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Viral Respiratory Infections 29

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Key features

- Global distribution of multiple pathogens causing similar diseases
- Varying burden geographically and seasonally
- Spectrum of pathogens from established, endemic human-adapted viruses to emerging, highly pathogenic viruses from animal reservoirs with pandemic threat
- Clinical disease from common cold to severe lower respiratory tract infection with systemic dissemination
- Severe disease can occur in all age groups but young children, the elderly and the immunocompromised are more at risk for severe disease (during the recent H1N1 influenza pandemic pregnant women and young adults were especially at risk)

INTRODUCTION

Globally, acute respiratory illnesses caused by viruses and bacteria are the most frequently occurring illnesses in all age groups. Disease is mostly limited to the upper airways and is self-limiting, but a small percentage can progress to lower respiratory tract infections as bronchiolitis and pneumonia. Children and elderly people are at increased risk, especially in developing countries. Childhood pneumonia is the leading single cause of mortality in children aged less than 5 years. The incidence in this age group is estimated to be 0.29 episodes per child-years in developing countries and 0.05 episodes per child-years in developed countries. This translates into about 156 million new episodes each year worldwide, of which 151 million episodes are in the developing world. Pneumonia is responsible for about 19% of all deaths in children aged less than 5 years, of which more than 70% take place in sub-Saharan Africa and Southeast Asia. On the other side of the age spectrum, pneumonia is also a major cause of morbidity and mortality in older people, with an annual incidence for non-institutionalized patients estimated at between 25 and 44 per 1000 population – up to four times that of patients younger than 65 years of age.

The most important etiologic agents of severe lower respiratory illness are bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, and viruses such as respiratory syncytial virus (RSV) and influenza virus. Viruses are more important in mild upper and middle respiratory tract infections and in bronchiolitis in children, whereas bacteria are the main cause of pneumonia, especially in adults. Clinical syndromes considerably overlap and there is increasing evidence of bacterial-viral co-infections and of bacterial pneumonia being secondary to a viral respiratory tract infection [1–4].

A wide range of viruses from different families can cause respiratory infections; the most important are the ortho- and paramyxoviridae, picornaviridae, coronaviruses and adenoviruses. Recent etiological studies from tropical and subtropical regions are summarized in Table 29-1 [5–13].

EPIDEMIOLOGY

With some notable exceptions described below, most respiratory viruses are spread from person-to-person by the respiratory route – to a varying extent by large droplets, small-particle aerosols and by fomites with hand contamination and subsequent self-inoculation. Patients are most infectious early in disease: at symptom onset or even before. Secondary attack rates may be especially high in semi-closed populations, for example among schoolchildren, inpatients and nursing home residents. Children play a major role in respiratory virus outbreaks among families and communities. Frequent handwashing and covering of the mouth when coughing or sneezing may partially prevent transmission.

Many of the viruses display significant seasonal variation, especially in temperate regions. Influenza virus and RSV epidemics occur in the winter months in temperate regions. In tropical areas, seasonal patterns are less clear: viruses may circulate throughout the year and peaks may coincide with either lower temperatures or increased rainfall. Parainfluenza virus 3 causes epidemics in the spring, while viruses 1 and 2 do so in autumn and early winter in temperate regions [14].

ORTHOMYXOVIRIDAE: INFLUENZA A, B AND C VIRUSES

Orthomyxoviridae are divided into three genera: A, B and C. Influenza A viruses are further subtyped based on the two major antigens: hemagglutinin (HA; H1–H16), responsible for host receptor binding/cell entry; and neuraminidase (NA; N1–N9), responsible for cleavage of the HA-receptor complex to release newly formed viruses. Key amino acids in these proteins, particularly in HA, are associated with host specificity and transmissibility in humans. Aquatic birds are the natural reservoir of influenza A viruses, harboring all possible subtypes. A selection of subtypes has established endemicity among a range of land and water mammals (e.g. humans, pigs, horses, seals; Fig. 29.1). Influenza B and C viruses are mainly human pathogens, with rare reports of influenza B virus infection in dogs, cats, swine and seals. Influenza C rarely causes human infections and will not be further discussed.

Yearly epidemics of influenza are caused by influenza A and B viruses with mutations in the regions of the HA and NA genes that encode antigenicity, allowing them to escape the hosts' immunity against parent strains (antigenic drift).

