Novel Avian Influenza A Virus Infections of Humans

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KEYWORDS

- Avian influenza • H5N1 • H5N6 • H7N9

KEY POINTS

- Signs, symptoms, complications of human infection with avian influenza A viruses are nonspecific; suspicion is based on a recent history of poultry exposure or close exposure to a symptomatic person.
- Respiratory specimens for testing depend on the specific virus, time from illness onset, and the patient's symptoms and disease severity.
- Influenza tests available in clinical settings do not distinguish influenza A viruses of animal origin from seasonal influenza A viruses.
- Clinical specimens must be sent to a public health laboratory for specific testing for seasonal and avian influenza A viruses.
- Clinical management is based on prompt implementation of recommended infection prevention and control measures, antiviral treatment, and supportive care of complications.

INTRODUCTION

Influenza A viruses are RNA viruses with a segmented genome and are subtyped on the basis of the 2 virus surface glycoproteins, hemagglutinin (H) and neuraminidase (N), into 16 H and 9 N subtypes. More recently, additional virus subtypes have been discovered in bats, but these subtypes are of uncertain significance for humans. Influenza A viruses naturally circulate in a range of avian and mammalian species, including in humans. The greatest diversity of virus subtypes are found in aquatic waterfowl, which are regarded as the natural reservoir of influenza A viruses. Influenza A viruses of 3 subtypes—H1N1, H2N2, and H3N2—have been endemic in humans. Influenza A H1N1 caused the 1918 pandemic and circulated in humans

until 1957 when a new pandemic H2N2 virus replaced it; which was in turn replaced by an H3N2 virus in 1968. The most recent pandemic was in 2009, caused by a 'swine-origin' H1N1 virus. Currently, influenza A subtypes H1N1 and H3N2 co-circulate in humans as seasonal influenza A viruses. Pandemics arise when novel influenza A viruses containing virus hemagglutinins from swine or birds emerge and spread efficiently and in a sustained manner among an immunologically naïve human population. In addition, avian and animal influenza A viruses may cause sporadic zoonotic human infections and disease without acquiring the ability for sustained human-to-human transmission. However, such infections cause global public health concern because they may cause significant morbidity and mortality; but the even greater concern is that they pose potential pandemic threats. Swine-origin H1 and H3 viruses have also caused zoonotic infections, but are not discussed in this article.

EPIDEMIOLOGY

Sporadic human infections with avian influenza A viruses of multiple subtypes have been increasingly detected since 1997, in part because the surveillance and laboratory capacity for molecular analyses have improved worldwide, but also because changes in poultry production marketing practices have increased the opportunity for the emergence and dissemination of potentially zoonotic viruses. The classification of avian influenza A viruses as highly pathogenic avian influenza (HPAI) or low pathogenicity avian influenza (LPAI) viruses is based on specific molecular criteria and pathogenicity in birds. Past pandemics have arisen from LPAI viruses. Although HPAI viruses have important agricultural and economic implications, both HPAI and LPAI virus infections have caused a wide range of mild to fatal human disease (**Tables 1** and **2**). Therefore, for public health impact, focus is on the virus subtype rather than virus pathogenicity in birds.

Although diverse avian influenza A virus subtypes have caused zoonotic infections (see **Tables 1** and **2**), virus subtypes H5N1 and H7N9 have caused the highest impact, both numerically and in disease severity. The first instance of a zoonotic avian influenza A virus causing severe disease was in 1997 in Hong Kong when 18 cases of H5N1 virus disease were detected leading to 6 deaths.[1] Human cases were preceded by outbreaks in poultry. The outbreak in Hong Kong was stopped by the slaughter of all poultry in markets and farms in Hong Kong in December 1997. H5N1 viruses continued to circulate and evolve among poultry in the wider region. Zoonotic disease was again observed in early 2003 with 2 deaths among 2 confirmed and 1 probable case.[2] H5N1 virus spread via the poultry trade to affect poultry in 10 countries in Asia by 2004.[3] By 2005, the virus also was established in wild migratory birds and spread via bird migration to infect poultry in Central Asia, South Asia, the Middle East, and parts of Africa. Although these poultry outbreaks were stamped out successfully and repeatedly in some countries (eg, Japan, Malaysia), they became enzootic within poultry in others, evolving into antigenically distinct and genetic diverse clades leading to zoonotic disease.[3] As of May 2019, 861 human cases of H5N1 virus infection and 455 deaths had been reported from 17 countries since November 2003, and the cumulative case fatality proportion among reported H5N1 cases has remained greater than 50%, although few cases have been reported worldwide since 2016.[4,5] Since 2013, H5N1 viruses of clade 2.3.4.4 have undergone reassortment with other avian influenza A viruses to generate H5N6, H5N8, and other related subtypes. More recently, H5N6 has become the dominant H5 lineage virus circulating in China, sometimes causing zoonotic disease.[6]

Table 1
LPAI A virus subtypes reported to cause human illness and associated clinical syndromes

Subtype	Patient Characteristics	Clinical Syndromes	Illness Severity	Countries	Years (Illness Onset)
H6N1	Young adult	Moderate lower respiratory tract disease	Moderate	Taiwan	2013
H7N2	Adults	Upper respiratory tract illness, conjunctivitis, lower respiratory tract disease	Mild to moderate	US; UK	2002, 2003, 2007, 2016[a]
H7N3	Adults	Upper respiratory tract illness, conjunctivitis	Mild	UK; Canada	2004, 2006
H7N4	Elderly adult	Pneumonia	Moderately severe	China	2017
H7N7	Adults	Conjunctivitis	Mild	US; UK	1980,[b] 1996
H7N9	All ages	Upper respiratory tract illness, lower respiratory tract disease, critical illness with multiorgan failure	Mild to severe; majority with severe to critical illness with mortality in hospitalized patients at 40%	China; exported cases identified in Hong Kong Special Administrative Region of China, Taiwan, Malaysia	2013–2018
H9N2	Young children and adults with influenza-like illness; one immunosuppressed adult with bilateral pneumonia	Upper respiratory tract illness, lower respiratory tract disease	Mild to moderately severe, fatal outcome in 1 case	China; Hong Kong Special Administrative Region of China; Bangladesh; Egypt, Oman	1998, 1999, 2003, 2007, 2008, 2009, 2011, 2013–2017, 2019
H10N7	Adults	Conjunctivitis and upper respiratory tract illness	Mild	Australia	2010
H10N8	Middle-aged and elderly adults	Severe pneumonia, critical illness with multiorgan failure	Critical illness, fatal outcome in 2 of 3 cases	China	2013, 2014

As of May 2019; excludes asymptomatic infections, infections reported by sero-epidemiology studies, or infections with illness not specified in published reports.
   [a] One case of an avian-lineage H7N2 virus was transmitted from a cat to a human causing mild respiratory illness.
   [b] One case of conjunctivitis occurred in a researcher through close contact with a seal that was experimentally infected with a virus that was antigenically similar to an H7N7 virus of avian origin.

Table 2
HPAI A virus subtypes reported to cause human illness and associated clinical syndromes

Subtype	Patient Characteristics	Clinical Syndromes	Illness Severity	Countries	Years
H5N1	All ages, primarily children and young adults	Upper respiratory tract illness, lower respiratory tract disease, encephalitis, respiratory failure, ARDS, multiorgan failure	Mild to critical illness; majority with severe to critical illness with mortality >50%	Hong Kong Special Administrative Region of China; China; Vietnam; Thailand; Cambodia; Indonesia; China; Turkey; Iraq; Azerbaijan; Egypt; Djibouti; Nigeria; Laos PDR; Nepal; Pakistan; Myanmar; Bangladesh; Canada (imported from China)	1997, 2003–2017, 2019
H5N6	Adults	Upper respiratory tract illness, severe pneumonia, respiratory failure, ARDS, multiorgan failure	One case with mild illness; most cases with critical illness, mortality >50%	China	2014–2018
H7N3	Adults	Conjunctivitis	Mild	Canada; UK; Mexico; Italy	2004, 2006, 2012, 2013
H7N7	All ages	Hepatitis, conjunctivitis, upper respiratory tract illness, severe pneumonia, respiratory failure, ARDS, multiorgan failure	Mild to critical illness with fatal outcome in one adult; majority with mild illness (conjunctivitis)	UK; the Netherlands, Italy	1959, 1996, 2003, 2013
H7N9		Pneumonia, respiratory failure, ARDS, multiorgan failure	Critical illness, high mortality	China	2016–2017, 2019

As of May 2019; does not include asymptomatic infections, infections reported by sero-epidemiology studies, or infections with illness not specified in published reports.

Abbreviation: ARDS, acute respiratory distress syndrome.

In 2003, an outbreak of HPAI H7N7 virus in poultry was associated with zoonotic disease affecting 89 people in the Netherlands, most of them presenting with conjunctivitis, others with influenza-like illness, and 1 fatal pneumonia in a veterinarian. There was evidence of limited human-to-human transmission to family members of persons directly exposed to infected poultry.[7]

A novel H7N9 virus caused zoonotic disease in eastern China in the early spring of 2013.[8] Six epidemics of human cases of H7N9 virus infection (1564 laboratory-confirmed cases and 612 deaths) occurred in China through September 2017, typically during the fall, winter, and spring months, including a very large fifth epidemic during 2016 to 2017.[9,10] As of May 2019, 1568 laboratory-confirmed H7N9 virus infections acquired in China had occurred since 2013. Being an LPAI virus, H7N9 caused little or no illness in poultry and spread to multiple provinces in China. The seasonal increase in human cases corresponded with a seasonal increase in virus circulation among poultry. The cumulative case fatality proportion among reported H7N9 cases has remained approximately 40% since 2013.[9] The H7N9 virus acquired properties of an HPAI virus in 2016 causing disease in poultry. This led to the introduction of a bivalent H5N1/H7N9 vaccination program in poultry in China leading to a decrease in virus activity in poultry[11] and a marked reduction of zoonotic H7N9 disease since 2017.[10] Only 2 H7N9 cases were reported in 2018, and 1 case was reported in the early spring of 2019.[12]

Most surveillance for human infections with avian influenza A viruses has been hospital based and focused on collecting respiratory specimens for virologic testing from patients with severe disease (eg, pneumonia of unknown etiology). The recognition of clinically mild infections comes from sporadic cases identified through routine influenza surveillance among outpatients with influenza-like illness,[13,14] testing of ill persons with poultry exposures during large outbreaks of avian influenza follow-up of close contacts of confirmed cases (eg, H7N9), and sero-epidemiologic studies.[7,15,16] Therefore, asymptomatic and clinically mild illness cases of infections with avian influenza A viruses are likely underestimated, the true denominator of all infections is unknown, and the case fatality proportions for hospitalized patients are likely a substantial overestimate of the overall case fatalities for different virus infections.[17,18]

Serologic studies conducted among poultry workers,[19–34] persons exposed to poultry,[35–40] close contacts of confirmed cases,[41–44] health care providers,[45–47] and the general population[20,23,39,48,49] suggest that, although the findings vary by virus subtype, except for poultry workers, human infections with avian influenza A viruses are generally infrequent. However, because some infected persons with mild illness may not mount a detectable antibody response, and limited data on the kinetics of the antibody response for HPAI H5N1 and LPAI H7N9 virus infections suggest that antibody titers decrease over time,[50] sero-surveys may underestimate some human infections with avian influenza A viruses.

