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Summary

The epidemic has been geographically focused in China, and is associated with exposure to infected poultry.

Five annual epidemic waves of human cases occurred during 2013 to 2017, with the largest wave occurring in 2016 to 2017. Three sporadic human cases were reported in 2018, and only one case was reported in the first half of 2019.

The risk to public health is low; however, the pandemic potential of this virus is concerning. Case clusters of limited human-to-human transmission have been described, but there is no evidence of sustained transmission.

Infection prevention and control measures for routine care include standard, droplet, and contact precautions. Particulate respirators are recommended for aerosol-generating procedures.

There is a high cumulative case-fatality proportion of approximately 39% among hospitalised patients with laboratory-confirmed infection.

Reverse transcription polymerase chain reaction of respiratory tract samples at a designated public health laboratory is the recommended diagnostic test.

Treatment involves supportive care, specialised intensive-care management, and prompt administration of a neuraminidase inhibitor.

Definition

Avian influenza A viruses are generally confined to birds but have infected other mammals and some viruses have crossed the species barrier to sporadically infect humans. Highly pathogenic avian influenza (HPAI) A(H5N1) virus is capable of causing severe multi-system disease in birds, humans, and other mammals.[1] Until 2017, Asian lineage A(H7N9) virus infections in birds were associated with only asymptomatic infection or mild illness (characterised as low-pathogenic avian influenza [LPAI]). In February 2017, the detection of Asian lineage HPAI A(H7N9) viruses was reported for the first time in the People’s Republic of China (hereafter referred to as China), in samples from human cases, and from poultry and their environments.[2] [3] Regardless of pathogenicity assessments in birds, Asian lineage LPAI A(H7N9) virus typically causes severe illness in infected humans.[4]

Following the detection of Asian lineage LPAI A(H7N9) virus infection in humans in eastern China in March 2013, A(H7N9) viruses that are genetically similar to isolates from human cases were detected in poultry and environmental samples obtained from live animal markets in China.[5] [6] Investigations of isolated clusters of human infections where zoonotic transmission was thought to be unlikely suggest that human-to-human transmission may occur with Asian lineage LPAI A(H7N9) viruses, although transmission appears to be limited and non-sustainable to date.[3] [7] [8] [9] [10] [11] Nosocomial transmission, including patient-to-healthcare worker, and patient-to-patient, has been reported for Asian lineage LPAI A(H7N9) viruses.[12] [13] [14]

Epidemiology

In late March 2013, three human cases of novel influenza A(H7N9) virus infection were reported by Chinese health authorities. This was the first time A(H7N9) virus infection had been identified in humans and the first time a low-pathogenic avian influenza (LPAI) virus infection had caused critical illness with fatal outcomes in humans. As of June 2019, the current risk to the public’s health posed by Asian lineage A(H7N9) virus is low; however, the pandemic potential of this virus is concerning. Influenza viruses constantly change and it is possible that this virus could evolve to gain the ability to spread easily and sustainably among people, triggering a widespread pandemic.

Five distinct epidemic waves of Asian lineage A(H7N9) virus infections were observed in humans in China between 2013 and 2017. Between October 2017 and June 2019, only a small number of sporadic human cases were reported in 2018 and the first half of 2019. Human infections with A(H7N9) virus have generally coincided or overlapped with annual outbreaks of seasonal influenza in China, with sporadic cases detected at other times of the year.

Between 2013 and 2017 an increase in cases was reported annually, peaking in the fifth wave (2016 to 2017). From March 2013 to August 2017, 1557 cases of human infection with Asian lineage A(H7N9) virus were reported, with 759 reported during the fifth wave. From 2013 to 2017, 39% of the reported cases were fatal. There has been a marked decline in reported cases since the end of the fifth wave, with only 4 cases reported between October 2017 and June 2019. The decrease in reported cases is associated with decreased Asian lineage A(H7N9) virus detections in birds and the environment. Closure of live bird markets in urban areas contributed to reducing human exposures to A(H7N9) virus and zoonotic transmission. However, closure of live bird markets has also been reported to result in the spread of A(H7N9) virus among poultry to other areas. It is likely that implementation of a bivalent H5-H7 poultry vaccination programme in China has contributed to the sharp reduction in human infections with A(H7N9) viruses.

The majority of Asian lineage A(H7N9) virus infections in humans have occurred in the eastern half of mainland China, although cases have also been reported by provinces in south-west and north-west China. Large case-series have shown that all evaluated case-patients had histories of recent travel to affected provinces in mainland China. Asian lineage A(H7N9) virus infections have been detected outside China, with one case reported by Malaysia in February 2014, two cases reported by Canada in 2015, and five cases reported by Taiwan between 2013 and 2017. All of these cases were travel-associated and the infections were thought to have been acquired in mainland China.

Between February 2013 and June 2019, 616 of 1568 patients have died (case-fatality proportion 39%). The proportion of fatalities has been similar for each of the epidemic waves. Severity-of-illness data from the second wave revealed that 218 of 219 patients who attended medical services required admission to hospital and 191 of 218 (87.6%) hospitalised patients were reported to have severe respiratory complications or critical illness. Estimates of symptomatic case-fatality risk suggest that Asian lineage LPAI A(H7N9) virus infection is more likely to cause death than seasonal influenza A(H1N1)pdm09 virus infection, but is less likely to cause death than highly pathogenic avian influenza (HPAI) A(H5N1) virus infection.

In one large case-series, the mean age at presentation was 55.5 years (range 2-91 years) and infection had occurred more commonly in men than in women (male:female ratio 2:1). High frequencies of comorbidities have been observed in infected patients, and the presence of at least one comorbidity has been identified as a risk factor for infection with Asian lineage LPAI A(H7N9) virus. However, the risk of death is not...
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greater among those with comorbidities than in those without underlying chronic conditions. From 2013 to 2017, the number of incident cases had shifted from predominantly older to middle-aged adults and from urban locations to semi-urban and rural areas; however, the severity of illness among hospitalised patients had not changed.[51]

Chickens appear to be most susceptible to Asian lineage LPAI A(H7N9) virus infection, but the virus has been detected in other poultry species including ducks and quail. Although pigs can be infected, exposure to pigs has not been implicated in the epidemiology of human infections with Asian lineage LPAI A(H7N9) virus.[66] [67] [68] Many infected patients reported contact with poultry or markets where live birds are sold and/or slaughtered. Genetic similarity has been demonstrated in Asian lineage LPAI A(H7N9) viruses isolated from patients and Asian lineage LPAI A(H7N9) viruses obtained from live chickens in epidemiologically linked markets.[5] Chickens and ducks account for most positive detections of Asian lineage A(H7N9) LPAI in studies of live poultry markets, but Asian lineage A(H7N9) LPAI virus RNA has also been detected in samples from quail and pigeons, as well as in environmental and water samples obtained from the same markets.[69] Songbirds and small terrestrial birds have been shown to be susceptible to infection with Asian lineage LPAI A(H7N9) virus, but their role in zoonotic transmission to humans is not known.[70] The prevalence of LPAI and HPAI Asian lineage A(H7N9) virus infections in migratory birds within China and elsewhere remains unclear. Asian lineage LPAI A(H7N9) virus was detected in a healthy tree sparrow in Shanghai, but the virus was not detected in over 2000 samples from other wild birds in Shanghai that were tested in the same study.[71] This suggests that monitoring of infection in non-poultry birds is required and that infection in migratory birds or export of infected poultry could spread Asian lineage A(H7N9) viruses beyond China. The emergence of Asian lineage A(H7N9) viruses with high-pathogenicity properties reflects, by definition, increased pathogenicity in birds, but not necessarily in humans. Human infection with Asian lineage A(H7N9) virus after exposure to sick and dying birds may serve to increase awareness of the potential increased risk and lead to earlier health-seeking or diagnosis. No difference in disease severity has been seen among people with Asian lineage HPAI or LPAI A(H7N9) virus infection.[25] [72]

Retrospective epidemiological analyses suggest that at least 75% of confirmed Asian lineage LPAI A(H7N9) virus-infected case-patients had recent contact with domestic poultry.[73] An ecological study utilising statistical modelling suggested that deliberate closures of poultry markets were effective in curtailing human outbreaks of Asian lineage LPAI A(H7N9) virus infections in several Chinese cities.[55] In contrast to HPAI A(H5N1), many Asian lineage LPAI A(H7N9) virus infections have occurred in urban areas and have not been associated with rearing or slaughtering ‘backyard’ poultry. Asian lineage LPAI A(H7N9) virus infection does not cause sickness or death in poultry, leading to ‘silent’ zoonotic transmission. By contrast, the recently emerged Asian lineage HPAI A(H7N9) virus does cause sickness and death in poultry, similar to HPAI A(H5N1) virus infection. The UN Food and Agriculture Organization reported that from October 2016 to June 2019, 290 samples from birds and the environment tested positive for A(H7N9) virus, with 44 (15%) identified as HPAI and the remainder identified as LPAI viruses.[53] It is not clear yet as to whether the HPAI virus will become the predominant circulating Asian lineage A(H7N9) virus in poultry in China, but if it becomes prevalent, then outbreaks in poultry should be easier to detect.

A study of 396 poultry workers from areas where Asian lineage LPAI A(H7N9) virus is known to circulate among poultry found that 25 of 396 (6%) workers had detectable antibodies (haemagglutinin inhibition titres ≥80) against A(H7N9) virus. By contrast, antibodies were not detected in over 1000 samples tested from the general population.[74] Other retrospective studies have reported lower seroprevalence of antibodies to A(H7N9) virus or low incidence and seroconversion among Chinese poultry workers.[75] [76] [77] An
additional retrospective study did not find serological evidence of A(H7N9) virus infection in poultry workers from eastern China prior to November 2012.\[78\]

Experimental models of infection reveal that Asian lineage, avian-origin LPAI A(H7N9) virus can replicate in ferrets, mice, pigs, and non-human primates. Droplet transmission of Asian lineage LPAI A(H7N9) virus does occur in ferret models, but compared with A(H1N1)pdm09 virus, transmission in ferrets appears to be less effective. Despite epidemiological investigations linking infections in humans to infections in chickens, Asian lineage LPAI A(H7N9) virus replicates poorly in chickens and could not be transmitted efficiently from infected chickens to naive chickens (or ferrets) in experimental models. Genetic analysis of Asian lineage LPAI A(H7N9) viruses revealed substitutions associated with mammalian adaptation, but it is likely that additional adaptations would be required to facilitate efficient human-to-human transmission.

Case-clusters of confirmed infection have been detected in China, but to date there is no evidence of sustained human-to-human transmission of Asian lineage A(H7N9) virus.[11] [48] [79] Fatal Asian lineage LPAI A(H7N9) virus infection in a healthcare worker has been reported, but a confirmed source of infection was not identified and there was no known contact with a confirmed case.[80] Nosocomial transmission, including patient-to-healthcare worker, and patient-to-patient, is possible with human infections with novel influenza A viruses, and has been reported for Asian lineage LPAI A(H7N9) viruses.[12] [13] [14] Therefore, specific infection prevention and control measures, including droplet and airborne precautions, should be implemented as soon as possible for any patient who is a suspected case of novel influenza A virus infection, including Asian lineage A(H7N9) virus, to prevent healthcare-associated transmission.

Other avian influenza A viruses (e.g., H5, H6, H7, H9, H10 viruses) have caused human illness ranging from mild (e.g., conjunctivitis, uncomplicated influenza-like illness) to fatal disease.[16] [17] [18] [22] [81] [82] [83] [84] [85] [86] [87] [88]

**Aetiology**

The natural reservoir for influenza A viruses is wild aquatic birds, such as ducks and geese. Most influenza A virus subtypes identified to date, including 18 haemagglutinin and 11 neuraminidase subtypes, have been identified among birds.[89] Influenza A(H17N10) and A(H18N11) viruses have been identified in bats.[89] [90] Other animal species can also be infected by influenza A viruses, including pigs, marine mammals, horses, dogs, cats, and penguins.