New lineages of influenza A virus emerge every few decades, resulting in global pandemics with varying severity owing to the absence of immunity in the human population. New human viruses have emerged through re-assortment of gene segments in animal hosts infected with two different viruses (antigenic shift – 1918 Spanish flu: H1N1; 40–100 million deaths, 1957 Asian flu: H2N2; 2 million deaths and 1968 Hong Kong flu: H3N2; 500,000 deaths) [19]. After

TABLE 29-1 Results of Recent Etiological Studies on Respiratory Viral Infections in Tropical and Subtropical Regions

Country	Years	Setting	Patients	Method	Disease	Number	RSV	hMPV	FluA	FluB	PIV1	PIV2	PIV3	PIV4	Adeno	Entero	Corona				Rhino	Boca	KI-WU
																	NL63	*HKU1*	*229E*	*OC43*			
Korea	2000–2005	H	Children	RT-PCR	LRTI	515	122	24	24	9	9	0	32	X	35	X	8	X	X	X	30	58	X
Bangladesh	2000–2001	O	Children	Serology	ARI	107	3	20	10	14	0	0	9	X	4	X	X	X	X	X	X	X	X
India	2002–2004	HO	Children	Antigen/ Culture	LRTI	385	101	X	21		8				4	X	X	X	X	X	X	X	X
Iran	2001–2002	H	Children	Antigen	ARI	202	26	X	16	7	13	13	32	X	12	X	X	X	X	X	X	X	X
Brazil	2001–2003	O	Adults	Antigen/ RT-PCR	ARI	420	10	24	52	37	1	1	2	X	17	9	X	X	6	12	103	X	X
Brazil	2003	H	Children	RT-PCR	LRTI	336	81	60	17	0	2	0	28	X	23	X	X	X	X	X	X	X	X
Brazil	2003–2005	H	Children	Antigen/ RT-PCR	CAP	184	28	X	17		31				5	9	X	X	X	X	39	X	X
Nepal	2004–2007	HO	Children	RT-PCR	CAP	2219	334	93	164	84	98	17	129	X	X	X	X	X	X	X	X	X	X
India	2005–2007	HO	Children	RT-PCR	LRTI	301	61	11	9	0	10	17	22	X	X	X	X	X	X	X	X	X	X
Brazil	2006–2007	HO	Children	RT-PCR	ARI	205	4	8	6	0	0	0	0	0	2	X	4	1	0	3	38	7	2
Hong Kong	2005–2006	H	Children	RT-PCR	ARI	475	40	7	34	16	19	6	14	3	23	2	X	X	16	2	17	X	X
Singapore	2005–2007	H	Children	Antigen/ RT-PCR	ARI	500	59	29	4	2	4	0	8	X	1	X	3		X	X	X	40	X
Singapore	2006–2007	O	Adults	RT-PCR	ARI	1354	0	9	326	159	1	0	4	0	5	X	X	X	0	1	15	X	X
Vietnam	2007–2008	H	Children	RT-PCR	ARI	958	217	43	146	2	7	5	36	X	49	X	X	X	X	X	270	19	X

Adeno, Adenovirus; ARI, Acute Respiratory Infection; CAP, Community Acquired Pneumonia; Entero, Enterovirus; FluA, influenza virus A; FluB, influenza virus B; H, Hospitalized; hMPV, human metapneumovirus; HO, Hospitalized and Outpatients; LRTI, Lower Respiratory Tract Infection; O, Outpatients, PIV, parainfluenza virus; RSV, respiratory syncytial virus; RT-PCR, Reverse Transcription-Polymerase Chain Reaction; Corona, Coronavirus; Rhino, Rhinovirus; Boca, Bocavirus, KI-WU, KI and WU polyomaviruses.

