Influenza

Christian Sandrock

1 Introduction

Influenza is a dynamic, widespread virus that causes disease in a broad range of hosts with far-reaching public health effects. The influenza virus belongs to the genera *Orthomyxoviridae* and causes an acute respiratory tract illness in children and adults. Influenza undergoes frequent and extensive genetic changes, allowing for a yearly seasonal pattern of recurrent infections along with the development of novel subtypes that have the potential to create larger pandemics. More recently, avian subtypes have begun to cause disease in humans who have had direct contact with infected birds. Unfortunately, resistance to antiviral agents has emerged over the last few years. Influenza is one of the most influential viruses in history, and will undoubtedly continue to affect public health and challenge clinicians and policymakers in the future.

2 Basic Virology

2.1 Viral Structure

Influenza A, *B*, and *C* are the most important genera of the *Orthomyxoviridae* family. *Influenza A* is responsible for human pandemic outbreaks and seasonal epidemics, and *Influenza B* is responsible for increasing numbers of cases of seasonal disease. *Influenza C* causes rare human disease, mostly in children. Influenza viruses are enveloped, single-stranded RNA viruses with a segmented genome. The eight RNA segments of the genome encode for 11 viral proteins, including the polymerase proteins (PB1, PB2), matrix proteins (M1, M2), and the surface glycoproteins hemagglutinin (HA) and neuroaminidase (NA) (Table 1). *Influenza A* viruses are classified into subtypes on the basis of the antigenic properties of the HA and NA

C. Sandrock (✉)
University of California Davis Health System, Sacramento, CA, USA
e-mail: cesandrock@ucdavis.edu

A.G. Mainous III, C. Pomeroy (eds.), *Management of Antimicrobials in Infectious Diseases*, Infectious Disease, DOI 10.1007/978-1-60327-239-1_6,

glycoproteins expressed on the surface of the virion. To date, 16 HA and 9 NA subtypes have been identified and are found in 144 different combinations (e.g., H1N1, H3N2, H5N1) (Table 1) [1, 2].

Table 1 Characteristics of influenza viruses

	Influenza A	Influenza B	Influenza C
Genetic structure	8 segments	8 segments	7 segments
Viral proteins	10 total	11 total	9 total
Unique viral protein	M2	NB	HEF
Antigenic determinants	Hemagglutinin (HA) and neuroaminidase (NA)	HA and NA	HA and NA
Genetic change	Antigenic shift and drift	Antigenic drift	Antigenic drift
Host range	Avians, humans swine, marine mammals, horses	Humans	Humans and swine
Human epidemiology	Pandemics and seasonal epidemics	Seasonal epidemics	No seasonality

The HA glycoprotein mediates attachment and entry of the virus by binding to sialic acid receptors on the cell surface. The binding affinity of the HA to the host sialic acid allows for the host specificity of *Influenza A*. Once inside the cell, viral replication begins immediately with the cessation of host cell protein synthesis. The NA glycoprotein allows the spread of the virus by cleaving the glycosidic linkages to sialic acid on the host cells and the surface of the virus. The virus is then spread via bodily fluids or through direct contact with secretions. Viral synthesis and release occurs for approximately 12–24 h, and then eventual cell death occurs due to cessation of host protein synthesis and cell-mediated apoptosis driven by the influenza infection [2].

2.2 Genetic Changes

Influenza A viruses are highly variable, due to molecular changes in the RNA segments that occur through a number of mechanisms; the most important are point mutation (antigenic drift) and RNA segment reassortment (antigenic shift). Like other RNA viruses, the *Influenza A* viruses lack proofreading ability and are therefore subject to point mutations. These individual mutations in the viral genome cause minor changes in the antigenic character of the virus, with amino acid changes in HA and NA of principal importance. This drift occurs as the virus travels and replicates through a susceptible population. Subsequent disease caused by a new strain created from antigenic drift is less severe than with a novel strain, as partial immunity within the population often remains, but the extent of the seasonal epidemic varies yearly [2–4].

Reassortment occurs when a host cell is infected with two or more *Influenza A* viruses and leads to the creation of a novel subtype containing a new HA or NA that is immunologically distinct from that of the previous circulating strains. The

three major pandemics that have occurred in the last century (1918 H1N1, 1957 H2N2, and 1968 H3N2) have been associated with reassortment. As *Influenza A* is host-specific, a less specific host, or "mixing vessel," that is more susceptible to all subtypes is required. Pigs, which possess receptors for both the human and avian subtypes, are a traditional "mixing vessel," but any species, including humans and wildlife, can potentially play a similar role. In the 1957 (H2N2) and 1968 (H3N2) pandemics, a pig was implicated as the intermediate host for viral "mixing" of two strains. Recent infections of humans with avian subtypes of *Influenza A* (e.g., H5N1) have heightened concerns that humans can function as a "mixing vessel" after direct infection from birds [2–4].

2.3 Virulence Features

Severe clinical findings occur with certain subtypes, for example, the 1918 H1N1 and some avian subtypes. The virulence factors responsible for severe disease outbreaks are becoming better understood. First, the binding location may determine the extent of local inflammation and severity of disease. Human virus subtypes H1, H2, and H3 bind to α-2,6 linkages found in human upper respiratory epithelium. Humans also have a smaller number of α-2,3 linkages, mostly located in their lower respiratory tract and conjunctivae; these are the preferred binding sites of the avian subtypes. Thus, binding of an avian subtype is more likely to occur in the lower respiratory tract and thus presents as pneumonia rather than as upper respiratory symptoms (Table 2) [5]. Second, local and systemic cytokine release varies with subtypes. In a mouse model of an engineered 1918 H1N1, significantly higher levels of specific cytokines, most notably IL-2, IL-6, and TNF were found locally and systemically [1, 5]. Additionally, the NS1 protein, which antagonizes host cell interferon, appears to have had increased activity. These characteristics of the deadly 1918 virus have also been found with the most recent severe human infections with influenza caused by the avian subtype H5N1 [1]. Finally, influenza viral replication is usually limited largely to the respiratory tract, but in some subtypes (e.g., H5N1) viremia has been detected, adding to the burden of disease [5].