Exported Cases

Several human cases of infection with avian influenza A viruses acquired in China have traveled overseas and were diagnosed elsewhere. A traveler who returned to Alberta, Canada, from a 3-week visit to Beijing, China, was hospitalized with pneumonia, progressed to respiratory failure with meningocencephalitis, and died.[51] H5N1 virus was identified in this patient's upper and lower respiratory tract and cerebrospinal fluid specimens. H7N9 virus infections acquired in China, leading to mild or critical illness, have been identified in returned travelers in Taiwan[52] and Canada,[53] and in a tourist in Malaysia.[54]

Exposure Risk Factors

Most human infections with avian influenza A viruses have been sporadic and linked to recent direct contact or close exposure with domestic poultry, including raising back-yard poultry or visiting a live poultry market (**Table 3**).[55–65] Contact with dead wild swans (defeathering) was the source of infection for some cases of H5N1 virus infection in Azerbaijan.[66] However, the source of exposure is not always determined for some cases of human infection with avian influenza A viruses.[64,67] Live avian influenza A viruses have been identified in poultry carcasses sourced in endemic areas. Although cooking destroys virus infectivity, contamination from the carcass before cooking may contribute to some of the cases of zoonotic avian influenza A virus infection with no history of direct exposure to live poultry.[68] Virologically confirmed infection with avian-lineage H7N2 virus was identified in an ill veterinarian who had exposure to ill cats.[69,70] A researcher developed virologically confirmed conjunctivitis with an H7N7 virus that was antigenically related to an avian influenza A virus after close exposure to an experimentally infected seal.[71]

Infection of the human respiratory tract is likely initiated by inhalation of aerosolized avian influenza A viruses or contact transmission to mucus membranes, including conjunctivae, depending on the specific characteristics of the virus (eg, tropism for receptors with sialic acids attached to galactose by α2,6 linkages primarily in the upper respiratory tract vs sialic acids attached to galactose by α2,3 linkages primarily in the lower respiratory tract),[72] host factors (eg, age, immune function, and underlying comorbidities) and exposure (eg, virus dose, single or multiple exposures). Some avian influenza A(H7) viruses have tropism for ocular receptors and conjunctivitis has been reported in persons with H7N2, H7N3, and H7N7 virus infections.[73] In regions with enzootic poultry infections, human exposures to avian influenza A viruses such as H5N1, H5N6, and H7N9 has been extensive, but zoonotic disease is stochastic and rare. The reasons for this disconnect between exposure and disease are unclear.

Human-to-Human Transmission

Multiple clusters of epidemiologically linked human cases of H5N1 virus infection have been reported worldwide, beginning with the first outbreak described in Hong Kong

Table 3	
Exposure risk factors for human infections with avian influenza A viruses	
Risk Factor	**Viruses**
Direct contact with infected well-appearing poultry or poultry products	LPAI A viruses
Direct contact with infected sick or dead poultry or poultry products	HPAI A viruses (eg, H5N1, H5N6, H7N7, H7N9)
Close exposure to infected well-appearing poultry	LPAI A viruses
Close exposure to infected sick or dead poultry	HPAI A viruses (eg, H5N1, H5N6, H7N7, H7N9)
Visiting a live poultry market	LPAI A viruses (eg, H7N9); HPAI A viruses (eg, H5N1)
Raising backyard poultry	LPAI A viruses (eg, H7N9); HPAI A viruses (eg, H5N1, H5N6)
Close, unprotected, prolonged exposure to an ill person with avian influenza A virus infection and respiratory illness	LPAI A viruses (eg, H7N9); HPAI A viruses (eg, H5N1)

during 1997. Most cases in clusters have had recent exposure to birds, usually domestic poultry, suggesting a common exposure source.[66,67,74,75] However, some cases in clusters had close exposure to a symptomatic index case without poultry exposure. Although there is no laboratory test to confirm human-to-human transmission, epidemiologic investigations have concluded that limited, nonsustained human-to-human transmission of avian influenza A viruses likely occurred in some clusters in households or health care settings primarily among blood-related family members[67,76–79] This included 2 clusters of third-generation spread in Indonesia[80] and Pakistan.[81] Transmission has likely occurred through prolonged, unprotected close exposure to a symptomatic infected person. Similarly, at least 40 clusters of epidemiologically linked cases of H7N9 virus infection, mostly attributed to poultry exposures, were identified in China during 2013 to 2017.[82] In some of these clusters, probable limited, nonsustained human-to-human LPAI H7N9 virus transmission likely occurred in households[82–84] and in health care settings, including between blood-related family members as well as between unrelated patients.[85,86] There has been no increase identified in the transmissibility of H7N9 viruses among humans since emergence in 2013.[82,87] Probable, limited, nonsustained human-to-human transmission of HPAI H7N7 virus was also reported among family members in a few households in the Netherlands during 2004.[7]

Host Factors

The median age for reported human cases of infection with HPAI H5N1 virus is substantially younger than for infection with LPAI H7N9 virus among hospitalized patients. It has been postulated that these different age distributions are consistent with immunologic imprinting with an individual's first influenza A virus infection (belonging to either group 1 or group 2 virus hemagglutinin subtypes) and subsequent protection against future infection with influenza A viruses in the same hemagglutinin subtype grouping (group 1 or group 2).[88]

Age may also influence disease severity and thus, case detection and reporting. Older age or age 60 years or older is associated with fatal outcomes from H7N9 virus infection.[89–92] Among children with H5N1 virus infection, case fatality proportion was lowest in those aged 5 years or younger.[74] Among persons with H7N9 virus infection, mild illness was observed in young children.[64] The majority of H9N2 virus infections have occurred in children, and most cases have resulted in mild to moderate disease in patients in China, Hong Kong, Egypt, and Bangladesh.[93,94]

In contrast with H5N1 virus infection, risk factors for severe H7N9 disease include having a chronic medical condition (eg, obesity, chronic obstructive pulmonary disease, immunosuppression).[61–63,65] This finding may imply that infection in younger healthy persons occurs undetected and unreported. Epidemiologically linked clusters of H7N9 cases in China were identified in each epidemic from 2013 to 2017. Similarly, clusters of H5N1 cases have been identified in multiple countries. In zoonotic H5N1 disease, the occurrence of small clusters predominantly among blood-related family members has raised the suggestion of a genetic susceptibility.[95]

CLINICAL ISSUES
Clinical Spectrum

The clinical spectrum of infection with avian influenza A viruses is wide and depends on the specific virus and host characteristics, ranging from asymptomatic, mild focal illness (conjunctivitis), uncomplicated upper respiratory illness, to fulminant pneumonitis with multiorgan failure and sepsis leading to fatal outcomes (see **Tables 1** and **2**).

Most avian influenza A virus subtypes that have infected people have resulted in mild to moderate illness. Only a few viruses (H5N1, H5N6, H7N9) have caused a high proportion of severe illness (**Table 4**).

Asymptomatic infections have been identified by serology for several different avian influenza A viruses, although few such infections have been confirmed virologically.[16,96,97] In follow-up of household contacts of a confirmed H5N1 case, the case's adult daughter had a throat specimen collected that yielded H5N1 virus 6 days after slaughtering a chicken, and had evidence of seroconversion without experiencing any illness symptoms.[96]

Conjunctivitis has been reported for HPAI H5N1,[74,98] LPAI H7N2,[99] LPAI H7N3,[100,101] HPAI H7N3,[15,102] LPAI H7N7,[103] HPAI H7N7,[7,104] and LPAI H10N7[105] virus infections. Mild to moderate uncomplicated upper respiratory tract illness has been reported for infections with HPAI H5N1 (particularly in children),[67,74,77,106–108] HPAI H5N6,[109,110] LPAI H7N2,[69,111] LPAI H7N3,[102] HPAI H7N7,[7] LPAI H7N9,[13,14] LPAI H9N2,[93,94] and LPAI H10N7[105] viruses. Lower respiratory tract disease has been reported for HPAI H5N1,[112,113] HPAI H5N6,[114,115] LPAI H6N1,[116] LPAI H7N2,[117] LPAI H7N3, LPAI H7N4,[118] HPAI H7N7,[119] LPAI H7N9,[120] HPAI H7N9,[121] LPAI H9N2,[94] and LPAI H10N8[122] virus infections. Respiratory failure, refractory shock, acute respiratory distress syndrome, and multiorgan failure have been reported for infections with HPAI H5N1,[112,113] HPAI H5N6,[110,115] HPAI H7N7,[119] LPAI H7N9,[120] HPAI H7N9,[121,123] and LPAI H10N8[122,124] viruses. Fatal outcomes have occurred with HPAI H5N1,[60,112,113] HPAI H5N6,[110,115] HPAI H7N7,[119] LPAI H7N9,[120] HPAI H7N9,[121,123] LPAI H9N2,[125] and LPAI H10N8[109,122] virus infections.

