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Review

Human swine influenza A [H1N1]: Practical advice for clinicians early in the pandemic

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SUMMARY

The influenza pandemic the world was waiting for may have arrived, but the early indications are that the first wave of human swine influenza A [H1N1], also referred to as H1N1 Mexico 09 or "swine flu", is highly transmissible but of no greater virulence than seasonal influenza to date. The new swine flu H1N1 virus is a mixture of avian, porcine and human influenza RNA. With twenty thousand confirmed cases worldwide and 117 deaths within 7 weeks of the first acknowledgement of a possible pandemic by Mexican and WHO experts, the mortality rate is less than 0.1% and the majority of deaths centred upon the origin of the epidemic in Mexico [83%]. Swine flu is thus far a relatively mild illness seen predominantly in those who are healthy and under 25 years of age, perhaps reflecting protection from previous human influenza exposure in older people. As the virus spreads internationally, border protection issues have surfaced and public health initiatives are being progressively rolled out to minimise the transmission. Vaccines are being developed which will be trialled in the coming months with a likely availability by August 2009, in time for the northern hemisphere autumn and winter. Vigilance without alarm appears to be the recommendation so far.

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INFLUENZA VIRUSES

Influenza A viruses are negative stranded RNA viruses of the Orthomyxoviridae family.[1] There are eight segmented RNA components in the genome which encode for ten proteins. These proteins include two glycosylated proteins on the cell surface, haemagglutinin [H] and neuraminidase [N], which facilitate viral attachment and release from host cells.[1] These determine the manner in which influenza A virus strains are coded [eg H1N1]. The additional proteins include two non-structural proteins involved in the life cycle of the virus, three proteins involved in virus replication, a nucleoplasmid protein and two membrane proteins.[2] The influenza virus is capable of considerable genetic variability, allowing it to mutate frequently and easily as a result of its polymerase chains inefficient "proof-reading" abilities and the segmented genome which allows reassortment of genetic material.[1] Thus, the current human swine influenza A includes genetic material from influenza A viruses that have infected pigs, birds and humans [triple reassortment]. Importantly, this is not a static process, so every generation of the influenza A virus strain will have further alterations in the genetic composition.

As pigs can be infected with both avian and human strains of influenza A, and various reassortments have been isolated from pigs, it has been proposed that they may act as intermediate hosts for novel strains which have the potential to generate epidemic or pandemic strains.[3] Whilst viral reassortment is critical for the evolution of a novel virus, its virulence is affected by additional factors which include transmissibility, host adaption, tissue trophism and virus replication efficiency.[1] These factors are multigenic in nature. It must be emphasised that there is no risk of contracting influenza from eating pork.

HISTORY OF INFLUENZA EPIDEMICS

Following several likely influenza epidemics in the nineteenth century, there were three influenza epidemics during the twentieth century that resulted in millions of deaths. Indeed the 1918-1919 flu epidemic killed more people in 12 months than the previous four years had claimed in World War I. The three 20th century epidemics included the 1918-19 Spanish 'Flu, the 1957 Asian 'Flu and the 1968 Hong Kong 'Flu. Each began in the Northern hemisphere spring with a first wave of moderate impact followed by a second wave of devastating proportions in the following autumn and a third, smaller peak in the winter.[4,5] International mobility of people, certainly by ship after World War I and with the advent of airline travel over the last fifty years, has been implicated in the spread of influenza viruses in epidemics. More recently, evidence to support this claim has been suggested in relation to air travel in the United States.[6]

HOW DOES A PANDEMIC DIFFER FROM AN EPIDEMIC?

Perhaps one consequence of a vaccine preventable condition such as seasonal influenza A that is often overlooked is its

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severity: it is responsible for approximately 35,000 deaths per year in the United States.[2,4] Nonetheless, there are two key factors to be considered determining whether an epidemic infection can be considered to be a pandemic. Firstly, the term pandemic is used to describe a disease that is epidemic throughout the world at approximately the same time. Secondly, a pandemic occurs when a completely new virus emerges, one that has demonstrated a dramatic change [antigenic shift] which is out of keeping with the usual rate of change [antigenic drift].[7]

HOW DID HUMAN SWINE INFLUENZA A [H1N1] EVOLVE?

