Influenza

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Abstract

Influenza is one of the commonest infections in human populations, and causing substantial morbidity and mortality globally. The influenza virus is divided into different types and subtypes, three of which are currently circulating widely in humans: influenza A(H3N2) and influenza B. The virus undergoes constant evolution, leading to annual seasonal winter epidemics in temperate countries and necessitating annual updates to the vaccine. Rarely, completely new influenza viruses can emerge in human populations, giving rise to influenza pandemics. Children aged <5 years (especially those <2 years) and those with underlying illness such as cardiac, respiratory and severe neurologic disease have an increased risk of severe outcomes associated with influenza. Pregnant women have an increased risk of severe influenza. Complications may involve the respiratory tract (e.g. otitis media or pneumonia) or, less commonly, other organ systems (e.g. encephalitis or myocarditis). Specific antiviral treatment should be offered as soon as possible for hospitalized children with presumed or confirmed influenza and for influenza of any severity for children at high risk of severe complications of influenza without waiting

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for laboratory confirmation. Antiviral treatment is usually not warranted for uncomplicated influenza as this is usually self-limiting. Annual influenza vaccination should be offered to all individuals at increased risk for complications of influenza. Vaccine cannot be given to children aged <6 months but maternal influenza immunization during pregnancy is recommended and can confer protection to the young infant.

2.1 Introduction

Influenza is one of the commonest infections in human populations, infecting a significant percentage of the population each year and causing substantial morbidity and mortality globally. While seasonal influenza is an important cause of morbidity and mortality, novel influenza virus strains can emerge with the potential to cause global pandemics. Children are a common source of inluenza transmission in the community and form an important risk group for severe influenza illness (particularly infants and children with underlying chronic illnesses).

2.2 Virological Data

Influenza viruses are enveloped viruses from the family *Orthomyxoviridae* [1]. Influenza has a negative sense RNA genome divided into eight segments. The segmented genome allows for exchange of genes between influenza viruses of the same type through genetic reassortment. Two types of influenza viruses, influenza A and B, cause epidemic disease in humans. The influenza A viruses are divided into subtypes and influenza B viruses into lineages based on their antigenic structure. The influenza A subtypes are differentiated based on characteristics of the haemagglutinin (HA) and neuraminidase (NA) surface antigens. Haemaglutinin is responsible for virus attachment during the early stages of infection and is the main antigen against which the host immune response is directed. Neuraminidase facilitates the release of mature virus from the cell surface.

Currently there are two influenza A subtypes (influenza A(H3N2) and influenza A(H1N1)pdm09 and two influenza B lineages (Yamagata and Victoria) co-circulating globally in human populations. Influenza A viruses of at least 17 HA and 9 NA subtypes have been isolated from animals such as birds, pigs, horses and dogs. Because many different HA and NA subtypes can circulate in animals, animals such as birds and pigs may be the reservoir of emerging influenza virus subtypes which can infect humans [1]. Several of these subtypes such as influenza A(H7N1) or influenza A(H5N2) can cause severe illness and even death in individuals in close contact with animals but are not able to be efficiently transmitted from person-to-person [2].

Antigenic drift is the emergence of new influenza virus antigenic variants as a result of point mutations and recombination which occurs during viral replication [1]. This frequent emergence of antigenic variants contributes to seasonal influenza epidemics and leads to the requirement for annual assessment of the need to update
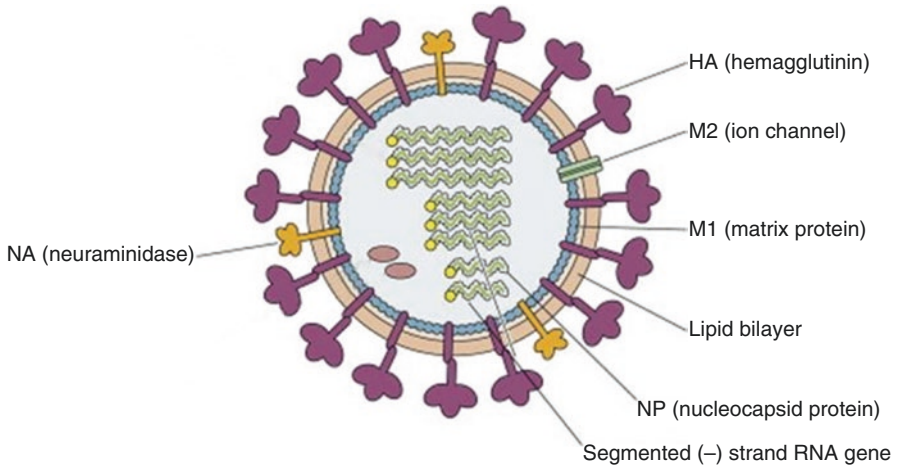
Fig. 2.1 The structure of influenza virus. Credit to virology blog: about viruses and viral disease by Vincent Racaniello http://www.virology.ws/2009/04/30/structure-of-influenza-virus/

the viruses included in the influenza vaccine. Antigenic shift is a term for larger genetic changes which occur infrequently in influenza A viruses. New, or substantially different, influenza A virus subtypes which emerge in humans, have the potential to cause pandemics if they are efficiently transmitted between humans in the presence of little or no pre-existing population immunity [2] (Fig. 2.1).

