices will be expected to fax a report to UKTIS on a weekly basis, including ‘null

reporting' if no cases have been identified for that week. Subsequently, only women in the community providing written consent will be asked to provide further health information.

UKTIS is permitted to store patient data on the existing database under Section 60 of the Health and Social Care Act 2001 to enable surveillance and follow up of pregnancy outcomes of cases where exposure to a potential teratogen in has been reported. This data is obtained from health care professionals involved in the patient's care. UKTIS does not offer counselling or advice directly to members of the public.

Recruitment in hospitals (UKOSS):
The hospital based component of the research is a non-interventional (descriptive) study only. UKOSS collects only anonymised information and accordingly the central team will not seek to collect any names, addresses, dates of birth, hospital or NHS numbers in order that none of the participants are individually identifiable. Duplicate cases will be identified by comparing a woman's year of birth, reporting hospital and expected date of delivery and follow-up with reporting clinicians. Patients will be managed by their usual clinical team and will receive the usual management for their hospital of delivery. Information will be collected from the clinical team responsible for each patient after the initial diagnosis. The management of each woman participating will not be altered in any way by participation in the study. The anonymised information will be used to calculate incidence rates and identify means to further improve patient care. This UKOSS methodology has received the approval of the London Multi-centre Research Ethics Committee (study reference 04/MRE02/45). The National Information Governance Board (formerly Patient Information advisory Group, PIAG) has judged that collection of information only, for the purpose of studying incidence and identifying means to improve patient care, which is not individually identifiable and does not lead to any change in management for the individual patient is acceptable without requiring individual patient consent[24].

4.10.2 Patient testing and follow-up

Women self reporting or reported through their GPs will be provided with written information about the study, and will be given the opportunity to discuss any concerns they may have or to ask questions about the study. For most participants, these discussions will be by telephone with the research team at UKTIS. In some network-associated practices, informed consent may be obtained directly by local health professionals. Potential participants will be made aware that participation in the study is voluntary, that they may withdraw from the study at any point and that these decisions will not affect their routine clinical care. It will also be made clear at the point of enrolment that 1 in 7 pregnancies miscarry and 2 to 3 out of every 100 children are born with a birth defect, and that the study does not imply that influenza infection and/or antiviral treatment during pregnancy is causative of either of these outcomes.

The GP/midwife will be asked to alert the research team should the status of the patient change after initial notification, to avoid the small risk of contacting individuals who may have died. Similarly, pregnancy outcome will be confirmed through the GP practice or obstetric unit involved before contacting the patient regarding pregnancy outcome.

H1N1 testing will be offered on a research basis to women who have not been tested as part of their routine care. Women will be advised that not all swabs will be analysed, and that the test result will be used for research purposes only, and not to inform individual patient clinical care. There will be no guarantee that the result of these tests is fed back to the participating women or their referrer, or of a timescale within which testing will occur. Consent will be sought to store the sample for future tests to further characterise influenza viruses that may be present.

All advertising of the dedicated participant's telephone line will clearly state that the service is purely to enable women to self-report influenza or antiviral exposure in pregnancy and will not offer a medical assessment or give advice. A pre-recorded message at the start of the call will direct callers who are seeking medical advice to NHS Direct (England and Wales) or NHS 24 (Scotland).

5 Project timetable and milestones

5.1 Timetable

Aug-Sept 2009	Obtain necessary approvals, develop web-based reporting systems
Sept 2009	Systematic Literature Review
Sept 2009 −Jan 2010	Data collection.
Oct 2009−Feb 2010	Ongoing data analysis, production of management guidance and dissemination.
Nov 2009	Commence data collection on AH1N1v vaccination
Jan-Feb 2010	Report– outcomes of H1N1v infection in pregnancy
April 2010 – Feb 2011	Ongoing data collection on infant outcome at six months
Feb – April 2011	Data analysis and report of outcomes for A H1N1v vaccination in pregnancy

5.2 Milestones

Sept 2009	Approvals completed, data collection commenced
Oct 2009	Systematic Review completed, first guidance for clinicians
Nov 2009	First data analysis, revised guidance issued
Dec 2009	Ongoing data analysis, revised guidance issued
Feb 2010	Final report and guidance: Management and outcomes of H1N1v infection in pregnancy

6 Expertise

The research team has the necessary expertise to carry out this comprehensive national study, including clinical pharmacology and pharmacoepidemiology (SHLT), teratology (SHLT, LY, SS), public health (ELF, MK, JK), systematic reviewing (MK, JK, PB), congenital malformations (JK) perinatal epidemiology and statistics (MK, JK, PB), obstetric surveillance (MK), guideline development (JK, PB) and obstetrics (PB).

