Seasonal, avian and pandemic influenza viruses

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Abstract

- Influenza viruses cause annual outbreaks of human respiratory tract disease, particularly affecting the very young and the old. Seasonal influenza is due to influenza A/H3N2 and A/H1N1, and influenza B.
- Antigenic drift and shift are typical of influenza viruses, allowing them to avoid immunity due to vaccination or prior infection.
- Pandemics due to novel influenza strains have occurred throughout history.
- Waterbirds are the natural host of influenza viruses. There is currently a large outbreak of avian influenza A/H5N1 infection in Asia, Europe and Africa. Humans have been infected with influenza A/H5N1 following close contact with infected poultry. Although the number of cases is low, the mortality is high.
- Vaccination for prevention, and antiviral drugs for treatment, are readily available for the management of influenza.
- National and state plans for pandemic responses have been developed.
- Australian Defence Force personnel are at risk of seasonal (and pandemic) influenza. Policies that guide surveillance, outbreak management, seasonal vaccination and pandemic planning are important for effective influenza responses.

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INFLUENZA IS A SEASONAL epidemic respiratory tract disease occurring during the colder months in temperate climates. In tropical and sub-tropical countries, infections occur throughout the year, often with one or two peaks of increased activity. Severe worldwide pandemic outbreaks occur at 10–40-year intervals. There have been three pandemics in the 20th century: the "Spanish" influenza of 1918–1919, which claimed more than 50 million lives, and the 1957 "Asian" and the 1968–1969 "Hong Kong" pandemics, which each resulted in 1–2 million deaths. Influenza-related terms are defined in Box 1.

The influenza viruses

The influenza viruses are members of the *Orthomyxoviridae* family — enveloped viruses containing a segmented single-stranded RNA genome. There are three main human influenza virus genera: influenza A is associated with the annual winter outbreaks and past pandemics, B is also associated with winter outbreaks, and C may cause mild common cold-like illness.[1]

Influenza A and B viruses have two major glycoprotein antigens that penetrate the lipid envelope: haemagglutinin (H) and neuraminidase (N). The H gene is responsible for virus attachment to the target cell, and the N gene assists with virion maturation and release.[2] There are 16 H and 9 N types, all circulating (often asymptomatically) in waterbirds.[3] Influenza viruses may move across into domestic poultry, with influenza A/H5 and A/H7 strains associated with high pathogenicity. Influenza A/H5N1 has been associated with the largest epizoonosis ever recorded, with birds affected in eastern, south-eastern and central Asia, Europe and Africa. Other influenza A subtypes can infect and become established in mammals, including horses (as demonstrated by the equine influenza A/H3N8 outbreak in eastern Australia in 2007) and pigs. Only three H (H1, H3, H2) and two N (N1 and N2) influenza A subtypes circulate in humans. Influenza B is limited to humans.[2]

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Genetic and antigenic variability is a prominent feature of influenza. *Antigenic drift* is the process whereby the surface glycoproteins undergo continuous antigenic variation due to point mutations in the H and N genome segments. This allows the viruses to escape vaccination or prior infection-induced immunity, and contributes to the seasonal variations in influenza activity and changes in vaccine strains. *Antigenic shift* is where new influenza A subtypes emerge in humans. It is due to reassortment of RNA segments between different avian, porcine or human strains, or adaptation of an avian strain to humans (as occurred with the 1918 pandemic).[1,2]

Influenza A/H5N1, first isolated in 1996 from a goose in Guangdong Province, China, caused severe poultry losses and occasional human infections associated with poultry exposure in Hong Kong in 1997. An aggressive poultry cull appeared to control this outbreak, but from 2003 the virus moved throughout south-eastern and eastern Asia, to Russia, central Asia and the Middle East (in 2005), Europe (2005), Africa (2006) and the Indian subcontinent (2006).[4] A combination of legal and illegal poultry and wild bird trade and transport by migratory waterbirds has contributed to the rapid spread of this virus.

The World Health Organization has confirmed 348 human cases from 14 Asian and African nations with 216 deaths, a 63% mortality rate. Most cases have been from Indonesia,

1 Definitions

Influenza: respiratory illness caused by human influenza viruses (influenza A/H3N2 or A/H1N1, influenza B, rarely influenza C).