Table 2 Characteristics and pathogenicity of *Influenza A* viruses

Viral features	
HA subtypes	16
NA subtypes	9
Predominant human subtypes	H1, H2, H3
Avian subtypes	H1–H16
Highly pathogenic avian influenza (HPAI) subtypes	H5 and H7
Conversion to high pathogenicity	Basic amino acid insertion in HA
Avian sialic acid-galactose linkages	α-2,3 linkages
Human sialic acid-galactose linkages	α-2,6 linkages

H or HA, hemagglutinin; HPAI, highly pathogenic avian influenza; NA, neuraminidase.

2.4 Pathogenicity Characteristics of Avian Influenza Viruses

In avian subtypes of *Influenza A*, the viruses are also characterized by their pathogenicity. Highly pathogenic avian influenza (HPAI) is defined by the World Organization for Animal Health (OIE) as any influenza that causes severe disease or death in domestic poultry. HPAI viruses, with very few exceptions, are of the H5 or H7 subtype, but not all H5 and H7 subtypes are HPAI viruses. The potential pathogenicity of H5 and H7 subtypes can be evaluated by sequencing the HA gene, since pathogenicity is associated with the presence of multiple basic amino acids at the HA cleavage site (Table 2). A change from a low pathogenic H5 or H7 subtype to a highly pathogenic form may occur upon introduction into poultry and is thought to occur primarily as a result of insertion of basic amino acids in the HA cleavage site. Molecular studies have shown that the 1918 human pandemic H1N1 subtype originated as a low pathogenic avian virus. In contrast, current human cases of H5N1 worldwide are the result of a highly pathogenic avian influenza virus.

2.5 Host Immune Responses to Influenza Virus

Immunity to influenza occurs through a number of steps. Initially, a large cytokine response occurs, characterized predominantly by IL-2, IL-6, and interferon gamma production. This leads to extensive local inflammation with neutrophils and macrophages infiltrating the sub-epithelium of the respiratory tract. Particularly with avian subtypes, this leads to a hemophagocytic syndrome and severe diffuse alveolar damage, causing the clinical findings of severe pneumonia and respiratory failure. Within the alveolar macrophages and pneumocytes, MHC I upregulation leads to antigen presentation of the hemagglutinin and other subcapsular proteins. This eventually leads to natural killer cell destruction of infected cells and the development of neutralizing antibodies (largely against HA) by day 14 of infection. When compared to human subtypes H1 and H3, infection with avian subtype H5N1 appears to infect lower respiratory tract cells, inhibit NK cell function, deplete lymphocytes, inhibit MHC class I upregulation, and inhibit cell apoptosis [2].

3 Epidemiology

3.1 Seasonal Influenza

Influenza follows a seasonal pattern with outbreaks occurring yearly in the winter months. *Influenza A* viruses predominate, with a H3N2 subtype currently making up the majority of isolates. *Influenza B* viruses are isolated more frequently late in the season and are more likely to be found in children [2]. *Influenza B* viruses are the most commonly reported influenza type in Europe, while both *Influenza A* and *Influenza B* viruses predominate in Asia and the southern hemisphere. Outside of the

winter season, influenza occurs infrequently. In temperate tropical regions, influenza can occur at lower levels throughout the year. Furthermore, summertime outbreaks of influenza have occurred on cruise ships or in individuals returning from areas of increased activity [2, 4]. *Influenza A* outbreaks typically begin abruptly, they peak over a 2–3 week period, and they last for 2–3 months. The earliest indication of influenza activity is an increase in febrile respiratory illnesses, usually in children and then adults.

The factors that determine the extent and severity of outbreaks vary yearly. The susceptibility of the population, as determined by the prevalence of antibodies to circulating virus, clearly plays a major role. Additionally, the virulence of the seasonal strains differ each year, and thus their efficiency of transmission or their ability to cause symptomatic infection will vary as well.

Influenza B outbreaks are generally less extensive and are associated with less severe disease when compared to *Influenza A* outbreaks. *Influenza B* has been reported most frequently in schools, military camps, and chronic care facilities. As with *Influenza A*, population immunity and the intrinsic virulence of the virus will affect severity in a given season. *Influenza C* causes very sporadic disease, mainly in children, without seasonality [2, 4].

3.2 Avian Subtypes

Over the past two decades, the incidence of avian subtypes of *Influenza A* directly infecting humans has dramatically increased. Land use changes, cultural practices, and worldwide poultry outbreaks have contributed to this increase. Initially, sporadic cases of avian influenza in humans occurred in both the United States and United Kingdom with subtype H7N7 (Table 3). Only a few cases of self-limiting conjunctivitis were reported in patients in each country, at the time of a poultry outbreak. The patients had each had contact with a sick bird without the appropriate protective equipment. Then, in 1997, a large-scale HPAI H5N1 outbreak occurred among poultry in Hong Kong farms and markets, and direct human disease occurred, with 18 documented human cases and 6 fatalities. Two subsequent poultry outbreaks in Hong Kong in 1999 and 2003 with HPAI H5N1 occurred without human cases until 2003, when two members of a family in Hong Kong contracted HPAI H5N1. In December of 2003, HPAI H5N1 surfaced in poultry in Korea and China, and from 2003 to 2006 the poultry outbreak spread worldwide. Human cases of HPAI H5N1 followed the poultry outbreak, with over 300 cases and 170 deaths to date [1, 6].

