

**Review of Maternal  
Deaths in the United  
Kingdom related to  
A/H1N1 2009 Influenza**

**December 2010**

## **Contents**

<b>Section</b>		<b>Page</b>
	Acknowledgements	3
<b>1</b>	Introduction and context	4
<b>2</b>	Methodology	6
<b>3</b>	Description of maternal deaths	7
<b>4</b>	Place, timing and cause of death	8
<b>5</b>	Presenting symptoms and signs	9
<b>6</b>	Indication and timing of hospital admission	11
<b>7</b>	Initial management on hospital admission	12
<b>8</b>	Infection control	15
<b>9</b>	Involvement of the multidisciplinary team	16
<b>10</b>	Medication	17
<b>11</b>	Clinical complications	19
<b>12</b>	Admission to high dependency or intensive care unit	20
<b>13</b>	Gestation and mode of delivery, and pregnancy outcome	21
<b>14</b>	Post-mortem examination	22
<b>15</b>	Conclusions	23
	References	25
	Appendix A	27

## Acknowledgements

### Author

Jo Modder, Consultant Obstetrician UCL Elizabeth Garrett Anderson Institute for Women's Health and UCLH NHS Foundation Trust

### Other contributors

- Amy Sullivan, Research Fellow, CMACE – Review of literature and contribution to methodology chapter
- Anna Springett, Senior Data Analyst, CMACE – data analysis
- Alison Miller, Programme Director, CMACE – facilitation of panel reviews
- Dr Imogen Stephens, Clinical Director, CMACE

### Panel Review Group

Gwyneth Lewis (Chair)	Public Health
Maureen Baker	General practitioner
Barbara Bannister	Infectious diseases
Tom Clutton-Brock	Intensivist
Mervi Jokinen	Midwife
Boon Lim	Obstetrician
Sebastian Lucas	Pathologist
Patrick O'Brien	Obstetrician
Nicola Savage	Midwife
Ann Seymour	Lay representative
Farah Siddiqui	Obstetrician
William Tong	Virologist
Susan Tuck	Obstetrician
David Williams	Obstetric physician

### Other acknowledgements

We would like to express our thanks to all maternity Unit staff who completed and returned data collection forms, the CMACE regional office staff who were involved in the collection of data and the staff in the affiliated nations of Scotland, Northern Ireland and Wales.

### Funding

The work was funded as part of the Maternal Death Enquiry by the National Patient Safety Agency; the Department of Health, Social Services and Public Safety of Northern Ireland; NNHS Quality Improvement Scotland (QIS); and the Channel Islands and the Isle of Man. The views expressed are those of CMACE and not those of the funding bodies.

## 1 Introduction and context

Influenza is a contagious respiratory illness caused by influenza viruses. It is transmitted by droplet inhalation, contact with infected objects or surfaces, or direct contact with an infected person. Clinical symptoms and signs can range from mild to severe and it can lead to mortality. There are three main types of influenza virus: A, B and C, with only influenza A being associated with pandemics. There are different subtypes of influenza A dependent on the identity of the haemagglutinin (H) and neuraminidase (N) glycoproteins on the surface of the viral envelope. Influenza A outbreaks may be caused by different viral subtypes, or by the same subtype which has developed changes in the haemagglutinin amino-acids. In addition, different viruses can exchange one or more of their eight RNA segment (genetic reassortment). Confirmed influenza pandemics in the last century have included the 1918 pandemic (Spanish influenza), which appeared to be transmitted from humans to swine; the 1957 A/H2N2 pandemic (Asian influenza); and the 1968 A/H3N2 pandemic (Hong Kong influenza).

The first reported outbreak of A/H1N1 2009 influenza occurred in Mexico City in March 2009, and the H1N1/09 virus was identified in April 2009, being identified as a combination of bird, swine and human influenza viruses. The first two UK cases were confirmed in the same month, and a pandemic was declared by the World Health Organisation on 11 June 2009, with nearly 30,000 confirmed cases worldwide at that time. In the UK, an influenza vaccination programme against A/H1N1 2009 influenza commenced on 21 October 2009.

Previous studies have shown that pregnant women have an increased risk of influenza complications.<sup>1-3</sup> In the recent A/H1N1 2009 pandemic, there was a four times higher rate of hospital admission in pregnant women compared to the general population<sup>4</sup>, and a seven times higher risk of admission to an intensive care unit.<sup>5</sup> Although numbers are small, it has also been suggested that the 2009 pandemic was associated with a higher number of maternal deaths than expected.<sup>4,6</sup>

Between 1 April 2009 and 13 January 2010, 12 maternal deaths in the UK and one maternal death in the Republic of Ireland in women with a diagnosis of A/H1N1 2009 influenza, were reported to the Centre for Maternal and Child Enquiries (CMACE). Eight of these deaths, all of which had polymerase chain reaction (PCR) confirmation of A/H1N1 2009 infection, were assessed by a central review panel using confidential enquiry methodology.

From July 2009, a number of guidance documents have been produced in the UK for health professionals and maternity services<sup>7-12</sup>, and in October 2009 the Department of Health (DH), England and the Royal College of Obstetricians and Gynaecologists (RCOG) published clinical management guidelines for pregnancy in relation to pandemic A/H1N1 2009 influenza.<sup>13</sup> The recommendations contained in the guidance documents were used as standards against which to assess clinical care provided to women in this enquiry (see Appendix A).

The Chief Medical Officer's bulletin (England) has highlighted that the H1N1/09 virus is likely to be the predominant strain in the 2010/2011 influenza season<sup>14</sup>, and it is vital that lessons are learned from the maternal deaths that have occurred in order to minimise the risk of future mortality. It is also anticipated that the learning points in this report will be relevant to any future pandemic caused by another viral strain.

Recognising the potential for A/H1N1/2009 to cause further serious morbidity and mortality amongst pregnant women in the 2010/2011 influenza season, the

## CONFIDENTIAL NOT FOR CIRCULATION

Department of Health/Health Protection Agency (HPA) has modified its advice on seasonal flu vaccination for this winter period. All pregnant women (not just those otherwise deemed at clinical risk) have now been advised to receive the trivalent seasonal flu vaccine for 2010/11 (which contains A/H1N1/09) during this influenza season, provided they have not already received A/H1N1/2009 (swine influenza) vaccine. In addition, relevant prescribing regulations have now been updated for the prescribing of antiviral medication in primary care during periods when national surveillance schemes indicate that influenza A or B is circulating. Pregnant women are now included in those considered 'at clinical risk' from seasonal influenza and eligible to receive antiviral medication. It is important that all healthcare professionals involved in the care and management of pregnant women, at all stages and in all settings, are aware of this advice and encourage all pregnant women to receive immunisation and / or antiviral medication as appropriate. The HPA advice 'H1N1 winter flu: Urgent advice for providers of maternity services' can be viewed at <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/PandemicInfluenza/PandemicH1N1Influenza/SIGuidanceIndex/>

## 2 Methodology

CMACE Regional Offices in England, Wales and Northern Ireland receive notifications of maternal deaths from NHS Trusts, Local Supervising Authority Midwifery Officers (LSAMO), and from other sources such as the local or national media. In Scotland maternal death case ascertainment is achieved using information from the General Register Office for Scotland (GROS), the Reproductive Health Programme of NHS Quality Improvement Scotland and the wider clinical community.

