Children, avian influenza H5N1 and preparing for the next pandemic

A Nicoll

ABSTRACT
The emergence of avian influenza A/H5N1 viruses has driven pandemic preparations to become government priorities across Europe. To date these viruses have remained poorly adapted to humans and the risk of a pandemic based on H5N1 is unquantifiable. However, the risk of a future pandemic is 100%. Preparations are essential and without these many avoidable deaths will occur. Children will be affected at least as much as adults and may play an important role in amplifying transmission. Pharmacological and public health interventions focused on children will save lives through suggested community measures such as pre-emptive closures of schools, and need to be considered carefully, balancing benefits against negative consequences. Child health services will be hugely stressed by any pandemic but also have the potential to save many lives. The challenge will be to deliver core services in the face of major staff illnesses. Detailed local business continuity planning will be essential.

Infectious disease is one of the great tragedies of living things – the struggle for existence between two different forms of life – incessantly the pitiless war goes on, without quarter or armistice – a nationalism of species against species
Hans Zinsser, Rats, lice and history, 1935

During influenza pandemics many millions of people become ill when a novel influenza A virus (a pandemic strain) spreads worldwide, and some of these people die from the infection or its complications. Pandemics vary in their pathogenicity (the case fatality rate or CFR) and the groups affected (table 1). In the United States contemporary planning estimates are that moderate (Hong Kong or Asian flu-like) and severe (Spanish influenza-like) pandemics would result in 200 000 and 1.9 million additional deaths and 265 000 and 9.9 million hospitalisations, respectively.1 Scaling these figures up to the European Union (EU) population of half a billion would mean between 350 000 and 3.2 million additional deaths and 440 000 and 16.5 million hospitalisations in the EU.

Children could constitute up to 40% of all cases.8 Although a smaller proportion of these patients will require hospitalisation than the elderly and those with other pre-disposing conditions, children with chronic ill health will be especially vulnerable and child health services will be severely tested. In addition, at the peak of local epidemics up to 20% of staff will be unavailable due to ill-health or having to care for ill members of their own families.9 Without good preparation these short but high levels of illness will cause much wider problems beyond the health services, with potential social and economic disruption, threats to the continuity of essential services, reduced production levels, shortages and distribution difficulties for goods and utilities. There could be major economic losses amounting to between 1% and 4% of the annual gross national product depending on the severity of the pandemic.10 11 Difficulties in maintaining business and service continuity will be worse if the virus affects working age populations as it did in 1918–19 (table 1). Therefore, such issues have to be considered by those responsible for delivering child services in primary and secondary care during a pandemic.

This review will consider what is known of how children are affected by A/H5N1 viruses (human bird flu), how children will be affected in the next pandemic, their potential role as amplifiers of infection in a pandemic and their importance in some of the suggested countermeasures. Finally, there will be some comments about how child services should prepare for functioning in a moderate to severe pandemic. However, it is necessary first to describe the ecology of influenza viruses, animals and Homo sapiens.

THE ORIGINS OF PANDEMICS
Three groups of influenza viruses (A, B and C) affect humans. However, it is the A viruses that cause serious pandemics; B viruses are only found in humans, produce milder illness and smaller outbreaks (although they especially affect children), while C viruses cause the common cold. The viruses are further classified according to the combination of types of haemagglutinin glycoprotein (H1–16) and neuraminidase enzymes (N1–9) found on their surfaces (so A/H1N1, A/H1N2, etc). The natural hosts of the A viruses are wild waterfowl, where they exist as many different types (A viruses circulating currently are types H1N1, H1N2, H5N2).

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A virus forming a pandemic strain has the following characteristics:
1. It can infect humans, in whom it can reproduce and produce pathology.
2. It is a virus to which many or most humans have no immunity (eg, from prior exposure to a similar virus).
3. It can transmit from human to human efficiently.

When all three conditions occur, the pandemic strain sweeps the world causing a variable level of pathology (table 1). The pathogenicity of the pandemic strain then seems to wane as rising proportions of the population acquire immunity, most from being infected (some older people may have immunity from previous pandemics) and some from receiving a vaccine which includes a component prepared against the pandemic strain (a pandemic vaccine). The pandemic strain frequently displaces a pre-existing strain from the seasonal influenza epidemics and can then dominate the subsequent winter epidemics which are usually considerably more intense following each pandemic.12