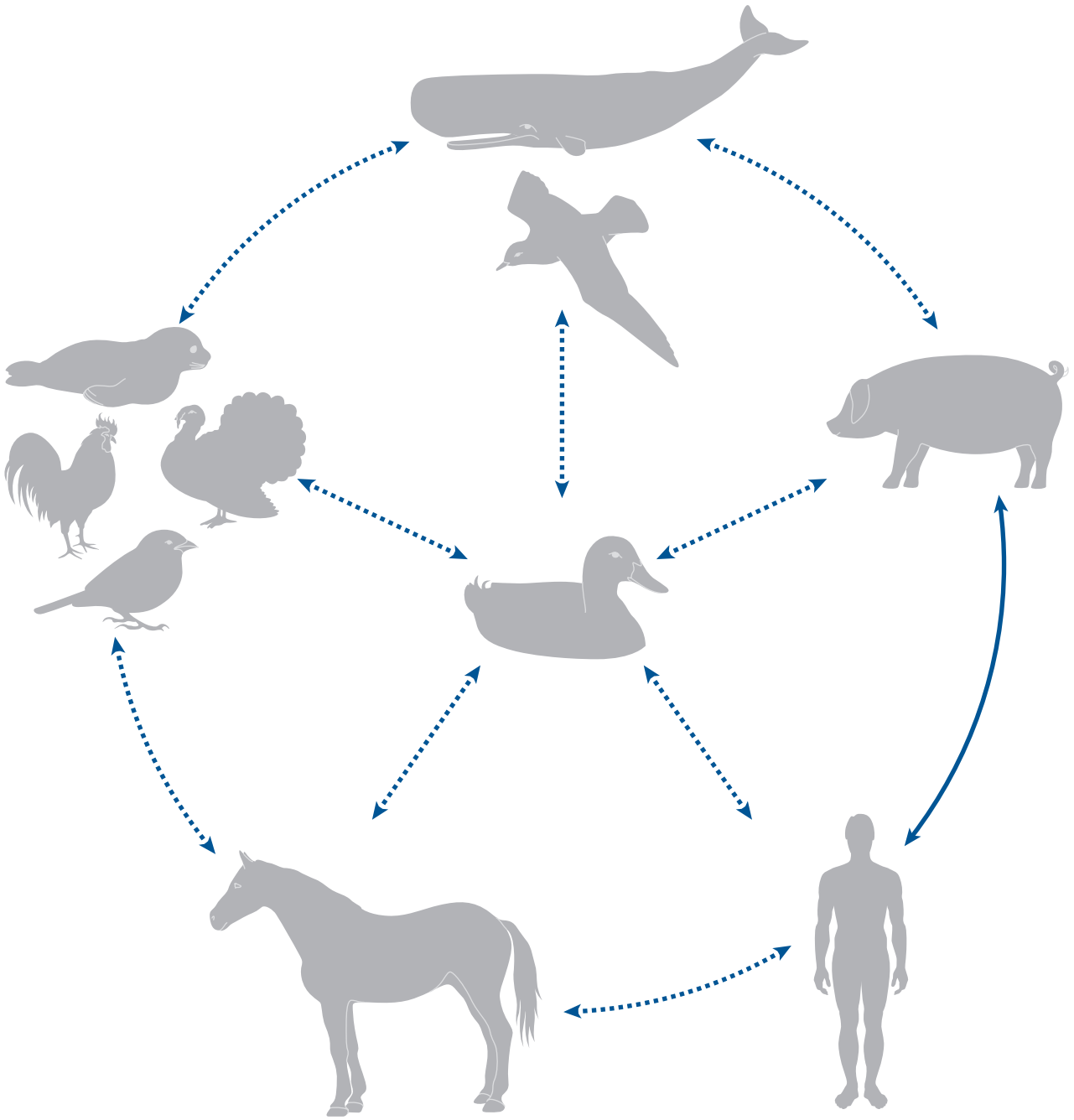

FIGURE 29.1 The reservoir of influenza A viruses. The working hypothesis is that wild aquatic birds are the primordial reservoir of all influenza viruses for avian and mammalian species. Transmission of influenza has been demonstrated between pigs and humans (solid lines). There is extensive evidence for transmission between aquatic birds and other species including pigs and horses and indirect transmission to humans through pigs and evidence for direct transmission to humans from chickens *(with permission from Elsevier Ltd, Encyclopedia of Virology 2nd edition; 1999; pp 824-829).*

such an introduction, the new virus becomes the dominant circulating lineage of influenza A. One exception was the re-introduction of H1N1 in the human population in 1977, which was possibly caused by an escape from a research laboratory. Since 1977, two lineages of H1N1 and H3N2 influenza A viruses have been co-circulating among humans, causing yearly seasonal epidemics worldwide (Fig. 29.2). Influenza B viruses co-circulate with influenza A viruses and also cause yearly epidemics but have not been associated with pandemics.

In 2009, a novel lineage of H1N1 influenza A virus emerged, most likely from pigs, in North America and caused a worldwide pandemic of relatively mild influenza. At the time of writing, the pandemic has passed and around 18,000 people died from infection during the pandemic phase. The virus has now become established as a seasonal virus, has largely replaced the former H1N1 virus and is co-circulating with H3N2.