2.3 Epidemiology Including Pandemics

2.3.1 Burden of Disease

It is estimated that 5–20% of the population become infected with influenza each year and about 20% of these develop symptomatic illness. Rates of influenza infection are highest in children aged 5–15 years [3]. Annually in children aged <5 years there are approximately 90 million new cases of influenza, 20 million cases of influenza-associated acute lower respiratory tract infection (ALRI) (13% of all cases of paediatric ALRI) and one million cases of influenza-associated severe ALRI (7% of all severe ALRI) globally [4]. Between 28,000 and 111,500 influenza-associated deaths in children <5 years are estimated to occur each year, with 99% of these occurring in developing countries. Influenza is associated with approximately 10% of respiratory hospitalizations in children <18 years worldwide ranging from 5% in children aged <6 months to 16% in children aged 5–17 years [5]. Influenza-associated hospitalization rates are more than three times higher in developing than industrialised countries. The incidence and mortality associated with influenza can vary substantially from year-to-year as a result of different circulating types and subtypes with differing propensity to cause severe illness. Years in which influenza A(H3N2) predominates may typically be associated with increased risk of severe disease [6].

People of all ages may develop symptomatic influenza infection but the highest rates of influenza-positive influenza-like illness (ILI) are seen in children aged 2–17 years [7]. School-age children are an important source of infection in the community and influenza outbreaks can occur in schools during the influenza season [8]. During the influenza season, influenza is an important cause of school absenteeism. Illness in children can cause a substantial economic burden as a result of caregiver absenteeism from work to care for ill children as well as outpatient visits in children and can lead to additional antibiotic courses being prescribed. Hospitalizations and mortality during the influenza season can be substantial. In severe influenza seasons, the large number of medical care visits as a result of influenza can overwhelm health systems.

2.3.2   Groups at Risk for Severe Disease

The highest rates of influenza-associated hospitalizations and deaths are typically seen in individuals aged ≥65 years, <5 years and those with underlying medical conditions that confer an increased risk for severe influenza [9]. Children aged <2 years and, to a lesser extent, those aged 2–5 years have increased rates of influenza-associated hospitalization and mortality compared to older children. Children with underlying illnesses, particularly cardiac, respiratory and severe neurologic disease have an increased risk of severe outcomes associated with influenza. A study from South Africa, found that amongst children aged <5 years, malnutrition, prematurity and HIV infection were associated with increased odds of influenza-associated hospitalization [10]. HIV-infected children have an approximately two times elevated risk of influenza hospitalization and are more likely to die of influenza once hospitalized compared to HIV-uninfected children [11, 12].

Pregnant women have an increased risk of severe influenza. Some studies suggest that influenza in pregnancy may be associated with adverse outcomes in infants born to these women (such as low birth weight, pre-term birth and stillbirth), but others have disputed this [13].

2.3.3   Seasonality

In temperate climates influenza typically causes annual seasonal epidemics in the winter months, between April and September in the Southern Hemisphere and between October and April in the Northern Hemisphere [9, 14]. In more tropical climates influenza commonly circulates year-round with two or more peaks which may coincide with climatic events such as the rainy season [15]. This may present challenges for decision-making around the best time to vaccinate and which vaccine formulation (the Northern or Southern Hemisphere) should be used (see section on vaccines) [16]. The start, peak, size and duration of the influenza season may vary substantially from year-to-year. Seasonal influenza can give rise to outbreaks in closed settings such as schools, these can occur at any time of year but are more common during the influenza season [9].

2.3.4   Pandemic Influenza

Influenza pandemics are caused by the emergence and spread in human populations of a new influenza A virus with either a new or substantially altered HA or NA combination against which there is little or no immunity in humans, which is easily transmitted between humans and causes clinical illness in humans [1]. The emergence of a pandemic influenza strain is unpredictable and can occur through two mechanisms. Firstly, a host could be simultaneously infected with two different influenza virus subtypes which could allow for exchange of genetic material or reassortment and the emergence of a new subtype. For example this could occur if a pig were infected by both a human and avian origin influenza subtype simultaneously with genetic exchange leading to the emergence of a virus adapted to spread in humans, but with HA and/or NA not currently circulating in humans. The second way that novel subtypes can emerge is if avian or other animal adapted subtypes are directly transmitted to humans and then undergo adaptation to allow transmission between humans. Currently some avian influenza virus subtypes such as influenza A(H5N2) can be transmitted to humans, usually following close contact with poultry, and cause severe infections. However, these viruses are not adapted for efficient transmission from person to person and therefore have not given rise to a new pandemic strain [2]. Global surveillance for new influenza virus strains is essential for early identification of novel strains to allow a global public health response.