Three major pandemic strains have emerged in the last 100 years. Other influenza viruses have emerged and affected humans, but they either only had mild pathogenicity and/or only affected certain age groups (table 1). Some, mostly H1N1 type viruses, which have emerged in the 20th century have not caused pandemics but have required inclusion in the seasonal vaccines. In 1977 one H1N1 virus emerged, perhaps escaping from a laboratory, and spread world wide, mostly affecting children and adolescents (table 1). Virological archeology suggests that all three important pandemic strains started after some genetic material from an animal (bird) virus combined with that from a human influenza virus to produce the pandemic strain, with Spanish influenza having the clearest relationship with an animal influenza (table 1). As a result, there has been major international concern since 1997, when a novel avian virus group (the A/H5N1 viruses) emerged in China and showed an ability to infect and kill humans. The concern intensified after 2003 when the virus extended its geographical range to infect birds in over 50 countries, becoming endemic in domestic poultry in a few places, and so increased the risk of human infection.24 25 However, to date these viruses have remained in poultry (China, Egypt, Indonesia, Thailand and Viet Nam) account for nearly 90% of these cases. A total of 213 people are known to have died, a case fatality rate of around 60%. Serology testing suggests there are only a few asymptomatic or mild cases. Fortunately person to person transmission has been uncommon and very limited. Children, adolescents and young women are disproportionately represented among the cases, probably because almost all infections come from close contact with sick chickens and ducks, and the care of domestic poultry is traditionally a task for younger members of families and women in the endemic countries. Clinical trials, the children and adults present with a severe febrile respiratory illness and sometimes also with diarrhea, which can progress to multi-organ involvement. Treatment with antivirals and other agents has not been conclusively shown to result in a positive outcome, although there are now some observational data pointing to benefit from early treatment of young patients in Egypt. However, most cases have only come to the attention of health care services at a late stage, so experience is limited. Much remains to be discovered about the behaviour of the A/H5N1 viruses. However, to date these viruses have remained influenza viruses of birds since they are poorly adapted to humans than the H5N1 avian influenza and in the past were considerably less pathogenic. The highest recorded all age case fatality rate (CFR) during a pandemic was the 2–3% observed in 1918–19. However, when combined with attack rates of up to 50%, even the low CFRs observed in 1957 and 1968 (under 0.2%) resulted in many additional child deaths (table 1).

Table 1 Pandemics of the 20th century (reproduced with permission from the European Centre for Disease Prevention and Control, http://ecdc.europa.eu/Health_topics/Pandemic_Influenza/stats.html)

<table>
<thead>
<tr>
<th>Pandemic (date and common name)</th>
<th>Considered area of emergence</th>
<th>Influenza A virus type</th>
<th>Estimated reproductive number*</th>
<th>Estimated case fatality rate</th>
<th>Estimated attributable excess mortality worldwide</th>
<th>Age groups most affected (simulated attack rates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918–19 Spanish influenza</td>
<td>Unclear</td>
<td>H1N1</td>
<td>1.54–1.83</td>
<td>2–3%‡</td>
<td>20–50 million$</td>
<td>Young adults†</td>
</tr>
<tr>
<td>1957–8 Asian flu</td>
<td>Southern China</td>
<td>H2N2</td>
<td>1.50</td>
<td>&lt;0.2%‡</td>
<td>1–4 million†</td>
<td>Children most affected**</td>
</tr>
<tr>
<td>1968–9 Hong Kong flu</td>
<td>Southern China</td>
<td>H3N2</td>
<td>1.28–1.56</td>
<td>&lt;0.2%‡</td>
<td>1–4 million†</td>
<td>Across all age groups††</td>
</tr>
</tbody>
</table>

*The average number of people infected by a single case of influenza in a fully susceptible population.
‡Hall, et al; Kilbourne, Johnson et al; Glezen; Chin et al; Davis et al