Influenza A viruses can infect many types of animals including horses, pigs, birds, whales and seals.[7] The origins of swine flu date back to the 1918-19 influenza A epidemic. From that time both pigs and humans were infected with influenza A strains, with epidemics occurring in each species periodically. Following the 1968 Hong Kong 'Flu human H3N2 influenza A emerged and pigs became infected. Over the subsequent 30 years there were influenza A epidemics in pigs in Europe and Asia before this strain reached the United States in 1998.[8] Sporadic cases of human infection with swine influenza have been reported over the last 10 years, with 12 cases of human infection with swine influenza in the USA between December 2005 and February 2009.[9]

In contrast to human influenza A viruses, the antigenic evolution of swine viruses has occurred at a rate approximately six times slower than that of human viruses.[8] This has lead to relative stability when preparing swine influenza virus vaccines, as opposed to the necessity for yearly alterations in the annual influenza virus immunisation which aims to provide protection against the three most likely human influenza A virus strains. What experts had not expected was a sudden mixture of the genetic material of human and swine viruses, given that recent attention had focussed on the potential for avian influenza A H5N1 viruses to infect humans.[7]

Analysis of the viral genome of the human swine influenza A [H1N1] virus has indicated that it has derived from a mixture of the previously identified common swine viruses isolated in North America, Europe and Asia from the late 1990s.[10,11]

DIAGNOSTIC TRAIL

A novel strain of human H1N1 influenza A virus was identified in Mexico in April 2009[11] following informal reports of a "mysterious" influenza like illness centred upon the town of La Gloria which had infected an estimated 60% of the population of 3000 residents and been responsible for 2 deaths in March.[12] During early April 2009, further cases were suspected in other regions of Mexico, prompting an alert to the WHO to be made on April 10th by the Global Public Health Intelligence Network [GPHIN].[12] Whilst initial reports were in the Mexican Spanish language media, the first reports in the English language media appeared on April 21st following the confirmation of a novel influenza A H1N1 in two children living near San Diego, California four days earlier based upon testing carried out by the Centres for Disease Prevention and Control [CDC]. Neither child had been exposed to pigs. Thus, within a period of 6-8 weeks from the appearance of early cases noted by clinicians, the genetic make-up of the virus was determined and the unexpected origins of the reassorted genes had become apparent.

Between April 15 and May 5 2009, the virus had spread rapidly through Mexico, into 41 States in the USA and resulted in 642 confirmed cases in the USA.[12] The virus had reached Canada and Europe by the same time and by May 27th had reached 46 countries with 92 deaths [80 in Mexico and 10 in the USA].[12] Despite border protection measures with screening of inbound aircraft passengers, remote countries were not spared and even 'geographically remote'Australia had reported 50 confirmed cases in a total of 12,954 cases worldwide by May 27th, 2009, climbing to 882 cases out of a worldwide total of 19,273 by June 5th, 2009,[13]

CASE DEFINITION

The case definition will vary between countries with few cases of swine flu compared to those with many cases such as Mexico, the USA and Canada. It is important to remember that the case definition will be refined during the course of the epidemic. By way of example, for countries such as Australia with currently only 400 cases, the New South Wales Department of Health[14] defines a suspected case of H1N1 Influenza 09 (human swine influenza) virus infection as a person with:

- An **acute febrile respiratory illness** (defined as temperature of 38 °C or greater OR a good history of fever, AND recent onset of at least one of the following symptoms: rhinorrhoea, nasal congestion, sore throat or cough), with onset within 7 days of travel to Mexico, USA, Canada, Japan or Panama (countries to be updated where evidence of local transmission).

  OR
- An **acute respiratory illness** (defined as recent onset of at least one of the following symptoms: rhinorrhoea, nasal congestion, sore throat or cough with or without fever) within 7 days of close contact with a person who is a **confirmed** case of H1N1 Influenza 09 (human swine influenza) virus infection or a suspected case with an influenza A positive test result.

In contrast, the June 1st 2009 operational definition offered by the US Centre for Disease Control and Prevention differs because of established local transmission [15]. It uses the definition of influenza like illness as used for seasonal influenza purposes by public health investigators. Consequently, cases of swine flu are divided into confirmed, probable or suspected cases.

Influenza-like-illness (ILI) is defined as fever (temperature $\geq$ 100 °F [37.8 °C]) and a cough and/or a sore throat in the absence of a known cause other than influenza.