Although HPAI H5N1 is the largest outbreak, other notable avian subtypes have caused human disease in recent years. In 2003 in the Netherlands, a large poultry outbreak of H7N7 subtype resulted in 89 cases of influenza disease among poultry workers and a veterinarian; there was one death (the veterinarian). Two cases of conjunctivitis caused by subtype H7N3, a low pathogenicity strain, occurred among poultry workers during a Canadian outbreak in 2004. Finally, in 1999 and again in 2003, *Influenza A* subtype H9N2 caused a mild, self-limiting respiratory infection

in children during a poultry outbreak. Clearly, HPAI H5N1 is the largest and most significant poultry and human avian influenza outbreak recorded, but other subtypes have caused significant diseases as well (Table 3) [6].

Table 3 Influenza subtypes associated with human infection and disease

Influenza subtype
Seasonal subtypes
H1N1
H2N2
H3N2
Avian subtypes
H5N1
H7N7
H7N3
H9N2

Human cases of avian influenza have been mostly acquired by direct transmission from infected birds to humans. In each of the outlined outbreaks, the humans have consumed undercooked or raw poultry products or they have had direct contact with infected poultry or contaminated fomites. All birds have been ill or dead, and transmission has only been documented from domesticated poultry or waterfowl. No transmission to humans from wild birds has been reported. Thus far, human-to-human transmission has occurred in a few cases and with poor efficiency. During the 1997 HPAI H5N1 Hong Kong outbreak, one household contact of an ill poultry worker became infected. Health-care worker studies at the time also showed a 3.7% seroprevalance rate for H5 antibodies among the workers caring for the ill during the outbreak (0.5% in controls). During the 2003 worldwide HPAI H5N1 outbreak, two family clusters were suspected, and in 2004 one case of daughter to mother transmission was confirmed in Thailand. An additional family cluster from Indonesia with eight infections from a single source was also suspected in 2007 [1]. Three subsequent studies of health-care workers in Thailand, Vietnam, and China all showed not nosocomial transmission. Finally, in 2003 during the H7N7 outbreak in the Netherlands, three cases of household contacts with minimal disease were reported [1, 6].

3.3 Pandemic and Novel Strains

Novel strains of influenza develop through reassortment or antigenic drift. If the novel strain has little immunity in the general population, if it causes disease, and it is transmittable from human to human, then the likelihood for a pandemic is high. The advent of a pandemic may initially be noted by severe cases, particularly in young, lower risk adults, and an elevated mortality. The number of cases may be exceedingly high and also may occur outside of the winter season. Additionally, the excess mortality related to influenza may be higher in the first or second season. For

example, in North America, the majority of influenza-related deaths in 1968/1969 and 1969/1970 occurred during the first pandemic season [2, 4].

4 Clinical Features

4.1 Seasonal Influenza in Adults

Infection by influenza begins by inhalation of virus-containing respiratory secretions from an infected person through small-particle aerosols or through direct contact with the virus. Respiratory secretions of infected persons that contain large amounts of virus are transmitted through sneezing, coughing, and talking. Viral spread and survival increases with lower temperatures and humidity. After initial infection, viral replication appears to occur only in the respiratory tract [7].

Influenza infections have a broad spectrum of presentation, ranging from afebrile respiratory illnesses similar to the common cold to illnesses with systemic signs and symptoms. After an incubation period of 1–2 days, influenza often begins with the abrupt onset of fever, headache, myalgias, and malaise. These symptoms are accompanied by respiratory tract illness with cough and sore throat. A few physical findings may be noted in uncomplicated influenza. Fever, flushing, and mild cervical lymphadenopathy may be present and are more frequent in younger patients. The respiratory examination is often normal, but on occasion, rales may be present. Uncomplicated influenza usually improves over 2–5 days, although the illness may last for 1 week or more. Some patients have persistent symptoms of weakness or easy fatigability, referred to as postinfluenza asthenia, which last for several weeks.

In certain individuals, particularly those at high risk, complications may occur [7]. Individuals at high risk for complications include those with renal disease, underlying pulmonary disease, and cardiovascular disease. Patients receiving immunosuppressive agents as well as those in chronic care facilities are also at risk. Pneumonia is the most common complication and can either be a primary or secondary pneumonia. Primary influenza pneumonia occurs when influenza directly infects the lower respiratory tract, with the disease usually being relatively severe. Those with cardiac and underlying pulmonary disease, such as obstructive lung disease, are the most susceptible to primary pneumonia. Secondary pneumonia, which is more common than primary pneumonia, occurs when bacteria invade and infect the lower respiratory tract after loss of the upper respiratory tract cilia's natural clearance mechanism. The most common complicating bacterial pathogens are *Pneumococcus*, *Haemophilis influenzae,* and *Staphylococcus aureus*. Over the past few years, methicilin-resistant *Staphylococcus aureus* has become an increasing factor. Clinically, patients with a secondary bacterial pneumonia often improve from their initial influenza and then subsequently worsen, as the secondary bacterial pneumonia worsens. Bacterial pneumonia following an influenza infection accounts for over 25% of all influenza-related deaths. Other complications of influenza include myositis, rhabdomylitis, encephalitis, transverse myelitis, and Guillain–Barré syndrome [2, 7].