CHILREN AND AVIAN INFLUENZA H5N1

By the end of 2007 there had been 346 confirmed human cases of A/H5N1 infection reported to WHO from 14 countries, although five countries where the infection seems to be endemic in poultry (China, Egypt, Indonesia, Thailand and Viet Nam) account for nearly 90% of these cases. A total of 213 people are known to have died, a case fatality rate of around 60%. Serology testing suggests there are only a few asymptomatic or mild cases. Fortunately person to person transmission has been uncommon and very limited. Children, adolescents and young women are disproportionately represented among the cases, probably because almost all infections come from close contact with sick chickens and ducks, and the care of domestic poultry is traditionally a task for younger members of families and women in the endemic countries. Clinically, the children and adults present with a severe febrile respiratory illness and sometimes also with diarrhea, which can progress to multi-organ involvement. Treatment with antivirals and other agents has not been conclusively shown to result in a positive outcome, although there are now some observational data pointing to benefit from early treatment of young patients in Egypt. However, most cases have only come to the attention of health care services at a late stage, so experience is limited. Much remains to be discovered about the behaviour of the A/H5N1 viruses. However, to date these viruses have remained influenza viruses of birds since they are poorly adapted to humans than the H5N1 avian influenza and in the past were considerably less pathogenic. The highest recorded all age case fatality rate (CFR) during a pandemic was the 2–3% observed in 1918–19. However, when combined with attack rates of up to 50%, even the low CFRs observed in 1957 and 1968 (under 0.2%) resulted in many additional child deaths (table 1). The...
clinical experience of children in pandemics is not well described in the literature, but clinical effects and features in children and adults do not differ fundamentally. Also, since young children’s first contact with influenza virus is when they encounter seasonal influenza, their clinical responses to pandemic and seasonal influenza are similar. The illnesses commonly experienced by children include headache, malaise, myalgia, loss of interest in food, sore throat, cough, sneezing and nasal discharge. Mild and asymptomatic infections do occur, but complications are more common in pandemic than seasonal influenza. Children with other underlying medical conditions have worse disease. The respiratory system shows the most complications with otitis media, croup, bronchitis and pneumonia (including secondary bacterial infections) occurring. There are a plethora of other occasional complications including neurological (Reye’s syndrome, confusion, convulsions, psychosis, neuritis, Guillain-Barre syndrome, transverse myelitis, encephalomyelitis and coma) and cardiac (myocarditis and pericarditis) symptoms and a miscellaneous group (toxic shock syndrome, myositis, myoglobinuria and renal failure).

Pandemics are not standard and differ in their severity and whom they affect. Children can play especially important roles as amplifiers of infection when they experience high attack rates. The three 20th century pandemics have varied considerably in the importance of transmission among children (table 1 and fig 1). Like seasonal influenza, all three have impacted on the very young and the elderly. However, the 1918–19 pandemic particularly affected older children and young adults and there were spectacular accounts of rapid onset death from overwhelming primary infection involving pneumonia. Case fatality rates in young adults reached 3% and 4–5% in infants. In contrast, the 1957–8 pandemic especially affected children and adolescents with unusually high attack rates of over 50% in school-age children but a relatively low CFR of under 0.2% (table 1 and fig 1). Perhaps because of the spread among children, the pandemic developed rapidly in the UK. Finally, the 1968–9 pandemic affected all age groups to similar extents and had a much slower onset in the UK. It also had a CFR of under 0.2% (table 1 and fig 1).

Figure 1  Age specific attack rates for 20th century pandemics (reproduced with permission from Glass et al).

HOW INFLUENZA TRANSMITS: REDUCING THE DAMAGE AND PROTECTING CHILDREN

The influenza virus spreads via the respiratory route from person to person through talking, coughing or sneezing of large infectious droplets among people who are in close contact (risk declines significantly beyond 1 m). It also spreads through hand to face contact if hands are contaminated with the virus and by hand to face contact after touching an infected person or surface contaminated with infected secretions. However, contrary to common belief influenza is not very infectious. Even without intervention or significant immunity in the population, one person generally only infects about 1.4–1.8 others (although higher rates can be observed in closed communities such as schools or residential homes). The disease has a short incubation period, typically 2–3 days (with an outside range of 1–4 days) and it is this short serial interval rather than high infectivity that accounts for influenza’s ability to spread rapidly. Data are sparse on how much spread takes place from asymptomatic versus symptomatic patients and when people become infectious. Too much may be inferred from studies of viral excretion rather than actual transmission patterns. However, it is thought that sufferers are most infectious early in their illness, although a few are probably somewhat infectious before the onset of clinical symptoms, and it is considered that people remain infectious for 4–5 days thereafter, although their infectiousness rapidly declines. Children (and adults with impaired immune systems) can excrete virus for 7 or more days. Some people can be infected without showing symptoms and may shed virus and therefore pass on the infection.

CHILD FOCUSED COUNTERMEASURES

Influenza is a difficult infectious disease to control, especially among children assembled together in schools and day care who are less able to practice the recommended personal protective measures (table 2) of regular hand washing, good use of tissues and early self-isolation. Hand washing is considered important as washing with alcohol hand disinfectant or ordinary soap and water readily deactivates the virus. Once a pandemic virus has started to spread worldwide, its containment is considered impossible and all but the most isolated or isolatable communities can expect to be affected. However, a variety of measures can be undertaken to achieve mitigation (damage reduction) and ensure that productive businesses and vital services are sustained (table 2). The specific objectives are:

1. to reduce the total number of cases,
2. to delay and flatten the peak of local epidemics so that it is easier to maintain essential production and services,
3. to protect the most vulnerable from disease and death.