The 1918 pandemic of influenza A(H1N1) is widely acknowledged as the most severe in recent times with an estimated >20 million deaths worldwide. Other recent pandemics (1957, Asian flu H2N2 and 1968 Hong Kong flu H3N2) have been associated with a lower death toll [17]. A characteristic of pandemic influenza strains is the shift in the age distribution of deaths from predominantly affecting the extremes of age (young infants and the elderly) to mortality in young adults aged 20–40 years [17]. Although influenza pandemics can cause substantial mortality, the annual cumulative deaths each year, associated with seasonal mortality, far outweigh this burden.

In 2009, a novel influenza A virus, influenza A(H1N1)pdm09 emerged in the human population and caused a global pandemic. This virus, was antigenically distinct from the H1N1 virus which had been circulating in human populations from 1997 to early 2009 and was thought to have entered the human population from pigs (hence the colloquial name "swine flu"). The overall mortality burden of this strain was estimated at between 123,000 and 203,000 deaths globally, similar to the annual mortality burden from seasonal influenza, although this strain did exhibit the characteristic pandemic age shift, disproportionately affecting individuals aged 20–40 years [18]. Subsequently, influenza A(H1N1)pdm09 has been circulating in human populations and immunity in the population has built up. Influenza A(H1N1)pdm09 has become the predominant H1N1 seasonal train, replacing those that previously circulated and behaves like any other seasonal influenza virus [9].

2.4   Transmission and Pathogenesis of Disease

Influenza is predominantly spread person-to-person by large droplets and through direct contact with respiratory secretions [19]. The contribution of airborne transmission is unclear. The incubation period for influenza typically ranges from 1 to 4 days (median 2 days) [20]. Influenza virus is typically shed from the nasopharynx for up to 5 days after illness but viral shedding may be longer in severely ill individuals, young children and immunocompromised individuals. The reproductive number for influenza is between 1 and 2 and the serial interval usually estimated at 2–3 days.

An individual's susceptibility to infection and disease will depend on host characteristics including preexisting cellular or humoral immunity to influenza [20]. Young children may have no pre-existing immunity to influenza, but older children and adults have often been exposed to circulating influenza several times before and may also have pre existing immunity from vaccination. Natural immunity is not fully protective, largely because of the variability of influenza HA and NA.

Influenza virus replication predominantly occurs in the respiratory tract columnar epithelial cells, with infection leading to loss of cilia and cell death [20]. Damage to the respiratory tract as well as immunologic changes can lead to increased susceptibility to bacterial superinfection. Viremia with influenza is relatively uncommon although constitutional symptoms are a prominent feature of clinical disease.

2.5   Clinical Manifestations

In most children influenza infection results in acute self-limiting upper respiratory tract (URT) symptoms, however, systemic manifestations are not uncommon [21]. Factors that influence clinical presentation include: age of the child, previous influenza exposure, vaccination status, underlying disease states or co-morbidities, as well as viral factors.

Children are considered important influenza "vectors" and are often responsible for introducing the virus into their homes and broader social settings [22].

Influenza classically presents with the sudden onset of systemic (fever, myalgia, headache, and malaise) and URT symptoms (sore throat, cough, rhinitis). Since many patients do not have all these typical symptoms, accurate clinical diagnosis is challenging particularly in the younger pre-verbal child and outside of the influenza season [23].

A large study evaluating the clinical presentation of influenza in children found that almost all (95%) had fever; cough (77%) and rhinitis (78%) were also very common, but much lower proportions experienced headache (26%) or myalgia (7%) [24]. Younger children have not yet been exposed to influenza very often and so have yet to acquire immunity to a substantial repertoire of circulating seasonal influenza strains. They, therefore, are more likely to develop severe or complicated disease [25]. Further, they are less likely to manifest with classic symptoms, experience higher fevers (not uncommonly associated with febrile convulsions), less prominent URT involvement and more gastro-intestinal symptoms (vomiting, diarrhea, abdominal pain, loss of appetite).

Examination may be completely normal in some children, others may manifest with tachypnea, conjunctival injection, nasal inflammation and discharge, or cervical lymphadenopathy. Oropharyngeal findings are often limited, even in those children complaining of a sore throat [24].

Symptoms of uncomplicated influenza usually start improving within a few days, but symptoms lasting more than a week are not uncommon. Cough, in particular, may persist for a number of weeks, but steady improvement can be expected [26].

The differential diagnosis of influenza largely depends on the presenting symptoms and clinical findings, but includes other respiratory viruses (rhinovirus, coronavirus, respiratory syncitial virus, human metapneumovirus, adenovirus, parainfluenza) and some bacterial URT infections (*Streptococcus pyogenes*, Mycoplasma). The clinical manifestations of these conditions are very similar, regardless of the implicated pathogen [27]. All influenza strains may result in severe illness and knowing which infection a particular child has, is not helpful in predicting their disease course.

Complications may involve the respiratory tract (e.g. otitis media, pneumonia) or, less commonly, other organ systems (e.g. encephalitis, myocarditis). Otitis media may occur in as many as 50% of cases; this may be related to the influenza virus itself or secondary infection with bacteria or other viruses [24, 28]. Symptoms of acute otitis media generally present a few days after onset of influenza symptoms.

