33 Viral Respiratory Infections

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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 H1N1pdm09 influenza pandemic, pregnant women and young adults were especially at risk, whereas the annual avian H7N9 outbreaks in China and MERS-CoV mostly affect the elderly).

INTRODUCTION

Acute respiratory illnesses are the most frequently occurring illness in all age groups globally. Disease is mostly limited to the upper airways and is self-limiting, but a small percentage can progress to lower respiratory tract infections (LRTIs) as bronchiolitis and pneumonia. Children and elderly people are at increased risk, especially in low- and middle-income countries (LMICs).

Childhood pneumonia is the leading cause of mortality in children under 5 and has an incidence of 0.29 episodes per child-year in LMICs and 0.05 in high-income countries. This translates into 156 million new episodes annually worldwide, of which 151 million are in LMICs. Pneumonia killed 920,136 children under 5 in 2015, accounting for 16% of all deaths of children under 5. 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 at 25 to 44 per 1000, up to four times that of patients under 65.

The most important etiologic agents of severe LRTI are bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* and viruses such as respiratory syncytial virus (RSV) and influenza virus. Efficacious vaccines are available against the two bacteria and the influenza virus. Viruses are more important in mild upper and middle respiratory tract infections (RTIs) and in bronchiolitis in children, whereas bacteria are the main cause of pneumonia, especially in adults. Despite this, RTIs—because of the difficulty of making a rapid diagnosis of the etiologic agent—are often treated with antibiotics and are responsible for a large part of inappropriate and appropriate use of antibiotics in humans. Clinical syndromes overlap considerably, and there is increasing evidence of bacterial-viral co-infections and of bacterial pneumonia being secondary to viral RTI.[1-6]

ETIOLOGY

A range of different viruses can cause RTIs; the most important are the ortho- and paramyxoviridae, picornaviridae, coronaviruses, and adenoviruses. Although it is generally accepted that the majority of mild RTIs are viral, recent systematic reviews and meta-analyses of the published literature showed that in adults, 25% of patients with community-acquired pneumonia was viral. This percentage is higher in children, particularly children under 5, due to the large proportion of cases caused by RSV. In adults, the contributions of identified viral etiologies were 8% for influenza viruses, 6% for rhinoviruses, 3% for coronaviruses, and 2% for RSV. In children under 5 with LRTIs, strong causal associations for RSV, influenza viruses, parainfluenza viruses, and metapneumovirus were found in comparison with healthy controls, and less so for adenoviruses, bocaviruses, and coronaviruses.[7,8]

Orthomyxoviridae: Influenza Viruses

Orthomyxoviridae are divided into four genera: A–D. Influenza A viruses are further subtyped based on the two major antigens: haemagglutinin (HA; H1–H18) and neuraminidase (NA; N1–N11), that are responsible for host receptor binding/cell entry and cell exit, respectively. Key amino acids in these proteins, especially 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, except H17, H18, N10, and N11. These were recently identified in bats, suggesting birds are not the only reservoir. A selection of subtypes has established endemicity among land and water mammals (e.g., humans, pigs, horses, seals; Fig. 33.1). 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 influenza D viruses mostly infect cattle 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 due to the absence of immunity in the human population. New human viruses have emerged through antigenic drift in avian viruses (1918 Spanish flu: H1N1, 40–100 million deaths) or through reassortment of gene segments in animal hosts infected with two different viruses (antigenic shift; 1957 Asian flu: H2N2, 2 million deaths; 1968 Hong Kong flu: H3N2, 500,000 deaths). After such an introduction, the new virus becomes the dominant circulating lineage. Two notable exceptions were the reintroduction of H1N1 in the human population in 1977, possibly caused by an escape from a research laboratory, and the introduction in 2009 of a novel lineage of H1N1 influenza A virus, most likely from pigs, in North America, causing a relatively mild pandemic (with an estimated 100,000–400,000 deaths) and generating massive attention from both the public health communities and the general public and replacing only the 1977 H1N1 lineage. Currently, H1N1pdm09 and H3N2 influenza A virus are co-circulating with influenza B viruses and continue to cause yearly seasonal epidemics worldwide. The timing, extent, and direction of either "drift" or "shift" have so far been completely unpredictable. With no animal reservoirs to provide such new antigens, shift does not occur in influenza B and thus major epidemics do not occur (Fig. 33.2).[1,2]

