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Influenza, respiratory syncytial virus and SARS

Catherine Thompson

Maria Zambon

Abstract

Acute lower respiratory tract infections (LRTIs) are a major worldwide health problem, particularly in childhood. About 30–50% of acute LRTIs are viral in origin; of these, influenza and respiratory syncytial virus are associated with the greatest disease burden in humans. Many different influenza A viruses occur naturally in animal reservoirs, and present a constant threat of zoonotic infections and global pandemics. The pandemic (H1N1) influenza virus that emerged in humans in 2009 contained a unique combination of genes originating in swine and the global human population was highly susceptible to the novel strain. The emergence of the severe acute respiratory syndrome coronavirus in 2003, and the ensuing worldwide epidemic, highlights the fact that respiratory viral infections in humans may originate in animals. Preventative measures for influenza include annual vaccination and treatment with antiviral drugs such as the neuraminidase inhibitors oseltamivir and zanamivir. Subtype-dependent resistance to antivirals can develop and should be closely monitored.

Keywords flu; H1N1; influenza virus; LRTI; pandemic; respiratory infection; respiratory syncytial virus; RSV; SARS coronavirus

Influenza

Influenza viruses are small (80–120 nm diameter), contain RNA and are enveloped. There are three types – A, B, and C. Type A is further classified according to the properties of the surface proteins haemagglutinin and neuraminidase. All A subtypes are found in aquatic birds, which are the natural reservoir (Figure 1); only a few subtypes circulate in humans and other mammals. Type B and C influenza have only one subtype and are restricted to humans.

Seasonal illness, epidemics and pandemics

Influenza viruses circulating in humans (A H1N1, H3N2, B and C) cause respiratory tract disease. Influenza A is generally considered to be clinically more severe than influenza B; influenza C causes only a mild illness confined to the upper respiratory tract. Circulation of influenza A and B viruses in humans

Catherine Thompson BSc PhD is a Healthcare Scientist in the Respiratory Virus Reference Unit at the Health Protection Agency Centre for Infections, London, UK. Competing interests: none declared.

Maria Zambon MA PhD FRCPath is Director of the Health Protection Agency Centre for Infections, London, UK. Competing interests: none declared.

What's new?

- First identified in April 2009, the novel influenza H1N1 virus quickly spread worldwide leading to the declaration of the first influenza pandemic in more than 40 years
- Neuraminidase inhibitor antiviral drugs have been developed for treatment of influenza. Oseltamivir-resistant seasonal influenza virus emerged globally in untreated people in 2007/08, highlighting the unpredictability of the influenza virus

(Figure 2) causes unpredictable seasonal epidemics of disease in temperate climates, with excess population morbidity and mortality, usually occurring between October and March in the northern hemisphere and lasting about 6–8 weeks.¹ In the UK, 5000–10,000 deaths are associated with influenza A and B epidemics every year, and more than 20,000 in severe years. Widespread pandemics of severe disease occur less frequently, occurring on at least three occasions in the last century (1918, 1957, 1968), and have been associated with high mortality. In April 2009 a novel (H1N1) influenza virus emerged in humans and quickly spread worldwide leading to the declaration of the 2009 influenza pandemic.