Avian influenza A viruses can infect tissues of the respiratory and gastrointestinal tracts of birds, which have receptors with sialic acid bound to galactose by alpha-2,3 linkages.[26] [91] Asian lineage low-pathogenic avian influenza (LPAI) A(H7N9) virus was detected for the first time in humans in March 2013. Unlike highly pathogenic avian influenza (HPAI) A(H5N1), Asian lineage LPAI A(H7N9) virus is associated with asymptomatic or sub-clinical infection in birds, making surveillance of outbreaks in poultry difficult. Closely related gene sequences were found in A(H7N9) viruses obtained from wild ducks in South Korea in early 2011, although it is not clear precisely when genetic reassortment events occurred between different viruses to give rise to Asian lineage A(H7N9) virus detected in 2013.[6] [29] [92] In 2017, Asian lineage HPAI A(H7N9) virus was detected in human respiratory specimens, poultry, and environmental samples, indicating evolution from Asian lineage LPAI A(H7N9) virus during circulation among poultry.[2] [42] [93]

Other influenza A viruses are also subject to genetic reassortment. Previous pandemic viruses are believed to have emerged in human populations through mutation from a zoonotic reservoir virus (1918 H1N1);
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genetic reassortment between LPAI avian influenza A viruses and seasonal influenza A viruses (1957 H2N2, 1968 H3N2); and genetic reassortment between triple reassortant swine influenza A(H1N1) and other swine influenza A viruses (A[H1N1]pdm09).[94] [95] A potential exists for Asian lineage A(H7N9) virus to undergo reassortment events with co-circulating seasonal influenza A viruses.

**Pathophysiology**

Like other influenza A viruses, the Asian lineage low-pathogenic avian influenza (LPAI) A(H7N9) virus binds to receptors bearing sialic acid residues. A(H7N9) viruses have been shown to attach to both human upper and lower respiratory tract epithelial cells,[96] facilitated by binding to alpha-2,6-linked sialic acid residues (the receptors to which human seasonal influenza viruses bind) and alpha-2,3-linked sialic acid residues (the common avian influenza A virus receptors). Alpha-2,3 receptors are primarily, but not entirely, distributed in the human lower respiratory tract, whereas alpha-2,6 receptors are the predominant receptor in the human upper respiratory tract. Ex vivo studies suggest that A(H7N9) virus is better adapted and replicates more efficiently than highly pathogenic avian influenza (HPAI) A(H5N1) virus in human respiratory tract tissues.[97] Unlike other avian influenza viruses, Asian lineage LPAI A(H7N9) virus binds to ciliated epithelial cells of the nasal concha, trachea, and bronchus, in addition to the expected avian pattern of binding to alveolar epithelial cells, alveolar macrophages, and club cells (also known as bronchiolar exocrine cells or Clara cells) in the terminal bronchioles. The binding patterns of examples of Asian lineage A(H7N9) viruses have also been studied ex vivo in tissues obtained from ferrets, macaques, mice, pigs, and guinea pigs; wider tissue tropism is seen overall compared with HPAI A(H5N1) virus. It should be noted that the binding pattern of Asian lineage LPAI A(H7N9) virus in ferret tissues is markedly different from binding patterns in human tissues, with only limited attachment of Asian lineage LPAI A(H7N9) virus to ferret tracheal and bronchial epithelial cells.[98] This may help explain, at least in part, why airborne transmission of Asian lineage LPAI A(H7N9) virus between ferrets appears to be possible but is inefficient,[34] [99] [100] but does not explain the apparent inefficient transmission between humans. Experimental infection of ferrets is associated with shedding of high titres of Asian lineage LPAI A(H7N9) virus for 6 to 7 days, and shedding is seen in pigs for 6 days. Transmission did not occur between infected pigs and naive pigs or ferrets in the same model.[100]

Mice infected with Asian lineage LPAI A(H7N9) virus isolated from infected humans experience induction pro-inflammatory cytokines in serum and lung secretions, and during early infection cytokine levels positively correlate with virus load in the lungs. However, Asian lineage LPAI A(H7N9) virus appears to be less pathogenic than HPAI A(H5N1) virus in mice.[101] Increased levels of pro-inflammatory cytokines and chemokines have been observed in serum obtained from patients in the acute phase of Asian lineage LPAI A(H7N9) virus infection.[35] Serum levels of interleukin (IL)-6 and inducible protein-10 (IP-10) may positively correlate with severity of illness.[102] Others have shown that levels of pro-inflammatory cytokines in bronchoalveolar lavage fluid tend to be greater than levels in plasma and that patients with higher plasma levels of IL-6, IL-8, and macrophage inhibitory protein 1-beta (MIP-1-beta) were more likely to have more severe illness or fatal outcomes.[103] Similar to findings in seasonal and pandemic influenza,[104] [105] Asian lineage LPAI A(H7N9) virus-infected patients with the interferon-induced transmembrane protein-3 (IFITM3) rs12252-C, complement decay-accelerating factor (CD55) rs2564978, and toll-like receptor (TLR3) rs5743313 genetic polymorphisms are more likely to have severe disease.[103] [106]

In addition to detection in respiratory tract secretions, Asian lineage LPAI A(H7N9) virus RNA has been detected in blood, urine, and faeces in fatal and non-fatal cases.[107] [108] The virus has been detected in multiple extrapulmonary organs in mouse and ferret models, including in brain and cardiac tissue, but
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has not been detected in the small number of human cerebrospinal fluid samples that have been analysed. Reactive haemophagocytosis has been reported at autopsy.[107] Whether human infection with Asian lineage HPAI A(H7N9) virus will result in increased extrapulmonary spread and clinical manifestations (e.g., central nervous system disease) compared with Asian lineage LPAI A(H7N9) virus infection is not yet known.

Avian influenza A viruses, including Asian lineage A(H7N9) virus, can potentially be transmitted to humans through different modalities.

- Direct or close exposure to infected sick or dead poultry or poultry products is thought to be the major risk for transmission of avian influenza A viruses to humans, including Asian lineage A(H7N9).[7] [55]
- Inhalation of aerosolised material (e.g., poultry faeces) containing infectious Asian lineage A(H7N9) virus is a possible route of transmission from poultry to humans.[109]
- Self-inoculation of the mucous membranes after direct contact with material containing Asian lineage A(H7N9) virus (touching or cleaning infected birds), or indirect (fomite) contact transmission from surfaces contaminated with poultry faeces or products containing Asian lineage A(H7N9) virus to mucous membranes, are other possible routes of transmission.[109]
- Consumption of uncooked poultry products, including blood from infected birds, has been identified in field investigations of HPAI A(H5N1) outbreaks as a potential risk factor for infections in humans, but it remains uncertain as to whether A(H5N1) and other avian influenza A viruses can cause infections via the human gastrointestinal tract.[1] [110]
- The handling and preparation of infected uncooked meat may pose a greater risk, although quantified risk estimates are not available.

Classification

Pathogenicity

Avian influenza A virus strains are classified as low-pathogenic avian influenza (LPAI) or highly pathogenic avian influenza (HPAI) using criteria that include molecular analyses and assessment of pathogenicity in experimentally infected chickens. Notably, the terms LPAI and HPAI do not describe, or necessarily correlate with, the severity of illness caused by infection in humans.

- Most avian influenza A viruses are LPAI viruses and cause asymptomatic infection or mild disease in infected poultry. LPAI H6N1, H7N2, H7N3, H7N4, H7N7, H7N9, H9N2, H10N7, and H10N8 virus strains have infected humans causing disease ranging from conjunctivitis to non-fatal upper respiratory and lower respiratory tract disease, to severe lower respiratory tract disease and death (H7N9, H10N8).[15] [16] [17] [18] [19] [20] [21]
- All HPAI viruses identified to date are of the H5 and H7 subtypes and can cause severe illness in poultry. HPAI virus infections in humans have ranged from asymptomatic to severe or fatal disease. Rare, sporadic human cases of HPAI virus infection have been detected, for example with H5N1, H5N6, H7N3, and H7N7 viruses, and have caused a wide spectrum of illness from conjunctivitis (including H7N3 and H7N7 viruses) to acute respiratory distress syndrome and fatal outcomes (such as H7N7 and H5N1 viruses).[22] [23] [24]
- During 2013 to 2016, all human cases of A(H7N9) virus infection were caused by LPAI viruses. From February 2017, Asian lineage A(H7N9) viruses with genetic characteristics of HPAI were detected in 3 human cases, and environmental and poultry samples, in China.[2] [25]
Virology

Asian lineage A(H7N9) is a reassortant virus that contains genetic material from other avian influenza A viruses. The LPAI form of Asian A(H7N9) virus was the first LPAI virus to cause a significant outbreak of severe and fatal illness in humans. The RNA segment encoding the haemagglutinin is derived from a Eurasian A(H7) avian virus found in ducks and the segment encoding the neuraminidase is similar to avian A(H11N9) and other avian A(H7N9) viruses, which may have infected migratory birds. Six internal RNA segments are closely related to A(H9N2) viruses isolated from poultry in China, and at least two subclades of LPAI A(H7N9) virus have been identified.[26] [27]

Analysis suggests that multiple, sequential reassortment events occurred to form the novel Asian lineage LPAI A(H7N9) virus, probably taking place in ducks and chickens. The animal reservoirs for Asian lineage A(H7N9) virus that have infected humans have not been confirmed, but the virus has been detected in samples from domestic birds sold in live poultry markets in eastern and southern China.[5] [28] Asian lineage LPAI A(H7N9) virus can infect chickens, ducks, quail, pigeons, and geese; experimentally infected quail can transmit Asian lineage LPAI A(H7N9) virus to other quail.[29] The virus replicated in ferrets, mice, and non-human primates following experimental infection. Although the virus has genetic markers of mammalian adaptation, Asian lineage LPAI A(H7N9) virus appears to be less transmissible than A(H1N1)pdm09 virus in a ferret model of infection and transmission.[26] [27]

The Asian lineage LPAI A(H7N9) virus has demonstrated genetic and antigenic evolution since it emerged in 2013, which is not unexpected or unusual for influenza A viruses. Two main sub-lineages of the Asian lineage A(H7N9) LPAI virus have been described, demonstrating different geographical presence within China: the Yangtze River Delta sub-lineage and the Pearl River Delta sub-lineage.[3] [30] Additionally, the detection of insertion mutations at the multi-basic cleavage site of the viral haemagglutinin gene, reported in February 2017, signifies the emergence of an Asian lineage HPAI A(H7N9) virus.[2] [3] The cleavage site of HPAI A(H5N1) viruses has been shown to be a virulence factor in mammals (including humans); by contrast, experimental induction of the HPAI cleavage site in an A(H3N2) virus did not increase virulence in a ferret model of infection. There is some evidence that HPAI A(H5N1) viruses may have reduced airborne transmissibility,[31] [32] and are associated with a lower viral burden,[33] [34] compared with LPAI A(H5N1) viruses. There is no evidence currently to suggest that the Asian lineage HPAI A(H7N9) virus is associated with increased severity of disease in humans, nor increased transmissibility from birds to humans or between humans, but additional studies and monitoring of this evolving virus are required.

