Respiratory Viral Pathogens[☆]

Philipp P Nelson, Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University Marburg, Marburg, Germany; University Hospital Giessen and Marburg GmbH, Universities of Giessen and Marburg Lung Center (UGMLC), Marburg, Germany

Nikolaos G Papadopoulos, Department of Allergy, 2nd Pediatric Clinic, University of Athens "P&A Kyriakou" Children's Hospital, Athens, Greece; Department of Allergy, University of Athens "P&A Kyriakou" Children's Hospital, Athens, Greece; Division of Infection, Immunity & Respiratory Medicine, Royal Manchester Children's Hospital, University of Manchester, Manchester, United Kingdom

Chrysanthi Skevaki, Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University Marburg, Marburg, Germany; University Hospital Giessen and Marburg GmbH, Universities of Giessen and Marburg Lung Center (UGMLC), Marburg, Germany

Structure and Taxonomy

Picornaviridae

The family of *Picornaviridae* comprises several viruses associated with respiratory tract infections. Members of this family form non-enveloped, icosahedral virions with approximately 30 nm in diameter and a single linear, positive-sense RNA genome of 7–10 kb. It encodes for a polyprotein containing the four capsid proteins VP1-4 and the seven non-structural proteins 2A-C and 3A-D in the precursor proteins P1 and P2, respectively (Zell et al., 2017). VP1, 2, and 3 are highly variable surface proteins which interact with antiviral antibodies. VP4 is confined to the interior of the capsid and is closely associated with the viral RNA (Fig. 1).

Rhinoviruses (RVs) belong to the genus *Enterovirus* and probably represent the most abundant human pathogenic microorganisms universally (Mäkelä et al., 1998). Genetically, they are classified into the species RV-A, RV-B, and RV-C and further divided into distinct types by sequence variances of VP1. These types have been formerly called serotypes and were based on their antigenic properties (McIntyre et al., 2013). So far, around 80, 30, and 55 types have been described for RV-A, RV-B, and RV-C, respectively (see website of the picornavirus study group). Most RV-A and all RV-B use intercellular adhesion molecule (ICAM)-1 as cell entry receptor (major group), while the remaining RV-A bind low density lipoprotein receptor (LDL-R, minor group). RV-C attaches to cadherin-related family member 3 (CDHR3) (Royston and Tapparel, 2016).

Coxsackie viruses (CV), enteroviruses (EV) and echoviruses (E) all belong to the species *Enterovirus A-D*, but only a few types are associated with respiratory illnesses. Commonly, these are CV-A21, EV-C104, EV-C105, EV-C109, EV-C117, and EV-C118 of the species EV-C, as well as EV-D68 of the species EV-D. CV-A21 and EV-D68 are also associated with neurological symptoms like flaccid paralysis similar to the related polio virus. Among others, EV-A71 (EV-A) and E1-7 (EV-B) are occasionally associated with respiratory diseases. EV-A71 is also a frequent cause of hand-foot-mouth disease (Royston and Tapparel, 2016).

Human parechoviruses (HPeVs) belong to the species *Parechovirus A* in the genus *Parechovirus*. Based on VP1, 19 types with different pathogenicity have been defined (see website of the picornavirus study group). While HPeV1 and 2 are associated with mild gastrointestinal and respiratory symptoms, HPeV3 may lead to sepsis-like illnesses mainly in neonates and infants (Dunn, 2016).

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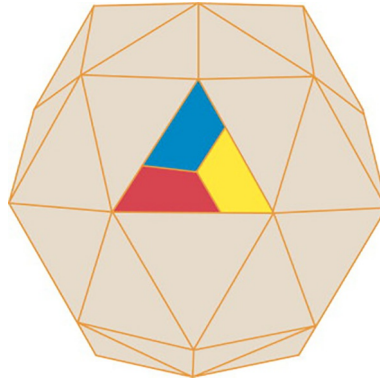
Fig. 1 *Rhinovirus* (RV). The rhinovirus capsid is arranged in an icosahedron composed of 60 copies of each of the three subunits VP1-3 (shown in red, blue, and yellow). Reproduced with permission from Papadopoulos NG and Skevaki CL (2006) Viruses of the lung. In: *Encyclopedia of Respiratory Medicine*, 483–488, https://doi.org/10.1016/B0-12-370879-6/00494-4.