An initial notification form, the Maternal Death Notification, is completed by the Regional Office in contact with the notification source. A minimum dataset, the Maternal Death Surveillance Form, is then received from the notification source which includes information on demographics, underlying medical conditions and circumstances surrounding the death.

From September 2009, a Flu Addendum was added to the Maternal Death Notification. The question "Was the woman diagnosed as having influenza A/ H1N1 (swine flu)?" was asked for every maternal death in the UK upon notification to CMACE, and if this was the case, a short questionnaire completed. Notification based on clinical diagnoses as well as virological confirmation of A/H1N1 2009 influenza was accepted at this stage, in order to ensure that no cases were missed. Maternal deaths due to A/H1N1 2009 influenza were defined as deaths occurring during pregnancy or up to 6 months following termination, miscarriage or delivery, where A/H1N1 2009 influenza was confirmed prior to 42 days after the end of pregnancy. For the women who died prior to the Flu Addendum being available, the Regional Offices were already aware of the influenza-related maternal deaths in their area and obtained retrospective information from the units to complete the Flu Addendum.

Complete medical records were requested for all maternal deaths after notification. These included antenatal and intrapartum clinical records, correspondence, investigation results and post mortem reports where applicable. All medical records were fully anonymised and made available to members of the review panel prior to the meeting, together with the Maternal Death Notification and Surveillance forms, the Flu Addendum, and any completed sections of the Maternal Death Report (MDR1) form (completed by local clinicians at the maternity unit notifying the death).

The review panel for the eight cases in this report was a multidisciplinary group of 11 health professionals including a Chair, and a lay representative. A range of disciplines was represented including obstetrics, infectious diseases, obstetric medicine, critical care, pathology, virology, midwifery and general practice. A number of observers from CMACE also attended the meeting but did not participate in the discussions.

A semi-structured enquiry proforma was used to capture both factual information and the views of the panel about the clinical circumstances and the care provided. Information was transcribed onto electronic and hard copies of the proforma by two members of the CMACE project team. Data was entered into an Access database and imported into Microsoft Excel. All data was re-checked against the medical records by the lead author.

### 3 Description of maternal deaths

The eight women in this review presented with symptoms between May and October 2009, and their dates of death ranged from June to December 2009.

All the maternal deaths were notified to CMACE within nine days of death, with the average being five days after death.

There were three additional women in the UK and one in the Republic of Ireland that died prior to the panel meeting, but it was not possible to obtain the anonymised medical records prior to panel review.

#### 3.1 Socio-demographics and co-morbidities

The eight women who died had a median age of 28.5 years (range 17 – 39 years). Four women were White British, three were Asian and one was Black African. The median Body Mass Index (BMI) was 23.5 kg/m<sup>2</sup> (range 14.2 - 36.6 kg/m<sup>2</sup>). Median parity was 2 (range 0 – 6) and all women had singleton pregnancies.

Co-morbidities including asthma, neuro-developmental and neurological conditions, chronic lung and heart disease, blood, kidney, liver disorders, metabolic and endocrine conditions, weakened immune systems and morbid obesity, can increase the risk of influenza complications.<sup>15</sup> In Australia and New Zealand, 27.9% of patients diagnosed with A/H1N1 2009 influenza had a co-existing clinical condition and this was independently associated with death in hospital (OR 2.56, 95% CI 1.52-4.30, p<0.001).<sup>5</sup> In Victoria, Australia, co-morbidities were present in 51% of pregnant women admitted to hospital with A/H1N1 2009 influenza, with asthma, obesity and diabetes being most frequently described.<sup>16</sup>

Five of the eight women in this review had clinically important co-morbidities and these are described in Table 1.

**Table 1**  
**Maternal co-morbidities in UK maternal deaths related to A/H1N1 2009 Influenza**

Co-morbidities
Childhood asthma (not currently active), obstetric cholestasis
Paraplegia, anaemia
Previous cerebrovascular accident (CVA), smoking 20 cigarettes per day
Underweight (BMI 17), smoking 10 cigarettes per day
Obese (BMI 36.6)
Underweight (BMI 14.2), scoliosis, hyperemesis gravidarum, anaemia

#### 4 Place, timing and cause of death

All eight women died in an intensive care unit.

All of the women died in the postpartum period, at a median of 16 days (range 0-56 days) after delivery.

The cause of death<sup>a</sup> was recorded as

- H1N1 influenza (2 cases)
- ARDS / severe respiratory failure (4 cases)
- Intra-cerebral bleed secondary to anticoagulation for extracorporeal membrane oxygenation (ECMO) (2 cases)

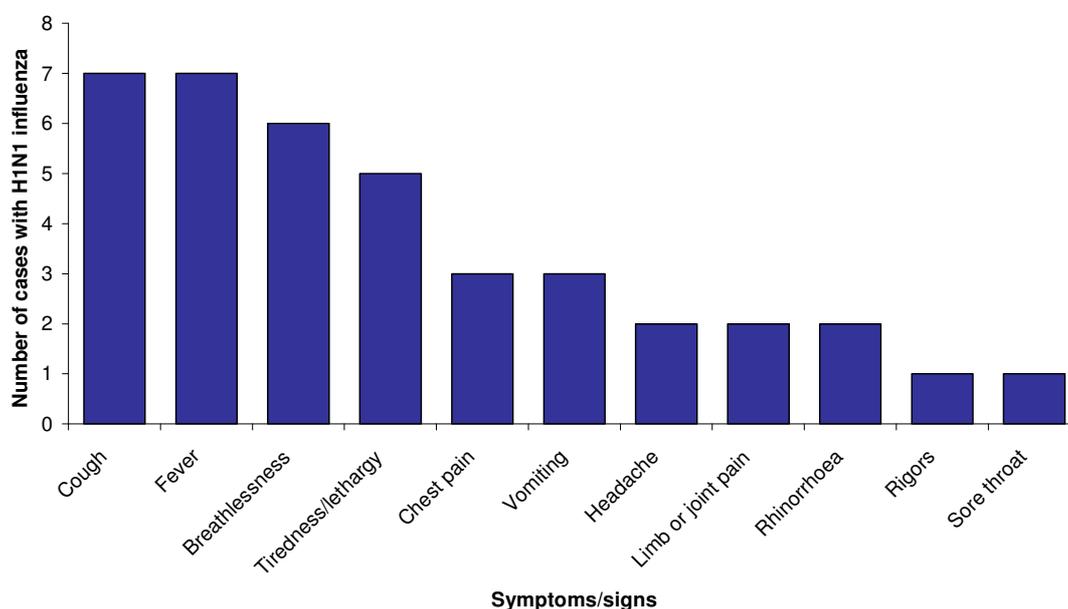
All eight women were tested for A/H1N1 2009 influenza by polymerase chain reaction (PCR) testing and all had positive results. However, two of the eight women had an initial false negative result and then tested positive on repeat testing 5 days and >1 week later respectively.

