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Review

# Recent Human Metapneumovirus Outbreak in East Asia: The Time to Shift Immunological Gears is Now

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**Abstract:** Recently, there has been a significant outbreak of clinical pneumonia caused by the Human Metapneumovirus, particularly in Northern regions of the People's Republic of China, causing thousands of hospitalisation cases. Such an outbreak has grown fresh concerns with regards to a potential spread of the novel infectious disease to several other world countries and causation of public health-related difficulties that may be similar in nature with the effects of the SARS-CoV-2-induced COVID-19 pandemic, which occurred from March 2020 to March 2022 before the disease finally became endemic in nature. Throughout the COVID-19 pandemic, a novel immunological research narrative was developed, in which a wider inclusion of natural immunity-based elements was recommended as part of an update in general approaches contained by immunotherapeutic and vaccine-related clinical research. Particularly, it has been suggested that a fairly decreased concentration of Type I and Type III elements from the host interferon system be placed in the central area of the natural immunity-based immunisation and immunisation adjuvance. Several clinical trials have confirmed the important position of such interferon system elements in the natural immunity department responsible for immunising functions. Given the fact that major components of the natural immune system have recently shown to display considerable adaptive immunity-like traits, such as specificity and long-term "memory", natural immunity-based vaccination may now be deemed as scientifically plausible, contrary to initial scientific projections that they can only constitute vaccine adjuvants. Approaches as such may include a low dose of Type I and Type III Interferon-, and perhaps protollin-based treatment of nasopharyngeal tissues, as well as of natural and adaptive lymphocytes, and of plasmacytoid dendritic cells also, which represent both factories for Type I and Type III Interferons, as well as valid immune system-based vaccine candidates against infectious and oncologic diseases, alongside natural and adaptive lymphocytes. Such components of the immune system may be utilised in combination to confer the most effective version of such an overall candidate of a clinical response. Other vaccine candidates may involve live-attenuated viral genomes either lacking the interferon-suppressive genes or containing them as the only slightly active genetic regions, with the overall purpose of stimulating an evolutionary push of the interferon-encoding genes to outcompete the already advanced stages of microbial evolution, whose stronghold seems to be largely upon the host interferon system. Other approaches may also involve the development of live-attenuated pathogen-derived vaccines that have Interferon I and III-encoding genes inserted into the viral genome as its sole active genetic components. There may be a novel, experimental process involving the isolation of Rhinoviral agents during the beginning of local, seasonal outbreaks and perhaps inducing their weakening as well, prior to the performance of a small-scale gene editing through the insertion Type I and Type III Interferon-encoding genes into the viral genome, prior to its release back into the local environment. Such a process may turn the virus into a vaccine, as the immune system would automatically be activated once the virus undergoes receptor-mediated endocytosis and starts expressing its genes. If such a procedure is performed accurately and matches all bioethical guidelines, then the Rhinovirus-induced infectious disease in the upper respiratory tract may be prevented in many cases and probably even become gradually eradicated in the end.

**Keywords:** human metapneumovirus; outbreak; immune escape; R0 rate; polymorphic microbes; single-nucleotide polymorphism; natural immunity; adaptive immunity; immune evolution;

microbial evolution; adaptation; interferons; dendritic cells; lymphocytes; microbial genome; gene editing

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## Introduction

The human metapneumovirus, which is abbreviated as hMPV, constitutes a member of the Pneumoviridae family and the Metapneumovirus genus, and represents an enveloped, negative-sense, single-stranded RNA-based virus that causes lower respiratory tract clinical illness, particularly in children aged 0-5, and the fact that the immune systems of young children may not have been exposed to many related microbial agents could explain such a phenomenon. Despite the development of fresh fears with regards to a possible repetition of a pandemic scenario, the case-fatality ratio of hMPV-induced infectious disease is visibly lower than the one of COVID-19, making it less likely that the disease will become a deadly pandemic. Furthermore, unlike SARS-CoV-2, which represents a novel viral species, HMPV existed for several years beforehand, as it was only a novel viral variant that started spreading more aggressively in the North of the People's Republic of China. Nonetheless, the clinical symptoms of the disease are similar in nature, the lethality rate of the infectious disease remains high within hospital settings of Intensive Care (ICU), with average estimates of 22% (Choi S. H. et al., 2019). Moreover, the hMPV viral agent also has a slightly higher rate of human-to-human transmission than the H1N1 Influenza A virus ( $R_0$ : 1.1-1.4), which does urge public health authorities to locally re-develop insignificant measures to help adults and children alike prevent the spread of the disease, through the wearing of face coverings, recommendation of people in affected geographical settings to practice social distancing and for clinical patients to stay at home until their recovery (Hacker K. et al., 2022). Scientific researchers may already be in the process of obtaining the genomic data of the virus and starting vaccine-based innovations, as it is likely that humanity has significantly learned her lessons from the SARS-CoV-2-induced COVID-19 pandemic, when only a few months were required from the viral disease to turn from a local outbreak-based epidemic into a pandemic. At the same time, it is important for all sides of genuine research efforts to be equally taken into consideration during the process of scientific investigation and clinical innovation, given the fact that novel, major discoveries occurred regarding the resolution of functional immunity in both innate and adaptive immune departments. It seems that the problem which enables novel infectious viruses to cause significant clinical illness is centred around gaps in the bridging between innate and adaptive immune pathways, which increasingly encourage immunological researchers to build a broader and firmer bridge of signalling between first-line and third-line immune elements. Such a scenario involves major improvements in both the timing and the methodology contained by such signal-based immune bridging and could be accurately described through a novel concept named "United Immune System".

