Clinical Guidelines for Patients with an Influenza like illness during an Influenza Pandemic

British Thoracic Society
British Infection Society
Health Protection Agency

Version 5.0
Last updated: 15 October 2005

CONTENTS

1 INTRODUCTION

1.1 Scope and Purpose

This document contains guidance for health professionals regarding the treatment of pandemic influenza, agreed by experts from the British Thoracic Society, the British Infection Society and the Health Protection Agency. It is published as official UK guidance by the Department of Health in England and covers treatment in hospitals and the community, of both adults and children. It is intended for use in the UK in event that the World Health Organisation declares that an influenza pandemic has started,(1) and the Department of Health in England (UK-wide lead agency on pandemic influenza, including the devolved administrations) has declared UK Pandemic Alert Level 2 (cases of pandemic influenza identified within the UK – see Appendix 1).(2)

This guidance should be read in conjunction with UK Infection Control Guidance for Pandemic Influenza,(3) (document to be published) the Department of Health UK Pandemic Influenza Contingency Plan,(2) Operational Guidance for Health Service Planners,(4) and the Operational Framework for stockpiling, distributing and using antiviral drugs in the event of pandemic influenza.(5)

To facilitate preparedness planning, this document has been written in advance of the emergence of the next influenza pandemic, at a time when the identity of the causative virus remains unknown, based on the best evidence available from previous pandemic and interpandemic periods. Thus the guidance may evolve as clinico-pathological information on the eventual pandemic virus emerges. Therefore, once an influenza pandemic is underway, users are strongly urged to ensure that they refer to the most up-to-date version of these guidelines (from web-based access points).

1.2 Context

Seasonal influenza is a familiar infection in the UK, especially during winter. Every year strains of influenza (type A or B) circulate, giving rise to clinical consultations in primary care (age-specific impact varies by season), episodes of hospital treatment (mainly in older persons and young children, but occasionally in working age adults), and deaths (mainly in the elderly). Treatment in primary care and hospital may be required due to the direct effects of influenza virus infection or its possible complications, most commonly secondary bacterial pneumonia. Increases in GP consultations for influenza-like illness and winter bed pressures are frequently associated with periods of known community influenza activity.(6)

Pandemic influenza occurs when a new influenza A virus subtype emerges which is markedly different from recently circulating subtypes and strains, and is able to:

- infect humans;
- spread efficiently from person to person;
- cause significant clinical illness in a high proportion of those infected.

Because the virus is novel in humans, a high proportion of the population will have little or no immunity, producing a large pool of susceptible persons; accordingly the disease spreads widely and rapidly.

Influenza pandemics occur sporadically and unpredictably. In 1918 a devastating and unusual pandemic caused by influenza A/H1N1 (‘Spanish flu’) killed between 20 and 40

million people worldwide. Other pandemics that followed had a less devastating impact but were nevertheless severe. Influenza A/H2N2 ('Asian flu') emerged in 1957 and H3N2 ('Hong Kong flu') in 1968; both produced roughly 1 million excess deaths worldwide.(7)

The circumstances still exist for a new influenza virus with pandemic potential to emerge and spread, and the longest interval so far recorded between pandemics is 39 years (1918-1957). The unpredictability of the timing of the next pandemic is underlined by the occurrence of several large outbreaks of highly pathogenic avian influenza associated with epizootic transmission to humans.(8) By far the most serious has been the massive and unprecedented outbreak of highly pathogenic influenza (A/H5N1) affecting poultry in East and South East Asia in late 2003, which is still continuing. This outbreak has so far been associated with a small number of human cases but a high proportion of deaths. Recently, epidemiological and virological changes have been reported from northern Viet Nam which may indicate that the virus is beginning to adapt to humans.(9) Although the emergence of an A/H5N1 strain with capacity to spread efficiently between humans is neither inevitable nor imminent, international concern has increased regarding the possibility that avian influenza A/H5N1 may evolve to produce the next pandemic.

Other events and developments that inform the creation of this guidance are the development and licensing of a new class of drug (neuraminidase inhibitors) active against influenza, and UK government's recent announcement of plans to procure 14.6 million treatment courses of oseltamivir (Tamiflu®)(10) for use in the UK in the event of a pandemic.

1.3 Who are these guidelines aimed at?

These guidelines are offered for the guidance of all UK hospital doctors and primary care physicians. In the event of a pandemic, it is envisaged that all health care practitioners, regardless of individual specialisation, may be involved in the management of patients with influenza. It is intended that these guidelines also be of value to health care practitioners who do not usually manage patients with influenza but may be called upon to do so in a pandemic situation. Modification of some recommendations at a local level may be necessary in specific instances.

These guidelines are not relevant for the management of patients affected by seasonal influenza, sporadic acute exacerbations of chronic obstructive pulmonary disease, lower respiratory tract infections or community acquired pneumonia (CAP).

1.4 Grading of recommendations

The recommendations offered in the current guidelines are based on a matrix of evidence centred mainly around seasonal influenza, expert opinion and group consensus. Grading of these recommendations based on the strength of the evidence base was deemed inappropriate.

2 EPIDEMIOLOGY AND HEALTH IMPACT PROJECTIONS

Summary

1. The scale and severity of illness (and hence consequences) caused by pandemic influenza generally exceed those of even the most severe winter epidemics.
2. Mortality in the UK is likely to exceed 50,000 deaths, possibly appreciably higher.
3. Besides the elderly, excess mortality is also likely in younger adults and children.
4. Modelling studies suggest that after a case occurs in Hong Kong, because of international travel, it will take less than one month for the virus to reach the UK.
5. Once cases begin to occur in the UK it will take only 2 – 3 weeks before activity is widespread and roughly a further 3 weeks (6 weeks after initial cases in UK) until activity peaks.
6. It is possible that there will be more than one epidemic wave (with an interval of several months) and, if a second wave occurs, it may be more severe than the first.
7. Cumulative clinical and serological attack rates across all waves together may be in the order of 25% and 50% respectively.
8. Increases in demand for health care services are likely to be very substantial in both primary care and hospital settings.

2.1 Introduction

When an influenza pandemic occurs, a substantial proportion (possibly all) of the population is likely to be non-immune, producing a large pool of susceptible persons. In past pandemics, the scale and severity of illness (and hence consequences) have been variable but broadly of a higher order than even the most severe winter epidemics. It is reasonable to expect this to be the case with the next pandemic as well.

2.2 Excess Mortality

Excess mortality due to influenza occurs in most winter seasons but is especially marked during epidemics. The average annual excess mortality attributable to influenza in recent years is around 12,000 deaths per annum in England and Wales,(11) although there is considerable yearly variation and some years are notably much higher than the average (est. 26,000 in 1989/90 epidemic). Excess mortality in England and Wales associated with the three pandemics of the 20th century has also varied widely; this was estimated at 198,000 civilians in 1918/19, and 37,500 in 1957/58. In 1968/69 and 1969/70 (both seasons considered to be associated with the influenza A/H3N2 pandemic) there were an estimated 31,000 and 47,000 deaths respectively.(7) Therefore the extent of mortality associated with the next pandemic cannot be reliably predicted although it is reasonable to plan for a scenario worse than a severe winter epidemic of normal influenza.

2.3 Age distribution of morbidity and mortality

Typically, there are changes in the age-distribution of cases compared with seasonal influenza. Mortality, which in typical seasonal influenza is usually confined to age groups over 65 years, tends to be increased in younger age groups. The size of any increase in morbidity and mortality and the extent to which a shift in age distribution occurs depends on a variety of factors including the nature of the pandemic virus and pre-existing immunity but appears to be a consistent phenomenon.(12) Therefore clinicians can expect to see relatively larger amounts of influenza-related illness in younger adults compared with normal winter

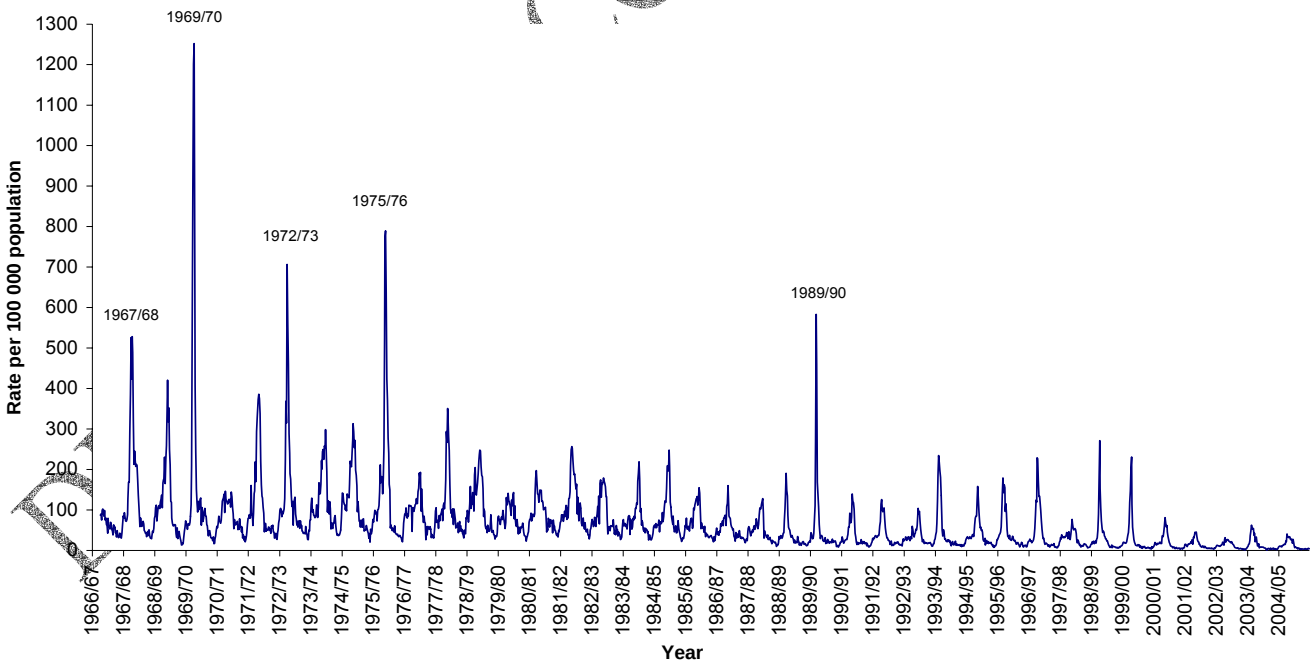
activity. At least one third of all excess deaths may be expected in persons under 65 years of age.

2.4 Geographical and temporal spread

Virological and clinical surveillance of influenza have improved markedly since the last pandemic in 1968. However the extent of international travel has also grown. Modelling studies using transmission characteristics based on the 1968/69 pandemic and international air-traffic data from 2002 indicate that the approximate delay between a first case in Hong Kong and first introduction to UK will be less than one month.(13) In terms of the spread within the UK, it will probably take only 2-3 weeks from the initial introduction(s) until activity is widespread and a further 3 weeks (6 weeks from initial UK cases) until activity peaks.

The temporal and spatial spread of a pandemic strain is important, particularly in terms of the demand placed on healthcare services. Pandemic activity taking the form of a brief but severe peak in cases will be more difficult for all services to cope with, compared with an identical number of cases distributed over a longer time course. For example, during the A/H3N2 pandemic a long first wave occurred in the winter of 1968/9 with morbidity and mortality approximately at the same level as the previous seasonal influenza; but in the following winter of 1969/70 a short and more severe epidemic occurred with a three-fold higher peak in general practice consultation rates and a four-fold higher peak in mortality attributed to influenza, bronchitis and pneumonia. The high peak in consultation rates is well illustrated in the figure below.

Figure 2.1 RCGP Index for Influenza & Influenza-like Illness, 1966 and 2005 (Year marked at start of season i.e. Week 40 (October))



2.5 Pandemic waves

In 1918/19 the A/H1N1 pandemic occurred in three distinct epidemic waves: early spring 1918, autumn 1918 and late winter 1919. The second wave was by far the largest and case-fatality rates were also higher than in the first wave. The A/H3N2 pandemic caused an

epidemic wave in the winter of 1968/69 but a more severe one in 1969/70. In contrast, the second wave of the 1957/58 pandemic in the UK was very small in comparison to the first.(7) Thus it should be considered a possibility that more than one wave of influenza will occur within a few months of the emergence of a pandemic virus and a subsequent wave could be worse than the first.

2.6 Health impact projections

It is impossible to reliably predict with precision the level of excess mortality that will be experienced in the next pandemic. However Table 2.1 illustrates the broad range of excess mortality that it is reasonable to consider, based on various realistic combinations of case fatality rate and clinical attack rates derived from previous pandemics and epidemics.

Table 2.1a Range of possible excess deaths based on various permutations of case-fatality rates and clinical attack rate for England and Wales.

Overall case fatality rate	Clinical attack rate		
	10%	**25%**	**50%**
0.37%	19,300	**48,400****	96,700
1.00%	51,700	129,200	258,400
1.5%	77,100	192,700	385,400
2.5%	129,200	323,000	645,900

Table 2.1b Range of possible excess deaths based on various permutations of case-fatality rates and clinical attack rate for the U.K.

Overall case fatality rate	Clinical attack rate		
	10%	**25%**	**50%**
0.37%	21,500	**53,700**	107,500
1.00%	56,700	141,800	283,700
1.5%	85,100	212,800	425,500
2.5%	141,800	354,600	709,300

A case fatality rate of 0.37% corresponds to the aggregate rate observed in recent epidemic seasons (1989/90, 1991/92, 1993/94, 1995/96, 1996/97, 1997/98 and 1998/99) and the 1957 pandemic, although the overall case-fatality rate observed in the 1918-19 pandemic was in the region of 1-2%. A clinical attack rate of around 25% corresponds to the approximate clinical attack rate seen in all three previous pandemics of the 20th century. Thus, a figure of at least 50,000 excess deaths is likely.

Using mathematical projections it is possible to illustrate the potential impact of the next pandemic, but these do not amount to accurate predictions. The table below summarises the number of events that might be expected by a GP with 1,000 patients on his/her list and by a PCT serving a population of 100,000 persons.

Table 2.2 Estimated burden of illness attributable to pandemic influenza over the entire pandemic based on a 25% clinical attack rate and illustrative case hopitalisation and case fatality rates of 0.55% and 0.37% respectively. Health Care Contacts represent the equivalent of GP consultations outside the pandemic period. It is envisaged that individuals experiencing symptoms will be diverted away from GPs in a pandemic. GP consultations represent the remaining contacts required to deal with complications and with young children (see text for explanation). Figures are rounded and represent work additional to normal background health service activity. (Figures in parentheses illustrate the range from 10% (lower limit) to 50% (upper limit) attack rates.)

Population	People with clinical symptoms/ Health Care contacts	GP consultations	A&E presentations	Minimum excess hospitalisations	Minimum excess deaths
Population of 1,000	**250** (100-500)	**25** (10-50)	**13** **(5-25)**	**1** (0-3)	**1** (0-2)
Population of 100,000	**25,000** (10,000-50,000)	**2,500** (1,000-5,000)	**1,250** (500-2500)	**140** (50-300)	**90** (40-180)

**approximate figures.*

Using the same assumptions, the table below illustrates the number of events by week over an assumed 15-week (single wave) pandemic period in a typical PCT population of 100,000. Most major acute trusts receive patients from a catchment area spanning several PCTs and the figures below require pro-rata adjustment before applying to individual hospitals.

Table 2.3 Demand for Health Care Contacts by primary care unit: The table shows weekly totals for the number of new clinical cases, and thus potential demand for Heath Care Contacts, per 100,000 population, and per PCT, community pharmacy, GP practice or GP list of various sizes (see footnote for definition of 'small', 'medium' and 'large' as they are used in the table).

Period	Clinical cases	Cases per 100,000	% of total cases	Cases per PCT			Cases per pharmacy			Cases per GP practice			Cases per GP		
				Small	Medium	Large	Small	Medium	Large	Small	Medium	Large	Small	Medium	Large
Week 1	21,367	36	0.1%	28	54	109	1	2	3	1	2	3	0	1	1
Week 2	30,400	51	0.2%	40	77	155	2	3	4	2	3	5	1	1	1
Week 3	121,886	205	0.8%	162	310	620	7	11	18	8	13	19	3	3	4
Week 4	464,219	780	3.1%	617	1,181	2,360	28	41	67	29	49	72	10	12	15
Week 5	1,569,434	2,638	10.6%	2,086	3,992	7,977	94	137	226	99	166	242	33	42	52
Week 6	3,206,013	5,388	21.6%	4,261	8,155	16,295	192	280	462	203	339	494	67	85	106
Week 7	3,147,669	5,290	21.2%	4,183	8,007	15,999	189	275	454	199	333	485	66	84	105
Week 8	2,122,779	3,568	14.3%	2,821	5,400	10,790	127	185	306	134	224	327	44	56	70
Week 9	1,444,925	2,428	9.7%	1,920	3,676	7,344	87	126	208	91	153	223	30	38	48
Week 10	1,122,055	1,886	7.5%	1,491	2,854	5,703	67	98	162	71	119	173	23	30	37
Week 11	778,167	1,308	5.2%	1,034	1,980	3,955	47	68	112	49	82	120	16	21	26
Week 12	387,404	651	2.6%	515	985	1,969	23	34	56	25	41	60	8	10	13
Week 13	232,944	392	1.6%	310	593	1,184	14	20	34	15	25	36	5	6	8
Week 14	128,240	216	0.9%	170	326	652	8	11	18	8	14	20	3	3	4
Week 15	97,498	164	0.7%	130	248	496	6	9	14	6	10	15	2	3	3
All weeks	**14,875,000**	**25,000**	**100%**	**19,770**	**37,839**	**75,606**	**891**	**1,299**	**2,145**	**942**	**1,572**	**2,292**	**311**	**396**	**494**

Note:
In the above table, 'small', 'medium' and 'large' refer to the 2.5th, 50th and 97.5th percentiles for the population served by a PCT, community pharmacy, GP practice or GP list, as follows:

Population	PCT	Pharmacy	GP practice	GP list
small	80,000	3,600	3,800	1,200
medium	150,000	5,200	6,300	1,600
large	300,000	8,600	9,200	2,000

2.7 Health care delivery modes

Even though it is impossible to predict with certainty the impact of the next pandemic, based upon the available epidemiological and modelling information, it is clear that it will generate demands for health care which may saturate or overwhelm normal NHS acute services for a period of time, perhaps several weeks or months. Accordingly, it should be anticipated that the NHS (in common with all health systems around the world) will need to revert to emergency arrangements. These are laid out in further detail in Operational Guidance for Health Service Planners,(4) and the UK Operational Framework for stockpiling, distributing and using antiviral drugs in the event of pandemic influenza.(5) With regard to the delivery of medical care for patients with influenza this is normally achieved through:

- GP treatment of community patients 'well' enough to be managed in the community
- Hospital care in acute medicine for persons considered too ill to be managed at home.

In the event of a pandemic the following additional care settings may have to be considered as the threshold for hospital admission rises:

- Treatment of patients in the community (who would normally receive care from a GP) by other health care professionals (nurses, paramedics, pharmacists etc.) following treatment guidance laid out in the this publication and using Prescription-only medicines according to Patient Group Directives (PGDs)

- Treatment of patients in their own homes or in temporary intermediate care facilities by a GP, following treatment guidance laid out in this publication when, under normal circumstances, such patients would have been admitted for hospital care

- Treatment of severely ill patients in hospital by medical and nursing teams who do not normally manage patients with influenza or community acquired pneumonia, in areas of the hospital not normally used for providing medical care (for example, surgical teams and bed space diverted from routine elective work towards pandemic response).

CHAPTER i

Clinical Guidelines for Adults with Influenza like illness during an Influenza pandemic

Section	Title
3	Clinical Features
4	General management in the Community
5	Severity assessment and criteria for hospital admission
6	General investigations
7	Microbiological investigations
8	General management in Hospital
9	Antiviral therapy
10	Antibiotic therapy

3 CLINICAL FEATURES

3.1 How reliable is a clinical diagnosis of influenza infection during a pandemic?

The clinical manifestations of infection by influenza viruses are diverse, ranging from asymptomatic infection to fulminant respiratory distress leading to respiratory failure and death. Furthermore, the presence of an influenza-like illness (ILI) comprising of a combination of fever, cough, sore throat, myalgia and headache is not specific for influenza infection. Other respiratory pathogens that may present with an ILI include viruses such as respiratory syncytial virus (RSV), adenovirus, rhinovirus and parainfluenza virus, as well as bacterial pathogens such as *Chlamydia pneumoniae, Legionella* sp., *Mycoplasma pneumoniae* and *Streptococcus pneumoniae*.(14-16)

Studies that have examined the value of a clinical definition of ILI in the diagnosis of influenza infection have not always used the same clinical definition for an ILI and have included different study populations, making comparison between studies complicated. A systematic review of the literature in this area identified the three-fold combination of the presence of fever, cough and acute onset to be the most predictive clinical features. The accuracy of this clinical definition was higher in persons aged 60 years and above compared to patient groups without age restrictions (positive likelihood ratio (95% CI) 5.4 (3.8 to 7.7) vs 2.0 (1.8 to 2.1)).(17) The probability of influenza infection also increases with increasing level of fever.(18;19)

Importantly, the predictive value of clinical definitions based on an ILI increases when influenza virus is known to be circulating in the community.(15;17;20) In cohort studies, correlation of ILI with laboratory-confirmed influenza infection ranges from 25 – 45% while in clinical trials, rates of 70% have been consistently reported.(15;21-23)

These findings relate to influenza infections during interpandemic periods. During a global influenza pandemic, when a pandemic strain is known to be circulating locally in an immunologically susceptible population, the presence of an ILI would be expected to be highly predictive for influenza infection. (However, the extent to which a clinical diagnosis of ILI becomes predictive during a pandemic will also be determined by the behaviour of the public- if many, who would not normally present to a health professional, are prompted to present, then the predictive value of a clinical diagnosis of ILI will be reduced.)

Box 3.1 Clinical Case Definition (October 2005):

The presence of fever and new (or, in those with chronic lung disease, worsening) cough of acute onset in the context of influenza circulating in the community.

(Important note - This definition may be modified once a pandemic occurs.)

3.2 What are the clinical features of uncomplicated influenza?

The following description will relate mainly to interpandemic influenza A infections. Influenza B and C are not considered pandemic threats. Different strains may be associated with different clinical presentations and disease severity. For instance, there is evidence to suggest that the H3N2 subtype causes more severe disease than H1N1 subtype.(24) **The spectrum of clinical disease associated with a new influenza A subtype (eg. a pandemic strain) cannot be determined currently and may differ from that described for interpandemic influenza**.

The incubation period prior to the onset of symptoms is commonly 2 – 4 days (range 1 – 7 days). In adults, the illness typically presents as an abrupt onset of fever accompanied by other a range of other symptoms as listed in Box 3.2. (25-29)

Box 3.2 Range of symptoms associated with uncomplicated influenza infection

- cough (~85%)
- malaise (~80%)
- chills (~70%)
- headache (~65%)
- anorexia (~60%)
- coryzal symptoms (~60%)
- myalgia (~53%) and
- sore throat (~50%).

Fever is the paramount symptom and may reach 41°C although more usually it ranges between 38 – 40 °C. The peak occurs within 24 hours of onset and lasts typically for 3 days (range 1 – 5 days).(25-29) The cough is generally dry although in up to 40% of cases it may be productive. A productive cough together with chest tightness and substernal soreness is more common in patients with underlying chronic lung disease. Myalgia affects mainly the back and limbs. Gastrointestinal symptoms such as vomiting and diarrhoea are uncommon (<10%) in adults. Abdominal pain is rare.

Clinical findings include a toxic appearance in the initial stages, hot and moist skin, a flushed face, injected eyes and hyperaemic mucous membranes around the nose and pharynx. Tender cervical lymphadenopathy is found in a minority (~10%) of cases. Wheezing or lung crackles are recognised findings (~10%) more commonly noted in patients with coexisting chronic lung disease.

Although the overall clinical picture of uncomplicated influenza in any specific age group is similar for different influenza A subtypes, the frequency of certain symptoms may vary. For instance, during the 'Asian' pandemic of 1957 (H2N2), headache and sore throat were frequent initial symptoms.(30)

In uncomplicated infection, the illness usually resolves in 7 days although cough, malaise and lassitude may persist for weeks.