<sup>a</sup>The death certificate was available for six out of eight women.

## 5 Presenting symptoms and signs

Figure 1 shows the presenting symptoms and signs of the eight women. Fever and cough were almost universal (apart from one woman who presented with maternal collapse), and five women had a fever  $>38^{\circ}\text{C}$ . Breathlessness was noted to be present in six of the eight women. These findings are consistent with previous observational data of pregnant women with A/H1N1 2009 influenza in the USA and Australia, with fever present in 84-97%, cough in 93-100% and breathlessness in 37-41% of women.<sup>4,6,16</sup> Rhinorrhoea, sore throat and joint pains were uncommon in this group of women.

**Figure 1**  
**Symptoms and signs at initial presentation in maternal deaths related to H1N1 influenza**

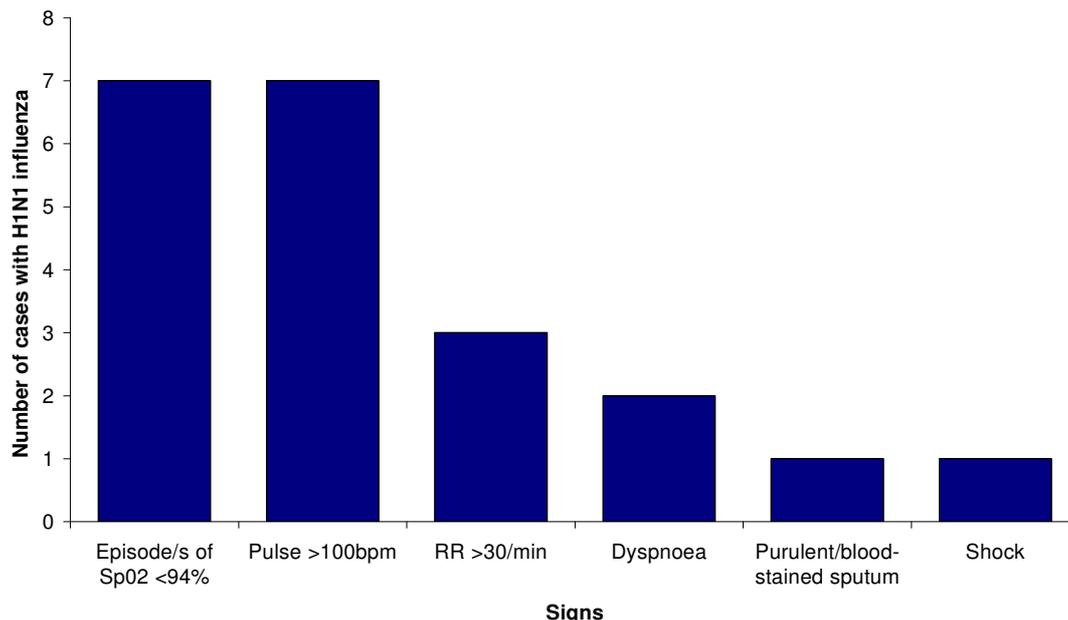


For two out of the eight cases it was documented in the medical records that a family member or close contact had had an influenza-like illness within the seven days prior to presentation.

None of the women were documented to have received a seasonal flu vaccine in 2008/2009. None of the women had received a specific A/H1N1 2009 Influenza vaccine as in all eight cases the initial presentation occurred prior to the start of the A/H1N1 2009 UK vaccination programme on 21<sup>st</sup> October 2009.

Figure 2 indicates the women who had signs of severe H1N1 influenza at presentation. The most consistent signs were a tachycardia  $>100$  beats per minute and episodes of hypoxia, which occurred in seven women. It should be noted that none of the three women with a respiratory rate  $>30$  per minute on admission were documented in the medical records to be dyspnoeic, but it is likely that overall five women had shortness of breath.

**Figure 2**  
**Signs of severe disease at presentation in maternal deaths related to H1N1 influenza**



### 5.1 Unusual clinical presentations

Two of the women had extremely rapid deterioration in respiratory function. In the first case, there was a few days' history of coryza and a one-day history of vomiting which apparently improved on the morning of presentation; however in the afternoon of the same day she was cyanosed and had severe hypotension, tachycardia and extremely low oxygen saturations on admission to hospital. In the second case, the woman had normal oxygen saturations on admission with no signs of dyspnoea. However, an hour later her O<sub>2</sub> saturation had dropped significantly (on air) and after eight hours she was hypoxic on 50% inspired oxygen, with the decision being taken at that time for delivery and mechanical ventilation. Louie et al have previously reported that pregnant women with A/H1N1 2009 influenza frequently presented with mild or moderate symptoms but then had rapid clinical deterioration.<sup>6</sup>

One woman who presented with signs of shock had simultaneous A/H1N1/09 influenza and bacterial septicaemia.

Six of the eight women were noted to have a raised C-reactive protein (CRP) ranging from 68 – 112 at first admission, although it is traditionally viewed that CRP is not usually raised in viral infections. A seventh woman developed a raised CRP of 105 on the day after admission and there was no documentation of CRP in the eighth case, possibly due to the severity of the woman's clinical condition on admission. Two women presented with pleuritic chest pain – this has not been noted in previous studies of pregnant women with A/H1N1 2009 influenza.<sup>4,16</sup>

## 6 Indication and timing of hospital admission

All eight women were admitted to hospital prior to death. Six women were admitted due to respiratory symptoms and signs and two were admitted for obstetric reasons. The first of these women was admitted for planned induction of labour at term for obstetric cholestasis and developed shortness of breath, low oxygen saturations and pyrexia  $>38^{\circ}\text{C}$  following emergency caesarean section; at this time she volunteered a 3-day history of cough. The second woman went into spontaneous preterm labour and delivered during ambulance transfer to hospital. Soon after admission she was noted to have a fever  $>39^{\circ}\text{C}$  and gave a three-day history of cough and feverish symptoms. It is possible that her respiratory illness may have precipitated preterm delivery.

Of the six women presenting initially with respiratory symptoms, four were admitted more than 48 hours but less than seven days after onset of symptoms, and one woman was admitted more than seven days after onset of symptoms. In this case the woman presented to her general practitioner (GP) with a history of a few days' cough. She was prescribed zanamivir (Relenza) but did not take the medication, and presented to hospital a week after her symptoms had started. At her first hospital presentation she was prescribed antibiotics and discharged home. She re-presented two days later with increasing shortness of breath, tachycardia  $>100$  beats per minute, and decreased oxygen saturation.

In one case it was not possible for panel members to definitely identify the time interval between onset of symptoms and admission to hospital.

The review panel considered that in some cases there was evidence of a delay in hospital admission; in one case the GP did not recognise the symptoms of possible H1N1 influenza, and in two further cases the hospital team did not consider the possibility of H1N1/09 influenza, with consequent discharge of the patient on oral antibiotics. In a fourth case a woman with postnatal onset of symptoms was discharged on oral antibiotics and re-admitted after 3 days.

