

# Postgraduate Course ERS Munich 2006

## Avian influenza and SARS: updates on the big stories

# Avian influenza



## Educational aims

- › To update clinicians on the epidemiology and clinical manifestations, including complications, of avian influenza.
- › To update on the options for treatment.

## Summary

To date, all outbreaks of the highly pathogenic form of avian influenza have been caused by viruses of the H5 and H7 subtypes. The virus can improve its transmissibility among humans *via* reassortment, in which genetic material is exchanged between humans and avian virus during coinfection of a human and a pig. It can also go through a more gradual process of adaptive mutation during subsequent infections of humans. All evidence to date indicates that close contact with dead birds is the principal source of human infection with the H5N1 virus.

Limited evidence suggests that some antiviral drugs, notably oseltamivir, can reduce the duration of viral replication and improve prospects of survival, provided that they are administered within 48 hours, ideally 12 hours, following symptoms onset. This review aims to give an overview of this topical and interesting issue.

*This article was modified with permission from WHO publications and presented at an ERS Postgraduate Course held at the 2006 ERS Congress in Munich. Original slides, web casts and original material from the course can be found at [www.ers-education.org](http://www.ers-education.org)*



## Key points

- › In many patients, the disease caused by H5N1 may follow an unusually aggressive clinical course, with rapid deterioration and high fatality.
- › The incubation period is around 2–8 days and possibly as long as 17 days.
- › Diarrhoea, vomiting and abdominal pain have been reported as early symptoms.
- › Almost all reported patients develop pneumonia.

## The disease in birds

Avian influenza is an infectious disease of birds caused by type A strains of the influenza virus. The disease occurs worldwide. While all birds are thought to be susceptible to infection with avian influenza viruses, many wild bird species carry these viruses with no apparent signs of harm.

Other bird species, including domestic poultry, develop disease when infected with avian influenza viruses. In poultry, the viruses cause two distinctly different forms of disease: one common and mild; the other rare and highly lethal.

In the mild form, signs of illness may be expressed only as ruffled feathers, reduced egg production or mild effects on the respiratory system. Outbreaks can be so mild they escape detection unless regular testing for viruses is in place.

In contrast, the second and far less common highly pathogenic form is difficult to miss. First identified in Italy in 1878, highly pathogenic avian influenza is characterised by sudden onset of severe disease, rapid contagion and a mortality rate that can approach 100% within 48 hours. In this form of the disease, the virus not only affects the respiratory tract, as in the mild form, but also invades multiple organs and tissues. The resulting massive internal haemorrhaging has earned it the lay name of "chicken Ebola".

All 16 haemagglutinin (HA) and nine neuraminidase (NA) subtypes of influenza viruses are known to infect wild waterfowl, thus providing an extensive reservoir of influenza viruses perpetually circulating in bird populations. In wild birds, routine testing will nearly always identify some influenza viruses. The vast majority of these viruses cause no harm.

To date, all outbreaks of the highly pathogenic form of avian influenza have been caused by viruses of the H5 and H7 subtypes. Highly pathogenic viruses possess a tell-tale genetic "trade mark" or signature (a distinctive set of basic amino acids in the cleavage site of the HA) that distinguishes them from all other avian influenza viruses and is associated with their exceptional virulence.

Not all virus strains of the H5 and H7 subtypes are highly pathogenic, but most are thought to have the potential to become so. Recent research has shown that H5 and H7 viruses of low pathogenicity can, after circulation for sometimes short periods in a poultry population, mutate into highly pathogenic viruses. Considerable circumstantial evidence has long suggested that wild waterfowl introduce avian

influenza viruses, in their low pathogenic form, to poultry flocks, but do not carry or directly spread highly pathogenic viruses. This role may, however, have changed very recently: at least some species of migratory waterfowl are now thought to be carrying the H5N1 virus in its highly pathogenic form and introducing it to new geographical areas located along their flight routes.

Apart from being highly contagious among poultry, avian influenza viruses are readily transmitted from farm to farm by the movement of live birds, people (especially when shoes and other clothing are contaminated), and contaminated vehicles, equipment, feed and cages. Highly pathogenic viruses can survive for long periods in the environment, especially when temperatures are low. For example, the highly pathogenic H5N1 virus can survive in bird faeces for at least 35 days at low temperature (4°C). At a much higher temperature (37°C), H5N1 viruses have been shown to survive in faecal samples for 6 days.

For highly pathogenic disease, the most important control measures are rapid culling of all infected or exposed birds, proper disposal of carcasses, the quarantining and rigorous disinfection of farms, and the implementation of strict sanitary or "biosecurity" measures. Restrictions on the movement of live poultry, both within and between countries, are another important control measure. The logistics of recommended control measures are most straightforward when applied to large commercial farms, where birds are housed indoors, usually under strictly controlled sanitary conditions, in large numbers. Control is far more difficult under poultry production systems, in which most birds are raised in small backyard flocks scattered throughout rural or peri-urban areas.

