# Respiratory Viruses May Take Over the World

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The respiratory system and circulatory system work together to provide oxygen and release carbon dioxide. Damage to either one of these systems can make a person vulnerable to respiratory infections. The external environment we live in also contributes to our survival. Air quality is one of the environmental factors that we have control over and can prevent respiratory diseases from increasing. The World Health organization (WHO) have guidelines for air quality; and 91 percent of the world's population live in areas where air quality exceeds those limits (7). Air pollution, toxic particles and tobacco smoke are common contributors to an unhealthy respiratory system. Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide (7). So, you can see why adding contagious respiratory viruses to our world can make survival complicated. Influenza and the recent COVID-19 are not the only respiratory viruses that are active and concerning. I will discuss other respiratory viruses that circulate during the flu season and get less attention in the public news. Patients often manifest the same symptoms of influenza and COVID-19 but test negative for both viruses. The overlap of respiratory symptoms caused by different respiratory viruses can make diagnosis and treatment difficult. Please do not overlook or exclude the following viruses: respiratory syncytial virus (RSV), human metapneumovirus, rhinovirus, adenovirus, human parainfluenza virus and human coronavirus. Some of these respiratory viruses have a high mortality and morbidity among immunocompromised adults and children in the United States (2). While exploring the antiviral therapies, clinical symptoms, mode of transmission, risk factors and diagnostic lab testing of these respiratory viruses, we will appreciate the importance of winning the battle against global respiratory disease.

Diagnostic laboratory tests are important for determining the most beneficial treatment for the patient. Most of the respiratory viruses cause the same symptoms so identification of the specific virus causing the infection is vital for the correct diagnosis. There are Nucleic Acid Amplification Tests (NAATS) or molecular pathology tests on the market that perform identification of multiple viruses simultaneously (15,16,17) The methodology and technology of NAATS are replacing traditional virology laboratory tests because of the shorter turn-around times, increased accuracy, increased percent sensitivity and increased percent specificity (14,15). The higher specificity and sensitivity of the test result correlates with relevant diagnostic data and appropriate therapy. Bacterial infections can be immediately ruled out and the misuse of antibiotics controlled. NAATS has significantly changed healthcare's approach to the diagnosis of respiratory tract infections. For example, conventional viral culture takes 5 to 7 days for results and rapid cell culture takes 48 hrs. (14,15). Other traditional lab tests NAATS are replacing Rapid Antigen Direct tests (RADTS) and Direct Fluorescent Antibody tests (DFA). RADTS and DFA have lower sensitivities and are limited to the type of virus detected (14,15). For instance, with some RADTS the sensitivity of RSV is between 50 to 98 percent and only RSV or Influenza A/B is detected (14,15). Since a decrease in the sensitivities of a test can cause false negative lab results, physicians could prescribe the wrong medication or order more ancillary tests without the correct diagnosis. False positive test results could also happen if the test methodology is not specific enough. There are many excess healthcare expenditures with false negative or false positive results. Sending a sample to a reference lab for confirmatory testing could introduce error and increase the costs. Over prescribed antibiotics is already increasing the cost of healthcare by creating resistant super bugs. An inaccurate or incomplete test result could increase the patient's length of stay in the hospital or increase nosocomial outbreaks. One of the disadvantages of NAATS, compared traditional viral tests, is the higher cost (16,17). The higher cost might be worth it if the total cost of patient care is lowered. While traditional or conventional viral testing definitely have a niche, they are becoming less popular. Different NAATS manufactures offer respiratory viral panels which are sensitive, specific and offer a wide range of viral targets(16,17,18) Prodesse, Film Array, GenMark and Luminex are competitive and offer the accuracy of RT-PCR(16,17,18). The viruses that are often included in the one test panel are as follows: Adenovirus, Coronaviruses (multiple serotypes), Human Metapneumovirus,

Human Rhinovirus/Enterovirus, Influenza (multiple serotypes), Parainfluenza (multiple serotypes), Respiratory Syncytial Virus.

