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Respiratory viruses: Preventive and therapeutic approaches to diverse pathogens

ABSTRACT

Viral respiratory diseases affect millions of individuals worldwide each year. Annual vaccinations are recommended by the World Health Organization for some of them, such as influenza and more recently for the coronavirus disease of 2019 (COVID-19) and respiratory syncytial virus, with the goal of reducing disease severity and limiting transmission. In the context of infection and vaccination, it is of primary importance to evaluate the immune response to pathogens to shed light on the mechanisms of protection.

KEY POINTS

Next-generation vaccines need to be effective in all populations, including high-risk populations such as infants, the elderly, and those affected by comorbidities.

It is estimated that during the 2022–2023 influenza virus season, more than 26 million cases of influenza virus infection occurred in the United States, with 290,000 hospitalizations and 18,000 deaths.

The fusion protein is sufficient and necessary for development of respiratory syncytial virus infection both in vitro and in the case of natural infection.

Like influenza viruses, SARS-CoV-2 has shown the ability to mutate, leading to the emergence of new variants with potentially altered transmissibility, virulence, or ability to evade immunity.

Cutting-edge, computational modeling (eg, artificial intelligence-driven) and multidisciplinary approaches are indispensable to understanding the dynamics of the immune responses and develop next-generation vaccines and therapies against infectious pathogens.

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This century has been the target of multiple waves of deadly and infectious disease outbreaks, some of them with a pandemic impact causing numerous deaths. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of 2019 (COVID-19) pandemic has had a devastating impact on our lives, spanning global health and sociopolitical and economic fronts. Preceding COVID-19 were outbreaks from the severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2003, the swine-origin H1N1 influenza pandemic in 2009, the Middle East respiratory syndrome coronavirus in 2012, the Ebola virus disease epidemic in West Africa in 2013 to 2016, and the recent Zika virus disease epidemic in 2015. Some of these still represent a threat, as they can re-emerge and potentially cause epidemic or pandemic outbreaks. An additional concern is climate changes that have an impact on vector distribution, such as those transmitted by arthropods. An example is the recent dengue epidemic outbreak in Brazil, which is challenging the country's healthcare system.[1]

These outbreaks all caused considerable morbidity and mortality, with pandemic events involving multiple countries and affecting the population at a global level. Low- and lower-middle-income countries are primarily affected by infectious diseases and have the fewest available resources to counter them. Moreover, morbidity and mortality associated with malaria, human immunodeficiency virus (HIV) infection, neglected tropical diseases, and tuberculosis remain high. Persistent emerging and re-emerging infections further contribute to infectious disease-associated deaths, especially in the above-mentioned countries and in addition to ongoing seasonal and endemic infections. Some pathogens, like the Epstein-Barr virus, the human herpesvirus 8, and the hepatitis C virus, are associated with development of chronic infections and severe sequelae, including cancer, especially in immunocompromised subjects. As in the case of emerging infections, no vaccines or

broadly effective immunotherapies exist to prevent these infections; this deficit poses an urgent medical need, especially in areas of the world where access to treatment is challenging.

RESPIRATORY INFECTIONS: PRIMARY ROLE IN EPIDEMIC AND PANDEMIC EVENTS

The World Health Organization estimates that even in nonpandemic times, acute respiratory infections (ARIs) kill approximately 3.9 million people per year worldwide,[2] with viral ARIs a leading cause of morbidity and mortality. The overwhelming majority of deaths and severe illness episodes are due to ARIs of the lower respiratory tract. These infections affect all age groups, but particularly impact vulnerable populations such as the very young, the elderly, pregnant women, and those with chronic medical conditions such as metabolic syndrome or immunocompromising conditions.[3] Historical data have demonstrated that the burden of infectious diseases is disproportionately borne by those of racial and ethnic minority groups and those of lower socioeconomic status, suggesting that these groups should also be included in our definition of vulnerable or high-risk populations.[4] For the most vulnerable populations, the long-term complications of viral ARIs include risk of secondary bacterial infections, pneumonia, bronchitis and bronchiolitis, and asthma exacerbations.

In addition to increasing the risk of secondary bacterial infections, respiratory viruses are implicated in about half of community-acquired pneumonia in children, greater than 90% of bronchiolitis cases in infants,[5] and 85% to 95% of asthma in children,[6,7] with similar trends observed in adults.[8] Susceptibility to and impact from respiratory virus infections can be much worse in certain populations as highlighted by health disparities and inequalities associated with the SARS-CoV-2 pandemic, but prophylactic vaccines or effective antiviral treatments against viral respiratory infections are either still unavailable or provide only limited protection.