Lower respiratory tract complications may include the following [21, 29]:

- Laryngo-tracheo-bronchitis ("croup")
- Bronchiolitis
- Pneumonia—especially in children <2 years of age, often mild but may be severe, rapidly-progressive and occasionally fatal, particularly if associated with secondary bacterial infection (usually *Streptococcus pneumoniae* or *Staphylococcus aureus*). A variety of radiographic appearances have been described
- Acute exacerbation of asthma—this is the most common respiratory tract complication of influenza.

Central nervous system involvement can include the following [30–32]:

- Aseptic meningitis
- Acute cerebellitis
- Transverse myelitis
- Guillain-Barré syndrome
- Febrile seizure
- Necrotizing encephalitis
- Postinfectious encephalitis (also referred to as acute disseminated encephalomyelitis).

Neurologic complications appear to be more common in younger children and in those with underlying neurologic and neuromuscular disease. Following the rapid decline in aspirin use over the last few decades, influenza-associated Reye syndrome is now rare.

Mild transient myositis is common with influenza infection; it is more likely with influenza B and is associated with moderate elevations in creatine kinase levels [24]. Acute myositis is an important, severe, but rare, complication of influenza infection [33]. It presents with extreme muscle tenderness, often involving the calf muscles, extreme elevations in creatine kinase as well as significant myoglobinuria.

2.5.1 Diagnostic Testing

During influenza season, influenza should be considered in all children presenting with suggestive clinical features—this includes those already admitted to hospital, as nosocomial transmission of influenza is well described. Influenza should still be considered outside of the influenza season, particularly in travelers and children residing in tropical and sub-tropical climates where year-round influenza transmission occurs.

Accurate clinical diagnosis of influenza is challenging, particularly in younger children. The lack of specific signs or symptoms results in patients receiving diagnoses of "influenza-like illness" or "viral upper respiratory tract illness" unless further diagnostic testing is undertaken. This degree of diagnostic uncertainty should be acknowledged, however, since most such cases are self-limiting and management is largely supportive, there is usually no need to obtain a precise microbiological diagnosis.

Currently available diagnostic tests for influenza include the following [23, 34]:

- **Rapid, point-of-care, antigen detection tests**
  A number of different tests are currently available, although they remain unavailable in many settings. They provide results within 30 min, and, when used appropriately, are helpful in confirming influenza infection. In general, they are insufficiently sensitive to reliably exclude the disease. Further, their performance will depend on which antigens are expressed by currently circulating strains. When influenza activity is low, positive results are likely to be false-positives, however, their positive predictive value improves as influenza activity increases. Conversely, during periods of high influenza activity, false-negatives are more likely and may warrant additional testing in some patients.

  Since diagnostic confirmation seldom affects management of such children, the use of these tests is generally not recommended in low-resource settings and should be used judiciously in better-resourced areas. When used, it should be clear in the clinician's mind as to how the result is going to alter treatment: positive results can potentially reduce antibiotic usage and allow for early use of antivirals in those at high risk of complications or severe disease. However, it is important to recognize that the identification of influenza does not exclude the presence of bacterial co-infections.
- **Polymerase Chain Reaction (PCR) tests**
  These tests are currently considered to be the most reliable for the diagnosis of influenza in children. Amongst the available options, they are the most sensitive and specific. They can be performed on most respiratory samples, most commonly

nasopharyngeal aspirates or swabs. They are also able to differentiate influenza A and B, as well as subtypes of influenza A.

More recently, point-of-care PCR assays have becomes available in some developed world settings. They are performed on nasal swabs and can supply a reliable result in as little as 15 min. While, not currently available in most developing world settings, if more affordable they could become an important new influenza diagnostic.

Since the live attenuated influenza vaccine contains influenza genetic material, recent receipt of this vaccine will also result in a positive PCR test.

- **Immunofluorescence tests**
  These are also performed on nasal or nasopharyngeal swabs and allow for the direct or indirect detection of influenza antigens. Influenza A and B can be differentiated, however, the sensitivity of these tests is moderate and, particularly during periods of high transmission, negative tests may need to be repeated using a more sensitive methodology (PCR or culture).

- **Viral culture**
  Viral culture takes at least 48–72 hours and so has limited utility in the routine diagnosis of influenza. However, they are helpful as part of surveillance activities and isolates can be used to inform annual vaccine planning.

- **Serological assays**
  A variety (hemagglutination-inhibition, enzyme-linked immunosorbent assay (ELISA), and complement fixation assays) of serological assays can be performed but are of limited diagnostic value as they require acute and convalescent sampling. A fourfold increase in titre allows for a retrospective influenza diagnosis to be made. Their primary role is as a research tool.

2.6   Therapeutic Options

Antivirals are available for the specific treatment of influenza. Two classes of anti-influenza drugs are available: neuraminidase inhibitors (e.g. oseltamivir, zanamivir) and M2 inhibitors (e.g. amantadine, rimantadine). Both classes are inactive against all other respiratory viruses. Resistance can emerge in circulating influenza virus strains and for this reason antiviral resistance should be constantly monitored through surveillance and recent guidance consulted for the latest antiviral resistance profiles.

- **Neuraminidase inhibitors** [35]
  Neuraminidase inhibitors prevent the release of new virions from influenza infected cells and are active against both influenza A and B.

