Respiratory viral infections – impact on sport and exercise medicine

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ABSTRACT

Respiratory viruses are the most frequent causative agents of disease in humans and thus also in elite athletes. The COVID-19 pandemic has recently emphasized the entire spectrum of respiratory tract infections worldwide. Understanding the basic elements of respiratory viral infections is a fundamental requirement from the perspective of etiological diagnostics, treatment, and prevention strategy planning, as well as resource allocation.

Keywords: respiratory virus, acute respiratory infection, common cold, exercise, sport, athletes

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Abbreviations: ARI – acute respiratory infection; Ct value – cycle threshold value; EBV – Epstein-Barr virus; HEPA filter– high efficiency particular air filter; IOC – International Olympic Committee; NAAT – nucleic acid amplification test; POCT – point of care test; PCR – polymerase chain reaction; RT - reverse transcription

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INTRODUCTION

Respiratory viruses are the most frequent causative agents of disease in humans and the most common reason to seek medical care. Globally, acute respiratory infections (ARIs) represent an enormous social and disease burden with 17 billion cases and an estimated 120 million disability-adjusted life years annually (41, 162). In a 9-month follow-up study with 15112 participants, febrile ARIs led to an overall reduction in exercise equivalent to 15% of the active US population becoming completely immobilized for 1 day (106). The importance of viral respiratory tract infections has been emphasized recently because of the emergence of the coronavirus disease COVID-19 leading for 2020 and 2021 to an estimated half a billion cases and 15–18 million excess deaths (20, 114). Diagnostics for respiratory virus detection has evolved from viral culture tests to the current standard nucleic acid amplification tests (NAATs), to multiplex point-of-care tests (POCT), and now at-home tests (8, 18, 137). The clinical impact of viral diagnostics has been shown in numerous studies (179). The main value of viral testing has been to differentiate between viral and bacterial infections, to reduce unnecessary antibiotic use and to detect influenza and COVID-19 for possible antiviral treatment (96, 144, 147, 181). However, what is not well understood is the relative contribution of the various modes of transmission of different viruses (79, 91, 105, 174).

In this review we provide a clinically relevant overview of the epidemiology, clinical manifestations, transmission, virological diagnosis, and prevention of acute respiratory viral infections. At the end of relevant section, we provide a brief conclusion on the impact of the topic on sport and exercise medicine.

RESPIRATORY VIRUSES

There are ten different respiratory virus groups circulating constantly in the community: rhinoviruses, human coronaviruses (seasonal 229E, OC43, HKU1, NL63, and the emerged SARS-CoV-2), respiratory syncytial viruses, influenza viruses (A, B and C), adenoviruses, enteroviruses, parainfluenza viruses (types 1–4), human metapneumoviruses, human bocaviruses, and Epstein-Barr virus (EBV). They are all recognized as being adapted to efficient person-to-person transmission (12, 18, 58, 117, 165). There are hundreds of sub- and serotypes of these viruses but the clinical significance of more detailed diagnostic recognition of viruses is low. Rhinoviruses and seasonal coronaviruses are the most common viruses constituting 60–80% of detected viruses from patients with acute respiratory illness (1, 13, 118).

Viruses are formed by a single- or double stranded nucleic acid (DNA or RNA) which is surrounded by a protein capsid. RNA viruses include rhinoviruses, coronaviruses, influenza viruses, parainfluenza viruses, respiratory syncytial viruses, metapneumoviruses and enteroviruses. Adenoviruses, bocaviruses and EBV are DNA viruses. Most human respiratory viruses have an outer envelope composed of lipids and proteins. The most common respiratory virus, rhinovirus is small (diameter 30 nm) non-enveloped virus, as well as adenoviruses, bocaviruses and enteroviruses. There are 3 rhinovirus species, A, B and C. The total number of rhinovirus types is 169 (65). The other common respiratory virus, human coronavirus (Figure 1) is enveloped virus with a diameter of 80–120 nm and around 30 kilobases long genomes, the largest among the known RNA viruses (36).

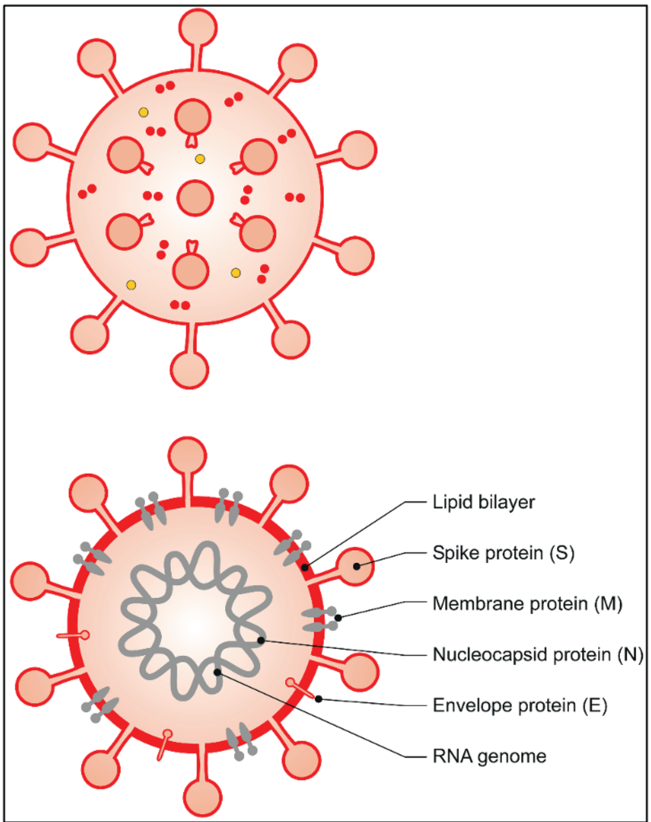

Figure 1. Schematic depiction of the coronavirus structure.

DISEASE BURDEN

In family studies conducted over 50 years ago, the annual frequency of ARI in young adults was 2.3–4.8 episodes (110). In a recent study in the USA (13), 26 households with 105 individuals were followed for one year with weekly symptom diaries and the collection of nasal swabs for viral diagnostics. In 26 of the participants aged between 18–39 years, the mean rate of ARI episodes was 4.6 and a virus was detected in 6.3 episodes per person per year, i.e. approximately 30% of the infections were asymptomatic. Children younger than 5 years of age were virus positive half of the year (50% of the weeks of the follow-up) and young children in the household were considered to be the major risk factor for virus transmission. In an internet-based surveillance 125 participants between 15–34 years of age reported an average of 3.7 ARIs during a 1-year period (3). The annual mean number was recently estimated to be globally 2.25 episodes (71). In young adults (18–49 years of age), a lower incidence of 0.46 was recently reported in a 5-year text message study (158). It is worth noting, that respiratory viruses induce recurrent infections because they do not elicit long-term protective immunity (32, 138).