Amino acid substitutions associated with reduced susceptibility to neuraminidase inhibitor antivirals have also been detected sporadically in Asian lineage A(H7N9) viruses,[35] [36] [37] [38] [39] [40] [41] including some of the more recently detected HPAI viruses.[2] For viruses where sequence analysis has been performed, the proportions with reduced susceptibility have been similar between different annual waves of Asian lineage A(H7N9) virus activity.[2] [42] Genetic analysis of 83 recent Asian lineage A(H7N9) viruses identified amino acid substitutions associated with reduced susceptibility in three viruses: two with R292K and one with A246T (N2 numbering).[2] Viruses with the R292K amino acid substitution demonstrate resistance to oseltamivir and reduced susceptibility to zanamivir and peramivir.[37] Some isolates have demonstrated reduced susceptibility to oseltamivir but not to peramivir.[43] Although reporting of associated clinical data is incomplete, some viruses with reduced susceptibility appear to have emerged following or during use of neuraminidase inhibitors for treatment in the affected individuals.[42] Several amino acid substitutions that confer reduced susceptibility to neuraminidase inhibitors do not confer a virus fitness cost (i.e., replication of Asian lineage HPAI A(H7N9) virus is not reduced) in cell lines in vitro.[44] Sequencing data suggest that all Asian lineage A(H7N9) viruses are inherently resistant to adamantane antivirals (amantadine and rimantadine) because they all possess the S31N amino acid substitution.
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It should be noted that the North American wild bird lineage HPAI A(H7N9) virus, detected in commercial poultry flocks in Tennessee, US, in March 2017, is genetically distinct from the Asian lineage A(H7N9) virus. North American wild bird lineage LPAI A(H7N9) virus has also been detected in poultry in the US; no human infections have been identified to date with either the HPAI virus or the LPAI A(H7N9) virus in the US. Other distinct LPAI A(H7N9) viruses were detected in wild birds prior to the emergence of Asian lineage A(H7N9) virus in 2013.[45]

Case history

Case history #1

A previously healthy 68-year-old Chinese man develops acute-onset fever (body temperature >38.8°C [>102°F]) and fatigue for two days. He had visited a local live poultry market one week before onset of symptoms to buy fresh chicken meat for a meal he prepared for his family. None of his family experience similar symptoms. Over the following two days he remains febrile, and develops a new, productive cough. He becomes increasingly short of breath, so his daughter takes him to the local hospital. A chest radiograph reveals multilobar, patchy lung infiltrates. A full blood count reveals a normal white cell count but lymphopenia, and the platelet count is below the normal range. C-reactive protein, alanine aminotransferase, and aspartate aminotransferase are all found to be elevated. A nasopharyngeal swab collected upon hospitalisation is tested for a panel of influenza and other respiratory viruses. Influenza A(H7N9) virus infection is confirmed by reverse transcription polymerase chain reaction (RT-PCR).

Case history #2

A 45-year-old Chinese-Australian woman with hypertension and diabetes mellitus develops progressive fever, headache, non-productive cough, and shortness of breath on minimal exertion, five days after returning to Australia from central China. She had stayed with relatives in a small city to celebrate Chinese New Year, but had not visited any live poultry markets. Her husband, who did not travel with her, has coryzal symptoms only. On arrival to the emergency department, she is tachypnoeic, tachycardic, and hypotensive, and has oxygen saturations of 90% on room air. She coughs while being assessed and then vomits. Auscultation reveals decreased breath sounds at the base of her left lung. A chest radiograph demonstrates patchy infiltrates in lower zones of both lung fields and a focus of dense consolidation in the right lower lobe. Laboratory findings include leukocytosis, lymphopenia, anaemia, thrombocytosis, and hypoxaemia. C-reactive protein, lactate dehydrogenase, and procalcitonin are all elevated, but the creatine kinase level is normal. She deteriorates rapidly, requiring intubation and mechanical ventilation 8 hours after being admitted to hospital. A computed tomography scan of her thorax is performed, revealing bilateral ground glass changes and dense consolidation of the left lower lobe and a small pleural effusion. Clinical specimens including combined nose and throat swabs and endotracheal aspirates are tested by RT-PCR for a panel of influenza and other respiratory viruses daily. While day 1 specimens test negative for respiratory viruses, the day 2 endotracheal aspirate tests positive for presence of influenza A(H7N9) virus.

Other presentations

Mild influenza-like illness without organ dysfunction has been described, but is uncommon. In the first three months of the 2013 outbreak, a large surveillance system in mainland China assessed patients...
Avian influenza A(H7N9) virus infection

presenting to outpatient services and emergency departments with influenza-like illness.[46] Asian lineage low-pathogenic avian influenza (LPAI) A(H7N9) virus infection was confirmed in five patients, three of whom had mild illness (fever and upper respiratory tract symptoms) and did not require hospitalisation. Two of the patients were young children and one was a 26-year-old adult. Diarrhoea or vomiting was reported in 14% in one case series, although not as isolated symptoms. Unlike infection with other avian influenza A(H7) viruses, initial conjunctivitis has not been reported. Similar to highly pathogenic avian influenza (HPAI) A(H5N1) and complicated seasonal influenza A(H1N1)pdm09 virus infections, most patients with Asian lineage A(H7N9) virus infection present with symptoms consistent with moderate or severe community-acquired pneumonia.
**Approach**

Clinico-epidemiological evaluation is required to guide diagnostic testing for Asian lineage A(H7N9) virus infections. In most H7N9 cases there is history of exposure to poultry in endemic areas, including visiting markets where poultry are sold live or slaughtered or through contact with backyard chickens, which can be useful in case recognition because the clinical and radiological features are non-specific and mimic other causes of viral and bacterial pneumonia.

If there is concern that a patient might be infected with Asian lineage A(H7N9) virus, recommended infection prevention and control precautions should be implemented as soon as possible, including patient isolation and the use of personal protective equipment by healthcare workers and family member carers (face mask, goggles, disposable gown, and gloves). Due to the potential to cause severe disease, suspected H7N9 infection is notifiable, and public health experts should be involved early. Positive laboratory results for human infection with any avian influenza A virus should also be reported to the World Health Organization (WHO) under the International Health Regulations.


**Background**

Influenza disease in humans is caused primarily by infection of the respiratory tract by influenza viruses. Of four known types of influenza viruses, three types (A, B, C) are known to infect humans, with influenza A and B virus infections most clinically significant. Seasonal influenza epidemics during colder periods in temperate climates result in a spectrum of illness, from asymptomatic infection to upper respiratory tract illness with or without fever and exacerbation of chronic illness, and may progress to severe and fatal complications.

Patients with Asian lineage A(H7N9) virus infection can present with signs and symptoms of pneumonia similar to those caused by other pathogens (including influenza A[H1N1]pdm09 and other seasonal influenza A or B viruses). There is a wide spectrum of disease ranging from asymptomatic infection,[113] to sub-clinical or only mild symptoms,[46] [114] to severe respiratory compromise and death.[115] However, most patients with Asian lineage A(H7N9) virus infection have required hospitalisation for management of pneumonia and/or respiratory failure.[4] [7] [37] In contrast to the late clinical presentation that is seen with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection, some Asian lineage low-pathogenic avian influenza (LPAI) A(H7N9) virus-infected patients have presented to medical care soon after onset of symptoms. Similar to HPAI A(H5N1) cases, initiation of antiviral therapy has been delayed in many patients with LPAI A(H7N9) virus infection (median 6 days; range 0-15 days).[7] [37] [116]

Given that human infection with Asian lineage A(H7N9) virus appears to be rare (even among people with high-risk exposures within China) diagnostic evaluation and therapy must consider alternative aetiologies.

**History**

The median incubation period of Asian lineage LPAI A(H7N9) viruses in infected humans following poultry exposures has been estimated to be between 3 to 4 days and 6 days (range: 1-10 days) in different studies.[7] [117] [118] In all countries, Asian lineage A(H7N9) virus infection should be considered in patients who develop acute febrile respiratory illness within 10 days of potential exposure to the virus.
Avian influenza A(H7N9) virus infection

**Diagnosis**

Exposure risks include a history of travel within 10 days of symptom onset to an area where Asian lineage A(H7N9) viruses are known to be circulating in animals (e.g., poultry) or humans, or exposure to wild or domestic animals or having visited environments in affected areas, such as markets or farms where live animals (especially poultry) are kept, sold, or slaughtered. Asian lineage A(H7N9) virus infection should also be considered in healthcare workers and close contacts who develop compatible symptoms within 10 days of contact with a suspected or confirmed case of Asian lineage A(H7N9) virus infection. To date, all acquisition of A(H7N9) virus infection in humans has occurred in China. The WHO advises that clinicians in China and neighbouring countries should consider testing for Asian lineage A(H7N9) virus infection in hospitalised patients with severe unexplained acute respiratory illness. Similarly, because exported cases of Asian lineage A(H7N9) virus infection acquired in China have been identified in Taiwan, Malaysia, and Canada, a history of potential exposure to poultry should be asked of any patient who has recently travelled to China and presents with severe unexplained acute respiratory illness.

Early illness is manifested by signs and symptoms consistent with a febrile upper respiratory tract infection. A dry or productive cough and dyspnoea are common symptoms. Non-specific symptoms consistent with influenza-like illness have been reported (headache, sore throat, myalgia, and fatigue). Clinical progression to severe lower respiratory tract disease occurs in many patients during days 3 to 6 of illness. Clinically mild disease (fever and symptoms of upper respiratory infection) has been described. At admission, most patients have fever and clinical findings similar to community-acquired pneumonia. In a series of 111 patients, 13.5% reported diarrhoea or vomiting.[116]

Most patients admitted to hospital with Asian lineage LPAI A(H7N9) virus infection have experienced severe lower respiratory tract disease, often with multi-organ dysfunction or failure (renal, respiratory, hepatic, and cardiac). Other reported complications include haemophagocytosis, shock requiring vasopressor support, and disseminated intravascular coagulation. Acute respiratory distress syndrome and/or multi-organ failure is a common feature of fatal cases.[4] [7] [37] [107] [108] [116] Clinical data for Asian lineage HPAI A(H7N9) virus infections are limited, due to the small number of cases identified and reported.[25] [72] [119] [120]

**Physical examination**

Physical examination findings in severe illness associated with Asian lineage A(H7N9) virus infection are usually similar to those seen in severe pneumonia due to other aetiologies. They typically include raised body temperature ≥38°C (≥100.4°F), tachypnoea, and abnormalities on chest auscultation (which may include rales, wheezing, and focal decreased breath sounds). Based on clinical experience of severe influenza A virus infections, clinicians should be aware of atypical presentations of Asian lineage A(H7N9) virus infection such as altered mental status, seizures, and febrile diarrhoeal illness progressing to pneumonia.

Mild illness with Asian lineage A(H7N9) virus infection may be indistinguishable from uncomplicated human influenza virus infection. Physical examination findings include upper respiratory tract and constitutional signs and symptoms such as fever, cough, headache, and malaise. In contrast to illness caused by other influenza viruses, initial conjunctivitis appears to be uncommon in Asian lineage A(H7N9) virus infection.

**Initial investigations**

Because Asian lineage A(H7N9) virus infection is much less common than infection due to other respiratory viruses including seasonal influenza viruses, it is critical that diagnostic evaluation also includes work-up for a broad range of more common disease processes that may also present as febrile
respiratory illness, and investigation for endemic pathogens from the region where infection may have occurred.

First-line evaluation of patients suspected of having Asian lineage A(H7N9) virus infection should include the following.

- **Laboratory tests**, including at least an FBC with differential, basic chemistries, and hepatic enzymes: common findings in severe cases may include normal white cell count or mild leukopenia, lymphopenia, and mild to moderate thrombocytopenia, but these laboratory findings are not present in all cases and are unable to differentiate between illness caused by Asian lineage A(H7N9) virus and illness caused by other respiratory pathogens.
- **Chest radiograph**: lung infiltrates may be present, but a normal chest radiograph does not exclude the possibility of Asian lineage A(H7N9) virus infection.
- **Pulse oximetry**: should be performed in patients with dyspnoea to assess their oxygenation status, as well as arterial blood gas analysis if considered necessary.
- **Sputum Gram stain and bacterial culture, and blood culture**: should be performed as part of the evaluation for community-acquired primary bacterial pneumonia and potential bacterial co-infection. Urinary antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* may also be considered.
- **Respiratory virus testing** depending upon local surveillance and epidemiological data (e.g., seasonal influenza A and B viruses): other respiratory virus testing may be indicated (e.g., for respiratory syncytial virus, parainfluenza virus, and multiple virus aetiologies in immunocompromised patients).
- **Patients presenting with atypical signs and symptoms** (e.g., affecting gastrointestinal or neurological systems) should receive a suitable work-up directed at alternative aetiologies for those processes.
- **Local or national guidelines for safely obtaining and testing samples** should be followed. Guidance is available from the WHO website if local/national guidelines are not immediately available. [WHO: WHO information for molecular diagnosis of influenza virus - update.](https://www.who.int/influenza/gisrs_laboratory/molecular_diagnosis/en/)

We recommend that clinicians consider more common causes of influenza-like illness and community-acquired pneumonia whenever they encounter a patient they suspect has Asian lineage A(H7N9) virus infection. As always, work-up should be directed towards abnormal clinical findings. Other travel-associated infections relevant to the area visited should also be considered, as appropriate.