A **confirmed case** is defined as a person with an influenza-like illness with laboratory confirmed novel influenza A (H1N1) virus infection by one or more of the following tests:

1. real-time, reverse transcriptase polymerase chain reaction [RT-PCR] on the viral throat or nasal swab
2. viral culture on the same sample which is slower, and therefore not the preferred test

A **probable case** is defined as a person with an influenza-like-illness who is

- positive for influenza A, but negative for human H1 and H3 by influenza RT-PCR

A **suspected case** is defined as a person who does not meet the confirmed or probable case definition, and is not novel H1N1 test negative, and is/has:

- a previously healthy person $<$ 65 years hospitalized for ILI

  OR
- ILI and resides in a state without confirmed cases, but has travelled to a state or country where there are one or more confirmed or probable cases

  OR
- ILI and has an epidemiologic link in the past 7 days to a confirmed case or probable case

CLINICAL PRESENTATION

The symptoms of human swine influenza A infection are identical to those of seasonal influenza in that there will be fever, sore throat, nasal congestion, body aches, headache, chills and fatigue. However, more commonly reported in swine influenza infection at 25% are symptoms of vomiting and diarrhoea.[12]

CONFIRMING THE DIAGNOSIS OF HUMAN SWINE INFLUENZA A H1N1

A rapid diagnosis of infection with the swine influenza virus is essential to minimise spread of the condition, protect the patient from developing complications by treating with antivirals and to inform the public health response.[15] The typical steps involved may include:

1. Does the illness in the patient meet the current case definition for possible swine influenza?
2. If so, then the patient is isolated. The need to confirm the diagnosis and how this will be done is explained. A throat and nasal swab for viral PCR testing and viral culture is collected and sent to a reference laboratory for testing [Table 1].
3. Testing will involve the health care worker wearing personal protective equipment which will typically include gown, gloves, eye protection [goggles or a face-shield], mask and hand-hygiene products.
4. The patient is sent home for isolation pending the result of the test. Most public health units would consider the use of an antiviral at the time of presentation or when the diagnosis was confirmed with a rapid diagnostic [PCR] test.

In testing laboratories, the viral sample [throat swab or nasal swab] is cultured and set up for PCR testing. Using techniques which amplify and simultaneously detect specific nucleic acid sequences, rapid detection of viral nucleic acid sequences is achieved. The reliable technique is called real time polymerase chain reaction [RT-PCR] and the result is available within 24 hours.[16]

Table 1
Collection of nasal and throat swabs {derived from 14}

Nasal Swab [collected from the nasal septum, not just the anterior nares]
• Stand to one side of the child, who may be on a parent's lap.
• Have the patient's head resting against a firm surface [eg parent's chest].
• Place non-dominant hand against the patient's forehead and thumb on the tip of the nose.
• Use a viral culture swab and insert the swab into the closest nostril horizontally, approximately 1-2 cm for a child.
• Place lateral pressure on the swab in order to collect cells from the nasal septum.
• Rotate the swab completely twice [720 degrees] to collect cells, not mucous.
• Place swab into viral transport medium in tube, label [name, date of collection and source: nose] and send to the laboratory.
Throat Swab
• Stand to one side of the patient who may be on a parent's lap.
• Ensure the child's head is resting against a firm surface [eg parent's chest].
• Place your non-dominant hand on the parent's forehead.
• Ask the child to open their mouth widely and say "argh".
• Use a viral culture swab and insert the swab into the mouth avoiding any saliva.
• Place lateral pressure on the swab in order to collect cells from the tonsillar fossa at the side of the pharynx.
• Rotate the swab completely twice [720 degrees] collecting epithelial cells and not saliva.
• Place the swab directly in the viral transport medium, label [name, date of collection and source: throat] and send to the laboratory.

WHO IS AT RISK OF MORE SEVERE ILLNESS?

The early reports have demonstrated that 80% of affected people are below 25 years of age.[12,15] The illness has been mild in the majority of the 15,000 cases reported to June 1st 2009, with comparatively few of those infected needing hospitalisation.[15] Nonetheless, as with seasonal influenza, those considered at higher risk include the very young [< 5 years], the elderly [>65 years], pregnant women, people of any age with chronic conditions that include asthma, heart disease or diabetes and those who are immunosuppressed [on medication or with HIV].[12,15]