Influenza-like illness: acute febrile respiratory tract illness with systemic features. This can be caused by human influenza viruses or a wide range of other respiratory pathogens.

Avian influenza: infectious disease of birds caused by influenza A viruses. Severe disease (as occurs with influenza A/H5N1) is called highly pathogenic avian influenza.

Human A/H5N1 infection: zoonotic (and very occasional human-to-human) transfer of influenza A/H5N1 from infected birds to humans.

Pandemic influenza: widespread and readily transmissible human infection with a new influenza A subtype to which humans are not immune.

Vietnam, Egypt, China, and Thailand (Box 2).[5] Nearly all human infections have been acquired from direct contact with affected poultry, and there has been very limited human-to-human spread. Both avian and human influenza A/H5N1 strains have shown significant genetic and antigenic drift (but no genetic reassortment with seasonal influenza strains), complicating vaccine development and diagnostic testing.[6]

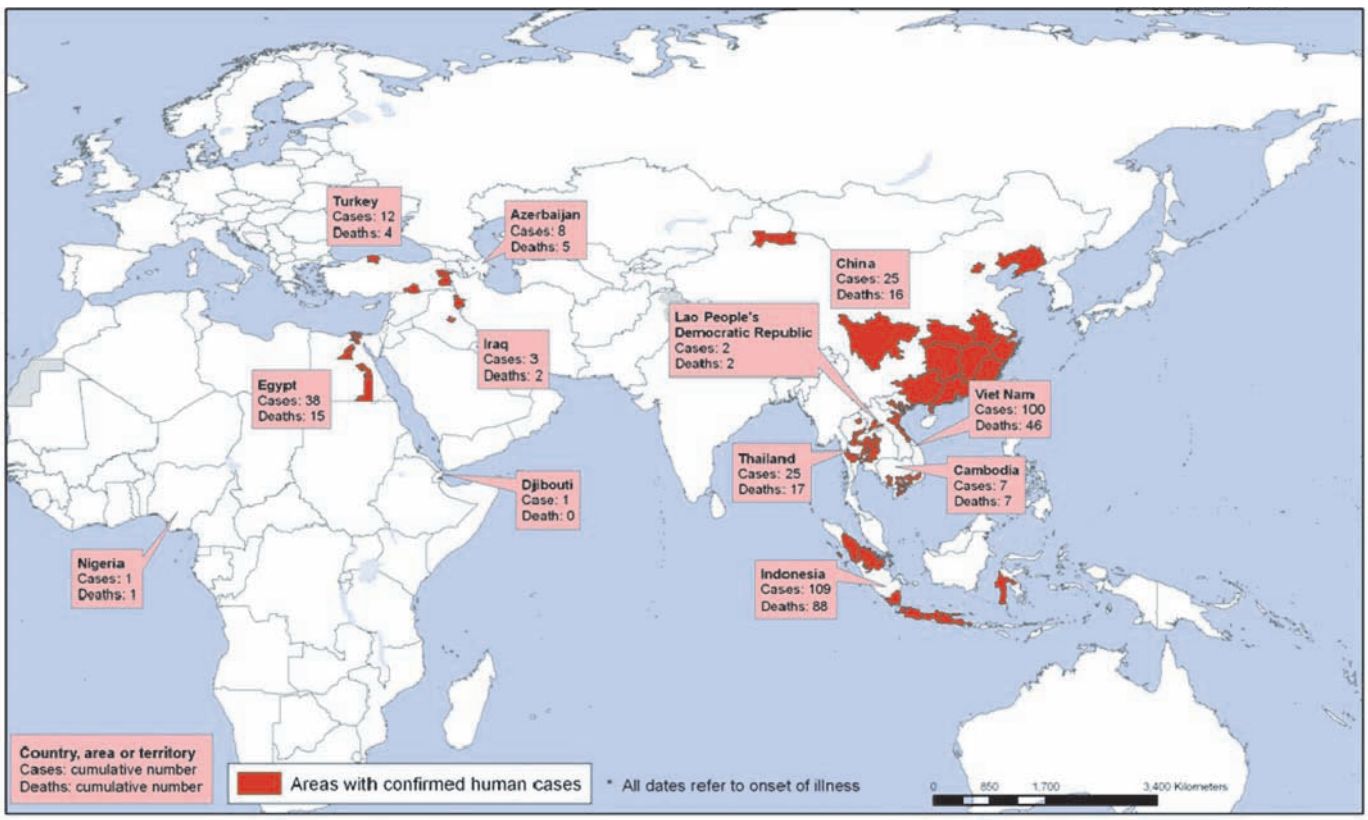
Although there has been extensive spread of avian influenza A/H5N1 and some human infection in recent years, it does not necessarily follow that this strain will cause the next pandemic. The attack rate and severity of clinical disease during a pandemic will be determined by the intrinsic properties of the virus, the immunological status of the affected individual, and the success of medical and social interventions.