When culling (the first line of defence for containing outbreaks) fails or proves impracticable, vaccination of poultry in a high-risk area can be used as a supplementary emergency measure, provided quality-assured vaccines are used and recommendations from the World Organisation for Animal Health (OIE) are strictly followed. The use of poor-quality vaccines or vaccines that poorly match the circulating virus strain may accelerate mutation of the virus. Poor-quality animal vaccines may also pose a risk for human health, as they may allow infected birds to shed virus while still appearing to be disease free.

Apart from being difficult to control, outbreaks in backyard flocks are associated with a

heightened risk of human exposure and infection. These birds usually roam freely as they scavenge for food and often mingle with wild birds or share water sources with them. Such situations create abundant opportunities for human exposure to the virus, especially when birds enter households or are brought into households during adverse weather, or when they share areas where children play or sleep. Poverty exacerbates the problem: in situations where a prime source of food and income cannot be wasted, households frequently consume poultry when deaths or signs of illness appear in flocks. This practice carries a high risk of exposure to the virus during slaughtering, defeathering, butchering and preparation of poultry meat for cooking, but has proved difficult to change. Moreover, as deaths of birds in backyard flocks are common, especially under adverse weather conditions, owners may not interpret deaths or signs of illness in a flock as a signal of avian influenza and a reason to alert the authorities. This tendency may help explain why outbreaks in some rural areas have smouldered undetected for months. The frequent absence of compensation to farmers for destroyed birds further works against the spontaneous reporting of outbreaks and may encourage owners to hide their birds during culling operations.

### The role of migratory birds

During 2005, an additional and significant source of international spread of the virus in birds became apparent for the first time. Scientists are increasingly convinced that at least some migratory waterfowl are now carrying the H5N1 virus in its highly pathogenic form, sometimes over long distances, and introducing the virus to poultry flocks in areas that lie along their migratory routes. Should this new role of migratory birds be scientifically confirmed, it will mark a change in a long-standing stable relationship between the H5N1 virus and its natural wild-bird reservoir.

Evidence supporting this altered role began to emerge in mid-2005 and has since been strengthened. The dying-off of more than 6,000 migratory birds, infected with the highly pathogenic H5N1 virus, that began at the Qinghai Lake nature reserve in central China in late April 2005, was highly unusual and probably unprecedented. Prior to that event, wild bird deaths from highly pathogenic avian influenza viruses were rare, usually occurring as isolated cases found within the flight distance of a poultry outbreak. Scientific studies comparing viruses from different outbreaks in birds have found that

viruses from the most recently affected countries, all of which lie along migratory routes, are almost identical to viruses recovered from dead migratory birds at Qinghai Lake. Viruses from Turkey's first two human cases, which were fatal, were also virtually identical to viruses from Qinghai Lake.

### Countries affected by outbreaks in birds

The outbreaks of highly pathogenic H5N1 avian influenza began in South-East Asia in mid-2003 including: the Republic of Korea, Vietnam, Japan, Thailand, Cambodia, the Lao People's Democratic Republic, Indonesia, China and Malaysia.

In late July 2005, the virus spread geographically beyond its original focus in Asia to affect poultry and wild birds in the Russian Federation and adjacent parts of Kazakhstan. Almost simultaneously, Mongolia reported detection of the highly pathogenic virus in wild birds. In October 2005, the virus was reported in Turkey, Romania and Croatia. In early December 2005, Ukraine reported its first outbreak in domestic birds. Figure 1 is a map showing the different areas throughout the world which have reported a confirmed occurrence of H5N1 in poultry and wild birds since 2003.