Clinical Presentation

The clinical presentation varies by the specific virus infection, host characteristics, and time from illness onset to medical care. However, signs, symptoms, and

Table 4
Summary of clinical and clinical laboratory findings reported in patients with severe disease from avian influenza A virus infection

Admission clinical findings	History of fever and cough (productive cough, shortness of breath, dyspnea, chest pain, hypoxemia are associated with severe pneumonia), myalgia; diarrhea, malaise, headache, sore throat can occur, but are less common. Radiographic findings: bilateral patchy, interstitial, lobar, and/or diffuse infiltrates, ground glass opacities, consolidation, air bronchograms
Admission laboratory findings	White blood cell count may be low or normal; lymphopenia and moderate thrombocytopenia are common; neutropenia and elevated alanine aminotransferase associated with H5N1 mortality.
Clinical complications during hospitalization	Respiratory failure, acute respiratory distress syndrome, refractory hypoxemia, pleural effusion, cardiac failure, acute kidney injury/renal failure, multiorgan failure, septic shock, rhabdomyolysis, spontaneous miscarriage in pregnant patients, disseminated intravascular coagulation, encephalitis, bacterial co-infection, fungal co-infection, pneumothorax.
Laboratory findings during hospitalization	Elevated lactate, creatinine kinase, hepatic transaminases; hypoalbuminemia, leukopenia or leukocytosis

Associated with H5N1, H5N6, or H7N9 virus infections.

complications associated with avian influenza A virus infection are nonspecific and overlap with those caused by other respiratory pathogens, including seasonal influenza A and B viruses. Patients with avian influenza A(H7) virus infections can present with unilateral conjunctivitis only or also with fever and upper respiratory tract symptoms. The incubation period is not well-characterized for human infection with most avian influenza A viruses, but is estimated to be approximately 3 to 5 days after exposure to infected poultry for H5N1[126,127] and H7N9[127–129] virus infections, with a wider range in clusters with limited human-to-human transmission of H5N1 virus.[76,77]

In early illness with H5N1, H5N6, or H7N9 virus infections, fever or feverishness is usually present; cough, and malaise, myalgia, headache, and sore throat also may be present.[115,120,130] Gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea are variable,[60,77,120,131] but conjunctivitis is uncommon.[74,115,120] Atypical presentations have included fever and diarrhea before signs and symptoms of lower respiratory tract disease or encephalitis developed.[132,133] Dyspnea, shortness of breath, tachypnea, productive cough, and chest pain are associated with severe pneumonia. Many patients with H5N1, H5N6, or H7N9 virus infections have presented to medical care with severe pneumonia and hypoxemia approximately 5 to 7 days after illness onset.[4,64,112,113,115,123]

Routine laboratory findings are nonspecific and leukopenia, lymphopenia, and moderate thrombocytopenia are associated with more severe H5N1 disease[60,113] and lymphopenia is commonly observed at admission, but white blood cell counts may be normal initially for patients with H7N9 virus infection.[120] A high neutrophil to lymphocyte ratio 24 hours after hospital admission of H7N9 patients was independently- associated with mortality.[134] Other abnormalities reported in severely ill patients with H5N1, H5N6, or H7N9 virus infections include hypoalbuminemia[77] and elevated levels of hepatic transaminases,[60,112,113,115,120] creatinine kinase,[98,112,115,120] and lactic dehydrogenase.[112,115,120] Radiographic findings in patients with H5N1, H5N6, or H7N9 virus infections hospitalized with pneumonia include bilateral patchy, interstitial, lobar, and/or diffuse infiltrates, ground glass opacities, consolidation, pleural effusion, air bronchograms, and pneumothorax.[60,112,115,120,135]

Complications

Respiratory complications of H5N1, H5N6, or H7N9 virus infections include pneumonia, respiratory failure, and acute respiratory distress syndrome.[60,112,115,120,135] Extrapulmonary dissemination and isolation of H5N1 virus from blood, cerebrospinal fluid, brain tissues, lower respiratory tract tissues, gastrointestinal tract tissues (ileum, colon, rectum), rectal swabs, stool, ureter, and axillary lymph node have been reported.[133,136,137] Detection of H7N9 viral RNA was reported in stool.[138] Extrapulmonary complications owing to H5NI or H7N9 virus infections include cardiac failure,[60,112,120] acute kidney injury,[60,112,120] encephalitis,[51,133,139] myelitis,[140] rhabdomyolysis,[120,141] multiorgan failure and sepsis,[112,120,142] disseminated intravascular coagulation,[112,113,120,143] and spontaneous miscarriage in pregnant patients.[112] A 36-week gestational infant survived after emergency Cesarean section delivery of a critically ill pregnant woman with H5N1 virus infection who died.[144] Obstructive hydrocephalus[139] and Reye syndrome with aspirin administration[145] have been reported in pediatric cases of H5N1 virus infection. Co-infection with bacterial pathogens has been reported at hospital admission in H7N9 patients,[146] and nosocomial infection and ventilator-associated pneumonia with bacterial and fungal pathogens can occur.[8,120,147,148,149] Nosocomial bacterial infections were more common in 6 fatal cases than in 6 survivors of H7N9 virus infection.[138] H5N1 virus infection in persons with HIV has been reported.[60,150]

Neutropenia and elevated alanine aminotransferase at admission were associated with mortality for H5N1 patients in an observational study.[113] Septic shock with severe hypoxemia was an independent risk factor associated with mortality in H7N9 patients in another observational study.[151] Refractory hypoxemia is a major cause of death in H7N9 patients.[120]

Pathogenesis and pathology findings

In severe disease, the pathogenesis of H5N1, H5N6, and H7N9 virus infections is driven by high viral levels and prolonged replication in the lower respiratory tract and aggravated by innate immune dysregulation. Higher viral levels in nasal and throat swabs are associated with adverse clinical outcomes in H5N1 disease.[152] H5N1 virus infects ciliated and nonciliated tracheal epithelial cells with tropism for α2,3-linked sialic acid receptors in the lower respiratory tract,[153] and H7N9 virus has affinity for α2,6-linked sialic acid receptors in the upper respiratory tract, but preferentially binds to α2,3-linked sialic acid receptors in the lower respiratory tract.[154] Patients with severe and fatal lower respiratory tract disease have prolonged H5N1 viral replication.[153] High-dose corticosteroid treatment is associated with prolonged detection of H7N9 viral RNA.[155,156] In vitro and ex vivo studies indicate that H5N1, H5N6, and H7N9 viruses induce inflammatory mediators,[114,157–167] and data from critically ill patients indicate that virus infection of the respiratory tract triggers a dysregulated proinflammatory cytokine and chemokine response, resulting in inflammatory pulmonary damage and multiorgan injury.[2,115,168–170] H5N1 virus induces higher levels of proinflammatory cytokines and chemokines than H7N9 and seasonal influenza A viruses and infection of endothelial cells as shown in mice and ferrets may also contribute to pulmonary vascular leakage and viral pneumonia.[171,172] Limited autopsy studies have described extrapulmonary dissemination of H5N1 and H5N6 viruses,[153,173] including evidence of infection of cerebral neurons, placenta, T lymphocytes in lymph nodes, cytotrophoblasts of placental chorionic villi and fetal macrophages (transplacental transmission)[153]; pulmonary findings of diffuse alveolar damage and interstitial fibrosis for H5N1, H5N6, and H7N9 virus infections[60,138,174–179]; and other organ findings of hepatic central lobular necrosis, acute renal tubular necrosis, lymphoid depletion, and reactive hemophagocytic syndrome for H5N1 or H7N9 virus infections.[2,138,153,176,180]

CLINICAL MANAGEMENT
Infection Prevention and Control Measures

Prompt isolation and implementation of infection prevention and control measures is essential to decreasing the risk of nosocomial transmission of patients with avian influenza A virus infection associated with severe and fatal illness (eg, H5N1, H5N6, H7N9, H10N8 viruses). The Centers for Disease Control and Prevention recommend placement of patients with suspected avian influenza A virus infection associated with severe illness in a negative pressure respiratory isolation room and implementation of standard, contact (including googles), and airborne (use of fit-tested N95 respirator or higher level of respiratory protection) precautions for health care personnel[181] while providing care, including collecting respiratory specimens. The World Health Organization recommends personal protective equipment (medical mask, eye protection, gown, and gloves), performing adequate hand hygiene, and use of a separate adequately ventilated or airborne precaution room (isolation in mechanically or naturally ventilated rooms with 12 air changes per hour and controlled direction of airflow), and use of a respirator for aerosol-generating procedures.[182] Patients should wear a medical mask when outside of isolation rooms.

Diagnosis

Because the signs, symptoms, and clinical findings are nonspecific, clinical suspicion of avian influenza A virus infection (all subtypes with at least 1 human infection; see **Tables 1** and **2**) is based on eliciting a history of (1) recent poultry exposure in a virus enzootic region, in particular, visiting a market where live poultry are sold or slaughtered, or at small farms or inside/outside homes (where poultry are raised), or (2) recent close exposure to a symptomatic person with suspected or confirmed avian influenza A virus infection (eg, viruses in which limited human-to-human transmission has been reported, namely, H5N1, H7N7, and H7N9). The optimal respiratory specimens to collect depends on the time from illness onset to presentation, the presumed site of the major pathology and the patient's disease severity. For example, although a nasopharyngeal specimen might be sufficient for detecting some avian influenza A viruses associated with upper respiratory symptoms, a throat swab specimen has a higher yield for detecting H5N1 virus in patients without severe lower respiratory tract disease. For hospitalized patients, the collection of respiratory specimens from multiple respiratory sites, including sputum, can increase the likelihood of detecting avian influenza A virus infection. For critically ill patients with respiratory failure receiving invasive mechanical ventilation, an endotracheal aspirate or bronchoalveolar lavage specimen should be collected for testing.

Commercially available influenza tests available in clinical settings, including molecular assays, detect influenza A and B viruses but do not specifically distinguish between seasonal influenza A viruses circulating among people worldwide and zoonotic avian influenza A viruses. Therefore, respiratory specimens must be sent to a public health laboratory for specific testing for avian influenza A virus subtypes by reverse transcriptase polymerase chain reaction (eg, H5, H7, H9) and additional analyses, such as genetic sequencing. Antigen detection tests are less sensitive than reverse transcriptase polymerase chain reaction assays for detecting avian influenza A virus infection. Serologic testing of paired acute and convalescent sera can yield a retrospective diagnosis, but must be performed at a specialized public health or research laboratory.

Discharge Criteria

No guidelines exist on discharge criteria for hospitalized patients with avian influenza A virus infection, but key criteria are clinical recovery with demonstration of clearance of viral RNA from the respiratory tract.