Pathogenic features

The major viral targets are ciliated epithelial cells in the mucous layer of the respiratory tract. The receptor is sialic acid — human influenza viruses bind to cell sialic acid linked to galactose by an α-2,6 linkage, whereas avian strains bind to an α-2,3 linkage (although the "shape" of these sugar linkages may be more important than the specific linkage).[7] Major changes in receptor tropism with influenza A/H5N1 strains have not been noted to date, even though recent studies indicate that there are avian influenza receptors in the human lower respiratory tract.[8]

A feature of highly pathogenic avian strains is the generalised ability of cell proteases to cleave the H molecule into its active subunits; this explains the systemic nature of infection in infected birds. Adaptation to different species is also affected by changes in the polymerase PB2 region. Compared with human strains, influenza A/H5N1 hyperinduces a range of inflammatory cytokines, contributing to the "cytokine storm" or "sepsis syndrome" observed in human disease.[7,9]

2 Areas with confirmed human cases of avian influenza A/H5N1 since 2003



Clinical features of influenza infection

Incubation and transmission

The typical incubation period for influenza is 1–3 days. Adults can be infectious from the day before symptoms begin until about 5 days after. Children may be infectious for 10 or more days after symptom onset, and severely immunocompromised people can shed virus for weeks to months.[10,11] Transmission is mostly by virus-containing droplets, where larger droplets ($\geq 5\,\mu m$) are generated and propelled a distance of about 1 m to land on the mucous membranes or conjunctivae of another person. Direct and indirect contact transmission is also common, whereas airborne transmission of smaller droplets is less common.

The incubation period for human influenza A/H5N1 infection may be up to 8 days.[7] Human influenza A/H5N1 infections have occurred following direct contact with infected poultry and raw poultry products or contaminated surfaces. Human-to-human transmission is rare and has occurred only after very close and prolonged contact with an infected person.

Clinical presentation of seasonal influenza

Uncomplicated influenza is characterised by acute onset, upper respiratory tract symptoms (eg, dry cough, sore throat) and prominent constitutional features (eg, fever, headache, myalgias, anorexia and malaise). Some patients may present with a relatively mild respiratory illness similar to the common cold. The highest attack rates are in school-aged children, with the highest rate of serious illness in the 6–12-months age group.[12]

Physical signs are few in uncomplicated influenza, and include fever, tachycardia, facial flushing, conjunctival injection, excessive tearing, clear nasal discharge, coughing, pharyngeal hyperaemia, and mild cervical lymphadenopathy. One hospital series found that only half the patients with proven influenza satisfied the criteria for influenza-like illness (temperature > 37.8° C, cough or sore throat), so a high index of suspicion is required.[13] Chest examination is usually unremarkable.