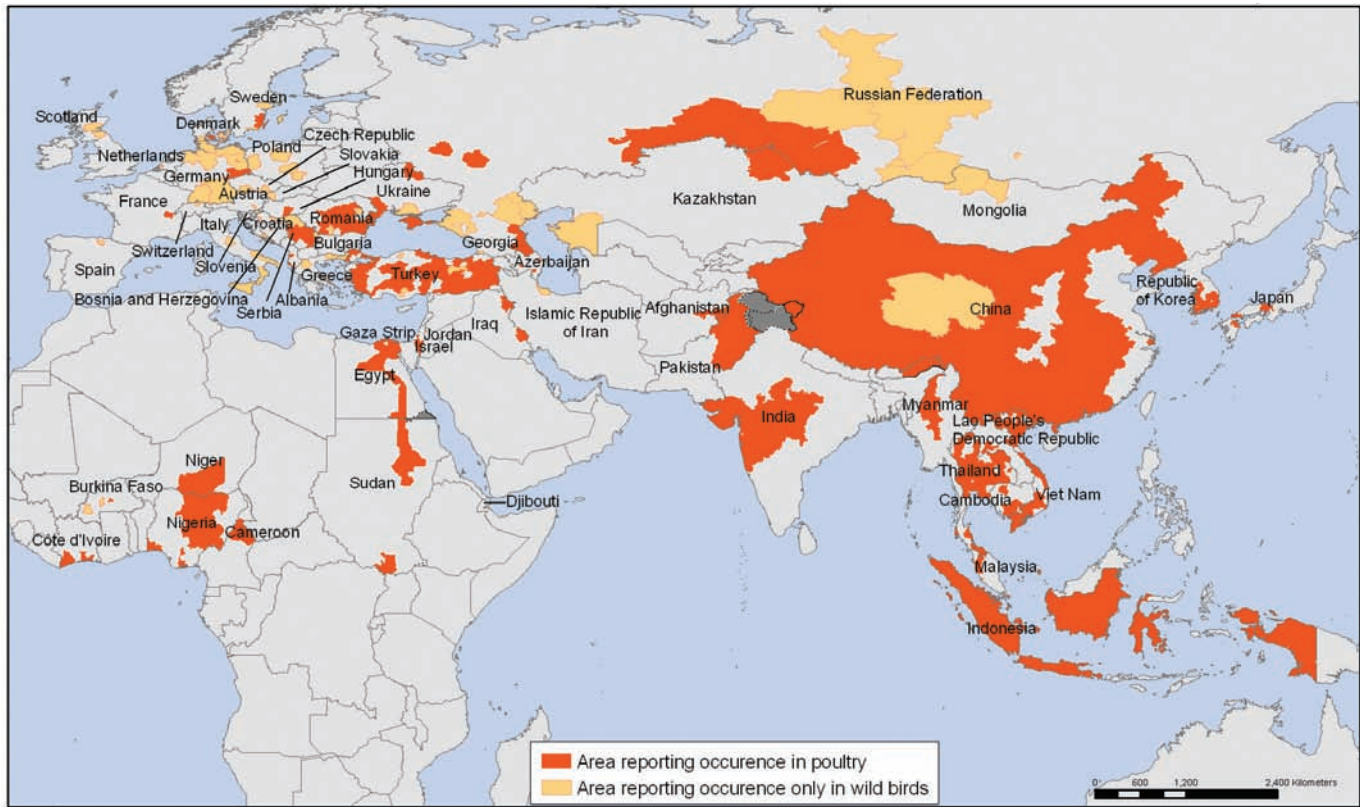
Further spread of the virus along the migratory routes of wild waterfowl is anticipated. Moreover, bird migration is a recurring event. Countries that lie along the flight pathways of birds migrating from central Asia may face a persistent risk of introduction or re-introduction of the virus to domestic poultry flocks.

Prior to the present situation, outbreaks of highly pathogenic avian influenza in poultry were considered rare. Excluding the current outbreaks caused by the H5N1 virus, only 24 outbreaks of highly pathogenic avian influenza have been recorded worldwide since 1959. Of these, 14 occurred in the past decade. The majority have shown limited geographical spread, a few remained confined to a single farm or flock, and only one spread internationally. All of the larger outbreaks were costly for the agricultural sector and difficult to control.

## The disease in humans

### History and epidemiology

Influenza viruses are normally highly species specific, meaning that viruses that infect an individual species (humans, certain species of birds,



**Figure 1**  
*Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003. Status as of 14.10.2006. Figure reproduced with permission from WHO.*

pigs, horses and seals) stay "true" to that species and only rarely spill over to cause infection in other species. Since 1959, instances of human infection with an avian influenza virus have been documented on only 10 occasions. Of the hundreds of strains of avian influenza A viruses, only four are known to have caused human infections: H5N1, H7N3, H7N7 and H9N2. In general, human infection with these viruses has resulted in mild symptoms and very little severe illness, with one notable exception: the highly pathogenic H5N1 virus.

Of all the influenza viruses that circulate in birds, the H5N1 virus is of greatest present concern for human health for two main reasons. First, the H5N1 virus has caused by far the greatest number of human cases of very severe disease and the greatest number of deaths by crossing the species barrier to infect humans. Figure 2 shows a map of all occurrences of H5N1 avian influenza since 2003.