3.3 What complications are associated with influenza infection?

Influenza virus infection has been associated with worsening in the clinical condition of patients with a range of existing medical conditions, such as, heart failure, diabetes, coronary heart disease, asthma and chronic obstructive airways disease (COPD).

In addition, specific complications associated with influenza infection regardless of co-existing medical conditions are recognised (Table 3.1). Based on data from interpandemic influenza, certain persons are identified as being at high risk from influenza-related complications. Such patients are similar to the group currently recommended for influenza vaccination by the Department of Health. These include those of all ages with chronic respiratory disease including asthma, chronic heart disease, chronic renal disease, chronic liver disease, immunosuppression due to disease or treatment, or diabetes mellitus, and all those aged 65 years or older, or those in long stay residential care (see Appendix 2).

In the course of a pandemic, it may emerge that the patient group at high risk of complications differs from the group currently identified. In such circumstance, details of the 'high risk' patient group will be altered according to relevant clinico-epidemiological data.

Table 3.1: Complications associated with influenza infection in adults

Complication	Incidence	Comments
Respiratory		
Acute bronchitis	Common	More common in elderly and those with chronic medical conditions.
Primary viral pneumonia	Uncommon	Onset within 48 hours of start of fever.
Secondary bacterial pneumonia	Common	Typically occurs 4 – 5 days after onset of illness.
Cardiovascular		
ECG abnormalities	Common	Non-specific T wave and rhythm changes, ST segment deviation. Mostly not associated with cardiac symptoms.
Myocarditis	Rare	
Pericarditis	Rare	
Muscle		
Myositis	Uncommon	Occurs during early convalescence
Myoglobinuria and renal failure	Rare	
Central Nervous System		
Encephalitis/ encephalopathy	Rare	Occurs within first week of illness. More common in children and in Japan.
Transverse myelitis	Very rare	
Guillian-Barre syndrome	Very rare	
Others		
Otitis media	Uncommon	Much more common in children
Toxic shock syndrome	Rare	
Parotitis	Very rare	

3.3.1 Influenza-related pneumonia

The incidence of pneumonia (defined as a combination of respiratory symptoms and signs supported by chest radiographic changes consistent with infection) complicating influenza infection varies widely, from 2% to 38%, and is dependent on viral and host factors.(25-27) Pneumonia generally occurs more frequently and with greater severity in patients with pre-existing chronic cardiac and respiratory conditions.

Patients who develop pneumonia may present with symptoms and signs indistinguishable from pneumonia related to other viral and bacterial pathogens. In the context of an influenza pandemic, the presence of an ILI *and* new or worsening dyspnoea should prompt a careful examination for the presence of complicating pneumonia. Two main types of influenza-related pneumonia are recognised; primary viral pneumonia and secondary bacterial pneumonia.(25-28)

(A) Primary viral pneumonia.

Patients with primary viral pneumonia typically become breathless within the first 48 hours of onset of fever. An initially dry cough may become productive of blood-stained sputum. Cyanosis, tachypnoea, bilateral crepitations and wheeze on chest examination and leucocytosis are usual. The commonest chest radiographic abnormality is of bilateral interstitial infiltrates predominantly in the mid-zones, although focal consolidation is also well recognised. Rapid clinical deterioration with respiratory failure may ensue.(31) The mortality in hospitalised patients is high (>40%) despite maximum supportive treatment on intensive care.(25-28) In the majority of fatal cases, death occurs within 7 days of hospital admission.

(B) Secondary bacterial pneumonia

Secondary bacterial pneumonia is more common (up to four times) than primary viral pneumonia. Typically, symptoms and signs of pneumonia develop during the early convalescent period (4 – 5 days from onset of initial symptoms). In others, symptoms of pneumonia blend in with the initial symptoms of influenza. Chest radiography usually demonstrates a lobar pattern of consolidation. Mortality rate ranges from 7% to 24%,(25-29;32) although some small studies report higher mortality rates.

The spectrum of pathogens implicated is similar to that observed in CAP and includes *Streptococcus pneumoniae*, S*taphylococcus aureus*, *Haemophilus influenzae* and Groups A,C and G beta-haemolytic streptococci.(27;28;33-35) Different pathogens have predominated at different times. For instance, in the 1918 pandemic, *H influenzae*, beta-haemolytic streptococci and *S pneumoniae* were the predominant pathogens isolated. In contrast, during the 1957 pandemic, *Staphylococcus aureus* was the predominant organism isolated (up to 69% of cases).(25) In 1968, *Streptococcus pneumoniae was* the predominant pathogen (48%) followed by *Staph aureus* (26%) and non-typeable *H influenzae(*11%).(34) Importantly, *Staphylococcus aureus* was identified two and a half times more frequently during the 1968 pandemic compared to pneumonia occurring in the interpandemic period.(34;36)

Secondary staphylococcal pneumonia is associated with a higher incidence of lung abscess formation (14% vs 2%) and carries a poorer prognosis compared to non-staphylococcal pneumonias (mortality 47% vs 16%).(25;29;32;37)

(C) Mixed viral-bacterial pneumonia

Bacterial and viral pneumonia can occur concurrently. In these instances, the chest radiograph may demonstrate lobar consolidation superimposed on bilateral diffuse lung infiltrates. The mortality rate in mixed viral – bacterial pneumonia is high (>40%), as for primary viral pneumonia.(25-28)

3.3.2 Cardiovascular

Minor abnormalities on ECG such as ST segment deviation, T wave changes and rhythm disturbances have been described in uncomplicated influenza illness. They have been reported in up to 81% of patients hospitalised with influenza.(25) Most do not have cardiac symptoms. Myocarditis and pericarditis are occasionally encountered in severe illness.(38;39) Post mortem evidence of necrotising myocarditis has been reported in patients without clinically significant myocarditis in the antemortem period.

3.3.3 Myositis

In contrast with myalgia affecting the back and limbs which is common on initial presentation, myositis generally develops after the subsidence of the acute upper respiratory tract symptoms. The gastrocnemius and soleus muscles are typically involved with pain and tenderness to palpation. Complete recovery usually occurs in 3 days. Elevation in serum creatine phophokinase is recognised.(40;41) Rarely, this is associated with myoglobinuria and renal failure.(42;43) Myositis is more commonly described in children than adults.

3.3.4 Central Nervous System

Central nervous system (CNS) involvement in adults is uncommon. Most reports originate from Japan and occur in children.(44;45) The main clinical syndrome is an encephalitis or encephalopathy manifesting in the form of decreased consciousness and seizures about 3 days (range 0 – 7 days) following the onset of upper respiratory tract symptoms. Focal neurological signs such as paresis, aphasia, choreoathetosis and cranial nerve palsies are less common. Cerebrospinal fluid (CSF) examination may be normal or reveal an elevation in protein or white cell count. Imaging by CT or MRI may be normal and if so, is indicative of a good prognosis and full recovery may be anticipated.(46) Young age and abnormal CT/MRI findings are associated with a poor outcome including death or recovery with severe neurological sequelae. [A fuller description is given in Section 11.2.6]

Acute necrotising encephalopathy is a rare fulminant syndrome associated with multifocal brain lesions that is described mainly in Japan.(46) Other rare manifestations include transverse myelitis and Guillain-Barre Syndrome.(47;48)

Reye's syndrome, characterised by an encephalopathy, acute fatty liver, association with aspirin use and high mortality (~40%), is a special situation that is almost exclusively seen in children and adolescents.(46) Nevertheless, physicians managing adults are advised to be aware of this complication. [A fuller description is given in Section 11.2.6]

3.3.5 Others

Other complications rarely encountered in adults with influenza A infection include toxic shock syndrome in conjunction with secondary *Staphylococcus aureus* infection(49;50) and parotitis.(51) Otitis media is more commoner encountered in children than adults.

3.4 What are the clinical features associated with human infection by avian influenza A (H5N1)?

The first recorded instance of human infection by avian influenza H5N1 occurred in May 1997 in Hong Kong. The first patient was a 3 year old child who presented initially with symptoms of fever, sore throat and abdominal pain. He later developed Reye's syndrome, ARDS, multi-organ failure and eventually died.(52) A total of 18 persons were subsequently infected before the outbreak ended in December 1997.(53;54) Half the patients were aged 18 years and below and only 2 were aged over 50 years. Abdominal symptoms, such as diarrhoea, vomiting and abdominal pain, were described in a number of patients 10(56%). Eleven (61%) had a severe illness characterised by pneumonia occurring within 14 days of symptom onset, lymphopenia, deranged liver function tests and a high mortality (6 (55%) of 11 patients with pneumonia). Secondary bacterial infections were not identified as the cause of the pneumonias.

The clinical features of patients infected by the re-emergent avian influenza A (H5N1) in 2004 were very similar to those described in 1997. (Table 3.2) Once again, children and young adults were the main groups affected. Gastrointestinal symptoms were common. The presence of lymphopenia and deranged liver function tests were again associated with the development of a severe primary viral pneumonia.(55)

From 26 December 2003 to 10 October 2005, 117 cases had been reported to the WHO, 91 cases occurring in Viet Nam, 17 in Thailand, 5 in Indonesia and 4 in Cambodia. In the initial period, mortality was very high (December 2003 to March 2004, 24 (68%) of 35 cases). In latter months, crude mortality rate has been lower (December 2004 to October 2005, 28 (38%) of 73 cases.) (56).

3.4.1 Summary

The spectrum of human illness associated with avian influenza A (H5N1) infection is not fully known. The proportion of persons with asymptomatic or mild illness compared to those with illness warranting hospital admission is difficult to determine. Recent evidence suggests that mild or subclinical infections are not very common.

In patients who are symptomatic, an ILI similar to that associated with inter-pandemic influenza A (H1N1 or H3N2) infection is recognised. In addition, gastrointestinal symptoms are present in a relatively large proportion of both adult and paediatric cases. This contrasts with the relatively low incidence of gastrointestinal symptoms in seasonal influenza. The majority of patients develop a severe primary viral pneumonia usually associated with lymphopenia, thrombocytopenia and deranged liver function tests. Renal failure and multi-organ failure may develop subsequently. Mortality is high.

Should influenza A (H5N1) acquire efficient human-to-human transmission capabilities, it may result in an influenza pandemic. In such an event, the clinical features of human disease may alter.

Table 3.2: Clinical features of human H5N1 infection (adapted from refs (54;57))

	Children (16 years and under)			Adults (>16 years)		
	1997 Hong Kong	2004 Vietnam	Total (%)	1997 Hong Kong	2004 Vietnam	Total (%)
Number	7	7	14	5	3	8
Male	3	3	6 (43)	1	3	4 (50)
Mean age (years)	4.1	10.3	-	36.4	21.7	-
Fever	7	7	14 (100)	5	3	8 (100)
Headache	1	NK	1 (7)	1	NK	1 (13)
Sore throat	2	NK	2 (14)	1	NK	1 (13)
Rhinorrhoea	4	NK	4 (29)	2	NK	2 (25)
Dyspnoea	NK	7	7 (50)	NK	3	3 (38)
Cough	4	7	11 (79)	4	3	7 (88)
Sputum	0	2	2 (14)	2	3	5 (63)
Diarrhoea	1	4	5 (36)	1	3	4 (50)
Vomiting	2	NK	2 (14)	2	NK	2 (25)
Abdominal pain	1	NK	1 (7)	1	NK	1 (13)
Deranged LFTs	2	5 of 5	7 of 12 (58)	4	1 of 1	5 of 8 (63)
Rasied ALT	1	5 of 5	6 of 12 (50)	3	1 of 1	4 of 8 (50)
Thrombocytopenia	1	6	7 (50)	3	3	6 (75)
Lymphopenia	5	7	12 (85)	5	3	8 (100)
Leucopenia	2	7	9 (64)	2	3	5 (63)
Bacterial infection			0 (0)			0 (0)
CXR pneumonia	1	7	8 (57)	4	3	7 (88)

NK = not known or reported

4 GENERAL MANAGEMENT IN PRIMARY CARE

4.1 Overview

Management decisions should be based primarily on:

- an assessment of illness severity
- identification of whether the individual is in an 'at risk' group
- current advice from DOH/local public health officials based on the epidemiology of the pandemic

Patients who are not considered to be at high risk and who have no features suggesting severe disease or complications may not need to be seen in face to face consultations by a primary care clinician.

Patients with features of severe disease or serious complications will need assessment and may need admission to hospital.

4.2 Triage.

A significantly increased demand for advice and consultation should be anticipated. Practices may make a number of arrangements to deal with this, including:

- Telephone triage and advice, which may be nurse-led
- Triage and advice immediately after reception at the practice
- Nurse-led prescribing of antiviral medication or antibiotics, according to patient group directives (PGDs)
- Making arrangements to provide domiciliary services for some patients who are unwell at home, but who may be able to avoid hospital admission
- Possibly making arrangements for patient care in intermediate-level community facilities, again to avoid hospital admission

It may be useful for the triage system to include criteria for suspecting that a patient does NOT have influenza features (such as large, tender lymph nodes in the neck, white spots on the tonsils, or non-respiratory symptoms eg urinary tract symptoms).

4.2.1 Patients without influenza-like illnesses

With widespread concern during a pandemic, there are likely to be significantly higher consultation rates for all respiratory tract infections (e.g. febrile colds, sore throat with temperatures) which are normally managed well at home using over the counter remedies. Demand management in both the practice and the PCT will be crucial to avoid the service's capacity to triage care being overwhelmed.

Patients with non-ILIs who would normally self-medicate should be advised not to seek medical care where possible to minimise the chance of contracting influenza during a visit to the surgery reception room. (see UK Infection Control Guidance for Pandemic Influenza) This will also enable patients with ILI to be appropriately recognised and treated.

A sensible use of GP practice time will be to manage patients in the high risk groups (see Appendix 2) and those with complications. The PCT should make other arrangements for treating those with clinical influenza who are previously well, in addition to making it clear that antivirals will only be available for those fitting a strict clinical definition of influenza (see Section 9).

Recommendations

- **Health professionals should use a nationally agreed clinical definition when diagnosing influenza (see Box 3.1)**
- **PCTs and practices should formulate triage arrangements in advance of a pandemic to allow GPs to predominantly assess high risk patients and those developing complications.**
- **PCTs and practices should formulate plans according to UK Infection Control Guidance for Pandemic Influenza(*to be published*) to minimise the contact of patients without ILI with patients suffering from ILI in practice waiting rooms.**

4.3 General advice and symptomatic treatment

All patients presenting in general practice with symptoms suggestive of influenza (except perhaps those in whom urgent admission is required) should be given general advice and advice on symptomatic treatment. It is important that clinicians identify and address individual concerns and expectations, provide information about the illness, and provide information about what patients can do to help themselves and when they should seek further help.

4.3.1 Addressing the patients agenda

Influenza can present with quite severe symptoms which may result in considerable anxiety or expectations of treatment to 'cure' the illness. These *concerns* and *expectations* are likely to be heightened in the event of a pandemic. Furthermore, in a pandemic situation, patient's *ideas* about their illness are likely to be affected by the experiences of others they know or even the stories they have heard through friends, neighbours or the media. Failure to identify and address the patients unique ideas about their illness, and their main concerns, is likely to lead to dissatisfaction, and may result in increased rates of re-consultation, leading to an increased drain on primary care resources at a time when they are likely to be stretched.

In order to effectively deal with these issues, it will be necessary for primary care clinicians to use all of their skills in identifying the patient's agenda. Developing an interested, concerned manner is as important as the specific questions asked.

4.3.2 Providing information about the illness

Like addressing the patients agenda, providing the patient with accurate information about the nature of the illness, symptoms to expect, and the likely course of the illness, is extremely important in conditions, such as Influenza, that are for the most part self limiting. Some useful facts that can be provided to the patient are included in Box 4.1.

Box 4.1 Information about Influenza to provide to patients

- Influenza is caused by a number different types of 'influenza' viruses.
- The incubation period is 1-4 days and infected adults are usually contagious from the day before to 5 days after illness onset.
- Fever usually declines after 2-3 days and normally disappears by the 6th day.
- Cough, weakness and fatigue can persist for 1-2 weeks and up to 6 weeks.
- Antibiotics do not benefit most people with influenza but are sometimes needed to treat secondary infections.

4.3.3 Providing information about symptomatic treatment

There is little scientific evidence for most symptomatic and self-help treatment, but experience suggests that some of the following may help, and are unlikely to cause harm.

- Treatment of fever, myalgias and headache with Paracetamol or Ibuprofen
- Rest
- Drink plenty of fluids
- void smoking
- Consider: steam inhalation, short course of topical decongestants, throat lozenges, saline nose drops

4.3.4 Providing information about when patients should seek further help, and modify help-seeking behaviour

GPs should share information with patients about best use of medical services and specific advice should be given about when they should seek further help. Possible examples of what should prompt a patient to re-consult are given in Box 4.2.

Box 4.2 Examples of what should prompt patients to re-consult

- Shortness of breath at rest or while doing very little
- Painful or difficult breathing
- Coughing up bloody sputum
- Fever for four to five days and not starting to get better (or getting worse)
- Started to feel better then developing high fever and feeling unwell again
- Drowsiness, disorientation or confusion.

5 SEVERITY ASSESSMENT AND CRITERIA FOR HOSPITAL REFERRAL

5.1 Which patients require hospital referral?

Patients with uncomplicated influenza infection usually do not require hospital referral. Patients who might require hospital admission fall into two main groups; those with worsening of a pre-existing medical condition and those with an influenza-related complication.

5.1.1 Worsening of pre-existing medical condition

Patients who experience a worsening or clinical deterioration of pre-existing medical problems due to influenza infection should be managed according to recommended best practice for the medical condition in question. For instance, a patient with an acute exacerbation of COPD triggered by influenza infection should be managed according to current NICE Guidelines for COPD.(58)

Those with a worsening of a pre-existing condition are likely to be in a group at 'high risk' of influenza-related respiratory complications and consequently at risk of hospitalisation or death (Appendix 2). This group should be promptly reassessed if the illness is getting worse to consider hospital referral.

5.1.2 Influenza-related pneumonia

Pneumonia is the commonest influenza-related complication requiring hospital admission. Patients complaining of new or worsening dyspnoea should be carefully assessed for signs of pneumonia. If pneumonia is diagnosed, disease severity assessment according to the BTS CAP Guidelines 2004 (CRB-65 score) is recommended and hospital referral made accordingly.(59) (Table 5.1) The CRB-65 score is offered as a clinical assessment tool and does not replace clinical judgement.

In addition, in view of the rapid and fulminant course of primary viral pneumonia, patients with pneumonia who have bilateral chest signs (crackles or wheeze) should be referred to hospital for further assessment, including a chest x-ray.

5.1.3. Other complications

Other influenza-related complications are uncommon. There are no specific recommendations relating to criteria for hospital admission or disease severity assessment in these cases.

Recommendations

- **Patients with clinically defined uncomplicated influenza infection would be expected to make a full recovery. They require good symptomatic management, access to antiviral treatment, information about the natural history, and advice as to when to re-consult.**

- **Patients with new or worsening symptoms - particularly shortness or breath or recrudesecent fever not responding to treatment - should be examined to assess the presence and severity of influenza-related pneumonia.**

- **Patients with worsening of pre-existing comorbid medical conditions should be managed according to best practice for that condition with reference to published disease-specific guidelines, if available.**

- **In patients with influenza-related pneumonia clinically, hospital referral and assessment should be considered for patients with a CRB-65 score of 1 or 2 (particularly score 2) and urgent admission for those with CRB-65 score of 3 or more.**

- **Patients with bilateral chest signs of pneumonia should be referred to hospital for further assessment regardless of CRB-65 score.**

Table 5.1 Severity assessment used to determine the management of influenza-related pneumonia in patients in the community (CRB-65 score)

Score 1 point for each feature present:
• **C**onfusion (Mental Test Score of ≤ 8, or new disorientation in person, place or time.)
• **R**espiratory rate ≥ 30/min
• **B**lood pressure (SBP < 90mmHg or DBP ≤ 60mmHg)
• Age ≥ **65** years

CRB-65 score	Recommended action
0	Likely suitable for home treatment
1 or 2	Consider hospital referral, particularly with score 2
3 or 4	Urgent hospital referral

5.2 What severity assessment strategy is recommended for patients referred to hospital with influenza-related pneumonia?

The CURB-65 severity assessment tool as described in the BTS CAP Guidelines 2004 is recommended for the stratification of hospitalised patients with influenza-related pneumonia into disease severity groups.(59) (Table 5.2) In addition, the presence of diffuse bilateral lung infiltrates on chest radiography consistent with primary viral pneumonia is an adverse prognostic feature. Such patients should be treated as for severe pneumonia. In all instances, clinical judgement is essential when assessing disease severity.

Recommendations

- **Patients with bilateral lung infiltrates on chest radiography consistent with primary viral pneumonia should be managed as having severe pneumonia regardless of CURB-65 score.**

- **In hospital, patients with influenza-related pneumonia and who have a CURB-65 score of 3 or more are at high risk of death and should be managed as having severe pneumonia.**

- **Patients who have a CURB-65 score of 2 are at increased risk of death. They should be considered for short stay inpatient treatment or hospital supervised outpatient treatment. This decision is a matter of clinical judgement.**

- **Patients who have a CURB-65 score of 0 or 1 are at low risk of death. They can be treated as having non-severe pneumonia and may be suitable for home treatment.**

5.3 When should transfer to a High Dependency Unit (HDU) or Intensive Care Unit (ICU) be considered?

The indications for transfer to HDU or ICU are no different in patients with influenza infection compared to other patients. Most patients who might require HDU/ICU care will have influenza-related pneumonia or a severe exacerbation of underlying comorbid illness eg. exacerbation of COPD. In a pandemic situation when HDU/ICU beds may not be readily available, prioritisation of patients on an individual basis matched against available resources will be expected.

Recommendations

- **Patients with primary viral pneumonia *or* a CURB-65 score of 4 or 5 should be considered for HDU/ICU transfer.**
- **General indications for HDU/ICU transfer include:**
    a. **persisting hypoxia with PaO_2 <8Kpa despite maximal oxygen administration**
    b. **progressive hypercapnia**
    c. **severe acidosis (pH<7.26)**
    d. **septic shock**
- **Patients with influenza admitted to Intensive Care Unit should be managed by specialists with appropriate training in Intensive Care, Respiratory Medicine and Infectious Diseases.**

Table 5.2 Severity assessment used to determine the management of influenza-related pneumonia in patients admitted to hospital (CURB-65 score)

Score 1 point for each feature present:

• **C**onfusion (Mental Test Score of ≤ 8, or new disorientation in person, place or time)
• **U**rea > 7 mmol/l
• **R**espiratory rate ≥ 30/min
• **B**lood pressure (SBP < 90mmHg or DBP ≤ 60mmHg)
• Age ≥ **65** years

CURB-65 score*	Recommended action
0 or 1	Likely suitable for home treatment
2	Consider short in-patient stay or hospital supervised out-patient treatment
3 or more	Manage in hospital as severe pneumonia

***NOTE: New bilateral lung shadowing on CXR consistent with primary viral pneumonia should be taken as a feature of severe pneumonia regardless of CURB-65 score.**

6 GENERAL INVESTIGATIONS

6.1 What general investigations should be done in the community?

Recommendations

- **General investigations, including a chest x-ray, are not necessary for the majority of patients managed n the community.**

6.2 What general investigations should be done on all adults referred to hospital?

6.2.1 Radiology

In acute uncomplicated influenza the chest X-ray is usually normal. When primary viral pneumonia occurs as a complication, particularly in elderly adults the chest X-ray often shows multiple infiltrates or consolidation. Cavitations or pleural changes suggest bacterial superinfection. In combined viral-bacterial pneumonia, the clinical features typically appear later than primary viral pneumonia and the chest X-ray often shows cavitation or pleural effusions. Secondary bacterial pneumonia usually occurs after apparent improvement from the viral infection; the chest -ray may show consolidation.