Orthomyxoviridae

Orthomyxoviridae's major representatives are the influenza viruses, which are grouped into four genera with one member per genus: influenza A virus (IAV, *Alphainfluenzavirus*), influenza B virus (IBV, *Betainflunenzavirus*), influenza C virus (ICV, *Gammainfluenzavirus*), and the recently discovered influenza D virus (IDV, *Deltainflunezavirus*). While IAV has a wide host range with water fowl as main reservoir, IBV mainly infects humans. ICV and IDV have also zoonotic potential but cause mostly mild respiratory diseases (Asha and Kumar, 2019). *Orthomyxoviridae* form enveloped, spherical or pleomorphic virions with 80–120 nm in diameter. Their linear, negative-sense RNA genome has a total length of 10–15 kb and is divided into eight (IAV, IBV) and seven (ICV, IDV) segments, respectively. It encodes for up to 12 proteins, among others, in IAV and IBV, hemagglutinin (HA) and neuraminidase (NA) for attachment, cell entry, and release of new particles. The NA and HA proteins are regularly subjected to small changes, which are capable of producing viral strains causing annual epidemics. This phenomenon is called "antigenic drift," while "antigenic shift" is the process by which a sudden major change in the HA or NA proteins of IAV occurs due to genetic reassortment (King, 2011). Instead of HA and NA, which bind and cleave sialic acid (*N*-acetylneuraminic acid), ICV and IDV express one combined protein, the hemagglutinin-esterase-fution glycoprotein (HEF). This protein requires an acetylated derivative of *N*-acetylneuraminic acid for attachment to the host cells (Su et al., 2017) (Fig. 2).

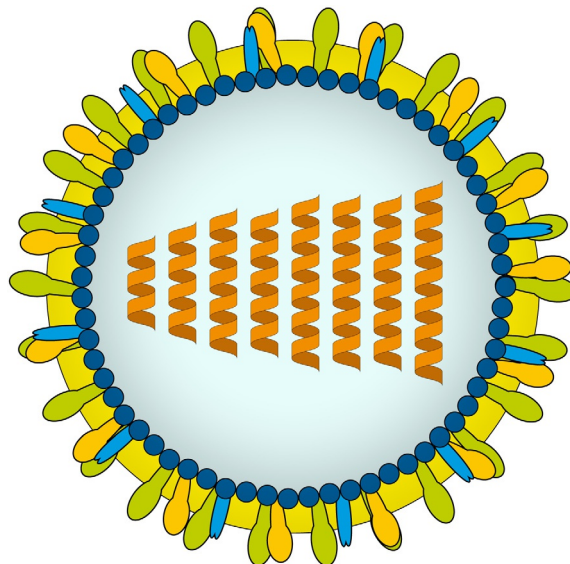**Fig. 2** *Influenza virus.* Schematic representation of an influenza A virus (IAV). Hemagglutinin spikes (green) radiate all over the surface and are interspersed by neuraminidase (yellow) and matrix protein M2 (light blue). The latter are embedded in the envelope's lipid bilayer(light yellow), which in turn surrounds a layer of matrix protein M1 (dark blue). The segmented RNA (orange) of the virus is located in the interior.

Paramyxoviridae

Human parainfluenza viruses (HPIVs) are respiratory viruses in the family of *Paramyxoviridae*. They have enveloped, pleomorphic but mostly spherical virions with a diameter of 300–500 nm. The single, linear, negative-sense RNA genome consists of 14.5–20 kb in a helical nucleocapsid. For efficient replication, the genome length is confined to multiples of 6 nucleotides. Among others, it encodes for the glycosylated fusion (F) protein and the glycosylated receptor-binding protein (RBP), also called haemagglutinin-neuraminidase (HN) protein, which binds to neuraminic acid on the cell surface.