Individuals at increased risk of complications include those with chronic cardiac or pulmonary disorders (eg, cystic fibrosis, asthma, chronic airways limitation, cor pulmonale, bronchopulmonary dysplasia), residents of chronic-care facilities, including nursing homes, people with chronic medical conditions (eg, diabetes mellitus, renal insufficiency, haemoglobinopathy, immunodeficiency and immunosuppression), women in the second or third trimester of pregnancy, and people older than 65 or younger than 2 years. Complications of seasonal influenza in children include febrile seizures, laryngotracheobronchitis or "croup", bronchiolitis, pneumonia, apnoea, otitis media, sinusitis, nausea, vomiting, diarrhoea, abdominal pain, lethargy and poor feeding. Various central nervous system features such as apnoea, opisthotonos, meningeal irritation, and seizures can manifest in up to 20% of infants. Other non-pulmonary complications include myositis and rhabdomyolysis, encephalitis, transverse myelitis, aseptic meningitis, Reye syndrome, myocarditis and pericarditis. Presentation in the elderly may be atypical, with delirium, falls, immobility, lethargy and incontinence.[12]

Pneumonia is the major complication of influenza. This can be primary pneumonia, where virus infection directly involves the lung parenchyma. Presentation is often abrupt and dramatic, progressing within 24 hours to severe pneumonia with respiratory failure and shock. Mortality is about 10%–20%; people with non-fatal cases recover 5–16 days after onset, but residual lung damage is frequent. Combined viral–bacterial pneumonia is at least three times more common than viral pneumonia, from which it is clinically indistinguishable. This diagnosis requires isolation of pathogenic bacteria, usually *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*. Mortality is about 10%. Secondary bacterial pneumonia is clinically easier to differentiate from combined viral–bacterial pneumonia, as patients typically initially improve and then deteriorate with features suggestive of bacterial pneumonia including chills, rigors, increased productive cough, pleuritic chest pain and dyspnoea. Mortality is about 7%.[12] Rapid and severe pneumonia in otherwise healthy adults was well described during the 1918 pandemic; more recent review of records suggests that secondary bacterial pneumonia was common.[14]

Clinical presentation of human influenza A/H5N1

Most cases of confirmed influenza A/H5N1 infection have been in previously healthy young children or adults, probably reflecting the age-related behaviours that facilitate exposure to infected poultry or birds. Mortality has been higher in young and middle-aged adults rather than the elderly or very young. This contrasts with seasonal influenza, for which mortality is highest among those at the extremes of age. This age distribution is similar to the 1918 Spanish influenza epidemic, in which mortality rates were higher among young adults.[15]

The main clinical presentation is fever (typically > 38° C) and an influenza-like illness with prominent lower respiratory tract symptoms; most patients (> 88%) have had pulmonary infiltrates at time of diagnosis.[16] This pneumonic process most likely represents a primary viral pneumonia. Gastrointestinal manifestations are common compared with seasonal influenza; watery diarrhoea has preceded respiratory manifestations by up to 1 week.[17] Encephalitic presentation has been described.[7] Most hospitalised patients with influenza A/H5N1 infection have required ventilatory support within 48 hours of admission as well as intensive management for multi-organ failure.[18,19] Empirical therapy has generally consisted of antiviral agents, alone or with corticosteroids, and broad-spectrum antibiotics. Initiation of antiviral drugs, often relatively late in the disease, has not resulted in any apparent reduction in mortality, although early initiation of antivirals does confer some benefit.[16,18,19]

Laboratory investigations

A definitive diagnosis of seasonal human influenza A or B is made by the isolation of the virus or its detection by properly validated antigen detection or nucleic acid testing (NAT) methods. A presumptive diagnosis can be made by a validated rapid antigen (or point-of-care) test.[20] Rising influenza-specific antibody levels in acute and convalescent sera confirm recent

infection, while a high antibody level in convalescent serum usually indicates recent infection in the context of a consistent clinical illness and community influenza activity. There is little in the full blood examination, renal and liver function tests that allows influenza to be differentiated from other viral respiratory tract infections.[12]

Surveillance of influenza isolates is needed for vaccine development. Worldwide, this laboratory surveillance is undertaken by the WHO Global Influenza Network. Australia is well served by this system, with a WHO Collaborating Centre in Melbourne (http://www.influenzacentre.org) and three National Influenza Centres in Sydney, Melbourne and Perth.[20]

Although similar laboratory criteria apply to influenza A/H5N1 or other potential pandemic viruses, NAT specific for the pandemic strain is the test of choice, at least in the initial stages.[21] Virus isolation can also be used, but has a turnaround time of 3–5 days, compared with hours or days with NAT. The direct and rapid antigen tests are quick (15 minutes to 2 hours), but do not differentiate between pandemic and seasonal strains. The Public Health Laboratory Network, which includes the major jurisdictional public health laboratories in Australia, has taken an active role in developing laboratory protocols for an influenza pandemic. The pathology guidelines in the *Australian health management plan for pandemic influenza* (http://www.health.gov.au) discuss the various laboratory issues, including specimen collection and transport, and testing methods and strategies.