## 7 Initial management on hospital admission

### 7.1 H1N1 influenza testing

The DH/RCOG clinical management guideline for pandemic H1N1 influenza<sup>13</sup> recommends that all patients admitted to hospital with influenza-like illness should be tested for A/H1N1 2009 influenza in order to facilitate appropriate treatment and infection control precautions, with priority being given to virological confirmation of H1N1 in high-risk groups such as pregnant women, patients admitted to critical or high dependency care or those with influenza-related pneumonia.

All eight women had positive virological confirmation of H1N1 influenza using polymerase chain reaction (PCR) testing of nasal swabs. Two women initially had false negative swab results.

The panel noted a delay in testing for three women, ranging from two to five days after hospital admission (or readmission where this occurred). In a further woman the wrong swabs were initially used. The main underlying issue appeared to be a lack of consideration of H1N1/09 influenza as a possible diagnosis.

### 7.2 Initial assessment

It is important that health professionals assessing pregnant women are aware that symptoms and signs may be caused by influenza.

All eight women had assessment of oxygen saturation by pulse oximetry on admission.

For five women, there was initially a failure to consider H1N1 influenza as a possible cause of the presenting symptoms. In these women, bacterial pneumonia was considered to be the probable diagnosis and antibiotics commenced. In one instance, H1N1 influenza was noted to be 'unlikely' on initial assessment, but was then documented as the main diagnosis after review by a second clinician. In another case with respiratory signs and multiple areas of shadowing, consolidation and effusion on chest X-ray, the differential diagnosis documented included tuberculosis, pulmonary embolism and Legionnaire's disease, but not A/H1N1 09 influenza.

### 7.3 Excluding possible differential diagnoses

Severe symptoms and signs of influenza (dyspnoea, chest pain on breathing, purulent or blood stained sputum, respiratory rate >30 per minute, hypoxia with SpO<sub>2</sub> ≤ 94%, persistent tachycardia >100bpm, dehydration and shock, rigors, seizures, altered conscious level) may be also be caused by other medical or obstetric conditions such as urinary tract infection, co-existing bacterial pneumonia, chorioamnionitis or pulmonary embolism. The DH/RCOG guideline states that in the event of any severe signs or symptoms, other differential diagnoses should be excluded.<sup>13</sup>

Five of the eight women had appropriate steps taken to exclude possible differential diagnoses. In one case, however, a chest X-ray was not requested for three days following admission although the woman had signs of possible pneumonia. It is unclear whether this was due to concerns about fetal and/or maternal irradiation. In a further case, no investigations were performed to exclude pulmonary embolus although the woman presented with pleuritic chest pain. One woman had a tachycardia of 130pm and the panel felt that a creatine kinase test should have been done to exclude myocardial infarction.

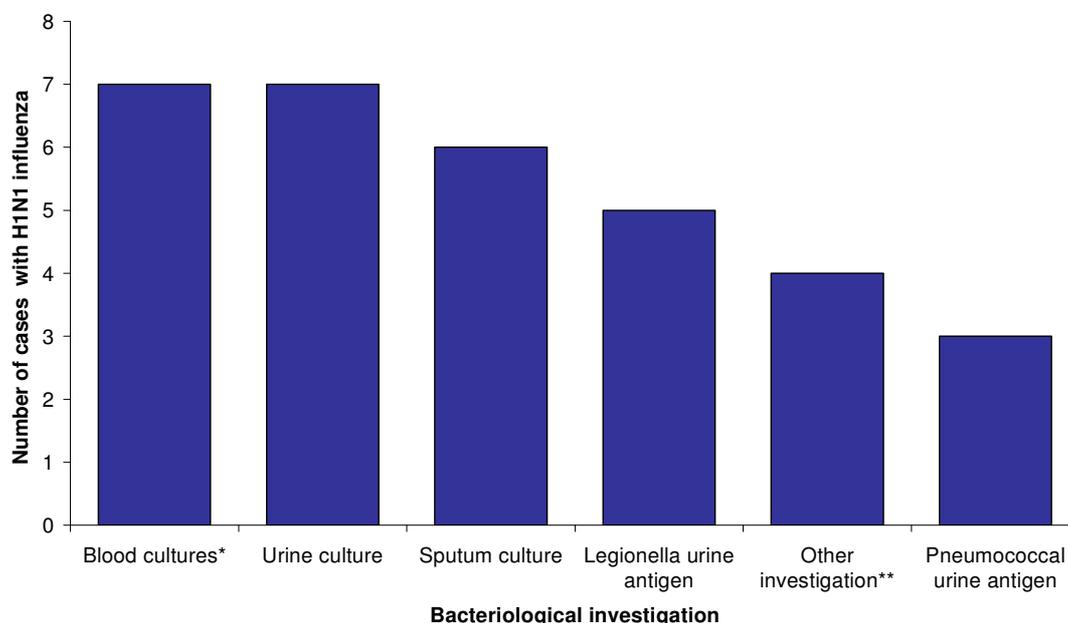
For one woman, computed tomography pulmonary angiogram (CTPA) was considered in order to exclude pulmonary embolus, but was not carried out until late the following morning with a resulting significant diagnostic delay.

### 7.4 Bacteriological investigations

The DH/RCOG guideline recommends the following bacteriological investigations as a minimum: blood cultures; sputum culture; pneumococcal and legionella urine antigen (where available locally).<sup>13</sup>

Figure 3 shows information obtained from panel enquiry data on the bacteriological investigations which were carried out for the eight women. The majority of women had urine, sputum and blood cultures (one woman declined blood cultures). Legionella and pneumococcal urine antigens were tested for in five and three women respectively. This information was not validated from the case notes.

**Figure 3**  
**Bacteriological investigations prior to maternal death related to H1N1 influenza**



\*one was offered but declined by woman

\*\*other bacteriological investigations included MRSA swabs, atypical infection screen and tests for tuberculosis.

## CONFIDENTIAL NOT FOR CIRCULATION

### **7.5 Management plan**

Once H1N1 influenza was diagnosed, there was evidence of a clear management plan in the medical records for five out of eight women who died. A sixth woman had a clear management plan but only after admission to the intensive care unit.

## 8 Infection control

A recent systematic review of physical interventions to reduce the spread of respiratory viruses showed that wearing masks, gloves, gowns and frequent handwashing all significantly reduce the risk of severe acute respiratory syndrome.<sup>17</sup> The advice for health professionals and the algorithm for management of influenza in pregnancy, prepared by the RCOG, Royal College of Midwives (RCM) and Department of Health in August 2009, recommended that if a woman with suspected or confirmed H1N1 influenza was admitted to hospital, the hospital Infection Control team should be informed<sup>7</sup>; and the DH/RCOG guideline recommends that full infection control measures should be observed for suspected cases pending laboratory results, with isolation preferred to cohorting.<sup>13</sup>

For two of the eight women who died, there was documented evidence in the medical records that the hospital infection control team had been informed of their admission. Three out of eight women were nursed in isolation; for a further four women it was not possible to assess this from the medical records. One of the women was not nursed in isolation, and in this case the nursing records noted that medical staff had advised against barrier nursing as H1N1 influenza was unlikely and the presumptive diagnosis was bacterial pneumonia.

For two women it was documented in the care plan that provision had been made for both the woman and health care personnel to wear surgical masks.