Antiviral Treatment

There are no randomized controlled trials (RCTs) of antiviral treatment of patients with avian influenza A virus infection. No clinical or virologic benefit of double-dose versus standard-dose oseltamivir was found in an RCT conducted in 326 hospitalized patients with influenza, including 17 H5N1 patients.[183] Mortality was very high (88%) among the enrolled H5N1 patients.[183] Observational studies of patients with H5N1 or H7N9 virus infections have reported survival benefit of antiviral treatment with a neuraminidase inhibitor (NAI), usually oseltamivir monotherapy, particularly when treatment is initiated early in the clinical course.[74,113,149,184–188] One observational study reported no benefit of combination NAI treatment (oseltamivir and peramivir) compared with oseltamivir for hospitalized H7N9 patients.[189] Most severely ill H5N1, H5N6, and H7N9 patients have been admitted more than 5 days after illness onset, with late initiation of NAI treatment. One observational study reported that

delayed administration of NAI treatment was an independent risk factor for prolonged H7N9 viral shedding.[156]

Currently, NAI treatment is recommended as soon as possible in patients with suspected avian influenza A virus infection, even before laboratory confirmation, because there may be a long delay until specific testing results are received. Recommended NAI dosing is the same as for the treatment of patients with seasonal influenza. Combination treatment with 2 NAIs is not recommended. The duration of antiviral treatment should continue until there is no evidence of viral shedding and be guided by testing results of respiratory tract specimens, particularly lower respiratory tract specimens, in ventilated patients. The emergence of antiviral resistance to NAIs should be considered in patients with prolonged viral replication with no decrease in viral load. Analyses of genetic markers associated with decreased antiviral susceptibility or resistance can be performed on viral RNA and phenotypic antiviral susceptibility testing on virus isolates at specialized public health reference laboratories.

The emergence of oseltamivir-resistant viruses containing an H275Y mutation in viral neuraminidase has been reported during oseltamivir treatment of H5N1 patients with sustained viral replication, clinical deterioration, and fatal outcomes,[190] and in an H5N1 patient who had received oseltamivir chemoprophylaxis followed by oseltamivir treatment and recovered.[79] Similarly, the emergence and sustained replication of H7N9 viruses with an R292 K mutation in viral neuraminidase confers resistance to NAIs.[158,191–193] This mutation confers high-level resistance to oseltamivir and moderately decreased sensitivity to peramivir and zanamivir.[194] Most H5N1, H5N6, and H7N9 viruses circulating among poultry are resistant to the adamantane antivirals (amantadine and rimantadine). Novel antivirals such as favipiravir and baloxavir marboxyl have not been used therapeutically in zoonotic avian influenza A virus infections, but may need to be considered in the event of NAI resistance.[194]

Adjunctive Therapy

Immunotherapy with convalescent plasma has been administered to a very small number of hospitalized H5N1 patients. The source of the convalescent plasma was recovered survivors of H5N1 virus infection[112,195] for 2 critically ill patients with respiratory failure receiving invasive mechanical ventilation and an H5N1 vaccine recipient for another patient[78] with pneumonia receiving noninvasive ventilation, all of whom also received antiviral treatment and survived. Convalescent plasma from a recovered survivor has also been administered to a hospitalized H7N9 patient with respiratory failure receiving invasive mechanical ventilation with no improvement from oseltamivir treatment.[196] The patient also received other medications, including methylprednisolone, and survived.[196] No conclusions can be made on the clinical benefit of convalescent plasma treatment from such limited uncontrolled data, but further studies of the clinical benefit of immunotherapy as an adjunctive treatment to antiviral therapy are warranted. IVIG has been administered to some H7N9 patients on an uncontrolled basis.[149]

No RCTs have been conducted of corticosteroid treatment for any patients with avian influenza A virus infection. Observational studies have suggested an increased mortality risk with corticosteroid treatment of H5N1[113] and H7N9[197] patients, and high-dose corticosteroids have been implicated with increased H7N9 mortality risk.[155] High-dose corticosteroids were also reported to be an independent risk factor for prolonged H7N9 viral shedding in an observational study of 478 patients with H7N9.[156] The clinical benefit or harm of low-dose or moderate-dose corticosteroid treatment for hospitalized patients with avian influenza A virus infection is unknown. However, given the observational data to date, high-dose corticosteroids should be avoided, and corticosteroids should only be administered for treatment of septic shock.

There are very limited and inconclusive observational data about the benefit of probiotic treatment of patients with H7N9 virus infection.[198–200] Salicylates should not be administered to patients with suspected or confirmed avian influenza A virus infection because of the risk of Reye syndrome.[145]

Advanced Organ Support

No RCTs are available, but advanced organ support has been administered to most critically ill hospitalized patients with H5N1, H5N6, or H7N9 virus infections, especially invasive mechanical ventilation for respiratory failure.[110,113,115,120] In H7N9 patients with acute respiratory distress syndrome, extracorporeal membrane oxygenation has been administered on an uncontrolled basis.[120,201–208] H7N9 patients with acute kidney injury have also required renal replacement therapy.[120] Plasma exchange has been used in combination with continuous venovenous hemofiltration to reduce levels of cytokines and chemokines.[209] Artificial liver therapy has been used in management of some H7N9 patients.[149]

Immune responses

During the acute illness, most H5N1 patients typically mount a robust neutralizing antibody response 14 or more days after onset.[42] In 4 H5N1 survivors of severe disease, although specific hemagglutination inhibition and neutralizing antibody titers increased from 15 days after illness onset and declined by 5 to 12 months, titers were detectable for 3 to 4 years after onset.[210] A follow-up study of 11 H5N1 patients who survived severe disease reported that 70% had a positive neutralizing antibody titer after 2 weeks and all had a neutralizing antibody titer of 1:80 or greater by 3 weeks after illness, with titers peaking at 1 to 2 months and declining by 10 to 12 months.[50]

During the acute illness, most critically ill H7N9 patients mounted a robust humoral immune response with a seroprotective titer of neutralizing antibodies ($\geq$1:40) detected significantly earlier (median, 10.5 days) in survivors than in fatal cases (median, 14 days).[211] Other studies in H7N9 survivors have reported variable kinetics and antibody titers after recovery declining, though still detectable at 1 year after illness.[212,213] T-cell (CD^8+/$CD4^+$ T-cell memory) responses are reported to play an important role in recovery from disease.[214,215]

Long-term follow-up

Few studies have assessed long-term clinical follow-up of survivors of severe or critical illness owing to avian influenza A virus infections. During follow-up of 2 adult H5N1 patients who recovered from respiratory failure and ventilator-associated bacterial pneumonia, 1 patient had bilateral patchy, as well as fibrotic reticular and linear opacities noted at 7 months that mostly had resolved by 12 months after illness onset.[216] However, the more severely ill patient had ground-glass shadows, reticular opacities, linear fibrotic opacities, interlobular thickening and intralobular lines at 12 months that persisted at 24 months after onset. Of 5 adult patients who survived H7N9 virus infection and were followed for approximately 5 to 7 months after diagnosis, only one reported mild respiratory symptoms, but all had bilateral lower lung abnormalities such as interlobular septal thickening, subpleural linear opacities, and some had cystic changes on a computed tomography scan.[217] For 3 of these 5 patients who had pulmonary function testing, 1 patient had near normal pulmonary function, but 2 patients had abnormalities in forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and carbon monoxide diffusing capacity. A cohort study of 56 adult H7N9 patients followed for

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Box 1
Gaps in the clinical management of zoonotic influenza A virus infections

- Lack of point-of-care or rapid diagnostic tests with high accuracy that can specifically identify avian influenza A viruses in respiratory specimens in a time frame relevant to inform clinical decision making.
- Lack of clinical data from randomized controlled trials on combination treatment with a neuraminidase inhibitor and an antiviral with a different mechanism of action, as well as combined with immunodulatory therapy.
- Lack of a standardized approach to clinical management of hospitalized patients with avian influenza A virus infection, such as advanced organ support of critically ill patients, and management (eg, low tidal volume lung protective strategies for acute respiratory distress syndrome).
- Lack of prospective, multiyear, multicountry, multiregional clinical influenza research networks that can serve as platforms for coordinating detailed clinical data collection, and for implementation of randomized clinical adaptive trials of interventions (pharmacologic and nonpharmacologic) for patients with seasonal influenza; sporadic patients with avian influenza A virus infections could also be enrolled.

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2 years reported that although pulmonary function and chest computed tomography findings improved by 6 months after hospital discharge and most had returned to work, most patients had persistent abnormalities.[218] At 1 year after discharge, 42% had pulmonary fibrosis and 52% had parenchymal opacities, with bronchiectasis noted in 24% and pleural thickening reported in 22%, and 55% had evidence of ventilation dysfunction and 78% had an abnormal carbon monoxide diffusing capacity at 24 months (**Box 1**).[218]

SUMMARY

A high index of suspicion and early diagnosis of avian influenza A virus infection is essential to initiating interventions (antiviral treatment; infection prevention and control measures) as soon as possible to reduce transmission risk from symptomatic persons to close contacts, including health care personnel. Clinical suspicion relies on eliciting a history of recent exposure to poultry or to sick persons with suspected or confirmed avian influenza A virus infection. Diagnosis requires the collection of appropriate respiratory specimens, ideally from the lower respiratory tract when available, for specific testing for seasonal and avian influenza A virus subtypes at specialized public health laboratories. Patients with suspected infection should be isolated immediately and patients with lower respiratory tract disease should be placed on airborne precautions if possible, and NAI antiviral treatment should be started as soon as possible even before specific testing results are available. Corticosteroids and salicylates should be avoided and clinical management is focused on supportive care of complications, including nosocomial bacterial or fungal infections. Sporadic human infections with avian influenza A viruses resulting in mild to severe illness are expected to continue to occur in persons with close exposures to infected poultry and other birds. Options to decrease human exposure to enzootic avian influenza include interventions in live poultry markets, which serve as a major source of zoonotic infection and virus amplification.[219] Because zoonotic avian influenza A viruses pose potential pandemic threats, it is important to risk assess these viruses to prioritize countermeasure development such as vaccines.[220]

