13
What the Paediatrician Needs to Know When Pandemic Influenza Arrives in Clinical Practice

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1 Introduction

1.1 The Media Outbreak

Avian (H5N1) influenza or "bird 'flu" has received considerable attention in both the medical literature and the mass media in the last few years. Despite the tabloids' portrayal of an imminent threat, to date there have been relatively few cases in humans in spite of large numbers of infected poultry (Hien et al. 2004). However, this may be falsely reassuring. Most indications suggest that it is just a matter of time until the next influenza pandemic occurs (Osterholm 2005). In the words of the UK Chief Medical Officer: "most experts believe that it is not a question of whether there will be another severe influenza pandemic but when" (Department of Health 2005). Although experts are agreed that a future influenza pandemic is almost inevitable, its timing is unpredictable and it is uncertain whether the virus responsible will be H5N1 or another, novel, influenza strain (Osterholm 2005). A recent editorial described avian influenza as a "predicament of extraordinary proportions" (Anonymous 2006). The next influenza pandemic will have a dramatic impact on all levels of health care including the everyday work of doctors. This chapter focuses on the clinical aspects of pandemic influenza about which paediatricians need to be familiar.

2 The Impact of Pandemic Influenza

2.1 How Many People will be Affected?

There have been ten influenza A pandemics in the past 300 years, of which the last three have been the best studied. The pandemic of 1918 (H1N1) "Spanish Influenza" killed 50–100 million people, with more than half of deaths occurring in healthy people between 18 and 40 years of age (Osterholm 2005). In the

following two pandemics – in 1957 (H2N2; "Asian influenza") and 1968 (H3N2; "Hong Kong influenza") – the mortality was strikingly lower, with each pandemic killing approximately one million people (Hien et al. 2004). This highlights the association between the virulence of virus subtype and mortality. Death rates are also determined by various other factors including clinical attack rates, R_0 (basic reproduction number), vulnerability of affected populations and the effectiveness of preventive measures. It is therefore impossible to predict with accuracy the impact of the next pandemic. Best-case scenarios, modelled on the mild pandemic of 1968, predict global deaths in the range of 2–7.4 million (World Health Organization 2005a). Should a virulent H5N1 become the next pandemic strain, evidence suggests that this strain would mimic the 1918 pandemic with estimates up to 360 million deaths globally (Osterholm 2005). As of September 2007, there have been 327 confirmed cases (with 199 deaths) of H5N1 avian influenza (World Health Organization 2006b). The mortality rate of 60% is remarkably high, but may decrease in a pandemic. The 1918 Spanish influenza which had an estimated mortality rate of 2.5% (Hien et al. 2004).

2.2   How Fast will Pandemic Influenza Spread?

In a pandemic situation it is likely that influenza would strike in several waves, each lasting approximately 15 weeks with a cumulative clinical attack rate of up to 25% of the population (Department of Health 2005). In the first wave, it is expected that the number of cases would rise exponentially within a few weeks. Second and third waves, which may be weeks or months apart, with possible increased virulence may occur, as has been the case during past pandemics (Department of Health 2005; World Health Organization 2005a). Previous pandemics spread around the globe in 6–9 months. Given the pace and dimensions of international travel today, it is likely that pandemic influenza will spread more rapidly, reaching all continents in less than 3 months (World Health Organization 2005a).

The World Health Organisation (WHO) has defined stages in the evolution of an influenza pandemic ranging from phase 1 (inter-pandemic) to phase 6 (pandemic). During 2006 and 2007, WHO declared a phase 3 (pandemic alert) stage, which is defined as "no or very limited human-to-human transmission." The next phases are "evidence of increased" (phase 4), "significant" (phase 5) and "efficient and sustained" (phase 6) "human-to-human transmission" (World Health Organization 2005b).

2.3   Is Human-to-Human Transmission Likely to Occur?

In birds there has been a substantial rise in the number of cases of H5N1 influenza during the past few years, with an expanding range of infected avian species, (Perkins and Swayne 2002). In mammals the broadening of the host

range including infection of felids, mice, pigs and ferrets has also been documented (Chen et al. 2004; Kuiken et al. 2004). To date, human H5N1 avian influenza has occurred almost exclusively as a result of bird-to-human transmission (Tran et al. 2004; Beigel et al. 2005). Human-to-human transmission has been associated with two family clusters of H5N1 avian influenza (Tran et al. 2004). The first documented human-to-human transmission occurred in September 2004 in Thailand. An 11-year-old girl infected her mother and aunt, who both provided unprotected nursing care and subsequently developed respiratory symptoms. Autopsy tissue from the mother and nasopharyngeal and throat swabs from the aunt were positive for H5N1 by reverse transcriptase-polymerase chain reaction (RT-PCR). No other routes of transmission could be identified (Ungchusak et al. 2005).

At the time of the most recent pandemic, which emerged in China in 1968, the population of that country comprised 790 million humans, 5.2 million pigs and 12.3 million poultry. Today these populations have increased to 1.3 billion, 508 million and 13 billion respectively (Osterholm 2005). This potent mix of people, pigs and poultry creates the perfect conditions for genetic reassortment to create a novel influenza virus strain (antigenic shift). However, recent evidence suggests that reassortment is probably less dangerous than expected in the case of H5N1 avian influenza. In an animal model in ferrets – who have a similar α-2,6 sialic acid receptor predominance on respiratory epithelial cells as humans – transmission of H5N1 reassorted influenza virus was poor (Maines et al. 2005).