Four types of HPIVs are known: HPIV-1 and 3 belong to the genus *Respirovirus* in the subfamily of *Orthoparamyxovirinae*, HPIV-2 and 4, like mumps virus, to the genus *Orthorubulavirus* in the subfamily of *Rubulavirinae* (Rima et al., 2019).

Pneumoviridae

Viruses of the family of *Pneumoviridae* form enveloped, spherical or filamentous virions with 100–200 nm in diameter, which contain a single, linear, negative-sense RNA genome. This genome is bound in a complex with the nucleocapsid (N) protein, the polymerase (L), and a necessary co-factor (P). The glycosylated fusion (F) and attachment (G) proteins in the envelope mediate cell entry. In contrast to paramyxoviruses, almost all pneumoviruses lack a hemagglutinin and neuraminidase (Rima et al., 2017).

Human respiratory syncytial virus (HRSV or RSV) belongs to the genus *Orthopneumovirus*. The genome of ~15 kb contains 10 genes for 11 proteins, two of them being non-structural proteins (G protein, two groups, RSV-A and RSV-B, are distinguished (Pangesti et al., 2018).

Another pneumovirus is human metapneumovirus (HMPV) in the genus *Metapneumovirus*. It forms paramyxovirus-like pleomorphic to spherical particles of 150–600 nm diameter. The genome of HMPV comprises roughly 13 kb and encodes for 9 proteins (Shafagati and Williams, 2018).

Coronaviridae

Until the beginning of the 21st century, only two human coronaviruses (HCoV-229E and OC43) were known. Since then, many other members of the family of *Coronaviridae* have been indentified, most of them infecting animals and only four others infecting humans: HCoV-NL63 and HKU1 cause respiratory diseases worldwide, severe acute respiratory syndrome (SARS) coronavirus was discovered in an outbreak in 2003–2004, and Middle East respiratory sondrome (MERS) coronavirus, so far constricted to the Arabian Peninsula.

Coronaviruses form enveloped, spherical virions with a diameter of 120–160 nm. The size of the single, linear positive-sense RNA genome ranges between 26 and 32 kb, which represents the largest genome of known RNA viruses. The trimeric glycosylated spike (S) protein forms characteristic 15–20 nm long protrusions, which mediate receptor binding and membrane fusion. Common to all coronaviruses are also the membrane (M) and envelope (E) glycoproteins and the nucleocapsid (N) protein. Depending on the species, other proteins are included, e.g., a hemagglutinin-esterase (HE) for reversible attachment to *O*-acetylated sialic acid in HCoV-OC43 and HKU1. During replication, two polyproteins are produced from the replicase gene and then cleaved into several small products; among them nsp1, which is used for genus demarcation (King, 2011). High estimated mutation rates and possible genetic recombinations during replication increase the probability of the emergence of new (zoonotic) coronaviruses (Su et al., 2016) (Fig. 3).

HCoV-229E (subgenus *Duvinacovirus*) and HCoV-NL63 (subgenus *Setracovirus*) belong to the genus *Alphacoronavirus*. The four other coronaviruses belong to the genus *Betacoronavirus*. HCoV-OC43 and HCoV-HKU1 are subspecies of the species *Betacoronavirus 1* in the subgenus *Embecovirus*. MERS-CoV is a member of the subgenus *Merbecovirus* and SARS-CoV of the subgenus *Sarbecovirus* (Walker et al., 2019).

The cell entry receptor differs between those viruses as well. HCoV-229E binds human aminopeptidase N (APN, CD13) while HCoV-NL63 and SARS-CoV use angiotensin-converting enzyme (ACE) 2 as their receptor. According to their HE protein, HCoV-OC43 and HKU1 use 9-*O*-acetylated sialic acids attached to cell surface proteins. MERS-CoV requires dipeptidyl peptidase 4 (DPP4, CD26) for cell entry (Hulswit et al., 2019; Raj et al., 2013).

Adenoviridae

Human adenoviruses (HAdV) belong to the genus *Mastadenovirus* and are further classified into 6 species (A-G) with more than 100 types identified so far (Lion, 2019). The symptoms of an infection vary between different types and range from respiratory disease to diarrhea or conjunctivitis.

