Pandemic H1N1 influenza: a threat to infant health

This article outlines the cause of the current global 'swine flu' pandemic and describes the clinical consequences of infection to infants and young children. The clinical management of infants with influenza is discussed and clinically effective infection prevention and control measures are explained. Comprehensive and relevant online resources are provided for healthcare professionals to ensure that they remain up-to-date with this fast moving pandemic.

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Keywords

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Key points

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1. The emergence of new influenza viral strains is a regularly occurring natural phenomenon that will, on occasion, cause a global pandemic.
2. Influenza viruses are principally transmitted by large virus-laden respiratory droplets and by direct and indirect contact with hands and surfaces contaminated with respiratory secretions.
3. Infants, especially those under the age of six months, are at significant risk of severe influenza-associated complications.
4. Pandemic H1N1 2009 influenza vaccination during pregnancy can indirectly protect infants from maternal transmission.
5. Antiviral treatment with oseltamivir can be safely used for infants who have pandemic H1N1 2009 influenza.

Influenza viruses have endangered public health for centuries and recurrent patterns of annual epidemics of seasonal influenza (winter 'flu) and less frequent influenza pandemics are very familiar. Due to their sudden emergence and their capacity for rapid transnational spread, influenza pandemics are among the most frightening and potentially cataclysmic threats to global public health.

The Centers for Disease Control and Prevention (CDC) in the United States (US) report that children who are less than one year of age are at higher risk for complications associated with seasonal human influenza virus infection compared to older children and that the risk of influenza complications is especially high for children less than six months of age. CDC also noted that children less than one year old were also found to be at an increased risk of complications during previous influenza pandemics[1]. Early UK data indicated that critical illness associated with pandemic (H1N1) 2009 influenza in children principally affected those over the age of five years with coexisting medical conditions or disease processes (co-morbidities)[2]. Other more recent UK data showed that children under the age of five years without co-morbidities are also at risk of severe disease[3]. This is not surprising as the immaturity of the immune system in infants and very young children leads to a physiological immunodeficiency that enhances their vulnerability to severe disease and secondary viral and bacterial infections.

Influenza viruses

Two types of orthomyxoviruses cause influenza in humans; influenza A and influenza B. The genetic material of these viruses is organised in the viral genome as eight separate segments of ribonucleic acid (RNA) containing a total of ten genes. The genome is enclosed within a lipoprotein envelope (lipid bilayer) and the outer surface of the envelope is studded with two types of glycoprotein spikes known as haemagglutinin (HA) and neuraminidase (NA) (**FIGURE 1**). These are antigenic and when these viruses infect a person they provoke an immediate immune response which results in the activation and deployment of antibodies and cytotoxic cells. The antibodies are precisely designed to perfectly combine with the exact structural characteristics of the external glycoproteins and neutralise the virus, while the cytotoxic cells are devised to identify, target and then kill cells infected with virus.

Drifting and shifting

Surface glycoproteins, particularly HA, progressively undergo minor antigenic

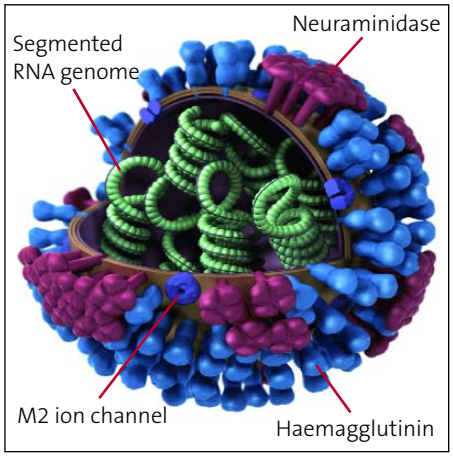

FIGURE 1 2009 Influenza A(H1N1) virus – Courtesy of the Centers for Disease Control and Prevention,2009.

changes as a result of random replication errors, a process known as 'antigenic drift.' This happens because influenza genes, comprised of RNA, are more prone to small point mutations that occur during viral replication than are genes composed of deoxyribonucleic acid (DNA). When the HA gene mutates during replication, the surface glycoprotein it encodes also changes and a new viral strain is produced.

As antibodies are strain-specific, those previously made in response to another strain will be ineffective in neutralising a new viral variant that emerges as a result of antigenic drift. This is the reason why the trivalent seasonal influenza vaccine is adjusted each year in order to ensure that the immunogenic components of the vaccine accurately reflect the 'drifted' viruses currently in circulation.

In addition to the gradual changes in the glycoproteins of both viruses as a result of antigenic drift, type A viruses (but not type B viruses) are able to undergo an abrupt and massive alteration in the structural characteristics of their surface glycoproteins, a phenomenon known as an 'antigenic shift.' As this involves the reassortment of larger sections of genetic information than in the relatively minor point mutations responsible for slow antigenic drift, it is less likely to give rise to new biologically successful influenza A subtypes. However, when they do emerge, these new subtypes are the basis of a potential pandemic as there will always be large populations of immunologically naïve humans who will be susceptible to the new subtype[4].