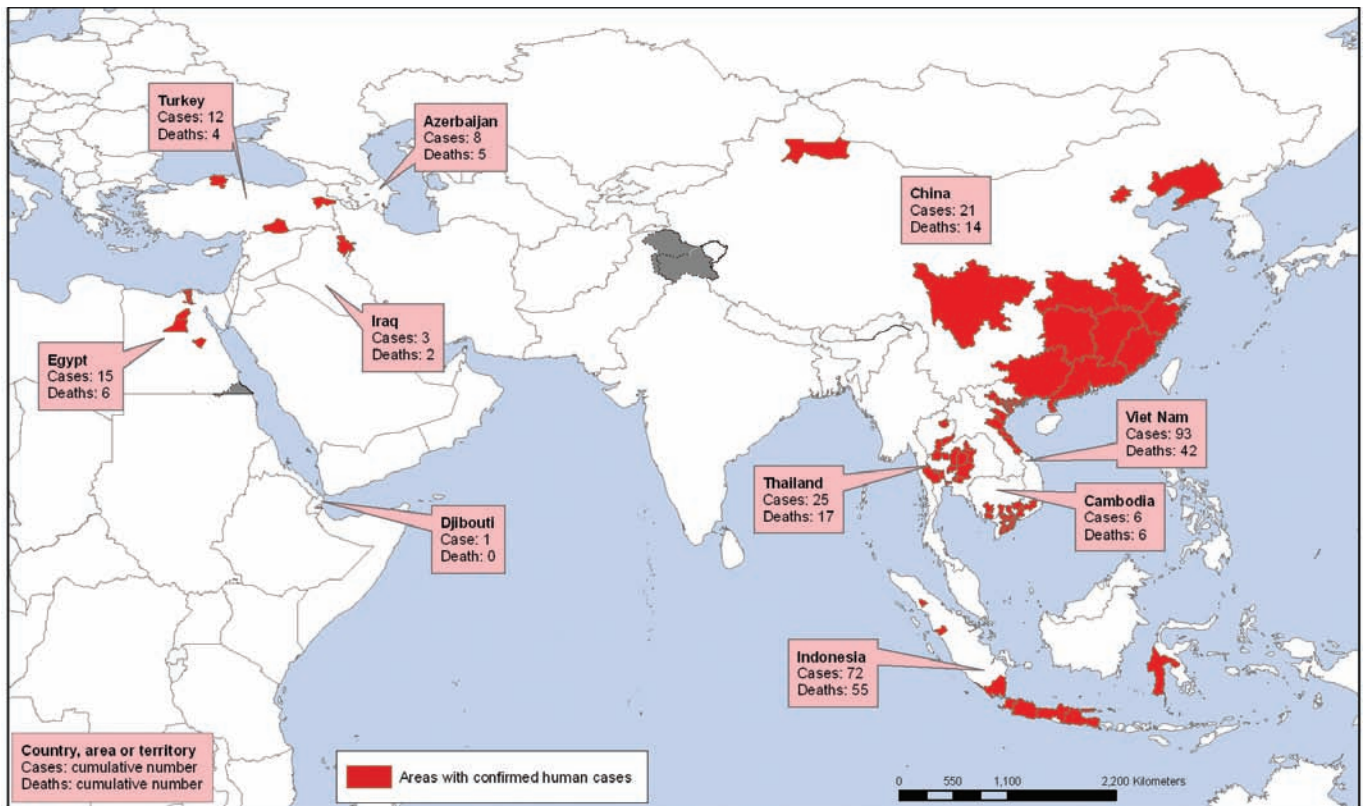
A second implication for human health, of far greater concern, is the risk that the H5N1 virus (if given enough opportunities) will develop the characteristics it needs to start another influenza pandemic. The virus has met all prerequisites for the start of a pandemic save one: an ability to spread efficiently and sustainably among humans. While H5N1 is presently the

virus of greatest concern, the possibility that other avian influenza viruses, known to infect humans, might cause a pandemic cannot be ruled out.

The virus can improve its transmissibility among humans *via* two principal mechanisms. The first is a "reassortment" event, in which genetic material is exchanged between human and avian viruses during co-infection of a human or pig. Reassortment could result in a fully transmissible pandemic virus, marked by a sudden surge of cases with explosive spread.

The second mechanism is a more gradual process of adaptive mutation, whereby the capability of the virus to bind to human cells increases during subsequent infections of humans. Adaptive mutation, expressed initially as small clusters of human cases with some evidence of human-to-human transmission, would probably give the world some time to take defensive action, if detected sufficiently early.

During the first documented outbreak of human infections with H5N1, which occurred in Hong Kong in 1997, the 18 human cases coincided with an outbreak of highly pathogenic avian influenza, caused by a virtually identical virus, in poultry farms and live markets. Extensive studies of the human cases determined that direct contact with diseased poultry was the



source of infection. Studies carried out in family members and social contacts of patients, health workers engaged in their care and poultry cullers found very limited, if any, evidence of spread of the virus from one person to another. Human infections ceased following the rapid destruction (within 3 days) of Hong Kong's entire poultry population, estimated at ~1.5 million birds. Some experts believe that this drastic action may have averted an influenza pandemic.