Recommendations

- **A chest x-ray should be obtained during assessment of a suspected case of influenza seen in the hospital setting (accident and emergency department or acute admissions ward).**
- **In those patients who are subsequently followed up in a hospital outpatient clinic or by a general practitioner a repeat chest X-ray should be obtained at around 6 weeks if respiratory symptoms or signs persist or where there is a higher risk of underlying malignancy (especially smokers and those over 50 years of age).**
- **Further investigations including a CT thoracic scan and bronchoscopy should be considered if the chest X-ray remains abnormal at follow up (ref BTS CAP guidelines).**

6.2.2 Blood tests

In those patients severe enough to present to secondary care then the following tests may be useful.

- Full blood count: a leucocytosis with left shift may occur in those with primary viral pneumonia, mixed viral-bacterial pneumonia or secondary bacterial pneumonia. Lymphopenia has been noted in human cases of severe avian H5N1 influenza.
- Urea and electrolytes may reveal evidence of hypo or hypernatraemia or renal impairment.
- Liver function tests are usually normal.
- Creatine kinase (CK) may be elevated in those with severe myalgia.

C reactive protein (CRP) is unlikely to be helpful except where superimposed bacterial infection is suspected(59). However the diagnostic value of CRP in lower respiratory tract infections remains controversial.(60)

Recommendations

- **The following blood tests should be obtained in patients admitted to hospital:**
    a. **Full blood count**
    b. **Urea, creatinine and electrolytes**
    c. **Liver function tests**
    d. **Creatine kinase (if myositis is suspected)**
- **In patients with suspected secondary bacterial infection, the C-reactive protein (CRP) level may aid diagnosis.**

6.2.3 Other tests

Recommendations

- **Pulse oximetry should be carried out in all patients presenting to secondary care.**
- **If the oxygen saturation is below 92% then arterial blood gases should be obtained.**
- **An electrocardiogram (ECG) should be obtained in all patients with cardiac or respiratory complications.**

6.2.4 Lung function tests

In acute uncomplicated influenza larger airway function remains normal. However there is often an increase in bronchial reactivity which may persist for many weeks after resolution of the infection.(61) Lung function tests are unnecessary in most patients.

7 MICROBIOLOGICAL INVESTIGATIONS

7.1 Introduction

The guidelines provided below are based on the assumption that when cases are first occurring in the UK as part of a global pandemic, it will be possible to perform full microbiological investigations in all new cases of influenza-like illness and influenza-related pneumonia. As case numbers rise, possibly to pandemic levels, full or indeed any microbiological investigation will become increasingly difficult. Thus, data on the relative frequency of different bacterial causes of influenza-related pneumonia and their antimicrobial susceptibilities amongst investigated cases gathered earlier in the pandemic should be available to guide and refine empirical antimicrobial therapy choices for cases occurring later in the pandemic.

The most likely pathogens implicated in influenza-related pneumonia are *Streptococcus pneumoniae*, *Staphylococcus aureus, Haemophilus influenzae* and to a lesser extent beta-haemolytic streptococci (see Section 3.3). In the early phases (UK Alert Levels 1,2 and 3 – see Appendix 1) of a pandemic microbiological diagnostic approaches should focus on confirming influenza as the primary illness, defining bacterial causes of influenza-related pneumonia and optimizing both specific (for individual patients) and general (for populations) antimicrobial treatment recommendations. In later pandemic phases (UK Alert Level 4) with the much higher caseloads anticipated, microbiological investigation should be focused on patients with severe influenza-related pneumonia unresponsive to empirical antimicrobial therapy. Actual and practical local level transition to less intense microbiological investigation may occur at UK Alert Level 3 in some regions as the number of local cases is likely to vary between regions.

PRIMARY CARE

7.2 What microbiological investigations should be undertaken for patients in the community?

The aim of microbiological investigations early in a pandemic (UK Alert Levels 1, 2 and 3) will be to confirm that Influenza A is circulating in the local community. Once a pandemic is established (UK Alert Level 4), microbiological investigations are not recommended routinely or likely to be available readily. Routine testing for bacterial pathogens is not recommended at any stage.

Recommendations

- **Where possible, early in a pandemic (UK Alert Levels 1,2 and 3), nose and throat swabs in virus transport medium should be collected from patients and submitted to the local laboratory.**
- **Once a pandemic is established (UK Alert Level 4), microbiological investigations are not recommended.**

IN HOSPITAL

7.3 Early in a pandemic (UK Alert Levels 1, 2 and 3), what microbiological investigations should be undertaken for hospitalised patients?

It will be necessary to perform full microbiological investigations on all hospitalised cases, including patients with severe and non-severe influenza-related pneumonia, in order to;

- confirm influenza as the primary infection,
- optimize treatment options for the patients investigated and
- define the most common bacterial causes of influenza-related pneumonia and their antimicrobial susceptibility patterns.

The latter data will help to inform empirical antimicrobial therapy of subsequent cases for which microbiological investigation may not be undertaken fully, or at all.

7.3.1 Virology

In influenza, rapid virological tests, viral culture and PCR of respiratory samples will yield positive results between 1 and 7 days after illness onset. However, if presentation is more than 7 days after the onset of influenza-like illness then such sampling and testing is unhelpful. Instead, serum samples for serological testing for evidence of recent influenza infection is recommended.

Specific detailed microbiological guidance for taking and handling specimens from individuals at risk of avian influenza prepared by Prof Maria Zambon of Health Protection Agency (HPA) Centre for Infections is available at;
http://www.hpa.org.uk/infections/topics_az/avianinfluenza/guidance/microbiological_guidance.htm

7.3.1 Bacteriology

Bacteriological investigations are only recommended in patients with influenza-related pneumonia. *Legionella pneumophila* infection is not normally associated with influenza-related pneumonia, despite this Legionella urine antigen tests should be performed on severe CAP cases in the early stages of an outbreak/incident in order to confirm Legionella infection is not the reason for a local increase in pneumonia admissions. These recommendations are modified from those contained in the British Thoracic Society Community Acquired Pneumonia (BTS-CAP) Guidelines 2001 Thorax 2001;**56** (suppl iv) see Sections 5.7, 5.8 and 5.9 (pp iv23-iv28) and the 2004 Update (see pages 4-5) both available at; http://www.brit-thoracic.org.uk/iqs/bts_guidelines_pneumonia_html

Sputum investigative efforts must be focused on quality samples (i.e. those from patients who are able to expectorate purulent samples, *and* have not received prior antibiotic treatment) and not dissipated on large numbers of poor quality samples. It is important to acknowledge that the criteria for quality samples may only be met for a minority of admissions. Laboratories should offer a reliable Sputum Gram stain for appropriate samples, as on occasions this can give immediate indication of likely pathogens. The most likely influenza-related pneumonia pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* all of which may present a characteristic appearance on Gram stain of purulent sputum. Laboratories performing sputum Gram stains should adhere to strict and locally agreed criteria for interpretation and reporting of results.

Recommendations (Early in a pandemic: UK Alert Levels 1,2 and 3)

A. VIROLOGY – ALL PATIENTS

- **Nose and throat swabs in virus transport medium should be collected from all patients and submitted to the local laboratory. The relevant laboratory should be notified of the suspected diagnosis and there should be close liaison over sample collection, handling and transport.**
- **Rapid testing by direct immunofluorescence or rapid EIA test, virus culture and/or PCR should be undertaken according to local availability and/or referred to an appropriate laboratory**
- **If presentation is <u>more than 7 days after onset of illness</u>, an 'acute' serum (5-10mLs clotted blood) should be collected and a 'convalescent' sample (5-10mLs clotted blood) obtained after an interval of not less than 7days. The two sera should be examined serologically for evidence of recent influenza infection.**

B. BACTERIOLOGY – PATIENTS WITH INFLUENZA-RELATED PNEUMONIA

- **The following bacteriological tests should be performed:**
    1. **Blood culture (preferably before antibiotic treatment is commenced)**
    2. **Pneumococcal urine antigen (20 mls urine sample)**
    3. **Legionella urine antigen (20 mls urine sample)**
    4. **Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from patients who:**
        a. **are able to expectorate purulent samples, *and***
        b. **have not received prior antibiotic treatment.**

        Sputum samples should be transported rapidly to the laboratory.
    5. **Paired serological examination for influenza/other agents. Acute serum should be collected and a 'convalescent' sample obtained after an interval not less than 7days (both 5-10mLs clotted blood) and the two sera stored for subsequent testing.**

7.4 Once a pandemic is established (UK Alert Level 4), what microbiological investigations should be undertaken for hospitalised patients?

In a pandemic situation, virological investigations are not recommended routinely and in a pandemic situation may not be available readily. The diagnosis of influenza will be based on clinical findings. If influenza-related pneumonia is present, the degree of microbiological investigation will be directed by disease severity and the presence of co-morbidities.

In influenza-related pneumonia, examination of sputum should be considered for patients who do not respond to empirical antibiotic therapy. This will be particularly relevant if *Staph aureus* is identified as a common influenza-related pneumonia pathogen during the early phase of the pandemic as, in contrast to *S pneumoniae* and *H influenzae,* antimicrobial susceptibilities of this organism are less predictable and empirical choices more speculative.

<u>Recommendations (Once a pandemic is established: UK Alert Level 4)</u>

A. VIROLOGY – Not routinely recommended.

B. BACTERIOLOGY - PATIENTS WITH INFLUENZA-RELATED PNEUMONIA

(I) Non-severe pneumonia (CURB-65 Score 0,1 or 2)

- **Sputum samples should be sent for Gram stain culture and antimicrobial susceptibility tests in patients who do not respond to empirical antibiotic therapy.**

(II) Severe pneumonia (CURB-65 Score 3, 4 or 5)

- **Specific investigations should include:**
  1. **Blood culture, preferably before antibiotic treatment is commenced**
  2. **Pneumococcal urine antigen (20mls urine)**
  3. **Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from patients who:**
     a. **are able to expectorate purulent samples, *and***
     b. **have not received prior antibiotic treatment.**

     Sputum specimens should be transported rapidly to the laboratory.
  4. **Paired serological examination for influenza/other agents. 'Acute' serum should be collected and a 'convalescent' sample obtained after an interval not less than 7 days (both 5-10mLs clotted blood) and the two sera stored for subsequent testing.**
  5. **Tracheal or endotracheal aspirate samples, if available, should be sent for Gram stain, culture and antimicrobial susceptibility testing.**

8 GENERAL MANAGEMENT IN HOSPITAL

8.1 Introduction

Initial management will depend on the assessment of the reason for admission, the presence of complications, and the impact of the influenza on any pre-existing disease, or psychosocial factors. For instance, some elderly patients may require admission for social reasons.

In broad terms, the most likely clinical reasons for admission will be (in order of frequency):

Lower respiratory tract complications

- Non pneumonic bacterial exacerbation of chronic lung disease such as COPD (possibly with a mixed viral infection)
- Secondary bacterial pneumonia
- Mixed bacterial and viral pneumonia
- Primary viral pneumonia

Cardiac complications

- Exacerbation of pre-existing cardiac disease with cardiac failure and/or arrhythmia
- Primary myocarditis

Other complications

- Exacerbation of other pre-existing disease, such as diabetes mellitus
- Neurological complications
- Rhabdomyolysis
- Severe sinusitis

The initial management is likely to most usually involve that of respiratory and cardiac complications, especially pneumonia and these are discussed below. Management of other less common primary influenzal complications (such as rhabdomyolysis, encephalopathy) is not covered.

8.2 What initial management strategy should be offered to patients with respiratory and cardiac complications?

All influenza patients admitted to hospital with abnormal cardiorespiratory symptoms and signs, including influenza-related pneumonia should have a chest radiograph, and electrocardiogram and should have oxygenation assessed by pulse oximetry, preferably whilst breathing air (see Section 6). Those with SaO_2 <92% should have arterial blood gas measurements, as should all patients with features of severe illness. Knowledge of the inspired oxygen concentration is essential to the interpretation of blood gas measurements and should be clearly recorded with the blood gas result.

Continuous oxygen therapy is indicated for those patients with PaO_2 <8 Kpa, hypotension with systolic BP <100 mmHg, metabolic acidosis with bicarbonate <18 mmol/l or respiratory distress with respiratory rate >30/min.(62) The aim of oxygen therapy should be to maintain PaO_2 at >8 Kpa or SaO_2 >92%. Unless complicated by severe chronic obstructive pulmonary disease with ventilatory failure, high concentrations of oxygen of 35% or greater are indicated and can be safely used.

High concentration oxygen therapy given to patients with pre-existing chronic obstructive pulmonary disease who may have CO_2 retention can reduce hypoxic drive and increase ventilation-perfusion mismatching. In such patients initial treatment with low oxygen concentrations (24-28%) should be progressively increased on the basis of repeated arterial blood gas measurements, the aim being to keep PaO_2 >6.65 Kpa without causing a fall in arterial pH below 7.26,(63) in line with the management strategy recommended in the NICE COPD Guidelines(58). Non-invasive ventilation (NIV) may often be of value. Non-invasive ventilation in patients with pneumonia but without co-existing COPD has not been shown to influence mortality. The use of NIV in such patients should not delay the institution of invasive ventilation if appropriate.(59;64)

Patients should be assessed for volume depletion and may require IV fluids. The potential for influenza to cause cardiac decompensation, either through exacerbation of pre-existing cardiac disease or from a primary myocarditis should be borne in mind, with any complicating heart failure and arrhythmias being managed in the usual way.

Physiotherapy may be of benefit in selected patients with excess bronchial secretions, particularly those with concurrent chronic obstructive pulmonary disease. In cases of severe illness requiring prolonged hospital admission, increased nutritional support whether enteral, parenteral or via naso-gastric feeding should be arranged.

Recommendations

- **Hypoxic patients should receive appropriate oxygen therapy with monitoring of oxygen saturations and inspired oxygen concentration with the aim to maintain $PaO_2 \geq 8$ Kpa and $SaO_2 \geq 92\%$. High concentrations of oxygen can safely be given in uncomplicated pneumonia.**
- **Oxygen therapy in patients with pre-existing chronic obstructive pulmonary disease complicated by ventilatory failure should be guided by repeated arterial blood gas measurements. Non invasive ventilation may be helpful.**
- **Patients should be assessed for cardiac complications and also volume depletion and their need for additional intravenous fluids.**
- **Nutritional support should be given in severe or prolonged illness.**

8.3 What monitoring should be conducted during hospital stay?

Pulse, blood pressure, respiratory rate, temperature, oxygen saturation (with a recording of the inspired oxygen concentration at the same time) and mental status should be measured initially at least twice daily. This is most conveniently performed using an Early Warning Score (EWS) chart, which all ward staff should be familiar with. Those with severe illness, requiring continuous oxygen or cardiovascular support, should be monitored more frequently.

Failure to improve clinically within 48 hours should result in a full clinical reassessment and failure to improve over 4 days is an indication to repeat the chest radiograph.

Recommendations

- **Temperature, respiratory rate, pulse, blood pressure, mental status, oxygen saturation and inspired oxygen concentration should be monitored and recorded initially at least twice daily and more frequently in those with severe illness or requiring regular oxygen therapy.**
- **An Early Warning Score system is a convenient way to perform this.**
- **In addition to a full clinical reassessment, a chest radiograph should be repeated in patients who are not progressing satisfactorily.**

8.4 When can patients be safely discharged from hospital?

There will be considerable pressure to discharge patients early during a pandemic. The type and availability of out-of-hospital facilities will dictate hospital discharge decisions. Some guidance regarding simple parameters to review when considering hospital discharge can be obtained from a recent US prospective, multi-centre, observational cohort study of 680 patients admitted to hospital with CAP(65) and are offered as advice for all patients admitted with influenza-related respiratory complications.

Recommendations

- **Patients should be reviewed before 24 hours of discharge home. Those with more than 2 of the following unstable clinical factors should consider remaining in hospital:**
  a. **temperature > 37.8^{o}C**
  b. **heart rate > 100/min**
  c. **respiratory rate > 24/min**
  d. **systolic blood pressure <90mmHg**
  e. **oxygen saturation < 90%**
  f. **inability to maintain oral intake and abnormal mental status.**

8.5 What arrangements should be made for follow up after hospital discharge for influenza and by whom?

It is usual practice to arrange "routine" hospital clinic follow up and repeat the chest radiograph at around 6 weeks after discharge for acute respiratory illness such as pneumonia. However, there is no evidence on which to base a recommendation regarding the value of this practice in patients who have otherwise recovered satisfactorily. It is also not known whether there is any value in arranging clinical follow up in a hospital clinic rather than with the patient's general practitioner. During an influenza pandemic situation, it is likely that only patients who developed complications or who had significant worsening of their underlying disease will be offered clinical review at one or other venue.

At discharge, patients should be offered access to information about their take home medication, smoking and lifestyle advice as appropriate, potential future complications and action to take in the event of a relapse of symptoms.

Recommendations

- **Follow up clinical review should be considered for all patients who suffered significant complications or who had significant worsening of their underlying disease, either with their general practitioner or in a hospital clinic.**
- **At discharge or at follow up, patients should be offered access to information about their illness, take home medication and any followup arrangements.**
- **It is the responsibility of the hospital team to arrange the follow up plan with the patient and the general practitioner.**

9 USE OF ANTIVIRALS IN PANDEMIC INFLUENZA

9.1 What drugs should be used for antiviral treatment during a pandemic?

Oseltamivir (neuraminidase inhibitor) will be the mainstay for therapy in the pandemic. The M2 inhibitors, amantadine and rimantadine, are unsuitable for use for *treatment* due to the rapid emergence of resistance together with side-effects.

From clinical trial data accrued to date and based on seasonal, interpandemic influenza, the *anticipated* positive effect of antivirals in a pandemic will be:

(a) reduction of illness duration by 24 hours, and therefore more rapid mobilisation of affected individuals including essential workers
(b) a possible reduction in hospitalisation of infected individuals
(c) a reduction of subsequent antibiotic use by infected individuals

The evidence accrued to date does not suggest there will be a reduction of overall mortality. Therefore the major utility of antivirals will be to maintain the essential workforce, and reduce hospitalisation and antibiotic treatment of complications.

9.2 Who should be treated with antivirals (neuraminidase inhibitors) during a pandemic?

Recommendations

- **Individuals should only be considered for treatment with neuraminidase inhibitors if they have all of the following:**
  1. **an acute influenza-like illness**
  2. **fever (>38^{0}C**) *and*
  3. **been symptomatic for 2 days or less**

- **Treatment Schedule: Adults: Oseltamivir 75mg every 12 hours for 5 days. Dose to be reduced by 50% if creatinine clearance is less than 30ml/minute.**

- **EXCEPTIONS:**
  a) **Patients who are unable to mount an adequate febrile response eg. the immunocompromised or very elderly, make still be eligible despite lack of documented fever.**
  b) **Hospitalised patients who are severely ill, particularly if also immunocompromised, may benefit from antiviral treatment started more than 48 hours from disease onset. (This advice reflects the lack of robust evidence to guide the use of antivirals in such patients and places a high value on the potential benefits of antiviral therapy.)**

9.3 Delivery of antivirals in Primary Care.

National distribution arrangements are laid out in the UK Operational Framework for stockpiling, distributing and using antiviral drugs in the event of pandemic influenza.(3) The drug will be made available through these arrangements to pharmacies, PCTs and/or GP surgeries.

Recommendations

- **PCTs are encouraged to plan for the delivery of antivirals to the large numbers of previously healthy persons with an ILI via community health professionals, including community pharmacists.**
- **GPs should focus their efforts on assessment and management of those persons at high risk of complications (see Appendix 2) and patients developing complications.**

9.4 How do antivirals work?

Drugs available for treatment and prevention of infection by influenza are summarised in Table 9.1. There are four drugs available, the older agents, amantadine and rimantadine, and the neuraminidase inhibitors, oseltamivir and zanamivir.

Older Agents: The older agents, amantadine and rimantadine (rimantadine is not currently licensed in the UK), are related substances that act by blocking the ion-channel function of the influenza virus M2 protein. This protein, although a minor surface constituent of the influenza virus particles, is essential for virus replication. They are only active against influenza Type A. Amantadine is not recommended by NICE for treatment and/or prophylaxis of interpandemic influenza, so in the absence of national stockpiling, supplies of amantadine can be expected to be very low. H5 viruses in SE Asia are resistant to amantadine, so may play no role at all depending on the nature of the pandemic strain.

Neuraminidase inhibitors: Neuraminidase inhibitors have been developed that have a potent anti-influenza activity *in vitro* and also have clinical efficacy. They are active against both Type A and Type B influenza viruses. The neuraminidase (NA) surface protein of the virus is essential for the de-aggregation and release of newly synthesized virions from infected cells. Inhibition of this enzyme interrupts propagation of the influenza virus within the human respiratory tract.

Two neuraminidase inhibitors so far have been developed to the level of entry into the formulary:

- Zanamivir is a modification of Neu5Ac2en, a dehydrated neuraminic acid derivative.
- Oseltamivir is a similar molecule except it has a cyclohexene ring and replaces a polyglycerol moiety with lipophilic sidechains.

Oseltamivir can be taken by mouth, whereas Zanamivir. must be inhaled, using a Diskhaler device. An intravenous formulation of zanamivir has been developed but its efficacy has not been established. This may be relevant for the management of ventilator cases. Both drugs are active against both the influenza Type A and influenza Type B viruses.

9.5 What effect do antivirals have on the natural history of influenza?

Older agents: Both amantadine and rimantadine are effective for the treatment of Type A influenza virus infection if treatment is begun within 48 hours of the onset of illness. (66) Historical data show that they can shorten the illness by approximately one day but their efficacy or in preventing complications, hospitalisations, or deaths has never been established. Although these drugs are effective, their use in clinical influenza treatment has been limited as a result of their proclivity to induce viral resistance, and their side-effect profile.

Neuraminidase inhibitors:

9.5.1 Effect on symptoms

Several large clinical trials have demonstrated the utility of zanamivir and oseltamivir in treatment of adults with influenza in the community (Table 9.2). The evidence yielded by these studies has recently been reviewed by the Cochrane Collaboration.(67) Overall, neuraminidase inhibitors have been shown to shorten the duration of symptoms by one day. Across all studies, the time gained in returning to normal activities is half a day for laboratory-confirmed cases of influenza. The beneficial effect appears to be confined to patients in whom there is fever, (38^0C in the study reported by Nicholson et al, 2000 (68), and 37.8^0C in the study reported by the MIST group 1998(69)) and who are treated within 48 hours of the onset of symptoms. Oseltamivir has also been shown to have efficacy in children aged 1-12 years. In one study involving 452 children with proven influenza the median duration of illness was reduced by 36 h (26%) in oseltamivir compared with placebo recipients (101 h; 95% confidence interval, 89 to 118 vs. 137 h; 95% confidence interval, 125 to 150; P < 0.0001). Oseltamivir treatment also reduced cough, coryza and duration of fever.(70) The neuraminidase inhibitors may have the additional benefit of reducing transmission between hosts; in studies of experimental human influenza, zanamivir greatly reduced titres of virus cultured from the nasopharynx as well as the mean duration of viral shedding.(71)

9.5.2 Effect on outcomes

Virtually all studies on the efficacy of neuraminidase inhibitors to reduce complications have been conducted with oseltamivir, and this drug has been shown to have some effect on outcomes other than time to recovery. In a metanalysis of adults and adolescents with a virologically proven influenza illness, oseltamivir treatment reduced overall antibiotic use for any reason by 26.7% (14.0% vs 19.1% with placebo; P< 001) and the incidence of influenza-related chest infections such as bronchitis resulting in antibiotic therapy by 55% (4.6% vs 10.3% with placebo; P<.001). In those subjects considered at increased risk of complications, 74 (18.5%) of 401 placebo recipients developed a chest infection leading to antibiotic use compared with 45 (12.2%) of 368 oseltamivir recipients (34.0% reduction; P =.02). Hospitalization for any cause occurred in 18 (1.7%) of 1063 placebo recipients compared with 9 (0.7%) of 1350 oseltamivir-treated patients (59% reduction; P =.02). In contrast, among subjects with an influenza-like illness but without a confirmed influenza infection, the incidence of complicating chest infections (6.7% vs 5.3%), overall antibiotic use (19.7% vs 19.3%), or hospitalizations (1.7% vs 1.9%) was similar between placebo and oseltamivir recipients, respectively.(72) In a study of children aged 1-12 with proven influenza, children with proven, new diagnoses of otitis media arising as a complication of influenza were reduced by 44% (12% vs. 21%). The incidence of physician-prescribed antibiotics was significantly lower in influenza-infected oseltamivir (68 of 217, 31%) than placebo (97 of 235, 41%; P = 0.03) recipients.(70) So far, the neuraminidase inhibitors have not been extensively investigated in patients who are at the highest risk of serious complications of influenza. Such patients include the elderly and those with serious cardiopulmonary illness, such as chronic obstructive pulmonary disease. The neuraminidase inhibitors have not been associated with a reduction in mortality, but the clinical trials conducted so far have not been appropriate to measure this.