Successful laboratory diagnosis depends on collection of good quality respiratory tract samples. Samples should be collected early in the clinical illness (within the first 96 hours during maximal viral shedding), transported to the laboratory at 4° C for virus isolation or at room temperature for other assays, and processed rapidly. Combined nose (one collected deeply from each nostril) and throat swabs are the most practical sample to collect from adults. Nasopharyngeal aspirates can be obtained from young children, provided they can be collected safely. Serology can be used if other tests are negative, inadequate, or unavailable. However, serological diagnosis is retrospective, as it requires acute and convalescent (collected 4–6 weeks after onset) sera, and generally does not differentiate between circulating influenza A strains. Pandemic strain-specific serology is not routinely available.[20,21]

In human influenza A/H5N1 infections, virus is more readily detectable in lower respiratory tract samples, although upper respiratory tract samples are easier to collect. Virus has been detected in serum, faeces and cerebrospinal fluid, reflecting the systemic nature of influenza A/H5N1 infection. High viral load and viraemia are associated with increased mortality.[9]

Prevention and treatment of influenza

Vaccination

Prevention of seasonal influenza is based on vaccination, with the annual pre-winter vaccine designed with the influenza A/H3N2, A/H1N1 and B strains circulating in the previous winter. Vaccination is recommended for all individuals older than 65 years, people with chronic cardiac or suppurative lung diseases, and other chronic diseases requiring regular medical care, immunodeficiency, residents of long-term care facilities, and contacts of high-risk patients. Vaccine should also be administered to anyone else who wishes to reduce the likelihood of becoming ill with influenza.[22]

There are many problems in developing a pandemic vaccine.[23] A prototype vaccine will not be a perfect match for an emergent virus, the antigenic constitution of which may be uncertain until the pandemic actually occurs. A better-matched vaccine may take some 3–6 months into the pandemic to be produced. Some prototype influenza A/H5N1 vaccines have been poorly immunogenic, and it is likely that two doses will be required to optimise protection in humans. Issues related to vaccine production, determinants of protective immunity, vaccine regulation and approval, administration, stockpiling strategies, equitable worldwide access, and costs remain to be solved.

Antiviral drugs

Management of acute seasonal influenza is based on early use of the neuraminidase inhibitors oseltamivir and zanamivir. The neuraminidase inhibitors block the influenza neuraminidase that facilitates the release of newly formed virions from infected cells, thus reducing the spread of infection in the respiratory tract.[24] Neuraminidase inhibitors are effective against all nine neuraminidase subtypes and against influenza A and B. Oseltamivir is an oral preparation (capsule or liquid suspension), whereas zanamivir is delivered by inhalation using a diskhaler or, rarely, intravenous infusion. As the replication of influenza virus peaks 24–72 hours after illness onset, the neuraminidase inhibitors must be administered as early as possible after symptoms appear.[24] Both neuraminidase inhibitors have been evaluated in multiple double-blind, randomised controlled trials as treatment or prophylaxis for seasonal influenza in various patient populations. A review of pooled data from eight trials with 1180 participants found that oseltamivir and zanamivir reduce the duration of symptoms by an average of one day.[25] In children, a review of pooled data from randomised controlled trials showed that oseltamivir reduces the median duration of the symptoms of influenza by 36 hours. Oseltamivir also significantly reduces the number of complications, particularly otitis media.[26] When used as prophylaxis for 7–10 days, neuraminidase inhibitors were 74% effective compared with placebo in preventing naturally occurring cases of influenza and 60% effective in preventing cases of laboratory-confirmed influenza in household contacts of cases. Neuraminidase inhibitors have also been used as long-term (6 weeks) prophylaxis to prevent infection in elderly at-risk populations during winter.[24]

