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COMMENTARY

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Addressing the unmet needs: Optimized vaccine design for human metapneumovirus

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Human metapneumovirus (hMPV) has recently garnered widespread attention as one of the primary causes of respiratory infections across all age groups, especially for infants, the elderly, and immunocompromised individuals. The latest surveillance data indicates that hMPV was the second most prevalent respiratory pathogen among outpatients presenting with influenza-like symptoms in China in December 2024 (retrieved from www.chinacdc.cn). Reports have suggested that hMPV is associated with the acute exacerbations of underlying respiratory illness, including chronic obstructive pulmonary disease and asthma, and can even lead to severe infections in immunocompromised individuals. However, effective vaccines and antiviral agents targeting this virus remain unavailable.

hMPV is an enveloped, non-segmented, negative-sense single-stranded RNA virus belonging to the *Pneumoviridae* family. It shares a similar genomic structure to that of respiratory syncytial virus (RSV). Both RSV and hMPV are prevalent worldwide, primarily transmitted via droplets, and exhibit seasonal distribution characteristics. Their viral genomes encode a surface glycoprotein, the trimeric fusion (F) protein, which mediates fusion between the virus and host cell membranes during viral entry. The F protein facilitates viral attachment and fusion processes, and demonstrates strong immunogenicity. As the most crucial surface glycoprotein, the F protein is highly conserved among different subtypes of hMPV, making it an attractive target for the development of therapeutic monoclonal antibodies and vaccines.

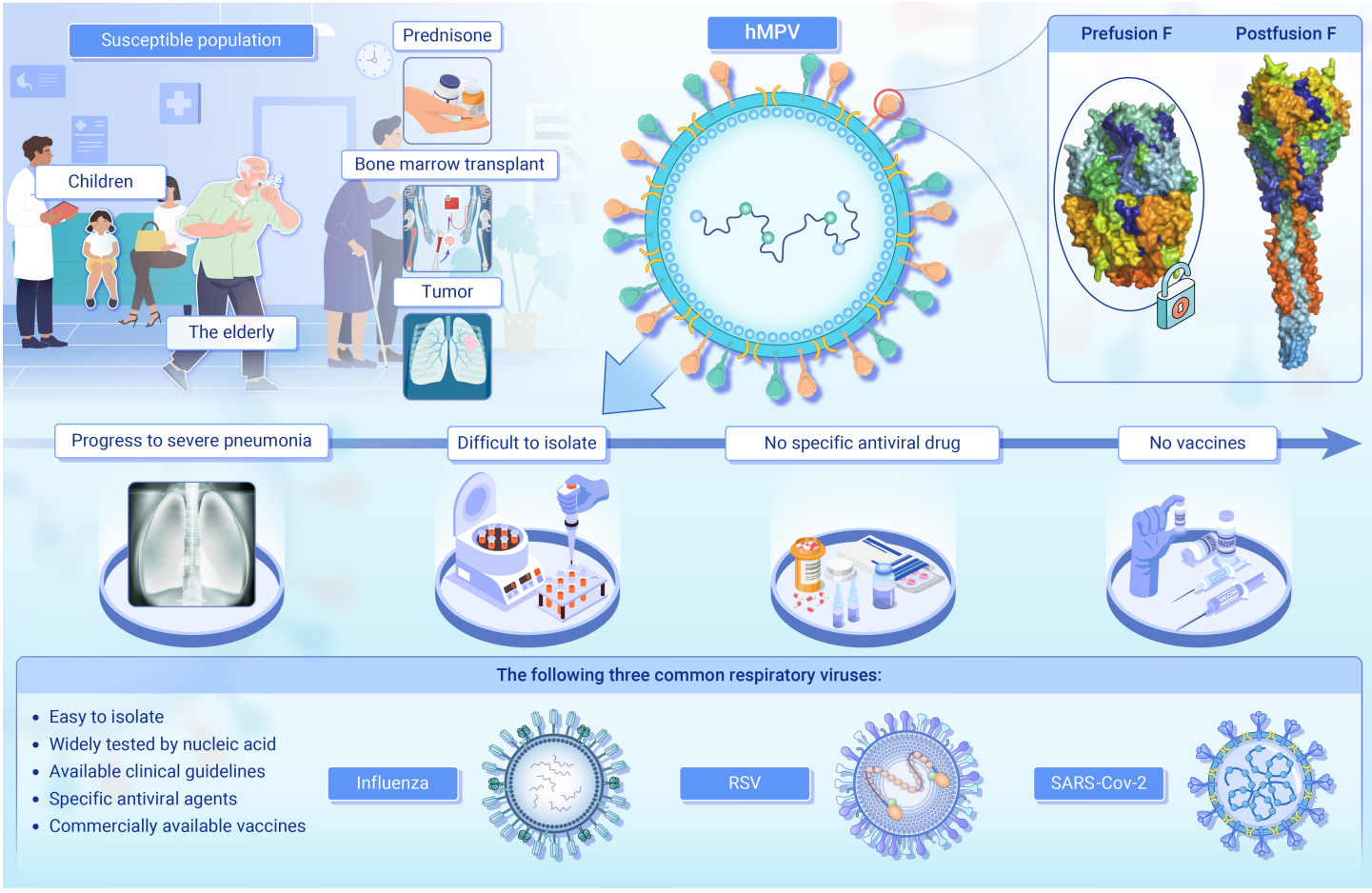

Figure 1. Comparisons of clinical diagnosis, treatment, and prevention of several respiratory viruses hMPV, human metapneumovirus; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