9.6 Will antivirals have activity against the pandemic strain of influenza virus?

It is not known for certain whether the neuraminidase inhibitors will be effective in pandemic influenza because their use has only been assessed in inter-pandemic influenza, where the virulence is moderate and there is some degree of host immunity. The antiviral acrtivity is likely to be adequate; *in vitro*, all neuraminidase inhibitors have been demonstrated to have a broad spectrum of activity against multiple avian influenza viruses.(73) The older agents, rimantadine and amantadine, were studied in both the 1968 Hong Kong pandemic and again when H1N1 influenza appeared in a pandemic in 1977. Their efficacy has been reviewed by Hayden.(66) When the older agents were given for 4-8 week periods *as prophylaxis* in a community setting, their protective efficacy against influenza illness averaged 70% compared

with placebo. This compares with 80-90% efficacy observed with the same agents in studies during the interpandemic period.

9.7 Can influenza virus develop resistance to the antivirals?

When amantadine or rimantadine are used to treat patients, resistant viruses emerge rapidly and approximatey 30% of treated children or adults will shed resistant variants starting 2-5 days after the onset of treatment.(71) The resistant viruses shed from these patients retain full virulence, infectivity and transmission potential. When contacts of cases treated with amantadine or rimantadine are given post-exposure prophylaxis with these older agents, the reduction in secondary cases is minimal.(74)

In contrast the frequency of emergence of resistance during treatment with the neuraminidase inhibitors is reported to be low. However, during studies of experimentally-induced influenza A/H1N1 infection in healthy adults, 4% of participants shed viruses with a histidine to tyrosine substitution at position 274 within the binding site of oseltamivir.(75) In these cases the volunteers had increased influenza viral load within the nasopharynx but there was no deterioration of symptoms. So far, there have been no proven instances of transmission of oseltamivir or zanamivir-resistant variants in field clinical trials, but the experience is relatively small currently. Sequence analysis of H5N1 human isolates from North Vietnam have revealed virus with a 274-Y (resistant) sequence. Although the isolate was not fully resistant, its IC50 for oseltamivir was shifted upwards and it is therefore less susceptible to oseltamivir than other H5N1 isolates that had been tested from the region. The patient from whom the virus was isolated was concurrently being treated with oseltamivir.

9.8 What side-effects occur during use of antivirals?

Both amantadine and rimantadine can cause nausea and vomiting in a small percentage of individuals receiving them (Table 9.1). Unfortunately amantadine is also associated with very unpleasant central nervous system side-effects including anxiety, depression, insomnia and hallucinations. The side-effects are dose-related and do resolve with discontinuation of the drug. In the case of the neuraminidase inhibitors, both drugs appear relatively safe. Zanamivir has very few side-effects, but can result in bronchospasm which might be potentially serious in patients with asthma. Oseltamivir, requires dose-reduction in patients with low creatinine clearance (< 30ml/min). Nausea occurs in 5-15% of oseltamivir recipients but is seldom severe enough to lead to drug discontinuation.

Table 9.3: Side-effects of oseltamivir

Main side-effects	Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea, headache, fatigue, insomnia, dizziness, conjunctivitis, nose-bleed, rash, ear disorders
Rare side-effects	Hypersensitivity reactions
Very rare side-effects	Hepatitis, Stevens-Johnson syndrome

10 ANTIBIOTIC MANAGEMENT

10.1 Introduction

Antimicrobial chemotherapy will be indicated primarily for respiratory complications due to secondary bacterial infections, principally influenza-related pneumonia. The majority of patients with exacerbations of chronic obstructive pulmonary disease (COPD) and other chronic lung conditions such as bronchiectasis, due to secondary bacterial will also require antimicrobial chemotherapy, as will some patients with severe sinusitis.

Few pneumonias and lower respiratory tract infections are defined microbiologically at initial assessment and hence most prescribing is empirical. In broad terms the antimicrobial management of these patients should follow the guidance offered in relevant national guidelines for the management of community acquired pneumonia and COPD, but modified in the light of the different range of pathogenic bacteria that may be implicated, specifically *Staph aureus* infection.

In the minority of cases, the aetiology may be determined after hospital admission, thereby permitting modification of the initial empirical regimen.

Although the pathogens responsible for community acquired pneumonia are diverse, in the case of bacterial pneumonia complicating influenza the principal pathogens which should be covered by any initial empirical antimicrobial therapy include: *S pneumoniae, H influenzae and Staph aureus*. The latter is said to be more common with combined viral-bacterial pneumonia, as some strains of staphylococci have synergistic effect with the virus. Gram negative enteric bacillary infection is also sometimes seen. Exacerbations of COPD will be largely associated with *S pneumoniae, H influenzae*, and *Moraxella catarrhalis.* Severity assessment and the association of pre-existing co-morbid disease is essential in predicting prognosis and in turn determines management, choice of antibiotic therapy and its method of administration (see Section 5).

10.2 Antibiotic resistance of respiratory pathogens

During an influenza pandemic this will be principally related to concerns about the local pattern of antimicrobial resistance of *Staph aureus,* and assessing the possibility of methicillin-resistant *S aureus* (MRSA) being present locally. Clinicians should be kept closely informed of any local shift in antimicrobial resistance patterns, both at the start and during a pandemic. *Staphylococcus aureus* is widely resistant to penicillin (76) and an increasing number are now methicillin-resistant (MRSA); when occurring in the community this generally reflects hospitalisation within the recent past or residence within a nursing home. Hence, β-lactamase unstable penicillins (penicillin G, aminopenicillins) and, in the case of MRSA, isoxazolyl penicillins (flucloxacillin, cloxacillin) and cephalosporins, are inappropriate for such infections. The true incidence of resistance among pathogens in the community is difficult to estimate since most laboratory samples come from selected populations. With this limitation in mind, the presence of β-lactamase production among *H influenzae* varies geographically but ranges from 2–17 % (77;78) in various parts of the UK. *M catarrhalis* has a high rate of β-lactamase production.

Antibiotic resistance among *S pneumoniae* is of concern world wide, owing to the dominance of this organism as a cause of community acquired pneumonia and because penicillin and macrolide resistance are frequently linked.(78;79) However to date it is not a common enough problem in the UK to influence initial antimicrobial management decisions.

Recent data provided by the HPA of antimicrobial sensitivities of respiratory pathogens isolated from blood and respiratory samples during the last 3-4 years (Robert George,

personal communication) found macrolide resistance amongst about 10-14% Methicillin sensitive *Staphylococcus aureus (*MSSA) isolates and 12-19% of *S pneumoniae.* Macrolides apart from clarythromycin have poor in vivo activity against *H influenzae*. By contrast, tetracycline resistance was around 5-8% for *S pneumoniae*, 3% for *H influenzae* and 2-8% for of MSSA.

Fluoroquinolones have activity against methicillin sensitive *Staphylococcus aureus* (MSSA): with MIC 90 figures of 1.0 mg/L for ciprofloxacin, 0.5 mg/L for levofloxacin and 0.12 for moxifloxacin.(80) Modern fluoroquinolones (oral moxifloxacin and oral and IV levofloxacin currently licensed in the UK) are therefore a possible choice for secondary bacterial infections following influenza where MSSA is a likely pathogen. A recent pharmacokinetic and pharmacodynamic in vitro study indicated that moxifloxacin 400mg od had advantages over ciprofloxacin 500mg bd or levofloxacin 500mg od in antimicrobial effects against *Staph aureus*.(81) The quinolones levofloxacin or moxifloxacin also provide cover against *S pneumoniae* and *H influenzae*. MRSA is an unlikely pathogen in the UK in the context of community acquired respiratory bacterial infection following influenza and fluoroquinolones are not sufficiently active against MRSA.

10.3 Formulation of these recommendations

There are no robust research studies available to provide evidence based guidance on the best empirical choice of antimicrobial therapy for bacterial complications of influenza. For these reasons the recommendations for treatment have been made on the basis of assessing a matrix of laboratory, clinical, pharmacokinetic and safety data, interpreted in an informed manner and taking account of other published guidelines.(82)

EMPIRICAL THERAPY – IN THE COMMUNITY

10.4 What are the principles and practice of empirical antibiotic choice for adults with bronchial complications of influenza without pneumonia managed in the COMMUNITY?

Features of an acute bronchitis, with cough, retrosternal discomfort, wheeze and sputum production are an integral part of the influenzal illness. In previously well individuals who do not have pneumonia or new focal chest signs antibiotics are not indicated.

If the illness is worsening, for instance with recrudescent fever or increasing breathlessness, a worsening bacterial bronchitis or developing pneumonia is possible and the use of antibiotics should be considered.

Those at high risk (see Appendix 2) of influenza-related complications and super-infection should be strongly considered for early ‘prophylactic’ antibiotics. The antibiotic prescription should come with clear instructions that the antibiotics should be used if the illness is not starting to settle after 24 hours or if there is worsening of symptoms. The potential advantages of this approach of ‘prophylactic’ antibiotics is to minimise rates of influenza-related complications and reconsultation.(83)

If, having started antibiotics, patients do not begin to improve over the next 48 hours of antibiotic treatment (or if they get worse) they should be advised to re-contact their GP for assessment of pneumonia and its severity (see sections 3 and 5).

Antibiotics should cover the likely bacterial pathogens including: *S pneumoniae, H influenzae, M catarrhalis and Staph aureus*.

The preferred first choice of antibiotic for non-pneumonic bronchial infections, including those patients with COPD, should include an effective oral β-lactamase stable agent such as co-amoxiclav, or a tetracycline, such as doxycycline. A macrolide (eg. erythromycin or clarithromycin) is an alternative for those intolerant of the preferred first choices, whilst remembering the possibility of antimicrobial resistance. Clarithromycin has better activity against *H influenzae* than azithromycin.

Recommendations

- **Previously well adults with uncomplicated influenza, or acute bronchitis complicating influenza, in the absence of pneumonia, do not routinely require antibiotics.**
- **Antibiotics should be considered in those previously well adults who develop significant worsening of symptoms (particularly recrudescent fever or increasing breathlessness).**
- **A prescription for prophylactic antibiotics should be strongly considered for patients at high risk of complications (see Appendix 2) - to be used if the illness is not starting to improve after 24 hours or there is worsening of symptoms (as above).**
- **Most patients can be adequately treated with a week's course of oral antibiotics**
- **The preferred choice of antibiotic needs also to cover infection with *Staph aureus* - for example either co-amoxiclav, or doxycycline.(see Table 10.0)**
- **A macrolide such as erythromycin (or clarithromycin) is an alternative choice in certain circumstances.**

10.5 What are the principles and practice of empirical antibiotic choice for adults with influenza-related pneumonia managed in the COMMUNITY?

The principles of antibiotic selection for patients with influenza-related pneumonia who can be managed in the community is similar to those for the management of sporadic community acquired pneumonia in general (BTS 2001, 2004), except that adequate cover for *Staph aurues,* in addition to cover for *S pneumoniae,* should be included in any empirical regimen.

For this reason oral co-amoxiclav or a tetracycline, such as doxycycline is the preferred regimen (Table 10.1).

A macrolide (eg. erythromycin or clarithromycin) is an alternative for those intolerant of the preferred first choices.

Recommendations (see Table 10.1)

- **Co-amoxiclav or a tetracycline is preferred.**
- **A macrolide (erythromycin or clarithromycin) is offered as an alternative choice for those intolerant of penicillins.**
- **Those with features of severe infection (ie. bilateral chest signs or CRB-65 score of 3 or more) should be urgently referred to hospital.(see Section 5)**
- **For those referred to hospital, GPs may consider administering antibiotics immediately where the illness is considered life-threatening or where delays (>2 hours) in admission are likely.**

Table 10.1 Preferred and alternative initial empirical antibiotic treatment regimens for adults with pneumonic and non-pneumonic lower respiratory tract infections (including exacerbations of COPD and acute bronchitis) complicating influenza managed in the community

PREFERED	ALTERNATIVE[a]
co-amoxiclav 625mg tds PO (for 1 week), OR doxycycline 200mg stat and 100mg od PO	Macrolide (erythromycin 500 mg qds PO *or* clarithromycin 500 mg bd [b] PO)

a) An alternative regimen is provided for those intolerant of or hypersensitive to preferred regimen

b) Clarithromycin may be substituted for those with gastrointestinal intolerance to oral erythromycin and also has the benefit of twice daily dosage and better cover against *H influenzae*.

Abbreviations: od = once daily; bd = twice; tds = 3 times; qds = 4 times

EMPIRICAL THERAPY – IN HOSPITAL

10.6 What are the principles and practice of empirical antibiotic choice for adults with bronchial complications of influenza without pneumonia managed in HOSPITAL?

The principles are similar to those outlined for such patients managed in the community. (Section 10.4)

In those with chronic lung disease, particularly COPD, bacterial exacerbation will be the commonest cause of admission. It is likely that all such patients sufficiently ill to require hospital admission with an exacerbation will require antibiotics. Management of their underlying condition, such as COPD, should follow standard guidelines, including the use of corticosteroids if indicated.

Antibiotics should cover the likely bacterial pathogens including: *S pneumoniae, H influenzae, M catarrhalis and Staph aureus*. Oral therapy should be sufficient for those without adverse severity features and who are able to take oral medication.

The preferred first choice of antibiotic for non-pneumonic bronchial infections should include an effective oral β-lactamase stable agent such as co-amoxiclav, or a tetracycline, such as doxycycline. A macrolide is an alternative for those intolerant of the preferred first choices, whilst remembering the possibility of antimicrobial resistance. Clarithromycin has better activity against *H influenzae* than azithromycin. A newer generation fluroquinolone (eg. levofloxacin or moxifloxacin) with enhanced activity against *S pneumoniae* is an alternative choice if there is increased likelihood of resistance or local issues that dictate such a choice (such as local concern regarding the prevalence of antibiotic associated enteropathy linked to β-lactam use).

Recommendations (see Table 10.2)

- **Previously well adults with acute bronchitis complicating influenza, in the absence of pneumonia, do not routinely require antibiotics.**
- **Antibiotics should be considered in those previously well adults who develop worsening symptoms (recrudescent fever or increasing dyspnoea).**
- **Patients at risk of complications or superinfection should be considered for antibiotics in the presence of lower respiratory features. These include patients**

who are within the group currently recommended for influenza vaccination (see Appendix 1).

- **Most patients can be adequately treated with oral antibiotics .**
- **The preferred choice includes co-amoxiclav or a tetracycline.**
- **A macrolide such as clarithromycin (or erythromycin) or a fluoroquinolone active against *S pneumoniae and Staph aureus is a*n alternative choice in certain circumstances.**

10.7 What are the principles and practice of empirical antibiotic choice for adults with non-severe influenza-related pneumonia managed in HOSPITAL?

Patients will be suffering from primary viral pneumonia, or combined viral-bacterial pneumonia, or secondary bacterial pneumonia. The features of each of these are covered in section 3.

All patients with pneumonic involvement should receive antibiotics. The principles of antibiotic selection for non-severe influenza-related pneumonia is similar to those for the management of sporadic community acquired pneumonia in general (BTS 2001, 2004), except that adequate cover for *Staph aureus* should be included in any empirical regimen. It is also not felt necessary to routinely provide cover for atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia sp*., *Coxiella burnetti*, *Legionella sp*.) during a pandemic as the large majority of patients will be hospitalised as a direct result of influenza and its complications caused by bacterial infection.

For these reasons oral co-amoxiclav or a tetracycline, such as doxycycline is the preferred regimen (Table 10.1). When oral therapy is inappropriate, parenteral co-amoxiclav or a second or third generation cephalosporin is offered as an alternative. Based on in-vitro data, the activity of selected cephalosporins against MSSA in the UK in descending rank order is cefuroxime (MIC90 1 – 2 mg/l) > cefotaxime (MIC90 2mg/l) > ceftriaxone (MIC90 16mg/l). (Robert George, personal communication) Only cefuroxime and cefotaxime are recommended as cephalosporins offering adequate MSSA cover within an empirical regimen.

A macrolide or one or the new fluoroquinolones, are identified as an alternative in hospitalised patients, in specific circumstances. These include those intolerant of penicillins, where local microbiological surveillance suggests they are better choices or where there are local concerns over *C difficile* associated diarrhoea. At the time of completing these guidelines, only levofloxacin and moxifloxacin are licensed and available in the UK for pneumonia.

Regardless of the regimen selected it is critical that the antibiotics be administered promptly (within 4 hours of admission), and in the case of the patient with severe pneumonia without delay, by the admitting doctor in the Admissions Ward or by the general practitioner if delays are expected in the hospital admission process. Delays in administration of antibiotics are related adversely to mortality in some studies, particularly when managing elderly patients. (84;85)

Following initial assessment and empirical therapy, progress should be monitored carefully. The route and choice of antibiotic treatment will require adjustment, either by stepping up and broadening the spectrum of microbiological activity in the light of clinical deterioration or as a result of positive microbiological information, or stepping down with improvement as discussed below. The review of antibiotic therapy forms an obvious and essential part of the regular clinical review of patients with community acquired pneumonia.

Recommendations (see Table 10.2)

- **Most patients can be adequately treated with oral antibiotics.**
- **Oral therapy with co-amoxiclav or a tetracycline is preferred.**
- **When oral therapy is contra-indicated, recommended parenteral choices include intravenous co-amoxiclav, or a second or third generation cephalosporin (cefuroxime or cefotaxime respectively).**
- **A macrolide (erythromycin or clarithromycin) or a fluoroquinolone active against *S pneumoniae and Staphylococcus aureus* is an alternative regimen for those intolerant of penicillins or where there are local concerns over *C difficile* associated diarrhoea. Currently levofloxacin and moxifloxacin are the only recommended fluoroquinolones licenced in the UK.**
- **Antibiotics should be administered within 4 hours of admission.**

10.8 What are the principles and practice of empirical antibiotic choice for adults with severe influenza-related pneumonia managed in HOSPITAL?

Mortality is greatly increased in those with severe pneumonia (Section 5). The illness may progress before microbiological information is available.

Preferred and alternative initial treatment regimens are summarised in Table 10.1. The recommendation of broad-spectrum β-lactam regimens plus a macrolide in those with severe influenza-related pneumonia is based on the following rationale:

a. While *S pneumoniae* and *Staph aureus* remain the predominant pathogens, Gram negative enteric bacilli, although uncommon, carry a high mortality.(86)
b. The recommended empirical regimen will offer double cover for the likely pathogens implicated in influenza-related pneumonia and there is some evidence to indicate that combination therapy is associated with better outcomes in severe pneumonia.(87)
c. Although there is no evidence of an increased incidence of infection by atypical pathogens in influenza-related pneumonia, in severe pneumonia, it is felt necessary to include cover for atypical pathogens, particularly Legionella sp. as it may not be possible at the outset to distinguish between patients with sporadic severe community acquired pneumonia in whom Legionella infection is important, and influenza-related pneumonia.

Parenteral administration of antibiotic is recommended in those with severe community acquired pneumonia regardless of the patient's ability or otherwise to take oral medication. This is to ensure prompt, high blood and lung concentrations of antibiotic.

A fluoroquinolone is offered as an alternative, despite limited data on their use in severe pneumonia.(88) Levofloxacin is the only licensed and available agent in the UK at the time of writing. It is marketed in parenteral and oral formulations. However, until more clinical experience is available we recommend combining it with another agent active against *S pneumoniae* and *Staphylococcus aureus* such as a broad spectrum β-lactam or macrolide when managing severe influenza-related pneumonia.

Recommendations (see Table 10.2)

- **Patients with severe pneumonia should be treated immediately after diagnosis with parenteral antibiotics.**
- **An intravenous combination of a broad spectrum beta-lactamase stable antibiotic such co-amoxiclav or a second (eg cefuroxime) or third (eg cefotaxime) generation**

cephalosporin together with a macrolide (clarithromycin or erythromycin) is preferred.

- **An alternative regimen includes a fluoroquinolone with enhanced activity against pneumococci together with a broad spectrum β-lactamase stable antibiotic or a macrolide. Currently levofloxacin is the only such fluoroquinolone licenced in the UK.**

10.9 When should the IV route be changed to oral?

There can be no rigid recommendation concerning the timing of transfer to oral therapy and further studies of this area are needed.(89) Any decision must be individualised on the basis of assessing all factors, including the absence of any contraindications to oral administration, the availability of any microbiological information regarding aetiology of the infection and clear evidence that the patient is responding to initial therapy. The recommended guideline is that oral therapy be considered in a patient who has shown clear evidence of improvement and whose temperature has resolved for a period of 24 hours.

Recommendations

- **Patients treated initially with parenteral antibiotics should be transferred to an oral regimen as soon as clinical improvement occurs and the temperature has been normal for 24 hours, providing there is no contra-indication to the oral route.**

10.10 How long should antibiotics be given for?

Until there are more precise methods to reliably identify microbiological and clinical end-points, the duration of therapy will remain subject to clinical judgement and custom. For these reasons the duration of therapy will vary by individual patient, disease severity and speed of resolution.

Recommendations

- **For most patients admitted to hospital with non severe and uncomplicated pneumonia, 7 days of appropriate antibiotics is recommended.**
- **For those with severe, microbiologically undefined pneumonia, 10 days treatment is proposed. This should be extended to 14 to 21 days where *S aureus* or Gram negative enteric bacilli pneumonia is suspected or confirmed.**

10.11 Failure of initial empirical therapy

In those patients who fail to respond to initial empirical therapy, several possibilities need to be considered, the first of which is whether the correct diagnosis been made. Radiographic review is recommended for the community and hospital-managed patient. This may also indicate complications of pneumonia such as pleural effusion/empyema, lung abscess or worsening pneumonic shadowing, which will be more common in the presence of staphylococcal infection.

The initial empirical antibiotic regimen may need to be reassessed. However compliance with, and adequate absorption of an oral regimen should first be considered.

Microbiological data should be reviewed and further specimens examined, with a view to excluding *Staph aureus* and Gram negative bacillary infection.

In the hospital managed, non-severely ill patient, changing to a new fluoroquinolone such as levofloxacin provides a second alternative.

In the severely ill patient already receiving a β-lactam/clarithromycin regimen, it is recommended that further staphylococcal cover is added to include cover for MRSA. In addition, urgent referral to a respiratory physician should be made for clinical assessment including the possible need for bronchoscopic sampling. Other rapid MRSA diagnostic techniques are in the evaluation stage.

Recommendations

- **For those with non-severe pneumonia in hospital on combination therapy, changing to a fluoroquinolone with effective pneumococcal and staphylococcal cover is an option.**
- **Adding further antibiotics effective against MRSA is an option for those with severe pneumonia not responding to combination antibiotic therapy.**

SPECIFIC PATHOGEN DIRECTED ANTIBIOTIC THERAPY

10.12 What are the optimum antibiotic choices when specific pathogens have been identified?

When a pathogen has been identified specific therapy as summarised in Table 10.3 is proposed. In transferring patients from empirical to pathogen targeted therapy, the regimen and route of administration will be determined by the continued need for parenteral therapy and known drug intolerance. These recommendations are again based on a synthesis of information, which includes *in vitro* activity of the drugs, appropriate pharmacokinetics and clinical evidence of efficacy gleaned from a variety of studies. The choice of agent may be modified following the availability of sensitivity testing or following consultation with a specialist in microbiology, infectious disease or respiratory medicine. Close liasion with the local microbiology service will be essential during a pandemic.

Currently *S pneumoniae* highly resistant to penicillin (MIC ≥4mg/L) is uncommon in the UK. However it is important that the situation is monitored and in future higher doses of penicillins or alternative regimens may need to be considered.

Staphylooccus aureus is an uncommon cause of sporadic community acquired pneumonia in the UK, but will assume much greater potential importance during a pandemic. Most community isolates are methicillin-sensitive although the recent increase in MRSA in hospitalised patients may result in subsequent readmission with an MRSA infection, secondary to influenza. Options for methicillin-sensitive and -resistant infections are based on parenteral administration in view of the serious nature of staphylococcal pneumonia.