  Oseltamivir is the most widely available member of this drug class and can be used for children and adults. It is dosed orally and is approved for both treatment and prevention of influenza. It is available both in capsule form and as a powder for suspension, although the suspension has a relatively short shelf life and is often substantially more expensive than the capsule. As a result, the capsule is the most widely used formulation. When the oral suspension is unavailable the capsule can be opened and diluted with sweetened liquids to provide the appropriate dose.

Zanamivir is predominantly available as an inhaled formulation, although intravenous zanamivir is available for investigational use, particularly for severely ill patients or those with suspected or confirmed oseltamivir-resistant virus. The inhaled preparation is contra-indicated in children with a history of wheezing or other chronic respiratory condition. Its use is not recommended for children younger than 5 years of age.

Peramivir is an intravenous neuraminidase inhibitor that is not approved for use in children and is not widely available.

Neuraminidase inhibitors are generally well tolerated. Common side effects include nausea, vomiting and rash, as well as bronchospasm with zanamivir. Neuropsychiatric symptoms have been linked to oseltamivir use, particularly in Japan, however, more recent evidence suggests no such causative link [36, 37]. Severe adverse reactions have been reported but are considered rare [38].

The mainstay of influenza prevention remains immunization, but in high risk situations, amongst partially or unimmunized children, chemoprophylaxis can be considered. Both pre- and post-exposure chemoprophylaxis have been advocated, however, concerns regarding induction of oseltamivir-resistance have tempered enthusiasm for this approach and their prophylactic use is increasingly discouraged.

Antiviral treatment should be offered as soon as possible for hospitalized children with presumed or confirmed influenza and for influenza of any severity for children at high risk of severe complications of influenza (Table 2.1) [39]. Timely oseltamivir treatment can reduce the duration of fever and symptoms. There are no prospective randomized controlled trials of treatment efficacy of neuraminidase inhibitors in hospitalized children and for severe outcomes but observational data suggest that treatment does reduce the risk of hospitalization and death, although there is some controversy in the literature (Table 2.2) [40]. Treatment should be initiated as early as possible. The benefit of any treatment is maximal early in the course of the disease and should be started within 48–72 hours of symptom onset. Influenza diagnosis may not have been confirmed within this timeframe and so treatment will often be initiated empirically prior to microbiological confirmation. Some evidence suggests benefit to those with very severe illness even when treatment is initiated later than 72 hours into the disease course. Therefore, in

Table 2.1 Children at high risk of severe influenza in whom influenza antiviral treatment is recommended by the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) current guidance [9, 39]

1. Children aged <2 years
2. Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
3. Persons with immunosuppression, including that caused by medications or by HIV infection
4. Persons who are receiving long-term aspirin therapy
5. American Indian/Alaska Native persons
6. Residents of chronic care facilities

Table 2.2 Currently recommended doses for neuraminidase inhibitors (modified from [39])

Medication	Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir		
Children aged ≥12 months		
Body weight		
<15 kg (≤33 lb)	30 mg twice daily	30 mg once daily
>15–23 kg (33–51 lb)	45 mg twice daily	45 mg once daily
>23–40 kg (>51–88 lb)	60 mg twice daily	60 mg once daily
>40 kg (>88 lb)	75 mg twice daily	75 mg once daily
Infants aged 9–11 months	3.5 mg/kg per dose twice daily	3.5 mg/kg per dose once daily
Term infants aged 0–8 months	3 mg/kg per dose twice daily	3 mg/kg per dose once daily for infants 3–8 months; not recommended for infants <3 months old unless situation is judged critical, because of limited safety and efficacy data in this age group
Preterm infants	1 mg/kg per dose, orally, twice daily, for those <38 weeks' postmenstrual age	
	1.5 mg/kg per dose, orally, twice daily, for those 38 through 40 weeks' postmenstrual age	
	3.0 mg/kg per dose, orally, twice daily, for those >40 weeks' postmenstrual age	
	For extremely preterm infants (<28 weeks), consult a pediatric infectious diseases physician	
Zanamivir		
Children (≥7 years for treatment, ≥5 years for chemoprophylaxis)	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily

patients with severe or complicated disease, treatment should be initiated even if >48 hours after illness onset. Children meeting the clinical criteria for treatment should be treated irrespective of whether they have been vaccinated.

Since influenza is generally a mild, self-limiting disease in previously well children, most such children will not require antiviral treatment even when they present soon after symptom onset. Treatment of such children increases the risk of adverse events, potentially increases the risk of resistance developing and may deplete medicine supply for those in greater need.

- **Adamantanes** [9, 39]
  These agents target the influenza A M2 protein, which is essential for efficient viral replication. They have no activity against influenza B and are not active

against currently circulating influenza A strains. As such, there use is not currently recommended for the treatment or prevention of influenza. It has been suggested that they may have a role, in combination with oseltamivir, for the treatment of oseltamivir-resistant influenza A.

