Understanding the Impact of Respiratory Viral Infections on Immunocompromised Populations

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Respiratory viruses burden the global healthcare system and significantly impact immunocompromised people, who comprise a substantial subset of the population. Respiratory viruses such as influenza virus, SARS-CoV-2 virus (COVID-19), and respiratory syncytial virus (RSV) infect our breathing passages (nose, mouth, lungs) and spread through direct contact with respiratory droplets.[1] These viruses can cause infections ranging in severity from mild to severe and, in some cases, result in hospitalization and death.[1] Immunocompromised individuals experience more severe effects from infections because their immune systems are weaker and likely dysregulated, reducing viral clearance.[2] Vaccines do not work as effectively for an immunocompromised individual as a healthy individual because they do not trigger a strong enough response from their immune system.[3] Additionally, the immunocompromised population is heterogeneous, including individuals with autoimmune disease, chronic disease, and even high-risk age groups like infants and the elderly.[1] Understanding how respiratory viruses affect the immunocompromised will allow us to shed light on this vulnerable group and identify strategies to better protect their health.

Viruses are incredibly complex microbes that can infect and kill millions of people. Our immune system has evolved mechanisms to combat viruses and prevent prolonged, severe illness. However, in immunocompromised people, the immune system is incapable of robust responses, leading to long recovery times and more critical symptoms.[4] For example, the respiratory syncytial virus (RSV) is a common virus that hospitalizes more than 100,000 older adults per year and causes around 10,000 deaths.[5] Most healthy individuals who get infected with RSV develop mild cold-like symptoms and recover within two weeks, whereas high-risk age groups like infants and the elderly are disproportionately affected due to their weaker immune systems, ending up with RSV bronchitis or pneumonia.[6] According to the Administration of Aging, there are over 70 million people over 60 years old in the United States, which means over fifteen percent of our population is in a high-risk age category.[7] When factoring in the percentage of infants, this percentage surpasses fifteen percent. It is essential to spread awareness about the effects of viruses on immunocompromised as there is a substantial population of people in the US who are more vulnerable to disease and require more attention from the public.

Overall, this paper will investigate the normal immune response to viral respiratory infections and the response and impact of viral disease on the immunocompromised. Specifically, it will focus on individuals with autoimmune diseases, chronic immune diseases, and people who fall into high-risk age categories. The goal is to explore the effects of respiratory viral disease on groups with weakened immunity to identify protective strategies for them.

Normal Immune Response to Viral Infections

To gain a deeper understanding and more holistic view of respiratory viral diseases and their impact on immunocompromised populations, we must investigate the distinct characteristics of a virus. Viruses are considered non-living, infectious agents that depend on infected host cells for replication. Though viruses cause similar symptoms as bacteria, a distinct difference between viruses and bacteria is that bacteria are single-celled and can survive independently.[8]

Coughing and sneezing are not the only ways a virus can travel; touching a contaminated area or surface and then rubbing your eyes, nose, or mouth can also lead to infection.[1] Symptoms of an infection include runny nose, sore throat, headache, and fatigue.[1] Additionally, we can classify a respiratory infection into two categories: upper and lower infection.[9] Upper respiratory infections affect our sinuses and throats, while lower respiratory infections affect our airways and lungs.[9] The latter is generally more severe and lasts longer because it impacts our lungs and chests, which can result in bronchitis, chest infection, or pneumonia.[9]

There are many steps involved in the viral infectious cycle. The process can be divided into three stages: entry, genome replication, and exit.[10] In the entry stage, the virus attaches to the host cell's plasma membrane and interacts with two proteins: the attachment factor and the viral receptor.[10] These proteins help the virus particle penetrate the membrane and enter the cell's cytoplasm.[10] After penetration, the virus particles move to a specific site in the cell with cellular machinery that allows them to replicate in the nucleus.[10] Following replication, the virus exits the cell either through cell lysis or budding through the plasma membrane.[10] The stages of entry, genome replication, and exit are complex but essential to understand for a thorough comparison of this process in a healthy immune system with a weakened one.