The M2 inhibitors (the adamantanes amantadine and rimantadine) have also been used for treatment and prophylaxis of influenza A. They block the influx of hydrogen ions through the M2-proton channel of influenza A, inhibiting the uncoating and release of free viral ribonucleoproteins into the cell cytoplasm. However, their central nervous system and gastrointestinal toxicity, ineffectiveness against influenza B,

and rapid development of resistance means that they are not often used.[12]

Antiviral drug resistance is a major concern when proposing widespread use of antiviral medications. Amantadine resistance has been found in human and avian influenza A/H5N1 strains in China, Thailand, Vietnam and Cambodia, although other variants found in Indonesia, China, Mongolia, Russia and Turkey remain sensitive.[27] Human influenza A/H3N2 and A/H1N1 strains are becoming increasingly resistant worldwide to the adamantanes.[28] Neuraminidase inhibitor resistance is less frequent, occurring in less than 1% of viruses isolated from adults and 5%–18% of treated children. Resistant strains are not generally associated with clinical deterioration except in rare cases of immunocompromised patients, and possibly in patients with influenza A/H5N1 infection.[29,30] Neuraminidase inhibitor resistance in vivo is usually due to mutations in the neuraminidase region, and in vitro involves the haemagglutinin region, leading to impaired enzyme activity. Although oseltamivir resistance in human influenza A/H5N1 infection has been documented, these mutations occurred in the context of late commencement of oseltamivir and suboptimal dosing regimens.[7,30] Circulating avian influenza A/H5N1 strains remain susceptible to neuraminidase inhibitors.[27,30]

A cornerstone of pandemic planning in Australia has been stockpiling antivirals for use in both treatment and prophylaxis. It is assumed (but unknown) that oseltamivir will improve clinical outcomes in treated patients; whether resistance will become a clinically important issue in a pandemic is uncertain. It is also assumed that there will be a community benefit from the short-term prophylactic use of neuraminidase inhibitors in preventing transmission and illness, and from long-term prophylaxis for health care and other essential workers.[31]

Pandemic planning

Although outside the scope of this review, infection control, public health, use of the National Medicines Stockpile, communication and psychosocial measures will be essential in managing a pandemic. The issues around government and community management are addressed in Commonwealth and state pandemic plans. These are designed for Australia, but recognise regional and international responsibilities.

What is the impact of influenza on the Australian Defence Force?

Influenza is an important illness in the young and otherwise healthy population characteristic of the Australian Defence Force, and outbreaks may significantly affect ADF functioning. A factor that exacerbates the effect of influenza in the military is close contact in closed environments. Outbreaks of seasonal influenza (and other respiratory or gastrointestinal viruses) with high attack rates have been observed in recent years in military barracks and naval vessels in Australia. Deployment of forces to areas of current influenza activity is also a risk, as are joint exercises between northern and southern hemisphere forces.

Control of influenza outbreaks in ADF facilities requires cooperation with local public health authorities to ensure accurate sample collection and laboratory confirmation, and appropriate use of antivirals. Reliable surveillance for influenza-like illnesses and reporting of outbreaks within the ADF is likely to more quickly alert medical staff to the presence of influenza, and so allow appropriate interventions.

There is increasing use of seasonal influenza vaccination in populations that fall outside the usual risk groups for severe influenza.[22] It could be argued that influenza vaccination should be annually given to all troops, irrespective of their region of deployment. Use of pandemic strain vaccination will depend on vaccine efficacy and availability during a pandemic.

Severe outbreaks occurred among Australian soldiers overseas and returning home by sea during the 1918 influenza pandemic, and returning troops contributed to the spread of the pandemic strain in Australia. The ADF are at risk of new pandemics of influenza, should they occur, and it is possible that ADF personnel may be part of pandemic management in Australia and overseas. A sensible pandemic management plan specific to the ADF (and cognisant of the *Australian health management plan for pandemic influenza*) would be the first response to a potential pandemic.

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Competing interests

None identified.

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