Adenoviruses are non-enveloped, double-stranded DNA viruses with a genome of 26–48 kb in icosahedral virions ranging from 70 to 90 nm in diameter (King, 2011). Fiber-like protrusions extend from each of the 12 penton base capsomers at the corners of the icosahedron. The knobs at the ends of these fibers confer attachment to the host cells, among others to coxsackie and adenovirus receptor (CAR) or membrane cofactor protein (MCP, CD46). While most HAdVs only use one of the two receptors, group D viruses use both receptors simultaneously (Khanal et al., 2018). During replication ~40 polypeptides are produced through alternative splicing (Fig. 4).
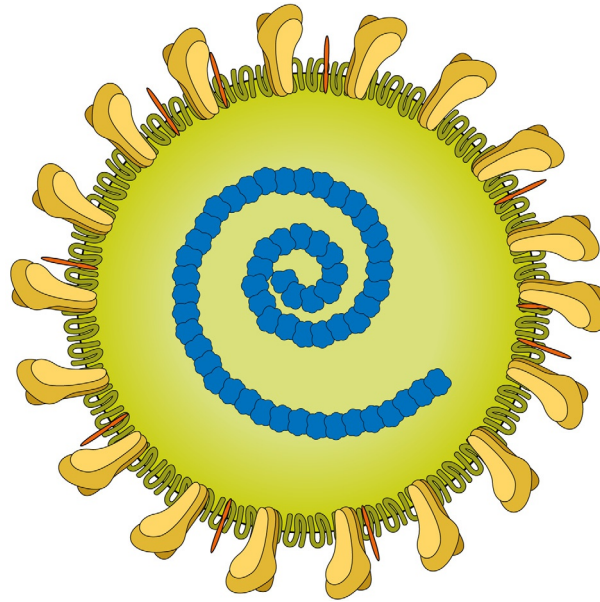
Fig. 3 *Coronavirus.* The membrane of coronaviruses comprises characteristic club-like spike (S) proteins (yellow). The membrane (M) protein (green) is the major constituent, while the envelope (E) protein (red) is less frequent. The linear RNA-genome forms a helical complex with the nucleocapsid (N) protein (blue).
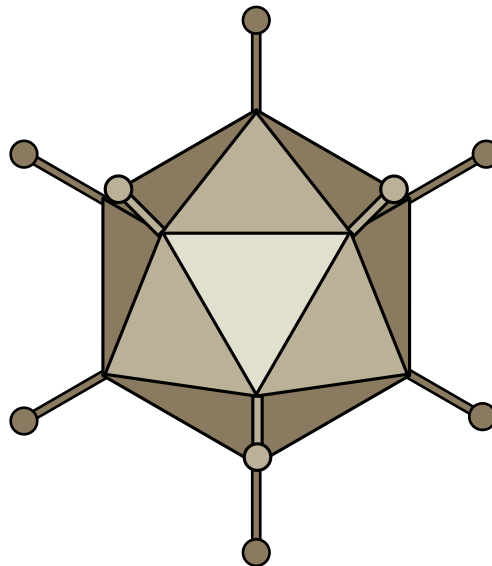

Fig. 4 *Adenovirus.* Adenoviruses are nonenveloped DNA viruses surrounded by an icosahedral capsid from which stalk-like structures, the fibers, protrude.

Polyomaviridae

Although most polyomaviruses (PyVs) have been associated with different types of tumors, two recently discovered polyomaviruses of the genus *Betapolyomavirus*, WUPyV and KIPyV, have been found in respiratory samples worldwide, most frequently in samples from immunocompromised patients. While both alpha- and betapolyomaviruses may infect humans, gamma- and deltapolyoma-viruses do not (Babakir-Mina et al., 2013).