Nevertheless, the properties of an influenza virus that increase transmissibility are poorly understood and it is also possible that, without re-assortment, a mutation of an influenza virus such as H5N1 could produce a strain adapted to humans. For example, the receptor binding specificity of influenza H5N1 virus can be altered through a change of one amino acid in the H5 protein (Gambaryan et al. 2006). There is evidence that the change of preferred binding of the influenza H5N1 virus to the specific receptor on human respiratory epithelial cells (sialic acid α-2,6) could be the critical event in the evolution of a human-to-human transmissible strain (Matrosovich et al. 2000, Wong and Yuen 2006).

3   Diagnosis and Clinical Features of H5N1 Avian Influenza

3.1   Differences Between Pandemic Influenza and Seasonal Influenza

Important differences between annual and pandemic influenza are summarised in Table 1. The remainder of this section relates to H5N1 avian influenza specifically.

Table 1 Key differences between seasonal and pandemic influenza

	Seasonal influenza	Pandemic influenza
Seasonality	Winter	Unpredictable; not always in winter
Clinical attack rate	Up to 10% of population	Up to 25% of population
Incubation	1–3 days	2–4 days (up to 10 days)[a]
Pattern of illness	"Typical" influenza illness	Wide spectrum of presentation and illness
Excretion of virus	Peak 1–3 days (up to 10 days) (Frank et al. 1981)	Up to 18 days (Beigel et al. 2005)[a]
Viral titres	Higher viral titre in nose	Higher viral titre in throat[a]
Highest mortality	<5 years and >65 years	All ages (in previous pandemics >50% deaths in healthy adults 18–40 years)
Case fatality rate	2.5% (Hien et al. 2004)	60% (World Health Organization 2006b)[a]
Antiviral treatment	For any person likely to have a life-threatening influenza-related illness; for persons >65 years of age	Likely to be an important component of treatment but efficacy uncertain
Prophylactic antiviral treatment	For persons who live or work in institutions in case of an institutional outbreak; exposed high risk persons within a family; persons with immuno-suppressive conditions who are not likely to mount adequate immune response to vaccination (Centers for Disease Control and Prevention 2006)	Optimal strategy for use of antivirals uncertain but likely to be used to protect health care workers and in strategy to contain initial outbreaks
Vaccine	Highly effective vaccine available and recommended annually	Will probably take up to 6 months to develop and distribute in best case scenario

[a]Specifically for H5N1 avian influenza

3.2   *Clinical Features*

3.2.1   **Clinical Features at Presentation**

More than half of H5N1 avian influenza cases have been in individuals under 18 years of age and a quarter have occurred in children under 10 years of age (Fig. 1). In the first published series of ten case of H5N1 avian influenza, of which eight subsequently died, the mean age was 13.2 years (range 5–24 years) (Tran et al. 2004). Significantly, none of these patients had any known pre-existing medical condition. Nine had clear evidence of either handling poultry or exposure to sick poultry the week before the onset of illness.
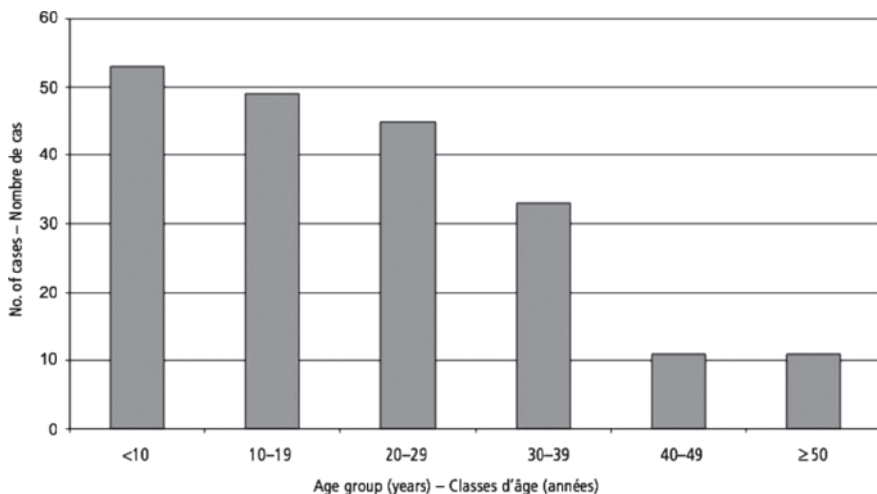
Fig. 1 Distribution of H5N1 cases by age group, as of April 2006 (n = 202) (World Health Organization 2006c)

The incubation period in H5N1 avian influenza is 2–10 days (Ungchusak et al. 2005). Patients present with initial symptoms of fever (38.5–40°C), an influenza-like illness (headache, myalgia, malaise) and lower respiratory tract symptoms (non-productive cough, shortness of breath). Upper respiratory tract symptoms and conjunctivitis are rare, in contrast to other types of influenza A. Diarrhoea (seven of ten patients in the first series (Tran et al. 2004)), vomiting, abdominal pain, pleuritic pain and bleeding from the nose or gums have all been reported early in the course of illness (Beigel et al. 2005). Dyspnoea develops a median of 5 days after the onset of symptoms (range 1–16 days) (Chotpitayasunondh et al. 2005) and respiratory distress, tachypnoea and inspiratory crackles are common. Most patients have required ventilatory support within 48 h of admission (Tran et al. 2004; Chotpitayasunondh et al. 2005).