Sporadic dead-end human infections of animal viruses are known to occur and have caused concern about the pandemic potential of these viruses. Swine H3N2, H1N1, and H1N2 viruses have
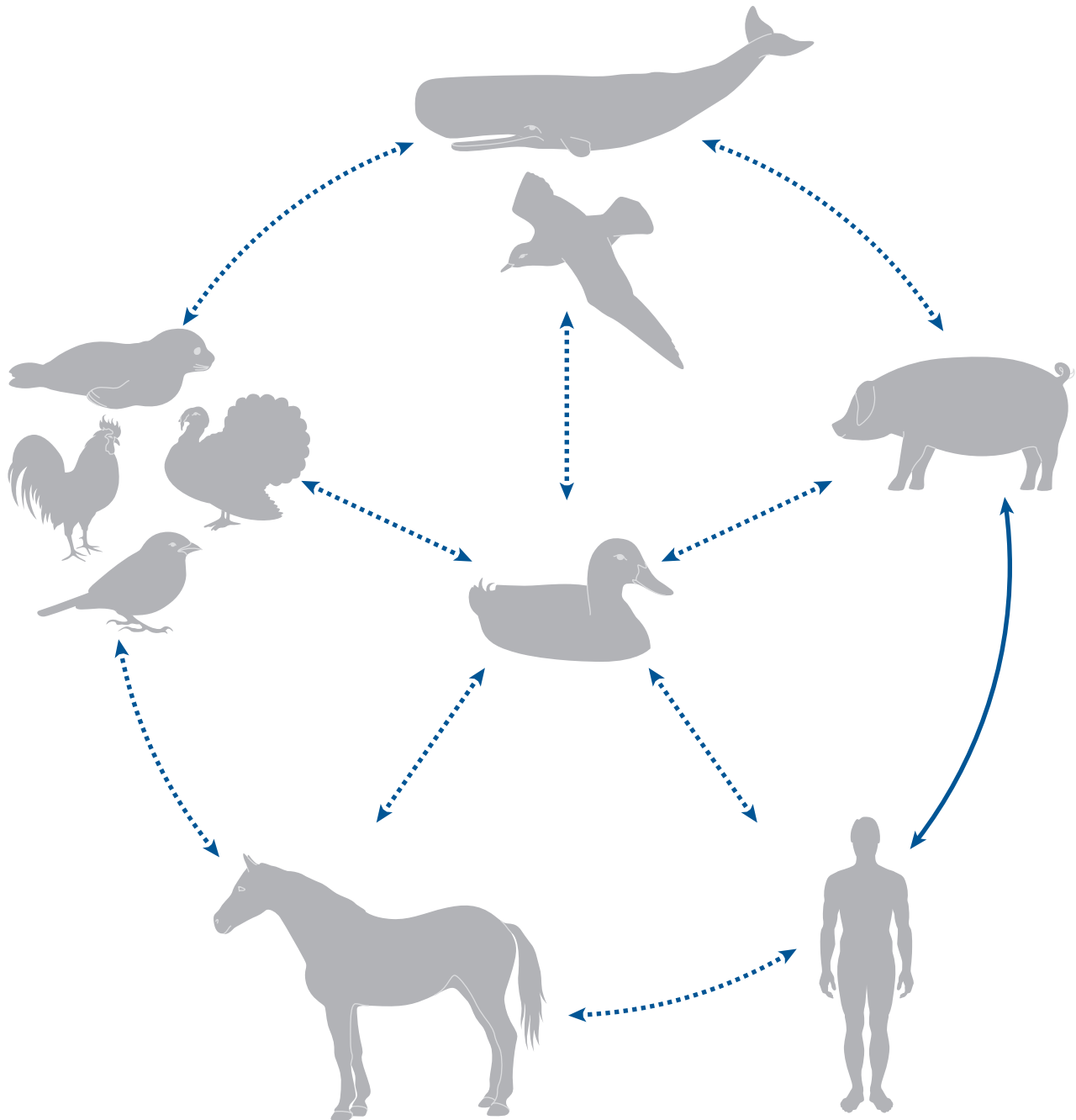
Fig. 33.1 The reservoir of influenza A viruses. The working hypothesis is that wild aquatic birds are the primordial reservoir of all influenza viruses for avian and mammalian species. Transmission of influenza has been demonstrated between pigs and humans (solid lines). There is extensive evidence for 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. (Reprinted with permission from *Encyclopedia of virology*, 2nd ed. 1999, Elsevier, Academic Press, Cambridge, MA, USA, pp. 824–829.)