UKTIS is experienced in this type of research; it is actively providing information on antiviral use during the current H1N1 pandemic and has drafted national guidance for management of H1N1 infection or exposure during pregnancy. This guidance already prompts health professionals to report affected pregnancies to UKTIS. The infrastructure is thus already in place for recording pregnancy details and fetal outcomes collected by letter or telephone, as are the necessary ethical approvals for the relevant databases and current methods of data collection.

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 226 hospitals throughout the UK. The infrastructure is thus in place to allow rapid identification of women hospitalized with H1N1 infection in pregnancy through an established active surveillance system.

In addition the project benefits from a wide range of collaborations. The study will be co-adopted by the Reproductive Health and Childbirth Network and the Primary Care Research Network. It has been discussed with both National leads of the Reproductive Health and Childbirth Network (Prof Steve Robson and Prof Steve Thornton) and Prof Wallace of the Primary Care Research Network. Each network will be involved in recruitment, and the subsequent consent and follow up of any patients accrued within the respective network. Collaboration with the HPA Virology Laboratory North East (Prof John McGee, Dr Manoj Valappil, Dr Andrew Sails) to undertake H1N1 testing on a research basis, provide expert virological opinion and act as lead laboratory of the HPA Regional Microbiology Laboratory Network (RMN) on this study has been agreed. The feasibility of a postal self testing system for H1N1 has been fully considered and discussed with the HPA laboratory in Colindale who are currently operating such a system for community influenza surveillance and who have agreed to share their expertise in this area. Links with the RMN will also ensure that any H1N1 positive samples are forwarded to Colindale for further analysis according to current surveillance practice, and that swabs for which an equivocal result is

obtained are also tested by one of the other HPA laboratories in order to ensure an accurate result and continue monitoring of possible viral mutation.

Dr Phillip Bryan of the Medicines and Healthcare Regulatory Agency (MRHA) will provide expertise on interpreting adverse reactions reported during this study, and assist with supplying information on adverse reactions associated with neuraminidase exposure in pregnancy reported via the MRHA.

Collaboration with non-UK Teratology organisations including the European Network of Teratology Information Services (ENTIS), European Teratology Society (ETS), Organization of Teratology Information Specialists (OTIS, USA), and Motherisk (Canada) will be formalised if the study is funded with a view to producing a meta analysis of the data collected by each of these centres.

Lastly, access to information on background congenital abnormality rates for the period of this study will be obtained from the British Isles Network of Congenital Anomalies Registers (BINOCAR) in collaboration with Dr Judith Rankin who also has extensive expertise in maternal and perinatal health.

We informed the manufacturers of both Oseltamivir (Roche) and Zanamivir (GSK) of our proposed study and are keen to work effectively with them on this project.

7 Service users

Within the timescale of the current pandemic, extensive consultation with service users has not been possible during the development of the project protocol. The planned project has been discussed with the NPEU advisory group, which includes both lay and professional representatives, and, if funded, lay representatives from UKOSS and UKTIS Steering Groups will be consulted about the development and acceptability of information and other materials.

8 Justification of support requested

The additional resource specified from the University of Newcastle is being sought for (a) additional information scientist/nursing staff for systematic review and to allow the logging and processing of data (1 wte, 6 months, £24k) (b) the development of a website to allow patients to enter and edit their own data directly (£14k), (c) funds to cover travel and administrative costs for collaborative work with other European Centres (£5k) and (d) Further publicity of the study with relevant health professionals (£5k) (e) statistical analysis costs (£5k). Note costs are approximate and include overheads.

At the time of submission of our expression of interest, H1N1 testing had been routinely carried out on all patients with suspected swine flu. As a result of the subsequent move from the containment to treatment phase by the Department of Health, diagnosis of H1N1 influenza is being made on clinical grounds. With the approach of autumn, it will become increasingly difficult to accurately differentiate between cases of

H1N1 and seasonal flu using clinical markers only. A further £30k is therefore being sought for H1N1 testing on a research basis.