Impact on sport and exercise medicine. An upper respiratory infection, presenting as a common cold before or during a major competition may ruin an athlete's long-term goal and, in addition, cause marked financial losses in professional sport. Some athletes may be exceptionally prone to respiratory viral infections and suffer prolonged symptoms (22, 56, 159). Genetic susceptibility to respiratory viral infections is, however, not well understood (89, 99). Heavy exercise and psychological stress are traditionally believed to increase the risk of infection, but clinical and virological evidence is lacking (33,45,144).

A recent review and meta-analysis of the International Olympic Committee (IOC) Consensus group reported an annual ARI incidence of 1.7 in athletes (26, 154). The incidence is lower or comparable with that of the normal population (3, 13, 110). The real occurrence of respiratory viral infections in athletes in different disciplines is rarely studied in long-term controlled studies with viral diagnostics (52, 144).

EPIDEMIOLOGY AND SEASONALITY

Respiratory viruses typically display three different patterns of occurrence: endemic, endemic with seasonal peaks, and epidemic (113). Adenoviruses are typically endemic as their prevalence is static, not exhibiting any significant rise or not fall. Many respiratory viruses are epidemic, displaying substantial seasonal variation, i.e. the prevalence occurs at regular up and down intervals (Figure 2). The most common respiratory viruses, rhinoviruses can be detected throughout the year, but distinct peaks occur in early autumn and in late spring. Four seasonal coronaviruses cause outbreaks in the winter months (85, 98). Influenza epidemics have been well known for a long time, the Spanish influenza pandemic of 1918–1919 as "the mother of all pandemics" (163). In temperate climates, influenza epidemics occur yearly with a peak prevalence in winter months in the Northern Hemisphere

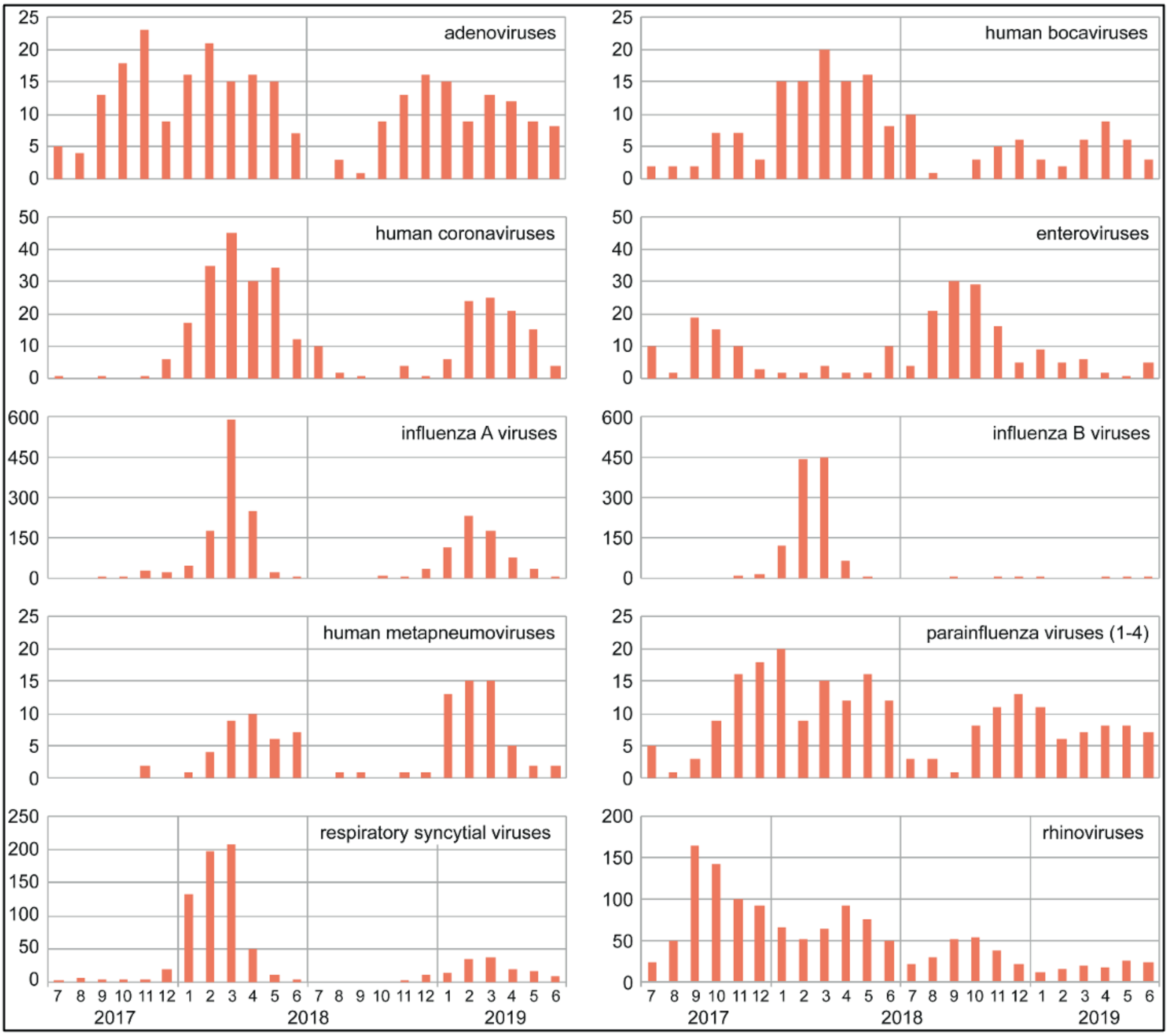

Figure 2. Seasonality of respiratory viruses. Monthly numbers of detections during two respiratory virus seasons (from July 2017 to July 2019) in Turku, Finland. Magnitudes are not comparable between viruses due to differences in the numbers of tests performed. Data from the Turku University Hospital Laboratories, Department of Clinical Microbiology.

and in summer months in the Southern Hemisphere. Globally, annual epidemics of influenza cause 3–5 million cases of severe illnesses and about 500 000 deaths, mostly among the elderly (63). Respiratory syncytial virus, the leading cause of lower respiratory tract infections in children, induces regular severe epidemics. In most countries these infections occur annually during the winter months. Epidemics usually last 3–4 months (123). It must be stressed that during influenza or respiratory syncytial virus epidemics many other respiratory viruses like seasonal coronaviruses also circulate in the community and cause respiratory infections (98, 117). Whether SARS-CoV-2 establishes a seasonal pattern similar to other coronaviruses remains to be seen. Overall, viral lows tend to constantly occur during the summer months. In tropical areas, many respiratory viral infections are endemic, and some occur during the rainy season (39, 58). In the subtropics, e.g. China and Hong Kong, influenza A may occur in two yearly epidemic (183).