The immune system is our primary defense mechanism against viruses and bacteria.[11] It is one of the most complex biological systems known to us.[11] When a virus or bacteria enters our body, it triggers immune responses from both the innate and adaptive immune systems.[11] The innate immune system acts quickly to clear pathogens (minutes to hours) while the adaptive immune system forms a long-term response (days to weeks) that can provide long-term protection (lasting years) against pathogens.[12] The innate immune system, the more ancient immune system, comprises cell types such as neutrophils, macrophages, and dendritic cells.[11] It has evolved to respond quickly in minutes to hours against toxins and infectious agents.[13] Their components include physical and anatomical barriers like skin and mucous and epithelial cells which serve to separate the organism from the external environment.[13] On the contrary, the adaptive immune system takes days to weeks to respond, but it possesses T-cells and B-cells that effectively get rid of the virus.[11] Although the adaptive immune system takes longer to initiate a response, it is the body's strongest immune response.[11] Immune system cells can recognize the viruses with protein receptors at the outer plasma membrane.[11] Because the adaptive system has billions of pattern-recognition receptors capable of recognizing various viruses, it is challenging for pathogens to bypass the system without detection and destruction.[11] After an infection, our immune system gains memory of the specific virus and is able to kill the virus if the body is infected again.[12] Because we can develop immunity to viruses, symptoms are mild to none in our second infection of the same virus.[11]

The adaptive immune system is capable of defending our body from pathogens. However, because of the myriad of protein receptors in the immune system, there is a chance the immune system recognizes the body's own beneficial cells as foreign and attacks them, sometimes resulting in autoimmune disease.[11] Infections can be deadly for immunocompromised or immunosuppressed people with dysregulated immune systems. Because of their reduced ability to fight infections, the immunocompromised are at a higher risk in our community. Causes of a weakened immune system include AIDS, diabetes, genetic disorders, etc.[2] Moreover, treatments like radiation therapy or medications following organ transplants can also weaken the immune system.[2] A person with a weakened immune system might always have a cold, a slow wound healing process, frequent diarrhea or constipation, infections, or low energy levels.[14] While a healthy individual can fight off an infection in a week

or two, an immunocompromised individual might experience a prolonged infection that lasts for several weeks. According to the Centers for Disease Control and Prevention, the risk of death in hospitalized people with COVID-19 is 1.44 times greater for immunocompromised people than for others.[4] Another main risk factor for the immunocompromised is the inefficacy of vaccines to protect them from serious infection. For example, during the COVID-19 pandemic, immunocompromised patients were advised to get additional doses of the mRNA vaccine because a single dose may not mount a sufficient immune response.[15]

Table 1

Specific Immunodeficiencies Mentioned

Autoimmune disease	Systemic lupus erythematosus
Chronic diseases that affect the immune system	Lymphoma and persistent Epstein-Barr virus infection
People who fall into high-risk age categories	Adults greater than age 65 and infants from 0 to 6 months

Response and Impact of Viral Disease on People With an Autoimmune Disease

Autoimmune disease occurs when the immune system can not distinguish between foreign pathogens and host cells, triggering immune responses to host tissues, and causing significant damage to the body.[16] People with autoimmune diseases like systemic lupus erythematosus (lupus) or type 1 diabetes are especially susceptible to and more affected by viral infections as their overactive immune system targets host cells.[16] Consequently, autoimmune disease patients experience more severe symptoms during infection.[17]

Viral infection induces a robust immune response in the body. Still, when the immune system is dysregulated and can not control its response, it can target and harm beneficial host cells.[18] A mechanism called molecular mimicry plays a role in autoimmunity.[18] In this process, viral proteins that share structural similarities with self-peptides activate autoreactive T or B cells, which can shift the immune response to attack itself.[18] Although there are technological limitations and a lack of statistical power in the study of T-cells and B-cells, the concept of molecular mimicry may still help prevent and treat autoimmune diseases.[19]