## 9 Involvement of the multidisciplinary team

Good multidisciplinary working is vital in the context of pregnant women admitted with respiratory symptoms who are at risk of rapid clinical deterioration and who may be cared for in venues unfamiliar to some team members. The DH/RCOG guideline recommends that pregnant women admitted with respiratory complications should be managed jointly between the obstetric and medical teams, and an assessment made with respect to the best place to manage the woman. In the event of influenza complications, early involvement of the obstetric anaesthetists, respiratory physicians and haematologists is important in order to set out a clear management plan.<sup>13</sup>

In six out of eight women there was evidence of appropriate involvement of the obstetric anaesthetist, physician and haematologist following hospital admission. In the seventh case there was no documented evidence of haematology involvement from review of the medical records and in the eighth it was not possible to assess multidisciplinary involvement from the notes available. In one of the cases there was strong evidence of a lack of collaboration between obstetricians and intensivists, with no physical review being carried out by the obstetric team and inadequate senior obstetrician input. The passivity of obstetric involvement in this case was reflected by the fact that the intensivists were asked by the obstetrician to make the decision for delivery if they felt it was warranted by deterioration in the woman's clinical condition.

## 10 Medication

### 10.1 Type and duration of antiviral treatment

Oseltamivir (Tamiflu) and zanamivir (Relenza) are neuraminidase inhibitors effective against A/H1N1 2009 influenza. Zanamivir is usually administered by oral inhalation and is effective in the respiratory tract, but does not reach effective levels systemically. It is therefore recommended as first line treatment for pregnant women in order to minimise placental transfer to the fetus. However, for women with severe or complicated influenza or with a prior history of asthma or chronic pulmonary disease, oseltamivir is recommended as first line treatment.<sup>12</sup> The recommended duration of antiviral therapy is 10 days.

All the women received oseltamivir (Tamiflu). One woman also received intravenous zanamivir and another received ribavirin via nasogastric tube in view of the severity of her condition. The review panel considered that all eight women had received appropriate antiviral medication. There was evidence in the notes for six out of eight women that they had received a complete antiviral treatment course. It was noted that one woman received double the recommended dose of oseltamivir via nasogastric tube, this was documented to be due to concerns with absorption of medication from the gut.

### 10.2 Timing of antiviral treatment

The DH/RCOG guideline recommends that antiviral treatment should be commenced as early as possible, particularly within the first 48 hours of onset of symptoms.<sup>13</sup> Randomised controlled clinical trials have shown that oseltamivir and zanamivir will reduce the severity of seasonal influenza if commenced within 48 hours of illness onset.<sup>18-19</sup> In the A/H1N1 2009 influenza pandemic, it was noted that antiviral drugs commenced after 48 hours up to 7 days after onset of symptoms also appeared to reduce illness severity.<sup>20</sup>

Five of the eight women who died received antiviral medication between 48 hours and 7 days after the onset of symptoms, while three women first received antiviral medication >7 days after the onset of symptoms. In seven of the maternal deaths the review panel considered that there was an avoidable delay in commencing antiviral treatment. Factors contributing to this delay included:

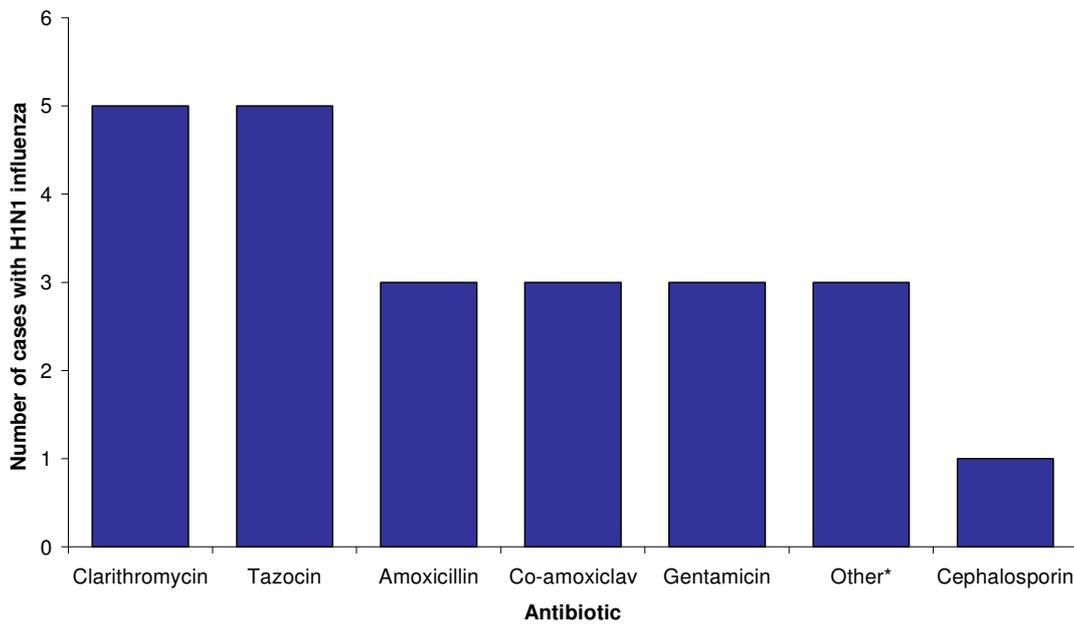
- delay in testing for H1N1 influenza
- patient non-compliance with medication prescribed by the GP
- the wrong swab used to test, necessitating repeat swabs
- initial false negative swab in two cases
- failure on the part of the health professionals to consider H1N1 influenza as a possible cause of the patient's symptoms
- decision taken by health professionals not to commence treatment until a positive H1N1 influenza swab had been received (in two cases this was based on advice from the microbiologist)

None of the eight women had any adverse effects ascribed to the antiviral treatment.

### 10.3 Antibiotic treatment

All eight women who died received intravenous antibiotic treatment, six to treat presumed bacterial pneumonia and two due to severe signs and symptoms of influenza. Figure 4 shows the types of antibiotics used. In seven out of eight cases, there was evidence from the medical records that the most appropriate antibiotic therapy had been discussed with a microbiologist. The duration of antibiotic treatment ranged from one day (in a woman who died less than 24 hours after admission) to 49 days, with a median of 17 days. For all eight women, the initiation, type and duration of antibiotic treatment was deemed appropriate by the review panel.