**Specific viral testing**

The recommended and definitive test for detecting Asian lineage A(H7N9) virus is reverse transcription polymerase chain reaction (RT-PCR) of respiratory specimens, including real-time or conventional RT-PCR, and using specific primers and probes. Asian lineage A(H7N9) virus strains have demonstrated genetic evolution over time, so testing by RT-PCR using up-to-date primers and probes is essential. However, RT-PCR for A(H7N9) viruses is usually not available in many clinical settings, where detection of non-subtyped influenza A virus is more typical. Many regional public health laboratories, most national laboratories, and some private laboratories can perform RT-PCR for A(H7N9) virus, or RT-PCR for avian A(H7) viruses with subsequent virus characterisation by genetic sequencing. If subtyping of a detected influenza A virus has been attempted locally, but seasonal A(H1) and A(H3) viruses could not be detected (‘unsubtypable influenza A’), the sample should be referred to a reference laboratory for further characterisation.
In non-intubated patients, the preferred respiratory specimens are nasal, nasopharyngeal, or oropharyngeal swabs. Healthcare workers collecting clinical specimens from patients with suspected A(H7N9) virus infection should follow recommended infection control precautions and use appropriate personal protective equipment.[20] [111] [121] [122]

Specific swabs are available to optimise the diagnostic yield for respiratory virus sampling (e.g., flocked Dacron swabs with plastic shafts that are placed in sterile viral transport medium). Using swabs with cotton tips or wooden shafts is not recommended because they may interfere with the RT-PCR assay. Swab specimens placed in bacterial transport medium (e.g., Amies swabs) are inappropriate samples for virus detection. Ideally, multiple respiratory specimens for testing should be collected from multiple respiratory sites from patients with suspected Asian lineage A(H7N9) virus infection, including over multiple days, because testing of single specimens may fail to detect Asian lineage A(H7N9) virus.

Intubated patients should also have endotracheal aspirates collected for Asian lineage A(H7N9) virus detection. Bronchoscopy and thoracocentesis are not recommended procedures for the sole purpose of collecting clinical specimens, but if collected for other diagnostic purposes, bronchoalveolar lavage fluid specimens and pleural fluid can also be tested.

National public health agencies have many useful online resources to assist clinicians to determine whether a particular patient should have clinical specimens tested for Asian lineage A(H7N9) virus, and typically they have medical officers available to consult and assist clinicians in the evaluation, testing, and case management of suspected or confirmed human Asian lineage A(H7N9) virus infection. The RT-PCR assay may take several hours to produce preliminary results, but transport time and testing logistics may delay testing results. Viral culture (isolation) should only be performed by an experienced, biosafety level 3-enhanced laboratory or greater following recommended personal protective equipment and infection control precautions.

Currently available, point-of-care, rapid influenza diagnostic tests lack satisfactory sensitivity and specificity for detecting A(H7N9) virus and, therefore, should not be used for diagnosis of Asian lineage A(H7N9) virus infection.[123] [124] [125] Molecular assays for influenza that are available in clinical settings have high sensitivity for detecting influenza A viruses in respiratory specimens, but cannot specifically identify or distinguish A(H7N9) virus from seasonal influenza A viruses.

Analysis of paired acute and convalescent sera, collected approximately 2 to 3 weeks apart and tested using specific serological assays, can potentially yield a retrospective diagnosis of Asian lineage A(H7N9) virus infection in a patient with clinically compatible illness, but cannot inform clinical management decisions. All positive tests on human clinical specimens for Asian lineage A(H7N9) virus should be confirmed by a designated public health reference laboratory. Positive laboratory results for human infection with any avian influenza A viruses (e.g., H7N9, H5N1, H5N6, H10N8 viruses) should be reported to the WHO under the International Health Regulations.

**History and exam**

**Key diagnostic factors**

**cough (common)**

- Present in most hospitalised patients and can be dry or productive. Haemoptysis was reported in 25% patients in one series.
Avian influenza A(H7N9) virus infection

**Diagnosis**

**typical influenza signs and symptoms (common)**

- Non-specific symptoms that are often associated with influenza including cough, fever, headache, myalgia, and fatigue have been reported in some clinically mild cases and as the initial symptoms prior to progression to lower respiratory tract disease. Sore throat and rhinorrhea appear to be less likely.

**dyspnoea (common)**

- Present in over 50% of hospitalised patients in a large published series.

**fever (common)**

- Usually temperature >38°C (>100.4°F) occurs early in the course of illness and may persist, especially with severe illness, but an absence of pyrexia does not exclude the possibility of infection.

**decreased breath sounds (common)**

- Frequency unknown, but common auscultatory finding in severe illness caused by other influenza A viruses. Signals decreased air movement through a part of the lung or lungs, and could indicate pulmonary consolidation, atelectasis, effusion, or acute respiratory distress syndrome.

**tachypnoea (common)**

- Frequency unknown, but common finding in severe illness caused by other influenza A viruses.

**Other diagnostic factors**

**vomiting, diarrhoea (uncommon)**

- Non-specific primary gastrointestinal symptoms have been reported in some A(H7N9) virus-infected patients.

**altered mental status (uncommon)**

- Non-specific neurological symptoms have been reported.

**Risk factors**

**Strong**

**environmental exposure to Asian lineage A(H7N9) virus**

- Many (but not all) patients with Asian lineage A(H7N9) virus infection report having visited or worked at a live poultry market in China. Some low-pathogenic avian influenza (LPAI) A(H7N9) virus-infected patients reported having direct or close contact with backyard poultry in rural areas of China. Most animal exposures involved poultry, but exposures to other birds and mammals have been reported.[7] Asian lineage A(H7N9) virus has been detected in chickens, ducks, and pigeons, but not in pigs. Asian lineage A(H7N9) virus RNA has been detected in goose meat and also in sewage obtained from a wet market.

**Weak**
close contact with infected humans

- As of February 2019, 40 case clusters of Asian lineage A(H7N9) virus infection have been reported since 2013, with most of the clusters containing no more than two individuals. Epidemiological investigations of family clusters suggest that most cases of Asian lineage A(H7N9) virus infection had poultry exposures. However, close and prolonged unprotected exposure, including providing basic care to an index case, is the most likely explanation for limited, non-sustained human-to-human transmission in some clusters; this has been reported after prolonged unprotected exposures in blood-related family members and in unrelated people, including nosocomial transmission (patient-to-healthcare worker, and patient-to-patient). The risk of human-to-human A(H7N9) virus transmission was similar during 2013 to 2017 and remains low.[11]

laboratory work with A(H7N9) virus

- Transmission of Asian lineage A(H7N9) virus to laboratory workers is not known to have occurred when appropriate laboratory health and safety measures have been followed.
- Biosafety level 2 practices and procedures are the minimum requirement for handling specimens suspected to contain Asian lineage A(H7N9) virus.[111] Biosafety level 3-enhanced containment standards are the minimum requirement for culture of suspected Asian lineage A(H7N9) virus.[111] A small serological survey of laboratory workers exposed to highly pathogenic avian influenza (HPAI) A(H5N1) virus with incomplete personal protective equipment use and adherence to biosafety precautions demonstrated no serological evidence of prior HPAI A(H5N1) virus infection.[112]
## Investigations