The reasons for the seasonality of respiratory viruses are not well understood. Three mechanisms have been proposed: 1. Environmental parameters. At low temperature and low humidity respiratory viruses in aerosols are more stable and transmissible. 2. Human behavior. Indoor activities, crowding, number of close contacts, opening of schools and traveling all increase person-to-person contacts and transmission of viruses. 3. Host defense. Antiviral immunity may have seasonal changes. The dry air in the wintertime impairs the function of cilia in the airway epithelium. Seasonal molecular changes in immunity have also been recorded. Importantly, the innate response to rhinovirus, the most common causative agent of the common cold, is lower at low temperatures (79, 91, 92, 113,121, 174).

The human-environmental interaction affecting the seasonality of respiratory viruses is complex. No single mechanism seems to be a major factor. In some countries like Finland, large respiratory syncytial virus epidemics occur only every other year in 2-year cycles suggesting that environmental factors may be less important (175). Recently, a great number of studies have shown that COVID-19

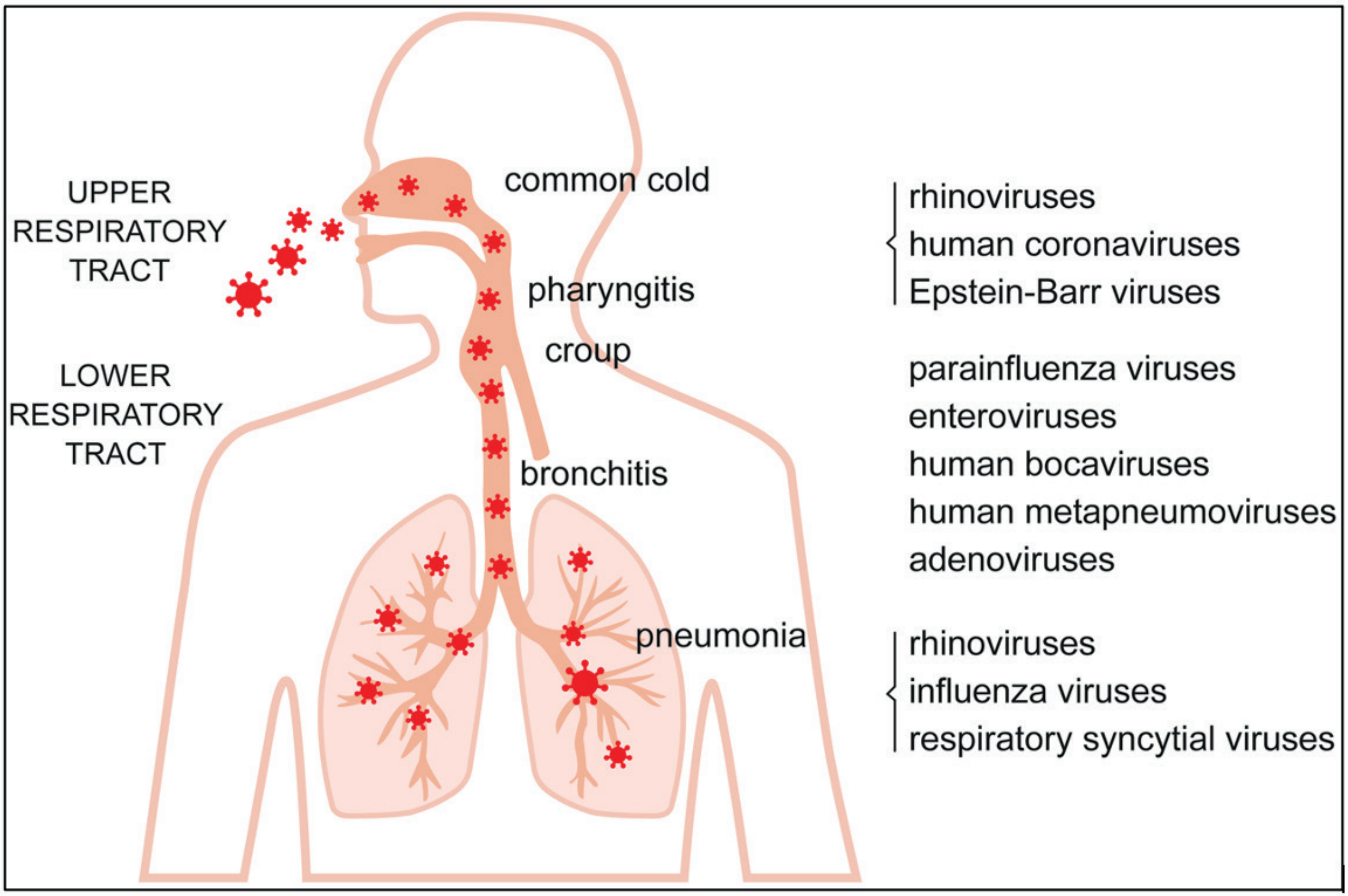

Figure 3. Human respiratory tract and the most common clinical presentations associated with different respiratory virus groups causing respiratory tract infections in humans. Classification of upper and lower respiratory tract infections is nonspecific because all respiratory viruses can cause both upper and lower respiratory tract infections.

prevention procedures, wearing masks, maintaining physical distancing and sanitizing, nearly eliminated the occurrence of other respiratory viral infections, most effectively influenza and respiratory syncytial virus epidemics (48, 124, 140, 182). Likewise, consistent with the reduction in preventive measures, the return of non-SARS-CoV-2 respiratory viruses has been observed (17, 51). These observations clearly support the important role of human behavior in the seasonality of respiratory viral infections. For example, the school calendar predictably drives seasonal variation in the prevalence of the common cold (rhinovirus) (34).

Impact on sport and exercise medicine. It is important to realize that seasonality affects much on athletes' susceptibility to respiratory viral infections. During winter games the athletes have a significantly increased risk for viral ARIs probably due to the marked environmental viral pressure in the community (27, 168, 170). Furthermore, high risk crowded indoor gatherings with poor ventilation are more common during wintertime (57).