REFERENCES

1. Chan PK. Outbreak of avian influenza A(H5N1) virus infection in Hong Kong in 1997. Clin Infect Dis 2002;34(Suppl 2):S58–64.
2. Peiris JS, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet 2004;363(9409):617–9.
3. Webster RG, Peiris M, Chen H, et al. H5N1 outbreaks and enzootic influenza. Emerg Infect Dis 2006;12(1):3–8.
4. Lai S, Qin Y, Cowling BJ, et al. Global epidemiology of avian influenza A H5N1 virus infection in humans, 1997-2015: a systematic review of individual case data. Lancet Infect Dis 2016;16(7):e108–18.
5. Organization WH. Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. 12 February 2019. 2019. Available at: https://www.who.int/influenza/human_animal_interface/2019_02_12_tableH5N1.pdf?ua=1. Accessed April 12, 2019.
6. Claes F, Morzaria SP, Donis RO. Emergence and dissemination of clade 2.3.4.4 H5Nx influenza viruses-how is the Asian HPAI H5 lineage maintained. Curr Opin Virol 2016;16:158–63.
7. Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet 2004;363(9409):587–93.
8. Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. N Engl J Med 2013;368(20):1888–97.
9. Wang X, Jiang H, Wu P, et al. Epidemiology of avian influenza A H7N9 virus in human beings across five epidemics in mainland China, 2013-17: an epidemiological study of laboratory-confirmed case series. Lancet Infect Dis 2017;17(8):822–32.
10. Organization WH. Influenza at the human-animal interface. Summary and assessment, 13 February to 9 April 2019 2019. Available at: https://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_09_04_2019.pdf?ua=1. Accessed April 12, 2019.
11. Wu J, Ke C, Lau EHY, et al. Influenza H5/H7 virus vaccination in poultry and reduction of zoonotic infections, Guangdong Province, China, 2017-18. Emerg Infect Dis 2019;25(1):116–8.
12. Yu D, Xiang G, Zhu W, et al. The re-emergence of highly pathogenic avian influenza H7N9 viruses in humans in mainland China, 2019. Euro Surveill 2019;24(21). pii=1900273.
13. Xu C, Havers F, Wang L, et al. Monitoring avian influenza A(H7N9) virus through national influenza-like illness surveillance, China. Emerg Infect Dis 2013;19(8):1289–92.
14. Zeng X, Mai W, Shu B, et al. Mild influenza A/H7N9 infection among children in Guangdong Province. Pediatr Infect Dis J 2015;34(1):104–7.
15. Lopez-Martinez I, Balish A, Barrera-Badillo G, et al. Highly pathogenic avian influenza A(H7N3) virus in poultry workers, Mexico, 2012. Emerg Infect Dis 2013;19(9):1531–4.

16. Chen Z, Liu H, Lu J, et al. Asymptomatic, mild, and severe influenza A(H7N9) virus infection in humans, Guangzhou, China. Emerg Infect Dis 2014;20(9): 1535–40.

17. Yu H, Cowling BJ, Feng L, et al. Human infection with avian influenza A H7N9 virus: an assessment of clinical severity. Lancet 2013;382(9887):138–45.

18. Feng L, Wu JT, Liu X, et al. Clinical severity of human infections with avian influenza A(H7N9) virus, China, 2013/14. Euro Surveill 2014;19(49) [pii:20984].

19. Ma MJ, Zhao T, Chen SH, et al. Avian Influenza A virus infection among workers at live poultry markets, China, 2013-2016. Emerg Infect Dis 2018;24(7):1246–56.

20. Wang X, Fang S, Lu X, et al. Seroprevalence to avian influenza A(H7N9) virus among poultry workers and the general population in southern China: a longitudinal study. Clin Infect Dis 2014;59(6):e76–83.

21. Yang P, Ma C, Shi W, et al. A serological survey of antibodies to H5, H7 and H9 avian influenza viruses amongst the duck-related workers in Beijing, China. PLoS One 2012;7(11):e50770.

22. Yang P, Ma C, Cui S, et al. Avian influenza A(H7N9) and (H5N1) infections among poultry and swine workers and the general population in Beijing, China, 2013-2015. Sci Rep 2016;6:33877.

23. Yang S, Chen Y, Cui D, et al. Avian-origin influenza A(H7N9) infection in influenza A(H7N9)-affected areas of China: a serological study. J Infect Dis 2014; 209(2):265–9.

24. Huo X, Zu R, Qi X, et al. Seroprevalence of avian influenza A (H5N1) virus among poultry workers in Jiangsu Province, China: an observational study. BMC Infect Dis 2012;12:93.

25. Shimizu K, Wulandari L, Poetranto ED, et al. Seroevidence for a high prevalence of subclinical infection with avian influenza A(H5N1) virus among workers in a live-poultry market in Indonesia. J Infect Dis 2016;214(12):1929–36.

26. Nasreen S, Uddin Khan S, Azziz-Baumgartner E, et al. Seroprevalence of antibodies against highly pathogenic avian influenza A (H5N1) virus among poultry workers in Bangladesh, 2009. PLoS One 2013;8(9):e73200.

27. Nasreen S, Khan SU, Luby SP, et al. Highly pathogenic Avian Influenza A(H5N1) virus infection among workers at live bird markets, Bangladesh, 2009-2010. Emerg Infect Dis 2015;21(4):629–37.

28. Dung TC, Dinh PN, Nam VS, et al. Seroprevalence survey of avian influenza A(H5N1) among live poultry market workers in northern Viet Nam, 2011. Western Pac Surveill Response J 2014;5(4):21–6.

29. Uyeki TM, Nguyen DC, Rowe T, et al. Seroprevalence of antibodies to avian influenza A (H5) and A (H9) viruses among market poultry workers, Hanoi, Vietnam, 2001. PLoS One 2012;7(8):e43948.

30. Ortiz JR, Katz MA, Mahmoud MN, et al. Lack of evidence of avian-to-human transmission of avian influenza A (H5N1) virus among poultry workers, Kano, Nigeria, 2006. J Infect Dis 2007;196(11):1685–91.

31. Wang M, Fu CX, Zheng BJ. Antibodies against H5 and H9 avian influenza among poultry workers in China. N Engl J Med 2009;360(24):2583–4.

32. Schultsz C, Nguyen VD, Hai IT, et al. Prevalence of antibodies against avian influenza A (H5N1) virus among Cullers and poultry workers in Ho Chi Minh City, 2005. PLoS One 2009;4(11):e7948.

33. Bridges CB, Lim W, Hu-Primmer J, et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. J Infect Dis 2002;185(8): 1005–10.

34. Wang Q, Ju L, Liu P, et al. Serological and virological surveillance of avian influenza A virus H9N2 subtype in humans and poultry in Shanghai, China, between 2008 and 2010. Zoonoses Public Health 2015;62(2):131–40.
35. Ly S, Horwood P, Chan M, et al. Seroprevalence and transmission of human influenza A(H5N1) virus before and after virus reassortment, Cambodia, 2006-2014. Emerg Infect Dis 2017;23(2):300–3.
36. Cavailler P, Chu S, Ly S, et al. Seroprevalence of anti-H5 antibody in rural Cambodia, 2007. J Clin Virol 2010;48(2):123–6.
37. Dejpichai R, Laosiritaworn Y, Phuthavathana P, et al. Seroprevalence of antibodies to avian influenza virus A (H5N1) among residents of villages with human cases, Thailand, 2005. Emerg Infect Dis 2009;15(5):756–60.
38. Wu J, Zou L, Ni H, et al. Serologic screenings for H7N9 from three sources among high-risk groups in the early stage of H7N9 circulation in Guangdong Province, China. Virol J 2014;11:184.
39. Xiang N, Bai T, Kang K, et al. Sero-epidemiologic study of influenza A(H7N9) infection among exposed populations, China 2013-2014. Influenza Other Respir Viruses 2017;11(2):170–6.
40. Khan SU, Anderson BD, Heil GL, et al. A systematic review and meta-analysis of the seroprevalence of influenza A(H9N2) infection among humans. J Infect Dis 2015;212(4):562–9.
41. Vong S, Ly S, Van Kerkhove MD, et al. Risk factors associated with subclinical human infection with avian influenza A (H5N1) virus–Cambodia, 2006. J Infect Dis 2009;199(12):1744–52.
42. Katz JM, Lim W, Bridges CB, et al. Antibody response in individuals infected with avian influenza A (H5N1) viruses and detection of anti-H5 antibody among household and social contacts. J Infect Dis 1999;180(6):1763–70.
43. Ma MJ, Ma GY, Yang XX, et al. Avian Influenza A(H7N9) virus antibodies in close contacts of infected persons, China, 2013-2014. Emerg Infect Dis 2015;21(4):709–11.
44. Liao Q, Bai T, Zhou L, et al. Seroprevalence of antibodies to highly pathogenic avian influenza A (H5N1) virus among close contacts exposed to H5N1 cases, China, 2005-2008. PLoS One 2013;8(8):e71765.
45. Schultsz C, Dong VC, Chau NV, et al. Avian influenza H5N1 and healthcare workers. Emerg Infect Dis 2005;11(7):1158–9.
46. Buxton Bridges C, Katz JM, Seto WH, et al. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. J Infect Dis 2000;181(1):344–8.
47. Uyeki TM, Chong YH, Katz JM, et al. Lack of evidence for human-to-human transmission of avian influenza A (H9N2) viruses in Hong Kong, China 1999. Emerg Infect Dis 2002;8(2):154–9.
48. Lin YP, Yang ZF, Liang Y, et al. Population seroprevalence of antibody to influenza A(H7N9) virus, Guangzhou, China. BMC Infect Dis 2016;16(1):632.
49. Ma C, Cui S, Sun Y, et al. Avian influenza A (H9N2) virus infections among poultry workers, swine workers, and the general population in Beijing, China, 2013-2016: a serological cohort study. Influenza Other Respir Viruses 2019;13(4):415–25.
50. Buchy P, Vong S, Chu S, et al. Kinetics of neutralizing antibodies in patients naturally infected by H5N1 virus. PLoS One 2010;5(5):e10864.
51. Rajabali N, Lim T, Sokolowski C, et al. Avian influenza A (H5N1) infection with respiratory failure and meningoencephalitis in a Canadian traveller. Can J Infect Dis Med Microbiol 2015;26(4):221–3.