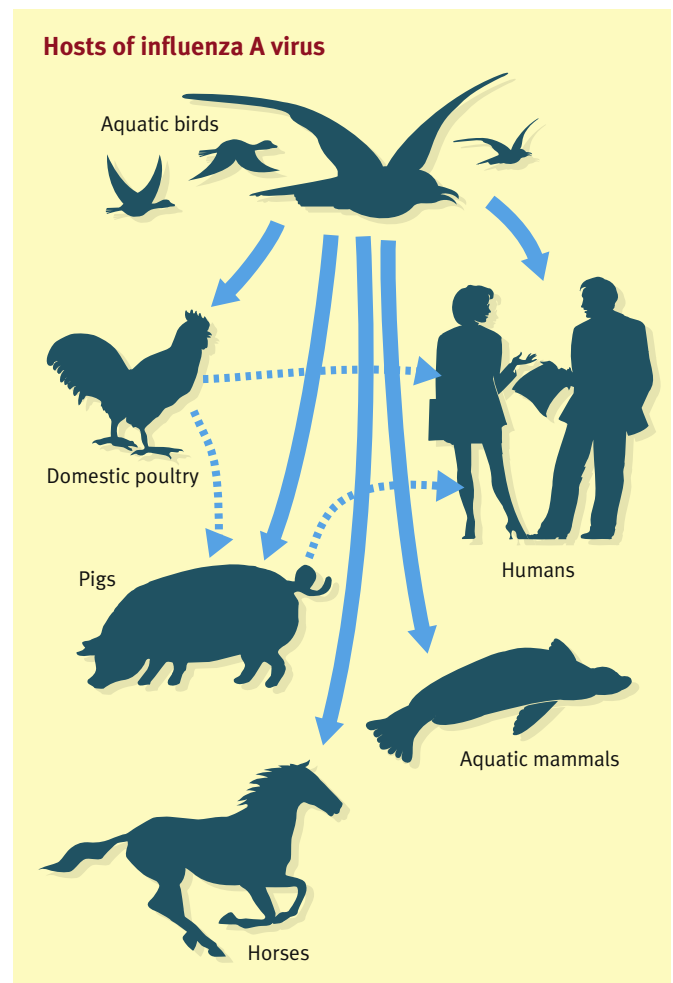


Figure 1

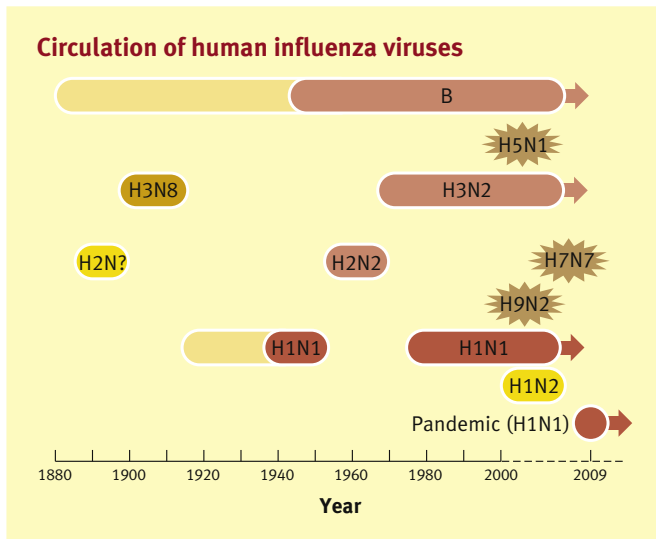


Figure 2

Clinical features

Influenza A and B illness in humans ranges from subclinical or mild upper respiratory tract symptoms to more severe illness including laryngotracheitis and pneumonia or, less commonly, death from respiratory system failure. The most common presenting symptoms are cough, high temperature, joint pain and general malaise (Figure 3). The rapid onset and short incubation period (about 48 h) are characteristic, though incubation can last up to 4 days. Individuals at greatest risk of complications are those with pre-existing cardiac and respiratory disease, the elderly, and those with impaired