Long-term complications from SARS-CoV-2 have been described but their origin, duration, and consequences remain mostly undefined.[9]

Need for effective vaccines for all populations

Prophylactic vaccines and effective antiviral treatments against viral respiratory infections are available but provide limited protection. Influenza, respiratory syncytial virus (RSV), and SARS-CoV-2 vaccinations elicit antibody responses in the elderly that are often compromised and wane, leading to poor protection in this high-risk population. Annual influenza vaccinations and, recently, SARS-CoV-2 booster vaccinations are recommended, especially for these high-risk groups.

Respiratory virus epidemics and pandemics are attributable to ongoing evolution and spillovers from animal reservoirs, respectively, as in the case of influenza virus and SARS-CoV-2. The emergence of variants is allowed by the continuous circulation of these viruses in the human population. It is a consequence of the diverse immune response among individuals, the incomplete protection conferred by currently available vaccines against the drifted virus strains, and the waning of the immune response following the exposure or vaccination.[10]

Given the widespread prevalence, a general lack of natural sterilizing immunity, and high morbidity and mortality rates of diseases caused by ARIs, a thorough understanding of the virus-host interactions during these respiratory infections is crucial. Considering the previous and current worldwide spread of influenza viruses and SARS-CoV-2, the human population can be considered universally pre-immune to these viruses with few exceptions, such as infants in their early years of life.[11,12] In fact, recent epidemiologic models suggest that virtually everyone in the developed world experiences their first influenza infection by age 5 with most hospitalizations occurring in children younger than 2 years.[13] Moreover, early-life exposure to influenza shapes the immune response to subsequent infections and vaccination through a phenomenon known as immune imprinting or original antigenic sin.[14–17]

What influences the immune response?

The fundamental mechanisms conferring this differential immune response as well as those determining its durability are unclear. Gender, ethnicity, and metabolic status have been shown to influence the immune responses to viruses, but the intrinsic factors associated and correlated with this differential immune response still need to be elucidated.[18] It is well known that a potent and broad-spectrum antibody response correlates with a higher survival rate following influenza infection; monoclonal antibodies (mAbs) featuring a potent and broad neutralizing activity (ie, able to block multiple viral strains and variants) have been shown to limit the disease severity in patients affected by SARS-CoV-2 infection.[19]

Prior to the SARS-CoV-2 pandemic, the leading causes of viral respiratory infections were RSV and influenza viruses; human metapneumovirus (HMPV)

and seasonal coronaviruses have been more recently recognized causes of severe disease in children and adults, respectively. Despite reports of influenza virus–SARS-CoV-2 coinfections, the feared influenza–SARS "Twindemic" did not occur. In fact, influenza virus and RSV levels decreased with the emergence of SARS-CoV-2,[20] and studies in China and New Zealand suggest that nonpharmaceutical interventions like lockdowns, mask mandates, and border closures may have also reduced seasonal influenza virus transmission.[20]

INFLUENZA VIRUSES

Numerous respiratory viruses cause symptomatic infections, but most hospitalizations and deaths are caused by influenza viruses, RSV, and HMPV. Since the SARS-CoV-2 pandemic, starting with the 2022–2023 influenza virus season, over 26 million cases of influenza virus have occurred in the United States, with 290,000 hospitalizations, and 18,000 deaths, including 125 pediatric deaths.[21,22]

Three types of influenza viruses (A, B, and C) can infect humans and fall into antigenically distinct subtypes: influenza A viruses (IAV) and lineages (influenza B [IBV], and C viruses). IAV and IBV cause significant morbidity and mortality in humans and are the current target of seasonal influenza vaccines. Seasonal IAV outbreaks are caused by 2 divergent subtypes, H1N1 and H3N2, for which immunity against 1 subtype does not confer immunity against the other. Moreover, IBV outbreaks are largely caused by the Victoria lineage. Influenza viruses undergo antigenic drift, a process in which viruses mutate their major surface glycoproteins to circumvent host antibody responses. Additionally, diverse IAV subtypes (ie, H1N1, H5N1) within the same cell can exchange genomic segments to generate antigenically novel influenza viruses.

Very recently, the discovery of H5N1 bird flu in US cattle and the news that at least 1 person in Texas has been infected, apparently through contact with infected cows, raised public concerns and caught influenza virologists by surprise.[23] However, it is well known that mammals can be infected by avian influenza strains; in many such cases, the symptoms are frequently severe or fatal.[24] This is possible thanks to the extreme variability of influenza viruses, allowing them not only to evade the immune response but also to adapt to species other than their original primary host. One of the primary viral determinants that allows this adaptability is the main surface protein of the virus, the hemagglutinin (HA).