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBC with differential</strong></td>
<td>leukopenia or normal WBC; lymphopenia; thrombocytopenia</td>
</tr>
<tr>
<td>• Described in majority of patients in case series.</td>
<td></td>
</tr>
<tr>
<td><strong>liver function tests (alkaline phosphatase, hepatic aminotransferases, bilirubin)</strong></td>
<td>elevated aspartate aminotransferase/alanine aminotransferase</td>
</tr>
<tr>
<td>• Described in majority of patients in case series.</td>
<td></td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>may be normal; may show infiltrates consistent with pneumonia in severe cases</td>
</tr>
<tr>
<td>• CXR alone cannot exclude or differentiate viral or bacterial pneumonia.</td>
<td></td>
</tr>
<tr>
<td>• Lung infiltrates are commonly bilateral, diffuse (lower, middle, and upper zones can be affected), and show both central and peripheral distribution.</td>
<td></td>
</tr>
<tr>
<td><strong>pulse oximetry</strong></td>
<td>may show hypoxia</td>
</tr>
<tr>
<td>• Indicated in patients with dyspnoea or suspected pneumonia.</td>
<td></td>
</tr>
<tr>
<td><strong>sputum Gram stain</strong></td>
<td>visualisation of infecting organisms if bacterial pneumonia or potential bacterial co-infection</td>
</tr>
<tr>
<td>• Primary bacterial pneumonia and potential bacterial co-infection should be evaluated. Co-infections have been reported in Asian lineage A(H7N9) virus-infected patients, but mainly hospital-acquired bacterial infections and ventilator-associated pneumonia.</td>
<td></td>
</tr>
<tr>
<td><strong>sputum and blood bacterial culture</strong></td>
<td>growth of infecting organism if bacterial pneumonia or potential bacterial co-infection</td>
</tr>
<tr>
<td>• Primary bacterial pneumonia and potential bacterial co-infection should be evaluated in severely ill patients.</td>
<td></td>
</tr>
<tr>
<td><strong>reverse transcription polymerase chain reaction (RT-PCR) of respiratory specimens for Asian lineage A(H7N9) virus and influenza A and B viruses</strong></td>
<td>positive for H7-specific viral RNA</td>
</tr>
<tr>
<td>• This is the test of choice for diagnosis of Asian lineage A(H7N9) virus infection using H7-specific primers and probes to detect Asian lineage A(H7N9) viral RNA in respiratory clinical specimens.</td>
<td></td>
</tr>
<tr>
<td>Both real-time and conventional RT-PCR assays can be used to detect Asian lineage A(H7N9) virus RNA at national laboratories, highly specialised local public health laboratories, or some academic centre laboratories. RT-PCR for Asian lineage A(H7N9) virus is not available in most clinical settings. A(H7)-specific primers and probes should be updated regularly. RT-PCR for influenza A alone cannot differentiate between infection with seasonal influenza A and avian influenza A viruses, but failure to detect influenza A virus RNA reduces the likelihood of Asian lineage A(H7N9) virus infection. Concurrent assays for seasonal influenza A (H3N2 and H1N1pdm09) and influenza B viruses are recommended. All non-subtypable influenza A laboratory positive test results, particularly in clinically ill patients or those with risk factors for novel influenza virus infection, should undergo further testing with appropriate RT-PCR primers (or sequencing, if required) to identify the specific virus infection.</td>
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</table>
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>• Testing of upper respiratory tract specimens (e.g., nasal swabs, throat swabs, nasopharyngeal swabs/aspirates), even with RT-PCR assays, may produce false-negative results due to differential virokinetics along the respiratory tract. In instances where Asian lineage A(H7N9) virus infection is strongly suspected, a lower respiratory tract sample (e.g., sputum, tracheal aspirate, bronchoalveolar lavage) should be considered if samples are available. Intubation, bronchoscopy, and thoracentesis should not be performed for the sole purpose of obtaining clinical specimens for A(H7N9) virus testing. Repeated testing is also advisable to minimise the effect of sampling error.</td>
<td></td>
</tr>
<tr>
<td>• H7-positive results from national laboratories should be confirmed at World Health Organization (WHO) collaborating influenza centres. The WHO also accepts results of RT-PCR assays for novel influenza A viruses from some national influenza laboratories.[130]</td>
<td></td>
</tr>
<tr>
<td>• It is important to note that commonly available rapid antigen tests are insensitive in detecting influenza virus infections, including A(H7N9) virus infections, and cannot specifically identify A(H7N9) virus.[131] Thus a negative rapid antigen test result cannot be used to rule out influenza virus infections. Commercially available molecular influenza assays available in clinics and hospitals have high sensitivity to detect influenza viruses, but cannot specifically identify A(H7N9) virus in respiratory tract specimens, or distinguish A(H7N9) virus from seasonal influenza A viruses.</td>
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### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>viral culture of respiratory specimens</td>
<td>positive for A(H7N9) virus</td>
</tr>
<tr>
<td>• Virus culture will not produce timely results for clinical management and must be performed in a biosafety level 3-enhanced (BSL 3+) laboratory. Viral culture can be performed at World Health Organization (WHO) avian influenza reference laboratories and WHO collaborating influenza centres.</td>
<td></td>
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<tr>
<td>• Viral culture is important for virological surveillance, antigenic monitoring for vaccine strain selection, and assessment and analyses of viral characteristics such as genetic reassortment, receptor binding affinity, and antiviral susceptibility.</td>
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<tr>
<td>• Clinical specimens testing positive for A(H7N9) virus RNA by reverse transcription polymerase chain reaction may be cultured by a WHO avian influenza reference laboratory or WHO collaborating influenza centre laboratory.[130]</td>
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</tbody>
</table>
## Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>serological testing for A(H7N9)-specific antibody for</td>
<td>fourfold increase in A(H7N9) virus-specific antibody in convalescent</td>
</tr>
<tr>
<td>retrospective diagnosis</td>
<td>serum when compared with acute serum</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serological testing to demonstrate Asian lineage A(H7N9)</td>
<td></td>
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<tr>
<td>virus infection is not routinely available; due to the</td>
<td></td>
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<tr>
<td>timelines involved, serological testing cannot inform</td>
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<tr>
<td>clinical management and should not be considered for</td>
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<tr>
<td>clinical diagnostic purposes.</td>
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<tr>
<td>• It can be performed in only a few specialised</td>
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<tr>
<td>laboratories, such as World Health Organization avian</td>
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<tr>
<td>influenza reference laboratories. The microneutralisation</td>
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<tr>
<td>assay is a highly sensitive and specific assay and</td>
<td></td>
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<tr>
<td>specifically assesses the presence of specific,</td>
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<tr>
<td>neutralising antibodies. The assay should be performed</td>
<td></td>
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<tr>
<td>only in biosafety level 3 enhanced (BSL 3+) laboratories.</td>
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<tr>
<td>• Other serological assays include horse red blood cell</td>
<td></td>
</tr>
<tr>
<td>haemagglutinin inhibition assay using live or betapropiolactone-inactivated</td>
<td></td>
</tr>
<tr>
<td>A(H7N9) virus under appropriate biosafety conditions.</td>
<td></td>
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<tr>
<td>• Properly timed acute and convalescent sera can yield</td>
<td></td>
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<tr>
<td>a retrospective diagnosis of Asian lineage A(H7N9) virus</td>
<td></td>
</tr>
<tr>
<td>infection. A fourfold increase in A(H7N9) virus-specific</td>
<td></td>
</tr>
<tr>
<td>antibody level after a 2- to 4-week period from the initial</td>
<td></td>
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<tr>
<td>blood draw is diagnostic of A(H7N9) virus infection in a</td>
<td></td>
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<tr>
<td>patient with clinically compatible illness.</td>
<td></td>
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<tr>
<td>• Serological tests using standard influenza hemagglutinin</td>
<td></td>
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<tr>
<td>inhibition assays are non-specific for A(H7N9) virus and</td>
<td></td>
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<tr>
<td>are not recommended.</td>
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## Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronavirus disease 2019 (COVID-19)</strong></td>
<td>• Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset. • Signs and symptoms are similar so it may be difficult to differentiate between the conditions clinically. • The situation is evolving rapidly; see our COVID-19 topic for further information.</td>
<td>• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for SARS-CoV-2 RNA. • It is not possible to differentiate COVID-19 from other causes of pneumonia on chest imaging.</td>
</tr>
<tr>
<td><strong>Community-acquired pneumonia</strong></td>
<td>• No differentiating signs / symptoms.</td>
<td>• Diagnostic studies should be considered based on local guidance as well as microbial patterns in a particular community. • Isolation of organisms such as <em>Streptococcus pneumoniae</em> and <em>Staphylococcus aureus</em> from sputum and blood culture, and through response to typical therapy. • CXR findings for typical pneumonia are consistent with consolidation. • Positive Asian lineage A(H7N9) virus-specific tests do not exclude the possibility of co-infections or bacterial super-infections. Bacterial co-infections have not been detected in most Asian lineage A(H7N9) cases; when they have occurred, bacterial species associated with hospital-associated infections and ventilator-associated pneumonia accounted for the majority of bacterial co-infections. Methicillin-resistant <em>S. aureus</em> (MRSA) co-infection has been reported. Co-infection with bacteria associated with community-acquired pneumonia is more...</td>
</tr>
</tbody>
</table>
## Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atypical pneumonia</strong></td>
<td>• No differentiating signs / symptoms.</td>
<td>• Confirmation of infection by atypical pathogens (including atypical pneumonia pathogens such as <em>Mycoplasma pneumoniae</em>, <em>Legionella pneumophila</em>, and <em>Chlamydophila pneumoniae</em>) by sputum culture, blood culture, or other specific tests.</td>
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<td></td>
<td></td>
<td>• A diagnosis of atypical pneumonia does not rule out Asian lineage A(H7N9) virus infection, but co-infection with Asian lineage A(H7N9) virus and atypical pneumonia pathogens has not been reported.</td>
</tr>
<tr>
<td><strong>Endemic respiratory infections</strong></td>
<td>• No differentiating signs / symptoms.</td>
<td>• Diagnostic tests confirming infection caused by an atypical pneumonia organism do not rule out Asian lineage A(H7N9) virus infection, but co-infection with Asian lineage A(H7N9) virus and endemic respiratory infections has not been reported.</td>
</tr>
<tr>
<td></td>
<td>• Respiratory infections due to pathogens endemic to the region where infection occurred should be considered (e.g., endemic mycotic infection, melioidosis in parts of Southeast Asia).</td>
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<tr>
<td><strong>Seasonal influenza A or B virus infection</strong></td>
<td>• More common cause of severe morbidity in young children, older adults, and people with underlying chronic medical conditions (e.g., cardiopulmonary disease, immunosuppressed). More likely to be a self-limiting condition with milder symptoms among previously healthy people.</td>
<td>• Confirmation by diagnostic testing of infection by another respiratory virus does not rule out Asian lineage A(H7N9) virus infection. Co-infections with Asian lineage A(H7N9) and seasonal A(H3N2) and seasonal A(H1N1)pdm09 viruses have been reported.[14] [134] [135] A nosocomial cluster induced by co-infections with avian influenza A(H7N9) and A(H1N1)pdm09 viruses occurred in two patients at a hospital in China.[14] The implications of such influenza virus co-infections on clinical outcomes are not clear. Because there is potential for virus reassortment,</td>
</tr>
<tr>
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<td>• No differentiating signs / symptoms, but severe lower respiratory tract disease can also occur among previously healthy children, young adults, pregnant women, and morbidly obese people.</td>
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<tr>
<td></td>
<td>• Seasonal influenza and Asian lineage A(H7N9) virus infection can have rapid</td>
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<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
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</tr>
<tr>
<td>Avian influenza A(H7N9) virus infection</td>
<td>Onset of fever, cough, and pneumonia.</td>
<td>Detection of other influenza A virus subtypes as part of an influenza surveillance programme is recommended. Rapid influenza diagnostic tests (antigen tests) lack sensitivity to detect influenza viruses and cannot distinguish between Asian lineage A(H7N9) A virus and other influenza A viruses, and should not be used to diagnose Asian lineage A(H7N9) virus infection. Commercially available influenza molecular assays have high sensitivity to detect influenza viruses in respiratory specimens, but cannot specifically identify A(H7N9) virus, or distinguish A(H7N9) virus from seasonal influenza A viruses.</td>
</tr>
</tbody>
</table>
| Respiratory syncytial virus infection (RSV) | - Most common cause of lower respiratory tract infection in children aged <1 year.  
- Significant and often unrecognised cause of lower respiratory tract infection in both older and immunosuppressed patients.  
- Gives rise to upper and lower respiratory symptoms that peak in 3 to 5 days and resolve within 7 to 10 days. | - Rapid assays using antigen-capture technology are the mainstay of the diagnostic algorithm, as the identification by culture can take from 4 days to 2 weeks.[136] Molecular detection methods (polymerase chain reaction) are used increasingly to detect RSV.  
- Confirmation by diagnostic testing of infection by another respiratory virus does not rule out Asian lineage A(H7N9) virus infection, but co-infection with Asian lineage A(H7N9) virus and other respiratory viruses has not been reported. However, co-infections with other respiratory viruses have been identified in patients infected with A(H1N1)pdm09 and seasonal influenza viruses. |
<p>| Middle East respiratory syndrome (MERS) | - No differentiating signs / symptoms. | - Laboratory tests (reverse transcriptase polymerase chain reaction) for MERS- |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Common Middle East respiratory syndrome coronavirus (MERS-CoV) symptoms are acute, serious respiratory illness with fever, cough, shortness of breath, and breathing difficulties. Most patients had pneumonia, respiratory failure, and acute respiratory distress syndrome. Many also had gastrointestinal symptoms (including diarrhoea) while others had kidney failure. Approximately more than one third of people identified with MERS-CoV to date have died.</td>
<td>CoV are not commonly available, but can be found at some international public health laboratories, particularly in regions affected by MERS-CoV infections. Between 2012 and 30 June 2019, 27 countries (Kingdom of Saudi Arabia, Jordan, Bahrain, Egypt, Iran, Kuwait, Lebanon, Oman, Qatar, the United Arab Emirates, Yemen, Algeria, Tunisia, Austria, France, Germany, Greece, Italy, the Netherlands, Turkey, the UK, China, the Republic of Korea, Malaysia, Philippines, Thailand, and the US) have reported 2449 laboratory-confirmed cases of human infection with MERS-CoV; more than one third have died. The majority of infections were acquired in the Middle East and 84% of cases were reported by the Kingdom of Saudi Arabia. Secondary-transmission cases are common and have also been reported by countries outside the Middle East, including 185 cases that occurred in the Republic of Korea, following a single imported case.</td>
<td>• Between 2012 and 30 June 2019, 27 countries (Kingdom of Saudi Arabia, Jordan, Bahrain, Egypt, Iran, Kuwait, Lebanon, Oman, Qatar, the United Arab Emirates, Yemen, Algeria, Tunisia, Austria, France, Germany, Greece, Italy, the Netherlands, Turkey, the UK, China, the Republic of Korea, Malaysia, Philippines, Thailand, and the US) have reported 2449 laboratory-confirmed cases of human infection with MERS-CoV; more than one third have died. The majority of infections were acquired in the Middle East and 84% of cases were reported by the Kingdom of Saudi Arabia. Secondary-transmission cases are common and have also been reported by countries outside the Middle East, including 185 cases that occurred in the Republic of Korea, following a single imported case.</td>
</tr>
</tbody>
</table>

• Nosocomial transmission is well recognised. The majority of infected healthcare workers (approximately 18% of all cases) have had mild or asymptomatic infection, but some fatal outcomes have been reported. Camels are the suspected primary source of zoonotic transmission to humans, but investigations are ongoing. When human-to-human transmission has occurred it has not been sustained.[137] [138] [139] [140]
Screening

There is no role for screening for any A(H7N9) virus infection in the asymptomatic population outside of epidemiological research studies.
**Approach**

There is no standardised approach for the clinical management of humans with Asian lineage A(H7N9) virus infection; supportive care and early initiation of neuraminidase inhibitor antiviral therapy are considered the mainstays of treatment, similar to the management of complicated seasonal influenza A and B, highly pathogenic avian influenza (HPAI) A(H5N1), and influenza A(H1N1)pdm09 virus infections.[141][142] Patients with severe illness due to Asian lineage A(H7N9) virus infection can present with clinical findings similar to those of pneumonia caused by other infectious aetiologies. Because human infection with Asian lineage A(H7N9) virus is rare (even among people with high-risk exposures) diagnostic evaluation and therapy should also consider alternative aetiologies.

Many local and national health departments, and the World Health Organization (WHO), have excellent online guidance documents. Many local health departments can directly assist clinicians to determine which people need testing, to facilitate testing, and to assist with case management.