3.2.2 Presentation with Delayed Respiratory Features

Of major importance is the observation that the clinical presentation of H5N1 avian influenza has a wide spectrum. One report from Vietnam documented siblings (a 9-year-old girl and her 4-year-old brother) who died following a presentation with severe diarrhoea, seizures and coma. Notably, both of them lacked any respiratory symptoms and both had normal chest radiographs on admission to hospital (de Jong et al. 2005a). H5N1 avian influenza virus was isolated from throat, stool, serum and cerebrospinal 'fluid. A presentation with watery diarrhoea (without blood or inflammation) preceding respiratory symptoms by 1 week has also been described (Apisarnthanarak et al. 2004).

3.2.3 Complications

Complications of H5N1 avian influenza include renal and liver dysfunction, cardiac compromise, supraventricular tachyarrhythmia (due to dilatation), myocarditis, pulmonary haemorrhage, pneumothorax, pancytopenia, Reye's syndrome, encephalopathy and sepsis syndrome (Tran et al. 2004; Beigel et al. 2005). Death is associated with acute respiratory distress syndrome (ARDS) and multi-organ failure due to a virus-induced "cytokine storm" (Osterholm 2005).

Death has occurred an average of 9–10 days after the onset of illness (range 6–30 days) (Beigel et al. 2005) and, similar to the 1918 pandemic, most patients have died of progressive respiratory failure associated with ARDS and a "cytokine storm" (Beigel et al. 2005; Osterholm 2005). The fatality rate among hospitalised patients is between 33% and 100%. In contrast to the H5N1 outbreak in 1997, in which most deaths occurred in patients older than 13 years of age, recent H5N1 avian influenza outbreaks have caused high rates of death among infants and young children with a case fatality rate of 89% reported among those younger than 15 years of age in Thailand (Chotpitayasunondh et al. 2005).

3.3 Radiology

Radiographic abnormalities in H5N1 avian influenza are present a median of 7 days after the onset of fever in almost all patients. Chest x-ray findings are very variable and include diffuse, multifocal or patchy infiltrates, interstitial infiltrates, and segmental and lobular consolidation with air bronchograms. Pleural effusions are uncommon (Beigel et al. 2005). Progression to respiratory failure and ARDS is associated with diffuse, bilateral, ground-glass infiltrates (Beigel et al. 2005).

3.4 Laboratory Features

3.4.1 Routine Investigations

Abnormalities detected on laboratory tests in H5N1 avian influenza include significant lymphopenia (median count 700/mm^3) and mild thrombocytopenia (median count 75,000/mm^3) (Tran et al. 2004), hyperglycaemia (Beigel et al. 2005). Lymphopenia and thrombocytopenia have been associated with a poor prognosis (Tran et al. 2004; Chotpitayasunondh et al. 2005).

3.4.2 Laboratory Confirmation

The following specimens from the upper respiratory tract are suitable for the diagnosis of H5N1 avian influenza: nasal swab, nasopharyngeal swab, nasopharyngeal

aspirate, nasal wash and throat swab. In addition, diagnosis can be made from other specimens including tracheal aspirate, bronchoalveolar lavage fluid, lung biopsy tissue, cerebrospinal fluid and faeces. H5-specific RNA is not detected in urine (Beigel et al. 2005). Viral excretion is prolonged and can be detected in throat-swabs up to 18 days after illness onset and in nasopharyngeal isolates from 1 to 16 days after onset. Viral loads detected in H5N1 avian influenza from pharyngeal swabs are at least 10 times higher than in H3N2 or H1N1 influenza (Beigel et al. 2005). Throat samples may have a better yield than nasal samples but the sensitivity and specificity of different samples and assays is not well defined (Beigel et al. 2005). Procedures for specimen collection, especially those involving potential aerosol generation, should be performed with appropriate precautions. WHO has produced detailed guidelines for the safe collection of specimens (World Health Organization 2005c).

H5N1 avian influenza can be confirmed in several different ways: rapid antigen test, viral isolation from culture, and the detection of H5-specific RNA with RT-PCR assays. Rapid antigen tests are less sensitive than RT-PCR. WHO laboratory criteria for confirmation require one or more of the following: a positive viral culture, a positive PCR assay, a positive immunofluorescence test for antigen (monoclonal antibody against H5), and at least a fourfold rise in H5-specific antibody titre in paired serum samples (Beigel et al. 2005).

3.5   When Should H5N1 Avian Influenza be Considered?

The possibility of H5N1 avian influenza should be considered in all patients with severe acute respiratory illness and those who present with serious unexplained illness (e.g. encephalitis or diarrhoea), who have had possible exposure to H5N1 avian influenza in the previous 2 weeks (i.e. all individuals who either live in or who have visited areas where H5N1 avian influenza has been identified in birds or other animals (Fig. 2)).