52. Lin PH, Chao TL, Kuo SW, et al. Virological, serological, and antiviral studies in an imported human case of avian influenza A(H7N9) virus in Taiwan. Clin Infect Dis 2014;58(2):242–6.
53. Skowronski DM, Chambers C, Gustafson R, et al. Avian Influenza A(H7N9) virus infection in 2 travelers returning from China to Canada, January 2015. Emerg Infect Dis 2016;22(1):71–4.
54. William T, Thevarajah B, Lee SF, et al. Avian influenza (H7N9) virus infection in Chinese tourist in Malaysia, 2014. Emerg Infect Dis 2015;21(1):142–5.
55. Zhou L, Liao Q, Dong L, et al. Risk factors for human illness with avian influenza A (H5N1) virus infection in China. J Infect Dis 2009;199(12):1726–34.
56. Mounts AW, Kwong H, Izurieta HS, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis 1999;180(2): 505–8.
57. Wan XF, Dong L, Lan Y, et al. Indications that live poultry markets are a major source of human H5N1 influenza virus infection in China. J Virol 2011;85(24): 13432–8.
58. Yu H, Feng Z, Zhang X, et al. Human influenza A (H5N1) cases, urban areas of People's Republic of China, 2005-2006. Emerg Infect Dis 2007;13(7):1061–4.
59. Dinh PN, Long HT, Tien NT, et al. Risk factors for human infection with avian influenza A H5N1, Vietnam, 2004. Emerg Infect Dis 2006;12(12):1841–7.
60. Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis 2005;11(2):201–9.
61. Li J, Chen J, Yang G, et al. Case-control study of risk factors for human infection with avian influenza A(H7N9) virus in Shanghai, China, 2013. Epidemiol Infect 2015;143(9):1826–32.
62. Liu B, Havers F, Chen E, et al. Risk factors for influenza A(H7N9) disease–China, 2013. Clin Infect Dis 2014;59(6):787–94.
63. Ai J, Huang Y, Xu K, et al. Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013. Euro Surveill 2013;18(26):20510.
64. Li Q, Zhou L, Zhou M, et al. Epidemiology of human infections with avian influenza A(H7N9) virus in China. N Engl J Med 2014;370(6):520–32.
65. Zhou L, Ren R, Ou J, et al. Risk factors for Influenza A(H7N9) disease in China, a matched case control study, October 2014 to April 2015. Open Forum Infect Dis 2016;3(3):ofw182.
66. Gilsdorf A, Boxall N, Gasimov V, et al. Two clusters of human infection with influenza A/H5N1 virus in the Republic of Azerbaijan, February-March 2006. Euro Surveill 2006;11(5):122–6.
67. Sedyaningsih ER, Isfandari S, Setiawaty V, et al. Epidemiology of cases of H5N1 virus infection in Indonesia, July 2005-June 2006. J Infect Dis 2007;196(4): 522–7.
68. Mao X, Wu J, Lau EHY, et al. Monitoring avian influenza viruses from chicken carcasses sold at markets, China, 2016. Emerg Infect Dis 2017;23(10):1714–7.
69. Lee CT, Slavinski S, Schiff C, et al. Outbreak of Influenza A(H7N2) among cats in an animal shelter with cat-to-human transmission-New York City, 2016. Clin Infect Dis 2017;65(11):1927–9.
70. Marinova-Petkova A, Laplante J, Jang Y, et al. Avian Influenza A(H7N2) virus in human exposed to sick cats, New York, USA, 2016. Emerg Infect Dis 2017; 23(12).
71. Webster RG, Geraci J, Petursson G, et al. Conjunctivitis in human beings caused by influenza A virus of seals. N Engl J Med 1981;304(15):911.

72. Shinya K, Ebina M, Yamada S, et al. Avian flu: influenza virus receptors in the human airway. Nature 2006;440(7083):435–6.
73. Belser JA, Lash RR, Garg S, et al. The eyes have it: influenza virus infection beyond the respiratory tract. Lancet Infect Dis 2018;18(7):e220–7.
74. Oner AF, Dogan N, Gasimov V, et al. H5N1 avian influenza in children. Clin Infect Dis 2012;55(1):26–32.
75. Chea N, Yi SD, Rith S, et al. Two clustered cases of confirmed influenza A(H5N1) virus infection, Cambodia, 2011. Euro Surveill 2014;19(25) [pii:20839].
76. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med 2005;352(4):333–40.
77. Kandun IN, Wibisono H, Sedyaningsih ER, et al. Three Indonesian clusters of H5N1 virus infection in 2005. N Engl J Med 2006;355(21):2186–94.
78. Wang H, Feng Z, Shu Y, et al. Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. Lancet 2008; 371(9622):1427–34.
79. Le QM, Kiso M, Someya K, et al. Avian flu: isolation of drug-resistant H5N1 virus. Nature 2005;437(7062):1108.
80. Organization WH. H5N1 highly pathogenic avian influenza: timeline of major events 17 March 2014. 2014. 2019. Available at: https://www.who.int/influenza/human_animal_interface/H5N1_avian_influenza_update20140317.pdf. Accessed April 11, 2019.
81. Organization WH. Human cases of avian influenza A (H5N1) in North-West Frontier Province, Pakistan, October-November 2007. Wkly Epidemiol Rec 2008; 83(40):359–64.
82. Zhou L, Chen E, Bao C, et al. Clusters of human infection and human-to-human transmission of avian Influenza A(H7N9) Virus, 2013-2017. Emerg Infect Dis 2018;24(2):397–9.
83. Qi X, Qian YH, Bao CJ, et al. Probable person to person transmission of novel avian influenza A (H7N9) virus in Eastern China, 2013: epidemiological investigation. BMJ 2013;347:f4752.
84. Xiao XC, Li KB, Chen ZQ, et al. Transmission of avian influenza A(H7N9) virus from father to child: a report of limited person-to-person transmission, Guangzhou, China, January 2014. Euro Surveill 2014;19(25) [pii:20837].
85. Chen H, Liu S, Liu J, et al. Nosocomial co-transmission of avian Influenza A(H7N9) and A(H1N1)pdm09 Viruses between 2 patients with hematologic disorders. Emerg Infect Dis 2016;22(4):598–607.
86. Zhang ZH, Meng LS, Kong DH, et al. A suspected person-to-person transmission of avian Influenza A (H7N9) case in ward. Chin Med J (Engl) 2017;130(10): 1255–6.
87. Wang X, Wu P, Pei Y, et al. Assessment of human-to-human transmissibility of avian Influenza A(H7N9) virus across 5 waves by analyzing clusters of case patients in mainland China, 2013-2017. Clin Infect Dis 2019;68(4):623–31.
88. Gostic KM, Ambrose M, Worobey M, et al. Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting. Science 2016; 354(6313):722–6.
89. Cheng QL, Ding H, Sun Z, et al. Retrospective study of risk factors for mortality in human avian influenza A(H7N9) cases in Zhejiang Province, China, March 2013 to June 2014. Int J Infect Dis 2015;39:95–101.
90. Ji H, Gu Q, Chen LL, et al. Epidemiological and clinical characteristics and risk factors for death of patients with avian influenza A H7N9 virus infection from Jiangsu Province, Eastern China. PLoS One 2014;9(3):e89581.

91. Xiao YY, Cai J, Wang XY, et al. Prognosis and survival of 128 patients with severe avian influenza A(H7N9) infection in Zhejiang province, China. Epidemiol Infect 2015;143(9):1833–8.

92. Sha J, Chen X, Ren Y, et al. Differences in the epidemiology and virology of mild, severe and fatal human infections with avian influenza A (H7N9) virus. Arch Virol 2016;161(5):1239–59.

93. Peiris M, Yuen KY, Leung CW, et al. Human infection with influenza H9N2. Lancet 1999;354(9182):916–7.

94. Cheng VC, Chan JF, Wen X, et al. Infection of immunocompromised patients by avian H9N2 influenza A virus. J Infect 2011;62(5):394–9.

95. Horby P, Sudoyo H, Viprakasit V, et al. What is the evidence of a role for host genetics in susceptibility to influenza A/H5N1? Epidemiol Infect 2010;138(11): 1550–8.

96. Le MQ, Horby P, Fox A, et al. Subclinical avian influenza A(H5N1) virus infection in human, Vietnam. Emerg Infect Dis 2013;19(10):1674–7.

97. Yang P, Lou X, Zheng Y, et al. Cytokines and chemokines in mild/asymptomatic cases infected with avian influenza A (H7N9) virus. J Med Microbiol 2016; 65(10):1232–5.

98. Oner AF, Bay A, Arslan S, et al. Avian influenza A (H5N1) infection in eastern Turkey in 2006. N Engl J Med 2006;355(21):2179–85.

99. Editorial team C. Avian influenza A/(H7N2) outbreak in the United Kingdom. Euro Surveill 2007;12(22):3206.

100. Nguyen-Van-Tam JS, Nair P, Acheson P, et al. Outbreak of low pathogenicity H7N3 avian influenza in UK, including associated case of human conjunctivitis. Euro Surveill 2006;11(18):2952.

101. Skowronski DM, Tweed SA, Petric M, et al. Human illness and isolation of low-pathogenicity avian influenza virus of the H7N3 subtype in British Columbia, Canada. J Infect Dis 2006;193(6):899–900 [author reply 900-91].

102. Tweed SA, Skowronski DM, David ST, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis 2004;10(12):2196–9.

103. Kurtz J, Manvell RJ, Banks J. Avian influenza virus isolated from a woman with conjunctivitis. Lancet 1996;348(9031):901–2.

104. Puzelli S, Rossini G, Facchini M, et al. Human infection with highly pathogenic A(H7N7) avian influenza virus, Italy, 2013. Emerg Infect Dis 2014;20(10):1745–9.

105. Arzey GG, Kirkland PD, Arzey KE, et al. Influenza virus A (H10N7) in chickens and poultry abattoir workers, Australia. Emerg Infect Dis 2012;18(5):814–6.

106. Kandeel A, Manoncourt S, Abd el Kareem E, et al. Zoonotic transmission of avian influenza virus (H5N1), Egypt, 2006-2009. Emerg Infect Dis 2010;16(7): 1101–7.

107. Brooks WA, Alamgir AS, Sultana R, et al. Avian influenza virus A (H5N1), detected through routine surveillance, in child, Bangladesh. Emerg Infect Dis 2009;15(8):1311–3.

108. Chakraborty A, Rahman M, Hossain MJ, et al. Mild respiratory illness among young children caused by highly pathogenic avian Influenza A (H5N1) virus infection in Dhaka, Bangladesh, 2011. J Infect Dis 2017;216(suppl_4):S520–8.

109. Zhang R, Chen T, Ou X, et al. Clinical, epidemiological and virological characteristics of the first detected human case of avian influenza A(H5N6) virus. Infect Genet Evol 2016;40:236–42.

110. Jiang H, Wu P, Uyeki TM, et al. Preliminary epidemiologic assessment of human infections with highly pathogenic Avian Influenza A(H5N6) Virus, China. Clin Infect Dis 2017;65(3):383–8.