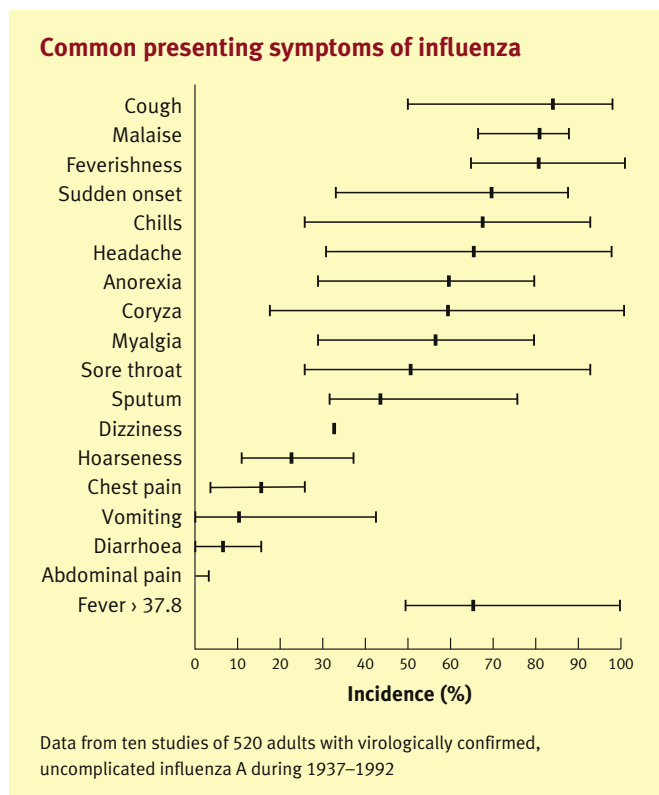


Figure 3

Groups at increased risk of complications of influenza

- Chronic respiratory disease
- Chronic heart disease
- Chronic renal failure
- Diabetes
- Immunosuppression from disease/treatment
- Asplenia/splenic dysfunction
- Frail elderly with co-morbidity

Table 1

immune systems (Table 1). The severity of the illness reflects pre-existing host immunity and the prevailing virus strain.

Virus variability

Protective immunity to influenza is conferred by antibodies. The ability of influenza to cause re-infections is related to the genetic mutability of the virus. In every replication round, mutant viruses are generated, some of which have a growth advantage because they can partially evade host immune responses. Variants capable of causing epidemics in susceptible populations emerge by a process termed 'antigenic drift'. New influenza A drift variants arise every 2–3 years; influenza B drift variants arise every 4–5 years.

Influenza as a zoonosis

The segmented nature of the influenza genome allows reassortment of segments when a single host is infected with more than one virus. This occurs regularly in aquatic birds, in which almost all combinations of influenza A virus segments can be detected, but is less common in mammals. It was previously thought that, for a novel subtype of influenza to arise in humans, reassortment of two virus subtypes had to occur in a mammal that could then transmit to humans. The pig was considered a suitable 'intermediate host', because both avian and human viruses, which differ slightly in their surface receptor requirements, can replicate in pigs. However, following transmission of H5N1 directly from birds to humans on 18 occasions in Hong Kong in 1997, and further zoonotic infections involving several different subtypes of influenza (Table 2), it is evident that cross-species barriers to transmission may be less stringent than was thought. Nevertheless, the requirements for adaptation of avian viruses to mammals are poorly understood. Cross-species transmission of novel subtypes into susceptible human populations (antigenic shift) are thought to be the source of pandemics of influenza.

Pandemic (H1N1) 2009

Influenza pandemics occur when a novel influenza virus, against which there is little or no pre-existing immunity, emerges and spreads in the human population. In April 2009 a novel influenza virus originating from swine was identified in humans in Mexico and the United States.² Individual cases were rapidly detected in other countries and following the onset of community transmission the World Health Organization (WHO) declared the start of the 2009 influenza pandemic. The pandemic (H1N1) 2009 virus has a unique combination of genes obtained from swine viruses from North America and Eurasia. Substantial antigenic differences between the seasonal H1N1 virus that has circulated

Bird-to-human transmission

| Place and date | Subtype | Number | Infection | Deaths |
|----------------------|---------|--------|-----------------------------|--------|
| • England, 1995 | H7N7 | 1 | Conjunctivitis | 0 |
| • Hong Kong, 1997 | H5N1 | 18 | Respiratory | 6 |
| • Hong Kong, 1999 | H9N2 | 2 | Respiratory | 0 |
| • Hong Kong, 2003 | H5N1 | 2 | Respiratory | 1 |
| • Netherlands, 2003 | H7N7 | 83 | Respiratory | 1 |
| • Hong Kong, 2003 | H9N2 | 1 | Respiratory | 0 |
| • Viet Nam, 2003–09 | H5N1 | 111 | Respiratory | 56 |
| • Thailand, 2004–06 | H5N1 | 25 | Respiratory | 17 |
| • Canada, 2004 | H7N3 | 2 | Respiratory, conjunctivitis | 0 |
| • Egypt, 2004 | H10N7 | 2 | Respiratory | 0 |
| • Indonesia, 2005–08 | H5N1 | 141 | Respiratory | 115 |
| • Egypt, 2006–09 | H5N1 | 87 | Respiratory | 27 |
| • England, 2006 | H7N3 | 1 | Respiratory, conjunctivitis | 0 |
| • UK, 2007 | H7N2 | 2 | Respiratory | 0 |
| • Hong Kong, 2007 | H9N2 | 1 | Respiratory | 0 |

Source of H5N1 data: WHO website (http://www.who.int/csr/disease/avian_influenza/en/index.html). Accessed 02.10.2009.

