

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 11.4) 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 progressive 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 irritability 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 $9/\text{ml}^3$ (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	Common (~10%)	The younger, the more likely to require hospital admission
Primary viral pneumonia		
Secondary bacterial pneumonia		
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	

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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.

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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