Hemagglutinin: permits infection, mutates frequently

Because HA allows the virus to attach and enter the target cells, it is the first viral determinant permitting a productive infection. HA is also the primary target of the host antibody response following infection as well as of vaccination, and HA therefore frequently mutates to evade these responses.

Structurally, HA is subdivided into 2 functionally distinct domains: the head and stalk. The head domain is highly variable, but contains the crucial regions that allow the virus to bind to target cells. It is therefore the target of the most potent neutralizing antibodies.[25] However, due to the variability of the head, antibodies endowed with a cross-reactive (ie, able to recognize and neutralize multiple influenza strains) and heterosubtypic (ie, able to recognize and neutralize multiple influenza subtypes) profile are rare.[26,27]

The stalk domain is highly conserved because of its functional importance in mediating viral membrane fusion. The stalk domain is targeted infrequently by neutralizing antibodies, and mutations within the stalk domain attenuate viral growth and pathogenesis. As a result, the stalk domain is highly conserved across group 1 IAVs (eg, H1, H2, H5) and among group 2 IAVs (eg, H3, H4, H7).

Strategies aimed at developing next-generation vaccines for influenza mainly target these 2 domains with the goal being a broadly protective immune response.[28,29]

Innovative approaches needed

Improving seasonal vaccines and developing universal influenza vaccines require innovative approaches to generate broadly reactive or cross-protective viral antigens combined with cutting-edge vaccine platforms. During a newly emerging influenza virus pandemic, there is little time to develop new vaccines for highly infectious strains, particularly when the human population has little or no existing pre-immunity to a new influenza virus subtype. Protective broadly reactive vaccines and mAbs derived from these vaccine immunogens are effective strategies for combating a newly emergent pandemic. These vaccines and mAbs can be produced, stockpiled, and administered quickly to infected patients or a community at risk for infection with a highly pathogenic avian influenza virus, such as strains of subtypes H5Nx.

Pandemic preparedness and the development of next-generation vaccines are linked. The objective is to either elicit broadly reactive, more universal

immune responses or to isolate and develop mAbs derived from the use of these new vaccines with the resulting products intended for immediate intervention against any subtype of influenza virus that may emerge now or in the future.

New tool: artificial intelligence

Artificial intelligence (AI) may accelerate the speed at which vaccines and immunotherapies (eg, mAbs) can be developed. An increasing number of papers in the scientific literature are describing the use of machine learning, AI, and quantum computing approaches for designing new vaccines and drugs for different types of diseases, including infectious diseases.[30–33] Routinely employed, these tools might make the "100 days mission," aspired by the Coalition for Epidemic Preparedness Innovations, a reachable and closer goal and provide the global community with vaccines and therapies that can be almost immediately deployed (in 100 days) in an epidemic or pandemic outbreak.

RSV AND HUMAN METAPNEUMOVIRUS (HMPV)

RSV and HMPV, which belong to the *Pneumoviridae* family, are leading causes of viral bronchiolitis and viral pneumonia in children and the elderly.[34] RSV infections in infants usually occur before age 2, causing approximately 58,000 hospitalizations and 100 to 500 deaths among children under 5 years old;[35] among adults over age 65,[36,37] RSV causes 177,000 hospitalizations and 14,000 deaths each year.[38,39] HMPV infection in children usually occurs before age 5; severe disease is common in immunocompromised patients, including lung transplant and hematopoietic stem-cell transplant recipients, with several deaths associated with viral infection.[40–42]

HMPV currently has no approved vaccine, but a vaccine for RSV was approved recently by the US Food and Drug Administration for use in people older than 60 years and in pregnant women. Moreover, new and more effective mAbs have been approved in Europe and the United States for prevention and treatment of RSV disease in select populations. Previously, the only available prophylactic and therapeutic treatment was palivizumab, a humanized mouse mAb.

Focus on fusion protein

As in the case of the influenza virus surface protein HA, the target of RSV and HMPV vaccines and mAbs is another viral surface protein: the fusion (F) protein. The F protein is necessary for RSV infection both in vitro and in natural infection. Upon attachment of the virus to the target cells, a remodeling process of the F protein is initiated. The protein transitions from a prefusion state (before virus attachment to the target cell) to the postfusion state (after virus attachment to the target cell) to cause fusion of virus and cell membranes and thus the entry of the virus into the target cell. An immune defense, whether mounted by the immune system or by vaccinologists and immunologists, must be directed against a moving target.