CLINICAL MANIFESTATIONS

Symptomatic infections

The symptoms of an ARI arise after an incubation period (the time between being infected with a virus and the onset of symptoms) of 1–5 days for most viruses (90). The common cold ("a cold") is the most common self-limited clinical manifestation of all respiratory viral infections. The clinical features include a sore throat, sneezing, a runny nose, nasal stuffiness, and a cough. Fever is not a common manifestation in adults (55). In addition to the common cold, the clinical presentations of ARI in adults include pharyngitis, tonsillitis, bronchitis, and pneumonia. Classification into upper and lower respiratory tract infections is partly artificial because symptoms like a cough commonly occur in both infections and all respiratory viruses can cause both upper and lower respiratory tract infections (Figure 3) (133, 152). The significant overlap in clinical symptoms that exist with the different viruses causing respiratory illnesses and the viral etiology of these illnesses means that they are unlikely to be reliably distinguished by their clinical features alone (101). Generally, the severity of the symptoms increases rapidly, peaks within 2–3 days and decreases soon after (31, 55, 180). The mean duration of the common cold is 7–10 days and in practice all patients make a full clinical recovery within 21 days after the onset of the symptoms (1, 133, 134, 143). In one study the mean duration of the cough was found to be 11 days (133). Clinically, the illness is usually mild (symptoms do not interfere with daily activities) or moderate (symptoms interfere with daily activities). Severe respiratory viral infections (symptoms prevent daily activities, require medical consultation or hospitalization) are rare and usually only occur in high-risk patients (4). Individuals at increased risk for disease severity include infants, senior citizens (>65 years old), obese individuals, patients with underlying respiratory conditions and those with a suppressed immune function. The duration of infectivity of different viral infections varies but are usually most infectious for 1–3 days and may continue up to 5–10 days after the onset of symptoms (55).

Asymptomatic infections

Many studies have shown that asymptomatic respiratory viral infections are much more common than has been understood earlier (67, 129). In the family study by Byington and associates, 44% of the 783 detected viral episodes were asymptomatic (13). In another family study investigating influenza transmission in families, 11% of the influenza positive individuals were asymptomatic (62). The high prevalence of asymptomatic SARS-CoV-2 positivity (up to 50% of the positive total) (136) and transmission of the virus from asymptomatic individuals have recently been addressed in several different studies (77). Some of the investigators consider respiratory viruses in asymptomatic subjects as innocent bystanders and consider the potential causal role of some viruses detected by PCR questionable (139). However, respiratory RNA viruses (with exception of coxsackieviruses) do not cause chronic asymptomatic infections and most probably meaningless carriage does not occur in healthy humans (171). To what extent an asymptomatic person can transmit the infection and how often asymptomatic infections develop into symptomatic infections is still unclear.

Clinical features of specific respiratory viruses

Although all respiratory viruses may cause upper and lower respiratory tract infections, they can also have typical clinical manifestations (Figure 3). The rhinovirus is the common cold virus causing about 50% of the cases and, in addition to upper respiratory tract infections rhinoviruses are associated with a wide range of clinical presentations. They are the most common cause of acute wheezing in children older than 2 years and acute asthma exacerbation in adults. They can cause pneumonia and induce exacerbation of chronic obstructive pulmonary disease (1, 64, 65, 117, 146).

Seasonal coronaviruses (non-SARS-CoV-2 coronaviruses) are common cold viruses (32, 85, 98). In one study coronaviruses were identified in 22% of young adult ARI patients with a cough and a chill (23). Coronaviruses may also induce severe respiratory infections in adults necessitating hospitalization and intensive care treatment (44, 173). The clinical spectrum of the SARS-CoV-2 infection varies from a mild common cold to severe pneumonia with respiratory failure and a multiple organ dysfunction syndrome. Originally, the major COVID-19 symptoms were fever, a persistent cough, fatigue, and a loss of or a change in taste or smell (46). Currently, with the dominance of the Omicron variant, the symptoms are usually mild including rhinorrhea, a sore throat, fatigue, and a headache; all these symptoms are also symptoms of all the other respiratory viruses (166). Thus, the majority of the non-hospitalized patients have an uneventful recovery. However, in one follow-up study of non-vaccinated patients at 12 months only 23% of patients (32% hospitalized) were completely free of symptoms (150). Fatigue, reduced exercise capacity, sleep difficulties and neuropsychiatric symptoms are the most common persistent symptoms after recovering from COVID-19 (109, 150).

Influenza ("flu") is characterized by the abrupt onset of fever, chills, myalgia, a headache, malaise, a sore throat, and rhinitis. A nonproductive cough may last 4–6 weeks after an acute illness (167). In one study 24% of the cases were asymptomatic or paucisymptomatic (had 1 symptom only) (62). A febrile illness with a cough or sore throat but without laboratory diagnosis of influenza is referred to as an influenza-like illness (106).

Worldwide, respiratory syncytial virus is the single most frequent cause of lower respiratory tract infections (bronchiolitis and pneumonia) in young children (47). In older children and young adults, a respiratory syncytial virus infection is a mild common cold (119). The main symptoms in healthy young adult military recruits were a sore throat (76%), sputum (73%), a cough (72%), tonsillar hypertrophy (68%), and rhinorrhea (56%) (126). In elderly people, respiratory syncytial virus infections are a significant cause of mortality, with over 6000 patients a year in the US alone (53).

The adenovirus induces symptomatic respiratory infection usually in children less than 5 years of age. Adenoviruses are also an important cause of childhood diarrhea. Infections are rare in adults but, interestingly, up to 80% of military recruits may experience an adenovirus infection occurring most commonly in training weeks 3 to 6. The clinical manifestations include fever, conjunctivitis, a sore throat, a cough, and pneumonia. An oral vaccine for adenovirus types 4 and 7 is effective but used only for the military basic training population in the US (97, 145).

Parainfluenza viruses are associated with upper and lower respiratory tract infections. They account for 75% of croup cases. Hoarseness, a barking cough, and inspiratory stridor are the classic signs (6, 141).

EBV seroconversion occurs usually during childhood. Clinically symptomatic infection may occur when primary infection is delayed. EBV is associated with approximately 8% of sore throat cases among adolescents (30). In young adults, EBV infection induces acute infectious mononucleosis with an incidence of 6–8 /1000 (30). The classic triad of symptoms includes fever, tonsillitis, and lymphadenopathy. Splenomegaly, palatal petechiae and fatigue are also common. EBV-induced mononucleosis is diagnosed by serology using a specific IgM test. Fatigue may persist for 4–6 months (14). Splenic rupture is a rare but potential complication. That is why physical activity, especially contact sport, is prohibited within the first 30 days of the illness (161).

Impact on sport and exercise medicine. In 6 etiological studies carried to date the etiology and clinical manifestations of respiratory viral infections in 178 athletes were comparable to those in young adults in the general population. Rhinoviruses, seasonal coronaviruses, influenza viruses, and respiratory syncytial viruses were the most commonly detected viruses (21, 49, 118, 156, 168, 170). The clinical manifestations were in practice only upper respiratory symptoms (the common cold) including a sore throat, a runny nose, and nasal stuffiness. The duration of ARI was 5–7 days, which agrees with the mean duration of 7 days reported by the IOC meta-analysis (153, 154).