Respiratory syncytial virus (RSV) is a member of the Paramyxoviridae family of single stranded, negative-sense RNA (3'-5") viruses and causes illness in children, infants, elderly or immunocompromised (1,3). While following the viruses' journey into the human body, it usually first enters the upper respiratory track followed by the lower respiratory tract. Incubation of RSV takes 3 to 5 days, during which time the virus starts replicating in the nasopharynx (1,5). Not only does the virus destroy the epithelium, but as the virus continues to multiply it causes infected cells to fuse with adjacent uninfected cells (1,3). Large multinucleated epithelial cells are formed called syncytia (1,3). Now the viral RNA can spread without forming complete viral particles (1). Since a weak humeral immune response is produced, the virus is not completely destroyed, and an upper respiratory tract infection develops (1,3). This causes symptoms like cough, nasal congestion, clear runny nose, an increase in oral secretions or drooling and low-grade fever (1,5). Symptoms could persist for 1 to 3 weeks before improvement. In 1 to 3 days after a runny nose is present, the virus could start replicating in the lower respiratory tract if the patient is elderly or immunocompromised (1). When the virus spreads to the bronchi and bronchioles, abnormal rapid breathing, (respiratory rate > 60-70 breaths per min.), shortness of breath and wheezing can occur (1). If the virus gets to the alveoli pneumonia may be evident (1). This could turn into respiratory distress when patient gasps for air with deep retractions. An increase in gastroesophageal reflux and a reluctance to ingest liquids or foods is also present. With severe complications, endotracheal intubation with mechanical ventilation is required. Asthma, COPD, and congestive heart failure is also present when the patient's illness worsens. Risk factors include adults older than 65 years, lung transplants, hematopoietic stem cell transplants and children under 1 year (1). The percentage of people with Respiratory illnesses in adults have increased since the introduction of molecular testing. It infects 3 to 5 percent adults annually. RSV causes 177000 excess hospitalizations and 14,000 deaths in the elderly per year in the United States (5). Older adults may be hospitalized if dehydration and shortness of breath occurs. People infected are contagious for 3 to 8 days. Although people with weakened immune systems can continue to spread the virus for 4 weeks after they stop showing symptoms. Transmission of RSV is through droplets from cough or sneeze to eyes, nose or mouth. Touching your face without handwashing can also cause infection. It can survive many hours on hard surfaces like tables and railings. Lives for shorter periods on soft surfaces like hands and linens. RSV infections occur during fall, winter, spring. National peak occurred week 5 or early February. Timing of the virus in a community can vary from year to year. Patients in high risk group demonstrated the greatest benefit of ribavirin based therapy at Upper respiratory tract infection stage (2). These same patients were at highest risk for progression to lower respiratory tract and death in absence of antiviral therapy.

Human Parainfluenza virus (HPIV), belonging to the Paramyxoviridae family and contains single-stranded negative sense RNA. HPIV includes 4 genetically different serotypes: HPIV-1 HPIV-2, HPIV-3, HPIV-4 and 2 subtypes HPIV-4a, and HPIV-4b. HPIV-1 is commonly found in children (11) HPIV-2 cause cold-like symptoms and lower respiratory tract illness. HPIV-3 is the most virulent and is associated w/bronchiolitis, bronchitis and pneumonia. A study performed by the institutional review board of university Feinberg school of medicine demonstrated that HPIV-3 accounted for 60% of hospitalized infections (2). The different serotypes also peaked at different times during the season. For example, HPIV-3 peaked in late spring, early summer (11) HPIV-4 is rare and causes mild to severe respiratory tract illness. Reinfections are very common, and people may get multiple HPIV infections in their lifetime. There is evidence to show mild recurrent and asymptomatic infections in immunocompetent adults. Documentation of Asymptomatic viral shedding in healthy males has also occurred (2). Older adults and immunocompromised have higher risk for severe infections. Data has shown that HPIV causes high morbidity in hospitalized adults. Most HPIV research has been done on children, so there is more to learn about how this virus causes illness in adults. Most of the cases have found the following symptoms in hospitalized adults: cold like infections such as runny nose, sore throat, and cough. These symptoms are expressed in adults with COPD, asthma, and congestive heart failure.