Table 2

since 1977 and the pandemic H1N1 virus meant the human population was highly susceptible to the new virus and it quickly became the dominant influenza strain circulating worldwide. It caused an unusual peak of influenza activity in many Northern hemisphere countries, including the UK, during the summer months when few influenza detections are usually made (Figure 4). In the Southern hemisphere during the normal winter influenza season, the pandemic strain rapidly became dominant.

Disease caused by the pandemic (H1N1) 2009 influenza virus is of moderate severity. Presentations range from mild, self-limiting illness, with typical symptoms of fever, cough and sore throat, to severe disease requiring hospitalization. Younger people appear to be more commonly affected, particularly for severe or fatal disease. This is in stark contrast to seasonal flu which generally has a greater impact on the over 65 years age group. Severe respiratory failure has been seen in a small proportion of cases and certain underlying medical conditions may present an increased risk of developing severe and fatal disease (Table 2). An increased risk for complications during pregnancy has also been documented.³

Control

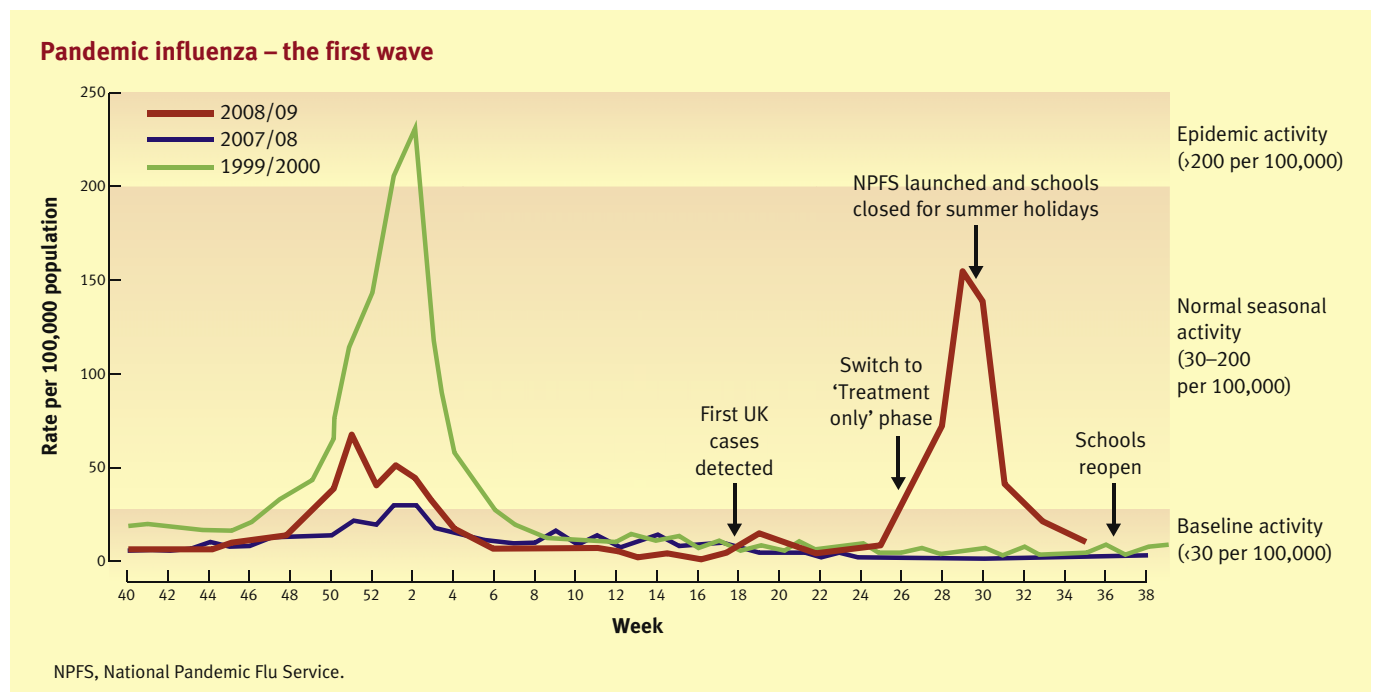
The presence of a large, mobile animal reservoir of influenza A virus suggests that eradication of this agent will be impossible. Control strategies focus on limiting the opportunities for cross-species transmission of novel subtypes; for example:

- housing domestic poultry in shelters to avoid contact with overflying migratory birds
- eliminating/reducing live bird markets
- housing aquatic birds and domestic poultry separately
- slaughtering domestic flocks infected with highly pathogenic influenza A viruses.