Type A viruses are further classified into subtypes according to the variations in these glycoproteins. Sixteen different haemagglutinin subtypes (H1-H16) and nine different neuraminidase subtypes (N1-N9) have been identified. Only H1, H2 and H3 and N1 and N2 influenza A viral subtypes are known to infect humans or cause serious outbreaks[5].

Strains of both influenza A and B viruses are involved in causing epidemics of seasonal influenza but only influenza A viruses are capable of causing global pandemics[6].

Pandemics

Three well-documented global influenza pandemics were experienced during the last century. The most infamous, the 1918-1919 'Spanish 'flu' pandemic, occurred when a new variant of influenza A(H1N1) virus emerged and within months infected half the world's population and caused the death of 100 million people[7]. Two further global pandemics followed, together killing two million people: the 1957-1958 'Asian 'flu,' pandemic caused by the emergence of influenza A(H2N2) virus; and a decade later, the 1968-69 'Hong Kong 'flu' pandemic, resulting from the emergence of influenza A(H3N2) virus[8].

The current influenza pandemic caused by a novel variant of influenza A(H1N1) has been long anticipated and the UK, along with other countries in the European Union (EU) and the industrially-developed world are now implementing well-rehearsed pandemic influenza preparedness plans and strategies for prevention, treatment, and infection control[9].

Pandemic H1N1 2009 influenza virus

The pandemic 2009 A(H1N1)influenza virus is a mixture of genetic material from other swine, bird and human influenza A viral strains[10]. This new variant has never before circulated in humans, it is not found in pigs or other animals and is only being transmitted between people.

The first cases of pandemic 2009 H1N1 influenza were identified in California and Texas in late March, 2009[11] although there is evidence that this new viral strain may have started circulating among people in January 2009[12]. In April 2009 further cases were identified in the US and Mexico[13] and within weeks the virus swept around the world[14]. As further continents experienced epidemics of influenza caused by this new viral strain, the World Health Organization declared a global influenza pandemic in June 2009[15].

Viral transmission

Influenza viruses spread from person to person via the respiratory route (droplet transmission) and also from hand-to-face contact if hands are contaminated by infectious respiratory secretions.

Droplet transmission easily occurs when an infected person generates and sprays uninfected persons with large respiratory droplets when talking, coughing or sneezing. Susceptible (ie non-infected) persons can only become infected by close personal contact as these droplets are too large to become buoyant and can only travel short distances (not more than 1m) through the air.

Transmission can also occur from contact with hands that have been contaminated, for example shaking hands with an infected person who has used their hands to cover their mouth and nose during coughing, or touching surfaces contaminated by infectious respiratory droplets. Influenza viruses can survive for 24 hours or more on stainless steel counters, table tops and washing up bowls[16]. Infection can occur when contaminated hands carry the virus to the nose or mouth where the virus can come into contact with and infect respiratory cells.

Although aerosol-generating procedures, such as endotracheal intubation, suctioning, nebuliser treatment or bronchoscopy can increase the risk of viral transmission by producing small particle aerosols, there is no reliable evidence that these are significantly involved in influenza transmission in any other circumstances[17,18]. However, some caution is needed here as other experts advise that small particle aerosols may play a more significant role in the transmission of influenza viruses then previously thought[19].

Consquences of infection

Most school children who become infected with pandemic H1N1 2009 influenza virus will either have asymptomatic infection or a relatively benign influenza-like illness with mild symptoms, such as fever, dry cough, fatigue, sore throat and headache.

Current or recent history of high fever (temperature >38°C) and two or more of the following:

- Cough
- Rhinorrhoea
- Sore throat
- Headache
- Widespread muscle and joint aches
- Vomiting
- Otitis media
- Diarrhoea
- Cerebral irritability and/or seizures (rarely)

Atypical features sometimes observed in children:

- Severe gastrointestinal symptoms, eg diarrhoea, nausea, vomiting, abdominal pain
- Haematemesis
- Photophobia
- Chest pain
- Epistaxis
- Croup
- Apnoea
- Rigors

TABLE 1 Features of pandemic 2001 H1N1 influenza in children[19].

The majority of these will rapidly recover within seven to ten days. However, a fraction of affected children will develop more serious clinical features (**TABLE 1**)[20]. Some very young children and infants can exhibit sudden severe collapse (apparent life-threatening episodes)[20,21] and in children under the age of one year, apnoea, reduced tone and poor feeding can occur with or without the classical features of influenza[20]. It is important to remember that children with influenza (seasonal or pandemic), unlike adults, may be at increased risk for complications and death, regardless of whether they have co-morbidities[20,22].