As is commonly known, elite athletes often train and compete while suffering from mild upper respiratory symptoms. The effect of a mild viral infection on performance and the health risks of physical exercise during infection

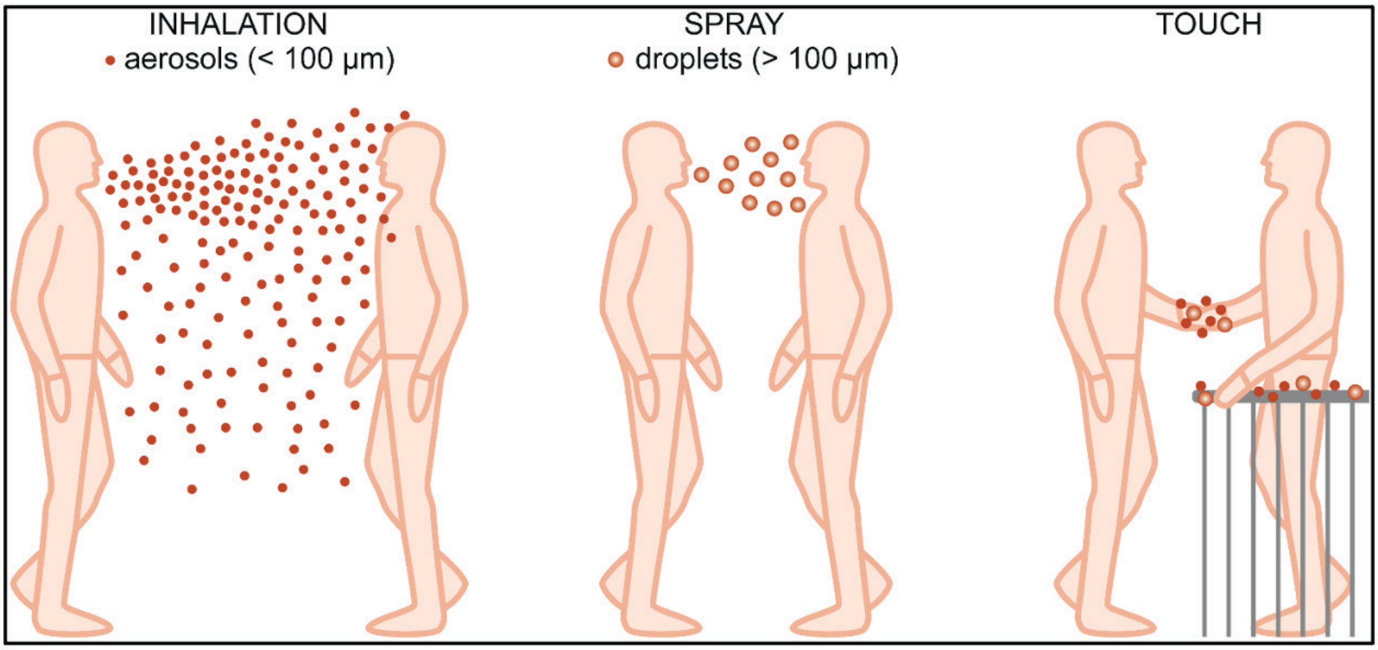

Figure 4. The transmission mechanisms of respiratory viruses: inhalation, spray, and touch.

are poorly understood (75). In one study on international swimmers, mild previous illness had trivial to small effects on competitive performances (135). The risk of myocarditis exists. However, of a total of 7988 athletes who recovered from COVID-19 the rate of myocarditis was 1% (108). In the absence of evidence-based return-to-sport protocols, clinicians rely on self-monitoring and the response to a gradually increased exercise regimen (153). No activity restriction is needed if an athlete has no cardiac symptoms such as chest pain, palpitation, or dyspnea (52, 83). The common-sense approach has not presented significant evidence of any harm to the athletes.

VIRAL-BACTERIAL CO-INFECTIONS

It has been well known for many years that a respiratory viral infection may pave the way for a secondary bacterial infection (acute otitis media, sinusitis, pneumonia) (35, 107, 112). Rhinovirus infection increases the acquisition and transmission of *Streptococcus pneumoniae* (74). We have shown that rhinovirus circulation in the community had an association with invasive pneumococcal disease in children (128). There is also evidence that mixed viral-bacterial infections induce a more severe clinical disease than individual bacterial or viral infections (100, 133, 143). As many as 20% to 60% of young children with respiratory viral infections develop bacterial acute otitis media (142). In young healthy adults, bacterial complications are rare. Bacterial sinusitis develops in only 1–2% of cases (73). In hospitalized patients with COVID-19 bacterial co-infections have been detected in 5–10% of the cases (111). It is of interest that pneumococcal vaccination confers moderate protection against respiratory viruses associated with lower respiratory tract infections in children and adults. Pneumococcal vaccination diminishes pneumococcal carriage which reduces the likelihood of acquiring respiratory viruses (94).

Impact on sport and exercise medicine. Bacterial co-infections of respiratory viral infections in athletes are uncommon and antibiotic treatment of ARI is rarely indicated (168, 169, 170).

TRANSMISSION

Recently, a simplification to 3 major routes of transmission has been proposed (104) (Figure 4):

1. Inhalation. Viral transmission occurs by direct inhalation of airborne particles (aerosols) containing viruses and viruses are deposited at various sites in the respiratory tract, depending on the size of the aerosol (105). Small aerosols are deposited straight onto the alveoli in the lungs. Aerosols are now defined as particles less than 100 µm in diameter. Aerosols are produced during breathing. It is of importance that speaking increases aerosol production by 35-fold, exercise, and heavy breathing by 60-fold, and coughing by 400-fold (79). Virus-laden aerosols can remain infectious in indoor air for hours and can be carried beyond 2 m from the infectious person and everywhere in the room without any safe distance (91, 174).

2. Spray. Particles with more than 100 µm in diameter are called droplets. Virus-laden droplets transmit the infection only when susceptible individuals are within 0.2 m of a talking infectious person. Sneezing and coughing propel the droplets further. Droplets settle down onto the ground within 2 m of the source person within a few seconds. Droplets transmit the infection through direct spray from the infector to the mucosa of the nose, eyes and mouth of the susceptible person (104).