PyVs are non-enveloped, icosahedral viruses of 40–45 nm diameter and contain a single, circular double-stranded DNA genome of ∼5 kb. Inside the virion, the genome is packed with histone proteins H2A, H2B, H3, and H4. The capsid consists of 72 pentameric capsomers of the major capsid protein VP1 and the two minor capsid proteins VP2 and VP3. Typically, the two regulatory proteins large and small tumor antigen (LTAg and STAg, respectively), which are expressed early during infection, are used for phylogenetic analyses (Moens et al., 2017). Even though detected frequently, a clear association between WUPyV and KIPyV on one hand and respiratory disease on the other hand is still missing (Babakir-Mina et al., 2013).

Parvoviridae

Parvoviridae are non-enveloped, icosahedral viruses of around 25 nm diameter. The capsid encloses a single, linear, mostly negative-sense DNA-genome with approximately 5.5 kb. The genome encodes for three capsid proteins (VP1-3) and five non-structural proteins (NS1–4, NP1). Human bocavirus 1 (HBoV1), a member of the species *Primate bocaparvovirus 1*, in the genus *Bocaparvovirus* and the subfamily of *Parvovirinae*, is strongly associated with upper and lower respiratory tract infections in young children. The related viruses, HBoV2-4, are only found in stool samples. By exploiting the cellular DNA repair machinery, HBoV1 is independent from the cell cycle for genome replication (Qiu et al., 2017).

Transmission and Mode of Infection

Generally, respiratory viruses are transmitted between humans by the following routes: direct or indirect contact to infected persons, via droplets, or by aerosols. The main route for each virus differs and is still in discussion (Kutter et al., 2018). In case of zoonotic MERS-CoV infection, the consumption of uncooked meat or milk from or direct contact to infected animals are other suspected routes (Song et al., 2019). Control of the transmission of respiratory infections may be partly achieved through adequate hygiene practices and avoidance of congregation and stress.

Upon entering a susceptible host through eyes, nose, or mouth, respiratory viruses replicate in nasopharyngeal epithelial cells or in the epithelium of the lower respiratory tract. In more severe cases, a subsequent systemic spreading of the virus is possible. The site of the deposition of inhaled particles also depends on their size. While inhalation of aerosols with influenza virus may lead to infection of the lower respiratory tract, larger droplets are retained in the upper respiratory tract (Paules and Subbarao, 2017).

Between respiratory viruses, patterns of infection differ, too. For example, epithelial infection by RVs has a "patchy" distribution and is not overtly cytotoxic, in contrast to many other respiratory viruses, including influenza viruses, paramyxoviruses, and adenoviruses, which cause extensive inflammation and epithelial shedding (Royston and Tapparel, 2016; Pawełczyk and Kowalski, 2017; Shim et al., 2017).

Several pathogen recognition receptors (PRRs) contribute to the detection of viral structures within the infected cell, among them specific toll-like receptors (TLRs), which bind viral nucleic acids and stimulate the production of type I interferons (Pichlmair and Sousa, 2007). One way of IAV to suppress interferon expression and finally cell death is the production of non-structural protein 1 (NS1) within a few hours after infection. NS1 binds viral RNA and prevents recognition by PRRs and inhibits expression of interferon-induced genes (Shim et al., 2017).

Respiratory virus infection causes an increase in both vascular permeability mediated by vasoactive amines and glandular secretion under the influence of cholinergic reflexes and neuropeptides. Several cytokines and chemokines have also been implicated in virus-induced inflammation. Inflammatory cells further aggravate events by release of additional mediators.

Humoral immunity is also activated in response to viral infections with production of serotype-specific antibodies. The nature of the response is associated with age, previous infection, and vaccination status of the host. Recovery from respiratory viral illness is usually achieved prior to the detection of specific antibodies indicating that cellular and/or non-specific immune responses are primarily responsible for viral eradication. Nevertheless, antibodies are able to provide protection from secondary infections. However, different aspects limit the protective effect of neutralizing antibodies against specific viruses: (a) the effect may not be long-lasting (e.g., for HMPV), (b) high mutation rates lead to the occurrence of escape-mutants (e.g., in influenza viruses), (c) many different serotypes of one virus are circulating and antibodies are lacking cross-reactivity (e.g., against other RVs).