The results of modelling suggest that some countermeasures should focus on children because they can amplify transmission, especially when crowded together in schools and care groups. The rationale is that lessening transmission among children may be especially effective in reducing the number of cases and flattening peak incidence. One of the commonly suggested community public health measures is reactive or even pre-emptive closures of schools and nurseries. One theoretical group has gone further and suggested that at the start of local transmission everyone under the age of 19 should be strictly confined to their homes for the duration of the pandemic, so-called protective sequestration. A variant of this extreme measure has been combined with other public health interventions in the USA.
### Table 2  Suggested countermeasures for a pandemic

<table>
<thead>
<tr>
<th>Countermeasures</th>
<th>Objectives</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal protective measures: early self-isolation, regular hand washing, respiratory hygiene (proper use and disposal of tissues), mask wearing and other protection in health care settings</td>
<td>Reducing the individual risk of acquiring or transmitting infection</td>
<td>Evidence base for all these measures is weak in relation to influenza</td>
<td>WHO Writing Group&lt;sup&gt;38&lt;/sup&gt;, ECDC&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Community public health measures: home working, pre-emptive school closures, reactive school closures, stopping mass gatherings, curtailing local travel</td>
<td>Reducing individual and community transmission risk</td>
<td>All measures have major problems of cost, practicability, acceptability and sustainability. Evidence base weak</td>
<td>WHO&lt;sup&gt;23&lt;/sup&gt;, Inglesby et al&lt;sup&gt;39&lt;/sup&gt;, Germann et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antivirals for early treatment (within 24 or 48 h) of symptomatic cases</td>
<td>Reducing disease and individual infectiousness to others</td>
<td>Evidence inferred from experience with seasonal influenza</td>
<td>Moscona&lt;sup&gt;38&lt;/sup&gt;, Halloran et al&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other therapeutic and supportive interventions</td>
<td>Reducing individual morbidity and mortality</td>
<td>British Infection Society et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Antivirals for prophylaxis of families</td>
<td>Reducing individual risk of acquiring and transmitting infection</td>
<td>Evidence inferred from experience with seasonal influenza</td>
<td>Germann et al&lt;sup&gt;38&lt;/sup&gt;, Ferguson et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Human A/H5N1 avian influenza (pre-pandemic) vaccines</td>
<td>Reducing individual risk of acquiring and transmitting infection</td>
<td>Assumes next pandemic is H5 based. Effectiveness may be low</td>
<td>Germann et al&lt;sup&gt;38&lt;/sup&gt;, Ferguson et al&lt;sup&gt;42&lt;/sup&gt;, WHO&lt;sup&gt;42&lt;/sup&gt;, ECDC&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>The pandemic vaccine</td>
<td>Reducing individual risk of acquiring and transmitting infection</td>
<td>Will not start to be available until 4 to 6 months after first isolation of pandemic strain</td>
<td>Germann et al&lt;sup&gt;38&lt;/sup&gt;, Ferguson et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Business continuity planning</td>
<td>Identifying and sustaining essential services and business</td>
<td>For example in hospitals stopping elective surgery and out-patients</td>
<td></td>
</tr>
</tbody>
</table>

into a package of community public health measures known as targeted layered containment.<sup>30</sup> However, not everyone agrees that school closures would be very effective, and this may depend on the characteristics of the pandemic (1957-like or 1968-like; see fig 1). The practicability, secondary effects and costs of all community public health measures, such as school closures, will have to be considered. Sustainability needs particular attention as measures would need to be continued for the 4–6 months of a pandemic.<sup>30</sup> Pharmacological countermeasures entail the use of antivirals and vaccines.<sup>38</sup> Early application of antivirals such as oseltamivir can reduce both the pathogenic effect and the transmission of seasonal influenza.<sup>39</sup>–<sup>41</sup> Because of the importance of transmission in the home, modelling suggests that when a case is suspected everyone in a family should be given antivirals.<sup>38</sup>–<sup>41</sup> Partially for this reason, many European countries have stockpiled large amounts of antivirals at national or regional levels. However, the practicalities of efficiently delivering antivirals at a population level within the required 24–48 h of first symptoms are challenging and the stockpile required can exceed 100% of the population.<sup>23</sup>–<sup>41</sup> Most authorities consider home stockpiling by families to be undesirable, although some European families did this following the concern over “bird flu” during the winter of 2005–6.<sup>43</sup>–<sup>46</sup> The recent surprising emergence of transmissible human seasonal influenza viruses which are highly resistant to oseltamivir has demonstrated that influenza can evade even this drug.<sup>47</sup>–<sup>49</sup> This is a reminder that the effectiveness of emerging influenza viruses including pandemic strains cannot be readily predicted and that too much reliance must not be placed on antiviral therapy alone. Multiple countermeasures, so called defence in depth (table 2) is what is required.