Lupus, a common autoimmune disease, can be characterized by a facial rash shaped like a butterfly's wings.[20] Usually, individuals are predisposed to developing the disease; however, external factors like infections, drugs, or sunlight can trigger its onset.[20] Those with lupus can have episodes or flares, which is when symptoms temporarily worsen and then improve or even disappear rapidly.[20] Additional signs of lupus include fatigue, joint pain, swelling, and fever. [20]

As mentioned before, external environments combined with genetics can cause one to develop lupus. Respiratory viruses like COVID-19 and influenza/flu have been reported to trigger systemic lupus erythematosus (SLE) flares. Disease flares are dangerous and can result in organ damage, which can lead to hospitalization and death.[21] According to a report published in 2021 analyzing the relationship between influenza infection and SLE flares, influenza infection

positively correlates with SLE flares, resulting in hospitalization.[21] In other words, a flu infection can cause a higher risk of SLE flares. Therefore, we must consider the possibility of SLE flares in patients during the first 7 days of influenza infection.[21] A case report published in 2022, on the contrary, researched the relationship between COVID-19 and systemic lupus erythematosus.[22] According to the report, there have been cases where COVID-19 infection caused autoimmune disease development.[22] In one case, a 53-year-old male patient developed SLE one month after COVID-19 infection.[22] At first, the patient complained about fatigue, wrist pain, and vomiting, but after examination, it was revealed that they were in acute renal failure due to SLE.[22] Overall, developing autoimmune diseases like SLE after a COVID-19 infection is rare but possible.[22]

Generally, respiratory infections significantly impact immunocompromised people with autoimmune diseases, as infections are external factors that can trigger the onset of lupus and other diseases. Specifically, in lupus, infections can increase the risk of flare-ups, which can be severe and require hospitalization.

Response and Impact of Viral Disease on People With Chronic Diseases That Affect the Immune System

Some diseases last a prolonged period and can be classified as chronic immune diseases. They are especially dangerous because they persist for an extended amount of time and often cannot be cured.

Hodgkin's lymphoma, or Hodgekin's disease, is a type of chronic immune disease that affects the lymphatic system, which plays a big role in the body's immune system.[23] The disease is a kind of cancer where infection-fighting white blood cells called lymphocytes multiply rapidly and uncontrollably, resulting in swollen lymph nodes and various tumor growths in the body.[23] There are two types of Hodgekin's lymphoma: classical Hodgkin's lymphoma and nodular lymphocyte-predominant Hodgkin's lymphoma.[23] Classical Hodgkin's lymphoma is more common, while the nodular lymphocyte-predominant Hodgkin's lymphoma is much rarer and requires less intensive treatment.[23] Several disease symptoms include lymphadenopathy (painless swelling of lymph nodes) in the neck, armpit, or groin, fever, and severe itching.[23] Though doctors are still unable to pinpoint the exact cause of lymphoma, they believe it involves DNA mutation in the lymphocytes that signals its own continual division and growth.[23] Besides DNA changes, the lymphoma cells attract healthy immune cells to protect their growth.[23] People with a family history of lymphoma, people who are infected with HIV, and people with a past Epstein-Barr infection have an increased risk of developing this disease.

Hematological malignancies (HMs) are cancers of blood-forming cells or tissues.[24] Researchers have determined that patients with Hodgkin's lymphoma, which falls under the category of HMs, have a high susceptibility to RSV, influenza virus, parainfluenza virus (PIV), and human metapneumovirus (hMPV).[25] During the winter months, when RSV and flu infections are most prevalent, immunosuppressed patients are at a higher risk of an upper respiratory tract infection (URTI).[25] In more severe incidences, these respiratory viruses can cause lower respiratory tract infection (LRTI) in patients with HMs, which is more severe and dangerous than an upper infection.[25] Increased mortality rates and progression into LRTI are associated with respiratory infection of RSV, influenza, PIV, and hMPV in patients with HMs.[25] Therefore, preventive strategies and measures should be used to prevent community outbreaks.