[WHO: avian and other zoonotic influenza](https://www.who.int/influenza/human_animal_interface/en/)


[CDC: information on avian influenza](https://www.cdc.gov/flu/avianflu/)

[CDC: avian influenza - information for health professionals and laboratorians](https://www.cdc.gov/flu/avianflu/healthprofessionals.htm)

**Unprotected exposure to a suspected or confirmed case: antiviral chemoprophylaxis**

The decision to use antiviral chemoprophylaxis should be considered on a case-by-case basis and guided by the nature of Asian lineage A(H7N9) virus exposure and the associated risk of developing infection. No prospective clinical trials exist to guide WHO antiviral chemoprophylaxis recommendations. The WHO does not recommend routine post-exposure antiviral chemoprophylaxis for Asian lineage A(H7N9) virus but states that it may be considered in asymptomatic individuals who have had substantial unprotected or prolonged exposure to an ill patient with Asian lineage A(H7N9) virus infection. Such individuals include those with risk factors for complications of influenza virus infection who have had close contact, and unprotected healthcare workers, especially those involved in aerosol-generating procedures.[143] Public Health England (PHE) and the Centers for Disease Control and Prevention (CDC) suggest that standard twice-daily treatment-dose regimens should be used for chemoprophylaxis, to decrease the risk of antiviral resistance developing.[144][145] When the decision is made to administer post-exposure antiviral chemoprophylaxis, it should be commenced as soon as possible following the potential exposure. The CDC recommends that 5 days of a neuraminidase inhibitor (twice-daily treatment dose) is administered when exposure was time-limited and not ongoing, but that 10 days (treatment dose) should be administered when exposure is likely to be ongoing (e.g., in a household setting). Regardless of whether or not antiviral chemoprophylaxis is administered, all close contacts should be monitored closely for signs and symptoms of influenza, and, if symptomatic, respiratory specimens should be collected for Asian lineage A(H7N9) virus testing as soon as possible.
Suspected human infection with Asian lineage A(H7N9) virus

When Asian lineage A(H7N9) virus infection is suspected, the appropriate course of action is to isolate the patient, and commence empirical neuraminidase inhibitor treatment as soon as possible (according to existing guidelines for seasonal influenza) while awaiting the results of specific diagnostic laboratory tests. Oral or enterically administered oseltamivir is the preferred primary treatment. Inhaled zanamivir might be used as an alternative regimen in non-intubated patients. It is important to note that Asian lineage A(H7N9) virus infection of humans appears to be rare even among exposed individuals, and physicians must consider alternative diagnoses when evaluating patients with suspected Asian lineage A(H7N9) virus infection.

Contacting local or national public health departments for guidance is highly recommended. Antiviral therapy should not be delayed by diagnostic specimen collection or laboratory testing.

Confirmed Asian lineage A(H7N9) virus infection

Most patients hospitalised with confirmed Asian lineage A(H7N9) virus infection have rapidly progressive viral pneumonia leading to acute respiratory distress syndrome (ARDS) with variable multi-organ failure. Based on observational data from treatment of patients with seasonal influenza, A(H1N1)pdm09, or HPAI A(H5N1) virus infection, early recognition of disease and initiation of antiviral and supportive therapies may improve clinical outcomes. Local or national public health departments should be contacted for guidance.

There is no standardised approach for the clinical management of humans with Asian lineage A(H7N9) virus infection, and WHO management guidelines are in development. In the absence of specific guidance, experience from the treatment of HPAI A(H5N1) and severe A(H1N1)pdm09 virus infection is helpful. For HPAI A(H5N1) virus infection, the WHO recommends that supportive care follow published evidence-based guidelines for the clinical syndrome present (e.g., septic shock, respiratory failure, and ARDS). According to the WHO, patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure, and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless indicated for other reasons (e.g., adrenal insufficiency, refractory septic shock) or as part of an approved research protocol.

Neuraminidase inhibitor antiviral therapy should not be delayed by diagnostic specimen collection or laboratory testing. Oral or enterically administered oseltamivir is the preferred primary treatment. No published controlled clinical trial data are available on efficacy of oseltamivir in treating Asian lineage A(H7N9) virus-infected patients, and observational data on the effectiveness of oseltamivir treatment for Asian lineage A(H7N9) virus-infected patients are very limited. One observational study reported that early initiation of neuraminidase inhibitor antiviral treatment shortened the duration of viral shedding and was associated with improved survival in A(H7N9) patients. Another observational study reported that mortality was significantly lower in patients treated with a neuraminidase inhibitor within 5 days of illness onset. One study reported that delayed initiation of neuraminidase inhibitor treatment was associated with prolonged A(H7N9) viral shedding. PHE and the CDC strongly recommend that oseltamivir therapy is started as soon as possible for patients with suspected or confirmed A(H7N9) virus infection, based on the experience of treating patients with complicated influenza A(H1N1)pdm09 and HPAI A(H5N1). Observational uncontrolled studies have suggested a survival benefit to early oseltamivir therapy in hospitalised A(H1N1)pdm09 and HPAI A(H5N1) virus-infected patients, especially when antivirals are started early in the clinical course, or before the onset of ARDS.

Treatment with oseltamivir for seasonal influenza virus infection in children under 1 year of age is recommended by the CDC and the WHO, and may be extrapolated to patients.
with Asian lineage A(H7N9) virus infection. The dosage for children is based on body weight. Serious adverse events were generally not reported during treatment of HPAI A(H5N1) virus-infected patients or in systematic reviews in adults with seasonal influenza. Inhaled zanamivir might be used as an alternative regimen in non-intubated patients. [142]

Clinicians can consider longer duration of oseltamivir treatment for patients with severe illness. To date, Asian lineage A(H7N9) virus isolates with de novo reduced susceptibility to oseltamivir (before oseltamivir exposure) have not been identified. De novo resistance to oseltamivir has been reported for A(H1N1)pdm09 and HPAI A(H5N1) virus infections, but appears to be rare. Emergence of oseltamivir, peramivir, and zanamivir resistance during treatment of patients with Asian lineage low-pathogenic avian influenza (LPAI) and HPAI A(H7N9) virus infections has been reported. [36] [37] [38] [40] [41] [120] [160] The Arg292Lys mutation, which has been the most commonly reported resistance mutation to date in Asian lineage A(H7N9) viruses, confers high-level resistance to oseltamivir and reduced susceptibility to zanamivir and peramivir. Where the clinical course remains severe or progressive despite at least 5 days of antiviral treatment, it is recommended that monitoring of Asian lineage A(H7N9) virus replication and shedding is performed, along with antiviral drug susceptibility testing. Combination oseltamivir and zanamivir treatment is not recommended for Asian lineage A(H7N9) virus infection because of potential mechanistic antagonism. [161] Data on use of investigational antivirals with different mechanisms of action than the neuraminidase inhibitors for treatment of patients with Asian lineage A(H7N9) virus infection are needed, but should be studied in clinical trials.

Giving M2 inhibitors (amantadine or rimantadine) or a cap-dependent endonuclease inhibitor (baloxavir marboxil) alone as a first-line therapy is not recommended. Virus isolates from humans demonstrate inherent resistance to M2 inhibitors. See Emerging treatments section for more detailed information on investigational antivirals.

**Infection control procedures**

Given the potential infectiousness and virulence of Asian lineage A(H7N9) virus, and because nosocomial transmission has been documented (e.g., patient-to-healthcare worker, and patient-to-patient) [12] [13] [14] enhanced infection prevention and control precautions are recommended. All infection prevention and control strategies include standard hand hygiene and respiratory precautions. There may be slight infection control recommendation differences between the WHO and some national public health organisations; therefore, if Asian lineage A(H7N9) virus infection is considered in a patient, it is recommended that clinicians consult national infection control guidelines. For example, the CDC recommends placement of a patient under investigation for Asian lineage A(H7N9) virus infection in an airborne infection isolation room and use of a respirator. [162]

For human infection with avian influenza A viruses, the WHO recommends using the following personal protective equipment before patient contact: [163]

- Clean, non-sterile, long-sleeved gown: if cloth gowns are used, a plastic apron should be added if splashing of blood or body fluids is anticipated
- Clean, non-sterile gloves
- Eye protection: eye visor or goggles, or a face shield
- Medical mask for routine care
- Particulate respirator (FFP3 or N95 standard) for aerosol-generating procedures.
Avian influenza A(H7N9) virus infection

Management

The recommended duration of the above precautions has not been defined for Asian lineage A(H7N9) virus-infected patients. However, for HPAI A(H5N1) virus infection, the recommended duration varies according to age group:

- People aged ≥12 years: 7 days after fever resolves
- Children aged <12 years: up to 21 days after symptom onset.

If the patient leaves hospital before this time, continued home quarantine is recommended.

Corticosteroids

The WHO advises against the use of corticosteroids in the management of patients with Asian lineage A(H7N9) virus infection because of the potential for increased risk of prolonged virus shedding, emergence of antiviral resistant virus strains, ventilator-associated pneumonia, and higher mortality. A retrospective study of 288 H7N9 patients in China reported that high-dose corticosteroid treatment was associated with increased mortality and longer median duration of viral shedding.[164] Corticosteroid use was associated with prolonged detection of A(H7N9) viral RNA in hospitalised patients.[151] In seasonal influenza virus infection, studies have demonstrated that corticosteroid use is associated with persistent viral replication 7 days after symptom onset.[165] One study reported that early use of glucocorticoids is a risk factor for critical illness and death with A(H1N1)pdm09 virus infection.[166] Another study reported that corticosteroids increased superinfection and deaths when controlled for indications in patients with seasonal influenza virus infections.[159] Corticosteroids are not recommended for the treatment of any influenza virus infection, but may be indicated for other reasons (e.g., asthma or COPD exacerbation, adrenal insufficiency, preterm labour, refractory septic shock).

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Initial</th>
<th>( summary )</th>
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<tbody>
<tr>
<td>unprotected exposed healthcare workers and close contacts of suspected/confirmed case</td>
<td>1st observation ± post-exposure neuraminidase inhibitor</td>
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<tr>
<th>suspected infection</th>
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<tr>
<td>1st isolation + neuraminidase inhibitor plus infection control</td>
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### Acute

**confirmed illness**

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<tr>
<td>1st</td>
<td>supportive care</td>
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<tr>
<td>plus</td>
<td>neuraminidase inhibitor</td>
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<tr>
<td>plus</td>
<td>infection control</td>
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( summary )
Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Avian influenza A(H7N9) virus infection

Management

Initial

unprotected exposed healthcare workers and close contacts of suspected/confirmed case

1st observation ± post-exposure neuraminidase inhibitor

Primary options

» oseltamivir: children ≥3 months of age: 3 mg/kg orally twice daily for 5-10 days; children >1 year of age and ≤15 kg body weight: 30 mg orally twice daily for 5-10 days; children >15-23 kg body weight: 45 mg orally twice daily for 5-10 days; children >23-40 kg body weight: 60 mg orally twice daily for 5-10 days; children >40 kg body weight and adults: 75 mg orally twice daily for 5-10 days

Not recommended for chemoprophylaxis in children <3 months of age unless the situation is judged to be critical.

Secondary options

» zanamivir: children ≥7 years of age and adults: 10 mg (2 puffs) inhaled twice daily for 5-10 days

Inhaled zanamivir is not appropriate for invasively ventilated patients, and should be used with caution in patients with lower respiratory tract involvement or obstructive lung disease, due to the risk of treatment failure and induction or exacerbation of bronchospasm.

The decision to use antiviral chemoprophylaxis should be considered on a case-by-case basis and guided by assessment of Asian lineage A(H7N9) virus exposure and subsequent risk of developing infection. No prospective clinical trials exist to guide interim World Health Organization (WHO) chemoprophylaxis recommendations. The WHO does not recommend routine post-exposure antiviral chemoprophylaxis for close contacts, but it may be considered under certain circumstances. Recommendations are based on chemoprophylaxis following exposure to other influenza virus subtypes, including A(H1N1)pdm09 and highly pathogenic avian influenza (HPAI) A(H5N1). Note that twice-daily administration (same as treatment dosing frequency is recommended) to reduce the risk of emergence of antiviral resistance.