As with complications from pneumonia, influenza mortality is highest in those with underlying comorbid disease or at the extremes of age. The elderly, particularly those in chronic care facilities, constitute the majority of deaths, followed by those over age 50 with underlying illnesses. Children under 1 year of age are the most vulnerable of the pediatric group [7].

4.2 Seasonal Influenza in Children

The incidence of influenza remains high in children, with 25–40% of school-aged children becoming infected each year. Uncomplicated influenza in children can present as in adults, but there is often more variability. Conjunctivitis, prolonged fever, oropharyngeal injection, nasal symptoms, and cervical adenopathy are more common. Additionally, respiratory symptoms, including shortness of breath, cough, and wheezing are increased. The clinical course for uncomplicated influenza in children is similar to adults, with symptoms usually resolving in 2–5 days [8].

As with adults, childhood complications from influenza usually occur in those with underlying medical conditions such as heart disease, congenital pulmonary disease (cystic fibrosis), hemoglobinopathies, and congenital metabolic abnormalities. Complications of influenza infection in children include pneumonia (both primary and secondary), otitis media, myositis, rhabdomyelitis, myocarditis, and neurological complications. Otitis media can occur in up to 50% of children with influenza. Secondary pneumonia can occur in healthy children as well as children with underlying conditions, and *Pneumococcus* and *Staphylococcus aureus* are the most common bacterial agents. Primary pneumonia is more common in children and can often be severe. The CDC began following severe pediatric cases of influenza in 2003, most of them manifested as pneumonia (23% were bacterial in nature). Half of these severe cases were in previously healthy children, and mortality was highest amongst those under age 6 months. Additionally, hospitalizations are higher among children when compared to adults, particularly for children under 6 months as well [8].

4.3 Avian Subtypes of Influenza A *in Humans*

The clinical manifestations of avian influenza in humans have ranged from mild conjunctivitis to severe pneumonia with multi-organ system failure. The median age of the cases in the 1997 HPAI H5N1 outbreak was 17.2 years, and, in the 2003–2006 Southeast Asian cases, it was 16 years (range 2 months to 90 years). The incubation period ranged from 2 to 8 days after contact with sick or dead birds. The predominant clinical findings appear to vary with each *Influenza A* subtype. For example, in the 2003 Netherlands outbreak (H7N7), where 92% of patients (82 of 89) presented with conjunctivitis and a minority had respiratory symptoms. However, with HPAI in Hong Kong in 1997, and in Southeast Asia currently, pneumonia progressing to multi-organ failure, ARDS, and death was the predominant finding. Reye's syndrome, pulmonary hemorrhage, and severe nausea, vomiting, and diarrhea can

occur in complicated cases. The clinical course of patients with HPAI H5N1 is rapid, with 68% of patients developing ARDS and multi-organ failure within 6 days of disease onset. The case fatality rate has ranged from 67 to 80%, depending on the series. Once patients reach the critical care unit, however, the mortality is 90%. The average time of death from disease onset is 9 to 10 days.

5 Diagnosis

The diagnosis of influenza ranges from recognition of clinical findings to viral isolation and subtype analysis. During a seasonal outbreak of influenza, clinical diagnosis by experienced clinicians has a relatively high degree of certainty. The findings of fever, cough, sore throat, and malaise have a positive predictive value of 79%. However, this predictive value is best in young adults, as the elderly and those with chronic underlying diseases may not present with traditional symptoms [7]. Additionally, sporadic cases of influenza (outside of the yearly season) are very difficult to differentiate from other respiratory illnesses. Thus, clinical findings are supportive, particularly in a seasonal outbreak, but cannot completely include or exclude the diagnosis of influenza [2, 9].

Therefore, a laboratory confirmation of influenza is the most reliable. Viral culture is the laboratory gold standard and is performed with nasal or oropharyngeal washes or with lower respiratory samples, such as bronchoalveolar lavage. Viral culture also allows for further subtype analysis if needed, but it does take 48–72 h and may not be well suited for immediate needs or initiation of medication administration. Rapid tests can be performed by immunofluorescence or enzyme immunoassays and have a sensitivity and specificity over 90% during seasonal outbreaks. Polymerase chain reaction-based assays are helpful for rapid diagnosis of new or avian subtypes and can additionally detect very low viral levels, which may be helpful after the initial 48 h of peak viral shedding. Finally, serology is helpful for retrospective analysis of exposure to certain strains or subtypes and is performed by complement fixation or enzyme-linked immunoabsorbant assay [9].

6 Treatment

Two classes of antiviral drugs, neuraminidase inhibitors and M2 inhibitors (adamantanes), are used for both the treatment and prevention of influenza. Due to resistance and side effects with the adamantanes, the neuraminidase inhibitors have become the mainstay of influenza antiviral treatment and prophylaxis [10].

6.1 Antivirals: Adamantanes

Amantadine and rimantadine are the two main drugs in the class of adamantanes (Table 4). These drugs target the M2 protein of *Influenza A*, which forms a protein

Table 4 Summary of antivirals for the treatment and prophylaxis of influenza

	Adamantanes	Neuraminidase inhibitors		
	Amantidine	Rimantidine	Oseltamivir	Zanamivir
Spectrum	Influenza A	Influenza A	Influenza A and B	Influenza A and B
Administration	Oral	Oral	Oral	Inhalation
Treatment dose	100 mg BID	200 mg QD	75 mg BID	10 mg BID
Prophylaxis dose	100 mg QD	100 mg QD	75 mg QD	10 mg QD
Side effects	Nausea, vomiting, CNS	Nausea, vomiting, CNS	Nausea, vomiting, psychiatric (children)	Bronchospasm, cough
Dose reduction	Renal dysfunction	Elderly	None	None
Generic	Yes	Yes	No	No
Pediatric indication	Yes (4–8 mg/kg/d)	Yes (5 mg/kg/d)	Over 1 year (1 mg/kg/d) for treatment and prophylaxis	Over age 8 (10 mg BID) for treatment, over age 5 for prophylaxis
Pregnancy schedule	C	C	C	C
Resistance in seasonal strains	Over 90%	Over 90%	1–5%	1%