111. Terebuh P, Adija A, Edwards L, et al. Human infection with avian influenza A(H7N2) virus-Virginia, 2002. Influenza Other Respir Viruses 2018;12(4): 529–32.
112. Yu H, Gao Z, Feng Z, et al. Clinical characteristics of 26 human cases of highly pathogenic avian influenza A (H5N1) virus infection in China. PLoS One 2008; 3(8):e2985.
113. Liem NT, Tung CV, Hien ND, et al. Clinical features of human influenza A (H5N1) infection in Vietnam: 2004-2006. Clin Infect Dis 2009;48(12):1639–46.
114. Li K, Liu H, Yang Z, et al. Clinical and epidemiological characteristics of a patient infected with H5N6 avian influenza A virus. J Clin Virol 2016;82:20–6.
115. Bi Y, Tan S, Yang Y, et al. Clinical and immunological characteristics of human infections with H5N6 avian influenza virus. Clin Infect Dis 2019;68(7):1100–9.
116. Wei SH, Yang JR, Wu HS, et al. Human infection with avian influenza A H6N1 virus: an epidemiological analysis. Lancet Respir Med 2013;1(10):771–8.
117. Ostrowsky B, Huang A, Terry W, et al. Low pathogenic avian influenza A (H7N2) virus infection in immunocompromised adult, New York, USA, 2003. Emerg Infect Dis 2012;18(7):1128–31.
118. Tong XC, Weng SS, Xue F, et al. First human infection by a novel avian influenza A(H7N4) virus. J Infect 2018;77(3):249–57.
119. Fouchier RA, Schneeberger PM, Rozendaal FW, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proc Natl Acad Sci U S A 2004;101(5):1356–61.
120. Gao HN, Lu HZ, Cao B, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. N Engl J Med 2013;368(24):2277–85.
121. Yang Y, Wong G, Yang L, et al. Comparison between human infections caused by highly and low pathogenic H7N9 avian influenza viruses in Wave Five: clinical and virological findings. J Infect 2019;78(3):241–8.
122. Chen H, Yuan H, Gao R, et al. Clinical and epidemiological characteristics of a fatal case of avian influenza A H10N8 virus infection: a descriptive study. Lancet 2014;383(9918):714–21.
123. Zhou L, Tan Y, Kang M, et al. Preliminary epidemiology of human infections with highly pathogenic Avian Influenza A(H7N9) virus, China, 2017. Emerg Infect Dis 2017;23(8):1355–9.
124. Zhang W, Wan J, Qian K, et al. Clinical characteristics of human infection with a novel avian-origin influenza A(H10N8) virus. Chin Med J (Engl) 2014;127(18): 3238–42.
125. Organization WH. Influenza at the human-animal interface. Summary and assessment 20 July to 3 October 2016. 2016. Available at: https://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_10_03_2016.pdf?ua=1. Accessed April 11, 2019.
126. Huai Y, Xiang N, Zhou L, et al. Incubation period for human cases of avian influenza A (H5N1) infection, China. Emerg Infect Dis 2008;14(11):1819–21.
127. Cowling BJ, Jin L, Lau EH, et al. Comparative epidemiology of human infections with avian influenza A H7N9 and H5N1 viruses in China: a population-based study of laboratory-confirmed cases. Lancet 2013;382(9887):129–37.
128. Virlogeux V, Li M, Tsang TK, et al. Estimating the distribution of the incubation periods of human Avian Influenza A(H7N9) virus infections. Am J Epidemiol 2015;182(8):723–9.
129. Virlogeux V, Yang J, Fang VJ, et al. Association between the severity of Influenza A(H7N9) virus infections and length of the incubation period. PLoS One 2016; 11(2):e0148506.

130. Uyeki TM. Human infection with highly pathogenic avian influenza A (H5N1) virus: review of clinical issues. Clin Infect Dis 2009;49(2):279–90.

131. Tran TH, Nguyen TL, Nguyen TD, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med 2004;350(12):1179–88.

132. Apisarnthanarak A, Kitphati R, Thongphubeth K, et al. Atypical avian influenza (H5N1). Emerg Infect Dis 2004;10(7):1321–4.

133. de Jong MD, Bach VC, Phan TQ, et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. N Engl J Med 2005;352(7):686–91.

134. Zhang Y, Zou P, Gao H, et al. Neutrophil-lymphocyte ratio as an early new marker in AIV-H7N9-infected patients: a retrospective study. Ther Clin Risk Manag 2019;15:911–9.

135. Feng F, Jiang Y, Yuan M, et al. Association of radiologic findings with mortality in patients with avian influenza H7N9 pneumonia. PLoS One 2014;9(4):e93885.

136. Buchy P, Mardy S, Vong S, et al. Influenza A/H5N1 virus infection in humans in Cambodia. J Clin Virol 2007;39(3):164–8.

137. Gao R, Dong L, Dong J, et al. A systematic molecular pathology study of a laboratory confirmed H5N1 human case. PLoS One 2010;5(10):e13315.

138. Yu L, Wang Z, Chen Y, et al. Clinical, virological, and histopathological manifestations of fatal human infections by avian influenza A(H7N9) virus. Clin Infect Dis 2013;57(10):1449–57.

139. Mak GCK, Kwan MY, Mok CKP, et al. Influenza A(H5N1) virus infection in a child with encephalitis complicated by obstructive hydrocephalus. Clin Infect Dis 2018;66(1):136–9.

140. Xia JB, Zhu J, Hu J, et al. H7N9 influenza A-induced pneumonia associated with acute myelitis in an adult. Intern Med 2014;53(10):1093–5.

141. Shi J, Xie J, He Z, et al. A detailed epidemiological and clinical description of 6 human cases of avian-origin influenza A (H7N9) virus infection in Shanghai. PLoS One 2013;8(10):e77651.

142. Pan M, Gao R, Lv Q, et al. Human infection with a novel, highly pathogenic avian influenza A (H5N6) virus: virological and clinical findings. J Infect 2016; 72(1):52–9.

143. Shu Y, Yu H, Li D. Lethal avian influenza A (H5N1) infection in a pregnant woman in Anhui Province, China. N Engl J Med 2006;354(13):1421–2.

144. Le TV, Phan LT, Ly KHK, et al. Fatal avian influenza A(H5N1) infection in a 36-week pregnant woman survived by her newborn in Sóc Trăng Province, Vietnam, 2012. Influenza Other Respir Viruses 2019;13(3):292–7.

145. Ku AS, Chan LT. The first case of H5N1 avian influenza infection in a human with complications of adult respiratory distress syndrome and Reye's syndrome. J Paediatr Child Health 1999;35(2):207–9.

146. Yang M, Gao H, Chen J, et al. Bacterial coinfection is associated with severity of avian influenza A (H7N9), and procalcitonin is a useful marker for early diagnosis. Diagn Microbiol Infect Dis 2016;84(2):165–9.

147. Luo H, Wang S, Yuan T, et al. Clinical characteristics from co-infection with avian influenza A H7N9 and Mycoplasma pneumoniae: a case report. J Med Case Rep 2018;12(1):77.

148. Liu WJ, Zou R, Hu Y, et al. Clinical, immunological and bacteriological characteristics of H7N9 patients nosocomially co-infected by Acinetobacter Baumannii: a case control study. BMC Infect Dis 2018;18(1):664.

149. Zheng S, Zou Q, Wang X, et al. Factors associated with fatality due to avian influenza A(H7N9) infection in China. Clin Infect Dis 2019. [Epub ahead of print].

150. Fox A, Horby P, Ha NH, et al. Influenza A H5N1 and HIV co-infection: case report. BMC Infect Dis 2010;10:167.
151. Yang Y, Guo F, Zhao W, et al. Novel avian-origin influenza A (H7N9) in critically ill patients in China*. Crit Care Med 2015;43(2):339–45.
152. Pawestri HA, Eggink D, Isfandari S, et al. Viral factors associated with the high mortality related to human infections with clade 2.1 influenza A/H5N1 virus in Indonesia. Clin Infect Dis 2019 [pii:ciz328].
153. Gu J, Xie Z, Gao Z, et al. H5N1 infection of the respiratory tract and beyond: a molecular pathology study. Lancet 2007;370(9593):1137–45.
154. Xiong X, Martin SR, Haire LF, et al. Receptor binding by an H7N9 influenza virus from humans. Nature 2013;499(7459):496–9.
155. Cao B, Gao H, Zhou B, et al. Adjuvant corticosteroid treatment in adults with Influenza A (H7N9) viral pneumonia. Crit Care Med 2016;44(6):e318–28.
156. Wang Y, Guo Q, Yan Z, et al. Factors associated with prolonged viral shedding in patients with Avian Influenza A(H7N9) virus infection. J Infect Dis 2018; 217(11):1708–17.
157. Guan Y, Poon LL, Cheung CY, et al. H5N1 influenza: a protean pandemic threat. Proc Natl Acad Sci U S A 2004;101(21):8156–61.
158. Hu Y, Lu S, Song Z, et al. Association between adverse clinical outcome in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance. Lancet 2013;381(9885):2273–9.
159. Hui KP, Chan LL, Kuok DI, et al. Tropism and innate host responses of influenza A/H5N6 virus: an analysis of ex vivo and in vitro cultures of the human respiratory tract. Eur Respir J 2017;49(3) [pii:1601710].
160. Chan MC, Chan RW, Chan LL, et al. Tropism and innate host responses of a novel avian influenza A H7N9 virus: an analysis of ex-vivo and in-vitro cultures of the human respiratory tract. Lancet Respir Med 2013;1(7):534–42.
161. Chan MC, Cheung CY, Chui WH, et al. Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells. Respir Res 2005;6:135.
162. Yu WC, Chan RW, Wang J, et al. Viral replication and innate host responses in primary human alveolar epithelial cells and alveolar macrophages infected with influenza H5N1 and H1N1 viruses. J Virol 2011;85(14):6844–55.
163. Meliopoulos VA, Karlsson EA, Kercher L, et al. Human H7N9 and H5N1 influenza viruses differ in induction of cytokines and tissue tropism. J Virol 2014;88(22): 12982–91.
164. Zeng H, Belser JA, Goldsmith CS, et al. A(H7N9) virus results in early induction of proinflammatory cytokine responses in both human lung epithelial and endothelial cells and shows increased human adaptation compared with avian H5N1 virus. J Virol 2015;89(8):4655–67.
165. Zhou J, Wang D, Gao R, et al. Biological features of novel avian influenza A (H7N9) virus. Nature 2013;499(7459):500–3.
166. Zhao C, Qi X, Ding M, et al. Pro-inflammatory cytokine dysregulation is associated with novel avian influenza A (H7N9) virus in primary human macrophages. J Gen Virol 2016;97(2):299–305.
167. Cheung CY, Poon LL, Lau AS, et al. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? Lancet 2002;360(9348):1831–7.
168. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. Nat Med 2006; 12(10):1203–7.