4   The Treatment of H5N1 Avian Influenza

The primary strategy for treatment of H5N1 influenza should be prevention. However, currently no commercially available vaccine against H5N1 avian influenza is available. In any case, the preparation of a vaccine against a novel strain will require several months and in the course of a pandemic, it is likely to take a minimum of 6 months before adequate supplies of vaccine are available. Therefore, effective antiviral agents are of major importance. There are two classes of drugs currently available for treatment and prophylaxis of influenza: the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (zanamivir and oseltamivir). Other drugs, such as peramivir, which is highly effective in vitro and in animal models are subject to further studies (McCullers 2006).
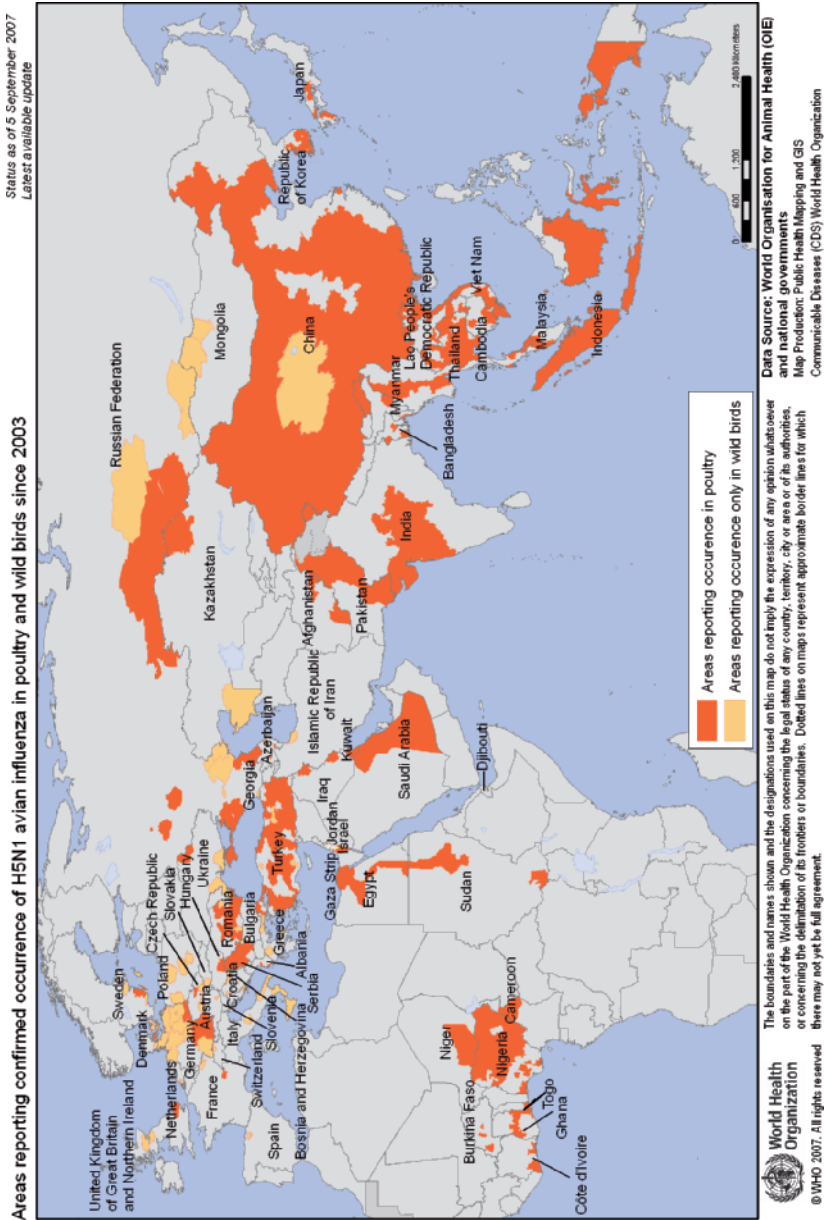
Fig. 2 Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003 (World Health Organization 2006c)

4.1   Adamantanes (M2 blockers)

Influenza virus enters host respiratory cells by endocytosis and it is then enclosed within endosomes in the cell. Subsequent acidification, through influx of H^+ ions through the M2 protein channel, is the precondition for release of the viral nucleic acid from the endosome into the cell (Fig. 3). At low concentrations, the adamantanes block the influx of H^+ ions through the M2 protein channel. This inhibits the uncoating of the virus (McKimm-Breschkin 2005; Hayden 2006; Pinto and Lamb 2006). At very high concentrations the adamantanes prevent the fusion of the virus and cell membrane by interfering with binding to hemagglutinin (McKimm-Breschkin 2005). Adamantanes may be cheaper than neuraminidase inhibitors, but they have significant limitations. They are only effective against influenza A viruses, as they exclusively block the A/M2 channel, which is not present on influenza B virus. The B/M2 channels on influenza B viruses are not affected by adamantanes (Pinto and Lamb 2006). Adamantanes are associated with gastrointestinal (nausea) and central nervous system (nervousness, anxiety, difficulty concentrating, insomnia and hallucinations (Harper et al. 2005; Jefferson et al. 2006)) adverse effects in 10–30% of patients (McKimm-Breschkin 2005). The greatest problem with this class of anti-influenza drugs is the rapid emergence (as early as day two of treatment) of resistance in up to 30% of patients (McKimm-Breschkin 2005). Furthermore, adamantane-resistant isolates can be transmitted to susceptible contacts and are pathogenic (Moscona 2005a; Wong and Yuen 2006).

4.2   Neuraminidase Inhibitors

4.2.1   Mechanism of Action

The neuraminidase inhibitors interfere with the release of influenza virus from infected host cells and thereby limit the spread of the infection (Moscona 2005a).