All evidence to date indicates that close contact with dead or sick birds is the principal source of human infection with the H5N1 virus. Especially risky behaviours identified include the slaughtering, defeathering, butchering and preparation for consumption of infected birds. In a few cases, exposure to chicken faeces when children played in an area frequented by free-ranging poultry is thought to have been the source of infection. Swimming in water where the carcasses of dead infected birds have been discarded or which may have been contaminated by faeces from infected ducks or other birds might be another source of exposure. In some cases, investigations have been unable to identify a plausible exposure source, suggesting that some as yet unknown environmental factor, involving contamination with the virus, may be implicated in a small number of cases. Some explanations that have been put forward include

a possible role of peri-domestic birds, such as pigeons, or the use of untreated bird faeces as fertiliser.

At present, H5N1 avian influenza largely remains a disease of birds. The species barrier is significant: the virus does not easily cross from birds to infect humans. For unknown reasons, most cases have occurred in rural and peri-urban households where small flocks of poultry are kept. Again for unknown reasons, very few cases have been detected in presumed high-risk groups, such as commercial poultry workers, workers at live poultry markets, cullers, veterinarians and health staff caring for patients without adequate protective equipment. Also lacking is an explanation for the puzzling concentration of cases in previously healthy children and young adults.

Research is urgently needed to better define the exposure circumstances, behaviours and possible genetic or immunological factors that might enhance the likelihood of human infection.

### Assessment of possible cases

Investigations of all the human cases in China, Indonesia and Turkey identified direct contact with infected birds as the most likely source of exposure. When assessing possible cases, the level of clinical suspicion should be heightened

**Figure 2**  
Affected areas with confirmed cases of human H5N1 influenza since 2003. Status as of 16.10.2006. Figure reproduced with permission from WHO.

for persons showing influenza-like illness, especially with fever and symptoms in the lower respiratory tract, who have a history of close contact with birds in an area where confirmed outbreaks of highly pathogenic H5N1 avian influenza are occurring. Exposure to an environment that may have been contaminated by faeces from infected birds is a second, though less common, source of human infection.

Not all human cases have arisen from exposure to dead or visibly ill domestic birds. Research published in 2005 has shown that domestic ducks can excrete large quantities of highly pathogenic virus without showing signs of illness. A history of poultry consumption in an affected country is not a risk factor, provided the food was thoroughly cooked and the person was not involved in food preparation. As no efficient human-to-human transmission of the virus is known to be occurring anywhere, simply travelling to a country with ongoing outbreaks in poultry or sporadic human cases does not place a traveller at enhanced risk of infection, provided the person did not visit live or "wet" poultry markets, farms or other environments where exposure to diseased birds may have occurred.

### Clinical features

In many patients, the disease caused by the H5N1 virus follows an unusually aggressive clinical course, with rapid deterioration and high fatality. Like most emerging disease, H5N1

influenza in humans is poorly understood. Clinical data from cases in 1997 and the current outbreak are beginning to provide a picture of the clinical features of disease, but much remains to be learned. Moreover, the current picture could change given the propensity of this virus to mutate rapidly and unpredictably.

The incubation period for H5N1 avian influenza may be longer than that for normal seasonal influenza, which is ~2–3 days. Current data for H5N1 infection indicate an incubation period ranging 2–8 days and possibly as long as 17 days. However, the possibility of multiple exposure to the virus makes it difficult to define the incubation period precisely.

Initial symptoms include a high fever, usually with a temperature higher than 38°C, and influenza-like symptoms. Diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported as early symptoms in some patients. Watery diarrhoea without blood appears to be more common in H5N1 avian influenza than in normal seasonal influenza. The spectrum of clinical symptoms may, however, be broader, and not all confirmed patients have presented with respiratory symptoms. In two patients from southern Vietnam, the clinical diagnosis was acute encephalitis; neither patient had respiratory symptoms at presentation. In another case, from Thailand, the patient presented with fever and diarrhoea, but no respiratory symptoms. All three patients had a recent history of direct exposure to infected poultry.

One feature seen in many patients is the development of manifestations in the lower respiratory tract early in the illness. Many patients have symptoms in the lower respiratory tract when they first seek treatment. On present evidence, difficulty in breathing develops ~5 days following the first symptoms. Respiratory distress, a hoarse voice and a crackling sound when inhaling are commonly noted. Sputum production is variable and sometimes bloody. Almost all patients develop pneumonia. During the Hong Kong outbreak, all severely ill patients had primary viral pneumonia, which did not respond to antibiotics. Limited data on patients indicate the presence of a primary viral pneumonia in H5N1, usually without microbiological evidence of bacterial supra-infection at presentation. Turkish clinicians have also reported pneumonia as a consistent feature in severe cases; as elsewhere, these patients did not respond to treatment with antibiotics.