3. Touch. Transmission is introduced by hands. Susceptible individuals shake hands with an infected individual whose hands are contaminated with a virus and then introduce the virus to his mucous membranes. The other possibility is to pick up the virus by hand from highly touched and contaminated surfaces (e.g. door handles, desks, elevator buttons, mobile phones). Respiratory viruses may remain infectious on surfaces from a few hours to several days (81, 82, 177). However, the

spread of respiratory viruses through touch in real-life is poorly documented

Transmission risk factors

Time spent in a crowded and poorly ventilated indoor space is the key determinant in the transmission of respiratory viral infections (105). Timing after the onset of infection is also critical, the highest frequency of transmission to contacts being most likely at the peak viral load and symptom severity (usually 1–3 days after the onset of symptoms) (40). Importantly, the risk of transmission is negligible outdoors (10). Close contact requires a 2-way face-to-face conversation of ≥3 words, close proximity, physical contact, or some combination of those criteria (57). Close contact has occurred when a person is less than 2 m away from the infector for 15 minutes or more over a 24-hour period (16). Potential high-risk transmission settings include a household, shared rooms, a concert, or a sporting event and public transportation vehicles like an aircraft, a bus, or a train. The household is the most common potential high-risk transmission setting. In our own study, we detected rhinovirus infections in 50% of the adults in families with a rhinovirus-positive index child (130). Secondary attack rates in families with a SARS-CoV-2 positive case vary from 22% to 43% (102). In a train, passengers seated next to a person with symptomatic SARS-CoV-2 were 10 times more likely to catch an infection compared to those sitting 3 seats away (60). The risk of influenza transmission on an aircraft is higher when a person is seated within 2 rows of an infector (88). On the other hand, on a 2-hour bus trip, 23 of 68 passengers were infected with COVID-19, but their seating was not significantly associated with the proximity to the index case (151).

Increasing evidence suggests that airborne transmission of numerous respiratory viruses is more prevalent than previously recognized (174). Transmissibility characteristics differ between respiratory viruses and one transmission route may dominate, for example, aerosols in COVID-19 (91, 105, 174). Studies carried out 15–25 years ago suggested that the major route of rhinovirus transmission is from the hands of an infected person to an intermediary surface or directly to the hands of the susceptible person. Recently, rhinoviruses and seasonal coronaviruses have been identified in exhaled breath and thus respiratory aerosols are now considered an important transmission route of these viruses (91, 92). Influenza transmission occurs primarily via spray and touch routes (7). Numerous studies have shown that inhalation of virus-laden aerosols is the major route of SARS-CoV-2 transmission and touch transmission is far less efficient (78, 91, 104, 105, 174).

Impact on sport and exercise medicine. It is well known that COVID-19 spread readily in sport teams like soccer and ice hockey (84, 157). Understanding the factors that shape susceptibility and transmission of viral ARIs in athletes is of fundamental importance to minimize the risk of infections. Behavioral factors may be more important than earlier understood to eliminating the risk of respiratory infection. For athletes, the frequent use of public and team transportation, human crowding, shared housing during the training camps and competitions, full-contact sports, heavy breathing and shouting by the infectees during the game and in the locker room may be important factors increasing airborne transmission. Interestingly, vigorous exercise generates smaller particles than speaking and aerosol particle emission may increase 172-fold during maximal exercise (116, 125).

DIAGNOSTICS

There are 4 major methods for the detection of respiratory viral infections: virus culture, antigen detection tests, nucleic acid amplification tests (NAATs, e.g. polymerase chain reaction (PCR) tests) and serology tests. The timeline of symptoms and diagnostic tests is shown in Figure 5. No test is absolutely accurate, meaning no test can be considered the gold standard (127, 132). It is noteworthy now that nasal mucus samples can be self-collected at home and mailed to a laboratory (149, 176).

Virus culture

In vitro cell culture for virus detection was developed in the 1940s. Different viruses induce their own particular changes in the susceptible cell lines. For many years, viral culture was considered the mainstay of viral diagnostics (61). However, viral culture requires technical expertise, is slow, time-consuming, and most importantly it has low sensitivity. In our study of 293 children with an acute respiratory infection, a viral culture detected the etiology in only 38% of the cases compared to 88% with all the 4 major methods, virus culture, antigen detection, PCR, and serology tests (68). Today, viral cultures are used in research laboratories but seldom for viral diagnostics (72).

Viral antigen detection

Protein antigens of viruses can be rapidly detected by visualizing (originally in infected cells by immunofluorescence) a specific antigen-antibody reaction. Today, a lateral flow immunoassay is the most common detection method (137). In this assay, a stationary line in a nitrocellulose paper strip is coated with an antibody against the virus. When the mucus sample containing the virus is placed on the well at the end of the strip, it becomes mixed with a secondary antibody conjugated with color particles as the liquid moves through the strip. The antigen-antibody complexes formed react with the stationary antibody and a visible line of color appears if the viral antigen is present in the sample. Several at-home rapid diagnostic tests have also recently emerged for influenza and the respiratory syncytial virus. Antigen tests are easy to use, they have a 15–20 minutes turnaround time, and they are inexpensive. However, it must be remembered that except for SARS-CoV-2, antigen tests for respiratory viruses are not recommended for adults due to the low sensitivity that is derived from low viral loads (9, 42, 80).

Nucleic acid amplifications tests

NAATs were developed during the 1990s and have become the workhorse of virus diagnostics. Briefly, DNA and/or RNA are purified from the sample, added to a mixture of nucleotides, oligonucleotide primers, probes, and a polymerase enzyme. As the target is often an RNA virus, PCR is preceded with a reverse transcription (RT) step converting RNA to a complementary DNA. RT-PCR can be performed as a single run by including the RT enzyme into the reaction. During PCR, progeny strands are synthetized by the action of the DNA polymerase. The target sequence is amplified in 35–45