caused infections in humans with limited human-to-human transmission. H6N1, H7N7, H7N3, H9N2, and H10N7 viruses have caused conjunctivitis and mild flulike illness in patients 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 occurred in Hong Kong, 6 of which were fatal. During the next 6 years no

human or animal cases were recorded. In 2003 the virus reemerged in China. Since then H5N1 viruses have become panzootic among poultry and wild birds and have caused 860 sporadic infections (454 fatal) in humans until 2015, most of whom reported close contact with wild birds or domestic poultry.

Furthermore, a total of 1566 cases (including 613 deaths) of human infection with avian influenza H7N9 have been reported from China, occurring in annual outbreaks between December and February since 2013. Human H7N9 infection is also zoonotic,
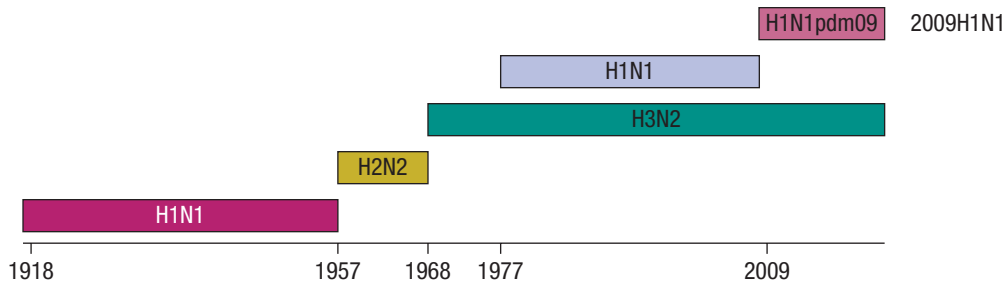
Fig. 33.2 Timeline of circulating subtypes of influenza A virus from 1918 onwards. In 1977, H1N1 was re-introduced and has since co-circulated with H3N2. In 2009, a new H1N1 lineage (pdm09) was introduced, which has replaced the former H1N1 subtype.

with no reported sustained human-to-human transmission, and mostly associated with exposure to live bird markets. Interestingly, human cases have been confined to parts of mainland China, and avian infection is limited to domestic poultry with little spillover to migratory birds and wild waterfowl. The case fatality of H7N9 is lower than H5N1, and associations with age and comorbidities are reported.[9–12]

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 for either. However, the continuous evolution and reassortment in these viruses (e.g., H5N8 viruses have spread globally within a few years among birds, without human cases, and H5N6 has become dominant among birds in parts of Asia and infected 19 humans in China, 6 of whom died) remains a cause for concern and warrants continuous monitoring and surveillance of these viruses in domestic poultry and wild birds.[6]

Paramyxoviridae: Respiratory Syncytial Virus, Parainfluenza Virus 1–4, Human Metapneumovirus

These six human viruses are the most important causes of LRTIs in children worldwide. RSV is the single most important cause of bronchiolitis and the leading cause of RTIs requiring hospitalization. Human metapneumovirus (hMPV) causes similar disease but less frequently, whereas the parainfluenza viruses are associated with bronchiolitis and croup. A recent study estimated that RSV caused 3.2 million hospitalizations and 59,600 deaths among children under 5, and 118,200 deaths among all age groups, annually.[13]

Infections 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 is incomplete, although reinfections tend to be milder. Severe disease is common from RSV and hMPV in the first year of life. Reinfection with RSV or parainfluenza viruses is also a common cause of pneumonia in elderly and immuno-compromised patients.