These measures may achieve some success in preventing zoonotic transmission of influenza A to humans, but have little impact on its annual cycle. Unprecedented levels of H5 circulating in domestic poultry in South East Asia and elsewhere present a high risk for emergence of a novel pandemic influenza A strain.

Immunization

Antibodies against haemagglutinin (and, to a limited extent, neuraminidase) can prevent disease caused by the same strain of virus. This is the basis of vaccination for influenza. Currently, most vaccines used worldwide are subunit vaccines. However,

**Figure 4** Reproduced courtesy of the Health Protection Agency (www.hpa.org.uk).

the high variability of influenza virus means that antibodies to one strain confer only limited protection against drift variants. Thus, influenza vaccines are given annually before the influenza season to boost pre-existing immunity, and the composition of the vaccine is updated regularly. In developed countries, the benefit of immunization has led to expansion of age-related vaccination policies. In the UK in 2000, vaccination was introduced for all individuals over 65 years of age, irrespective of pre-existing illness. Vaccination rates vary considerably between countries.

There is increasing interest in vaccination of children.⁴ Live attenuated influenza vaccines are particularly suitable, because they induce broader, long-lasting immunity. Child vaccination may also help to prevent transmission in the community in general.

Development of candidate pandemic vaccines and extensive testing of protocols as part of pandemic preparedness measures meant that vaccines for pandemic (H1N1) 2009 virus could be rapidly developed following the emergence of the novel virus.

Antiviral drugs

Despite the preventive efficacy of vaccination, the need for treatment of severe influenza remains.

Amantadine (or the related compound rimantadine) was, until recently, the only anti-influenza drug available. It selectively targets a viral protein (M2) and inhibits viral replication, but its use has been limited in the last 30 years, partly because of side effects (dizziness, confusion) that particularly affect the elderly, and also because drug-resistant mutants arise frequently and can be readily transmitted.

Neuraminidase inhibitors are a more recently developed, novel class of anti-influenza compounds (Table 3).⁵ They act on viral neuraminidase, prevent release of virus particles from infected cells, and are likely to be most efficacious when given early in illness. Since 2000, the UK National Institute for Clinical Excellence has recommended that neuraminidase inhibitors may be used for treatment and prophylaxis, with certain restrictions.

The neuraminidase inhibitor drugs have been used for treatment of pandemic (H1N1) influenza in community and hospital settings. Oseltamivir was widely used in the UK for treatment of confirmed cases and prophylaxis of close contacts during the early stages of the pandemic. As community transmission increased in the UK during July 2009, oseltamivir was prescribed

to people diagnosed with influenza through the National Pandemic Flu Service telephone health helpline (Figure 4). Neuraminidase inhibitors are frequently used for treatment of critically ill patients with pandemic influenza.

Antiviral drug resistance

During 2007 resistance to the neuraminidase inhibitor drug oseltamivir was detected in seasonal H1N1 influenza virus.⁶ The resistant strain was found globally in people who had not been treated with the drug. Clinical presentation did not appear to differ from infection with sensitive viruses, but circulation of the resistant strain had an impact on antiviral management of patients. The mutation conferring resistance was the well characterized H275Y change in the viral neuraminidase gene, which confers resistance to oseltamivir while sensitivity to zanamivir remains. Widespread community circulation of resistant virus was unexpected as it was previously shown that viruses with these mutations were at a disadvantage for replication and transmission. Further concern was also due to the fact that the neuraminidase inhibitors, and oseltamivir in particular, are the drugs of choice for clinical use against seasonal influenza and zoonotic H5N1 infections and were stockpiled by governments as a pandemic preparedness measure.

The pandemic (H1N1) influenza virus that subsequently emerged in April 2009 was sensitive to the neuraminidase inhibitor drugs and oseltamivir was widely used for treatment and prophylaxis. Sporadic detections of neuraminidase inhibitor resistant pandemic virus have been made in treated patients, often in immunocompromised people who can shed virus for a prolonged period.