Primary care

Advice from the Department of Health (DH) reassures that the majority of children with mild influenza-like illness who experience mild fever, coryza and new cough can be safely managed by parents and carers with fluids and antipyretics, such as paracetamol and ibuprofen. However, because the symptoms of influenza and serious bacterial infections are similar, especially in children under one year old, a general practitioner needs to examine all infants who are unwell with fever or influenza-like symptoms[20]. Infants who are ill with pandemic H1N1 2009 influenza should continue to breastfeed[23].

The DH advises that aspirin should not be given to children unless recommended by a medical specialist and that parents and carers should not use over-the-counter cough and cold medicines in children under the age of six years. The DH notes that there is little evidence that these preparations work and also cautions that they can cause side effects and allergic reactions in children[20].

Antimicrobial treatment

As they are at increased risk of severe complication, early empiric antiviral therapy with oseltamivir (Tamiflu®) should be considered for all infants and children under two years of age who have suspected or confirmed pandemic H1N1 2009 influenza[24-26]. Dosing instructions should exactly correspond to current guidance in the British National Formulary for Children (http://bnfc.org/bnfc/).

In some cases, empiric antibiotic therapy may also be prescribed but infants who are suspected of developing complications, eg lower respiratory tract infection, acute suppurative otitis media, need to be urgently examined by their general practitioner or referred to hospital[20].

Some infants and young children will develop significant influenza-associated complications, and others, potentially serious non-influenza illnesses. Consequently, parents need to be advised to seek further urgent medical advice if their child develops a rash or if their condition suddenly worsens. This means an urgent face-to-face clinical assessment in a clinical setting[20].

Secondary care

Assessment criteria for referral to hospital are not exclusive but include[20]:

- Signs of respiratory distress (dyspnoea, tachypnoea, nasal flare, grunting, indrawing of lower chest wall and severe recession)
- Peripheral oxygen saturation measured by pulse oximetry (SpO_2) less than or equal to 94%
- Dehydration or shock
- Any sign of sepsis
- Altered conscious level
- Seizures

In hospital, antiviral and, when appropriate, empiric antibiotic therapy will be prescribed. Oseltamivir is the antiviral agent of choice for infants and young children. Although some clinicians double the dose of oseltamivir in older critically ill children, DH guidance advises against doubling the dose in children under the age of one year[3,20].

Assessment criteria are used for consideration for escalation/referral to critical care facilities (**TABLE 2**) for those infants and young children with advancing respiratory distress, neurological disease, cardiovascular disease and shock, and the need for renal replacement[3].

It is beyond the scope of this article to describe the comprehensive intensive care required in the management of these infants but current detailed online guidance is available (**TABLE 3**). During this pandemic, demand has increased for the use of extra-corporeal membrane oxygenation (ECMO) to provide respiratory and cardiorespiratory support to infants. A detailed account of using this advanced technology for infants with reversible conditions that cannot be maintained by conventional respiratory support methods has been previously published in this journal[27].

- Hypoxaemia (SpO_2 <94%) resistant to high flow oxygen therapy.
- Worsening respiratory failure characterised by: severe recurrent, prolonged apnoea requiring resuscitation; worsening tachypnoea with gasping or grunting; or a rising pCO_2 on sequential blood gas analysis.
- Cardiovascular collapse/shock that does not respond to a fluid resuscitation (equal or greater than a total of 40mL/kg of 0.9% saline or Hartmann's).
- Encephalitis with coma (GCS <9) or seizures requiring intubation for air control

TABLE 2 Consideration for escalation/referral to critical care facilities in children[3,20].

- Department of Health (England). Pandemic H1N1 2009 Influenza: Clinical Management Guidelines for Adults and Children. October, 2009. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_107839.pdf
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TABLE 3 Online resources for the management of children with pandemic (H1N1) 2009 influenza and infection control precautions.

Immunisation

As mothers with influenza can easily transmit this infection to their newborn child, preventing them from contracting influenza in the first place offers significant protection to the infant. The most effective prevention measure is for all pregnant women to be immunised with both the seasonal vaccine and the pandemic H1N1 2009 influenza vaccine and to encourage breastfeeding after the baby is born. In addition, the passive transfer of maternal influenza antibodies, occurring both *in utero* and in breast milk from vaccinated mothers will offer additional protection to the newborn baby. When the infant is six months old, they should be vaccinated against pandemic H1N1 2009 influenza, as should all infants and young children over six months and under five years of age[28].

Infection control precautions

As discussed previously, influenza viruses are easily transmitted during close personal contact by large virus-laden respiratory droplets generated by an infected person during talking, coughing or sneezing, or by hand-to-face contact if the hands are contaminated with virus.