Costs from the University of Oxford are sought to cover administration of UKOSS data collection (£4.5k), programming and database management (£3.5k) and website design (£3k). In addition, funds are sought to cover the data analysis and clinical guidance development and review (£15k) together with printing and mailing of monthly cards and data collection forms, telephone and stationery costs (£2k). Estates and indirect costs are sought at the standard University rate.

Please note that this proposal is the result of a collaboration formed after each organisation had submitted separate expressions of interest for the call for research, both of which were shortlisted for submission as full proposals. The costs included therefore reflect the combined costs of the two projects, and therefore show an increase over the amounts in both the individual expressions of interest (submitted by Prof Thomas and Dr Knight), although we have been able to make cost savings by combining the projects as well as enhancing the scope of the proposed research.

NHS Service support costs are requested to cover clinician time completing the data collection forms, providing women with study information and obtaining consent to participate.

No additional funding for the protocol amendments is being sought from the NIHR. GlaxoSmithKline (GSK) and Baxter have agreed to provide resources for the AH1N1v vaccination arm of the study via the Newcastle Hospitals NHS Foundation Trust. This additional funding will be used to employ an additional information scientist for processing of data and producing reports; a study administrator; funds to cover postage, administrative costs, further advertising of the study and stationary; statistical analysis costs and funding to update the database with the additional data fields and to produce six month infant follow-up forms.

The CLRN have agreed to provide the required NHS Service Support costs for the requested protocol amendment.

9 Research Ethics Committee Approval

The original proposal was given favourable opinion by the County Durham and Tees Valley 1 Research Ethics Committee.

The protocol amendment relating to AH1N1v vaccination in pregnancy has been submitted for ethical review.

10 Project Management

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.

11 Research Governance

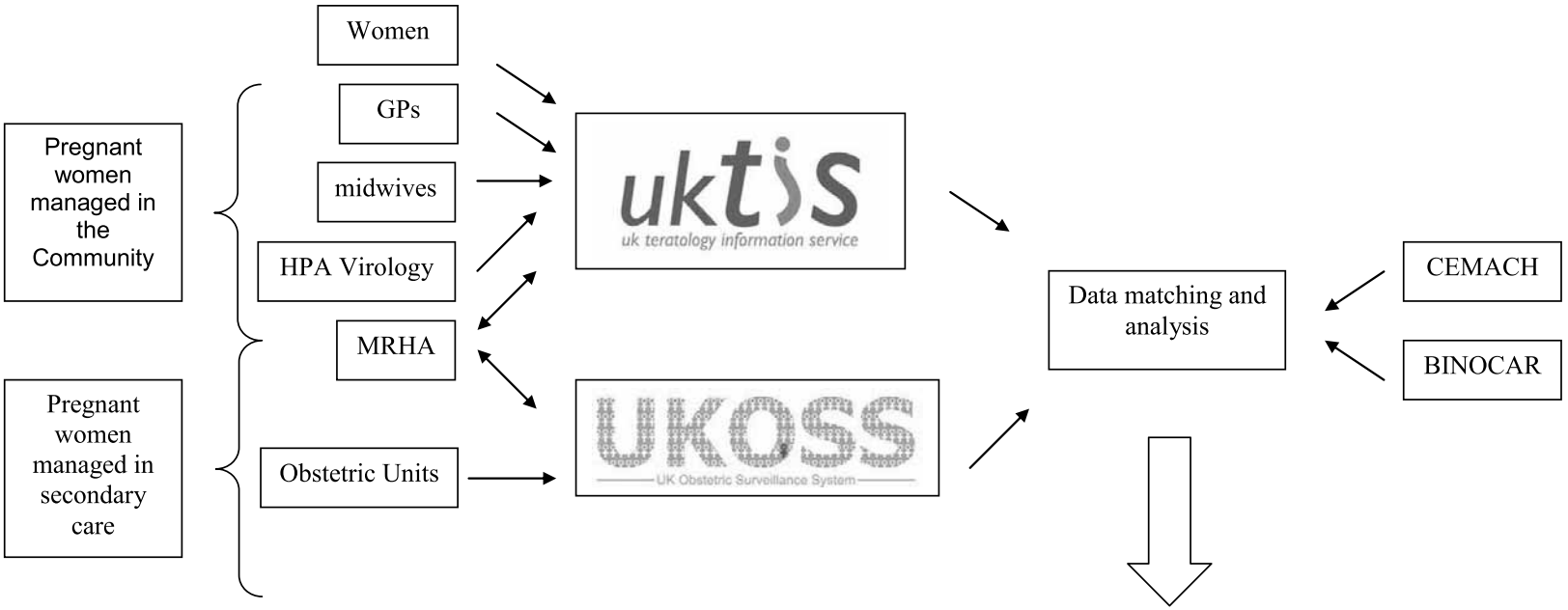
The Newcastle Upon Tyne Hospitals NHS Trust has agreed to sponsor the study.