169. Wang Z, Zhang A, Wan Y, et al. Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection. Proc Natl Acad Sci U S A 2014;111(2):769–74.
170. Guo J, Huang F, Liu J, et al. The serum profile of hypercytokinemia factors identified in H7N9-infected patients can predict fatal outcomes. Sci Rep 2015;5: 10942.
171. Hui KPY, Ching RHH, Chan SKH, et al. Tropism, replication competence, and innate immune responses of influenza virus: an analysis of human airway organoids and ex-vivo bronchus cultures. Lancet Respir Med 2018;6(11):846–54.
172. Tundup S, Kandasamy M, Perez JT, et al. Endothelial cell tropism is a determinant of H5N1 pathogenesis in mammalian species. PLoS Pathog 2017;13(3): e1006270.
173. Gao R, Pan M, Li X, et al. Post-mortem findings in a patient with avian influenza A (H5N6) virus infection. Clin Microbiol Infect 2016;22(6):574.e1-5.
174. Nakajima N, Van Tin N, Sato Y, et al. Pathological study of archival lung tissues from five fatal cases of avian H5N1 influenza in Vietnam. Mod Pathol 2013;26(3): 357–69.
175. Liem NT, Nakajima N, Phat IP, et al. H5N1-infected cells in lung with diffuse alveolar damage in exudative phase from a fatal case in Vietnam. Jpn J Infect Dis 2008;61(2):157–60.
176. Zhang Z, Zhang J, Huang K, et al. Systemic infection of avian influenza A virus H5N1 subtype in humans. Hum Pathol 2009;40(5):735–9.
177. Feng Y, Hu L, Lu S, et al. Molecular pathology analyses of two fatal human infections of avian influenza A(H7N9) virus. J Clin Pathol 2015;68(1):57–63.
178. Guo Q, Huang JA, Zhao D, et al. Pathological changes in a patient with acute respiratory distress syndrome and H7N9 influenza virus infection. Crit Care 2014;18(6):666.
179. Nicholls JM, Tsai PN, Chan RW, et al. Fatal H7N9 pneumonia complicated by viral infection of a prosthetic cardiac valve - an autopsy study. J Clin Virol 2014;61(3):466–9.
180. To KF, Chan PK, Chan KF, et al. Pathology of fatal human infection associated with avian influenza A H5N1 virus. J Med Virol 2001;63(3):242–6.
181. 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. 2019. Available at: https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm. Accessed April 11, 2019.
182. World Health Organization. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care. WHO Guidelines; 2014. Available at: https://www.who.int/csr/bioriskreduction/infection_control/publication/en/. Accessed April 11, 2019.
183. South East Asia Infectious Disease Clinical Research Network. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. BMJ 2013;346:f3039.
184. Kandun IN, Tresnaningsih E, Purba WH, et al. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. Lancet 2008; 372(9640):744–9.
185. Hanshaoworakul W, Simmerman JM, Narueponjirakul U, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. PLoS One 2009;4(6):e6051.

186. Adisasmito W, Chan PK, Lee N, et al. Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a Global Patient Registry. J Infect Dis 2010;202(8):1154–60.
187. Chan PK, Lee N, Zaman M, et al. Determinants of antiviral effectiveness in influenza virus A subtype H5N1. J Infect Dis 2012;206(9):1359–66.
188. Zheng S, Tang L, Gao H, et al. Benefit of early initiation of neuraminidase inhibitor treatment to hospitalized patients with Avian Influenza A(H7N9) virus. Clin Infect Dis 2018;66(7):1054–60.
189. Zhang Y, Gao H, Liang W, et al. Efficacy of oseltamivir-peramivir combination therapy compared to oseltamivir monotherapy for Influenza A (H7N9) infection: a retrospective study. BMC Infect Dis 2016;16:76.
190. de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med 2005;353(25):2667–72.
191. Marjuki H, Mishin VP, Chesnokov AP, et al. Characterization of drug-resistant influenza A(H7N9) variants isolated from an oseltamivir-treated patient in Taiwan. J Infect Dis 2015;211(2):249–57.
192. Ke C, Mok CKP, Zhu W, et al. Human infection with highly pathogenic Avian Influenza A(H7N9) virus, China. Emerg Infect Dis 2017;23(8):1332–40.
193. Kile JC, Ren R, Liu L, et al. Update: increase in human infections with novel Asian lineage Avian Influenza A(H7N9) viruses during the fifth epidemic - China, October 1, 2016-August 7, 2017. MMWR Morb Mortal Wkly Rep 2017;66(35):928–32.
194. Zhang X, Song Z, He J, et al. Drug susceptibility profile and pathogenicity of H7N9 influenza virus (Anhui1 lineage) with R292K substitution. Emerg Microbes Infect 2014;3(11):e78.
195. Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. N Engl J Med 2007;357(14):1450–1.
196. Wu XX, Gao HN, Wu HB, et al. Successful treatment of avian-origin influenza A (H7N9) infection using convalescent plasma. Int J Infect Dis 2015;41:3–5.
197. Ma W, Huang H, Chen J, et al. Predictors for fatal human infections with avian H7N9 influenza, evidence from four epidemic waves in Jiangsu Province, Eastern China, 2013-2016. Influenza Other Respir Viruses 2017;11(5):418–24.
198. Lu H, Zhang C, Qian G, et al. An analysis of microbiota-targeted therapies in patients with avian influenza virus subtype H7N9 infection. BMC Infect Dis 2014;14:359.
199. Qin N, Zheng B, Yao J, et al. Influence of H7N9 virus infection and associated treatment on human gut microbiota. Sci Rep 2015;5:14771.
200. Hu X, Zhang H, Lu H, et al. The effect of probiotic treatment on patients infected with the H7N9 influenza virus. PLoS One 2016;11(3):e0151976.
201. Liu C, Li J, Sun W, et al. Extracorporeal membrane oxygenation as rescue therapy for H7N9 influenza-associated acute respiratory distress syndrome. Chin Med J (Engl) 2014;127(9):1798.
202. Wang G, Zhou Y, Gong S, et al. A pregnant woman with avian influenza A (H7N9) virus pneumonia and ARDS managed with extracorporeal membrane oxygenation. Southeast Asian J Trop Med Public Health 2015;46(3):444–8.
203. Tang X, He H, Sun B, et al. ARDS associated with pneumonia caused by avian influenza A H7N9 virus treated with extracorporeal membrane oxygenation. Clin Respir J 2015;9(3):380–4.
204. Qian L, Zheng J, Xu H, et al. Extracorporeal membrane oxygenation treatment of a H7N9-caused respiratory failure patient with mechanical valves replacement history: a case report. Medicine (Baltimore) 2016;95(40):e5052.

205. Nie Q, Zhang DY, Wu WJ, et al. Extracorporeal membrane oxygenation for avian influenza A (H7N9) patient with acute respiratory distress syndrome: a case report and short literature review. BMC Pulm Med 2017;17(1):38.

206. Li H, Weng H, Lan C, et al. Comparison of patients with avian influenza A (H7N9) and influenza A (H1N1) complicated by acute respiratory distress syndrome. Medicine (Baltimore) 2018;97(12):e0194.

207. Huang L, Zhang W, Yang Y, et al. Application of extracorporeal membrane oxygenation in patients with severe acute respiratory distress syndrome induced by avian influenza A (H7N9) viral pneumonia: national data from the Chinese multicentre collaboration. BMC Infect Dis 2018;18(1):23.

208. Xie H, Zhou ZG, Jin W, et al. Ventilator management for acute respiratory distress syndrome associated with avian influenza A (H7N9) virus infection: a case series. World J Emerg Med 2018;9(2):118–24.

209. Liu X, Zhang Y, Xu X, et al. Evaluation of plasma exchange and continuous veno-venous hemofiltration for the treatment of severe avian influenza A (H7N9): a cohort study. Ther Apher Dial 2015;19(2):178–84.

210. Kitphati R, Pooruk P, Lerdsamran H, et al. Kinetics and longevity of antibody response to influenza A H5N1 virus infection in humans. Clin Vaccine Immunol 2009;16(7):978–81.

211. Zhang A, Huang Y, Tian D, et al. Kinetics of serological responses in influenza A(H7N9)-infected patients correlate with clinical outcome in China, 2013. Euro Surveill 2013;18(50):20657.

212. Guo L, Zhang X, Ren L, et al. Human antibody responses to avian influenza A(H7N9) virus, 2013. Emerg Infect Dis 2014;20(2):192–200.

213. Ma MJ, Liu C, Wu MN, et al. Influenza A(H7N9) virus antibody responses in survivors 1 year after infection, China, 2017. Emerg Infect Dis 2018;24(4):663–72.

214. Wang Z, Wan Y, Qiu C, et al. Recovery from severe H7N9 disease is associated with diverse response mechanisms dominated by CD8(+) T cells. Nat Commun 2015;6:6833.

215. Zhao M, Chen J, Tan S, et al. Prolonged evolution of virus-specific memory T cell immunity after severe avian Influenza A (H7N9) virus infection. J Virol 2018; 92(17) [pii:e01024-18].

216. Lu PX, Wang YX, Zhou BP, et al. Radiological features of lung changes caused by avian influenza subtype A H5N1 virus: report of two severe adult cases with regular follow-up. Chin Med J (Engl) 2010;123(1):100–4.

217. Tang XJ, Xi XH, Chen CC, et al. Long-term follow-up of 5 survivors after the first outbreak of human infections with avian Influenza A(H7N9) virus in Shanghai, China. Chin Med J (Engl) 2016;129(17):2128–30.

218. Chen J, Wu J, Hao S, et al. Long term outcomes in survivors of epidemic Influenza A (H7N9) virus infection. Sci Rep 2017;7(1):17275.

219. Peiris JS, Cowling BJ, Wu JT, et al. Interventions to reduce zoonotic and pandemic risks from avian influenza in Asia. Lancet Infect Dis 2016;16(2):252–8.

220. Cox NJ, Trock SC, Burke SA. Pandemic preparedness and the Influenza Risk Assessment Tool (IRAT). Curr Top Microbiol Immunol 2014;385:119–36.