   The neuraminidase enzyme – the target molecule of the neuraminidase inhibitor – is present on the cell surface of all influenza viruses. It cleaves the bond by which the surface viral protein hemagglutinin attaches to the host cell-surface receptor, sialic acid. Cleavage is essential for both viral entry into the host cell but more importantly for exit of viral progeny after replication within the host cell (Fig. 4) (McKimm-Breschkin 2005; Moscona 2005a; McCullers 2006). The neuraminidase inhibitors mimic the sialic acid cell-surface receptor preventing neuraminidase from cleaving host-cell receptors and, as a result, from releasing newly-replicated virus.

4.2.2   Administration

Neuraminidase inhibitors need to be taken as early as possible in the course of the illness and ideally within 72 h, as replication of influenza virus in the respiratory tract reaches its peak between 24 and 72 h after onset of symptoms. However, a recent report suggests that treatment may still be beneficial later, if there is evidence
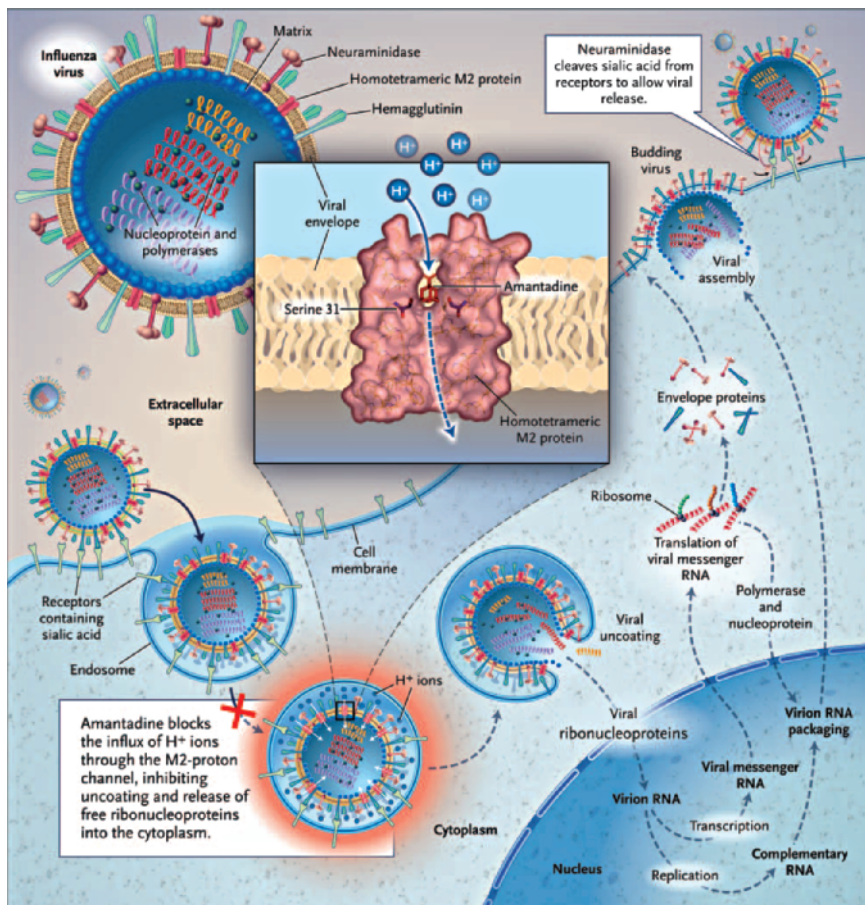
Fig. 3 Mechanism of action and development of resistance to M2 inhibitors. In the absence of amantadine, the proton channel mediates an influx of H+ ions into the infecting virion early in the viral replication cycle, which facilitates the dissociation of the ribonucleoproteins from the virion interior and allows them to be released into the cytoplasm and transported into the cell nucleus. In highly pathogenic avian viruses (H5 and H7), the M2-proton channel protects the hemagglutinin from acid-induced inactivation in the trans-Golgi network during transport to the cell surface. In the presence of amantadine, the channel is blocked and replication is inhibited. The serine at position 31 lies partially in the protein–protein interface and partially in the channel (see inset). Replacement of serine by a larger asparagine leads to the loss of amantadine binding and the restoration of channel function. Depending on the particular amino acid, other mutations at position 26, 27, 30, or 34 may inhibit amantadine binding or allow binding without the loss of ion-channel function. Inset courtesy of Rupert Russell, Phillip Spearpoint, and Alan Hay, National Institute for Medical Research, London (Hayden 2006) (with permission from the publisher, Copyright © 2006 Massachusetts Medical Society)