BID, twice daily; CNS, central nervous system; QD, once daily.

channel in the viral membrane that is essential for efficient viral replication. By blocking this ion channel, the virus is unable to fuse with the host cell membrane and thus replication is stopped. The adamantanes only have activity against *Influenza A*, as *Influenza B* lacks the M2 protein. Initial studies performed in young adults showed that both amantadine and rimantadine decreased the length of symptoms of influenza by approximately 24 h [10]. Additionally, the severity of fever and malaise was also decreased during the study. There was no effect on overall mortality or the development of complicated influenza in initial studies.

Both amantadine and rimantadine reach peak serum levels approximately 1–2 h after initial dose. Serum concentration is slightly higher with rimantadine, which has a half-life elimination of approximately 36 h. In the elderly, amantadine reaches higher serum levels and has a longer half-life of 16 h when compared to young adults. Rimantidine is metabolized and excreted by the liver and thus must be dose-adjusted in hepatic dysfunction. Amantadine is excreted unmetabolized in the urine, and if the creatinine clearance is below 50 ml/min, the dose must be reduced [10, 11].

The adamantanes are well tolerated by young adults [11, 12]. However, especially in the elderly, central nervous system side effects are common. These include anxiety, insomnia, confusion, and hallucinations and are more prominent with

amantadine. Increased seizure activity in those with a prior history has occurred. Finally, anticholinergic side effects of dry mouth and worsening glaucoma have also been reported. In initial studies with amantadine, the discontinuation rate was 13–17% (4–8% with placebo), largely based on the neurological side effects. Both amantadine and rimantadine have teratogenic effects in rat animal models and thus are not used in pregnancy [11].

6.2 Antivirals: Neuroaminidase Inhibitors

Oseltamivir and zanamivir are the two neuraminidase inhibitors currently used for prophylaxis and treatment of influenza (Table 4). The neuraminidase inhibitors prevent the release of virions from the host cell by acting as sialic acid analogs. By binding to sialic acid, they prevent hemagglutinin from binding to uninfected cells as well as inhibit sialic acid cleavage of progeny virions, reducing further spread. Due to their mechanism of action as a sialic acid analog, neuraminidase inhibitors are active against both *Influenza A* and *Influenza B* viruses [2, 10].

For treatment, Zanamivir is given by dry powder inhaler at 10 mg twice daily. Approximately 13% of the dose is deposited in the distal tracheal and bronchi while the remaining 78% remains in the oropharynx. Zanamivir concentrations remain 1,000 times the viral IC50 at 12 h after dosing. The small amount of drug that enters the systemic system is excreted renally. However, due to the low levels, no adjustment for renal dysfunction is required. In clinical studies with zanamivir administered twice daily for 5 days, the median time to alleviation of influenza symptoms was 1 day shorter compared to placebo [12, 13]. This occurred for both *Influenza A* and *B* but was dependent on time of administration. Benefit was seen when zanamivir was given within 30 h of the onset of symptoms. No benefit was demonstrated if administered after 30 h. Studies in immunocompromised hosts and in patients with severe cases of influenza were not performed, so in those settings where viral shedding and disease may last beyond 48 h, zanamivir may have some theoretical benefit. In high-risk patients, the development of influenza complications, especially asthma and bacterial pneumonia, was also diminished. The major side effect of zanamivir was asthma and bronchospasm and thus the drug should be used with caution in those with underlying lung disease.

Oseltamivir has good bioavailability and is administered as either a capsule or powder (for liquid suspension) at 75–150 mg twice daily. Bioavailability is 80% with a wide body of distribution, and a 100 mg does yields serum levels of 250 ng/ml with a half-life of 8 h. The drug is renally excreted and a dose reduction is recommended for a creatinine clearance less than 30 ml/min. In multiple clinical trials, oseltamivir reduced the median duration of symptoms of influenza (fever, cough, malaise) by 1–2 days when given within 24 h of onset of symptoms. The reduction of symptoms appeared to be greater in laboratory-confirmed *Influenza A* when compared to *Influenza B*. Complications, including pneumonia, bronchitis, sinusitis, and otitis media, were lowered by as much as 50% in adults and children. Antibiotic

use also was reduced in the oseltamivir group. As with zanamivir, oseltamivir is well tolerated, with only 15% of patients reporting nausea. In the past few years, particularly in pediatric cases from Japan, delirium and self-injury, including suicide, have been reported [8, 10]. Oseltamivir is pregnancy category C and there is limited data on pregnant patients; however, in a rabbit model, minor skeletal changes have been reported [12, 13].

6.3 Antiviral Resistance

Influenza resistance to the adamantanes occurs rapidly and is currently widespread, limiting their use in treatment and prophylaxis. In fact, the CDC currently does not recommend the use of the adamantanes unless susceptibility is known, such as in a focal outbreak. Resistance to both amantadine and rimantadine occurs through a single point mutation, leading to high-level resistance that confers to the entire class. Initially, resistance sometimes developed during therapy, starting as early as day 2–3 of drug administration. However, most recently, the CDC reported that 92% of *Influenza A* (H3N2) isolates in 2006 were resistant to adamantanes [10, 11]. All of the resistant isolates had a substitution at codon 31 of the M2 protein. This widespread resistance has developed from adamantane overuse in the clinical settings as well as use in poultry outbreaks over the years, thus nearly rendering this class useless [14, 15].