The development of a vaccine candidate for hMPV has been challenging. The mature F protein is a disulfide-linked F2/F1 heterodimer trimer that adopts a metastable pre-fusion (PreF) conformation, which subsequently undergoes a series of irreversible conformational changes to form a rod-shaped, stable post-fusion conformation. However, the post-fusion F conformation elicits weak or non-functional neutralizing antibody responses and

may cause adverse reactions, thereby rendering it unsuitable as a vaccine antigen. Conversely, the highly anticipated and most promising PreF conformation faces challenges of structural instability and low expression levels. To address these challenges, the development of vaccines for RSV and hMPV has long relied on interprotein disulfide bonds to stabilize the prefusion conformation of the F protein. However, this strategy often affects critical neutralizing epitopes. Although twenty years have passed since the first isolation and report of the virus, there is currently no commercially available vaccines against hMPV.

The recent success of the marketing RSV vaccines based on the rational design of a pre-fusion F protein sheds light on the development of hMPV vaccine. In 2024, Bakkers *et al* published a study on utilizing artificial intelligence to engineer the F protein with dual cleavage sites, enabling the screening of alternatives that stabilize the pre-fusion conformation at the natural folding interface of the native oligomeric trimer.[1] Consequently, they obtained a prefusion protein vaccine candidate that did not require a heterologous trimerization domain, exhibiting high expression levels and thermal stability. This protein candidate was capable of inducing high levels of cross-neutralizing antibody responses against two different genotypes of hMPV (A2 and B1), providing nearly complete protection of cotton rats against hMPV. A more recent study by Lee *et al* demonstrated that by optimizing a region known as the *buried acidic patch*, they were able to develop a stable prefusion trimer independent of interprotein disulfide bonds.[2] By incorporating rationally designed hydrogen-bond networks or hydrophobic interactions, they increased the proportion of pre-fusion trimers. This design not only maintains all critical neutralizing epitopes but also induces potent neutralizing antibody responses. This breakthrough offers novel insights into the development of more effective vaccines and lays the foundation for the rational design of vaccines against other viruses. Although these vaccine candidates still require additional preclinical studies and human trials, the structured-based rational design strategy targeting the pre-fusion conformation of stable F proteins has demonstrated considerable potential.

It is well-recognized that vaccine prevention is often more critical than treatment in many other viral infections. At the onset of the COVID-19 pandemic, effective antiviral drugs were scarce, whereas multiple vaccines were rapidly developed and marketed, significantly mitigating the progression of the pandemic. Annual influenza vaccines have been widely available for decades. Recently, RSV vaccines have been introduced in the United States, and will soon be available in other countries. Despite ongoing efforts by the researchers, no vaccine for hMPV is currently available. However, the aforementioned rationally designed vaccines are bringing new hope. Notably, given the genetic similarities and homology between RSV and hMPV, the realization of an RSV/hMPV bivalent vaccine based on this rationally designed prefusion conformation could potentially benefit a broader patient population. Additionally, a strategy based on rational design of the T-cell epitope is also under investigation.

Despite advancements in vaccine research, the overall lag in research and clinical management of hMPV infections remains a concern. Studies have shown that hMPV is associated with the development of severe pneumonia and even viral sepsis.[3,4] This is especially the case in patients after bone marrow transplant, as the mortality rate is up to 40% after hMPV infection.[5] Data from our institution reveal that over 60% of severe pneumonia cases associated with hMPV are accompanied by bacterial or fungal coinfections, and nearly half of these patients succumb to the illness (unpublished). This represents a significant issue of concern for global public health. In Figure 1, we compared the current diagnostic and treatment status of the four most common respiratory viruses: influenza virus, SARS-CoV-2, RSV, and hMPV. There are several notable points regarding hMPV. Firstly, the isolation and culture of hMPV in laboratory settings is more challenging, adding to the difficulties of research in this field. Briefly, for the cultivation of hMPV, nasopharyngeal specimens must be inoculated onto specific cell lines utilized in research laboratories and subjected to trypsin treatment to cleave the F protein of hMPV. Despite the application of current technologies, the success rate of viral isolation remains relatively low. Secondly, the primary detection method currently relies on viral nucleic acid testing, which is mainly conducted in surveillance laboratories and not yet widely available in major hospitals. Although metagenomic next-generation sequencing can assist in detection, its high cost limits its clinical application. Thirdly, there is a lack of antiviral drugs specifically targeting hMPV, resulting in limited therapeutic recommendations in current clinical guidelines. A few small-molecule antivirals have been reported in pre-clinical studies, but their clinical efficacy has yet to be tested.

Indeed, research in the field of hMPV infection remains notably scarce. The progress in vaccine research represents a promising start, and we eagerly anticipate further advancements in this area to contribute to the prevention and control of significant respiratory virus infections.

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DECLARATION OF INTERESTS

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