of ongoing viral replication. This was shown in four patients with H5N1 avian influenza who had a rapid decline in viral load, and who all subsequently survived, despite oseltamivir being initiated later than 72 h after illness onset (de Jong et al. 2005b).
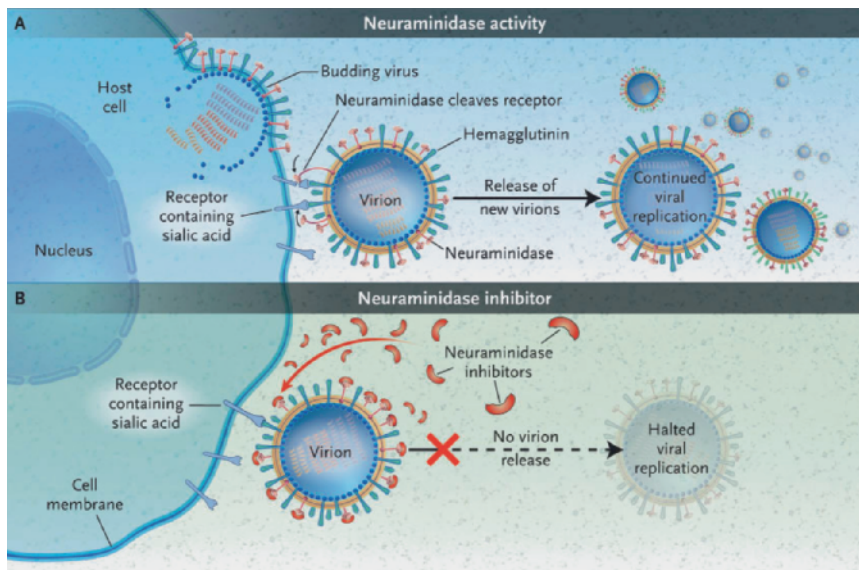
Fig. 4 Mechanism of action of neuraminidase inhibitors. Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells (Moscona 2005a) (with permission from the publisher, Copyright © 2005 Massachusetts Medical Society)

4.2.3 Formulations

Oseltamivir is available as a capsule or powder for liquid suspension with good oral bioavailability. After absorption and conversion through hepatic esterases, the active form (oseltamivir carboxylate) is widely distributed in the body with a half-life of 6–10h. The drug is excreted primarily through the kidneys thus requiring dosing modifications in patients with renal insufficiency (Moscona 2005a) (Table 2). Zanamivir is not bioavailable orally and is directly delivered to the respiratory tract through inhalation of a dry powder from a specially-designed device. Between 10% and 20% of the active component reaches the lungs and the rest is deposited in the oropharynx. Bioavailability in serum reaches a maximum of 2% (Moscona 2005a).

4.2.4 Effectiveness

Neuraminidase inhibitors are effective against all strains of influenza and their efficacy has been subject to numerous trials (Hayden et al. 1999; McKimm-Breschkin 2005; Moscona 2005a; Jefferson et al. 2006). Children with clinically-diagnosed influenza who received oseltamivir within 48h of onset of symptoms had the duration of their illness reduced by 36h (Whitley et al. 2001).

Table 2 Recommended daily doses for the treatment and prophylaxis of influenza in children (modified after Moscona 2005a; Harper et al. 2005)

	<1 year	1–6 years	7–11 years	>12 years	Renal insufficiency
Treatment Zanamivir		Not licensed for use under 7 years of age	10 mg (two inhalations) twice daily for 5 days	10 mg (two inhalations) twice daily for 5 days	No dose adjustment
Oseltamivir	Not licensed for use under 1 year of age	<15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	<15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	75 mg twice daily for 5 days	If creatinine clearance <30 mL/min: 75 mg once daily[a]
Prophylaxis Oseltamivir			Not approved for prophylaxis under 13 years of age	75 mg once daily for 7–10 days (Beigel et al. 2005)	If creatinine clearance <30 mL/min: 75 mg once every other day[a]

[a]Only evaluated in adults

Clinical trials on the efficacy of neuraminidase inhibitors for the treatment of H5N1 avian influenza have not been undertaken. In an animal model of H5N1 avian influenza-infected mice, both zanamivir and oseltamivir improved survival (Leneva et al. 2001). However, the predominant sialic acid on the cell surface receptor in mice is α-2,3 (in contrast to primarily α-2,6 in humans), which limits the interpretation of this study. In vitro studies in human survivors of H5N1 avian influenza have showed that the virus can generally no longer be cultured 2 or 3 days after starting oseltamivir (Beigel et al. 2005).

4.2.5   Adverse Effects

Neuraminidase inhibitors are associated with a low risk of adverse effects. Transient nausea, vomiting and abdominal pain occurs in up to 10% of patients treated with oseltamivir (Moscona 2005a). Cough and bronchospasm have been reported following treatment with zanamivir (Freund et al. 1999).

4.2.6   Dosing in Children

Table 2 details dosing of neuraminidase inhibitors, including dose adjustment in renal insufficiency.

Higher doses (150 mg twice daily) and longer treatment (7–10 days) may be considered in severe H5N1 influenza infections but no data have yet been published (Beigel et al. 2005).

The safety of oseltamivir in infants under 1 year of age has not been established yet. Of concern is the observation that juvenile rats accumulate high levels of oseltamivir in the central nervous system. Although the immature blood–brain barrier in infants could similarly lead to high levels of oseltamivir in the central nervous system, there have been no reports of adverse effects from oseltamivir use in infants. In addition, a retrospective study in Japan, in which 103 children younger than 1 year of age were treated with 4 mg/kg for 4 days, did not show any encephalopathy (Okamoto et al. 2005). Concerns about potential toxicity in pregnant women and breast-feeding mothers have also been raised (Moscona 2005a).

4.3   Resistance to Anti-Influenza Drugs

Resistant influenza virus can be isolated from approximately 1% of adults and 5% of paediatric patients treated with oseltamivir (Whitley et al. 2001; McKimm-Breschkin 2005). The emergence of oseltamivir-resistant H5N1 avian influenza can result from the substitution of a single amino acid in the N1 neuraminidase (tyrosine for histidine

at position 274: His274Tyr) (Ward et al. 2005). In a report of eight patients with H5N1 avian influenza in Vietnam, two had high-level resistance to oseltamivir with the His274Tyr mutation. This may have been associated with disease progression as both patients died. In the other two patients who died, one revealed wild-type 274H and in the other patient no sequences could be obtained from the specimen. In the four surviving patients none showed oseltamivir-resistant H5N1 virus (de Jong et al. 2005b).