Airborne transmission via small particle aerosols is generally only thought to be associated with influenza viral transmission during aerosol generating procedures (AGPs), such as bronchoscopy, endotracheal intubation, suctioning, non-invasive ventilation, and nebuliser treatments[17,18].

The consistent and appropriate use of transmission-based infection prevention and control precautions by healthcare workers can minimise the risk to both themselves and to their patients of becoming exposed to and infected with influenza viruses during episodes of healthcare.

Transmission-based precautions

National infection prevention and control guidance in England for minimising the risk of healthcare-associated infections in National Health Service hospitals and in primary and community care settings describe a set of standard principles that need to be applied at all times and with all patients[29,30]. These focus on hand hygiene, the safe use and disposal of sharps, and the correct use of personal protective equipment. However, to reliably interrupt the transmission of influenza viruses, more detailed additional transmission-based precautions are used in conjunction with the application of standard principles.

There are three types of transmission-based precautions. Droplet precautions and contact (direct and indirect) precautions are consistently used at all times to restrict the transmission of influenza viruses and in addition, airborne precautions are added to this infection control regimen when assisting with or undertaking AGPs. Pertinent infection prevention and control recommendations include the following:

Contact precautions

Standard principles for hand hygiene are used to prevent exposure by direct and indirect contact with contaminated surfaces and infected patients. The hands of infants and young children with influenza are always heavily contaminated because of frequent contact with their nose and mouth. This facilitates the contamination of their immediate environment which results in viral transmission to others who come into contact with these surfaces and articles. Consequently, good hand hygiene among health and social care providers and their patients is the single most important practice for reducing the transmission of infection in all healthcare settings. General recommendations for effective hand hygiene include:

- Hands must be decontaminated immediately before each and every episode of direct patient/client contact/care and after any activity or contact that potentially results in hands becoming contaminated.
- Hands that are visibly soiled or potentially grossly contaminated with dirt or organic material, ie following the removal of gloves, must be washed with liquid soap and water.
- Hands should be decontaminated between caring for different patients or between different care activities for the same patient. For convenience and efficacy, an alcohol-based handrub is preferable unless hands are visibly soiled.
- Hands should be washed with liquid soap and water after several consecutive applications of alcohol hand rub.
- When washing their hands, it is good practice for nurses and other healthcare workers in neonatal units to wash their hands and forearms up to the elbows.

Disposable plastic aprons should be worn if soiling of clothes/uniforms with patient respiratory secretions is anticipated and gloves should be worn if hand contact with respiratory or potentially contaminated surfaces is expected. Hands need to be decontaminated after removing aprons and gloves.

Droplet precautions

Protection against exposure to influenza viruses via large respiratory droplets is achieved by the use of fluid repellent surgical masks worn by healthcare workers for any close contact (that is, within 1m) with patients[31,32]. These masks provide a physical barrier and minimise contamination of the nose and mouth by respiratory droplets from patients. Disposable FFP3 respirators are not necessary unless healthcare workers are assisting with or conducting AGPs, as discussed previously. If FFP3 respirators are not available then FFP2 respirators should be used and all respirators need to be properly fit-tested before being worn.

Reducing the risk of transmission from mother to baby

As with general precautions, the DH recommends[33] that:

- Mothers should take steps to reduce the risk to their infant by washing their hands frequently with soap and hot water or a sanitiser gel and by using clean tissues to cover their mouth and nose when coughing or sneezing. Tissues should be binned after use.
- Mothers and infants should stay as close together as possible and be encouraged to have early and frequent skin-to-skin contact with their infants.
- Babies' hands should be washed if they have been in their mouths.
- Limit sharing of toys and other items that have been in infants' mouths. Wash thoroughly with soap and water any items that have been in infants' mouths.
- Keep dummies (including the dummy ring/handle) and other items out of adults' or other infants' mouths prior to giving to the infant.
- The available scientific evidence shows that the basic face masks do not protect people from becoming infected and that the best way of reducing the risk of transmission is by hand washing and using and disposing of tissues.

Environmental hygiene

As influenza viruses can survive on environmental surfaces for several hours, freshly prepared neutral detergent and

warm water should be used for cleaning healthcare environments, especially frequently touched surfaces. In addition to detergents, almost all commercially available disinfectants can inactivate influenza viruses, including alcohol, hydrogen peroxide, chlorine (bleach), chlorhexidine gluconate, and iodophors (iodine-based antiseptics). Influenza viruses are also easily destroyed by heat (75-100°C).

Further online resources

The DH[20], Health Protection Agency[3] and the CDC[1] have issued detailed online guidance for the clinical management of infants with pandemic H1N1 2009 influenza. In addition, the DH has developed comprehensive online pandemic influenza infection prevention and control guidance for healthcare staff in hospitals, critical care settings and in primary care[32,34]. Healthcare staff working in these areas should ensure that they are familiar with the recommendations in this guidance.

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