The WHO recommends close observation and post-exposure oseltamivir or zanamivir chemoprophylaxis for healthcare workers after unprotected close exposure to a symptomatic,
Management

Avian influenza A(H7N9) virus infection

**Initial**

suspected, or confirmed Asian lineage A(H7N9) case (within 2 m) in the healthcare setting, as well as for household members and close contacts of a person with suspected or confirmed Asian lineage A(H7N9) virus infection. Note CDC guidance states that unprotected exposure of healthcare workers is associated with moderate risk of infection and that chemoprophylaxis should be considered in this group.

» Treatment course: 5 days (if time-limited exposure, not ongoing) or 10 days (if exposure is ongoing).

<table>
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<tr>
<th>suspected infection</th>
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<tr>
<td><strong>1st</strong> isolation + neuraminidase inhibitor</td>
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</table>

**Primary options**

» oseltamivir: children <14 days of age: 3 mg/kg orally once or twice daily for 5 days; children 14 days to 1 year of age: 3 mg/kg orally twice daily for 5 days; children >1 year of age and ≤15 kg body weight: 30 mg orally twice daily for 5 days; children >15-23 kg body weight: 45 mg orally twice daily for 5 days; children >23-40 kg body weight: 60 mg orally twice daily for 5 days; children >40 kg body weight and adults: 75 mg orally twice daily for 5 days


**Secondary options**
### Initial

<table>
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<th>Management</th>
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| **» zanamivir**: children ≥7 years of age and adults: 10 mg (2 puffs) inhaled twice daily for 5 days  
Inhaled zanamivir is not appropriate for invasively ventilated patients, and should be used with caution in patients with lower respiratory tract involvement or obstructive lung disease, due to the risk of treatment failure and induction or exacerbation of bronchospasm.  
» When Asian lineage A(H7N9) virus infection is highly suspected, isolating the patient (either within a hospital or while being monitored at home, as per local public health policies) and starting empirical neuraminidase inhibitor treatment as soon as possible according to existing guidelines while waiting for the results of specific laboratory tests is appropriate. As of June 2017, oseltamivir resistance of Asian lineage A(H7N9) virus is uncommon, although resistance can develop rapidly during antiviral treatment and clinicians should be alert to this possibility.  
» It is important to note that Asian lineage A(H7N9) virus infections in humans appear to be rare, and physicians must consider alternative diagnoses when evaluating patients with suspected Asian lineage A(H7N9) virus infection.  
» During the 2009 H1N1 influenza pandemic, the World Health Organization (WHO) recommended the oseltamivir dose adjustments for children shown below. These dosages may be considered for the treatment of children with suspected Asian lineage A(H7N9) virus infection. The dosage for children is based on weight.  
» Oral or enterically administered oseltamivir is the recommended antiviral medication treatment.[146] Inhaled zanamivir might be used as an alternative regimen in non-intubated patients.[142]  
» Combination oseltamivir and zanamivir treatment is not recommended because of the potential for antagonism.[161]  

| plus infection control |  |
| Treatment recommended for ALL patients in selected patient group  
» Given the potential infectiousness and virulence of Asian lineage A(H7N9) virus, enhanced infection control precautions are recommended to prevent transmission by contact, droplet and airborne routes.  

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### Initial

This is achieved by measures including appropriate patient placement (e.g., respiratory isolation), protection of staff and other contacts by using correct personal protective equipment, appropriate cleaning and disinfection protocols, and control of waste and potentially contaminated materials. All infection control strategies include standard hand hygiene precautions. There may be slight infection control recommendation differences between the World Health Organization[^163] and some national public health organisations; therefore, if Asian lineage A(H7N9) virus infection is considered in a patient, it is recommended that clinicians consult national infection control guidelines.

[^163]: World Health Organization
Avian influenza A(H7N9) virus infection

Management

Acute
confirmed illness

1st supportive care

- Most patients hospitalised with Asian lineage A(H7N9) virus infection have had rapidly progressive pneumonia leading to acute respiratory distress syndrome (ARDS) and variable multi-organ failure.[37] [116] Based on experience of treating patients with severe illness caused by A(H1N1)pdm09 and highly pathogenic avian influenza (HPAI) A(H5N1) virus infections, early recognition of disease and rapid initiation of antiviral and supportive therapies may improve clinical outcomes.[158] [159] [169] [170] [171]

- While there is no standardised approach or specific guidance for the clinical management of humans with Asian lineage A(H7N9) virus infection, for HPAI A(H5N1) virus infection the World Health Organization (WHO) recommends supportive care that follows published evidence-based guidelines for the clinical syndrome present (e.g., septic shock, respiratory failure, and ARDS).[1] [147] According to the WHO, patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure, and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless indicated for other reasons (e.g., adrenal insufficiency, refractory septic shock) or as part of an approved research protocol.[148] Interim guidance on treatment of Asian lineage A(H7N9) virus infection is guided by experience of treating severe illness due to A(H1N1)pdm09 and HPAI A(H5N1) virus infections.

plus neuraminidase inhibitor

Treatment recommended for ALL patients in selected patient group

Primary options

- oseltamivir: children <14 days of age: 3 mg/kg orally once or twice daily for 5 days; children 14 days to 1 year of age: 3 mg/kg orally twice daily for 5 days; children >1 year of age and ≤15 kg body weight: 30 mg orally twice daily for 5 days; children >15-23 kg body weight: 45 mg orally twice daily for 5 days; children >23-40 kg body weight: 60 mg orally twice daily for 5 days; children >40 kg body weight and adults: 75 mg orally twice daily for 5 days
The WHO recommends once-daily dosing of oseltamivir in children <14 days of age; however, the CDC and the American Academy of Pediatrics recommend twice-daily dosing. Lower doses should be considered for infants who are not receiving regular oral feedings and/or those who have a concomitant medical condition that is expected to reduce significantly renal function.

Secondary options

» zanamivir: children ≥7 years of age and adults: 10 mg (2 puffs) inhaled twice daily for 5 days
Inhaled zanamivir is not appropriate for invasively ventilated patients, and should be used with caution in patients with lower respiratory tract involvement or obstructive lung disease, due to the risk of treatment failure and induction or exacerbation of bronchospasm.

» If exposure risk factors are present or suspected, empirical antiviral therapy should be initiated as early as possible. Antiviral therapy should not be delayed by diagnostic specimen collection or pending laboratory testing results. Oral or enterically administered oseltamivir is the recommended antiviral medication treatment.[1] [146] [152] [153] [154] Inhaled zanamivir might be used as an alternative regimen in non-intubated patients.[142]

» Modified regimens with higher doses of oseltamivir and longer duration of treatment may be considered on a case-by-case basis, but there are no available clinical trial data to reliably inform recommendations.[142] [172]

» Oseltamivir has been shown to be adequately absorbed following nasogastric administration to mechanically ventilated adults with severe A(H1N1)pdm09 and highly pathogenic avian influenza (HPAI) A(H5N1) disease.[173] [174]
Acute

» During the 2009 H1N1 influenza pandemic, the World Health Organization (WHO) recommended the dose adjustments for children shown below. These dosages may be considered for the treatment of children with suspected A(H7N9) virus infection. An adult dose of oseltamivir 150 mg twice-daily is often used for critically ill patients.[141] [142] Adjusting dosage is recommended for children and adults with renal impairment.[142] Oseltamivir is approved for use in patients aged 1 year or older.

» Combination oseltamivir and zanamivir treatment is not recommended because of the potential for antagonism.[161]

plus infection control

Treatment recommended for ALL patients in selected patient group

» Given the potential infectiousness of Asian lineage A(H7N9) virus and its ability to cause severe illness, enhanced infection control precautions are recommended to prevent transmission by contact, droplet, and airborne routes. This is achieved by measures including appropriate patient placement (e.g., respiratory isolation), protection of staff and other contacts by using correct personal protective equipment, appropriate cleaning and disinfection protocols, and control of waste and potentially contaminated materials. All infection control strategies include standard hand hygiene precautions. There may be slight infection control recommendation differences between the World Health Organization[163] and some national public health organisations; therefore, if A(H7N9) is considered in a patient, it is recommended that clinicians consult national infection control guidelines.
Emerging

Baloxavir marboxil

Baloxavir marboxil is a cap-dependent endonuclease inhibitor that inhibits influenza virus polymerase and, therefore, has a different mode of action to the neuraminidase inhibitors. It is approved in the US for the treatment of acute, uncomplicated influenza in people 12 years of age and older, and has also been approved in other countries. Inhibition of replication of avian A(H7N9) viruses has been demonstrated in vitro and in vivo,[175] but there are no data on efficacy in infected humans and no data on dosing or efficacy of baloxavir marboxil for treatment of hospitalised patients with seasonal influenza. Using baloxavir marboxil alone as a first-line therapy for A(H7N9) patients is not recommended. Markers of resistance to baloxavir marboxil emerged in 9.7% to 23.4% of participants in clinical trials of baloxavir marboxil for the early treatment of outpatients with seasonal influenza.[176] [177] [178] [179] A cap-dependent endonuclease inhibitor in combination with a neuraminidase inhibitor, with or without ribavirin, should be given only in the context of a controlled clinical research study.

M2 inhibitors

Giving M2 inhibitors (amantadine or rimantadine) alone as a first-line therapy is not recommended. Virus isolates from humans demonstrate inherent resistance to M2 inhibitors. M2 inhibitors have been used in combination with other antivirals (with possible synergistic action) to treat influenza A virus infections in experimental settings only. An M2 inhibitor in combination with a neuraminidase inhibitor, with or without ribavirin, should be given only in the context of a clinical research study.

Convalescent plasma

There is only one published case report of uncontrolled treatment and no clinical trials of convalescent plasma for treatment of Asian lineage A(H7N9) virus infection. In January 2015, a 45-year-old male patient with respiratory failure and confirmed Asian lineage A(H7N9) virus infection was treated with oseltamivir. Convalescent plasma collected from an H7N9 patient who had recovered from A(H7N9) virus infection 9 months earlier was added for treatment, with associated resolution of A(H7N9) virus shedding and full recovery.[180] In June 2006, a 31-year-old male patient with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection was treated with convalescent plasma that was obtained from a patient who had recovered from A(H5N1) illness earlier that year. HPAI A(H5N1) viral load from respiratory specimens decreased after 3 doses of convalescent plasma, with undetectable levels within 32 hours.[181] Two other HPAI A(H5N1) virus-infected patients who received convalescent plasma from a recovered A(H5N1) case or an A(H5N1) vaccine recipient have been reported.[182] A clinical trial assessing the use of A(H5N1) vaccine to generate levels of antibodies sufficient for use as convalescent plasma therapy has been completed.[183] Twenty-three patients received high antibody titre convalescent plasma as part of a prospective cohort study of 93 patients with severe influenza A(H1N1)pdm09 virus infection. Mortality in the treatment group was significantly lower than in the non-treatment group (20.0% vs. 54.8%; \( p = 0.01 \)). Reductions in respiratory tract viral load and serum cytokines were also seen.[184] Convalescent plasma therapy is experimental and not yet approved for clinical use in the treatment of illness caused by any influenza virus.