Sporadic, dead-end human infections of animal viruses are known to occur and have caused concern about the pandemic potential of these viruses. H7N7, H7N3 and H9N2 viruses have caused conjunctivitis and mild, flu-like illness in patients who were in close contact with infected birds or seals. In contrast, H5N1 avian influenza viruses have caused severe human respiratory illness in Asia and North Africa, with a mortality of over 50%. Highly pathogenic H5N1 viruses were first detected in birds in 1996 in China. Transmission to 18 humans

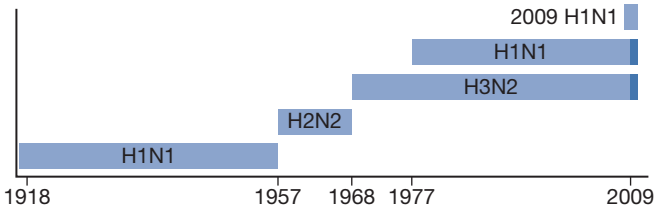

FIGURE 29.2 Timeline of circulating subtypes of influenza virus A from 1918 onwards. In 1977, H1N1 was reintroduced and has since then co-circulated with H3N2. In 2009 a new H1N1 lineage (pdm09) was introduced which has replaced the former H1N1 subtype.

occurred in Hong Kong, six of which were fatal. During the next 6 years, no human or animal cases were recorded. In 2003, the virus re-emerged in China. Since then, it has become panzootic among poultry and wild birds and, at the time of writing, has caused 584 sporadic infections (345 fatal) in humans, most of whom reported close contact with wild birds or domestic poultry. Despite their worldwide presence for many years, and the huge human–animal interface in Asia, no efficient human-to-human transmission episodes have been recorded. The possibility of mutations or re-assortment in these viruses remains a cause for concern and warrants continuous monitoring and surveillance of H5N1 viruses [15].

PARAMYXOVIRIDAE: RESPIRATORY SYNCYTIAL VIRUS (RSV), PARAINFLUENZA VIRUS 1–4 AND HUMAN METAPNEUMOVIRUS (HMPV)

These six human viruses are the most important causes of lower respiratory tract infections in children worldwide. RSV is the single most important cause of bronchiolitis and the leading cause of respiratory tract infections requiring hospitalization. Human metapneumovirus (hMPV) causes similar, but less frequent, disease, whereas the parainfluenza viruses are associated with croup.

Infections with these viruses are very common and virtually all children will have been infected with RSV by 2 years of age and by hMPV at 5 years of age. Immunity against all viruses is incomplete, although re-infections tend to be milder. Severe disease is common from RSV and hMPV in the first year of life. Re-infection with RSV or parainfluenza viruses is also a common cause of pneumonia in elderly and immunocompromised patients [6]. Other paramyxoviridae, such as rubeola virus (measles) or the zoonotic nipah virus may also be associated with respiratory disease as part of disseminated infection. These are discussed in separate chapters.

CORONAVIRUSES AND SEVERE ACUTE RESPIRATORY SYNDROME (SARS)-CORONAVIRUS

The four main human respiratory coronaviruses (229E, OC43, NL63 and HKU1) are associated with relatively mild upper respiratory infections and may cause 10–25% of episodes of common colds, but are less frequently implicated in severe infections requiring hospitalization.

In 2002–2003, a novel, severe form of pneumonia of unknown etiology emerged in Guangdong, China and was named Severe Acute Respiratory Syndrome (SARS). After smoldering for several months, the disease then spread rapidly across the world, facilitated by international air travel and a few so-called "super-spreaders", with the most notable outbreaks in Hong Kong and Toronto. Twenty-one percent of affected cases were healthcare workers. The rapidly identified culprit, SARS coronavirus, is thought to have jumped to humans from Civet cats (considered a delicacy in Asia) in live animal markets in Guangdong. Wild civet cats, however, do not carry these viruses but certain bat species have been implicated as the natural reservoir. The epidemic of SARS, with 8096 cases and 744 deaths in 29 countries across 5 continents, started in November 2002 and came to an end in July 2003. Few sporadic community- and laboratory-acquired infections, including limited person-to-person transmission, have been recorded since. SARS was characterized by fever and myalgia, rapidly progressing to a respiratory syndrome of cough and dyspnea followed by acute respiratory distress syndrome. Mortality was significantly lower in children.