2.7   Vaccines and Guidelines for Vaccination

2.7.1   Process of Annual Vaccine Selection

Because of the changing nature of influenza viruses, the World Health Organization (WHO) monitors the epidemiology of influenza viruses throughout the world through the Global Influenza Surveillance and Response System (GISRS). Separate recommendations are made for the Southern Hemisphere and Northern Hemisphere vaccine strains each year. Each year, towards the end of the influenza season, recommendations about strains to be included in the vaccine for each Hemisphere for the following influenza season are made.

2.7.2   Groups Recommended to Receive Annual Influenza Vaccination

Influenza vaccination can be given to any person who wishes to reduce the risk of becoming ill during the influenza season. Some countries such as the United States of America (USA) and United Kingdom (UK) recommend influenza vaccination for all children, or all individuals. In addition, special effort should be made to vaccinate children at risk of severe influenza listed in Table 2.3. Individuals such as healthcare personnel and childcare providers (especially those in contact with infants aged <6 months and children with underlying risk conditions) should be vaccinated to reduce the risk of transmission to high risk children. Lastly, pregnant women are recommended to receive influenza vaccination, to reduce the risk of severe illness in the mother, to provide direct protection to the young infant through trans-placental transfer of maternal antibodies and to reduce the risk of transmission of influenza from the mother to the young infant [41].

Table 2.3 Groups recommended for influenza vaccination of particular relevance in pediatrics (adapted from [39])

A. Children and adolescents at increased risk of severe influenza
1. All children and adolescents, including infants born preterm, who are 6 months and older (based on chronologic age) with conditions that increase the risk of complications from influenza including:
a. Asthma or other chronic pulmonary diseases, including cystic fibrosis
b. Hemodynamically significant cardiac disease
c. Immunosuppressive disorders or therapy

Table 2.3 (continued)

d. HIV infection
e. Sickle cell anemia and other hemoglobinopathies
f. Diseases that necessitate long-term aspirin therapy, including juvenile idiopathic arthritis or Kawasaki disease
g. Chronic renal dysfunction
h. Chronic metabolic disease, including diabetes mellitus
i. Any condition that can compromise respiratory function or handling of secretions or can increase the risk of aspiration, such as neurodevelopmental disorders, spinal cord injuries, seizure disorders, or neuromuscular abnormalities
j. Morbid obesity
k. Pregnancy
2. Children aged 6 months–59 months as this group (particularly those aged <24 months) has an increased risk of influenza-associated hospitalization and mortality
B. Individuals who come into contact with children at risk of severe influenza
1. All household contacts and out-of-home care providers of the following: children with high-risk conditions; and children younger than 5 years, especially infants younger than 6 months
2. All health care personnel (HCP)
3. All child care providers and staff; and
4. All women who are pregnant, are considering pregnancy, are in the postpartum period, or are breastfeeding during the influenza season

2.7.3 Available Influenza Vaccines (Table 2.4)

2.7.3.1 Trivalent Inactivated Vaccine (IIV3) and Quadrivalent Inactivated Vaccine (IIV4)

IIV3 has been available for many years and includes inactivated components of two influenza A (one each of influenza A(H1N1)pdm and influenza A(H3N2)) and one influenza B strains. Since the 1980s, two antigenically distinct influenza B lineages (Victoria and Yamagata) have been circulating globally. This is a limitation of IIV3, as protection may be reduced when the circulating influenza B strain is of the lineage which is not included in IIV3. The IIV4 includes an additional strain of the other influenza B lineage not included in TIV to make a total of four strains and thus potentially offers additional benefit of protection against both circulating influenza B lineages.

Inactivated influenza vaccines (IIV3 and IIV4) contain no live virus. Standard-dose IIV should contain 15 μg of each haemagglutinin antigen in each 0.5 mL dose. IIV3 and IIV4 are available in formulations for both intramuscular (IM) and intradermal (ID) use but the ID formulation is only licensed for use in individuals aged 18 years and older.

Two formulations of IIV3 manufactured using technologies that do not include eggs have become available in recent years, but neither is licensed for individuals aged <18 years. These are cell-culture based inactivated influenza vaccine and recombinant influenza vaccine.

Table 2.4 Types of influenza vaccines available for use in children (note this list is not comprehensive and other formulations may be available in some settings)

Type	Trade name	Manufacturer	Presentation	Age indications	Route
Trivalent IIV standard dose	Vaxigrip®	Sanofi Pasteur	0.5 mL liquid in a single-dose prefilled syringe	≥6 months	IM
	Influvac®	Abbott	0.5mL single dose prefilled syringe	≥6 months	IM
	Vaxigrip®	Sanofi Pasteur	5.0 mL multi-dose vial	≥6 months	IM
	Fluvac®	bioCSL	0.5 mL single dose prefilled syringe	≥9 years	IM
			5.0 mL multidose vial	≥9 years	IM
	Fluvirin®	Novartis vaccines and diagnostics	0.5 mL single-dose prefilled syringe	≥4 years	IM
			5.0 mL multidose vial	≥4 years	IM
Quadrivalent IIV standard dose	Fluzone®	Sanofi Pasteur	0.25 mL single dose prifilled syringe	6–35 months	IM
			0.5 mL single-dose prefilled syringe/0.5 single dose vial	≥36 months	IM
			5.0 mL multidose vial	≥6 months	IM
	Fluarix®	GlaxoSmithKline (GSK)	0.5 mL single dose prefilled syringe	≥3 years	IM
	Flulaval®	ID Biomedical Corp. of Quebec (distributed by GSK)	5.0 mL multidose vial	≥ 3 years	IM
Live attenuated influenza vaccine	FluMist Quadrivalent®	MedImmune	0.2 mL single-dose prefilled intranasal sprayer	2–49 years	IN