Recommendations

- **If a specific pathogen has been identified, the antibiotic recommendations are summarised in Table 10.3.**

Table 9.1
Antiviral agents for influenza

Antiviral Agent	Trade Name	Manufacturer	Influenza Spectrum	Route of Administration	Daily Dosage for Adults		Most Common Side Effects
					Prevention	Treatment	
Amantadine	Symmetrel Lysovir	Endo Pharmaceuticals (USA) Alliance (UK)	Type A	Oral	200mg	200mg	Gastrointestinal and central nervous system
Rimantadine†	Flumadine	Forest Laboratories (USA)	Type A	Oral	200mg	200mg	Gastrointestinal
Zanamivir	Relenza	GlaxoSmithKline	Types A and B	Oral inhalation	10mg	20mg	None
Oseltamivir	Tamiflu	Roche	Types A and B	Oral	75mg	150mg	Gastrointestinal

† Not available in the UK

Table 9.2

Neuraminidase inhibitors in the treatment of adults with community-acquired influenza – summary of trial data

Treatment	Patients (% with proven influenza)	Age range (mean)	Duration of illness	Reduction in days to alleviation of symptoms in patients with influenza (median)	Comments	Investigator
Inhaled zanamivir 10mg bid for 5 days	417 (63%)	≥13 years (32 years)	≤48 h	1 (5 vs 4) 3 (7 vs 4 in febrile)	3 days reduction in patients treated ≤30 h	Hayden *et al* (1997)(22)
Inhaled zanamivir 10mg bid for 5 days	455 (71%)	≥12 years (37 years)	<30 h and >30 h	1.5 (6.5 vs 5.0) 2.0 (6.5 vs 4.5 in febrile)	Reduced complications and antibiotics (15% vs 38%) in patients with underlying conditions. No effect in patients with symptoms > 30 h	MIST Study Group (1998)(69)
Oseltamivir 75mg or 150mg bid for 5 days	629 (60%)	18-65 years	≤ 36 h	1.4 (4.3 vs 2.9 vs 2.9)	Reduced complications	Treanor *et al* (2000)(23)
Oseltamivir 75mg or 150mg bid for 5 days	719 (66%)	18-65 years	≤ 36 h	1.2-1.5 days (4.9 vs 3.6 vs 3.4)	No difference between doses	Nicholson *et al* (2000)(68)

Table 10.2: Preferred and alternative initial empirical antibiotic treatment regimens and parenteral to oral switch regimens for pneumonic and non- pneumonic lower respiratory tract infections complicating influenza managed in HOSPITAL

PREFERRED	ALTERNATIVE [a]
[1] Hospital-treated, non-pneumonic bronchial complications (including exacerbations of COPD and acute bronchitis) requiring antibiotic therapy	
• co-amoxiclav 625mg tds PO, **OR** doxycycline 200mg stat and 100mg od PO	• Macrolide (erythromycin 500 mg qds PO *or* clarithromycin 500 mg bd [b] PO) **OR** Fluoroquinolone with enhanced pneumococcal activity e.g. levofloxacin 500 mg od PO *or* moxifloxacin 400mg od PO[c]
[2] Hospital-treated, not severe pneumonia	
• co-amoxiclav 625mg tds PO **OR** doxycycline 200mg stat and 100mg od PO	• Macrolide (erythromycin 500 mg qds PO *or* clarithromycin 500 mg bd [b] PO) **OR** Fluoroquinolone with enhanced pneumococcal activity e.g. levofloxacin 500 mg od PO *or* moxifloxacin 400mg od PO[c]
OR if IV needed	
• co-amoxiclav 1.2 g tds IV **OR** cefuroxime 1.5 g tds IV *or* cefotaxime 1g tds IV	• Macrolide (erythromycin 500 mg qds PO *or* clarithromycin 500 mg bd [b] PO) **OR** levofloxacin 500 mg od IV [c]
[3] Hospital-treated, severe pneumonia	
• co-amoxiclav 1.2 g tds IV *or* cefuroxime 1.5 g tds IV *or* cefotaxime 1g tds IV **PLUS** Macrolide (erythromycin 500 mg qds PO *or* clarithromycin 500 mg bd [b] PO)	• Fluoroquinolone with some enhanced pneumococcal activity e.g. levofloxacin 500 mg bd IV, PO [c] **PLUS, EITHER** Macrolide (erythromycin 500 mg qds PO *or* clarithromycin 500 mg bd [b] PO) **OR** Beta-lactamase stable antibiotic (co-amoxiclav 1.2 g tds IV *or* cefuroxime 1.5 g tds IV *or* cefotaxime 1g tds IV)

a) An alternative regimen is provided for those intolerant of or hypersensitive to preferred regimen, or where there are local concerns over *C difficile* associated diarrhoea related to beta- lactam use

b) Clarithromycin may be substituted for those with gastrointestinal intolerance to oral erythromycin and also has the benefit of twice daily dosage and better cover against *H influenzae*.

c) Levofloxacin and moxifloxacin are the only currently UK licensed fluoroquinolones with enhanced activity against *S pneumonia*, in addition to cover for *Staphylococcus aureus.* Levofloxacin comes in an oral and parenteral formulation and is licensed for severe pneumonia. Moxifloxacin comes in an oral formulation only in the UK and is not licensed for severe pneumonia. In the future other fluoroquinolones such as gemifloxacin and gatifloxacin are likely to extend this choice, when licensed in the UK.

Abbreviations: od = once daily; bd = twice; tds = 3 times; qds = 4 times: IV = intravenous; PO = oral

Switch from parenteral drug to the equivalent oral preparation should be made as soon as clinically appropriate, in the absence of microbiologically confirmed infection. In the case of the parenteral cephalosporins, the oral switch to co-amoxiclav 625 mg tds is recommended rather than to oral cephalosporins.

Table 10.3: Recommended therapy of most likely microbiologically defined causes of pneumonia complicating influenza.* Local specialist advice should always be sought

PATHOGEN	PREFERRED	ALTERNATIVE
S pneumoniae	amoxicillin 500 mg – 1.0 g[a] tds PO *or* benzylpenicillin 1.2 g qds IV	cefuroxine 0.75-1.5 g tds IV *or* cefotaxime 1-2 g tds IV *or* ceftriaxone 2g od IV *or* erythromycin 500 mg qds PO *or* clarithromycin 500 mg bd PO
S aureus	**Non-MRSA**: flucloxacillin 1-2 g qds IV ± rifampicin 600 mg od *or* bd, PO/IV **MRSA**: vancomycin 1 g bd IV (dose monitoring) ± rifampicin 600 mg od *or* bd PO/IV	Consult local microbiologist for further advice.
H influenzae	**Non-β-lactamase-producing:** amoxicillin 500 mg td or ampicillin 500 mg qds IV **β-lactamase-producing:** co-amoxiclav 625 mg tds PO *or* 1.2 g tds IV	cefuroxime 750 mg -1.5g tds IV *or* cefotaxime 1-2 g tds IV *or* ceftriaxone 2 g od IV *or* fluoroquinolone[b] PO *or* IV
Gram negative enteric bacilli	cefuroxime 1.5 g tds *or* cefotaxime 1-2 g tds IV *or* ceftriaxone 1-2 g bd IV	fluoroquinolone[b] IV *or* imipenem 500 mg qds IV *or* meropenem 0.5-1.0 g tds IV
P aeruginosa	ceftazidime 2 g tds IV ± gentamicin *or* tobramycin (dose monitoring)	EITHER ciprofloxacin 400 mg bd IV OR piperacillin 4 g tds IV ± gentamicin *or* tobramycin (dose monitoring)

CHAPTER ii

Clinical Guidelines for Children with Influenza like illness during an Influenza pandemic

Section	Title
11	Clinical Features in children
12	Severity assessment in children
13	General investigations for children admitted to hospital
14	Microbiological investigations for children admitted to hospital
15	General management of children admitted to hospital
16	Antiviral therapy in children
17	Antibiotic therapy in children

11 CLINICAL FEATURES IN CHILDREN

Summary

1. **The commonest presenting features of influenza during an epidemic are fever, cough and rhinorrhoea and, in older children, pharyngitis and headache.**

2. **The clinical features of influenza in children during a pandemic cannot be forecast.**

3. **Children with underlying respiratory or cardiac disease, immune compromise or who are non-ambulant are more likely to be severely affected.**

4. **The younger the child the more likely hospital admission will be needed.**

5. **The severe and life-threatening complications of influenza are likely to be**
   - **Bacterial pneumonia**
   - **ARDS**
   - **Encephalopathy or encephalitis presenting as seizures or altered mental status.**

11.1 What are the clinical features of uncomplicated influenza in children?

The clinical features of influenza presenting in a pandemic cannot be predicted as they appear to be dependent on the strain of influenza and, in some respects, the host. A new strain of influenza A responsible for an epidemic or pandemic may result in a different spectrum of clinical features than previous strains.(90;91)

Common features during previous epidemics have been described and depend on the age of the child. The studies of clinical features are hospital based and are therefore likely to reflect more severe illness. These are nevertheless informative as one of the main issues in a pandemic is which patients require hospital admission. In young children presenting to primary care in a non pandemic influenza season there are no specific clinical features that distinguish influenza from other winter viruses.(92)

(A) Previously healthy infants and children:

11.1.1 Neonates may present with non-specific signs of sepsis such as pallor, floppiness, (poor peripheral circulation, poor tone), lethargy, poor feeding, episodes of apnoea.(93). Fever may be the only presenting feature. A North American study identified influenza as the most common reason for children aged 0-60 days being admitted to hospital during an epidemic with fever as the only clinical feature.(94)

11.1.2 Infants and very young children (under 2 years) Fever may be the only presenting feature in this age group too. They may also be irritable and toxic and are more likely than older children to present with gastrointestinal symptoms such as diarrhoea and vomiting. Febrile convulsions, particularly repeated convulsions, are positively associated with influenza A.(95) Otitis media is also a common complication in children.(96) Admission rates for under 2s are 12 times higher than children aged 5-17.(97)

11.1.3 Older children The presentation does not differ significantly from adults. Common features are sudden onset of high fever, chills (76-100%), cough, headache, sore throat , fatigue (51-75%), nasal stuffiness and conjunctivitis (26-50%). Fever tends to settle 2-4 days later though a dry cough and clear nasal discharge last for 1-2 weeks.(93) A clinical prediction model from North America for influenza in children has shown that the triad of cough, headache and pharyngitis had a sensitivity of 80% and a specificity of 78% for a

positive viral culture for influenza.(98) The subjects, mean age 6 years, presented during an epidemic to a suburban emergency department with a febrile respiratory illness and one or more symptoms of influenza. A Finnish retrospective study of children referred to hospital from 1980-1999 with influenza confirmed by antigen testing reported that the median age for those with influenza A was 2 years. The most common features were cough, fever and rhinorrhoea.(96) These were also the commonest features reported in a Chinese study where the mean age of the subjects with influenza A was 4 years.(99)

(B) Children with underlying medical conditions

11.1.4 **Children with asthma and other chronic medical conditions**(100) (Table 11.1) and those who are not ambulant(101) experience substantial morbidity during influenza seasons with a disproportionate number requiring inpatient care and ventilatory support. Of the 22% of previously healthy children who are hospitalised with influenza in Texas during the winter of 1998-9, 75% are under 1 year old. Of the 60% hospitalised who had underlying conditions, only 27% were under 1 year.(102)

11.2 Complications and rarer clinical features

11.2.1 Pneumonia

As in adults, influenza can present with either primary viral pneumonia or bacterial pneumonia most commonly caused by *S pneumoniae* or *Staph aureus.* There is much less published about pneumonia complicating influenza in children.

An outbreak of severe pneumococcal pneumonia in children occurred in Iowa in the winter of 1995-6. This was coincident with an epidemic of influenza (H1N1). Compared with controls, patients were 12 times more likely to have experienced a recent influenza-like illness. There were also more likely to have family members with the illness and to have positive serology in the convalescent period. Many of these patients required chest drainage.(103)

Another study in 2002 of 202 children with proven influenza reported that 78 who had chest radiographs had either radiographic evidence of viral pneumonia or normal radiographs. No child had lobar pneumonia reported.(104)

Evidence from recent outbreaks of Avian influenza (H5N1) in Hong Kong and Vietnam suggests that while some children had mild disease,(105) others appeared to have multi-organ disease including acute respiratory distress syndrome (ARDS).(91) All children who developed progresssive pneumonia with ARDS died. There were no reports of bacterial pneumonia.

There is no reason to believe that, apart from ARDS, pneumonia complicating influenza presents differently from community acquired pneumonia in children.(59)

The general clinical indicators for severity assessment of lower respiratory tract infection are summarised in the BTS guidelines.(59) (Table 12.2) Failure to improve following 48 hours of antibiotics, or deterioration including a new, distinct spike of fever, should also be treated as severe and further complicating factors sought.

11.2.2 Croup. The clinical course of croup caused by influenza appears to be more severe than croup caused by the more common parainfluenza virus.(106) It is more likely to be complicated by bacterial tracheitis.(96)

11.2.3 Otitis media. Influenza is a well recognised cause of otitis media.(107) It is the commonest bacterial superinfection of influenza and is reported in approximately 25% patients aged <5 years.(108)

11.2.4 Bronchiolitis Influenza ranks second only to respiratory syncytial virus as a cause of bronchiolitis.(109) (reference currently incomplete) The clinical features are the same.(110)

11.2.5 Febrile convulsions Children with influenza may present with febrile convulsions. In a community study in the Netherlands, recurrent febrile seizures were positively related to influenza A. It was recommended that children who have had a previous febrile convulsion should be immunised against influenza A.(95)

11.2.6 **Encephalopathy and encephalitis** These complications are described in small case series.

11.2.6.1 Encephalopathy This is defined as depressed or altered level of consciousness including lethargy and/or extreme irratibility in younger children or significant change in personality or behaviour persisting beyond 24 hrs or confusion (older children). Encephalopathy usually presents as seizures within several days of the onset of fever.(111) Seizures at this point are usually the first symptom of involvement of the central nervous system. Febrile convulsions, which are more likely to be repeated with influenza than with other causes of fever, generally occur with the onset of fever. Disturbances of behaviour and neurological deficit have been reported. A rapid and severe clinical course is usual with encephalopathy and is thought to be due to brain oedema mediated by cytokines rather than by direct invasion of the brain. Steroids are therefore considered. 202 children with encephalopathy were recognised in Japan between 1997 and 2001. Death occurred in 31%, residual neurological deficit in 26% and full recovery in 43%.(112)

11.2.6.1.1 Reye's Syndrome

This is a rare childhood acute encephalopathy associated with liver dysfunction. The cause is unknown but it typically follows viral illness and there is a clear association with aspirin therapy: thus an innate susceptibility coupled with aspirin taken for relief of viral symptoms. Influenza (particularly influenza B) is commonly implicated.(113) There was a dramatic fall in incidence following warnings about aspirin use in children.(114) It is possible that children on long term aspirin treatment for medical conditions may be at increased risk if they develop influenza infection.

Reye syndrome is characterised by protracted vomiting and encephalopathy in afebrile patients with minimal or absent jaundice, and hepatomegaly in 50% of patients. It comprises:

- Acute noninflammatory encephalopathy with an altered level of consciousness
- Elevation of ammonia levels 24-48 hours after the onset of mental status changes. (the most frequent laboratory abnormality)
- Hepatic dysfunction with a liver biopsy showing fatty metamorphosis or a more than 3-fold increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST)

Neurological symptoms usually occur 24-48 hours after the onset of vomiting. Lethargy is usually the first neurologic manifestation. Diarrhoea and hyperventilation may be the first signs in children younger than 2 years.

Other Investigations: Head CT scanning may reveal cerebral oedema but results are usually normal. An electroencephalogram (EEG) may reveal slow wave activity in the early stages and flattened waves in advanced stages. Cerebrospinal fluid may or may not have increased opening pressure with WBCs fewer than 9/ml^3 (usually lymphocytes).

There is no specific treatment for Reye's Syndrome. Key aspects of management are correction of metabolic imbalance and reduction of intracranial pressure. Advice should be requested from a specialist in metabolic medicine. Many children have an underlying inborn error of metabolism. Mortality has fallen from 50% to less than 20% as a result of earlier diagnosis and more aggressive therapy.

11.2.6.1.2 Acute necrotising encephalopathy (ANE) occurs mainly in Japan where it was first described in 1995. An estimated 100 deaths per annum are related to central nervous system complications of influenza in Japan.(115) This suggests either a genetic predisposition for this complication or a variation in the strains of influenza circulating in Japan. ANE is characterised by high fever, convulsions and coma in children aged 1-5 years. The onset is 2-4 days after the respiratory symptoms and fewer than 10% of patients survive.(116) There are no specific markers although some patients have raised liver transaminases. In many the CSF is normal. Symmetrical multi-focal brain lesions are seen and bilateral thalamic involvement is characteristic and may be demonstrated on MRI.(116)

11.2.6.1.3 Encephalitis is defined as encephalopathy plus 2 of the following: fever of 38°C or higher, seizures, focal neurological findings, WBC>5cells/microlitre in CSF, EEG findings consistent with encephalitis, abnormal neuroimaging.(117)

11.2.6.1.4. Differential diagnoses must be considered when a child presents with altered level of consciousness or irritability.There is good evidence of an increased risk of meningococcal disease following influenza infection.(118) During a pandemic the focus will be on diagnosing influenza related illness. Other neurological conditions or drug toxicity, for example, may be missed.

11.2.7 Myositis A literature review of 316 cases of myositis(119) suggested that this was a complication mainly of schoolchildren. The calf muscles are predominantly affected. Rhabdomyolysis and renal failure are rare.

11.2.8 **Myocarditis and pericarditis** These are also rare complications but have been described in children with underlying medical conditions.(96)

Table 11.1 The most common underlying conditions in children admitted to hospital - Texas 1998-9 (102)

Asthma (42%)
Congenital anomalies mostly cardiac (28.5%)
Chronic lung disease of prematurity
Immunodeficiencies
Malignancies
Renal disease
Haemaglobinopathies
Diabetes (and other metabolic conditions)

Table 11.2 Complications of influenza in children

Complication	Incidence	Comments
Respiratory		
Otitis media	Very common	
Lung Bronchiolitis Primary viral pneumonia Secondary bacterial pneumonia	Common (~10%)	The younger, the more likely to require hospital admission
Croup	Presenting feature in ~5%(96)	Worse clinically than with parainfluenza
Central Nervous System		
Febrile convulsions	Common	May be repeated
Encephalopathy	Rare	Includes Acute Necrotising Encephalopathy, Reye's syndrome
Encephalitis	Rare	
Guillain-Barre	Rare	
Others		
Myositis	Rare	
Myocarditis	Rare	
Pericarditis	Rare	

12 SEVERITY ASSESSMENT IN CHILDREN

Summary : Appendix 5 – flow chart

12.1 Coughs and mild fevers --- *At Home*

An influenza pandemic is likely to occur during the winter season when other winter viruses such as RSV are also circulating. Many children will have coughs and mild fevers and should be managed in the usual way at home by parents with antipyretics and fluids. (Note: aspirin should not be used in children)

12.1 High fever (>38.5C) and cough or influenza like symptoms --- *Community Health professional*

Children with high fever (>38.5°C) and cough or influenza like symptoms will be seen by a community health professional (a nurse or doctor if aged < 7 years). If there are no features which put them at high risk of complications they should be treated with oseltamivir, and given advice on antipyretics and fluids. Children aged <1 year and those at risk of complications (Table 12.1) should be seen by a GP.

12.2 High fever (>38.5°C) and cough or influenza like symptoms PLUS at risk group ----- *GP/A & E consultation*

Cough and fever (or influenza like illness) and temperature >38.5°C AND
Children with chronic disease (see Table 12.1)
Or one of below features

- Breathing difficulties
- Severe earache
- Vomiting > 24 hours
- Drowsiness

These children may be considered at increased risk of complications and an antibiotic given as well as oseltamivir (in those >1 year of age) and advice on antipyretics and fluids. Children aged <1 year with none of the above features should be treated with antipyretics and fluids with a low threshold for antibiotics if they become more unwell.

12.3 When to refer for admission?

The most severely ill children should be referred for assessment for admission.
Indicators are:

- Signs of respiratory distress.
  - markedly raised respiratory rate
  - grunting
  - intercostal recession
  - breathlessness with chest signs

  (A useful severity assessment for respiratory distress is taken from the BTS pneumonia guidelines(59) Table 12.2)
- Cyanosis
- Severe dehydration
- Altered conscious level
- Complicated or prolonged seizure
- Signs of septicaemia – extreme pallor, hypotension, floppy infant

12.4 Assessment in hospital

Children will be triaged for admission to wards, HDU or PICU.

Most children admitted to hospital are likely to need oxygen therapy and/or intravenous support as well as antibiotics and oseltamivir. (See General Management section 15)

12.6 Indications for transfer to High Dependency or Intensive Care

1. the child is failing to maintain a SaO2 of >92% in FiO2 of >60%
2. the child is shocked
3. there is severe respiratory distress and a raised PaCO2 (> 6.5 KPa)
4. there is a rising respiratory rate and pulse rate with clinical evidence of severe respiratory distress with or without a raised PaCO2
5. there is recurrent apnoea or slow irregular breathing
6. there is evidence of encephalopathy

12.7 What to do when there are no PICU beds available?

In a pandemic situation paediatric high dependency and intensive care beds are likely to fill quickly and will be insufficient to meet demand . Children will have to be triaged on the basis of the severity of their disease a) acute and b) co-existing and the likelihood of their achieving full recovery. Early discussion with tertiary specialists in respiratory medicine, paediatric intensive care and paediatric infectious diseases for support in management is encouraged.

Table 12.1 Children at Risk for complications from Pandemic Influenza.

- Chronic respiratory disease
  Including asthma (on inhaled steroids and above) , cystic fibrosis, chronic lung disease of prematurity, bronchiectasis
- Congenital heart disease
- Chronic renal disease eg nephrotic syndrome, renal failure
- Chronic liver or Gastrointestinal disease, including inflammatory bowel disease
- Immunodeficiency
- Malignancy
- Diabetes and other metabolic conditions
- Haemoglobinopathy
- Neurological disease eg diseases with muscle weakness and cerebral palsy

Table 12.2 Respiratory Distress Severity Assessment

	Mild	**Severe**
Infants	Temperature <38.5°C Resp rate < 50breaths/min Mild recession Taking full feeds	Temperature >38.5°C Resp Rate >70 breaths/min Moderate to severe recession Nasal flaring Cyanosis Intermittent apnoea Grunting respiration Not feeding
Older children	Temperature <38.5°C Resp rate < 50breaths/min Mild breathlessness No vomiting	Temperature >38.5°C Resp Rate >50 breaths/min Severe difficulty in breathing Nasal flaring Cyanosis Grunting respiration Signs of dehydration

13 GENERAL INVESTIGATIONS FOR CHILDREN IN HOSPITAL

Summary recommendations

1. A full blood count with differential, urea, creatinine and electrolytes and liver enzymes and a blood culture should be done in all severely ill children.

2. A CXR should be performed in children who are hypoxic, have severe illness or who are deteriorating despite treatment.

3. Pulse oximetry should be performed in every child being assessed for admission to hospital with pneumonia

13.1 Are blood tests useful?

A low WBC is common in influenza A in children. (WBC<4 in 8-27%(96;105), WBC <5 in 24%(117)) with a lymphopenia (<1.5 in 41%(120);<1.0 in 40%(105)). In contrast a raised WBC (>15) is found in only 8-12% of cases.(96;105)

In the H5N1 cases reported from Vietnam(55) all 7 children had WBC < 4.0 (mean 2.44) and 6/7 had a lymphopenia <1.0 (mean 0.66). Six of the 7 children died. In contrast only 2 of the 7 children reported from Hong Kong died but they were both leukopenic and lymphopenic. The survivors had a mean WBC of 12.44 and lymphocyte count of 3.11.(54) Four of 5 cases reported from Thailand were lymphopenic.(121)

In Influenza A thrombocytopenia (<100) is found in 5-7%.(105;117) Thrombocytopenia was found in 4 /7 H5N1Vietnamese children.(55)

Liver transaminases are raised in 27% Influenza A(120) and were raised in 6/6 of those measured in Hong Kong H5N1 outbreak(54) and 5 /6 in those measured in Vietnam.(55)

C-Reactive Protein (CRP) is unhelpful in influenza with values <10 in 55%;(117) <20 in 72%(96) and >80 in only 5%.(96)

The CD4/CD8 ratio was inverted in the 2 children and 3 adults in whom it was measured in the Vietnam outbreak (mean 0.7 R 0.59-1.08) Two of these patients survived. (55)

Recommendation

- **A full blood count with differential, urea, creatinine and electrolytes and liver enzymes and a blood culture should be done in all severely ill children**.