Since it takes some months to develop and produce specific pandemic vaccines, they would not be available at the beginning of a pandemic. However, human avian influenza vaccines (sometimes called pre-pandemic vaccines) are potentially available, and it has been suggested that countries should stockpile a human vaccine based on the current H5N1 avian virus and use this if the pandemic starts in the hope that it will at least give recipients some protection against a human pandemic H5 strain.<sup>23</sup>–<sup>34</sup> Modelling studies have suggested that administering this vaccine preferentially to children might be especially valuable even with only 50% effectiveness.<sup>38</sup>–<sup>39</sup> Another group that would be a priority for such a vaccine would be health care staff. Persuading parents to accept a low effectiveness vaccine will be challenging, as will deploying and assessing the effectiveness and safety of a novel vaccine without phase 3 studies. This approach was successful with a meningococcal C vaccine in the UK,<sup>35</sup> but it would be particularly difficult during the stress of a pandemic. To date only two European countries (Finland and Switzerland) have committed to purchasing an H5 vaccine for their entire population. Other counties are considering the financial risk since it is not known when the next pandemic will occur and whether it will be based on an H5 virus.<sup>39</sup>

### PREPARING CHILD HEALTH SERVICES FOR A PANDEMIC

The UK has recently issued the first ever evidence-based guidance on how to treat adults and children infected with a pandemic virus.<sup>27</sup> Clinical guidance is essential but is only one element of preparations which have been described as the three Ps: planning, preparation and practice.<sup>3</sup> The broader health service preparations include identifying which child health services (in primary and secondary care) will be absolutely essential and should be preserved and which could be suspended under business continuity planning for up to 20% staff absenteeism.<sup>3</sup> The clinical guidance does not address the issue of planning for the additional kit and supplies that will be
needed. Requirements for intensive care and ventilation of severely ill children will increase and this cannot be simply addressed by purchasing additional equipment without considering how staff will be trained and redeployed to use it. Maintaining morale among workers will be crucial and it will be essential to ensure that medical and nursing staff are reassured that their health and that of their families is being as well protected as is practical. The recent (2007) EU-wide survey by ECDC for the Health Commissioner found that a good start had been made in health sector pandemic planning at the national level but that local preparedness was only just beginning.34 That is not a criticism, as preparing communities for a pandemic involves an intense programme of work lasting at least 5 years, starting with central planning and then flowing on to local preparation. To assist in this objective, ECDC employs some indicators of local preparedness when it works with European countries to assess and improve preparedness and these may prove helpful to those planning local services.35 Three of these indicators are:

1. If your national pandemic antiviral stockpile policy is designed to give early treatment to those with suspected pandemic influenza, can you yet demonstrate how at the local level 90% or more of citizens will be able to guarantee being able to receive antivirals within 48 if not 24 h of developing symptoms?

2. Have local health services identified the non-influenza related hospital and outpatient services that they will continue to deliver and those they will suspend during the height of a pandemic and how they will deliver the former in the face of up to 30% staff absenteeism due to ill health?

3. Have hospitals yet identified ways that they will increase their capacity for ventilating patients with influenza while at the same time maintaining minimal capacity for patients with other conditions, paying attention to the staff, training and supplies that will be needed as well as equipment?

CONCLUSION

Pandemic planning is different from preparing for most other health emergencies which are generally focal and short term. To be effective it has to involve all sections of society and every tier from international through national to local. There are great uncertainties about when and what sort of pandemic will occur. Indeed, it is quite possible that the pandemic will be mild (in 1977 a mildly pathogenic A/H1N1 virus emerged and particularly affected children worldwide but was so mild as to be scarcely termed a pandemic). The only certainty is that there will be another pandemic. Preparing for this needs to be a priority for child health services as for all society activity in Europe.

Competing interests: Currently the author is a seconded national expert at the European Centre for Disease Prevention and Control, Stockholm, Sweden (www.ecdc.europa.eu) where he is responsible for coordination of its influenza activities.

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