Respiratory viruses not only induce a local inflammatory reaction at the level of infected epithelial cells but may also act at a distance through neuronal pathways. All parasympathetic, sympathetic, and nonadrenergic noncholinergic nervous supply of the respiratory tree may be affected by viral infections, suggesting an important neuroimmune interaction, which may contribute to the virus-mediated reactive airway disease (Fig. 5).
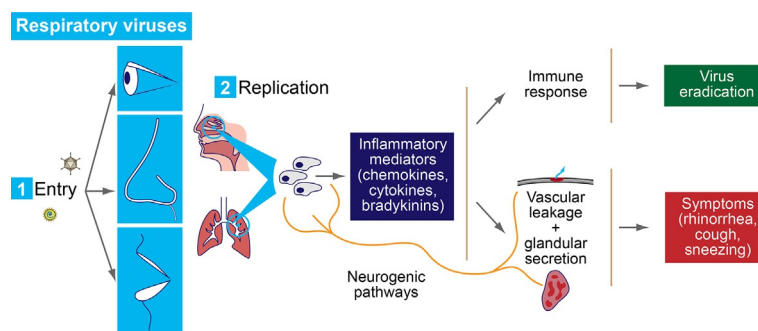
Fig. 5 Pathogenesis of respiratory viral infections. Respiratory viruses enter the human body mainly through the nose. Thereafter, they replicate in nasopharyngeal epithelial cells, but also in the lower respiratory tract. Immune mediators such as cytokines, chemokines, and bradykinins will both elicit an "immune" response leading to effective virus eradication and contribute to the development of associated symptomatology, through vascular leakage and increased glandular secretions. Neurogenic pathways are also involved in the development of clinical manifestations. Reproduced with permission from Papadopoulos NG and Skevaki CL (2006) Viruses of the lung. In: *Encyclopedia of Respiratory Medicine*, 483–488, https://doi.org/10.1016/B0-12-370879-6/00494-4.

Clinical Manifestations

Respiratory viruses are related to various distinct as well as non-specific clinical presentations. While acute infections are usually self-limited, severe forms may occur. There is considerable overlap between viruses and clinical presentations. Although differences exist, all agents may cause any of several clinical syndromes (Table 1). Among these, the common cold is by far the commonest with an enormous socioeconomic impact. Clinical presentation ranges from asymptomatic to upper respiratory tract (URT) symptoms such as nasal congestion, rhinorrhea, and nasopharyngeal irritation, lower respiratory tract symptoms such as cough, to systemic symptoms including general malaise, fever, headache, and sleep impairment depending on the viral culprit and host. The incubation period is 24–48 h and symptoms usually last for 5–7 days with a peak of viral replication before or together with the first clinical symptoms. The common cold is a rather benign clinical entity, which may however be complicated by secondary bacterial infections, otitis media, sinusitis, pneumonia, and asthma exacerbations; severe courses of disease and death may occur in young children and immunocompromised patients.

Viral URT infections often result in impairment of the function of the eustachian tube, which predisposes to the development of acute otitis media. The latter is one of the commonest infections among children and is very often attributed to viral etiology. Respiratory viruses may also predispose to nasopharyngeal bacterial colonization and alteration of the host's immune response. Finally, viruses may be responsible for antibiotic treatment failure in cases of concurrent bacterial and viral infections. Likewise, respiratory viruses have been implicated in the development of sinusitis, either directly as an extension of URT infection or as a result of secondary bacterial infection.

Laryngitis and laryngotracheobronchitis-croup have more frequently been associated with the parainfluenza virus group. Pneumonia in infants and young children is most commonly attributed to viruses. Disease burden is also significant among the elderly and the immunocompromised. RVs and RSVs are the agents most frequently isolated in viral pneumonias, although age, season, year, and other variations can be considerable. The presence of adenovirus is a risk factor for severe disease in infants. Influenza occurs in yearly winter epidemics and pandemics every 10–40 years resulting in enormous morbidity and mortality, especially among the very young, the elderly, and the immunocompromised. Infections with IBV or ICV are mostly milder than those with IAV (Paules and Subbarao, 2017). The zoonotic potential of IDV is yet unknown. So far, this virus could not be found in patients with respiratory symptoms although a high seroprevalence in people working with cattle has been observed (Su et al., 2017).