13.2 When to do a chest radiograph?

One of the largest studies of the value of chest radiography was undertaken in children aged between 2 months and 5 years with community acquired pneumonia managed as outpatients with time to recovery as the main outcome.(122) Chest radiography did not affect the clinical outcome in these children with acute lower respiratory infection. This lack of effect was independent of clinicians' experience. There are no clinically identifiable subgroups of children within the WHO case definition of pneumonia who are likely to benefit from a chest radiograph. The authors concluded that routine use of chest radiography was not beneficial in ambulatory children aged over 2 months with acute lower respiratory tract infection (LRTI.)

13.2.1 Observer agreement on radiographic signs of pneumonia

Clinicians basing the diagnosis of lower respiratory infections in young infants on radiographic diagnosis should be aware that there is variation in intraobserver and interobserver agreement among radiologists on the radiographic features used for diagnosis. There is also variation in how specific radiological features are used in interpreting the radiograph. A recent study on standardization of CXR interpretation in paediatric pneumonia illustrates the importance of standardised training.(123) The cardinal finding of consolidation for the diagnosis of pneumonia appears to be highly reliable(124) and reasonably specific for bacterial pneumonia (74% of 27 patients with alveolar shadowing had bacterial proven pneumonia)(125) but overall chest radiography is too insensitive to be useful in differentiating between patients with bacterial pneumonia and those whose pneumonia is nonbacterial.(126;127)

In the context of an influenza pandemic a CXR will not distinguish viral pneumonia from viral illness with bacterial superinfection and all children with signs of pneumonia should be treated with antibiotics.

Recommendation

- **A CXR should be performed in children who are hypoxic, have severe illness or who are deteriorating despite treatment**.

13.3 Who should have pulse oximetry?

Oxygen saturation (SaO2) measurements provide a noninvasive estimate of arterial oxygenation. Pulse oximetry will be a key tool in assessment and management and it is essential that it is used correctly and that users are aware of the possibility of artefactually low readings. The oximeter appears easy to use and requires no calibration. However, it requires a pulsatile signal from the patient. It is also highly subject to motion artefacts.
To obtain a reliable reading:

1. The child should be still and quiet
2. When using paediatric wrap around probes, the emitting and receiving diodes need to be carefully opposed
3. A good pulse signal (plethysmograph) should be obtained
4. Once a signal is obtained, the saturation reading should be watched over at least 30 seconds and a value recorded once an adequate stable trace is obtained

Recommendation

- **Pulse oximetry should be performed in every child being assessed for admission to hospital with pneumonia**

14 MICROBIOLOGICAL / VIROLOGICAL INVESTSIGATIONS FOR CHILDREN IN HOSPITAL

Summary Recommendations

(I) Early pandemic recommendations. (UK Alert levels 1-3)

A. Virology – all children

Nasopharyngeal aspirate or nose and throat swabs

B. Bacteriology – children with influenza related pneumonia

- **Blood culture (before antibiotic treatment is commenced)**
- **Sputum samples obtained from older children**
- **Paired serological examination for influenza/other agents.**

(II) Established pandemic recommendations (UK Alert level 4)

A. Virology – not routinely recommended

B. Bacteriology – children with influenza related pneumonia

- **Blood culture (before antibiotic treatment is commenced)**
- **Sputum samples obtained from older children**
- **Paired serological examination for influenza/other agents**

To be read in conjunction with Adult guidelines (section 7).

14.1 Introduction.

As with adults, the extent of virological and microbiological investigations undertaken in children should vary according to the stage of the pandemic and additionally according to the severity of an individual case. It should be noted however, that the clinical features of influenza in children are less characteristic than in adults (see section 1) and the need for special diagnostic tests is therefore greater.(96;128;129) A respiratory panel including influenza A and B, RSV, adenovirus, rhinovirus and parainfluenza 1,2,3 should be standard. The clinical features of human metapneumovirus infection may also be similar but current laboratory tests are limited.(120) Which tests are performed will vary according to the local laboratory but might include rapid antigen tests, immunofluorescence, culture, RT-PCR and serology. See Health Protection Agency guidance for further details.

14.2 Rapid influenza tests.

The utility of such tests has been demonstrated in studies where rapid knowledge of a diagnosis of influenza (within 10 minutes) has been shown to have an impact on clinicians` behaviour with respect to antibiotic use, performance of other tests and admission to hospital.(130;131) It may be imagined that in a pandemic situation such a test could result in earlier use of antiviral therapy and a more rational approach to hospital admission and to prophylaxis of contacts. However, using a molecular reference standard one test was shown to have low sensitivity (44%) but high specificity (97%) suggesting that its role might better be to “rule in” influenza rather than “ruling it out”.(132) Similar conclusions have been made with other commercial rapid tests.(133;134) As a reflection of this rapid antigen tests were positive in only 2 of 6 patients with avian influenza A (H5N1).(55)

14.3 Bacteriology

The need for bacteriological tests in cases of influenza with pneumonia is also logical and the range of pathogens similar to adults(36;103;135-139) except that legionella is extremely unlikely to occur in a previously healthy child and legionella-specific antigen testing is therefore unnecessary. The urinary pneumococcal antigen tests in children may lack both sensitivity and specificity and should be interpreted with care.(140;141) Sputum collection in children is also unreliable although in older children (eg > 12 years) it may be possible and should be handled as indicated for adults.

(I) Recommendations - Early pandemic (UK Alert levels 1-3)

A. Virology – all children

- **Nasopharyngeal aspirate or nose and throat swabs in virus transport medium should be collected from all patients and submitted to the local laboratory. The relevant laboratory should be notified of the suspected diagnosis and there should be close liaison over sample collection, handling and transport.**
- **Rapid testing by direct immunofluorescence or rapid EIA test, virus culture and/or PCR should be undertaken according to local availability and/or referred to an appropriate laboratory. Testing for influenza A and B, RSV, adenovirus, rhinovirus and parainfluenza 1,2,3 should be standard.**
- **If presentation is more than 7 days after onset of illness, an 'acute' serum (2-5 ml clotted blood) should be collected and a 'convalescent' sample (2-5 ml clotted blood) obtained after an interval of not less than 7days. The two sera should be examined serologically for evidence of recent influenza infection.**

B. Bacteriology – children with influenza related pneumonia

- **The following bacteriological tests should be performed:**
    1. **Blood culture (before antibiotic treatment is commenced)**
    2. **Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from older children who:**

       are able to expectorate purulent samples, *and*

       have not received prior antibiotic treatment.

       Sputum samples should be transported rapidly to the laboratory.
    3. **Paired serological examination for influenza/other agents. Acute serum should be collected and a 'convalescent' sample obtained after an interval not less than 7days (both 2-5 ml clotted blood) and the two sera stored for subsequent testing.**

(II) Recommendations - Established pandemic (UK Alert level 4)

A. VIROLOGY – Not routinely recommended.

B. BACTERIOLOGY - children with influenza related pneumonia

Specific investigations should include:

1. **Blood culture, before antibiotic treatment is commenced**
2. **Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from older children who:**

   are able to expectorate purulent samples, *and*

   have not received prior antibiotic treatment.

Sputum samples should be transported rapidly to the laboratory.

3. **Paired serological examination for influenza/other agents. 'Acute' serum should be collected and a 'convalescent' sample obtained after an interval not less than 7 days (both2-5 ml clotted blood) and the two sera stored for subsequent testing.**
4. **In an intubated patient tracheal or endotracheal aspirate samples, should be sent for Gram stain, culture and antimicrobial susceptibility testing as well as viral testing (listed above).**

Summary recommendations

1. **Where possible children should be cohorted using rapid virological tests**
2. **Patients whose oxygen saturation is 92% or less while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92%.**
3. **When children are unable to maintain oral intake supplementary fluids should when possible be given by the enteral route. Intravenous fluids in those with severe pneumonia should be given at 80% basal levels.**
4. **Children can be safely discharged from hospital when**
   - **Child is clearly improving**
   - **is physiologically stable**
   - **can tolerate oral feeds**
   - **respiratory rate is < 40/min (<50/min in infants)**
   - **awake oxygen saturation is >92% in air.**

15.1 Introduction

During an influenza pandemic children are likely to be admitted to hospital because of the severity of their disease and its complications or because of the impact of influenza on preexisting disorders such as cardiac, respiratory or neurological disease. Management of preexisting disorders is outside this guideline.

The most common reason for admission is likely to be

1. Lower respiratory tract disease with either a viral or bacterial or mixed pneumonia.

Other reasons for admission include

2. Severe gastroenteritis
3. Cardiac disease – viral myocarditis
4. Encephalitis

15.2 Triage

Children should be triaged to ward or HDU/PICU after severity assessment (section 12)

15.3 Cohorting

An influenza pandemic is likely to occur in the winter months when other winter viruses responsible for paediatric morbidity and hospital admission are circulating (such as RSV and adenovirus) Particularly in the early stages of a pandemic (UK Alert levels 1-3) it will be important to use rapid virological tests in an attempt to cohort influenza positive and RSV positive infants separately and to separate from other patients. See Health Protection Agency guidance.

15.4 Who needs oxygen?

Hypoxic infants and children may not appear cyanosed. Agitation may be an indication of hypoxia. Patients whose oxygen saturation is less than 92% while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92%. Nasal cannulae do not deliver a FiO2 more than around 40% even at flow rates of 2l/min in infants and 4l/min in older children. Alternative methods of delivering higher concentrations of humidified oxygen such as a head box or a venturi face mask may be necessary. If SaO2 >92% cannot be maintained with FiO2 of 60% then additional support such as CPAP, BiPAP or intubation and ventilation should be considered.

Recommendation : Patients whose oxygen saturation is 92% or less while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92%.

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15.5 Who needs fluids?

Children who are unable to maintain their fluid intake due to breathlessness, fatigue or gastroenteritis need fluid therapy. Where possible additional fluid should be by the enteral route and where nasogastric tube feeds are used, the smallest tube should be passed down the smallest nostril to minimize effects on respiratory status. Severely ill children may need intravenous fluids and if the child is in oxygen therapy intravenous fluids should be given at 80% basal levels (to avoid complications of inappropriate ADH secretion) and serum electrolytes should be monitored.

15.6 What monitoring is necessary?

The monitoring will depend on the child's condition. Severely ill children will need continuous monitoring of heart rate, respiratory rate, oxygen saturation and neurological status. All children on oxygen therapy should have four hourly monitoring including oxygen saturation.

15.7 Who needs physiotherapy?

Chest physiotherapy is not beneficial in previously healthy children with pneumonia. Children with underlying conditions such as cystic fibrosis or neuromuscular weakness will benefit from intensive physiotherapy

15.8 Management of fever and pain

Children with influenza are generally pyrexial and may have some pain, including headache, chest pain, arthralgia , abdominal pain, and earache from associated otitis media . Pleural pain may interfere with depth of breathing and may impair the
ability to cough. Antipyretics and analgesics can be used to keep the child comfortable and to help coughing.

15.9 When can children be safely discharged from hospital?

In a pandemic situation there will be great pressure on hospital beds. All children should be assessed for discharge at least twice daily. Children should not remain in hospital if they are receiving therapy that could be given in the community. In previously healthy children suitable discharge criteria would be:

1. child is clearly improving
2. is physiologically stable
3. can tolerate oral feeds
4. respiratory rate is < 40/min (<50/min in infants)
5. awake oxygen saturation is >92% in air.

15.10 Who needs follow-up?

Most children will make an uneventful recovery and not require follow up. Those with a prolonged illness may be followed up by their general practitioner. Only children with severe disease and/or at high risk of sequelae need hospital follow up. Children with lobar collapse should have a follow up CXR. Follow up CXRs after acute uncomplicated pneumonia are of no value where the patient is symptomatic.(142;143)

Section 16 ANTI-VIRAL THERAPY IN CHILDREN

Summary recommendations.

1. In the setting of a pandemic, children should only be considered for treatment with antivirals if they have <u>all</u> of the following:

- **an acute influenza-like illness (see definition in clinical section)**
- **fever (>38.5^{0}C) *and***
- **been symptomatic for no more than 2 days.**

2. Oseltamivir is the antiviral agent of choice.

3. In children who are severely ill in hospital oseltamivir may be used if the child has been symptomatic for <6 days.

To be read in conjunction with Adult guidelines (section 9).

16.1 Introduction

Five antiviral agents are theoretically available for the therapy of influenza in children: the M2 ion channel inhibitors amantadine and rimantadine (both administered orally and for influenza A only), the neuraminidase inhibitors oseltamivir (administered orally) and zanamavir (administered through an inhaler), and ribavirin (aerosolised).

16.2 Amantadine/rimantadine

The limitations of amantadine and rimantadine are detailed in the adult section, particularly in the context of a pandemic where resistance may already be present.(144) Both have been shown to be effective in the treatment of influenza A in children.(145) Concerns exist about the development of resistance during therapy for both agents.(145;146) A household study showed that treatment and prophylaxis with rimantadine resulted in rapid selection and transmission of drug resistant virus.(147)

16.3 Neuraminidase inhibitors

In a double-blind randomised, placebo controlled study 217 children (1-12 years of age) received oseltamivir with a resultant reduction in the median duration of illness, otitis media and need for antibiotic prescriptions.(70) The most common side effect was vomiting (5.8%). A systematic review and meta-analyses published in 2003 which included studies up to December 2001 included only 2 studies of zanamivir and 1 study of oseltamivir(70) in which these drugs were administered for treatment of influenza A or B in children < 12 years of age.(148) The reduction in the median time to alleviation of symptoms for influenza positive children when compared with placebo was 1.0 day (95% CI 0.4-1.6) for zanamivir and 1.5 days (0.8-2.2) for oseltamivir. Across all ages a 29% (10-44) relative reduction in complications requiring antibiotics was observed for zanamivir and for children specifically a 35% relative reduction was observed for oseltamivir. This was updated through to December 2002 in a Cochrane review.(149) Using its search criteria it identified 2 trials of oseltamivir (1 in healthy children(70) and 1 in children with asthma which was later published(150) and only 1 with zanamivir. Its conclusions were therefore the same with respect to median illness duration in healthy children. A significant reduction in complications (otitis media) was noted for oseltamivir while a trend to benefit was seen for zanamivir.(149) Vomiting was significantly more common among oseltamivir recipients than placebo recipients (15% vs. 9%). The review noted that there may be a difference in efficacy according to serotype with oseltamivir showing a significant reduction in time to resolution for influenza A (34%) but not B (8.5%).(149) With respect to children with asthma there was a trend to reduction in time to freedom from illness for oseltamivir recipients but this did not reach statistical significance. Oseltamivir appeared to result in a more rapid improvement in pulmonary function, and was well tolerated in children with asthma.(149;150) The Cochrane review concluded that oseltamivir was the preferred drug as it has shown a benefit with regard to secondary complications. It also concluded that there was no evidence of

benefit in at-risk children (i.e. asthma). From the perspective of pandemic use however, it should be noted that there was no evidence of harm in this group.

With regard to dosing of oseltamivir, pharmacokinetic studies have suggested that young children clear the drug faster than older children, adolescents and adults and therefore need higher doses.(151;152) The major practical issue with regard to zanamivir is its mode of administration limiting its use to children over the age of 5 years (FDA guidance: over 7 years of age).(149)

The development of resistance to oseltamivir in children may be more common than appreciated and more common than seen in adults. In one study resistance mutations were documented in 18% of 50 children.(152) This has implications for widespread use in a pandemic situation.

One particular issue with regard to paediatric use of oseltamivir is the apparent age limitation on its license (i.e. not for children < 1 year of age). This is particularly important because during epidemic years of all children with influenza it is children < 6 months of age who are most likely to be hospitalised.(153) The basis for this exclusion appears to be that rat data have shown high mortality in infant rats at 7 days of age when given a dose of 1000mg/kg together with high brain levels of oseltamivir, assumed to reflect the immature blood-brain barrier at this age. This is reflected in product literature and an FDA alert although there are no published data. As a result there are few human data in this age group as it was felt that it would be difficult to monitor CNS toxicity in this age group. However, because of a fear of encephalopathy due to influenza in young children Japanese paediatricians have been using it in infants and data on 102 consecutive infants from Japan revealed no encephalopathy or mortality in recipients.(154) A second Japanese report has just been published where 47 children <1year were treated (4mg/kg/day) showing similar efficacy for fever to a group of older children and no serious adverse effects.(155)

There are no data on the effectiveness of Oseltamivir if given more than 2 days from onset of illness. It is likely to be less effective and in particular to have little or no effect after 5-6 days of illness unless the child is immunosuppressed. Giving Oseltamivir to sick hospitalised patients is theoretically likely to decrease their infectivity and so may be useful but there are no data to support this.

16.4 Ribavirin

In a double blind placebo controlled study children hospitalized with influenza who had been ill ≤ 48 hours and who had a temperature ≥ 37.8 degrees C were randomised to receive either ribavirin or placebo. Sixty-two patients (35 in the placebo group, 27 in the ribavirin group) had a confirmed diagnosis of influenza. The time to reduction of temperature ≤ 38.3 degrees C for the ribavirin group was 8.9 hours compared with 22.6 hours for the placebo group (p = 0.04). There were no other differences detected between groups.(156) There have been no further published studies in the 11 years since this report thus ribavirin cannot be recommended at this time.

Recommendations

- **In the setting of a pandemic, children in the community should only be considered for treatment with antivirals if they have all of the following:**
  1. **an acute influenza-like illness (see definition in clinical section)**
  2. **fever (>38.5^{0}C) *and***
  3. **been symptomatic for 2 days or less.**

- **Oseltamivir is the anti-viral agent of choice.**

  Treatment Schedule for children over 1 year.
  Body weight 15kg or under ie <3 years : 30mg every 12 hours;
  Body weight 16-23kg i.e. < 7 years: 45mg every 12 hours;
  Body weight 24kg and over i.e. > 7 years : 75mg every 12 hours .

- **In children who are severely ill in hospital oseltamivir may be used if the child has been symptomatic for <6 days**.

  Oseltamivir may be considered for the treatment of infants < 1 year of age, especially those with severe influenza. This would need to be done following appropriate discussion with the parents highlighting the concerns from the animal data and the relative paucity of human data in this age group.

SECTION 17 ANTIBIOTIC THERAPY IN CHILDREN

Summary recommendations

1. Children a) who are at risk of complications of influenza or b) with disease severe enough to merit hospital admission during an influenza pandemic should be treated with an antibiotic that will provide cover against *S pneumoniae*, *Staph aureus* and *H influenzae*.
2. For children under 12 years co-amoxiclav is the drug of choice. Clarithromycin or cefuroxime should be used in children allergic to penicillin. For children over 12 years doxycycline is an alternative.
3. Oral antibiotics should be given provided oral fluids are tolerated.
4. Children who are severely ill with pneumonia complicating influenza should have a second agent added to the regime (eg clarithromycin or cefuroxime) and the drugs should be given intravenously to ensure high serum and tissue antibiotic levels.

These recommendations are based on the most likely anticipated scenarios but may need to be modified in the light of emerging information in an actual pandemic

17.1 Who should get antibiotics?

Secondary bacterial infections particularly pneumonia and otitis media are common in children with influenza. A case control study during an outbreak of severe pneumococcal pneumonia demonstrated that patients with severe pneumonia were 12 times more likely to have had an influenza like illness and 4 times more likely to have positive influenza serology than controls.(103) Infections with S*taphylococcus aureus* and *H influenzae* are also more common during influenza outbreaks.

A randomized controlled trial of antibiotics in 85 children aged 4 months to 11 years presenting with influenza like symptoms during an influenza epidemic showed a decreased incidence of pneumonia in the antibiotic treated group. (2.4% vs 16.3% p=0.031) (157) There was no change in duration of fever or incidence of acute otitis media. Interestingly only 1/7 of the cases of pneumonia in the placebo group was thought to be bacterial. The authors postulated that as bacterial proteases facilitate propogation and pathogenesis of influenza in a mouse model that decreasing bacterial numbers and hence protease levels in the lung may decrease viral pneumonia.

Another randomized trial of cephalosporins vs macrolides in 365 Japanese children with influenza like symptoms showed faster alleviation of fever (3.8+/-1.4 vs 4.3+/-1.4 days p=0.006) in the macrolide group and a decrease in number with CXR evidence of pneumonia (2 vs 13 cases p=0.002 ; 14/15 had interstitial changes).(158) The authors postulate that antinflammatory effects of macrolides may be responsible.

Recommendation

- **Children a) who are at risk of complications of influenza and b) Children with disease severe enough to merit hospital admission during an influenza pandemic should be treated with an antibiotic that will provide cover against *S pneumoniae*, *Staph aureus* and *H influenzae*.**

17.2 Which antibiotic?

The antibiotics of choice must cover the likely pathogens as above. Data from HPA 2004 indicate that in the UK <2.5% of *S pneumoniae* strains are penicillin resistant but 14.1% are erythromycin (macrolide) resistant. Similarly 14% of methicillin susceptible S*taph aureus* were erythromycin resistant. Only 76% of *H. influenzae* are susceptible to amoxicillin but >94% are susceptible to co-amoxiclav. There may be local variations to this data and clinicians should consult with their local microbiology department.

Recommendation

- **For children under 12 years co-amoxiclav is the drug of choice. Clarithromycin or cefuroxime should be used in children allergic to penicillin. For children over 12 years doxycycline is an alternative**.

17.3 What if the pathogen is known?

Rarely a blood culture or pleural tap will provide the pathogen. The antibiotics should then be specifically tailored eg benzyl penicillin iv or oral amoxicillin for *S. pneumoniae* and flucloxacillin or clindamycin for *S. aureus.*

17.4 Oral or intravenous?

A recent randomized controlled trial of the equivalence of oral amoxicillin vs iv benzylpenicillin in 252 children admitted to hospital with community acquired pneumonia showed no difference in duration of illness or complications.(159) Oral antibiotics should be given provided oral fluids are tolerated.

17.5 Antibiotic choice for severe or complicated pneumonia?

Children who are severely ill with pneumonia complicating influenza should have a second agent which provides good cover for gram positive organisms added to the regime (eg clarithromycin or cefuroxime) and the drugs should be given intravenously to ensure high serum and tissue antibiotic levels.

CHAPTER iii

Summary and synopses of recommendations

18 PRIMARY CARE SUMMARY

18.1 Scope and purpose of this section

18.1.1 This section contains advice and guidance for health professionals in primary care, in the event that the Department of Health has declared UK pandemic alert level 2 (indicating that cases of pandemic influenza have been identified in the UK, against a background of person to person transmission of the pandemic strain in the UK or other countries).

18.1.2 The advice in this section summarises the key elements found in the earlier Sections of this document. It is based on the best evidence available from previous pandemic and interpandemic periods. Thus the guidance may evolve as clinico-pathological information on the eventual pandemic virus emerges. Therefore, once an influenza pandemic is underway, users are strongly urged to ensure that they refer to the most up-to-date version of these guidelines (from web-based access points).

18.1.3 The advice is specific to a pandemic situation and does not apply to the management of seasonal increases in influenza, community acquired pneumonia, lower respiratory tract infections or exacerbations of COPD.

18.2 The impact of an influenza pandemic on primary care (refer to Section 2)

18.2.1 Estimates of case-numbers and excess deaths in a pandemic are based on the average attack rates and case-fatality rates calculated from the documented influenza pandemics which have occurred since 1900. They suggest a likely population attack rate of 25%, with a case-fatality rate of 0.37%, occurring in one, two or three annual waves of cases, with an individual wave lasting around 15 weeks.