In patients infected with the H5N1 virus, clinical deterioration is rapid. In Thailand, the time between onset of illness to the development of acute respiratory distress was ~6 days, with a range of 4-13 days. In severe cases in Turkey, clinicians have observed respiratory failure 3-5 days after symptom onset. Another common feature is multi-organ dysfunction. Common laboratory abnormalities include leukopenia (mainly lymphopenia), mild-to-moderate thrombocytopenia, elevated aminotransferases and with some instances of disseminated intravascular coagulation.

## Treatment

Limited evidence suggests that some antiviral drugs, notably oseltamivir (commercially known as Tamiflu®), can reduce the duration of viral replication and improve prospects of survival, provided they are administered within 48 hours following symptom onset. However, prior to the outbreak in Turkey, most patients have been detected and treated late in the course of illness. For this reason, clinical data on the effectiveness of oseltamivir are limited. Moreover, oseltamivir and other antiviral drugs were developed for the treatment and prophylaxis of seasonal influenza, which is a less severe disease associated with less prolonged viral replication. Recommendations on the optimum dose and duration of treatment for H5N1 avian influenza, also in children, need to undergo urgent review, and this is being undertaken by the WHO.

In suspected cases, oseltamivir should be prescribed as soon as possible (within 48 hours, ideally 12 hours, following symptom onset) to maximise its therapeutic benefits. However, given the significant mortality currently associated with H5N1 infection and evidence of prolonged viral replication in this disease, administration of the drug should also be considered in patients presenting later in the course of illness.

Currently recommended doses of oseltamivir for the treatment of influenza are contained in the product information on the manufacturer's website.

As the duration of viral replication may be prolonged in cases of H5N1 infection, clinicians

should consider increasing the duration of treatment to 7-10 days in patients who are not showing a clinical response. In cases of severe infection with the H5N1 virus, clinicians may need to consider increasing the recommended daily dose or the duration of treatment, keeping in mind that doses above 300 mg per day are associated with increased side-effects. For all treated patients, consideration should be given to taking serial clinical samples for later assay to monitor changes in viral load, to assess drug susceptibility and to assess drug levels. These samples should be taken only in the presence of appropriate measures for infection control.

In severely ill H5N1 patients or in H5N1 patients with severe gastrointestinal symptoms, drug absorption may be impaired. This possibility should be considered when managing these patients.

## Countries with human cases in the current outbreak

To date there have been just over 250 human cases. Most human cases have been reported in Asia. The first patients were from Vietnam and developed symptoms in December, 2003, but they were not confirmed as H5N1 infection until January 11, 2004. Thailand reported its first cases on January 23, 2004. The first case in Cambodia was reported on February 2, 2005. The next country to report cases was Indonesia, which confirmed its first infection on July 21, 2005. China's first two cases were reported on November 16, 2005. Confirmation of the first cases in Turkey came on January 5, 2006, followed by the first reported case in Iraq on January 30, 2006. All human cases have coincided with outbreaks of highly pathogenic H5N1 avian influenza in poultry. To date, Vietnam has been the most severely affected country, with more than 90 cases.

Altogether, more than half of the laboratory-confirmed cases have been fatal. H5N1 avian influenza in humans is still a rare disease, but a severe one that must be closely watched and studied, particularly because of the potential of this virus to evolve in ways that could start a pandemic.

# SARS

Severe acute respiratory syndrome (SARS) is a newly identified acute viral respiratory syndrome caused by a novel coronavirus (SARS-CoV), the SARS coronavirus (SARS-CoV), which is believed to have crossed the species barrier recently from animals to humans. It remains difficult to predict when or whether SARS will re-emerge in epidemic form, but clinicians should familiarise themselves with the varying clinical manifestations of this disease as highlighted in this update.

SARS was first recognised as a global threat in mid-March 2003. The first known cases of SARS occurred in the Guangdong province, China, in November 2002 [1, 2], and the World Health Organization (WHO) reported the last human chain transmission of SARS in that epidemic on July 5, 2003. The aetiological agent, the SARS-CoV [3–5], is believed to be an animal virus that crossed the species barrier to humans. This could have been caused by ecological changes, or changes in human behaviour providing increased opportunities for human exposure to the virus and virus adaptation, enabling human-to-human transmission [6]. By July 2003, the international spread of SARS-CoV had resulted in 8,098 SARS cases in 26 countries with 774 deaths [7]. The epidemic caused significant social and economic disruption in areas with sustained local transmission of SARS, and on the international travel industry in addition to the direct impact on health services. While much has been learnt about this syndrome since March 2003, our knowledge about the epidemiology and ecology of SARS-CoV infection and of this disease remains incomplete.