RSV is the major pathogen implicated in acute bronchiolitis in infants up to 1 year and is responsible for a great number of hospitalizations and deaths in this age group. In the second year of life, RV and HBoV become more frequent pathogens (Jartti et al., 2019). Host immune response skewed towards type 2 cytokine production seems to play a central role in the pathogenesis of the disease. Bronchiolitis is further associated with recurrent wheezing.

The great majority of acute asthma exacerbations in children and a considerable proportion in adults is preceded by a viral URT infection. Such exacerbations may often result in hospitalization. The most frequently isolated offending agent is RV, a fact that reflects the preponderance of the virus among common cold cases. Finally, exacerbations of chronic obstructive pulmonary disease may also have a viral etiology, most commonly due to RVs.

WUPyV and KIPyV have so far only been associated with increased sputum production and wheezing; a clear role as causative agent has not been shown (Cook, 2016).

Diagnosis, Vaccination, and Treatment

The diagnosis of respiratory viral infections relies upon clinical criteria and is further supported by laboratory techniques such as direct viral, nucleic acid or antigen detection, culture, and serology. Direct detection is based on the identification of whole virus or inclusion bodies with electron or light microscopy, respectively. Viral antigens may also be detected by the use of immunofluorescence and enzyme immunoassays but an adequate viral load is required. Viral cultures usually demonstrate the biological effects of an agent, such as the cytopathic effect or hemagglutination, in cultured cells. Culture methods, however, have drawbacks due to

Table 1   Disease syndromes of common respiratory viruses in upper and lower respiratory tract.

	Asthma	Bronchitis	Bronchiolitis	Common cold	Croup	Otitis/sinusitis	Pneumonia
Adenoviruses	*	*	**	*	*	*	**
Coronaviruses	**	*		**	*	*	**
Influenza	**	*	*	*	*	**	**
Parainfluenza	*	**	*	*	***	*	*
Rhinoviruses	***	*	*	***	*	**	*
RSV	*	*	***	*	**	**	**

The number of asterisks (*) is proportional to the relative frequency of the respective clinical presentation induced by each virus.
Papadopoulos NG and Skevaki CL (2006) Viruses of the lung. In: *Encyclopedia of Respiratory Medicine*, 483–488, https://doi.org/10.1016/B0-12-370879-6/00494-4.

their low sensitivity, extensive time length (days to weeks), and sometimes complex culture systems. Determination of specific viral antibodies in a host's blood sample and comparison between acute and convalescent phases of respiratory illness is another diagnostic modality, which is mainly used for epidemiological purposes. Serological tests include immunoassays, complement fixation, and passive agglutination assays as well as hemagglutination inhibition. Nucleic acid amplification tests (NAATs), like real-time polymerase chain reactions (real-time PCRs), are gaining more and more importance due to their high sensitivity and specificity, combined with low turnaround times. Together with antigen-based diagnostic tests, NAATs are used in point-of-care tests (POCTs), which are able to provide results much faster than lab-based tests and directly at the site of sample collection. In the field of genetic epidemiology and virus discovery, next-generation sequencing (NGS) became the method of choice, as no susceptible cell lines are required.

Usually, samples from the respiratory tract are taken for diagnostic purposes. These include swabs from nose or throat, nasopharyngeal aspirates, nasal washes, sputum, bronchial aspirates, and bronchoalveolar lavages. Upon infection with HPeVs or HAdVs systemic infections or other complications, e.g., gastrointestinal or neurological symptoms, may occur. In this case, additional specimens, ranging from stool, blood, urine, and cerebrospinal fluid, are taken (Olijve et al., 2018; Khanal et al., 2018).