Resistance in neuraminidase inhibitors appears to arise much more slowly and currently is significantly less, about 1–5% of isolates (Table 4) [15]. Resistance occurs with amino acid substitutions at either the NA or HA site. With NA mutations, a substitution of glutamine to glycine at position 119 in *Influenza A* and 117 in *Influenza B* results in decreased binding affinity at the NA active site. Cross-resistance is variable with this mutation, as resistance to oseltamivir was not conferred to zanamivir; when conferred, it has led to tenfold increase in the inhibitory concentration. Additionally, this mutation has yielded decreased viral infectivity and binding ability that was subsequently demonstrated in animal models [15]. Changes in the HA at or near the sialic acid binding site alter the viral binding and decrease the viral dependence on the NA. This change confers class resistance, as HA mutations to oseltamivir during treatment lead to a tenfold increase in the inhibitory concentrations of zanamivir. The development of resistance appears to be related to prolonged viral replication and shedding. In a few cases in high-risk patients (bone marrow transplant), therapy with oseltamivir led to resistance after receipt of the drug for 2 weeks, with two NA mutations and an M2 mutation conferring a 1,000-fold increase in zanamivir inhibitor concentrations. After therapy was terminated, the NA mutation disappeared but the M2 change persisted. Thus, therapy with prolonged viral shedding in certain hosts (e.g., immunocompromised) may lead to multiple mutations at the NA and HA sites, increasing resistance. However, thus far, there is no evidence that these mutations persist in the community [14, 15].

7 Prevention

7.1 Vaccine Basics

Influenza vaccination is the cornerstone of influenza prevention. Vaccine development, delivery, and administration to select groups can significantly impact the scope and severity of the influenza outbreak each season. Vaccine design and preparation are followed by targeted vaccination of high-risk groups and children, resulting in increased population immunity and a lower burden of disease. Human strains of *Influenza A* (H1N1, H3N2) and *Influenza B* circulate each year, and immunity develops from antibodies directed against the HA and NA surface glycoproteins. However, these glycoproteins vary each year (antigenic drift), making yearly vaccination paramount [16, 17].

As *Influenza A* and *B* undergo antigenic drift and shift, new variants emerge each year that are able to evade host immunity developed from vaccination or infection in prior years. Thus, worldwide surveillance of current strains is essential in order to estimate the most accurate HA and NA that will emerge the following year. Both the World Health Organization and the CDC estimate the strains available for vaccine development. Two major types of vaccines currently exist: an inactivated compound (TIV) and a live attenuated virus (LAIV). Both types of vaccines are trivalent, in that they contain the HA and NA for two *Influenza A* strains (H1N1, H3N2) and one *Influenza B* strain. The inactivated vaccine contains either whole virus or subvirion products, which are designed to ensure the presentation of a relevant HA and NA to the immune system. Inactivated influenza vaccine is given intramuscularly. The live attenuated virus is different as it is developed from a cold-adapted attenuated virus that contains the reassorted HA and NA of the selected strains. The LIV is administered by nasal mist spray and subsequently leads to replication of the virus in the distal upper respiratory tract (cold adaptation area). Thus, immunity develops through infection and subsequent antigen presentation [16, 17].

Vaccine manufacture takes approximately 6–9 months, so selection and development of influenza strains must begin in advance of the yearly influenza season. Therefore, vaccine mismatch can occur, reducing the efficacy of the vaccine and affecting the number and severity of influenza cases throughout the community. Additionally, developing a vaccine 6–9 months in advance means that policymakers must anticipate yearly usage, which can lead to shortages or extensive surpluses, depending on the year [16–18].

7.2 Vaccination in Adults

Vaccine efficacy depends largely on how closely the strain selected for the vaccine compares to the circulating strain during the yearly influenza season. Additionally, efficacy varies for the TIV and LAIV vaccines and according to the age of the individual and the presence or absence of underlying medical conditions. In a year when the vaccine and circulating strains are well matched, vaccine efficacy in healthy

adults can be up to 89% for *Influenza A* and 88% for *Influenza B* with the TIV. In years of a single strain mismatch, efficacy can drop to 50%. For the LAIV, reductions in febrile illness, respiratory illness, and missed workdays were significantly lower despite a mismatch between vaccine and circulating strains [16]. However, in a TIV-LAIV comparative trial, vaccine efficacy against serologically confirmed *Influenza A* was 74% for both TIV and LAIV, but TIV provided significantly better protection than LAIV for *Influenza B* (80% vs. 40%) [16, 18]. In a second trial conducted over 5 years, adults with *Influenza A* had 74% protection with TIV [16, 18]. With LAIV, 85% efficacy was noted with H1N1 subtype, but only 58% with H3N2. Both trials reported significant decreases in missed workdays, antibiotic use, and development of febrile illnesses, in addition to reducing serologically confirmed influenza [16, 18].

In high-risk groups, vaccination has shown additional benefits. In the elderly, vaccination efficacy has been reported to be as low as 50% [19], with outbreaks occurring in long-term care facilities among vaccinated individuals. However, vaccination is associated with significantly lower rates of hospitalization, pneumonia, and respiratory tract disease among these high-risk individuals. Mortality reduction in the elderly was not demonstrated in an individual study, but a meta-analysis suggested a slight reduction in the vaccination group [19]. Other at-risk groups, including patients with HIV infection or other chronic underlying diseases, receiving, immunosuppression, or experiencing pregnancy, have not been well studied in randomized trials and vaccine efficacy is more difficult to determine. However, due to their elevated risk for complicated influenza, vaccination is recommended in persons with these indications [19].