SARS is primarily spread by the respiratory route, but oral–fecal transmission has also been implicated. Why the SARS epidemic did not continue to spread is subject to much speculation. Explanations may include the fact that SARS is most infectious in a later stage of infection, allowing for timely containment, and an extraordinary worldwide public health effort to control spread [16].

PICORNAVIRUSES: RHINOVIRUSES, ENTEROVIRUSES AND PARECHOVIRUSES

Rhinoviruses are the most important cause of the common cold and may be associated with exacerbations of asthma and chronic bronchitis. Enterovirus and parechoviruses typically present with aseptic meningitis but are also associated with (mild) respiratory illness.

ADENOVIRUSES

Adenoviruses are a frequent cause of epidemic infective conjunctivitis in developing countries and of respiratory tract infections in children and young adults worldwide. Outbreaks can occur in closed communities such as day care centers and boarding schools, and among military recruits. Most adenoviral infections remain subclinical.

NATURAL HISTORY AND PATHOGENESIS

Acute respiratory viral infections usually start in the upper respiratory tract as the port of entry is the nose, mouth or eyes. Spread to the lower parts of the airways occurs within two to four days. Syndromes overlap considerably, are usually accompanied by symptoms such as fever, cough and malaise, and can be caused by any of the pathogens described above.

In developing countries in particular, crowding of large families in small houses, low levels of sanitation and personal hygiene, indoor and outdoor smoke pollution, malnutrition, vitamin and mineral deficiencies, and a high frequency of respiratory infections may have detrimental effects on the integrity of the respiratory mucosa, respiratory function and the immune status, making the patient more prone to repeated, and more severe, viral infection and to secondary bacterial infection. Old and very young age, including prematurity are additional risk factors for a more severe course.

CLINICAL FEATURES

Common Cold

The common cold, or coryza, is the most frequent disease worldwide. Specific symptoms include a runny or stuffed nose, sneezing and sore throat. Picorna- and coronaviruses are often involved. Symptoms are caused by local infection of the ciliated nasal mucosal epithelium cells and surrounding increased vascular permeability. Disease is usually self-limiting.

Pharyngitis

Sore throat often accompanies the common cold but is typically not the result of inflammation of the throat, rather it is caused by excretion of chemical inflammation mediators that stimulate pain nerve endings. Bacteria are a common cause of true pharyngitis, as are coxsackieviruses, Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

Acute Laryngotracheobronchitis (Croup)

Croup affects children under the age of 3 years; the hallmark symptoms are a barking cough and acute inspiratory stridor. Symptoms are caused by localized subglottic inflammation and edema leading to airflow impediment.

Tracheitis and Tracheobronchitis

These are most often caused by infection of the tracheal and bronchial epithelium by influenza A and B viruses and are characterized by tracheal tenderness, substernal discomfort on inhalation and nonproductive cough.

Bronchiolitis

This is a distinct syndrome of infants and young children. The major symptom is wheezing, accompanied by flaring of the nostrils, use of accessory respiratory muscles and cyanosis in more severe cases. Direct viral infection of the bronchiolar epithelial cells, followed by necrosis, infiltration of lymphocytes, submucosal swelling and increased mucus secretion results in the formation of dense plugs of debris that cause impediment of airflow, particularly expiratory. Children may experience repeated episodes of wheezing after recovery from bronchiolitis. Associations with later development of asthma and a causative role of the immune system in pathogenesis of bronchiolitis have been suggested.

Viral Pneumonia

Development of primary viral pneumonia, as described for influenza virus, is defined by dysfunctional gas exchange accompanying inflammation of the lung parenchyma, usually resulting in radiographic changes. There is acute generalized illness and a dry cough, rhinitis and conjunctivitis may be present. An increased respiratory rate is an early feature, with cyanosis developing in very severe disease. Viruses reach the small airways either through continuous spread or by inhalation of aerosols. Mucosal infection leads to destruction of epithelial cells, submucosal hyperemia, edema of the airways and hemorrhaging. Additional cellular infiltration and fibrin depositions may further compromise respiratory volume and gas exchange surface [17]. Viral pneumonia can be part of severe forms of measles and varicella, and may be secondary to generalized infections with EBV or CMV. In infections with New World hantaviruses, pulmonary symptoms are dominant but are, instead, caused by immune-mediated capillary leak.