Respiratory syncytial virus (RSV)

RSV (Figure 5) is a negative-sense, non-segmented, enveloped RNA virus of 100–300 nm diameter. It is best known as a cause of bronchiolitis in infants, but can cause respiratory tract infection in all age groups. Upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs) range in severity from subclinical infection to pneumonia and death. More than 60% of children have been infected with RSV by their first birthday and more than 80% by 2 years of age; thereafter, individuals are infected approximately every 3 years. RSV infections in adults are probably under-recognized, and the severity of RSV infection in the elderly may be much underestimated as a cause of pneumonia. About 5% of elderly individuals are thought to become infected with RSV every year.

Transmission

Transmission of RSV is primarily through large aerosol droplet or secretions, causing widespread nosocomial infection. Outbreaks in adult and paediatric facilities are difficult to control. RSV infection in immunocompromised individuals is severe and life-threatening; mortality may be 50–70% in adult bone marrow transplant recipients, in whom viral shedding may be prolonged.

Pathophysiology

RSV infects the respiratory epithelium, leading to increased goblet cell production of mucus. Dying infected ciliated epithelial cells combine with mucus to form plugs that block the airways; the consequences are most severe in very small babies with

Oral and inhaled neuraminidase inhibitors

| | Inhaled (zanamivir) | Oral (oseltamivir) |
|-------------------------|--|--|
| Pharmacokinetics | Active drug | Pro-drug |
| Site of action | Inhaled/topical | Oral/systemic |
| Delivery | Inhaler device | With food |
| Formulations | Bronchial/nasal/nebulized | Tablet and solution |
| Side effects | Rare bronchospasm events reported | Nausea (<5%) |
| Resistance | Low <i>in vivo</i> and <i>in vitro</i> | Resistance observed in seasonal H1N1 viruses |

Table 3

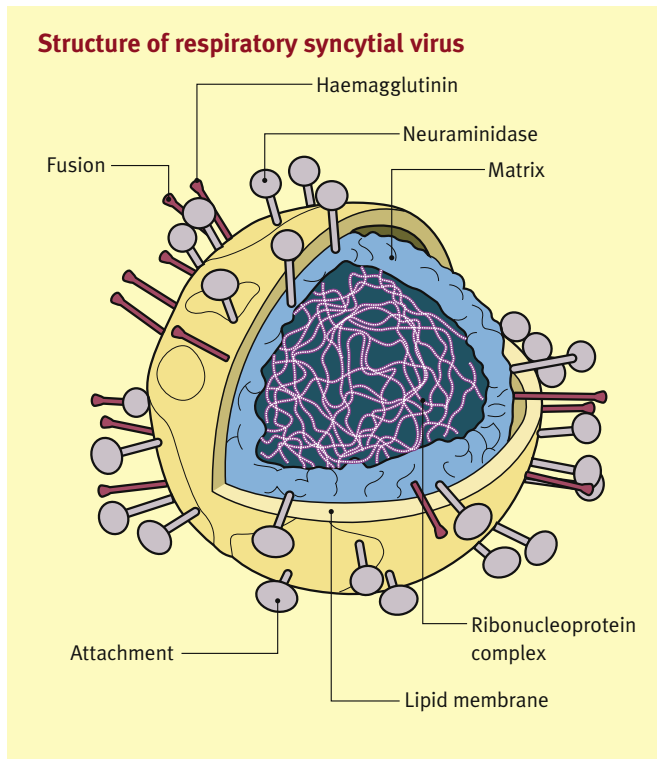


Figure 5

narrow airways. This leads to the characteristic signs and symptoms of atelectasis and the clinical syndrome of bronchiolitis. In RSV bronchitis and pneumonia, the peribronchiolar and interstitial infiltrate is characteristically lymphocytic.

Clinical features

The severity of RSV infection is related to age. In young infants, the illness is seldom asymptomatic and lasts for 1–3 weeks. Early signs of infection may include difficulty in feeding, nasal congestion, cough and otitis media compatible with URTI. Fever is often but not invariably present in RSV infection.