Adverse reactions vary for both the TIV and LAIV. Because the TIV is egg developed, allergy and anaphylaxis to egg protein can develop. Local reaction site inflammation and infection can also occur. An association between Guillain–Barré syndrome and influenza vaccination has been documented but was more prevalent with older preparations and with influenza infection itself [16]. The LAIV is also well tolerated, but due to its intranasal administration, rhinorrhea and nasal congestion are the most common side effects reported. In initial trials, wheezing, particularly in children under 4 months of age, was reported [16, 18]. Individuals with moderate to severe asthma were excluded from these studies.

The Advisory Committee on Immunization Practices at the CDC (Table 5) develops lists of targeted individuals for vaccination. Currently, these higher risk groups include those greater than 50 years of age, residents of a chronic care facility or nursing home, health-care providers, individuals with a chronic illness (pulmonary (including asthma), cardiovascular (excluding hypertension), renal, hepatic, hematologic, or metabolic disorders (including diabetes mellitus), or immunosuppression (including immunosuppression caused by medications or HIV infection)), and those who are pregnant. The LAIV is indicated for individuals aged 24 months to 49 years and should not be given to those patients with a chronic illness, pregnancy, history of Guillain–Barré syndrome, or immunosuppression. Thus, for individuals outside of the LAIV age group or with any contraindications, the TIV is the only form of vaccine indicated [18, 20].

Table 5 Targeted groups for influenza vaccination [18, 19]

Indication for vaccination	
Adults	Children
• Age > 50 years	• Age 6–59 months
• Resident of chronic or long-term facility (e.g., nursing home)	• Chronic and congenital pulmonary and cardiovascular disease (e.g., cystic fibrosis)
• Chronic illness (e.g., asthma, cardiovascular, renal, hepatic, hematologic, metabolic disorders (diabetes))	• Children on long-term aspirin therapy
• Immunosuppression (e.g., HIV, transplantation, medications)	• Children with difficulty controlling oral secretions (e.g., cognitive illness)
• Chronic neurologic disease (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, neuromuscular disorders)	• Metabolic and renal disorders
• Pregnancy during season	• Children in household of high-risk adult
• Health-care workers	• Healthy school children desiring vaccination
• Contacts of chronically ill	

7.3 Vaccination in Children

As for adults, vaccination efficacy in children is directly correlated with closeness in the match between the vaccine and seasonal strain [8, 18]. In studies with TIV, children over the age of 2 years had 59–65% protection against laboratory-confirmed influenza. In children under 36 months of age, efficacy appeared directly related to a history of prior influenza infection, as those with antibodies to *Influenza A* or *B* prior to vaccination developed a more robust response [16]. In addition to reduced rates of influenza infection, lower rates of otitis media and asthma exacerbation were also noted. Finally, children's immunity appeared to confer protection to other non-vaccinated household members, with an over 40% reduction in household members experiencing a febrile illness [21].

LAIV has efficacy rates of 30–93% depending on vaccine match, but with a close match, efficacy in children was around 93% [16]. Interestingly, protection in the second year after vaccination was 87%, even when the vaccine strain did not match, suggesting some increased protection against mismatched strains in children. As with TIV, cases of influenza acquired after vaccination were significantly milder. Multiple studies comparing LAIV to TIV in children show a 55% greater efficacy of LAIV than TIV, as assessed by laboratory-confirmed cases of *Influenza A*. Additional increased efficacy with LAIV in those with asthma (35%) and chronic respiratory infections (55%) was also noted. Finally, where vaccine mismatch occurred, LAIV was 35% efficacious while TIV provided no protection

[16, 18]. For *Influenza B*, the efficacy of LAIV and TIV was similar in these studies [38, 16, 18, 21].

The dosing for LAIV and TIV is different for children than for adults. The TIV dose is 0.5 ml intramuscularly and LAIV is 0.2 ml (0.1 ml per nostril). However, in children under 9 years of age, two doses of vaccine are recommended in the first year of vaccination, with only one dose needed in the years thereafter. Two doses provided optimal protection and efficacy (up to 93%); the first dose should be given a few months before the season, with the second dose 2–3 months after the first [8, 16, 18, 21].

The adverse events for TIV and LAIV are similar for children and adults. With TIV, local site reactions, including swelling, erythema, and pain can occur. Additionally, individuals with an egg allergy can develop anaphylaxis. Rash can also occur, and rarely seizures have been reported. Asthma exacerbations have not been associated with TIV. With LAIV, asthma exacerbations were initially thought to be associated, but post hoc analysis showed that the rates of asthma exacerbation in those with a history of mild asthma were similar in the two groups. Wheezing did initially appear to be increased among children aged 6–24 months in the LAIV group, along with hospitalization rates. However, further analysis suggested that medically significant wheezing and hospitalization were similar between the two groups. Overall, LAIV may increase the likelihood of wheezing but clinically significant asthma or hospital admission was not noted in the studies [8, 16, 18, 21, 22].

7.4 Antiviral Prophylaxis

Studies have been performed with both the adamantane and the neuraminidase classes of antivirals [10, 12]. Prior to the recent development of widespread resistance, the adamantanes provided adequate prophylaxis with a 50% reduction in laboratory-confirmed influenza and a 70% reduction in influenza-like illness when administered for 3–7 weeks. However, with the advent of widespread resistance, along with the efficacy and reduced side effects of the neuraminidase inhibitors, adamantanes are no longer recommended for prophylaxis. In certain situations, adamantanes may be indicated, such as in response to an outbreak in a chronic care facility where the virus is known to be susceptible to the drugs.