Factors which may favour the development of resistance include: the chemical structure of oseltamivir (Moscona 2005b), altered pharmacokinetics in severely ill patients, inadequate dosing, and reduced bioavailability resulting from diarrhoea. Prolonged therapy, higher doses or combination therapy may be of benefit (de Jong et al. 2005b). Murine studies indicate that, compared with a strain from 1997, the H5N1 avian influenza virus strain from 2004 requires higher doses and longer administration (8 days) to induce similar antiviral effects and survival rates (Yen et al. 2005). The transmissibility of oseltamivir-resistant H5N1 avian influenza strains is not yet known.

No influenza strains resistant to zanamivir have yet been isolated from immunocompetent patients after therapy (Moscona 2005b). The His274Tyr mutation does not lead to cross-resistance as the binding of zanamivir is not prevented by this mutation (McKimm-Breschkin 2002). Treatment regimens combining the two different neuraminidase inhibitors might be of benefit but to date there is insufficient evidence (Gupta and Nguyen-Van-Tam 2006).

Amantadine resistance in H5N1 avian influenza is associated with the presence of several mutations (Ser31Asn, Val27Ala, Leu26Ile), which result in loss of binding to M2 ion channel blockers. The distribution of amantadine-resistant H5N1 virus appears to be largely limited to Thailand, Vietnam and Cambodia. Most H5N1 isolates from China, Indonesia (Cheung et al. 2006), Mongolia, Russia and Turkey appear to be sensitive to amantadine (Hayden 2006). However, susceptible strains rapidly develop resistance. In addition, WHO states that current isolates of H5N1 avian influenza, in contrast to isolates from the 1997 outbreak, are highly resistant to amantadine and rimantadine, and that consequently these drugs should not be used in treatment (Beigel et al. 2005). The only role for amantadine may be in combination with neuraminidase inhibitors. In vitro studies suggest that combination chemotherapy with adamantanes and neuraminidase inhibitors reduces the emergence of drug-resistant influenza variants (Ilyushina et al. 2006).

4.4   Prophylaxis

Both zanamivir (Monto et al. 2002) and oseltamivir (Moscona 2005a) are effective for post-exposure prophylaxis in seasonal 'flu with a protective efficacy of 80% in children older than 1 year. In the 1968 pandemic, adamantanes were found to have a protective efficacy of 70%. The protective efficacy of neuraminidase inhibitors in a pandemic is expected to be at least as high (Moscona 2005a), but current data on the effectiveness of neuraminidase prophylaxis in a pandemic situation are lacking. It is thought that prophylactic use of neuraminidase inhibitors does not prevent

infection but efficiently limits viral replication and shedding. This is important because children are the main source of dissemination of influenza within the community, since they usually have higher viral loads and excrete viruses for longer periods (Moscona 2005b). As a result, children who receive oseltamivir for prophylaxis will be able to mount an immune response due to sub clinical infection, but will not be the hub for infectious spread (Dolin 2005; Smith et al. 2006).

4.5   Who Should be Treated?

Recommendations for the use of antiviral drugs in seasonal influenza are detailed elsewhere (Jefferson et al. 2006, Centers for Disease Control and Prevention 2006). During an influenza pandemic, depending on the number of cases, current supplies of neuraminidase inhibitors may be inadequate for any proposed strategy of prevention (e.g. around a localised outbreak or post exposure) and may not be sufficient for the treatment of even those with disease (Hayden 2004). One approach that has been proposed to maximise supplies is to reduce the required dose of neuraminidase inhibitors through the co-administration of probenecid. By reducing the renal clearance of oseltamivir, probenecid has the capacity to increase plasma levels by 50% (Howton 2006).

4.6   Additional and Other Treatments

Secondary bacterial infection is a common and serious complication of seasonal influenza. Rates of secondary bacterial infections in H5N1 avian influenza have not been defined, but *Staphylococcus aureus* and *Haemophilus influenzae* have been isolated from tracheal aspirates in patients with H5N1 influenza (Tran et al. 2004). WHO recommends that empirical treatment with broad spectrum antibiotics should be considered in patients with suspected H5N1 avian influenza (Beigel et al. 2005). Other drugs that have been used but for which there is currently no evidence of efficacy in the treatment of H5N1 avian influenza include ribavirin, corticosteroids, interferon alpha and intravenous immunoglobulin (Beigel et al. 2005; Wong and Yuen 2006).

4.7   Personal Stockpiling of Antiviral Drugs

A benefit of having a supply of antivirals at home is that treatment can be started soon after onset of symptoms, without any delay through access to medical services. However, if oseltamivir were dispensed in advance of an outbreak, it is likely that patients would misuse their stockpiles, possibly wasting it on illnesses other than influenza. Insufficient dosing and inadequate courses are of further concern. High rates of resistance (16%) have been shown in H1N1 influenza A virus isolated from

patients in Japan as a result of under-dosing (Ward et al. 2005). Patients' requests for a personal stockpile of oseltamivir place the physician in a difficult position in between the obligation to an individual patient and the demands of public health. Currently, there is no evidence of a benefit from personal stockpiling of antivirals and therefore an individual physician has no obligation to prescribe (Brett and Zuger 2005), and moreover, has an obligation from a public health viewpoint not to prescribe. Therefore, because personal stockpiles of oseltamivir will lead to improper use and shortages of supply they should be strongly discouraged.