The Ebstein-Barr virus (EBV), a type of herpes virus, can increase the risk of contracting Hodgkin's lymphoma.[23] According to the CDC, EBV is one of the most common human viruses in the world.[26] It is a ubiquitous disease related to the chronic infection of memory B cells and airway cells.[27] Typically, the virus spreads through bodily fluids like saliva, blood, and semen and

has fatigue, fever, and inflamed throat symptoms.[26] Furthermore, while EBV primarily causes infectious mononucleosis, also called mono or the kissing disease, it can also induce other illnesses such as Hodgkin's lymphoma.[26] After infection, the EBV virus becomes latent or inactive in the body but can reactivate in certain circumstances.[26] Because of their weakened immune system, immunocompromised people are more likely to develop symptoms if the EBV reactivates.[26] Epstein-Barr virus, in rare incidents, has triggered lymphoma as it is a potent agent with an oncogenic (cancer-causing) mechanism that promotes B-cell growth and possibly lymphomagenesis.[28] In immunosuppressed settings, patients who have recently received stem cell or organ transplants and thus have a weakened T-cell function can develop a higher risk of developing lymphoma from EBV.[28] Persistent infection of EBV weakens the immune system and makes one more vulnerable to respiratory viral diseases. result in Like EBV-induced lymphoma, other respiratory viruses can also have devastating long-term effects, particularly for immunocompromised individuals. Analyzing and studying these abnormal cases will push for more effective and safer treatments for the immunosuppressed and raise awareness of the dangerous possibilities the immunocompromised population faces daily.

Response and Impact of Viral Disease on People Who Fall into High-Risk Age Categories

Elders aged 65 years and older, as well as young children under 6 months, have relatively high hospitalization rates from respiratory viral infections.[5] Elders have a deteriorating immune system and likely have underlying health conditions, while infants have a developing immune system that has incomplete antiviral abilities.[5] Over the past few years, infants under 12 months and adults over 65 have been reported to have the highest rate of COVID-19-related emergency department visits.[38] Additionally, the highest number of visits to the department due to RSV is highest among infants under 12 months. [5] Evidently, older adults and infants both fall into high-risk categories for developing severe cases of illness.

Young children with an underdeveloped immune system may encounter dangerous viruses early on and have difficulty combating them. Children comprise 18% of all reported COVID-19 cases since the start of the pandemic.[29] Contrary to popular belief, older children do not get critically ill from COVID-19 and sometimes do not display symptoms.[29] The ones at risk are babies under age 1.[29] Many infants can get COVID-19 during childbirth or after delivery, both highly vulnerable times.[29] In some incidents, multisystem inflammatory syndrome in Children (MIS-C), a post-COVID condition, can occur 2-6 weeks after a young child is infected with COVID-19.[29] MIS-C causes inflammation in different body parts like the heart, lungs, and kidney.[29]A child might have the illness if they show symptoms of ongoing fever accompanied by stomach pain, diarrhea, bloodshot eyes, etc.[29] The condition is deadly but can get better through treatment and medical care.[29] In a study published in 2017, researchers investigated the long-term effects of RSV on young children.[30] The results concluded that contracting RSV in early childhood is associated with long-term wheezing, asthma, and impaired lung function.[30] Overall, babies under six months are more susceptible to severe respiratory viral infection, face more significant challenges and complications during infection, and may suffer the long-lasting aftermath of a virus.