18.2.2 This suggests that for a population of 1000 patients, 25 extra GP consultations and up to one excess death would be expected in the pandemic. A population of 100,000 might expect 2500 excess GP consultations, with 90 excess deaths (see Tables 2.2 and 2.3)

18.2.3 The numbers of consultations for influenza may be accompanied by a marked increase in consultations for related problems, including anxiety about symptoms which may or may not be caused by influenza, but reflect the concerns of patients, for their own health, for the health of household members and contacts, and concerning the availability of antiviral medication.

18.2.4 Information for patients will be available through a major campaign to provide public information through the media, and through the use of pre-prepared information algorithms for NHS Direct. Written material will be made available for use by patients and the public. It is hoped that this will reduce the burden of non-clinical work which falls on General Practice staff.

18.2.5 The clinical features of pandemic influenza (refer to Sections 3 and 11)

18.3.1 There is no reliable diagnostic feature of influenza.

18.3.2 The syndrome of influenza-like illness (ILI) described in Box 18.1, is strongly predictive of laboratory-confirmed influenza, especially when influenza is circulating in the community, as would be the case at UK Alert Levels 2 or more (see Appendix 1). The features of ILI are less frequently seen in children and younger adults but are still predictive of influenza, with a lower probability.

Box 18.1: **Clinical Case Definition (October 2005):**

The presence of fever and new (or, in those with chronic lung disease, worsening) cough of acute onset in the context of influenza circulating in the community.

(Important note - This definition may be modified once a pandemic occurs.)

18.3.3 While seasonal cases of influenza tend to present in children and the elderly, the age-range affects by pandemic influenza is likely to be broader, and different from that of seasonal influenza. Infants, small children and otherwise healthy adults may be seriously affected.

18.3.4 The range of clinical features in uncomplicated influenza is given in Section 3.2, Box 3.2. Features in a pandemic may differ from those seen in regular interpandemic (seasonal) influenza cases.

18.3.5 Tests for the diagnosis of influenza are only justified when the proportion of cases of influenza is low (14-20%) compared with other probable viral causes of ILI. (refer to Section 7.1) Therefore, early in a pandemic (UK Alert Levels 1,2 and 3) nasopharyngeal, or nose and throat, swabs in virus transport medium should be collected from all patients, where possible, and submitted to the local laboratory.

18.3.6 Once a pandemic is established (UK Alert Level 4), microbiological investigations are not recommended.

18.4 Severe and complicated influenza (refer to Sections 3.3 and 11.2)

18.4.1 Co-existing conditions such as asthma, COPD, cardiac failure, atrial fibrillation, coronary heart disease, diabetes mellitus, and chronic neurological conditions such as multiple sclerosis and epilepsy may be worsened by influenza infection.

18.4.2 The most common specific complications associated with influenza infection in adults are respiratory complications - acute bronchitis or influenza-related pneumonia. Other complications are listed in Table 3.1. Otitis media is the most common bacterial superinfection of influenza in children (see Table 11.2).

18.4.3 Influenza-related pneumonia can be caused primarily by influenza virus alone or by secondary bacterial infection. In addition to the usual well-recognised respiratory pathogens (predominantly *Streptococcus pneumoniae* and *Haemophilus influenzae)*, *Staphylococcus aureus* is a common cause of influenza-related pneumonia which can be severe. *Staph aureus* does not respond to treatment with amoxicillin and also has a significant rate of resistance to macrolide antibiotics (eg. erythromycin and clarithromycin).

18.5 Management of suspected pandemic influenza cases: early preparations and general measures (refer to Sections 2.7, 4 and 12)

18.5.1 **Triage.** A significantly increased demand for advice and consultation should be anticipated. Practices may make a number of arrangements to deal with this, including:

- Telephone triage and advice, which may be nurse-led
- Triage and advice immediately after reception at the practice
- Nurse-led prescribing of antiviral medication or antibiotics, according to patient group directives (PGDs)
- Making arrangements to provide domiciliary services for some patients who are unwell at home, but who may be able to avoid hospital admission
- Possibly making arrangements for patient care in intermediate-level community facilities, again to avoid hospital admission

18.5.2 Patients with non-ILIs who would normally self-medicate should be advised not to seek medical care where possible. PCTs and practices should formulate triage arrangements in advance of a pandemic to allow GPs to predominantly assess high risk patients and those developing complications.

18.5.3 **Patients at increased risk of severe disease or hospital admission.** These will be broadly the same patients as those who should receive routine annual influenza vaccination (see Appendix 2). Similarly, children with underlying respiratory or cardiac disease, immune compromise or who are non-ambulant are more likely to be severely affected. These patients should be promptly reassessed if the illness is getting worse to consider antibiotic treatment or hospital referral.

18.5.2 Pneumococcal vaccine. Patients over 65 years of age should already have been offered vaccination against *Streptococcus pneumoniae*, those who have not been vaccinated should be encouraged to have the vaccine before an influenza pandemic becomes established.

18.5.3 General advice to patients. Whether or not a patient has been prescribed antiviral drugs or antibiotics, they should be advised to self-manage their condition in the following ways:

- Stay at home and avoid contact with others until the feverish symptoms or elevated temperature have resolved
- Treat feverish symptoms, headache and myalgia with paracetamol, ibuprofen or (for patients over 16 years) aspirin
- Rest as much as possible while acute symptoms persist
- Drink plenty of fluids
- Avoid smoking
- Consider steam inhalation, short course of topical decongestants, throat lozenges.

18.5.4 The management of children in the community is summarised in Appendix 5.

18.6 Antiviral treatment (refer to Sections 9 &16)

18.6.1 The antiviral treatment of choice is oseltamivir (Tamiflu ™). This is given as a five-day course of oral tablets; 75mg twice daily for adults. Liquid suspension is available for children from the age of one year upwards.

Table 18.1: **Adult and child dosages of oseltamivir.**

Child aged >1yr; body weight 15kg or lower	30mg 12-hourly
15-23kg	45mg 12-hourly
24-40kg	60mg 12-hourly
Adult and child >40kg	75mg 12-hourly

(Dose to be reduced by 50% if creatinine clearance is less than 30ml/minute)

From clinical trial data accrued to date and based on seasonal, interpandemic influenza, the *anticipated* positive effect of antivirals in a pandemic will be:

(a) reduction of illness duration by 24 hours, and therefore more rapid mobilisation of affected individuals including essential workers
(b) a possible reduction in hospitalisation of infected individuals
(c) a reduction of subsequent antibiotic use by infected individuals

The evidence accrued to date does not suggest there will be a reduction of overall mortality.

18.6.2 Who should receive antiviral drugs? Ideally, antiviral treatment should be offered to every patient over the age of one year who

a) has an acute influenza-like illness
b) fever (38° C in adults, or 38.5 °C in children) *and*
c) presents within 48 hours of the onset of symptoms.

Note: Patients who are unable to mount an adequate febrile response eg. the immunocompromised or very elderly, make still be eligible for antiviral treatment despite the lack of documented fever.

18.6.3 There is no evidence of benefit for antiviral therapy commenced more than 48 hours after the onset of ILI in otherwise healthy patients. Immunosuppressed patients, including those on long-term corticosteroid therapy, may suffer more prolonged viraemia, and could possibly benefit from antiviral therapy commenced later than 48 hours after the onset of ILI. However, there is no evidence to support this hypothetical situation.

18.6.4 **Delivery of antivirals.** The drug will be delivered to PCTs via specific National distribution arrangements, and will be available through these arrangements to pharmacies or GP surgeries. PCTs are encouraged to plan for the delivery of antivirals to the large numbers of previously healthy persons with an ILI via community health professionals, while GPs should focus on those persons at high risk of complications (Appendix 2).

18.6.5 In the event of a shortage of antiviral drugs, the Department of Health will issue advice on the priority groups who should receive treatment. This will depend on evidence from previous pandemics, the epidemiological behaviour of the current pandemic and the real-time modelling of the effectiveness of antiviral treatment for various population groups. Information will be available through NHS websites, fax cascades and public information systems, including NHS Direct.

18.6.6 **Adverse effects of antiviral drugs.** The commonest adverse effect of oseltamivir is nausea. This can be managed with mild anti-emetic medication. Other side-effects are listed in Table 9.4.

18.7 Antibiotic treatment (refer to Sections 10.4 & 17)

18.7.1 Who should receive antibiotic treatment?

a) Patients in recognised high risk groups for severe and complicated influenza are at high risk of secondary bacterial infection (see Appendix 2). To reduce the burden on primary care of repeat consultations and potentially minimise influenza-related complications, it is recommended that these patients are offered prescriptions for 'prophylactic' antibiotics at their first consultation with clear instructions that the antibiotics should be used if the illness is not starting to settle after 24 hours or if there is worsening of symptoms.

b) **Patients who develop influenza-related pneumonia and acute bacterial otitis media.**

c) **Patients with significant worsening of symptoms** particularly recrudescent fever or increasing breathlessness.

18.7.2 Previously well adults with uncomplicated influenza or acute bronchitis complicating influenza, in the absence of pneumonia, do not routinely require antibiotics.

18.7.3 **Co-amoxiclav** is the preferred antibiotic for all ages. (Adult dose: 625 mg tds) In patients over 12 years of age, doxycycline is an alternative (Adult dose 200mg stat then 100mg po). See Appendix 7 for paediatric doses. (This empirical antibiotic regimen provides cover for *Staph aureus* in addition to the 'usual' respiratory pathogens.)

18.7.4 Most patients can de adequately treated with a week's course of antibiotic.

18.8 When to refer patients to hospital care (refer to Sections 5 & 12.4)

18.8.1 Patients with uncomplicated influenza infection usually do not require hospital referral.

18.8.2 Adults who experience a clinical deterioration of pre-existing medical problems (eg COPD) due to influenza infection should be managed according to recommended best practice for the medical condition in question.

18.8.3 In adults with influenza-related pneumonia clinically, hospital referral and assessment should be considered for patients with CRB-65 score of 1 *or 2.(*see Box 18.2)

18.8.4 Urgent hospital referral is recommended for adults with influenza-related pneumona and either a) bilateral chest signs of pneumonia or b) CRB-65 score of 3 or more.

Box 18.2: CRB-65 score - Severity assessment used to determine the management of influenza-related pneumonia in the community

Score 1 point for each feature present:
- **C**onfusion (Mental Test Score of ≤ 8, or new disorientation in person, place or time.)
- **R**espiratory rate ≥ 30/min
- **B**lood pressure (SBP < 90mmHg or DBP ≤ 60mmHg)
- Age ≥ **65** years

CRB-65 score	Recommended action
0	Likely suitable for home treatment
1 or 2	Consider hospital referral
3 or 4	Urgent hospital referral

18.8.5 Children who are severely ill, as indicated by signs of respiratory distress, cyanosis, severe dehydration, altered conscious level, complicated or prolonged seizure or sepsis, should be referred for assessment for admission (see Appendix 5).

19 MANAGEMENT OF ADULTS IN HOSPITALS- SYNOPSIS OF RECOMMENDATIONS

19.1 Scope and Purpose

19.1.1 This document is intended for use in the UK in event that the World Health Organisation declares that an influenza pandemic has started,[1] and the Department of Health in England (UK-wide lead agency on pandemic influenza, including the devolved administrations) has declared UK Pandemic Alert Level 2 (cases of pandemic influenza identified within the UK).

19.1.2 **These guidelines are not relevant for the management of patients affected by seasonal/ interpandemic influenza, lower respiratory tract infections, community acquired pneumonia or exacerbations of chronic obstructive pulmonary disease (COPD).**

19.1.3 Once an influenza pandemic is underway, users are strongly urged to ensure that they refer to the most up-to-date version of these guidelines (from web-based access points).

19.2 Severity assessment in hospital (see Appendix 4)

19.2.1 Patients with uncomplicated influenza infection would be expected to make a full recovery and do not require hospital care.

19.2.2 In uncomplicated infection, the illness usually resolves in 7 days although cough, malaise and lassitude may persist for weeks.

19.2.3 Patients with worsening of pre-existing comorbid medical conditions should be managed according to best practice for that condition with reference to published disease-specific guidelines, if available eg. COPD NICE guidelines.

(A) Influenza-related pneumonia

19.2.4 In hospital, patients with influenza-related pneumonia and who have a CURB-65 score of 3, 4 or 5 (see BOX 19.1) are at high risk of death and should be managed as having severe pneumonia.

19.2.5 Patients with bilateral lung infiltrates on chest radiography consistent with primary viral pneumonia should be managed as having severe pneumonia regardless of CURB-65 score.

19.2.6 Patients who have a CURB-65 score of 2 are at increased risk of death. They should be considered for short stay inpatient treatment or hospital supervised outpatient treatment. This decision is a matter of clinical judgment.

19.2.7 Patients who have a CURB-65 score of 0 or 1 are at low risk of death. They can be treated as having non-severe pneumonia and may be suitable for home treatment.

BOX 19.1: CURB-65 score

Score 1 point for each feature present:
- **C**onfusion (Mental Test Score of ≤ 8, or new disorientation in person, place or time)
- **U**rea > 7 mmol/l
- **R**espiratory rate ≥ 30/min
- **B**lood pressure (SBP < 90mmHg or DBP ≤ 60mmHg)
- Age ≥ **65** years

(B) High Dependency or Intensive Care Unit transfer

19.2.7 Patients with primary viral pneumonia *or* a CURB-65 score of 4 or 5 should be considered for HDU/ICU transfer.

19.2.8 General indications for HDU/ICU transfer include:
- persisting hypoxia with PaO_2 <8Kpa despite maximal oxygen administration
- progressive hypercarbia
- severe acidosis (pH<7.26)
- septic shock

19.2.9 Patients with influenza admitted to Intensive Care Unit should be managed by specialists with appropriate training in Intensive Care, Respiratory Medicine and Infectious Diseases.

19.3 General Investigations (see Appendix 3)

19.3.1 The following investigations are recommended in patients referred to hospital:

Test	Who this applies to
Full blood count	All patients
Urea and electrolytes	All patients
Liver function tests	All patients
Chest x-ray	All patients
Pulse oximetry	All patients. If <92% on air, then arterial blood gases.
ECG	Patients with cardiac and respiratory complications or comorbid illnesses.
C-reactive protein	If influenza-related pneumonia is suspected

19.3.2 In those patients who are subsequently followed up in a hospital outpatient clinic or by a general practitioner a repeat chest X-ray should be obtained at around 6 weeks if respiratory symptoms or signs persist or where there is a higher risk of underlying malignancy (especially smokers and those over 50 years of age).

19.3.3 Further investigations including a CT thoracic scan and bronchoscopy should be considered if the chest X-ray remains abnormal at follow up.

19.4 Microbiological investigations (see Appendix 3)

(A) Early in a pandemic (UK Alert Levels 1, 2 and 3)

19.4.1 ALL PATIENTS should have virological tests:

- **Nose and throat swabs** in virus transport medium.
- If presentation is more than 7 days after onset of illness, an 'acute' serum (5-10mLs clotted blood) should be collected and a 'convalescent' sample (5-10mLs clotted blood) obtained after an interval of not less than 7days.

19.4.2 PATIENTS WITH INFLUENZA-RELATED PNEUMONIA should also have the following bacteriological tests:

- **Blood culture** (preferably before antibiotic treatment is commenced)
- **Pneumococcal urine antigen** (20 mls urine sample)
- **Legionella urine antigen** (20 mls urine sample)
- **Sputum Gram stain, culture** and antimicrobial susceptibility tests on samples obtained from patients who:
  - i. are able to expectorate purulent samples, *and*
  - ii. have not received prior antibiotic treatment.
- **Paired serological examination for influenza/other agents**. Acute serum should be collected and a 'convalescent' sample obtained after an interval not less than 7days (both 5-10mLs clotted blood).

(B) Once a pandemic is established (UK Alert Level 4)

19.4.3 Virological tests are not routinely recommended.

19.4.4 PATIENTS WITH INFLUENZA-RELATED PNEUMONIA should have bacteriological tests in accordance to the severity of illness.

a. Non-severe pneumonia (CURB-65 Score 0, 1 or 2)

- No routine testing.
- In patients who do not respond to empirical antibiotic therapy, sputum samples should be sent for Gram stain culture and antimicrobial susceptibility tests.

b. Severe pneumonia (CURB-65 Score 3, 4 or 5, or bilateral CXR changes)

- **Blood culture**, preferably before antibiotic treatment is commenced
- **Pneumococcal urine antigen** (20mls urine)
- **Sputum Gram stain, culture** and antimicrobial susceptibility tests on samples obtained from patients who are able to expectorate purulent samples, *and* have not received prior antibiotic treatment.
- **Paired serological examination** for influenza/other agents. 'Acute' serum should be collected and a 'convalescent' sample obtained after an interval not less than 7 days (both 5-10mLs clotted blood).
- **Tracheal or endotracheal aspirate samples**, if available, should be sent for Gram stain, culture and antimicrobial susceptibility testing.

19.5 General Management (refer to Section 6)

(A) Initial management

19.5.1 Hypoxic patients should receive appropriate oxygen therapy with monitoring of oxygen saturations and inspired oxygen concentration with the aim to maintain $PaO_2 \geq 8$ Kpa and $SaO_2 \geq 92\%$. High concentrations of oxygen can safely be given in uncomplicated pneumonia.

19.5.2 Oxygen therapy in patients with pre-existing chronic obstructive pulmonary disease complicated by ventilatory failure should be guided by repeated arterial blood gas measurements. Non invasive ventilation may be helpful.

19.5.3 Patients should be assessed for cardiac complications and also volume depletion and their need for additional intravenous fluids.

19.5.4 Nutritional support should be given in severe or prolonged illness.

(B) Monitoring in hospital

19.5.5 Temperature, respiratory rate, pulse, blood pressure, mental status, oxygen saturation and inspired oxygen concentration should be monitored and recorded initially at least twice daily and more frequently in those with severe illness or requiring regular oxygen therapy. An Early Warning Score system is a convenient way to perform this.

19.5.6 In patients who are not progressing satisfactorily a full clinical reassessment and a repeat chest radiograph are recommended.

(C) Discharge and follow up

19.5.7 Patients should be reviewed 24 hours prior to discharge home. Those with more than 2 of the following unstable clinical factors should consider remaining in hospital:

- temperature > 37.8^{o}C
- heart rate > 100/min
- respiratory rate > 24/min
- systolic blood pressure <90mmHg
- oxygen saturation < 90%
- inability to maintain oral intake and abnormal mental status.

19.5.8 Follow up clinical review should be considered for all patients who suffered significant complications or who had significant worsening of their underlying disease, either with their general practitioner or in a hospital clinic.

19.5.9 At discharge or at follow up, patients should be offered access to information about their illness, take home medication and any follow up arrangements.

19.5.10 It is the responsibility of the hospital team to arrange the follow up plan with the patient and the general practitioner.

19.6 Use of antivirals (see Appendix 4)

19.6.1 Individuals should only be considered for treatment with antivirals (neuraminidase inhibitors) if they have all of the following:

- an acute influenza-like illness
- fever (>38^{0}C) *and*
- been symptomatic for 2 days or less.

19.6.2 Treatment Schedule: Adults - Oseltamivir 75mg every 12 hours for 5 days.
(Dose to be reduced by 50% if creatinine clearance is less than 30ml/minute)

19.6.3 Patients who are unable to mount an adequate febrile response eg. the immunocompromised or very elderly, may still be eligible for antiviral treatment despite lack of documented fever.

19.6.4 Hospitalised patients who are severely ill, particularly if also immunocompromised, may benefit from antiviral treatment started more than 48 hours from disease onset, although there is no evidence to demonstrate benefit, or lack of, in such circumstances.

19.7 Antibiotic Management (see Appendix 4)

(A) Bronchial complications without influenza-related pneumonia

19.7.1 Previously well adults with acute bronchitis complicating influenza, in the absence of pneumonia, do not routinely require antibiotics.

19.7.2 Antibiotics should be considered in those previously well adults who develop worsening symptoms (recrudescent fever or increasing dyspnoea) and have persisting purulent sputum.

19.7.3 Patients at risk of complications or superinfection should be considered for antibiotics in the presence of lower respiratory features. These include patients who are within the group currently recommended for influenza vaccination (see Appendix 2).

19.7.4 Patients with chronic lung disease, including COPD, should receive antibiotics in the presence of increased purulent sputum.

19.7.5 Most patients can be adequately treated with oral antibiotics.

19.7.6 The preferred choice includes co-amoxiclav or a tetracycline.

19.7.7 A macrolide such as clarithromycin (or erythromycin) or a fluoroquinolone active against *S pneumoniae and S aureus is* an alternative choice in certain circumstances.

(B) Non-severe influenza-related pneumonia

19.7.8 Most patients can be adequately treated with oral antibiotics.

19.7.9 Oral therapy with co-amoxiclav or a tetracycline is preferred.

19.7.10 When oral therapy is contra-indicated, recommended parenteral choices include intravenous co-amoxiclav, or a second or third generation cephalosporin (cefuroxime or cefotaxime).

19.7.11 A macrolide (erythromycin or clarithromycin) or a fluoroquinolone active against *S pneumoniae and Staphylococcus aureus* is an alternative regimen for those intolerant of penicillins or where there are local concerns over *C difficile* associated diarrhoea. Currently levofloxacin and moxifloxacin are the only recommended fluoroquinolones licenced in the UK.

(C) Severe influenza-related pneumonia

19.7.12 Patients with severe pneumonia should be treated immediately after diagnosis with parenteral antibiotics.

19.7.13 An intravenous combination of a broad spectrum beta-lactamase stable antibiotic such co-amoxiclav or a second (eg cefuroxime) or third (eg cefotaxime) generation cephalosporin together with a macrolide (clarithromycin or erythromycin) is preferred.

19.7.14 An alternative regimen includes a fluoroquinolone with enhanced activity against pneumococci together with a broad spectrum β-lactamase stable antibiotic or a macrolide. Currently levofloxacin is the only such fluoroquinolone licenced in the UK.

(D) Route and duration of antibiotic

19.7.15 Patients treated initially with parenteral antibiotics should be transferred to an oral regimen as soon as clinical improvement occurs and the temperature has been normal for 24 hours, providing there is no contra-indication to the oral route.

19.7.16 For most patients admitted to hospital with non severe and uncomplicated pneumonia, 7 days of appropriate antibiotics is recommended.

19.7.17 For those with severe, microbiologically undefined pneumonia, 10 days treatment is proposed. This should be extended to 14 to 21 days where *Staph aureus* or Gram negative enteric bacilli pneumonia is suspected or confirmed.

(E) Failure of empirical antibiotics

19.7.18 For those with non-severe pneumonia in hospital on combination therapy, changing to a fluoroquinolone with effective pneumococcal and staphylococcal cover is an option.

19.7.19 Adding further antibiotics effective against MRSA is an option for those with severe pneumonia not responding to combination antibiotic therapy.

20 MANAGEMENT OF CHILDREN – SYNOPSIS OF RECOMMENDATIONS

20.1 Scope and Purpose

20.1.1 This document is intended for use in the UK in event that the World Health Organisation declares that an influenza pandemic has started,[1] and the Department of Health in England (UK-wide lead agency on pandemic influenza, including the devolved administrations) has declared UK Pandemic Alert Level 2 (cases of pandemic influenza identified within the UK).

20.1.2 **These guidelines are not relevant for the management of patients affected by seasonal/ interpandemic influenza, lower respiratory tract infections or community acquired pneumonia.**

20.1.3 Once an influenza pandemic is underway, users are strongly urged to ensure that they refer to the most up-to-date version of these guidelines (from web-based access points).

20.1 Clinical features in children

20.1.1 The commonest presenting features of influenza during an epidemic are fever, cough and rhinorrhoea and, in older children, pharyngitis and headache. The clinical features may differ during a pandemic.

20.1.2 Children with underlying respiratory or cardiac disease, immune compromise or who are non-ambulant are more likely to be severely affected.

20.1.3 The younger the child the more likely hospital admission will be needed.

20.1.4 The severe and life-threatening complications of influenza are likely to be

- Bacterial pneumonia
- ARDS
- Encephalopathy or encephalitis presenting as seizures or altered mental status.