**Figure 4**  
**Antibiotic treatment in UK maternal deaths related to H1N1 influenza**

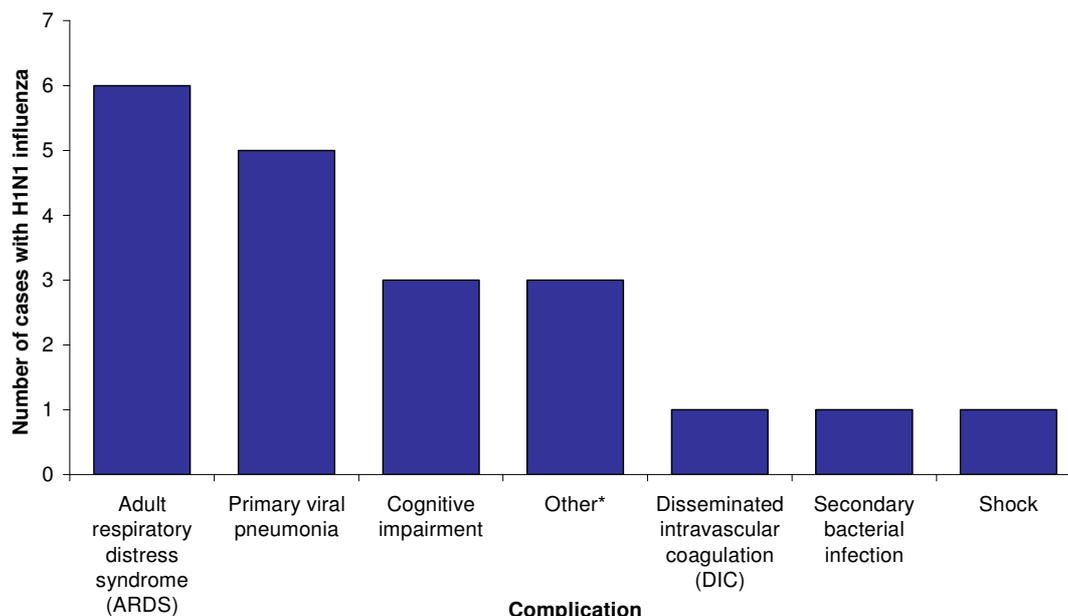


\*one case had fusidic acid, benzylpenicillin, vancomycin and imipenem, another had metronidazole and the third had piperacilin and meropenem

## 11 Clinical complications

Figure 5 shows the complications which occurred in the eight women who died. Primary viral pneumonia or adult respiratory distress syndrome were the commonest complications, whereas secondary bacterial pneumonia was only diagnosed in one case. Two women died of major intracerebral bleeds following anticoagulation for extracorporeal membrane oxygenation (ECMO).

**Figure 5**  
**Clinical complications in UK maternal deaths related to H1N1 influenza**



\*one case had rectus sheath haematoma, intraperitoneal and intracerebral bleed, another case had hypotension and oliguria and the third had pneumothorax and intracerebral bleed

The management of complications was felt by the review panel to be appropriate apart from

- a case of pneumonia where a chest X-ray was not carried out until 3 days after admission despite a presentation of fever, breathlessness, productive cough, bilateral expiratory wheeze on examination and a differential diagnosis of chest infection or pulmonary embolus. It was not clear from the notes whether a decision was made not to carry out a chest X-ray due to concerns about radiation exposure during pregnancy. When the chest X-ray was eventually done, it was noted to be very abnormal with widespread consolidation and pleural effusion.
- a case of ARDS where it was felt that extracorporeal membrane oxygenation (ECMO) should have been considered in view of the inability to achieve adequate oxygenation despite mechanical ventilation and 100% inspired oxygen.

## **12 Admission to high dependency or intensive care unit**

All eight women were admitted to an intensive care unit (ICU) due to respiratory complications and in one case, septicaemia. In two cases the review panel considered that there was a delay in admission. In one case there was evidence of severe pneumonia including low oxygen, but the severity of the woman's illness was not appreciated until she was reviewed by a consultant obstetrician. In the second case the severity of the woman's illness was not recognised by staff in the Accident & Emergency Department although she had a very high respiratory rate. All eight women, during ICU admission, had blood count and coagulation profile carried out in a timely manner and had appropriately early involvement of the haematologist.

All of the eight women who died required mechanical ventilation. Five women received special ventilatory support measures: three received extracorporeal membrane oxygenation (ECMO) and two received high frequency oscillation.

### **13 Gestation and mode of delivery, and pregnancy outcome**

The median gestation at delivery was 34.5 weeks (range 26 – 40 weeks). Three of the eight women went into spontaneous preterm labour at 26, 29 and 33 weeks respectively and had a vaginal delivery, two had induction of labour at term but proceeded to caesarean section and three had a planned caesarean section between 34 and 36 weeks gestation due to deteriorating maternal respiratory function. Six of the babies were live births, one was a stillbirth in a woman who presented with signs of shock and intrauterine death, and one died in the neonatal period.

#### **13.1 Consideration of timing and mode of delivery**

The consideration of timing and mode of delivery was thought to be appropriate for four of the five women who had their delivery expedited by induction of labour or planned caesarean section. In one case, however, appeared to be a lack of joint decision-making between the obstetricians and the intensivists; the decision for caesarean section was made by the ITU consultant and the caesarean was then performed by an obstetric SpR.

## **14 Post-mortem examination**

A post-mortem was planned and carried out for one of the maternal deaths, and included bacteriological and virological examination. The findings on post-mortem were strongly suggestive of viral pneumonia with diffuse alveolar damage and organisation, with little normal lung tissue remaining. There was no evidence of bacterial pneumonia, and a low level of H1N1/09 virus was detected in the lungs, a lymph node and in the blood.

## 15 Conclusions

This report provides information about the clinical characteristics and care provided to women who died due to A/H1N1 2009 influenza.

As with previous published reports, fever and cough were an almost universal presentation in this cohort, and shortness of breath was also common. The majority of women had no documented history of contact with influenza-like illness, compared to 32% of pregnant women in a population-based study in the USA.<sup>4</sup> Tachycardia and hypoxia were almost universal signs of severe disease. Only one woman had evidence of secondary bacterial infection, similar to the Californian cohort where two of 102 pregnant/postpartum women had microbiological evidence of bacterial co-infection with *Staphylococcus aureus*.<sup>6</sup>

Three of the women who died received extracorporeal membrane oxygenation (ECMO). ECMO is a system of cardiopulmonary bypass whereby blood is oxygenated externally and then returned to the body. ECMO decreases the risk of lung damage from high pressure ventilation and high oxygen concentrations which are required during conventional ventilation, and has been shown in a randomised controlled trial to significantly decrease morbidity at 6 months in adults with severe respiratory failure.<sup>21</sup> There are four ECMO centres in the UK, and of these Glenfield Hospital in Leicester provides care to adult patients. ECMO does carry a risk of serious complications consequent on anticoagulation and it is therefore usually reserved for patients 1) with severe but potentially reversible respiratory failure, 2) who have not responded adequately to conventional ventilation and 3) who have had less than seven days of maximum ventilation. In the UK, the third criterion was relaxed for pregnant women during the A/H1N1 2009 influenza pandemic, as they were on the whole a healthy population prior to infection, and ECMO was often the last resort. Of the 17 pregnant/postpartum women referred to the ECMO unit in Leicester during the pandemic, there were four deaths. The other women survived and were referred back to their index hospital. It is unlikely that there would have been any survivors in this group with severe respiratory failure if ECMO had not been offered.

There are some important learning points for healthcare professionals in this report. In many cases, there was late consideration of A/H1N1 2009 influenza as a diagnosis, with the possibility being actively discarded by clinicians in some instances. In two cases women presented initially with obstetric issues only, with the illness presenting insidiously following delivery: this highlights the importance of a high index of clinical suspicion. In addition, two women initially had false negative swab results. The rapid clinical deterioration noted in many cases makes early diagnosis even more important.