Similarly, adults over 65 years old experience serious consequences from respiratory diseases.[5] They have immune systems that do not function as well as others. In an aging immune system, there is a decreased ability to activate T cells, which are vital to eliminating virus particles and cancerous cells and generating sufficient immune memory responses.[31] Most deaths from respiratory viruses occur in the elderly as they have an increased risk of hospitalization.[5] Particularly, U.S. adults over 65 accounted for 62.9% of COVID-19-related

cases from January to February 2023.[39] And, people who are 75 years and older are nine times more likely to die from COVID-19 compared to people who are 18-39 years old.[5] In the case of the influenza virus, those 65+ are 3-5 times more likely to get a heart attack and 2-3 times more likely to get a stroke in the first two weeks of infection.[32] On the other hand, long COVID worsens preexisting health disorders like heart failure, lung disease, or dementia in older people.[33] As a result, during the COVID-19 pandemic, state health departments identified key protective strategies for high-risk age groups and other immunocompromised people to safeguard them from hospitalization and death.

Current Issues and Protective Strategies

Identifying high-risk groups in our community is our first step towards improving current protective and preventive strategies against respiratory viruses and infectious outbreaks. The immunosuppressed and immunocompromised population can include those with autoimmune diseases, chronic immune diseases, and infants under six months or elders over 65. Through extensive research, immunocompromised individuals with weakened immune systems were found to experience more significant and longer effects from respiratory infections. Immunization is one way to protect immunocompromised patients from infectious diseases.[34] However, because of concerns about adverse effects from vaccines, more attention on active clinical issues rather than prevention, and doubts about whether vaccines are worthwhile for the immunocompromised, many individuals susceptible to infections may not receive the vaccines they need to protect themselves.[34] In reality, although vaccines may only mount a partial response in people with weakened immune systems, they are still beneficial for protection.[34] Inactivated or killed vaccines with particles or strains of a dead virus are safe, moderately effective, and recommended for those with compromised immunity.[34] If the compromised individual does not receive the vaccine, their family members and healthcare workers should be immunized to decrease the risk of transmission.[34] Still, the lack of effective vaccines and the high cost of antiviral therapy for the immunocompromised underscore the need to increase awareness among our community about the effects of respiratory viral diseases on vulnerable groups.[25] During outbreaks and flu season, wearing masks and gloves, quarantining, adhering to contact isolation, and paying attention to overall hygiene are fundamental ways to protect oneself and others.[34]

During the COVID-19 pandemic, the CDC issued guidelines for people with weakened immune systems and cohabitants, listing preventative measures like obtaining the updated COVID-19 vaccine, washing hands, and spending time outside for better ventilation.[35] Although the immunocompromised gained access to vaccines earlier than the rest of the population due to their susceptibility to infection, vaccine inequality amongst populations of color can be especially detrimental for high-risk individuals.[36] If a group or a community has limited access to vaccines because of the lack of interpretation services, communication challenges, and reduced internet access that allows one to schedule vaccine appointments, it becomes perilous for the immunosuppressed in those populations as there may be higher viral transmission rates due to the lack of immunization.[36] As a result, combatting inequities in healthcare and vaccine distribution remains vital for overall health and safety, especially for those more vulnerable to disease.

Conclusion

Respiratory viral infections like COVID-19, influenza, and respiratory syncytial viruses tremendously impact human health, especially for immunocompromised people. These individuals have a weakened immune system and, thus, are more vulnerable to infections.

Respiratory infections can induce or worsen pre-existing health conditions and lead to long-lasting problems in the airway in individuals with autoimmune diseases, chronic immune diseases, and people who fall into high-risk age categories. However, through immunization and preventive measures like wearing masks, quarantining, and strictly adhering to health guidelines, risk factors can be significantly reduced in compromised populations. Education and awareness of the impact of respiratory viral disease are imperative in improving community engagement in the matter and helping strengthen protective strategies during a pandemic.[37] Specifically, ensuring access to vaccines and healthcare for populations of color should be a priority, as inequities and historical challenges to acquiring necessities impose dangers on vulnerable people in those communities.

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