Abnormal breath sounds, tachypnoea and hypoxaemia suggest lower respiratory tract involvement. Bronchiolitis and pneumonia are the two primary manifestations of progression to LRTI; they may be difficult to distinguish and can occur simultaneously. The clinical features of bronchiolitis are wheezing and hyperaeration, and these are characteristic of infants with RSV infection.

In the USA, RSV is estimated to cause 4500 deaths per year in children under 2 years of age. The risk of hospitalization in otherwise healthy under-2s is 0.5–2%, and 10–20% of children admitted to hospital require mechanical ventilation. These rates are higher in the first 6 months, and may be higher still in children with underlying acquired or congenital cardiopulmonary disease.

Older children and adults with RSV infection or re-infection usually have a milder or asymptomatic respiratory infection with a lower likelihood of LRTI. Adults with RSV-associated respiratory tract infections may experience prolonged symptoms. Disease in the elderly may be particularly severe; up to 50% develop pneumonia.

Investigations

RSV infection is often diagnosed on the basis of the clinical features. The certainty of the diagnosis is increased when RSV is known to be circulating in a seasonal epidemic. Chest radiography findings are non-specific and commonly include hyperaeration and peribronchial thickening, with areas of consolidation and interstitial infiltrates in patients with RSV pneumonia. There is a range of respiratory findings in immunocompromised adults, including pleural effusions. Laboratory diagnosis depends on detection of viral antigen in respiratory secretions by immunofluorescence, rapid antigen tests or culture of the virus. Serological tests are of little help in diagnosis of RSV infection, because they rely on the use of paired acute and convalescent sera.

Complications

Premature and very young infants are more likely to suffer acute apnoeic episodes and require assisted ventilation. Bronchiolitis and pneumonia are the major complications of RSV disease in young children. Children with congenital heart disease or chronic lung disease, and immunocompromised children and adults, are also at risk of severe disease.

Pneumonia is the major complication in adults and the elderly. Estimates of the incidence range from 10% in nursing homes to 55% in a hospital in-patient population; estimated mortalities in the elderly are 3–5% in the former and 10–20% in the latter.

RSV infection has very high mortality (50–70%) in severely immunocompromised individuals.

Management

Supportive care is the mainstay of management of RSV disease in infancy. Maintenance of oxygenation, hydration and nutrition is essential in hospitalized patients, and ventilatory support may be necessary in severe cases. A trial of bronchodilators may be beneficial. Controlled trials of corticosteroids and vitamin A supplementation have not proved efficacy in infant RSV disease.

Immunization

There are two subtypes of RSV – A and B. The surface glycoproteins F and G are the major antigens of the virus to which neutralizing antibodies are directed. Protective immunity to RSV is complex. Antibodies generated during natural infection are not necessarily protective. A high proportion of primary RSV infections occur before 6 months of age, when maternal antibody levels are highest. Overall, current (controversial) data suggest that neutralizing antibody to RSV is beneficial. Neutralizing antibody titres in human sera correlate inversely with the likelihood of hospitalization as a result of RSV infection, and neutralizing antibody titre correlates with a reduced risk of re-infection.

Immunoglobulin infusions with high neutralizing titres of antibody to RSV (RSVlg, Table 4) have been used to treat RSV illness in normal-risk and high-risk infants. In normal infants, there is little evidence to justify RSVlg for treatment of RSV infection. However, prophylaxis may be useful in high-risk infants (e.g. those with bronchopulmonary dysplasia). Assessment of risk is important, because intravenous RSVlg is contraindicated in congenital cyanotic heart disease. Recombinant humanized RSV monoclonal antibodies are now available for intramuscular treatment and prophylaxis of RSV. Early clinical

Use of intravenous respiratory syncytial virus immunoglobulin

- Consider for prophylaxis in infants < 2 years receiving oxygen therapy for bronchopulmonary dysplasia
- Infants born < 32 weeks with bronchopulmonary dysplasia are likely to benefit from 6–12 months' prophylaxis
- Infants born > 32 weeks with bronchopulmonary dysplasia may not benefit
- Should not be used in cyanotic congenital heart disease
- Not evaluated in paediatric or adult immunocompromised patients
- Main emphasis in nosocomial outbreaks should be infection control; efficacy is improved in such settings
- Initiate treatment before onset of respiratory syncytial virus season
- Defer live virus vaccines (e.g. MMR) until last dose

Table 4

data suggest that this preparation of passive antibodies may have wider application, with fewer limitations than RSVIg; however, it is extremely expensive.