The development of effective vaccines is hampered by the large number of viral serotypes. Currently, licensed vaccines are available only against influenza A and B viruses, as well as an oral live vaccine against HAdVs for U.S. military personell (Paules and Subbarao, 2017; Crenshaw et al., 2019). Following the regular recommendations of the World Health Organization (WHO), the composition of the seasonal influenza vaccines is updated every year to include the most important strains and to confer the best protection. However, as the actual frequency of the circulating influenza strains in each season may differ from this recommendation, the efficacy of these vaccines vary from year to year. Mostly, tri- and quadrivalent influenza vaccines, inactivated, live-attenuated, or recombinant vaccines are used. To overcome the need for a yearly vaccination, the search for alternative approaches and universal influenza vaccines is ongoing. Vaccine candidates against other respiratory viruses, like HRSVs, HPIVs, HMPV, and MERS-CoV are in development or under clinical investigation.

Over-the-counter remedies for the alleviation and reduction of duration of common cold symptoms include vitamin C, zinc, and echinacea, although these agents are only moderately effective. Nasal decongestants, first generation antihistamines, anticholinergic nasal sprays, oral and intranasal α-adrenergic agonists, inhalation of humidified hot air at 42–44 °C, nonsteroidal anti-inflammatory drugs, and cromones have been proposed for symptomatic relief with moderate results. A combination of specific antivirals with one or more anti-inflammatory drugs may offer the ideal therapeutic approach since it would both inhibit viral replication and block inflammatory events, although cost and compliance are considerable obstacles.

Current Antimicrobial Therapy

Unfortunately, only a limited number of antiviral agents against respiratory viruses is available, due to the frequent mutations resulting in the constant emergence of new and often resistant strains. Nevertheless, many new drugs and experimental approaches are under investigation (Papadopoulos et al., 2017).

The licensed antiviral chemotherapy against influenza viruses can be grouped into four classes, which prevent uncoating (adamantanes like amantadine and rimantadine), inhibit NA (e.g., oral oseltamivir and inhaled zanamivir), prevent membrane fusion (arbidol), and interfere with the viral RNA-dependent RNA polymerase (the broad-spectrum antiviral favipiravir). Adamantanes are only active against IVA, however, today all circulating seasonal strains of IAV are resistant against this antiviral, so the use is not recommended any more. NA inhibitors are available for treatment and prophylactic purposes, but prophylactic applications are more effective as randomized controlled trials showed only marginal effects on the duration of symptoms (Paules and Subbarao, 2017). New experimental antiviral agents target both the virus and the host, e.g., by inducing apoptosis only in infected cells (Shim et al., 2017). Another experimental host-targeted strategy, against infections with HBoV, is repurposing of kinase inhibitors developed for tumor treatments (Qiu et al., 2017).

Palivizumab is a monoclonal antibody against RSV F glycoprotein, which may be administered prophylactically to reduce the risk of severe bronchiolitis and hospitalization in specially vulnerable children, i.e. preterm infants and children with chronic lung or heart diseases (Jartti et al., 2019). The antivirals cidofovir and ribavirin have been used against RSV especially in immunocompromised patients, but little to no beneficial and many adverse effects have been observed. Consequently, their widespread use is not recommended (Khanal et al., 2018).

The clinical usefulness of the capsid binding antivirals pleconaril, vapendavir, and pocapavir against RVs still has to be shown. A high likelihood for drug resistances limits their clinical applicability (Papadopoulos et al., 2017).

A long-known effective compound against a variety of respiratory viruses and the resulting common cold is interferon alpha-2b, administered intranasally, before or shortly after exposure. However, due to its high cost, dosage frequency (six times daily), and side effects (mainly nasal irritation and bleeding) clinical application has been abandoned (Mossad, 1998).

Acknowledgments

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Relevant Websites

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www.ersnet.org—European Respiratory Society (ERS).
eswi.org—European Scientific Working group on Influenza (ESWI).
www.escmid.org/research_projects/study_groups/respiratory_viruses—European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group on Respiratory Viruses (ESGREV).

hadvwg.gmu.edu—Human Adenovirus Working Group.
talk.ictvonline.org—International Committee on Taxonomy of Viruses (ICTV).
www.picornaviridae.com—Picornavirus study group.
www.resvinet.org—Respiratory Syncytial Virus Network (ReSViNET).