Hospitalized HPIV patients have also been admitted with pneumonia. Transmission like other viral respiratory infections are spread by contact with droplets and is airborne when an infected person breathes, coughs, or sneezes. HPIVs may remain infectious in airborne drops for over an hour and surfaces for a few hours. Infectious seasons are during spring, summer and fall. There is no vaccine and no antiviral agents are licensed to treat at this time.

Human Metapneumovirus (HMPV) can infect the elderly and people with weakened immune systems. Spread by close contact with an infected individual or contact with contaminated area. Symptoms are similar to the common cold and lasts 2-5 days.(10). Again, transmission is via droplets from coughs, sneezes, or touching face after a contaminated doorknob. The virus follows a winter and spring season in united states. Again, it may develop into bronchiolitis, bronchitis or pneumonia. Adult risk factors include asthma, COPD, emphysema or any lung disease. Treatment involves comfort measures like inhaled corticosteroid, prednisone, and fever reducers. Vaccines are not available currently.

Adenovirus are non-enveloped double stranded DNA viruses. More than 50 serotypes cause human disease.(6) Because its relatively resistant to common disinfectants, it remains infectious for long periods on environmental Surfaces and medical instruments. Symptoms can include fever, sore throat, acute bronchitis, pneumonia, diarrhea, conjunctiva redness and flu-like symptoms. illnesses from this virus may include gastroenteritis, conjunctivitis (pink eye), cystitis, or neurologic disease. It causes ongoing illness in adenoids, intestines, and tonsils with no symptoms and sheds virus for weeks or longer. Usual clusters of respiratory illness or conjunctivitis by adenovirus is reportable to the local health department. Risk factors include existing lung or heart disease. Transmission is by respiratory droplets, close contact, and stool. It is also likely to spread in water such as community swimming pools and small lakes but less common. Historically, serotype 4 and serotype 7 causes acute respiratory illness in military recruits but lowered frequency due to vaccine in 2011. However, the vaccine is not available to the general public.

Rhinovirus is the most frequent cause of the common cold. Adults have average of 2 to 3 colds per year (19). Rhinovirus season is winter and spring (2). Symptoms include sore throat, runny nose, cough, sneeze, headaches, and body aches. Recovery is within 7 to 10 days. Adults with underlying respiratory illness, weak immune systems may develop severe illness like bronchitis or pneumonia. Rhinovirus frequently triggers sinus infections, ear infections and asthma. It is transmitted through air, close contact, stool, or respiratory secretions. Vaccine or antiviral therapy is currently unavailable.

There are 7 types of coronaviruses (CoV): 229E, NL63, OC43, HKU1, MERS-CoV, SARs-CoV, and SARS-CoV-2 (or COVID-19) (6). OC43 is the most detected CoV. CoV of animal origin transmitted to humans are MERS-CoV, SARs-CoV, and SARS-CoV-2 (or COVID-19) (6). All the human serotypes cause common cold symptoms. Coronavirus is the 2$^{nd}$ most frequent cause of the common cold after rhinovirus. It causes a range of illness, from asymptomatic, mild, moderate to severe. CoV follows a fall and winter season in the United States. Vaccine or antiviral therapy is currently unavailable.

Consequently, respiratory syncytial virus, rhinoviruses, adenoviruses, human coronaviruses, human parainfluenza viruses, and human metapneumoviruses are complicated to diagnose and treat due to the overlap of symptoms and routes of transmission. Bearing that in mind, influenza or COVID-19 can also overlap symptoms with the above-mentioned viruses and complicate treatment. Since influenza is on the NAATS respiratory viral panel already mentioned, doctors will have viral identification results within approximately one to three hours. COVID-19 is currently being identified by molecular methods but is not available on any of the NAATS respiratory viral panels to date. Antiviral therapy options have been researched and are available if influenza tests positive. These drugs must be given early in the incubation period for the drugs to have success. Antiviral therapy is not an option or successful for some of the other viruses listed above. Physicians and healthcare professionals rely heavily on accurate diagnostic lab tests for treatment and suppression of outbreaks in the hospital or community. Research and development in antiviral therapy are difficult, although there is hope

with new inventions down the pipeline. “Management of viral infections is challenging because viruses are intracellular parasites that use many of the hosts pathways to replicate and propagate.” “Therefore, antiviral agents need to target specific viral components to avoid potential damage to host cells.” (2).

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