IN intranasal, *IM* intramuscular, *IIV* inactivated influenza vaccine

2.7.3.2 Live-Attenuated Influenza Vaccine (LAIV)

LAIV is a live attenuated influenza vaccine which is administered intranasally and licensed for use in individuals aged 2–49 years of age. Since 2013 the LAIV has only been available in a quadrivalent formulation.

2.7.3.3 Adjuvanted Influenza Vaccine

Adjuvanted formulations of influenza vaccine are licensed for use in individuals aged ≥65 years in the USA but not currently in children [39]. They have been shown

Table 2.5 Recommended dosage of influenza vaccine for patients of different age groups

Age group	Dose	Number of doses
Adults and children 9 years of age and older	Adult dose (0.5 mL) IMI	Single dose
Children 3 years–8 years	Adult dose (0.5 mL) IMI	1 or 2 doses[a]
Children 6 months–2 years	0.25 mL (half an adult dose) IMI	1 or 2 doses[a]

Note: influenza vaccine is not recommended for infants <6 months of age. *IMI* intramuscular injection

[a]For individuals who have not previously received a total of ≥2 doses, or when vaccine status is unknown, two doses should be administered ≥1 month apart

to have a higher efficacy then IIV in a randomized controlled trial in children [42]. Adjuvants have several potential advantages over more traditional vaccine formulations including increased immunogenicity, potentially reducing the amount of antigen required. They elicit a more robust immune response and could potentially reduce the number of doses needed in children.

2.7.4 Influenza Vaccine Dosage and Administration

Children aged 6 months through 8 years should receive two influenza doses administered ≥4 weeks apart the first time influenza vaccine is administered. For young children who require two doses of influenza vaccine, vaccination should not be delayed to ensure that both doses are given with the same product. Any licensed, effective influenza vaccine product may be used for each dose. It is important to document all doses of influenza vaccine administered in the child's medical records. In temperate countries, influenza vaccine should be administered as soon as possible after the influenza vaccine becomes available.

The recommended dosage of influenza vaccine for patients of different age groups is described in Table 2.5 [9].

2.7.5 Influenza Vaccine Effectiveness

Influenza vaccine effectiveness depends on characteristics of those being vaccinated (age and health), whether there is a good match between the circulating viruses and the viruses contained in the vaccine, and on influenza types and subtypes circulating each year. In general, influenza vaccines work best among children ≥2 years and healthy adults. Older people (≥65 years), children <2 years and severely immunocompromised individuals often have poorer immune responses to inactivated influenza vaccine (IIV) compared with healthy adults. However, even for these people influenza vaccine still provides some protection. Other products, e.g. high-dose influenza vaccine and adjuvanted vaccines, have been shown to be more effective in certain groups [43] but these vaccines may not be available in all settings and are not licensed for use in all age groups.

There have been a number of studies of IIV effectiveness in children aged 6–59 months. For seasonal IIV in young children, two doses of influenza vaccine

provides better protection than one dose in the first season a child is vaccinated. Estimates of IIV efficacy in young children are limited and vary by season and study design. Efficacy is lower in children aged 6–23 months. Data are unclear as to the effectiveness in HIV-infected children aged <5 years [44].

A randomized controlled trial of LAIV3 in healthy children aged 15–71 found a vaccine effectiveness of 92% (95% CI 65–96%). Several other randomized controlled trials and observational studies have demonstrated high efficacy of LAIV3 against laboratory-confirmed influenza. Studies comparing efficacy of IIV and LAIV have generally found that LAIV has similar, or better efficacy, than IIV. Since 2013, LAIV4 has replaced LAIV3 as the available LAIV. Licensure was on the basis of immunogenicity studies. In 2016, conflicting findings on the effectiveness of LAIV emerged from different settings, with the USA withdrawing its recommendation for LAIV use in the 2016–2017 influenza season based on concerns of reduced effectiveness, particularly against the A(H1N1)pdm component of the vaccine [9]. Studies from Europe in the same seasons found moderate LAIV effectiveness, similar to that of IIV for the same year [45, 46] with recommendations for LAIV remaining unchanged in England and Europe.

Vaccinating individuals at risk of severe influenza may provide direct protection for these individuals. In addition, vaccinating individuals in close contact with people at risk for severe influenza may provide indirect protection through preventing transmission to high-risk individuals. Vaccinating children can protect children directly and the general population indirectly. This strategy is especially important for individuals in whom influenza vaccine is not indicated, such as children aged <6 months (who may be protected through maternal immunization) [47–49]. A randomized controlled trial conducted in South Africa has shown that when pregnant women receive the influenza vaccine, their risk of developing influenza is halved, as is the risk to their infants in the first 24 weeks of life [47]. The vaccine has been shown not only to be efficacious for prevention of influenza in both mothers and their infants, but also safe [47–49]. Vaccination of healthcare workers may decrease the risk of spreading influenza to their patients. Recent influenza vaccination does not preclude a diagnosis of influenza as the vaccine is not 100% effective.