20.3 Severity assessment in children (See Appendix 5)

20.3.1 Coughs and mild fevers --- Treated at home by parents with antipyretics and fluids
(Note: aspirin should not be used in children)

20.3.2 High fever (>38.5°C) and cough or influenza like symptoms --- Advice from community Health professional. If there are no features which put them at high risk of complications they should be treated with oseltamivir, and given advice on antipyretics and fluids. Children aged <1 year and those at risk of complications (Table 12.1) should be seen by a GP.

20.3.3 High fever (>38.5°C) and cough or influenza like symptoms PLUS at risk group ----- Seen by GP/A & E consultation.

Cough and fever (or influenza like illness) and temperature >38.5°C AND
Children with chronic disease (see Table 12.1)
Or one of below features

- Breathing difficulties
- Severe earache
- Vomiting > 24 hours
- Drowsiness

These children may be considered at increased risk of complications and an antibiotic given as well as oseltamivir (in those >1 year of age) and advice on antipyretics and fluids. Children aged <1 year with none of the above features should be treated with antipyretics and fluids with a low threshold for antibiotics if they become more unwell.

20.3.4 When to refer for admission?

Indicators are:

- Signs of respiratory distress.
  Markedly raised respiratory rate

grunting
□ecognize□ls recession
breathlessness with chest signs

- Cyanosis
- Severe dehydration
- Altered conscious level
- Complicated or prolonged seizure
- Signs of septicaemia – extreme pallor, hypotension, floppy infant

20.3.5 Assessment in hospital. Triage for admission to wards, HDU or PICU. Most children admitted to hospital are likely to need oxygen therapy and/or intravenous support as well as antibiotics and oseltamivir.

a) Indications for transfer to High Dependency or Intensive Care

- the child is failing to maintain a SaO2 of >92% in FiO2 of >60%
- the child is shocked
- there is severe respiratory distress and a raised PaCO2 (> 6.5 Kpa)
- there is a rising respiratory rate and pulse rate with clinical evidence of severe respiratory distress with or without a raised PaCO2
- there is recurrent apnoea or slow irregular breathing
- there is evidence of encephalopathy

20.3.6 What to do when there are no PICU beds available?
Children will have to be triaged on the basis of the severity of their disease a) acute and b) co-existing and the likelihood of their achieving full recovery.

20.4 General investigations for children in hospital

20.4.1 A full blood count with differential, urea, creatinine and electrolytes, and liver enzymes and a blood culture should be done in all severely ill children.

20.4.2 A CXR should be performed in children who are hypoxic, have severe illness or who are deteriorating despite treatment.

20.4.3 Pulse oximetry should be performed in every child being assessed for admission to hospital with pneumonia.

20.5 Microbiological/virological investigations in hospital

20.5.1 Early pandemic recommendations. (UK Alert levels 1-3)

A. Virology – all children
   - Nasopharyngeal aspirate or nose and throat swabs

B. Bacteriology – children with influenza related pneumonia
   - Blood culture (before antibiotic treatment is commenced)
   - Sputum samples obtained from older children
   - Paired serological examination for influenza/other agents.

20.5.2 Established pandemic recommendations (UK Alert level 4)

A. Virology – not routinely recommended
B. Bacteriology – children with influenza related pneumonia
   - Blood culture (before antibiotic treatment is commenced)
   - Sputum samples obtained from older children

- Paired serological examination for influenza/other agents

20.6 General management of children admitted to hospital

20.6.1 Where possible children should be cohorted using rapid virological tests.

20.6.2 Patients whose oxygen saturation is 92% or less while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92%.

20.6.3 When children are unable to maintain oral intake supplementary fluids should when possible be given by the enteral route. Intravenous fluids in those with severe pneumonia should be given at 80% basal levels.

20.6.4 Children can be safely discharged from hospital when

7. Child is clearly improving
8. is physiologically stable
9. can tolerate oral feeds
10. respiratory rate is < 40/min (<50/min in infants)
11. awake oxygen saturation is >92% in air.

20.7 Anti-viral therapy in children

20.7.1 In the setting of a pandemic, children should only be considered for treatment with antivirals if they have all of the following:

- an acute influenza-like illness (see definition in clinical section)
- fever (>38.5^{0}C) *and*
- been symptomatic for 2 days or less

20.7.2 Oseltamivir is the anti-viral agent of choice.

20.7.3 In children who are severely ill in hospital oseltamivir may be used if the child has been symptomatic for <6 days (but there is no evidence to demonstrate benefit or lack of it in such circumstances)

20.8 Antibiotic therapy in children

20.8.1 Children a) who are at risk of complications of influenza or b) with disease severe enough to merit hospital admission during an influenza pandemic should be treated with an antibiotic that will provide cover against *S pneumoniae*, *Staph aureus* and *H influenzae.*

20.8.2 For children under 12 years co-amoxiclav is the drug of choice. Clarithromycin or cefuroxime should be used in children allergic to penicillin. For children over 12 years doxycycline is an alternative.

20.8.3 Oral antibiotics should be given provided oral fluids are tolerated.

20.8.4 Children who are severely ill with pneumonia complicating influenza should have a second agent added to the regime (eg clarithromycin or cefuroxime) and the drugs should be given intravenously to ensure high serum and tissue antibiotic levels.

21 ACKNOWLEDGEMENTS, COMMITTEE MEMBERS AND AFFILIATIONS

21.1 Acknowledgements

Many people have helped with the preparation of these guidelines and our thanks go to them. In particular we would like to thank Dr Kevin Mortimer for expertly coordinating the reference database; Dr David Boldy, Chairman of the British Thoracic Society Standards of Care Committee; Mrs Sheila Edwards, Chief Executive of the British Thoracic Society for support and advice; Dr Claire Holt, Dr Minghzi Zhang and Dr Eri Papanikou for their help.

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Appendix 1

International Phases and their significance for the UK

International phases		Significance for UK
Interpandemic Period		
1	No new influenza virus subtypes detected in humans	
2	Animal influenza virus subtype poses substantial risk	UK not affected UK has strong travel/trade connections with affected country UK affected
Pandemic Alert Period		
3	Human infection(s) with a new subtype, but no new human to human spread to a close contact	UK not affected UK has strong travel/trade connections with affected country UK affected
4	Small cluster(s) with limited human-to human transmission but spread is highly localised, suggesting that the virus is not well adapted to humans	
5	Large cluster(s) but human-to-human spread still localised, suggesting that the virus is becoming increasingly better adapted to humans	
Pandemic Period		
6	Increased and sustained transmission in general population	**Alert level** **1** Virus/cases only outside the UK **2** Virus isolated in the UK **3** Outbreak(s) in the UK **4** Widespread activity across the UK
Post Pandemic Period		
	Return to interpandemic period	

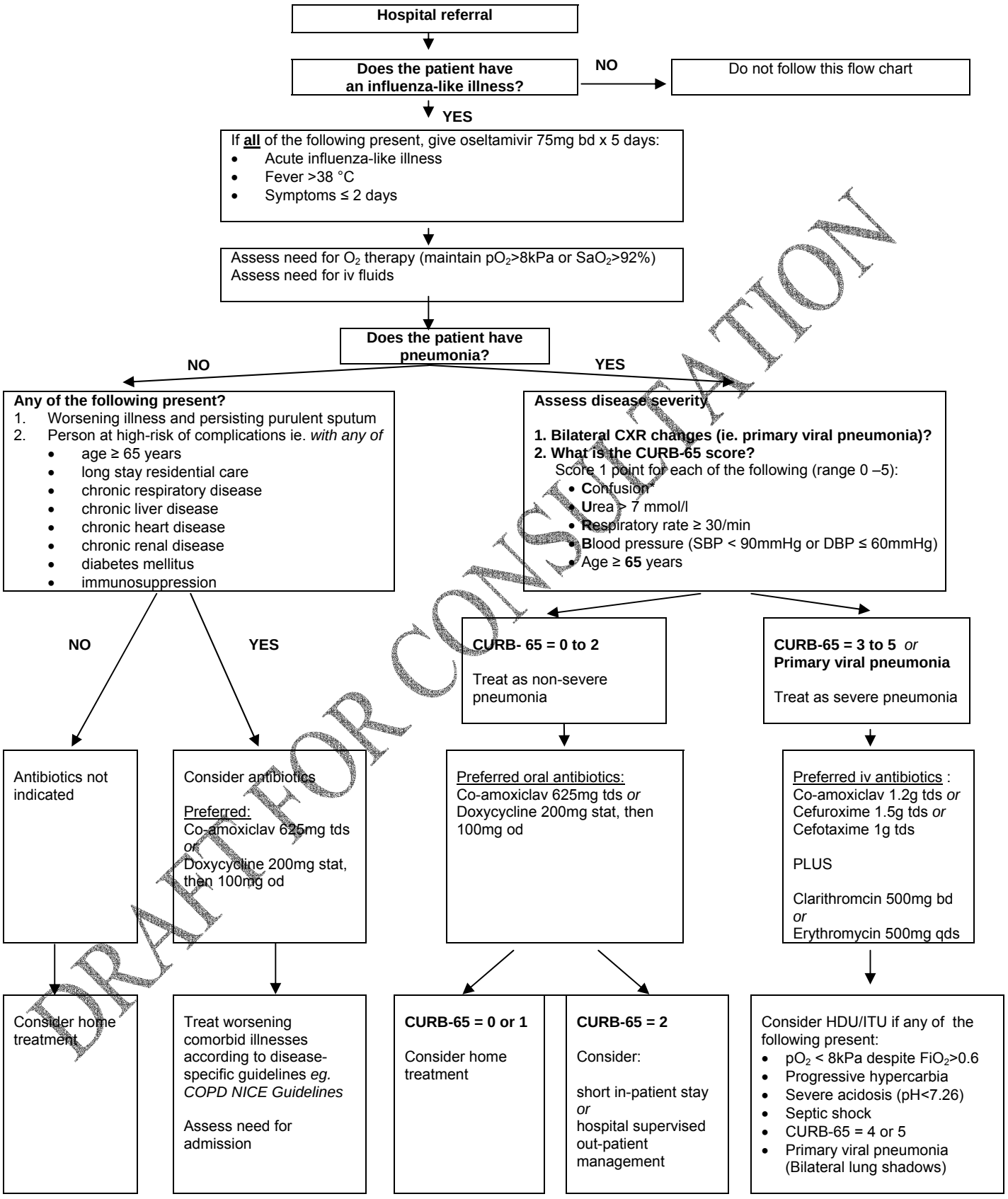
Appendix 2

Patients at high-risk of influenza-related complications*

CLNICAL RISK CATEGORY	EXAMPLES
Aged 65 years or older	
Chronic respiratory disease, including asthma	This includes chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema, and such conditions as bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Asthma requiring continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission. Children who have previously been admitted to hospital for lower respiratory tract disease.
Chronic heart disease	This includes congenital heart disease, hypertension with cardiac complications, chronic heart failure.and individuals requiring regular medication and/or follow-up for ischaemic heart disease.
Chronic renal disease	Including nephrotic syndrome, chronic renal□ecognize renal transplantation.
Chronic liver disease.	Including cirrhosis
Diabetes	Diabetes mellitus requiring insulin or oral hypoglycaemic drugs.
Immunosuppression	Due to disease or treatment. Including asplenia or splenic dysfunction, HIV infection at all stages, malignancy. Patients undergoing chemotherapy leading to immunosuppression. Individuals on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age) or for children under 20kg a dose of 1mg or more per kg per day. *However, some immunocompromised patients may have a suboptimal immunological response to the vaccine.*
Long-stay residential care homes residents	This does *not* include prisons, young offender institutions, university halls of residence.
Others	Doctors retain discretion in identifying additional individual patients who they recognise as at high risk of seri□ecognizess should they develop influenza; for example children on long term aspirin who are at increased risk of Reye's syndrome.

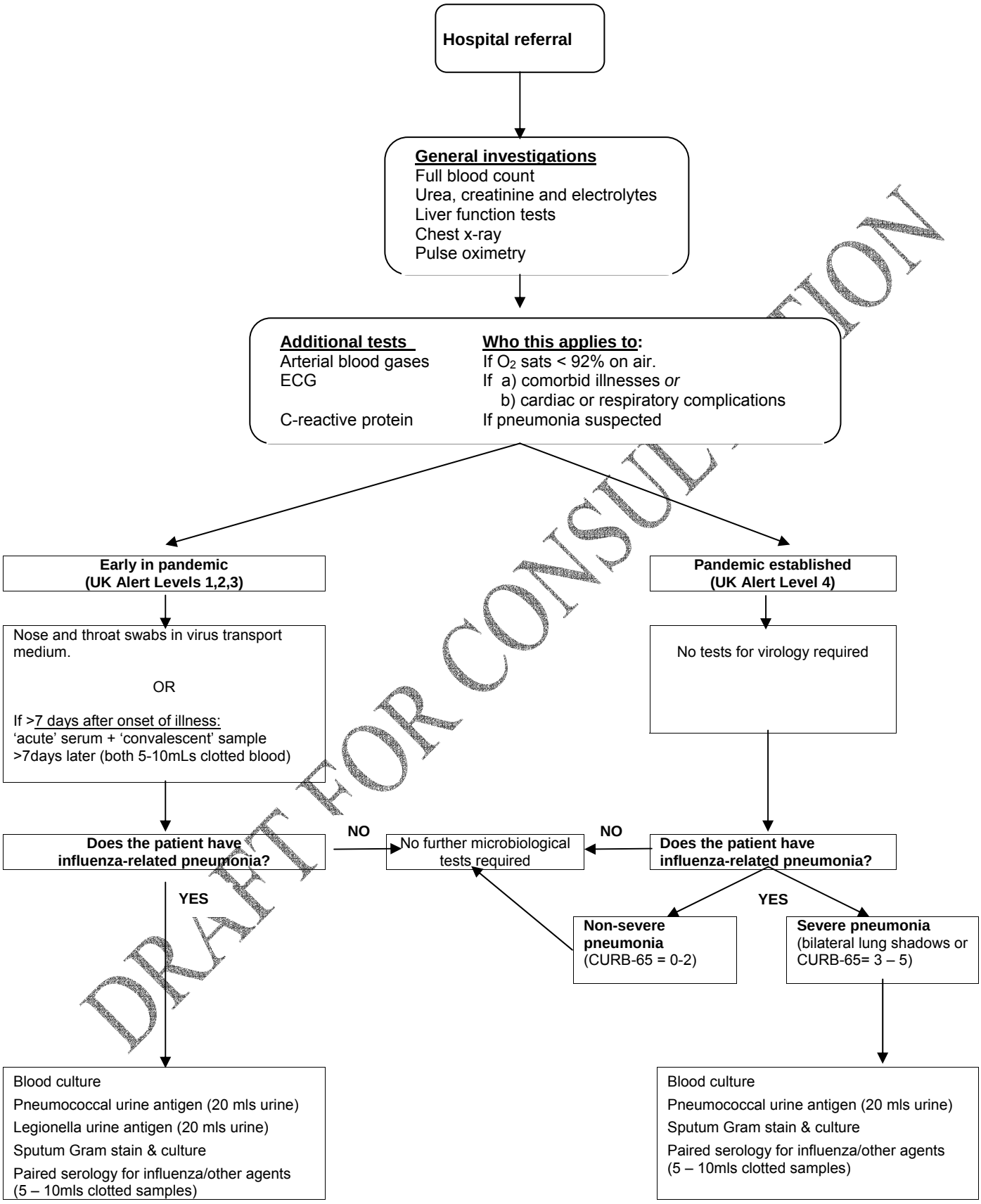
* The high risk groups described in this Appendix are largely based on data from interpandemic influenza. During the course of a pandemic, the definition of 'high risk groups' may differ. If so, details of the 'high risk' patient group will be altered according to relevant clinico-epidemiological data. Users are strongly advised to refer to the latest version of these guidelines at all times.

Appendix 3 **Pandemic Influenza: Initial MANAGEMENT of adults referred to HOSPITAL**

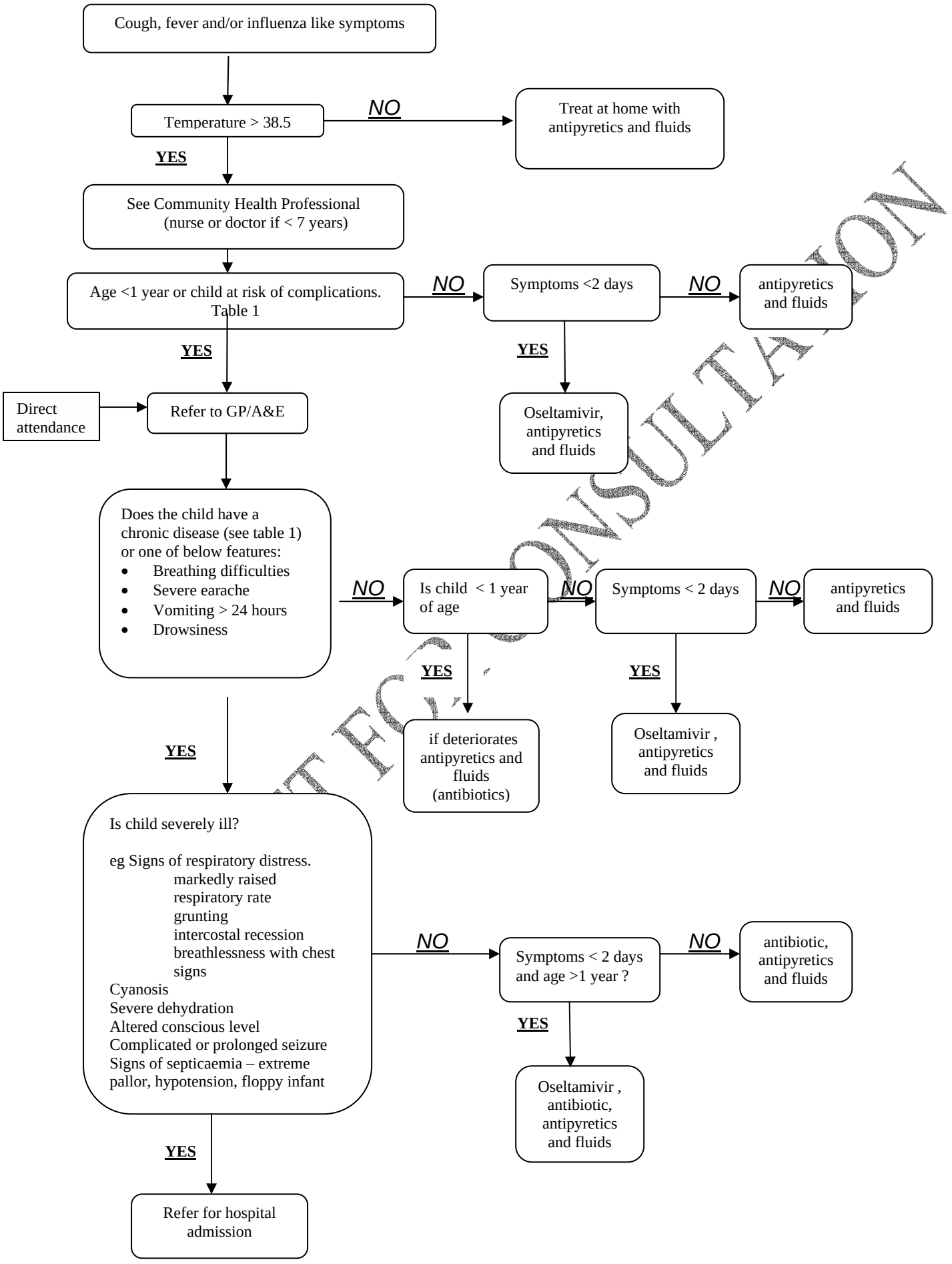


*Mental Test Score ≤ 8, or new disorientation in person, place or time

Appendix 4 **Pandemic Influenza: Initial INVESTIGATIONS for adults referred to HOSPITAL**

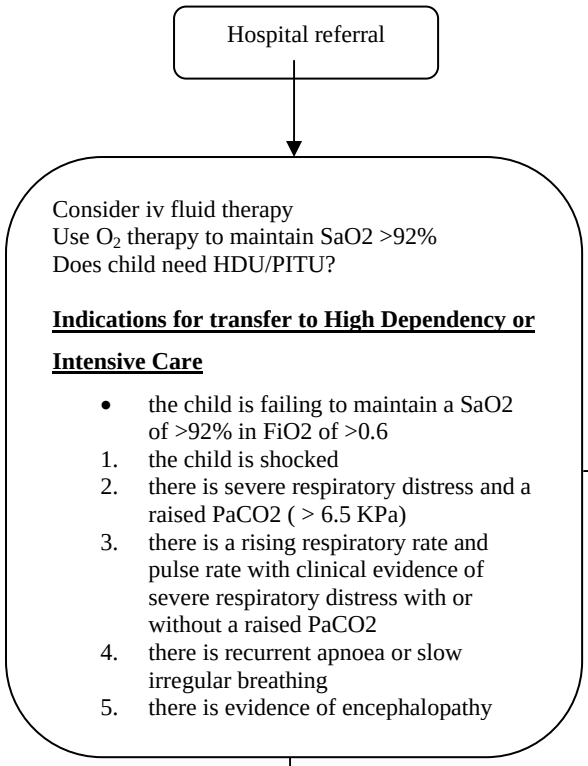


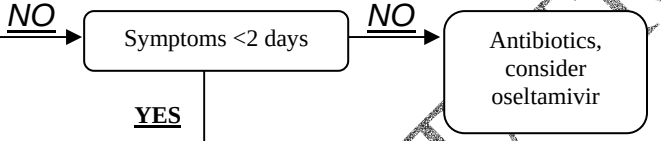
Appendix 5 **Pandemic influenza - Initial Assessment and Management of Children**

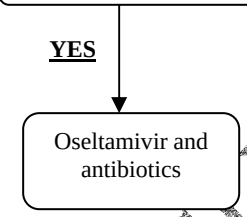


Appendix 6

Pandemic influenza - Management of children referred to hospital







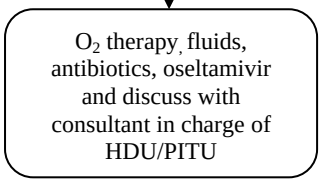


Table 1

Children at Risk for complications from Pandemic Influenza.

- Chronic respiratory disease
  Including asthma (on inhaled steroids and above) , cystic fibrosis, chronic lung disease of prematurity, bronchiectasis
- Congenital heart disease
- Chronic renal disease
  eg nephrotic syndrome, renal failure
- Chronic liver or Gastrointestinal disease
  Including inflammatory bowel disease
- Immunodeficiency
- Malignancy
- Diabetes and other metabolic conditions
- Haemoglobinopathy

. **Oseltamivir doses in children over 1 year**:

30mg every 12 hours (body weight <15kg ,<3years);

45mg every 12 hours (body weight 16-23kg, <7 years);

75 mg every 12 hours (body weight over 24kg,over 7 years)

Antibiotic doses

Co-amoxiclav

<1 year ---0.266ml/kg of 125/31 suspension tds
1-6 years ---5ml of 125/31 suspension tds
>6 years ---5ml of 250/62 suspension tds

If allergic
Clarithromycin

< 8.5kg –7.5mg/kg b.d.
1-2 years--- 62.5mg b.d.
3-6yrs ---125mg b.d.
7-9yrs---187.5mg b.d.
>10years ---250mg b.d.

Appendix 7 **Pandemic influenza - Antibiotic doses for children**

Co-amoxiclav

Age	Dose	Frequency	Type
1-12 months	2.5ml	tds	of 125/31 suspension
1-6 years	5ml	tds	of 125/31 suspension
7-12 years	5ml	tds	of 250/62 suspension
12-18 yrs	1tablet	tds	250/125
All ages	30mg/kg	tds	iv

Clarithromycin

Age	Dose	Frequency	Type
1-12months	2ml	bd	125mg in 5ml
1-2 years	2.5ml	bd	125mg in 5 ml
3-6 years	5ml	bd	125mg in 5 ml
7-9 years	7.5ml	bd	125mg in 5 ml
>10years	250mg	bd	tablet
All ages	5-7mg/kg	bd	iv

Cefuroxime

Age	Dose	Frequency	Notes
1 - 24months	125mg	bd	oral
2-12 years	250mg	bd	oral
All ages	20-30mg/kg	tds	iv

Doxycycline

Age	Dose	Frequency	Notes
>12 years	100mg	od	oral

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