Both oseltamivir and zanamivir have been studied extensively for prophylaxis (Table 4). Oseltamivir has been approved for once daily use as prevention and has been studied in household contacts, nursing homes, and the general community. When given Oseltamivir at 75 mg daily for 7 weeks, healthy, unvaccinated adults had 75% fewer cases of influenza as compared to those given placebo. In studies evaluating household contacts of known influenza cases, a risk reduction of 59% was seen. Finally, during an outbreak in nursing home residents who were vaccinated, oseltamivir markedly reduced the rate of influenza development. Zanamivir, when compared to placebo, has been shown to decrease rates of laboratory-confirmed influenza (2% vs. 6%) when given to young, unvaccinated adults. In household

contacts, influenza significantly reduced the rates of influenza (4% vs. 16%) when compared to placebo. The drug was well tolerated in these studies and no emergence of resistance was noted. Thus, antiviral prophylaxis with neuraminidase inhibitors is indicated for seasonal influenza in patients unable to receive or respond effectively to vaccination, household contacts, and contacts in high-risk groups during an outbreak [10, 12, 13].

In regard to pandemic influenza, little is known about the efficacy of antiviral prophylaxis. Because a pandemic will come in multiple waves affecting different populations, targeted prophylaxis will be difficult. Strain type, resistance, and virulence may all effect susceptibility, and the necessary length of prophylaxis will be unknown. Thus, the need for large amounts of neuraminidase inhibitors will be a limiting factor in providing protection and prophylaxis to all members of the community. Targeted prophylaxis algorithms and plans will need to be used instead to lessen the burden of disease and focus on the highest risk members of the community [17].

Key Points

- *Influenza A* and *B* cause a yearly influenza outbreak with variable respiratory disease ranging from mild to severe. Complications and death are highest in the elderly, children under 6 months, and high-risk individuals.
- Due to genetic changes, new strains of influenza emerge constantly, thus creating the possibility of a pandemic. Additional changes in the last two decades include the increased infection in humans by avian subtypes with high morbidity and mortality.
- Treatment of influenza is supportive, and if given early, antiviral treatment can reduce symptom time and complications. Due to recent emergence of widespread resistance to adamantanes, only the neuraminidase inhibitor class is currently recommended for treatment.
- Vaccination against influenza is the mainstay for prevention, with the elderly, children, and high-risk groups recommended for vaccination. Both inactivated and live attenuated virus vaccines are available. Prophylaxis with neuraminidase inhibitors can provide protection in high-risk groups.

References

1. Sandrock C, Kelly T (2007). Clinical review: Update of avian influenza A infections in humans. Crit Care 11:209
2. Hessen MT (2007). In the clinic. Influenza. Ann Intern Med 147:ITC10-1–ITC10-16
3. Ohmit SE, Victor JC, Rotthoff JR et al. (2006). Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med 355:2513–2522
4. Whitley RJ, Bartlett J, Hayden FG et al. (2006). Seasonal and pandemic influenza: Recommendations for preparedness in the United States. J Infect Dis 194(Suppl 2): S155–S161

5. Shinya K, Ebina M, Yamada S et al. (2006). Avian flu: Influenza virus receptors in the human airway. Nature 440:435–436
6. Beigel JH, Farrar J, Han AM et al. (2005). Avian influenza A (H5N1) infection in humans. N Engl J Med 353:1374–1385
7. Monto AS, Gravenstein S, Elliott M et al. (2000). Clinical signs and symptoms predicting influenza infection. Arch Intern Med 160:3243–3247
8. Westcar S, Chantler T (2007). Influenza: An overview with a paediatric focus. Community Pract 80:37–39
9. Ellis JS, Zambon MC (2002). Molecular diagnosis of influenza. Rev Med Virol 12:375–389
10. Antiviral drugs for influenza (2007). Med Lett Drugs Ther 49:85–86
11. Alves Galvao MG, Rocha Crispino Santos MA et al. (2008). Amantadine and rimantadine for influenza A in children and the elderly. Cochrane Database Syst Rev (1):CD002745
12. Monto AS (2006). Antivirals for influenza in healthy adults. Lancet 367:1571–1572; (author reply 3)
13. Whitley RJ (2007). The role of oseltamivir in the treatment and prevention of influenza in children. Expert Opin Drug Metab Toxicol 3:755–767
14. Halloran ME, Hayden FG, Yang Y et al. (2007). Antiviral effects on influenza viral transmission and pathogenicity: Observations from household-based trials. Am J Epidemiol 165:212–221
15. Monto AS, McKimm-Breschkin JL, Macken C et al. (2006). Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. Antimicrob Agents Chemother 50:2395–2402
16. Influenza vaccine 2007–2008 (2007). Med Lett Drugs Ther 49:81–83
17. Mossad SB (2007). Influenza update 2007–2008: Vaccine advances, pandemic preparation. Cleve Clin J Med 74:889–894
18. Campos-Outcalt D (2008). Vaccine update: New CDC recommendations from 2007. J Fam Pract 57:181–184
19. Bader MS (2007). Immunization for the elderly. Am J Med Sci 334:481–486
20. Bridges CB, Harper SA, Fukuda K et al. (2003). Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 52:1–34; quiz CE1-4
21. Whitley RJ, Monto AS (2006). Prevention and treatment of influenza in high-risk groups: Children, pregnant women, immunocompromised hosts, and nursing home residents. J Infect Dis 194(Suppl 2):S133–S138
22. Tosh PK, Boyce TG, Poland GA (2008). Flu myths: Dispelling the myths associated with live attenuated influenza vaccine. Mayo Clin Proc 83:77–84