In two cases the wrong type of swabs were initially used to test for influenza, necessitating repeat testing and leading to delays in diagnosis, and in two cases an incorrect decision was made to withhold antiviral treatment until a positive swab had been received. In some cases there was lack of a clear management plan, and in one case particularly there was evidence of poor multidisciplinary communication and joint decision-making.

There are a number of differential diagnoses in the presence of respiratory symptoms, and health professionals involved in providing care to pregnant women should be aware that imaging tests such as chest X-ray and CTPA are not contra-

## CONFIDENTIAL NOT FOR CIRCULATION

indicated in pregnancy. Any suspicion of pneumonia or thromboembolism should be investigated promptly and delays in imaging are inappropriate.

Vaccination is one of the main public health responses to influenza in general, and more recently to the A/H1N1 2009 influenza pandemic. Pregnant women are one of the high-priority groups for vaccination, however a previous study has shown that pregnant women have the lowest uptake of influenza vaccination.<sup>22</sup> In England, a joint letter in November 2009 from the Royal Colleges of General Practitioners (RCGP), Midwives (RCM) and Obstetricians and Gynaecologists (RCOG) to nurses and midwives highlighted that some health professionals were either refusing to immunize pregnant women against A/H1N1 2009 influenza or were strongly advising them against immunization. In the same month, the Department of Health communicated to all SHAs, PCTs and NHS Trusts that thiomersal-containing vaccines such as Pandemrix do not pose a risk during pregnancy.<sup>23</sup> In 2010 all pregnant women were included as an 'at clinical risk' population for severe illness and complications caused by seasonal influenza, and were advised to receive seasonal flu vaccination unless they had previously received A/H1N1/2009 monovalent influenza vaccine.

There may also be concerns on the part of women about the safety of antiviral medication during pregnancy, and one of the women in this study did not comply with antiviral medication prescribed by the GP, which unfortunately delayed commencement of treatment. Zanamivir has been shown to have a side-effect profile similar to placebo.<sup>24</sup> Oseltamivir has also been shown to be well-tolerated although one study noted a higher incidence of nausea and vomiting compared to placebo.<sup>25-27</sup> Recent changes to prescribing policy now permit antiviral medication to be prescribed in primary care for pregnant women, as this is considered clinically necessary and during periods where influenza A or B has been confirmed to be circulating.<sup>28</sup>

From the above, it is evident that the government, public health departments and health professionals need to continue to reassure the public including pregnant women that there is good evidence of safety for both flu vaccines and antiviral medication. In addition, the lessons learned from this enquiry should be disseminated to clinicians to ensure that front-line health services will be able to provide the most effective care to women in any future influenza pandemic.

## References

1. Freeman DW, Bamo A. Deaths from Asian influenza associated with pregnancy. *Am J Obstet Gynecol* 1959;78:1172-5.
2. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998; 148:1094-1102.
3. Dodds L, McNeil SA, Fell DB, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ* 2007; 176:463-468.
4. Jamieson DJ, Honein MA, Rasmussen SA et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009, published online July 29, DOI:10.1016/S0140-6736(09)61304-0
5. The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *NEJM* 2009;361:1-10
6. Louie JK, Acosta M, Jamieson DJ, Honein MA for the California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *NEJM* 2010;362:27-35.
7. Algorithm for management of influenza in pregnancy [accessed at RCOG website October 2009]
8. RCOG / RCM Guidance on Swine Flu for pregnant mothers (July 2009)
9. Clinical advice from the RCOG / RCM Pandemic Influenza Planning Group [accessed at RCOG website October 2009]
10. RCOG/RCM/DH Q&A: Managing pregnant women with suspected swine flu—advice for healthcare professionals [August 2009]
11. Department of Health. Pregnancy, breastfeeding and swine flu (updated 15 October 2009)
12. Department of Health. Updated September 2009. Pandemic Influenza: Recommendations on the use of antiviral medicines for pregnant women, women who are breastfeeding and children under the age of one year.
13. Department of Health and the Royal College of Obstetricians and Gynaecologists. October 2009. Pandemic H1N1 2009 Influenza: Clinical management guidelines for pregnancy.
14. Department of Health. Pandemic H1N1 (2009) influenza: CMO's Fortnightly Bulletin for Journalists, Issue 4, Thursday 4 March 2010
15. Centers for Disease Control and Prevention. People at high risk of developing flu-related complications 10 November 2009. [<http://www.cdc.gov/h1n1flu/highrisk.htm>], accessed 15 July 2010.

## CONFIDENTIAL NOT FOR CIRCULATION

16. Hewagama S, Walker SP, Stuart RL, Gordon C, Johnson PDR, Friedman ND, O'Reilly M, Cheng AC and Giles ML. 2009 H1N1 Influenza A and Pregnancy Outcomes in Victoria, Australia. *Clin Infect Diseases* 2010;50:686-690.
17. Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Foxlee R, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. *BMJ* 2009;339:b3675
18. Makela MK, Pauksens K, Rostila T et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomised, double-blind, placebo-controlled European study. *J Infection* 2000; 40 (1):42-8
19. Hayden FG, Treanor JJ, Fritz RS et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA* 1999; 282(13):1240-6
20. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009. *N Engl J Med* 2009; 361 (10.1056/NEJMoa0906695)
21. Peek G, Mugford M, Tiruvaipati R et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; 374: 1351-63.
22. Lu P, Bridges CB, Euler GL, Singleton JA. Influenza vaccination of recommended adult populations, US, 1989–2005. *Vaccine* 2008; **26**: 1786–93
23. A (H1N1) swine influenza: Phase Two of the Vaccination Programme – letter from Ian Dalton, National Director of NHS Flu Resilience. 19 November 2009
24. Lalezari J, Campion K, Keene O et al. Zanamivir for the treatment of influenza A and B infection in high-risk patients: A pooled analysis of randomized controlled trials. *Archives Int Med* 2001; 161(2):212-7
25. Hayden FG, Jennings L, Robson R et al. Oral oseltamivir in human experimental influenza B infection. *Antiviral therapy* 2000; 5(3):205-13
26. Treanor JJ, Hayden FG, Vrooman PS et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA* 2000; 283(8):1016-24.
27. Nicholson KG, Aoki FY, Osterhaus AD et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet* 2000; 355(9218):1845-50
28. H1N1 winter flu: Urgent advice for providers of maternity services 17<sup>th</sup> December 2010 HPA  
<http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/PandemicInfluenza/PandemicH1N1Influenza/SIGuidanceIndex/>

## Appendix A

### Guidance on H1N1 influenza during pregnancy

Guidance has been derived from the following RCOG and DH documents:

1. Algorithm for management of influenza in pregnancy [accessed at RCOG website October 2009]
2. RCOG / RCM Guidance on Swine Flu for pregnant mothers (July 2009)
3. Clinical advice from the RCOG / RCM Pandemic Influenza Planning Group [accessed at RCOG website October 2009]
4. Q&A: Managing pregnant women with suspected swine flu—advice for healthcare professionals (August 2009)
5. DH Pandemic Influenza: Antiviral medicines for pregnant and breastfeeding women and children under one year (updated September 2009)
6. DH Pregnancy, breastfeeding and swine flu (updated 15 October 2009)
7. DH/RCOG Pandemic H1N1 influenza 2009: clinical management guidelines for pregnancy (October 2009)