Few antiviral drugs are available for RSV. Ribavirin is a guanosine analogue that has been used widely, though its precise mode of action is uncertain and many clinical studies show conflicting results. Several studies have raised further doubts about the clinical effectiveness of ribavirin in infants and children at risk of severe RSV disease, and in ventilated children. In most centres, its use is now restricted to the immunocompromised or severely ill.

Several RSV vaccines (live attenuated, subunit and recombinant) are undergoing clinical trials. Development of safe vaccines has been impeded by poor understanding of the factors governing immune protection in different age groups,⁷ and early vaccination attempts in which more severe disease was seen in vaccinees. It is likely that there will be significant progress in future and that the types of vaccines suitable for different age groups may differ.

Severe acute respiratory syndrome (SARS)

SARS is an emerging viral infection. In 2003, detection of clusters of clinical cases of an unusually severe respiratory illness in South East Asia led to the description of a new syndrome and detection of a new coronavirus – SARS CoV.⁸ SARS CoV emerged in humans as a result of zoonotic infection. Civet cats and racoon dogs can be infected with the virus and are likely to have been the source of virus in the 2003 outbreaks. Bats have been identified as the host reservoir of many genetically diverse coronaviruses, including some that are related to SARS CoV, which is a strong indication that bats might be the natural reservoir of SARS CoV.

Transmission

SARS CoV spread worldwide within weeks in early 2003. The major route of transmission was respiratory, primarily through droplet, secretions and aerosol formation. About 60% of cases resulted from infection in healthcare settings, emphasizing the

SARS coronavirus infection

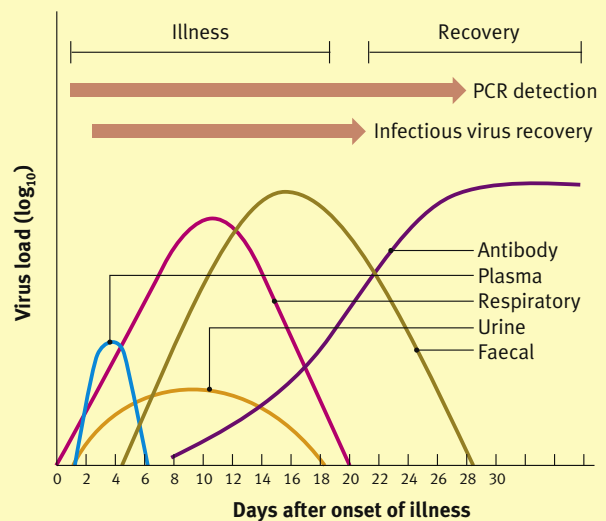


Figure 6

importance of close contact and exposure to bodily secretions. (The syndrome was noticed through unusual clusters of severe respiratory illness in hospital settings.)

Peak virus shedding is 7–12 days after the onset of illness (Figure 6). The virus is found in various body fluids. Infectious virus has not been recovered later than 21 days after illness onset. Neutralizing antibody is detected from about 10 days post-onset.

Risk factors for SARS CoV infection are:

- close contact with civet cats/racoon dogs
- eating/preparing civet meat
- laboratory work with SARS CoV
- contact with a known case of SARS.

Clinical features

Presentation is with fever and respiratory illness with cough and shortness of breath, progressing to acute respiratory distress syndrome and death in 10% of cases. Fatalities increase significantly over the age of 40 years; mortality is up to 40% in the over-50s. Onset of illness is 2–10 days post-infection, with a mean of about 5–6 days. About 60% of patients suffer later gastrointestinal symptoms of diarrhoea and vomiting.

Management and control

Specific control measures have not yet been developed, though work is in progress on antiviral drugs and suitable vaccines. During the 2003 epidemic, various non-specific therapeutic measures were used with variable success:

- corticosteroids
- antimicrobials to prevent secondary bacterial infection
- positive-pressure ventilatory support
- anti-inflammatory drugs
- infusion of antisera from convalescent patients.

The epidemic was controlled mainly through public health measures such as contact-tracing and quarantining. This policy was effective because there is little evidence of transmission before symptom onset, so infected individuals are easily identified. ♦

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