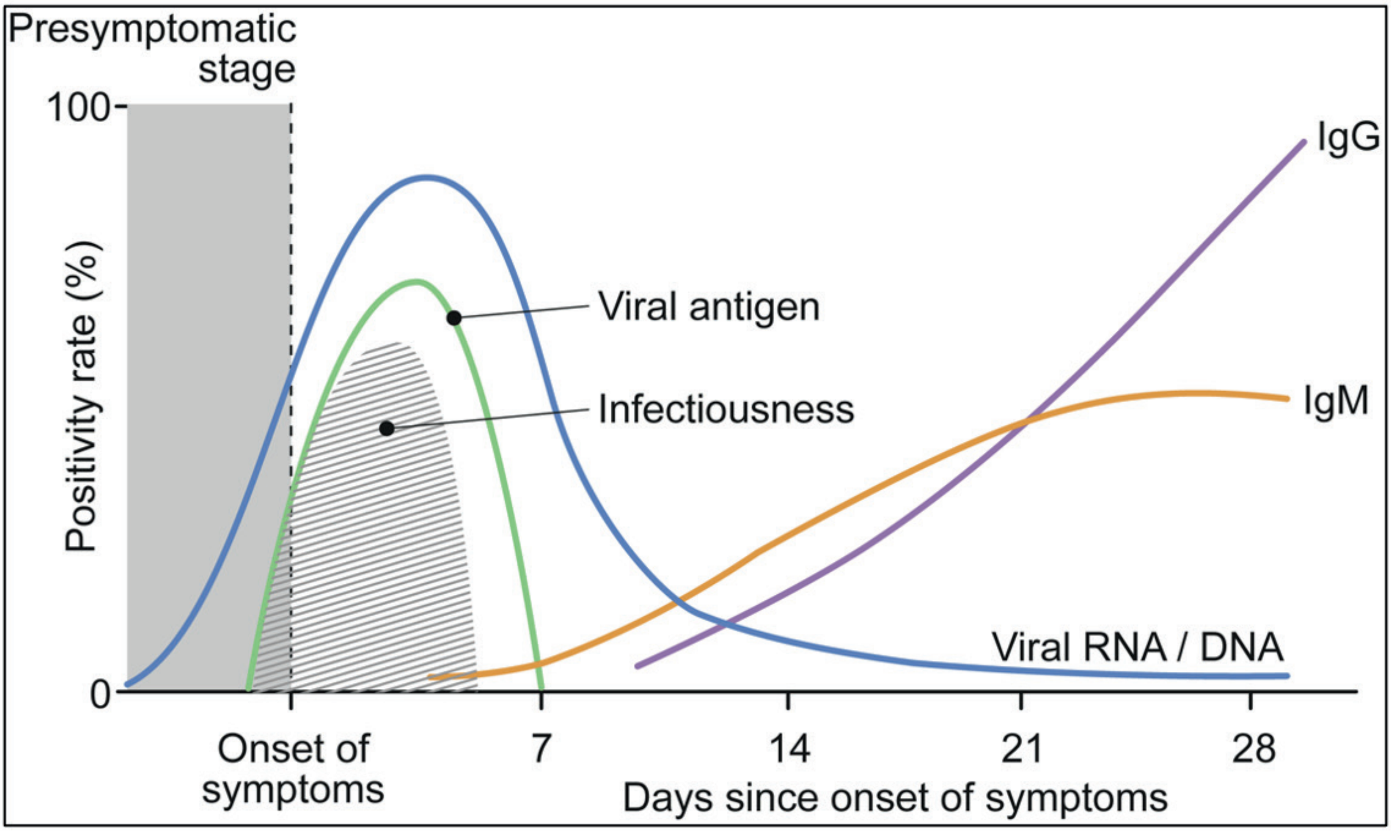

Figure 5. Generalized timelines for infectiousness, host immune response and optimal use of different diagnostic tests (nucleic acid amplification tests, antigen tests and serology) for respiratory viral infection.

temperature cycles. A fluorescent probe is used to demonstrate the reaction. PCR is highly sensitive and specific at detecting RNA or DNA of respiratory viruses. However, the sensitivity does not reach 100%. For example, PCR was able to detect only 80% of symptomatic influenza infections (86). This low sensitivity may be due to the nonoptimal timing of the sample, specimen quality and type and performance of the actual assay (86, 132). It is also possible, that there may be uncharacterized respiratory viruses awaiting discovery.

Virus sequencing is used in infectious disease epidemiology to decipher the genomic material of the virus for variant identification and to track the spread of infection. Sequencing has been especially important in the detection of various SARS-CoV-2 variants during the global spread of infections.

Multiplex PCR tests

Over the past decade, PCR tests have been multiplexed and nowadays it is possible to screen up to 16–20 respiratory viruses concurrently from a single mucus sample (155). The viral recovery rate with multiplex PCR is usually 40–60% (70, 158). The sensitivity of multiplex PCR tests is not as high as that of PCR tests for detecting a single virus. It should also be emphasized that in contrast to a positive virus culture a PCR test is not able to distinguish whether an infectious virus is present. Respiratory viruses do not induce chronic infections (171). PCR tests turn negative after acute infections usually within 1–2 weeks (viral shedding time) (Figure 5) (129). SARS-CoV-2 and bocavirus PCRs may stay positive months after an acute infection (66, 127). With the development of NAATs, it was found that in adults more than 1 virus can be detected in 5–10% of the samples. The clinical significance of viral co-infections is unclear (12, 120). In COVID-19, viral co-infections are detected in 5–10% of the cases. Co-infection with influenza was associated with an increased severity of infection (160).

The availability of the newly developed NAAT assays that can be used as POCT is increasing (8, 19). The FilmArray Respiratory Panel (BioFire Diagnostics, Salt Lake City, Utah) approved by the Food and Drug Administration is a popular test that in 45 minutes can detect 22 pathogens from a nasopharyngeal swab (61). We used FilmArray during a major winter sport event and detected respiratory viral infections on site in 88% of the 16 symptomatic cases in Team Finland. Six different viral infections were identified, all occurring at the same time in the Team (168).

Viral load

For most viruses, the current standard PCR assay for detection facilitates the estimation of the viral load in the sample. The number of cycles of the reaction at which an amplicon produces a detectable signal is the cycle threshold (Ct) value. The Ct value is inversely proportional to the amount of virus in the sample. The clinical use of Ct values expanded during the COVID-19 pandemic. It is well established that SARS-CoV-2 Ct values of <25 generally demonstrate an infectious virus (11, 69). With respect to the other respiratory viruses, the available studies have provided conflicting results about the correlation between the viral load and either infectiousness or a correlation to the severity of the illness (5, 37).

Serology

Serology tests detect specific IgM and IgG host antibody responses to an infectious virus (Figure 5). Specific IgM is of low value in respiratory virus diagnostics but will identify recent infection. A significant increase (2–4 fold) in the amount of specific IgG antibodies between acute phase and convalescent samples confirms the viral infection. Serology clearly enhances the diagnosis of respiratory viral infections, but serology is not used in everyday clinical practice because it necessitates an acute and convalescent serum sample taken 2–4 weeks apart.

Impact on sport and exercise medicine. Respiratory virus testing in athletes needs to be in a readily available format and much more widely utilized. Multiplex PCR tests are available as POCTs and permit diagnostics to be conducted at the site of the training camps and competitions (118, 168, 170).

Clinical value of virus diagnostics

Testing to treat is the optimal goal of virus diagnostics. Unfortunately, except for influenza and COVID-19, knowledge of the infecting viral agent does not usually alter the treatment; this is due to the fact, that clinically useful antiviral agents do not exist for other respiratory viruses. In hospitalized patients, the etiologic diagnosis is of importance to cohort patients, to avoid unnecessary further testing, to the use of antibiotics, and to prevent nosocomial infections (155). Additionally, laboratory confirmation of the etiology of a viral respiratory tract infection provides essential data for prevention strategies. The COVID-19 pandemic has also dramatically changed the significance of the detection of the viral etiologic agent among non-hospitalized patients.