	Guidance	Guidance reference
1	Pregnant women with any condition known to increase their risk from H1N1 influenza should take up the H1N1 influenza vaccine as soon as it is offered [e.g. asthma, other chronic pulmonary disease, chronic cardiac disease, diabetes, immunosuppression, chronic renal disease, neurological/neuromuscular disorder].	2
2	Routine post-exposure prophylaxis is not required for pregnant women with no symptoms.	4
3	If it is decided that a pregnant woman requires post-exposure prophylaxis due to family or other contact with a novel pandemic virus strain, Relenza is the preferred antiviral of choice.	5
4	If it is decided that a breastfeeding woman requires post-exposure prophylaxis due to family or other contact with a novel pandemic virus strain, Tamiflu is the preferred antiviral of choice.	5
5	Women should contact the Swine Flu information Line if they think they have symptoms of swine flu.	2
6	Women should contact their GP and inform their midwifery team if they think they have symptoms of swine flu.	1
7	If a woman has fever >38°C and at least 2 of the following symptoms (widespread muscle and joint aches; cough; headache; blocked or runny nose; sore throat; vomiting; watery diarrhoea) they should be prescribed antiviral treatment within 7 days of onset of symptoms and ideally within 48 hours.	1, 4 2, 7
8	Relenza (zanamivir) is the recommended antiviral treatment in pregnancy.	2, 4, 5

## CONFIDENTIAL NOT FOR CIRCULATION

9	Tamiflu (oseltamivir) is the recommended antiviral treatment for women with asthma; chronic pulmonary disease; who may have difficulty with an inhaled preparation; or severe, systemic or complicated H1N1 influenza.	4, 5, 7
10	Women who require antiviral treatment and are breastfeeding should take Tamiflu.	2,5
11	Fever should be controlled by taking paracetamol.	1, 2
12	Pregnant women who are taking antiviral treatment for suspected or confirmed H1N1 influenza, should either postpone their antenatal appointment if they are low risk; or arrange to attend at the end of the day or in an alternative location if they are high risk, in order to avoid contact with other mothers.	1, 4
13	Women should contact their GP or midwife if their symptoms are not improving after 7 days of antiviral treatment or if there is sudden worsening of symptoms.	1, 2, 4
14	Women who have any severe signs or symptoms (e.g. tachypnoea with respiratory rate >30; dyspnoea; hypoxia (SpO <sub>2</sub> ≤94%); chest pain on breathing; persistent tachycardia >100bpm; dehydration and shock; purulent or blood stained sputum; any other signs of sepsis; rigors; seizures; altered conscious level) should be referred by the GP or midwifery team to hospital for assessment.	1,7
15	In the event of any severe signs or symptoms as in 14. above, other differential diagnoses e.g. pulmonary embolism, viral myocarditis, UTI, should be excluded.	1
16	The following bacteriological investigations are recommended as a minimum: blood cultures; sputum culture; pneumococcal and legionella urine antigen (where available locally).	7
17	The use of pulse oximetry is essential to exclude hypoxaemia in women with severe signs or symptoms.	7
18	Empirical antibiotic therapy should be considered if there are signs of bacterial or respiratory tract infection; failure to respond to antiviral therapy; any underlying diagnoses; and severe H1N1 disease. Co-amoxiclav, or clarithromycin if penicillin-allergic, should be used.	7
19	The appropriate antibiotic therapy should be discussed with a microbiologist at the earliest opportunity.	7
20	If there is severe, microbiologically-undefined pneumonia, antibiotic therapy should be given for 10 days. This should be extended to 14 or 21 days where Staph aureus or Gram negative enteric bacilli pneumonia is suspected or confirmed.	7
21	If a woman with suspected or confirmed H1N1 influenza is	1, 4

## CONFIDENTIAL NOT FOR CIRCULATION

	admitted to hospital, the hospital Infection Control team should be informed.	
22	All pregnant women admitted to hospital with an influenza-like illness should be tested for H1N1 influenza to facilitate appropriate treatment and infection control precautions.	7
23	PCR should be used in preference to immuno-fluorescence to test for H1N1 influenza.	7
24	Pregnant women admitted with respiratory complications should be managed jointly between the obstetric and medical teams, and an assessment made with respect to the best place to manage the woman.	7
25	When intravenous fluids are commenced due to low BP and/or compromised urine output, a refractory response should lead to consideration of central venous cannulation and early initiation of inotrope support.	7
26	Women with suspected H1N1 influenza who are admitted to hospital should be nursed in isolation e.g. side room.	1, 4
27	Women with suspected H1N1 influenza admitted to hospital should wear a surgical mask.	1,
28	Staff caring for women with suspected H1N1 influenza should wear a surgical mask, plastic apron, gloves and eye protection if there is a risk of eye splash, with careful attention to hand washing and hygiene.	1, 4, 7
29	If possible, pregnant health professionals should avoid caring for women with suspected or confirmed H1N1 influenza.	4
30	The current obstetric practice of administering prophylactic antenatal corticosteroids (betamethasone 12mg 12 or 24 hours apart) in order to promote fetal lung maturity if preterm delivery is possible, should be continued.	7
31	If a pregnant woman is admitted with complications of influenza, early involvement of the obstetric anaesthetists, respiratory physicians and haematologists is important in order to set out a clear management plan.	7
32	In women with suspected or confirmed H1N1 influenza due for induction of labour or planned elective caesarean, this should be deferred for five days if medically appropriate, in order to give the woman time to recover and reduce the risk to staff and other women.	4, 7
33	Delivery of a woman with severe H1N1 influenza should be carried out after her clinical condition has been stabilised and other potential complications such as coagulopathy have been excluded or corrected.	7

## CONFIDENTIAL NOT FOR CIRCULATION

34	It is unlikely that pregnancies in the second or third trimesters will need to be terminated unless it is considered that continuation of the pregnancy will be detrimental to the woman's condition.	7
35	Women who have commenced Relenza during pregnancy and have delivered and are breastfeeding, should continue with Relenza; they should not switch to Tamiflu.	5, 7
36	Breastfeeding should be continued in women who are on H1N1 antiviral treatment or prophylaxis.	6, 7
37	If possible, additional formula milk should not be used for babies whose mothers are taking H1N1 antiviral treatment, in order to maximise maternal antibodies transferred to the baby.	6, 7
38	In women who require ITU admission for severe complications and signs of hypoxia: <ul style="list-style-type: none"> <li>• The anaesthetist should be involved early</li> <li>• Haematologist should be involved early</li> <li>• Platelets and coagulation profile should be checked</li> <li>• Delivery of the baby should be considered to aid supportive management of the mother.</li> </ul>	3
39	Women who have recovered from H1N1 influenza should be offered appropriate psychological support.	3
40	Clinicians are encouraged to seek post-mortem examination in fatal cases of influenza-like illness and influenza-related pneumonia.	7
41	Post-mortem examination should include comprehensive virological and bacteriological examination.	7