12 Dissemination and publication

It will be important to feedback the outcomes of the study to the clinicians who participated in providing information. This will be done through monthly guidance for management and a final report. The results will also be reported to the Scientific Advisory Committee of the RCOG, the Royal College of Midwives, the Royal College of General Practitioners and the Obstetric Anaesthetists Association. In the academic arena, the findings will be presented at specialist conferences, such as the British Maternal and Fetal Medicine Society and the Annual Conference of the Faculty of Public Health. The findings of this study will also be submitted for publication in peer-reviewed journals such as the British Journal of Obstetrics and Gynaecology. The NPEU reports directly to the UK Department of Health and has a distinguished record for influencing health policy both in the UK and worldwide.

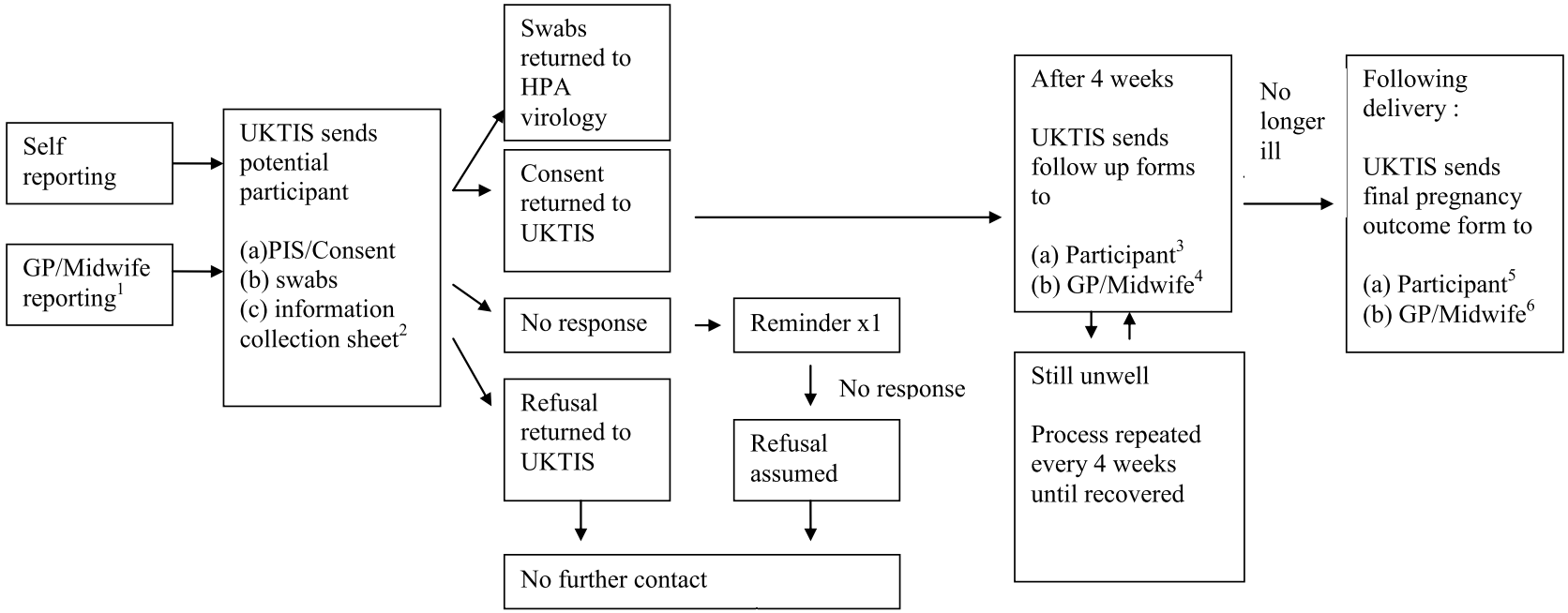
13 Flow Diagrams

(a) Overall study structure



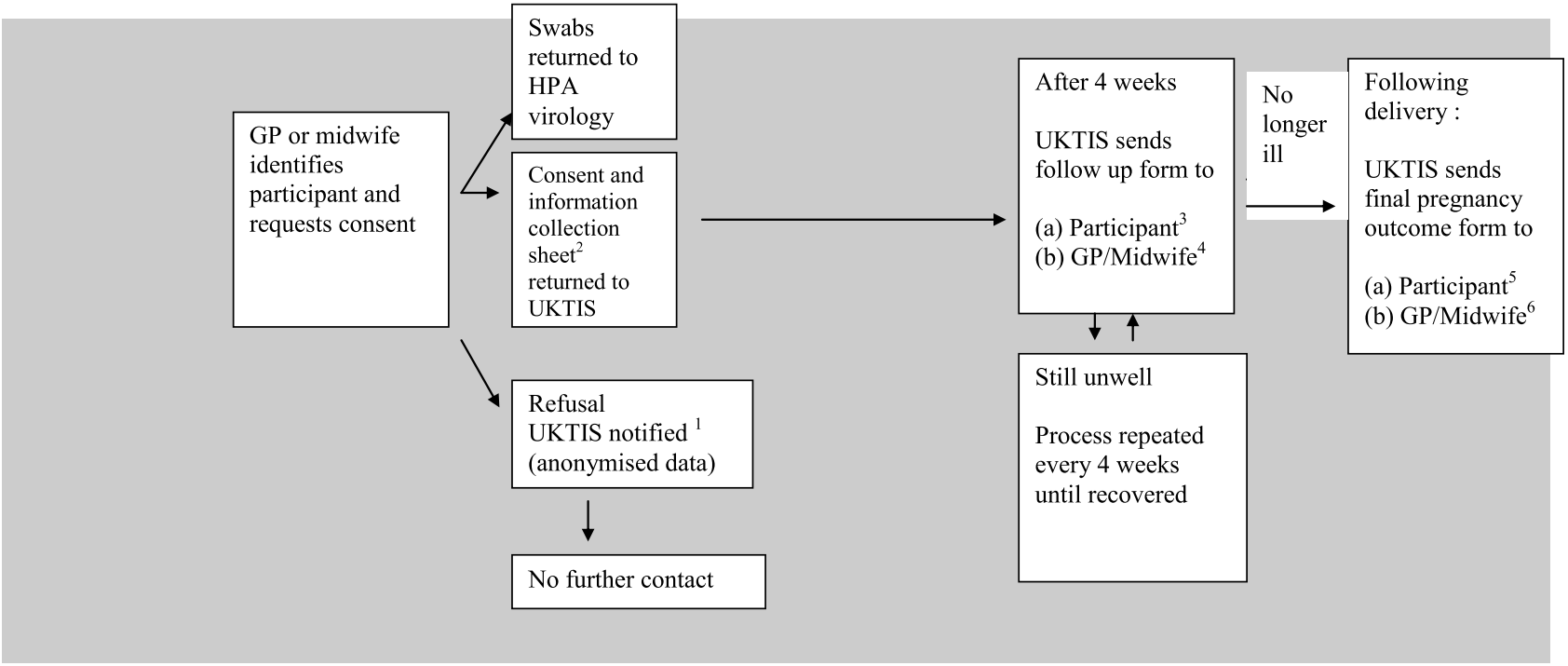
- **Oct 09 – Dec 09 Monthly review of emerging data to produce guidance on H1N1 management in pregnancy**
- **Feb 2010: Final report and guidance: Management and outcomes of H1N1v infection in pregnancy**

(b) Non-network recruiting in primary care



[1] Notification made using "UTKIS Antiviral Exposure in Pregnancy – Patient Reporting Form" (Appendix 1), [2] Initial information collection sheet - participant[Appendix 2], [3]Four week update form – participant [Appendix 3], [4] Four week update form – health professional [Appendix 4], [5] Final pregnancy outcome form – participant [Appendix 5], [6]Final pregnancy outcome form – health professional [Appendix 6]

(c) Network recruiting in primary care (provisional)



[1] Declined consent form (Appendix 7), [2] Initial information collection sheet [Appendix 2], [3]Four week update form – participant [Appendix 3], [4] Four week update form – health professional [Appendix 4], [4] Final pregnancy outcome form – participant [Appendix 5], [5] Final outcome form – health professional [Appendix 6]

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