Secondary bacterial pneumonia may follow any respiratory viral illness and presents as a recurrence or protracted fever and respiratory symptoms after initial recovery. *Streptococcus pneumoniae* and *Staphylococcus aureus* are common causes.

DIAGNOSIS

Epidemiologic characteristics, patient history, clinical features and accompanying signs and symptoms may give important clues in establishing the diagnosis of specific viral agents, but clinical syndromes overlap and are nonspecific. Diagnosis can only be reliably made by detection of virus, antigens or nucleic acids in respiratory or other specimens.

Rapid antigen tests exist for RSV and influenza virus, but these are, in general, not very sensitive (up to 70%). Viral culture is still considered the gold standard, but is complicated, cumbersome, slow and can also lack sensitivity. Instead, (reverse transcriptase)-PCR assays are rapid and sensitive and, when used in multiplex format, can detect most common respiratory viruses. Unfortunately, they are expensive by themselves and require even more expensive equipment, laboratory infrastructure and well-trained staff to be performed adequately, limiting their application in developing countries [17].

The identification of one viral agent does not rule out a double infection or mixed bacterial–viral infection. Recently, several novel viruses have been identified in the human respiratory tract (Bocavirus, WU and KI polyomaviruses, amongst several others). The exact significance of the role of these viruses as pathogens has yet to be established.

PREVENTION AND TREATMENT

Vaccines against influenza virus containing inactivated forms of the at-that-time predominant lineages of H3N2, H1N1 and B viruses are produced twice a year for the northern and southern hemispheres. Use in developing countries is limited because of the high cost and the need for annual re-vaccination. Vaccines for the other respiratory viruses are currently not available. Earlier attempts at the production of a formaldehyde-inactivated RSV vaccine were associated with more severe forms of disease in vaccinees.

Cidofovir is available for severe adenovirus infections but causes severe side effects and needs to be administered simultaneously with probenecid. Oral or aerosolized formulations of the broad-spectrum antiviral ribavirin inhibit replication of several respiratory viruses, including influenza virus and RSV; however, they are expensive, studies have not shown consistent benefit for patients with severe RSV infection and they should not be used routinely. Use of ribavirin in combination with other specific anti-influenza drugs for treatment of severe influenza infection has shown promising *in vitro* effects and is under investigation *in vivo*. Humanized anti-RSV immunoglobulins (palivizumab) are available for the prevention of RSV infection in high-risk groups (neonates and infants with congenital heart or lung disease), but are very expensive. Pleconaril was developed for the common cold and inhibits picornavirus replication, but the risks (reduction of efficacy of some hormonal contraceptives and drugs used to treat HIV) outweighed the benefits for its use in the prevention and treatment of uncomplicated infections.

The adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir) are specific antiviral drugs for influenza. The adamantanes and oseltamivir are available as oral preparations; zanamivir is administered through inhalation. Both have shown benefit in the prevention and treatment of uncomplicated influenza, especially when given early in the disease. For severe forms of influenza or H5N1 infection, treatment with oseltamivir is also of benefit when initiated in a later stage. The role of concomitant steroids for these infections is unclear. Oseltamivir was widely used in the developed world and, to a lesser extent, in the developing world to treat infection with 2009 H1N1. Development of resistance during treatment for both classes of drugs is a common phenomenon and is more frequently observed in children. In addition, the dominant lineages of H3N2 and H1N1 in the 2007–2008 season were resistant against adamantanes and oseltamivir, respectively. Resistance against zanamivir is rare, but its route of administration limits use in severe disease.

Parenteral formulations of oseltamivir and zanamivir, and two new neuraminidase inhibitors (peramivir and laninamivir) are under investigation for the treatment of severe influenza. Convalescent plasmatherapy, monoclonal antibodies and other forms of immunomodulation have shown promising results, warranting further evaluation in clinical trials. Supportive and, if needed, intensive care and various forms of oxygen supplementation for severe respiratory distress (tachypnea, retractions, cyanosis) are often the mainstay of treatment of respiratory viral infections. Extracorporeal membrane oxygenation (ECMO) is a last resort for maintaining oxygen saturation during severe viral pneumonia.

In some parts of the world (especially Southeast Asia), antibiotics are extensively used to treat any form of mild respiratory illness. Although there may be some benefit of the use of antibiotics in preventing secondary bacterial infection, over-the-counter availability of antibiotics, self-medication or medication by untrained pharmacy workers should be discouraged because of the selection and subsequent spread of resistance in commensal oral and gut flora.

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