TREATMENT

Antivirals

At present, there are no approved specific antiviral treatments for respiratory viruses other than influenza and SARS-CoV-2 viruses (24). Thus far, two first-generation oral antiviral treatments for coronaviruses have been approved for public use, molnupiravir (Lagevrio) and nirmatrelvir plus ritonavir (Paxlovid). They do not reduce the duration of symptoms but when started within 5 days of symptoms onset decrease markedly the need for hospitalization (147, 181).

Antiviral treatment with an oral neuraminidase inhibitor is recommended as soon as possible for influenza patients who are hospitalized and at risk of developing severe disease or who already have a severe, complicated, or progressive illness (15). Early (within 48 hours of illness onset) empiric antiviral treatment should also be considered for non-high-risk outpatients with suspected or confirmed influenza based on clinical judgment. The most common oral neuraminidase inhibitor for influenza is oseltamivir (Tamiflu®); while other options include inhaled zanamivir, intravenous peramivir, or oral baloxavir (15). It must be acknowledged that despite the widely accepted use of neuraminidase inhibitors, meta-analyses have shown only a modest benefit for influenza (28, 115).

Symptomatic treatment

The mainstay of the treatment for respiratory viral infection is to relieve symptoms. Effective treatment for reduction of symptom severity of viral ARI in adults is limited to over-the-counter analgesics and non-steroidal anti-inflammatory drugs intranasally or orally administered decongestants with or without antihistamines, intranasal ipratropium bromide and zinc lozenges (25, 55, 131). Antibiotics are an ineffective treatment for viral syndromes and antibiotic treatment is not indicated for adults with respiratory viral infections. Antibiotics are rather associated with potential side effects (55, 133). Antitussives have not been proven effective for cough and may even induce more harm than good (103).

Impact on sport and exercise medicine. In a recent study oseltamivir was successfully used in the treatment of influenza A outbreaks in two professional ice hockey teams (96).

PREVENTION AND CONTROL

Respiratory viral infections can be prevented by vaccination or by non-pharmacological measures to reduce transmission.

Vaccination

Vaccination is the most effective way to prevent respiratory viral infections but only two vaccines are generally available. There are three types of influenza vaccines: live attenuated, inactivated (split) whole virus, and subunit vaccine. Current seasonal influenza vaccines are multivalent with antigens from influenza A(H1N1), A(H3N2), B(Victoria), and B(Yamagata) viruses. The influenza vaccine is not an optimal vaccine because it must be given yearly and reformulated based on current circulating strains. More importantly, the effectiveness of influenza vaccines is not sufficiently adequate. During 2004–2020 the effectiveness varied from 10% to 60% (43, 122). In addition, vaccine coverage has remained far below the desired level. Influenza can also be effectively prevented by post-contact prophylaxis with oseltamivir (54).

The effectiveness (80–95%) and safety of COVID vaccines were demonstrated in a year, a record time for any vaccine (38). There is a small risk of cardiac complications after an mRNA COVID-19 vaccination, especially in young men (6 per 100 000 vaccine doses) (95). At the time of writing more than 13 billion COVID-19 vaccine doses have been delivered. Since the onset of the pandemic, new genetic variants such as Alpha, Beta, Gamma, Delta, and Omicron have emerged. Current vaccines provide little or no protection against infection with the dominant Omicron variant although they provide good protection against the severity of the disease (93). It is clear, that new vaccines (oral, nasal, inhaled) are needed.

Non-pharmacological measures

The goal of non-pharmacological measures is to minimize the interactions between susceptible and infected persons, which drive most of the viral transmission. Layered non-pharmacological preventive measures are needed to reduce the transmission of respiratory viral infections. With that in mind, it is easy to understand the importance of the following well-known measures: 1. face mask use has an effectiveness of 60–80% when both the infector and infectee use well-fitted masks (76, 79), 2. maintaining at least 1 m physical distance from other individuals, 3. avoiding nonessential crowded indoor spaces, 4. isolation of symptomatic individuals, 5.

enhancing hand hygiene by washing hands with soap for 20 seconds, 6. avoid handshaking and high-contact surfaces, 7. increasing room air ventilation e.g. opening the window and using high-efficiency particular air (HEPA) filters in closed recirculated air spaces (50), 8. active viral testing to detect community-incidence rates (59). Numerous studies have shown that these non-pharmacological preventive measures have globally controlled the spread of SARS-CoV-2 infections. Widespread use of these interventions also reduced the transmission of other respiratory viral infections including influenza virus and respiratory syncytial virus infections but less efficiently rhinovirus infections. Appropriately, it has been questioned which transmission-reducing behaviors (e.g. universal masking during the fall viral season and discontinuation of handshaking) will remain after the end of the COVID-19 pandemic to prevent the spread of other respiratory viruses. Recently, concurrent with the relaxation of government-enforced control measures, a reoccurrence of influenza viruses, respiratory syncytial virus, rhinovirus, and parainfluenza viruses has been reported (17, 51, 87). Unknown asymptomatic but infectious respiratory viral infections make prevention challenging.

Impact on sport and exercise medicine. Prevention of respiratory viral infections in athletes is a complex issue. We have no high-quality evidence of the efficacy of any single or layered intervention. The key aspects for athletes are their immunity, behavioral and environmental factors. It is generally agreed that for optimal immunity, the athlete has to balance training, nutrition and rest even though evidence of the clinical impact is lacking (172, 178). The layered mitigation procedures for COVID-19 effectively prevented the global transmission of non-SARS-CoV-2 infections in the community and subsequently in sport teams (148, 184). In the 2018 Winter Olympic Games, 45% of 44 athletes in Team Finland reported a common cold, while during the COVID-19 mitigation strategies in the 2022 Winter Olympics the corresponding percentage in 47 athletes was 6% (169). After the COVID-19 pandemic, athletes should consider using masks when traveling or when sick. Athletes who are unwell should be isolated until there is a clear improvement in symptoms (the first 1–3 days). During competitions maintaining over 2 m physical distancing is effective but may be difficult. The mitigation procedures should not induce additional psychological stress (33). Improved ventilation of indoor spaces like locker rooms is crucial. Carbon dioxide (CO_2) monitoring (<800 ppm), the use of HEPA filters for removing viruses and the use of ultraviolet radiation to inactivate viruses should be considered during respiratory viral outbreaks (2, 29, 164). Awareness of viral epidemics in both the homeland and travel destination may help to regulate the need for countermeasures.

CONCLUSIONS

In this review, we have covered the basic elements of respiratory viral infections, an entirety of which every clinician who treats ARI patients should be aware of. Concerning elite athletes, ARIs during a major competition main ruin years of hard work and cause marked financial losses not only for individual athletes but also at a team level. To prevent respiratory tract viral infections, all available and evidence-based preventive, and curative modalities against ARIs among professional athletes should be immediately implemented.

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