Because of the large year-to-year variability in influenza vaccine effectiveness depending on the circulating influenza strains, many countries publish annual estimates of influenza vaccine effectiveness using a test-negative case-control study design. A systematic review of test-negative case-control studies found that the pooled VE was 33% (95% CI 26–39) for H3N2, 54% (46–61) for type B, 61% (57–65) for H1N1pdm09, suggesting reduced protection of available vaccines against influenza A(H3N2) in recent years [50].

2.7.6   Contraindications to Influenza Vaccination [35, 39]

The IIV is an inactivated vaccine, and has a well-established safety record. It is safe for use in pregnancy and in children ≥6 months of age. Minor illness, with or without fever, is not a contraindication to influenza vaccine administration. Clinicians should always consult the manufacturer's package insert for current contraindications and precautions for particular products.

Contraindications to the administration of IIV include:

- A history of severe (anaphylactic) hypersensitivity to any components of the vaccine including, egg protein, or after previous dose of any influenza vaccine. Anaphylaxis is rare and a careful history will distinguish between anaphylactic reactions and allergic reactions like rashes. Mild egg protein allergy is not a contraindication for influenza vaccine
- Infants <6 months of age.

Precautions to IIV administration include:

- Persons with moderate to severe illness with or without fever should preferably be immunized after symptoms have resolved
- Person who developed Guillian-Barrè syndrome within 6 weeks of receiving an influenza vaccine.

Contraindications to the administration of LAIV include the following:

- Children 2–4 years of age with a history of recurrent wheezing or a medically attended wheezing episode in the previous 12 months because of the potential for increased wheezing after immunization
- Children with the diagnosis of asthma
- Children with a history of egg allergy
- Children who have received other live virus vaccines within the past 4 weeks; however, other live virus vaccines can be given on the same day as LAIV
- Children who have known or suspected immunodeficiency disease or who are receiving immunosuppressive or immunomodulatory therapies
- Children who are receiving aspirin or other salicylates
- Any female who is pregnant or considering pregnancy
- Children with any condition that can compromise respiratory function or handling of secretions or can increase the risk for aspiration
- Children taking an influenza antiviral medication (oseltamivir or zanamivir), until 48 hours after stopping the influenza antiviral therapy
- Children with chronic underlying medical conditions that may predispose to complications after wild-type influenza infection.

As for all vaccines, influenza vaccine should be administered in a setting where there is the ability to respond to acute hypersensitivity reactions.

2.7.7   Influenza Vaccine Adverse Events

The most common adverse events following intramuscular IIV administration are pain and tenderness at the injection site. Fever can occur in 10–35% of children aged <2 years within 24 hours of vaccination, but is much less common in older children. In trials, when IIV are administered, 16–20% of those vaccinated

experience local reactions in the arm, lasting for 1 or 2 days. Short-term reactions (mild fever, malaise and muscle pains) have been reported in a much smaller proportion in the first few hours following vaccination. Trials of the split and subunit vaccines show even fewer systemic reactions. There have been no strong temporal or causal associations of the current vaccines with more severe reactions. Anaphylaxis is very rare but does occur as with all vaccines. More severe adverse events, like Guillain-Barré syndrome have been reported with a particular vaccine in the 1970s but they are extremely rare. With the modern influenza vaccines, the causative risk is either found to be very rare (0.8 per million doses) [51] or there is no causal link found at all [52–54] and more association is found with influenza infection than vaccination [55]. An increased risk of fever and febrile seizures was reported from Australia in 2010 associated with the Southern Hemisphere IIV3 produced by CSL Biotherapeutics (now Sequirus) [39]. Following this, many countries do not recommend the CSL IIV3 for children aged <9 years.

Influenza vaccination during pregnancy has been shown to protect both the mother and her baby (up to 6 months old) against influenza [47, 48, 56, 57]. Influenza vaccination is safe in pregnancy and influenza vaccines have been administered to millions of pregnant women over many years and have not been shown to cause harm to pregnant women or their babies [58].

The most common adverse events associated with LAIV include runny nose or nasal congestion, headache, lethargy and sore throat. LAIV should not be administered to children with marked nasal congestion as this can reduce vaccine delivery. The safety of LAIV is not established in people with a history of asthma, diabetes mellitus, or other high-risk medical conditions associated with an elevated risk of complications from influenza. The use of LAIV in young children with chronic medical conditions is not recommended in the USA but is in some other countries.

2.7.7.1 Other Measures for Prevention of Influenza

Appropriate hand and respiratory hygiene (cough etiquette) has been shown to reduce influenza transmission in children in day-care or school [59]. Sick children and adults should remain at home and not attend school or work until symptoms have resolved to prevent transmission of influenza to others.

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