Other paramyxoviridae such as rubeola virus (measles) or the zoonotic Nipah virus are also associated with respiratory disease as part of disseminated infection. These are discussed in separate chapters.

Coronaviruses

The four main human respiratory coronaviruses (229E, OC43, NL63, and HKU1) are associated with relatively mild upper RTIs and may cause 10% to 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 most notable outbreaks in Hong Kong and Toronto, Canada. Twenty-one percent of affected cases were health care workers.

The culprit, SARS coronavirus, is thought to have jumped to humans in live animal markets in Guangdong. Civet cats, considered a delicacy in parts of Asia, in these markets were found to harbor the virus. Wild civet cats, however, do not carry these viruses, and instead 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 then.

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 include the fact that SARS is most infectious in a later stage of infection, allowing for timely containment, and an extraordinary worldwide effort to control spread.[14,15]

A decade later, another novel coronavirus was found to be associated with acute severe pneumonia in countries in the Middle East. The virus, called *Middle East respiratory syndrome* (MERS) coronavirus, has since caused >2100 infections, 750 of which were fatal, in 27 countries. Most cases originated from countries in the Arabian peninsula with rare travel-related spillovers, including one that caused a large health care facility–related outbreak in South Korea in 2015. More mild and asymptomatic cases are observed with MERS, and mortality is strongly associated with age and co-morbidities. The natural reservoir of MERS coronavirus is dromedary camels, and in Saudi Arabia half of cases are classified as primary, often associated with collection, preparation, and ingestion of milk or meat. The other half results from human-to-human transmission, often associated with health care facilities. Control of MERS coronavirus is difficult because of the stable natural reservoir and the presence of asymptomatic human spreaders. Vaccination of dromedary camels was proposed as an efficient intervention, but unfortunately neutralizing antibodies do not appear to protect against infection or viral shedding.[6,16]

Picornaviruses: Enteroviruses and Parechoviruses

Picornaviruses are the most common cause of infectious illness in humans. The more than 100 serotypes of rhinovirus species A–C (now classified as enteroviruses) are the most important causative agent of the common cold. Infections are usually mild and confined to the upper respiratory tract but may be associated with exacerbations of asthma and chronic bronchitis.

The more than 100 serotypes of enterovirus species A–D (Coxsackie A and B viruses, echoviruses, and enteroviruses) are mainly transmitted by the oral–fecal route and to a much lesser extent by respiratory droplets. Enteroviruses are a major cause of aseptic meningitis in children and adults but are also associated with the common cold, herpangina, and acute hemorrhagic conjunctivitis. Enterovirus D68 behaves more like a rhinovirus, as it replicates in the respiratory rather than the gastrointestinal tract and has caused a worldwide outbreak of relatively mild RTI in 2012–2014, but with epidemiologic links to acute flaccid paralysis.

Similarly, parechoviruses are another common cause of aseptic meningitis but are also implicated as frequent causes of (mild) respiratory illness.

Adenoviruses

Adenoviruses are a frequent cause of epidemic infective conjunctivitis in LMICs and of RTIs in children and young adults worldwide. Outbreaks of adenoviral respiratory infections can occur in closed communities such as daycare centers, boarding schools, and among military recruits. Most adenoviral infections remain subclinical. Two adenovirus serotypes are associated with gastroenteritis and diarrhea (serotypes 40 and 41).

EPIDEMIOLOGY

With the exceptions noted earlier, most respiratory viruses are spread from person to person by the respiratory route, to a varying extent by large droplets, small-particle aerosols, and fomites with hand contamination and subsequent self-inoculation. Patients are most infectious early in the disease or even before. Secondary attack rates may be especially high in semi-closed populations, like 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 lower temperatures, humidity, or rainfall.