Children appear more susceptible to swine flu. As with seasonal influenza, young children under the ago of two years may be more susceptible to infection and complications. Symptoms of more severe disease in young infants and children may include: apnoea, tachypnoea, dyspnoea, central cyanosis, dehydration, altered mental status and extreme irritability. Other predisposing conditions to more severe illness may include all children with immune suppression, chronic renal disease, structural heart disease, respiratory conditions [cystic fibrosis, asthma, bronchopulmonary dysplasia], neuromuscular disease, cerebral palsy or other conditions that may impair airway clearance or alter respiratory defence mechanisms. In addition, children with metabolic conditions who may not tolerate fasting such medium chain acyl-CoA dehydrogenase [MCAD] deficiency may be at a greater risk of a complicated course.[15]

Complications are rare but may include pneumonia, respiratory failure and death due to the virus. In addition, there is presumed to be a higher prevalence of secondary bacterial infections as with other influenza infections, and this may lead to otitis media, sinusitis and pneumonia.[15]

HOW INFLUENZA SPREADS

Influenza is transmitted through person to person spread of respiratory secretions. This occurs as respiratory droplets when an infected person coughs or sneezes in close proximity to others. The microscopic droplets are propelled through the air and deposited on the mouth or nose of people nearby. The hand of the person then spreads the droplets either to themselves or to others that are touched by the unwashed hands.[14,15]

MANAGING CASES OF SWINE FLU

The majority of people will be cared for by relatives at home as with seasonal influenza. Simple supportive care with the use of antiviral medication [see below] is recommended. Aspirin [acetylsalicylic acid] is avoided in children because of the risk of Reye's syndrome.[17,18] Cough and cold medications for children are not recommended as they are useless and may increase morbidity.[19] Nonetheless, as the CDC advises on its website[15] there are some simple measures that can be undertaken to manage the child comfortably at home [Table 2], to protect the carers from developing swine flu [Table 3] and simple measures to stay healthy [Table 4]. The secondary attack rate of 22%-30% for close contacts is suggested to be higher than seasonal flu at 5%–15%.[13] It is unclear whether this is attributable to low immunity in the community or specific virulence characteristics of the virus.

Additional considerations include the treatment of household contacts with antiviral medication which in the early stages is standard practice. The use of frequent hand washing with soap and water is essential for all family members and the use of an alcohol-based hand rub is a useful alternative. Household visitors should be discouraged.[15]

Table 2
Simple supportive measures when caring for a child with swine flu {derived from 15}

- Isolation for 7 days from the onset of symptoms or for 24 hours after resolution of symptoms.
- Avoid close contact with others while symptomatic.
- Obtain plenty of rest.
- Drink plenty of fluids to maintain hydration.
- Use simple analgesics for comfort and relief of fever [paracetamol or non-steroidal anti-inflammatory medications in standard doses on the side of the container].
- Use disposable tissues rather than handkerchiefs to blow or wipe the nose.
- If the person has to be in a common area of the house then they should wear a mask. Some authorities would advocate all family members in the house wear a mask.
- Clean hands with an alcohol based hand rub or with soap and water, especially after sneezing into hands or wiping the nose with a tissue.
- Seek expert medical attention if the child's condition deteriorates despite simple measures. This may reflect progression of the viral illness or possibly a secondary bacterial infection, particularly if after a period of improvement there appears to be an unexplained deterioration with recrudescence of fever.

Table 3
Simple supportive measures for the caregivers of children with swine flu {derived from 15}

- Avoid face to face contact with the sick person.
- When carrying sick children place them with their face resting on your shoulder away from your face so that they do not cough in your face.
- Wash hands frequently with soap and water.
- Consider the use of a disposable surgical facemask when you are in close proximity to the patient. Wash hands after removing the mask.
- Wash down surfaces with a disinfectant [especially bathroom surfaces, bedside tables and toys for children].
- Wash linen thoroughly using standard laundry powder/detergent and use tumble dry on a hot setting if possible. Clean hands after handling dirty linen.
- Wash eating utensils in detergent and hot water or with a dishwasher.
- Consider antiviral prophylaxis in discussion with your doctor.
- Monitor yourself for the symptoms of influenza.

Table 4
What you can do to remain healthy {derived from 14,15}

- Cover your nose and mouth with a tissue when you sneeze and then throw away the tissue and wash your hands.
- Avoid touching your eyes, nose and mouth.
- Stay home if you are sick.
- Avoid contact with sick persons.