5 Limiting the Spread of Influenza During a Pandemic

H5N1 avian influenza is transmitted through inhalation of respiratory droplets and droplet nuclei (dry droplets), by direct or indirect contact, or by contact with fomites. The relative efficiency of these different routes has not been defined (Beigel et al. 2005), but it is highly likely that the major mode of spread is through respiratory droplets expelled when coughing or sneezing (Bridges et al. 2003).

The possibility of person-to-person transmission of avian H5N1 influenza is of great concern since the case in Thailand, described above, in which there was apparent transmission to the child's relatives who provided unprotected care. Further transmission to health care workers did not occur in this case (Ungchusak et al. 2005). The current low risk of nosocomial transmission to health care workers is reassuring. However, in the advent of a pandemic, precautions to prevent human-to-human transmission would be critical for individuals caring for affected patients. In addition to standard and droplet precautions, the WHO recommends eye protection and, where possible, airborne precautions (World Health Organization 2006a).

Furthermore, respiratory hygiene, so-called "cough etiquette," is recommended by several health organisations, though it is of unproven efficacy. It involves covering coughs and sneezes with a disposable tissue, the use of masks if coughing and sneezing, and personal hand hygiene after contact with respiratory secretions (Centres for Disease Control and Prevention 2003; World Health Organization 2006a).

Contacts of a patient with proven or suspected virus should monitor their temperature and self-quarantine for a period of 1 week after their last exposure (Beigel et al. 2005). Household contacts of individuals with confirmed H5N1 avian influenza should receive post-exposure prophylaxis as described above (Beigel et al. 2005).

Travel restrictions and quarantine were not very effective in the previous three pandemics. However, banning of public gatherings and closure of schools may be effective in preventing the spread that is associated with close contact and crowding. Such measures may not need to be in place for prolonged periods, as pandemic influenza peaks have generally been short-lived. Preventing spread may lead to cases occurring over a longer time frame by flattening the epidemiological peak. The resulting fewer cases in any time period would decrease the burden on medical and other essential services (World Health Organization 2005a).

6 The Prevention of Pandemic Influenza

Controlling avian influenza in birds is a key tactic in preventing the emergence of pandemic influenza. Active surveillance in animals and humans is needed to monitor the evolution of potentially threatening avian viruses (Hien et al. 2004). In Hong Kong, for example, surveillance of influenza in poultry, recognition of early outbreaks and active surveillance in humans helped keep Hong Kong free of H5N1 avian influenza virus in humans for 7 years after the 1997 outbreak (Hien et al. 2004).

Vaccination remains the primary strategy for prevention of influenza and is beyond the scope of this chapter.

7 Conclusion

The world has its first opportunity to be prepared for the next influenza pandemic (Shortridge 2006). Understanding the epidemiology, clinical and laboratory features, and treatment and prophylactic strategies might provide a head start that will prevent the repetition of the mistakes in previous pandemics (Anonymous 2006).

8 Addendum

Subsequent to the completion of this manuscript in September 2006, new information about pandemic influenza had continued to be published at a high rate. Amongst the most interesting new developments are:

- Concerns about abnormal neuropsychiatric behaviour in adolescents receiving oseltamivir (2007)
- WHO recommendations on treatment and prophylaxis of H5N1 avian influenza, including a once daily dose of oseltamivir for the prophylactic treatment of children 1 to 12 years of age (Schunemann et al., 2007)
- The description of clades and subclades of H5N1 avian influenza virus with implications for resistance patterns and vaccine production (Webster and Govorkova, 2006)
- Confirmation that H5N1 avian influenza is predominantly a paediatric disease possibly explained by the presence of α-2,3 sialic acids in the upper airway tract in children (Goicoechea, 2007)

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Key web resources for pandemic and H5N1 avian influenza

Of the tens of millions of web sites with information about pandemic and H5N1 avian influenza available on the internet, many happy hours can be spent browsing the following sites that are amongst the most useful:

World Health Organisation

http://www.who.int/csr/disease/avian_influenza/en/index.html

http://www.who.int/csr/disease/influenza/nationalpandemic/en/index.html   (other countries' guidelines)

UK Health Protection Agency

www.hpa.org.uk/infections/topics_az/influenza/avian

www.hpa.org.uk/infections/topics_az/influenza/avian/microbiological_guidance.htm

UK Department of Health

http://www.dh.gov.uk/en/PandemicFlu/index.htm

UK National Health Service

http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=1565&sectionld=10

http://www.nhsdirect.nhs.uk/ articles/article.aspx?articleId=1303&sectionld=10

European Centre for Disease Prevention and Control

http://www.ecdc.eu.int

US National Library of Medicine and National Institute of Health

www.nlm.nih.gov/medlineplus/flu.html

US Department of Health and Human Services

http://www.pandemicflu.gov

Centers for Disease Control and Prevention

http://www.cdc.gov/flu

http://www.cdc.gov/flu/avian/index.htm

International Society of Infectious Diseases

http://www.promedmail.org

Miscellaneous

http://www.medscape.com/resource/influenza

http://www.influenzareport.com

http://www.fluwikie.com

http://www.fluwire.com

http://www.connotea.org/tag/AvianFlu

http://pandemicnews.blogspot.com/