CLINICAL SYNDROMES AND PATHOGENESIS

Acute RTIs 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 2 to 4 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 earlier.

Particularly in LMICs, 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 RTIs 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.

Common Cold

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

Pharyngitis

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

Acute Laryngotracheobronchitis (Croup)

Croup affects children under 3; 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 and are characterized by tracheal tenderness, substernal discomfort on inhalation, and non-productive cough.

Bronchiolitis

Bronchiolitis 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 increased mucus secretion results in the formation of dense plugs of debris that cause impediment of expiratory airflow. Children may experience repeated episodes of wheezing after recovery. Associations with development of asthma and a causative role of the immune system in pathogenesis have been suggested.

Viral Pneumonia

Development of primary viral pneumonia 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.

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 recurrent or protracted fever and respiratory symptoms after initial recovery. *S. pneumoniae* and *Staphylococcus aureus* are common causes.

DIAGNOSIS

Clinical history and examination may give important clues in establishing the specific viral diagnosis, but syndromes overlap and are non-specific. Etiologic diagnosis can only reliably be made by detection of virus, antigens, or nucleic acids in respiratory or other specimens, or retrospectively by demonstrating an immune response in paired serum samples.

Rapid antigen tests exist for RSV and influenza virus, but these are not very sensitive (up to 70%). Although viral culture is still considered the gold standard, it is complicated, cumbersome, slow, and lacks sensitivity; also it is not commonly used for clinical diagnostics anymore. Instead, molecular methods to detect pathogen nucleic acids are rapid and sensitive and, when used in multiplex format, can detect most common respiratory viruses. They are often still expensive and require even more expensive equipment, laboratory infrastructure, and well-trained staff to be performed adequately, thus limiting their application in LMICs, but simpler and more portable formats of molecular diagnostics are being developed.

The identification of one viral agent does not rule out double or mixed bacterial-viral infection. Recently several novel viruses have been identified in the human respiratory tract (Bocavirus, WU and KI polyomaviruses, and several others). The significance of these viruses as pathogens has yet to be established. With next-generation sequencing becoming more accessible for clinical diagnostics, including in LMICs, it is expected that many more such viruses will be discovered.

Another promising development is the use of rapid tests for biomarkers of bacterial or viral infection (C-reactive protein, procalcitonin, tumor necrosis factor-related apoptosis-inducing ligand [TRAIL], interferon gamma-inducible protein 10 [IP-10], Myxovirus resistance A [MxA]) to rule out the more severe bacterial etiology and prevent inappropriate antibiotic usage.

PREVENTION AND TREATMENT

Yearly vaccines against influenza virus are produced twice a year for the Northern and Southern Hemispheres containing the predominant lineages of H3N2, H1N1, and B viruses. The use in LMICs is limited due to the high cost and the need for annual revaccination. A live oral Adenovirus serotype 4 and 7 vaccine is used for military recruits in the USA, but is not in use for the general population or outside of the USA.

Vaccines for the other respiratory viruses are currently not available. Attempts at production of 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 anti-viral ribavirin inhibit replication of several respiratory viruses, including influenza virus and RSV, but is expensive and should not be used routinely. 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 its side effects outweighed the benefits for use in uncomplicated infections.

The adamantanes (amantadine and rimantadine) were options for prevention in outbreaks within closed communities of high-risk individuals and, less convincingly, for treatment of influenza A virus infections. However, these therapies have become obsolete, as most human and avian viruses are resistant.

Neuraminidase inhibitors such as oseltamivir and zanamivir, which inhibit influenza virus neuraminidase, are effective for treatment and prophylaxis of influenza. For uncomplicated influenza, treatment is generally not required, but if at all, neuraminidase inhibitors need to be given within 48 hours of onset for any clinical benefit. For severe influenza, influenza in the immunocompromised, and avian influenza, benefit can still be found when administered after 48 hours, and treatment should not be withheld in these cases.

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 is a last resort for maintaining oxygen saturation during severe viral pneumonia.[17,18]

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 sinusitis, otitis media, or pneumonia, over-the-counter availability of antibiotics, self-medication, or medication administration 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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