The natural reservoir of SARS-CoV has not yet been identified, but a number of wildlife species (the Himalayan masked palm civet (*Paguma larvata*) the Chinese ferret badger (*Melogale moschata*) and the raccoon dog (*Nyctereutes procyonoides*)) consumed as delicacies in southern China, have shown laboratory evidence of infection with a related coronavirus [2, 8]. Domestic cats living in the gardens of an

apartment block in Hong Kong were also found to be infected with SARS-CoV [9]. More recently, ferrets (*Mustela furo*) and domestic cats (*Felis domesticus*) were experimentally infected with SARS-CoV and found to efficiently transmit the virus to previously uninfected animals housed with them [10]. These findings indicate that the reservoir for this pathogen may involve a range of animal species. The masked palm civet is the wildlife species most often associated with animal-to-human transmission; however, whether the civet is the natural reservoir of SARS-like coronaviruses remains unproven.

Since July 2003, there have been four occasions when SARS has reappeared. Three of these incidents were attributed to breaches in laboratory biosafety, and resulted in one or more cases of SARS (Singapore [11–13], Taipei [14] and Beijing [15, 16]). Fortunately, only one of these incidents resulted in secondary transmission outside of the laboratory. The WHO recommends that each country ensures that the correct biosafety procedures are followed by all laboratories working with SARS-CoV and other pathogens [17], and that appropriate monitoring and investigation of illness in laboratory workers is undertaken.

The fourth incident (Guangzhou, Guangdong province, China [18–20]) resulted in four sporadic, community-acquired cases arising over a 6-week period. Three of the cases were attributed to exposure to animal or environmental sources, whereas the source of exposure is unknown in the remaining case. There was no further community transmission.



## Clinical description

### Aetiology

SARS is a disease caused by SARS-CoV.

### Epidemiology

Nosocomial transmission of SARS-CoV has been a striking feature of the SARS outbreak. The majority of the cases have been in adults. Children are less commonly affected than adults and usually have a milder illness [21]. The mean incubation period is 5 days, with a range of 2–10 days, although there are isolated reports of longer incubation periods. Cases outside the 2–10-day incubation period have not necessarily been subjected to rigorous and standardised investigation including serological confirmation. There have been no reports of transmission occurring before the onset of symptoms.

## Natural history

### Week 1 of illness

Patients initially develop influenza-like prodromal symptoms. Presenting symptoms include fever, malaise, myalgia, headache and rigors. No individual symptom or cluster of symptoms has proven specific. Although history of fever is the most frequently reported symptom, it may be absent on initial measurement.

### Week 2 of illness

Cough (initially dry), dyspnoea and diarrhoea may be present in the 1st week, but more commonly reported in the 2nd week of illness. Severe cases develop rapidly, progressing to distress and oxygen desaturation, with ~20% requiring intensive care. Up to 70% of patients develop diarrhoea, which has been described as large volume and watery without blood or mucus. Transmission occurs mainly during the 2nd week of illness.

## Clinical outcomes

Based on the analysis of data from Canada, China, Hong Kong SAR, Singapore, Vietnam and the USA during the 2003 epidemic, the case fatality ratio (CFR) of SARS is estimated to range from 0% to >50%, depending on the age group affected and reporting centre, with a crude global CFR of ~9.6%. Higher mortality has also been associated with male sex and presence of comorbidity in various studies.

## Radiological findings

Early chest radiography or computed tomography changes are observed in most patients as early as days 3–4 after the initiation of illness, in spite of the absence of respiratory signs. These typically show patchy consolidation, starting with a unilateral peripheral lesion, which progresses to multiple lesions or ground-glass appearance. Some lesions follow a shifting pattern. Features during the later stages have sometimes included spontaneous pneumothorax, pneumomediastinum, sub-pleural fibrosis and/or cystic changes.

## Haematological and biochemical findings

There are no haematological or biochemical parameters specific for SARS; however, studies have consistently highlighted the following.

### Haematological findings

Lymphopenia is common on presentation and progresses during the course of the illness. Sometimes thrombocytopenia and prolonged activated partial thromboplastin time are observed.

### Biochemical findings

Lactate dehydrogenase is frequently high and some reports have suggested an association with poor prognosis. Alanine aminotransferase, aspartate aminotransferase and creatine phosphokinase elevation are less frequently reported. Abnormal serum electrolytes have also been reported on presentation or during hospitalisation, including hyponatraemia, hypokalaemia, hypomagnesaemia and hypocalcaemia.

**Table 1** Criteria for laboratory confirmation of SARS-CoV infection

1. Detection of any of the following by a validated test, with confirmation in a reference laboratory:  
Serum antibodies to SARS-CoV in a single serum specimen OR  
A four-fold or greater increase in SARS-CoV antibody titre between acute- and convalescent-phase serum specimens tested in parallel OR  
Negative SARS-CoV antibody test result on acute-phase serum and positive SARS-CoV antibody test result on convalescent-phase serum tested in parallel **OR**
2. Isolation in cell culture of SARS-CoV from a clinical specimen, with confirmation using a test validated by CDC **OR**
3. Detection of SARS-CoV RNA by RT-PCR validated by CDC, with confirmation in a reference laboratory, from:  
Two clinical specimens from different sources OR  
Two clinical specimens collected from the same source on two different days

CDC: Centers for Disease Control and Prevention.