Intravenous neuraminidase inhibitors

Parenteral formulations of neuraminidase inhibitors have been developed and may be of use for specific clinical circumstances. Intravenous peramivir[185] [186] [187] is licensed in the US for early treatment of uncomplicated seasonal influenza in people aged 2 years and older, and is also approved in Japan, Europe, and the Republic of Korea. Common resistance mutations in seasonal influenza viruses that confer resistance to oseltamivir typically confer resistance to peramivir as well; oseltamivir-resistance mutations in Asian lineage A(H7N9) virus infection may also confer resistance to peramivir. Intravenous zanamivir was approved for the treatment of patients 6 months of age and older with complicated and potentially life-threatening influenza in Europe in 2019, but is not approved in the US. One study of intravenous zanamivir versus oral oseltamivir for treatment of seasonal influenza in hospitalised patients did not demonstrate...
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superiority.[188] During and after the 2009-10 H1N1 influenza pandemic, intravenous zanamivir was provided internationally by the manufacturer through a compassionate-use programme for patients with seasonal influenza who met specific prescribing criteria, but it is no longer available in the US. Although some oseltamivir-resistant influenza A viruses remain sensitive to zanamivir, some mutations can confer reduced susceptibility or resistance to zanamivir, in addition to oseltamivir and peramivir. A(H7N9) viruses resistant to all neuraminidase inhibitors have emerged during the treatment of some H7N9 patients in China.[37] [52] Multiple mutations can also occur; specialist antiviral susceptibility testing is recommended. The World Health Organization (WHO) recommends that treatment with intravenous neuraminidase inhibitors should be used in accordance with relevant emergency-use provisions.[142]

**Laninamivir**

Laninamivir is a new inhaled neuraminidase inhibitor that was approved in Japan for use against seasonal influenza. It is chemically similar to zanamivir, and is converted into its active form in the lungs where higher concentrations of the drug persist, permitting treatment of seasonal influenza with a single drug dose. Asian lineage A(H7N9) virus isolates appear to be sensitive to laninamivir in vitro.[99] Little is known about the clinical efficacy of laninamivir against Asian lineage A(H7N9) virus infection, and it is not currently recommended for this purpose.[189]

**Favipiravir**

Favipiravir is a new oral agent that has been approved in Japan for treatment of novel or re-emerging influenza virus infections in adults (limited to cases in which other anti-influenza virus drugs are ineffective or not sufficiently effective). The mechanism of action is inhibition of the RNA polymerase of influenza viruses.[190] Although in-vitro data have demonstrated inhibition of Asian lineage A(H7N9) low-pathogenic avian influenza (LPAI) viruses by favipiravir, informative clinical data on the use of favipiravir in the treatment of A(H7N9) virus infection or severe seasonal influenza are lacking.

**Ribavirin**

Although not licensed for the treatment of influenza in most countries, ribavirin has been demonstrated to increase efficacy of oseltamivir against some A(H5N1) viruses in mouse models.[191] However, studies of severe acute respiratory syndrome (SARS) coronavirus-infected patients treated with ribavirin have found strong associations between high-dose therapy and progressive haemolytic anaemia.[192] A WHO panel concluded that there is insufficient data on either its efficacy or safety to recommend its use for the treatment of influenza.[142] This conclusion may be extended to the treatment of A(H7N9) virus infection. Combination therapy using ribavirin with an M2 inhibitors and a neuraminidase inhibitor should be restricted to a clinical trial setting.

**Primary prevention**

The optimal means of containing Asian lineage A(H7N9) virus in communities and decreasing the risk to human health is unknown. However, the closure of live markets in affected areas, with prompt culling of poultry with Asian lineage A(H7N9) virus infection and disinfection of the contaminated environment, may help to contain outbreaks and disrupt zoonotic transmission. Vaccination of poultry with an H5/ H7 vaccine was correlated with a decline in detection of A(H7N9) viruses in vaccinated poultry and environmental specimens, and sharp reduction in human infections.[57] [58] The most effective way to prevent Asian lineage A(H7N9) virus infection of people is to minimise exposure to infected poultry. Unlike highly pathogenic avian influenza (HPAI) A(H5N1) virus infection, Asian lineage low-pathogenic avian influenza (LPAI) A(H7N9) virus infection causes asymptomatic or sub-clinical infection in poultry, making it impossible to identify infected poultry without laboratory testing. Asian lineage HPAI A(H7N9) virus has not yet replaced the LPAI virus, but if it does, outbreaks in poultry will be easier to detect.

The WHO and national public health agencies do not recommend travel restrictions to Asian lineage A(H7N9) virus-affected countries. It is recommended, however, that people avoid contact with poultry suspected of Asian lineage A(H7N9) virus infection, avoid animals in live food markets where an active Asian lineage A(H7N9) virus outbreak is occurring in poultry, and avoid contact with any surfaces that may
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be contaminated by faeces from poultry or other animals suspected of having Asian lineage A(H7N9) virus infection.

Currently, no vaccine is licensed to prevent Asian lineage A(H7N9) virus infections in humans. The WHO and partners are working on vaccine development, including tests of safety and immunogenicity, as part of pandemic preparedness plans. Healthcare workers are recommended to receive annual seasonal influenza vaccine to decrease the risk of nosocomial transmission of seasonal influenza viruses in the healthcare setting. Preventing seasonal influenza among people exposed to Asian lineage A(H7N9) virus may also decrease the theoretical risk of human co-infection with seasonal influenza A and Asian lineage A(H7N9) viruses and the associated risk of viral reassortment (an event that could lead to the emergence of a potential pandemic influenza A virus strain).

Most public health agencies consider the use of oral oseltamivir or inhaled zanamivir as antiviral chemoprophylaxis for primary prevention (pre-exposure prophylaxis) to be unnecessary if appropriate personal protective equipment and infection control precautions are followed. Some public health agencies may recommend pre-exposure prophylaxis in select individuals who are involved in responding to avian influenza virus outbreaks in birds.


Patient discussions

Any patient with suspected or confirmed Asian lineage A(H7N9) virus infection should be commenced on antiviral treatment as soon as possible and isolated in a hospital room, with strict adherence to local and national recommended infection control precautions. Instructions for discharge or home care and risk management of clinically mild illness with Asian lineage A(H7N9) virus infection should be provided by local or national public health departments to fit the needs of the particular case. The public health department will determine whether quarantine of exposed people, other forms of social distancing, and other pharmacological and non-pharmacological measures must be undertaken to minimise Asian lineage A(H7N9) virus transmission among exposed people in the community. Physicians should involve local or national public health agencies when managing Asian lineage A(H7N9) cases. Confirmed cases are notifiable under World Health Organization International Health Regulations.
Monitoring

Human illness caused by Asian lineage A(H7N9) virus infection is an acute infectious disease. Patients may experience prolonged virus replication and viral shedding, especially if they are immunosuppressed, and their hospital course may last up to 3 weeks or longer after disease onset. Once surviving patients have clinically improved and have been discharged, they may have immunity to subsequent infection by antigenically similar A(H7N9) virus strains, or decreased likelihood of severe illness if re-infected.

Long-term sequelae of acute respiratory distress syndrome include neuromuscular weakness, diminished lung function, post-traumatic stress disorder, and cognitive decline in older patients.[194] [195] A cohort study of 56 A(H7N9) patients who survived hospitalisation reported that although pulmonary function and chest computed tomography scan findings had improved by 6 months, most patients had persistent abnormalities 2 years after hospital discharge.[196]

The World Health Organization recommends close observation and post-exposure oseltamivir or zanamivir chemoprophylaxis for healthcare workers after unprotected close exposure to a symptomatic, suspected, or confirmed Asian lineage A(H7N9) case (within 2 m) in the healthcare setting, as well as for household and close contacts of a patient with suspected or confirmed Asian lineage A(H7N9) virus infection.

## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary influenza pneumonia</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Common complication of Asian lineage A(H7N9) virus infection.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment is with antivirals given as soon as possible, supplemental oxygen, and supportive therapy. Respiratory status should be monitored, and early ventilatory support considered.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>respiratory failure</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>This is a common complication of Asian lineage A(H7N9) virus infection, usually due to acute respiratory distress syndrome. Has been documented among all affected age groups.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiviral and supportive therapy is necessary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute respiratory distress syndrome</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>The most common cause of respiratory failure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence-based, lung protective ventilation strategies are recommended.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>multi-organ failure</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Multi-organ failure, including renal or cardiac compromise, is a common complication of severely ill Asian lineage A(H7N9) virus-infected patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive therapy is crucial, as is targeted therapy where applicable. Management should follow evidence-based management guidelines.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Septic shock requiring vasopressor support is a common complication of primary Asian lineage A(H7N9) virus infection.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment is supportive and should follow existing evidence-based guidelines for the management of septic shock.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>encephalitis</td>
<td>short term</td>
<td>low</td>
</tr>
<tr>
<td>Patients can have headaches, behavioural disturbances, and altered mental status, and may have seizures and coma, as a result of virus infection triggering cytokine dysregulation. Encephalitis is not recognised in Asian lineage A(H7N9) virus infection, but cases of central nervous system infection and detection of virus in cerebrospinal fluid have been described in severe illnesses caused by other influenza A viruses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The underlying infection should be treated with antivirals as soon as possible, and supportive care provided as indicated.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Follow up

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>death</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>Has occurred in approximately 39% of patients with confirmed Asian lineage A(H7N9) virus infection.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Community-acquired pneumonia**

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>variable</td>
<td>low</td>
</tr>
</tbody>
</table>

While co-infection with bacterial pneumonia pathogens (Staphylococcus aureus, Streptococcus pneumoniae, group A Streptococcus) is well described with seasonal influenza A or B virus infections, as well as with influenza A(H1N1)pdm09 virus infection, concurrent bacterial community-acquired pneumonia appears to be uncommon in patients with Asian lineage A(H7N9) virus infection.

In most cases, empirical therapies for bacterial pneumonia and influenza virus infection are initiated before the Asian lineage A(H7N9) diagnosis is confirmed. Antibacterial therapy should follow evidence-based treatment guidelines, conform to local/regional standards of care, and target common community-acquired pneumonia pathogens from the region where infection occurred.

**Hospital-acquired pneumonia**

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>variable</td>
<td>low</td>
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</tbody>
</table>

Common complication of mechanical ventilation and one of the most frequent of all healthcare-associated infections (HCAIs).[193] Relevant bacterial species-associated HCAIs, including ventilator-associated pneumonia, have been identified in some hospitalised patients with A(H7N9) virus infection.[116][150]

Evaluation and treatment should follow evidence-based guidelines and local/regional policies.

**Prognosis**

Between February 2013 and June 2019, approximately 39% of patients with confirmed Asian lineage A(H7N9) virus infection have died. Those who had progressive disease generally died from complications of acute respiratory distress syndrome (ARDS) and multi-organ failure. Early recognition of disease and early initiation of oseltamivir treatment may be associated with improved outcomes.

Management should follow evidence-based clinical care guidelines for ARDS, septic shock, and other critical care illness. No studies have assessed the long-term sequelae of Asian lineage A(H7N9) virus infection among survivors.
## Diagnostic guidelines

### Europe

**Avian influenza guidance, data and analysis**

**Published by:** Public Health England  
**Last published:** 2019

### North America

**Interim guidance for specimen collection, processing, and testing for patients with suspected infection with novel influenza A viruses associated with severe disease in humans**
[https://www.cdc.gov/flu/avianflu/healthprofessionals.htm](https://www.cdc.gov/flu/avianflu/healthprofessionals.htm)

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2014

## Treatment guidelines

### Europe

**Avian influenza: guidance, data and analysis**

**Published by:** Public Health England  
**Last published:** 2019

### International

**WHO portal for avian and other zoonotic influenza**

**Published by:** World Health Organization  
**Last published:** 2019

**WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses**
[https://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/](https://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/)

**Published by:** World Health Organization  
**Last published:** 2010

**Clinical management of human infection with avian influenza A(H5N1) virus**

**Published by:** World Health Organization  
**Last published:** 2007

**WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus**

**Published by:** World Health Organization  
**Last published:** 2006
**North America**

**Asian lineage avian influenza A (H7N9) virus** (https://www.cdc.gov/flu/avianflu/h7n9-virus.htm)

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2018


**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2017


**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2015

2. WHO: FAQs on human infection caused by the avian influenza A(H7N9) virus (https://www.who.int/influenza/human_animal_interface/faq_H7N9/en/) (external link)

3. CDC: avian influenza - information for health professionals and laboratorians (https://www.cdc.gov/flu/avianflu/healthprofessionals.htm) (external link)


7. CDC: information on avian influenza (https://www.cdc.gov/flu/avianflu/) (external link)
Key articles


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121. Centers for Disease Control and Prevention. Interim guidance for infection control within healthcare settings when caring for confirmed cases, probable cases, and cases under investigation for infection with novel influenza A viruses associated with severe disease. Jan 2014 [internet publication]. Full text (https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm)


133. World Health Organization. Laboratory procedures: serological detection of avian influenza A(H7N9) virus infections by modified horse red blood cells haemagglutination-inhibition assay. Dec 2013 [internet publication]. Full text (https://www.who.int/influenza/gisrs_laboratory/cnic_serological_diagnosis_hai_a_h7n9_20131220.pdf?ua=1)


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References


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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style
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