ANTIVIRALS

The most encouraging news for clinicians is that swine flu is treatable at all ages. The advantage of taking antiviral treatment within 48 hours of the onset of symptoms is that it may make the illness milder and it may also prevent serious complications of influenza infection. However, there is some suggestion that the antiviral therapy, even if commenced more than 48 hours after the onset of symptoms may afford some benefit, especially for hospitalised patients or people with co-morbidities considered to be at higher risk of complications.

The antivirals oseltamivir [Tamiflu®] and zanamivir [Relenza®] target the neuraminidase enzyme [NA], encoded by RNA segment 6, and these drugs are clearly effective against swine flu.[12,15] The other class of antivirals targets the M2 ion channel, encoded by RNA segment 7, and this includes amantidine and rimantidine. The early indications are that strains of swine flu are not sensitive to the adamantane ion channel inhibitors [amantidine and rimantidine].[20]

Table 5
Treatment doses of oseltamivir [Tamiflu®] for infants authorized by the FDA on April 27th 2009 {derived from 15,21}

Dose by age	Treatment dose for 5 days
< 3 months	12 mg twice daily
3-5 months	20 mg twice daily
6-11 months	25 mg twice daily

The standard dosing of oseltamivir {Tamiflu®}[21] for treatment of suspected or proven swine flu is summarised for infants in Table 5 and for children over a year of age in Table 6. The standard treatment dose of oseltamivir for adolescents and adults is 75 mg twice daily for 5 days. As with adults, it is recommended that treatment for children begins within 48 hours of exposure.[21]

In contrast, the dosing of oseltamivir for adolescents and adults to prevent swine flu within 48 hours of close contact with an infected person consists of 10 days of once daily therapy [75 mg]. The duration of protection lasts for as long as dosing is continued and safety and efficacy have been demonstrated for up to 6 weeks [FDA Tamiflu fact sheet]. Accordingly, the dose of oseltamivir for infants and young children following close contact with an infected person is a 10 day course of once daily treatment [ie half the 5 day treatment doses outlined in Table 5 and Table 6 for twice as long]. With regard to treatment, modifications [dose reductions] are needed for patients with significant renal impairment. The main side effects reported are nausea and vomiting and these may be reduced if oseltamivir is taken with food.[21]

MORTALITY

There is little doubt that the impact of swine influenza in the initial wave of the pandemic has been more modest than first feared. Deaths as of May 23rd [6 weeks after the first cases were confirmed] were limited to 17 in 10,053 proven cases in the USA,[14] with approximately 85 deaths in Mexico with 3000 proven cases and a handful of deaths in the other 39 countries with reported cases. There is clearly a time lag potential for the mortality rate to increase as the swine flu virus spreads, but the mortality rate at six weeks would appear no higher than seasonal influenza, although the demographic of those dying differs. Obviously, continued efforts at containment will be important to minimise the spread of swine flu and thereby minimise the risk of further mortality.

INTERNATIONAL RESPONSE TO THE THREAT OF A PANDEMIC: THE ROLE OF THE INTERNET

The clear impact of internet communication upon the co-ordinated response to the epidemic of swine influenza is

Table 6
Treatment doses of oseltamivir [Tamiflu®] for ≥ 1 year of age authorized by the FDA on April 27th 2009 {derived from 15,21}

Dose by age [years]	Dose by weight [kg]	Dose for 5 days	Number of bottles needed of oral suspension for 5 day course	Number of capsules needed for 5 day course
1-2	≤ 15	30 mg twice daily	1	10 capsules [30 mg]
3-5	15-23	45 mg twice daily	2	10 capsules [45 mg]
6-9	23-40	60 mg twice daily	2	20 capsules [30 mg]
≥ 10	> 40	75 mg twice daily	3	10 capsules [75 mg]

remarkable.[11] It has provided the general public with ready access to information via authoritative websites such as the CDC in the USA[14] and for clinicians from the same website as well as that provided by leading medical journals such as The Lancet[22] and the New England Journal of Medicine[23] as well as subscription medical summary search engines such as "Up to Date". Additional resources will no doubt emerge to keep us fully aware of what is happening around the world in real time, which can only be of benefit to all.

KEY POINTS

- Human Swine Influenza A [H1N1] is a highly transmissible infection which has predominantly affected children and young adults.
- The mortality in the early stages of the pandemic appears no worse than seasonal influenza A and it is young children and adults with significant chronic respiratory, cardiac and immunosuppressive conditions who appear at a greater risk of death.
- The neuraminidase inhibitors oseltamivir and zanamivir are effective for prophylaxis and treatment.

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