## Avian influenza

### Suggested further reading

Tran TH, Nguyen TL, Nguyen TD, et al. Avian Influenza A (H5N1) in 10 patients in Vietnam. *New Engl J Med* 2004; 350: 1179–1188.

Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998; 351: 467–471.

Chan PK. Outbreak of avian influenza A (H5N1) virus infection in Hong Kong in 1997. *Clin Infect Dis* 2002; 34: Suppl. 2, S58–S64.

### References

1. He J-F, Peng G-W, Zheng H-Z, et al. [An epidemiological study on the index cases of severe acute respiratory syndrome which occurred in different cities in Guangdong province.] In: Collection of papers on SARS published in CMA Journals. Beijing, Chinese Medical Association, 27 May 2003; pp. 44.
2. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 2003; 302: 276–278.
3. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1967–1976.
4. Peiris JSM, Lai ST, Poon LLM, et al. and SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; 361: 1319–1325.
5. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1953–1966.
6. Antia R, Rogoes RR, Koella JC, Bergstrom CT. The role of evolution in the emergence of infectious diseases. *Nature* 2003; 426: 658–661.
7. World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Based on data as of the 31 December 2003. [http://www.who.int/csr/sars/country/table2004\\_04\\_21/en/](http://www.who.int/csr/sars/country/table2004_04_21/en/)
8. Cyranoski D, Abbott A. Virus detectives seek source of SARS in China's wild animals. *Nature* 2003; 423: 467.
9. Ng SKC. Possible role of an animal vector in the SARS outbreak at Amoy Gardens. *Lancet* 2003; 362: 570–572.
10. Martina BE, Haagmans BL, Kuiken T, et al. Virology: SARS virus infection of cats and ferrets. *Nature* 2003; 425: 915.
11. World Health Organization. Severe acute respiratory syndrome (SARS) in Singapore, 10 September 2003. [http://www.who.int/csr/don/2003\\_09\\_10/en/](http://www.who.int/csr/don/2003_09_10/en/)
12. Biosafety and SARS incident in Singapore September 2003. Report of the Review Panel on New SARS Case and Biosafety. [http://www.moh.gov.sg/corp/sars/pdf/Report\\_SARS\\_Biosafety.pdf](http://www.moh.gov.sg/corp/sars/pdf/Report_SARS_Biosafety.pdf)
13. Lim PL, Kurup A, Gopalakrishna G, et al. Laboratory-acquired severe acute respiratory syndrome. *N Engl J Med* 2004; 250: 1740–1745.
14. World Health Organization. Severe Acute Respiratory Syndrome (SARS) in Taiwan, China, 17 December 2003. [http://www.who.int/csr/don/2003\\_12\\_17/en/](http://www.who.int/csr/don/2003_12_17/en/)
15. World Health Organization. SARS: one suspected case reported in China, 22 April 2004. [http://www.who.int/csr/don/2004\\_04\\_22/en/](http://www.who.int/csr/don/2004_04_22/en/)
16. World Health Organization. China's latest SARS outbreak has been contained, but biosafety concerns remain - Update 7, 18 May 2004. [http://www.who.int/csr/don/2004\\_05\\_18a/en/](http://www.who.int/csr/don/2004_05_18a/en/)
17. World Health Organization. Summary of the discussion and recommendations of the SARS laboratory workshop, 22 October 2003. <http://www.who.int/csr/sars/guidelines/en/SARSLabmeeting.pdf>
18. World Health Organization. Suspected severe acute respiratory syndrome (SARS) case in southern China, 28 December 2003. [http://www.who.int/csr/don/2003\\_12\\_28/en/](http://www.who.int/csr/don/2003_12_28/en/)
19. World Health Organization. New case of laboratory-confirmed SARS in Guangdong, China - Update 5, 31 January 2004. [http://www.who.int/csr/don/2004\\_01\\_31/en/](http://www.who.int/csr/don/2004_01_31/en/)
20. Liang G, Chen Q, Xu J, et al. Laboratory diagnosis of four recent sporadic cases of community-acquired SARS, Guangdong Province, China. *Emerg Infect Dis* 2004; 10: 1774–1781.
21. Hon KLE, Leung CW, Cheng WTF, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet* 2003; 361: 1701–1703.

## SARS

### Suggested further reading

[www.sarsreference.com](http://www.sarsreference.com) (3rd Ed). Kamps BS, Hoffman C, eds. SARS Reference. October 2003.

Background SARS picture Akira Yamaguchi