Most *Pneumovirus* vaccine candidates are focused on the F protein.[43] The success of these vaccines for RSV stems from lessons learned from an unfortunate vaccine trial in 1966, whereby a formalin-inactivated RSV vaccine candidate was given to children and induced the production of nonprotective antibodies. The vaccine resulted in enhanced disease upon natural RSV infection, leading to hospitalization of many vaccine recipients and 2 deaths. This failure has been attributed to the induction of inflammatory T cells, elicitation of antibodies directed toward nonprotective epitopes and actually facilitating the infection, and poor toll-like receptor stimulation. It was also discovered that formalin inactivation of RSV induces a conformational change in the RSV F protein from the prefusion to the postfusion conformation. Beginning with the stabilization of the RSV F protein in 2013, successes have occurred, including the development of several vaccine candidates and in-depth knowledge of RSV F epitopes.[44] Similarly, HMPV F was stabilized in the prefusion conformation, and the antigenic epitopes on the HMPV F protein were finally and successfully mapped.

As with influenza, machine learning and AI tools may help resolve potential issues related to the molecular structures of drug or vaccine targets, facilitating their prediction, and accelerating the development of vaccines and therapies. Several computational tools have been developed to achieve these goals, such as AlphaFold, Rosetta, ABodyBuilder, ABlooper, DeepAb, and IgFold.[45–48]

Compared to the influenza HA, the F protein is highly conserved among circulating RSV and HMPV strains, and approximately 30% is conserved between viruses. Studies of the antigenic epitopes on the RSV F and HMPV F proteins have shown that prefusion-specific antibodies are more frequent and potently neutralizing for the RSV F protein, while for HMPV F the prefusion and postfusion conformational states have been shown to elicit similar antibody responses.[49,50] Additionally, 3 antigenic sites are more conserved between the RSV and HMPV F proteins,

including antigenic sites IV, III, and V, identified by the isolation of mAbs that cross-neutralize both viruses. The mechanism by which these antibodies are elicited is unclear. For example, all previously isolated cross-neutralizing antibodies targeting antigenic site III are encoded by certain antibody genes, suggesting a conserved mechanism of recognition for both RSV and HMPV F by the human immune system.

Further, some prefusion-based RSV F vaccines can recall a subset of HMPV F antibodies. Understanding the epitope and structural basis for recognition by the immune system as well as tracking the generation of these cross-reactive antibodies will inform the development of novel cross-reactive vaccines.

CORONAVIRUSES AND SARS-COV-2

SARS-CoV-2 is the virus responsible for the COVID-19 pandemic that emerged in late 2019 in Wuhan, China. It belongs to the family of coronaviruses, which are enveloped RNA viruses known for causing respiratory illnesses in humans and animals. These respiratory illnesses can be caused by the so-called seasonal coronaviruses, which typically cause cold-like symptoms: runny nose, cough, and sore throat.

The coronaviruses have a characteristic structure with spike proteins protruding from their surface, giving it a crown-like appearance under electron microscopy, hence the name "corona" virus. Like HA and F proteins, these spike proteins are essential for the virus to bind to and enter host cells, particularly cells lining the respiratory tract.

In the case of SARS-CoV-2, the clinical manifestations of COVID-19 vary widely, ranging from asymptomatic or mild respiratory symptoms to severe pneumonia, acute respiratory distress syndrome, multiorgan failure, and death, particularly in high-risk populations such as older adults and those with underlying health conditions.

Mass vaccination campaigns have been under way globally to control the spread of SARS-CoV-2. The development of effective vaccines and immunotherapies (eg, mAbs) has been a breakthrough in the fight against COVID-19.[19,51] However, ensuring equitable distribution of vaccines, addressing vaccine hesitancy, and monitoring the emergence of vaccine-resistant variants will be critical in achieving herd immunity and preventing future outbreaks against SARS-CoV-2 as well as against any other emerging infectious pathogen or disease.

As with influenza viruses, SARS-CoV-2 can mutate, leading to the emergence of new variants with potentially altered transmissibility, virulence, or ability to evade immunity.[10] Continued surveillance and genomic sequencing are essential for monitoring the evolution of the virus and adapting public health measures and vaccine strategies accordingly.

Of special interest from a clinical perspective is the understanding of the long-term health consequences of COVID-19, often referred to as "long COVID," which are a priority for the healthcare systems worldwide. Research is ongoing to elucidate the mechanisms underlying persistent symptoms and complications in some individuals after recovering from acute infection.

Among the few positive aspects derived from the COVID-19 pandemic, there is the importance of the need for robust pandemic preparedness and response systems at local, national, and global levels. Investments in public health infrastructure, surveillance systems, research and development, and international cooperation will be crucial in mitigating the impact of future pandemics.

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