The fact that children aged 0-5 are primarily affected by the viral disease may further indicate that novel viruses and viral variants have specifically adapted to evade first-line immune signals, given that children seem to have sensitivity levels of interferon-based response that are above the average within the human population. The fact that such a viral variant emerged after the Omicron variants of SARS-CoV-2, which are also particularly adapted to the interferon system, may expose an evolutionary pattern within viral adaptations, as the majority of viral agents first hijack the host interferon system - both directly and indirectly - before it attacks the central, adaptive areas of the host immune system. On the other hand, adult patients with one or more underlying health conditions are also at risk of developing significant clinical illness due to the fact that their interferon system may not be as competent as the one of young adults with no significant comorbidities. Overall, decreased restrictions against a distribution of the viral load to neighbouring tissues and organs is often a major factor of the viral spread from the upper to the lower respiratory tract, which in turn

leads to the infection and inflammation of the bronchioles and alveoli, or in short, to the development of viral pneumonia. Such a viral spread may often also be a factor for the development of secondary infections in similar areas of the respiratory system due to the fact that the host immune system is already weakened by the generalised infective event. Likewise, it may now be deemed as substantially necessary for clinical researchers to shift gears in immunological and vaccine-based scientific investigations, perhaps by including such elements of the natural immune system more widely than before. In scientific progress, it is not a particular successful event that defines breakthrough, but exposure to the need of change, which ultimately defines such progressive trajectories observed throughout the history of scientific research. It may be that the initial discovery of vaccines that stimulate the development of adaptive immunity represents an initial gear of an overall journey of immunostimulatory, immunomodulatory and immunising processes that overall keep mankind in an evolutionary spot higher than pathogenic microbial agents.

## Discussion

Despite the fact that adaptive immunity represents the central sector of all immunity, it is the first-line, natural immune system that ultimately plays the foundational role of an adequate overall immune response; one that is relevant to the abilities of each microbial agent to hijack rates of immune recognition. Such phenomena have only recently been thoroughly investigated, due to the fact that adaptive immunity-based vaccines have shown to be highly successful throughout the past centuries, having saved hundreds of millions of human and animal lives worldwide, and that it was subsequently not needed for scientists to investigate the clinical context in a more profound manner. It was only in the recent decades that scientists were required to perform further research, as novel pathogenic agents were shown to cause clinical disease with high rates of consequences, in spite of such previous efforts. In other words, a missing “puzzle piece” was eventually observed, one that involves first-line immune signalling, despite the fact that such traditional vaccines have brought considerable positive effects upon natural immunity as well. Such a missing “piece” has become more evident with the occurrence of the SARS-CoV-2-induced COVID-19 pandemic, as the disease affected the general population far more than other recent epidemic and pandemic diseases that include the HIV-1-induced AIDS pandemic. Albeit, influential public health authorities did start suggesting a low dosage of Type I Interferon-based clinical approaches to prevent and/or treat AIDS in its very early stages. Likewise, there has already been an existing level of awareness regarding a potential update in vaccinology, perhaps to a level proportional to the current stages of microbial evolution, and the recent COVID-19 pandemic only increased such levels of awareness in a rather exponential manner. The facts that plasmacytoid dendritic cells, which are regarded as major factories of Type I and Type III Interferon glycoproteins, constitute major factors of immune system-based vaccination and that the natural and adaptive immune systems actually display a major intertwine of specificity and “memory”-like traits, may imply the possibility that such interferon glycoproteins also constitute important factors of immune system-based vaccination against oncological diseases and, implicitly, of several infectious diseases induced by polymorphic microbes (Paunescu V., 2011). Such applications may bring considerable prophylactic and early therapeutic effects against diseases like COVID-19, AIDS and perhaps also human metapneumovirus-induced pneumonia.

The context of the overall evolutionary battle between human and animal immune systems, and polymorphic microbial agents may prove to be more complex in nature than previously estimated. The process of microbial evolution comprises three methodologies in which pathogenic agents use the immune system to their advantage: the molecular self-camouflaging of the microbial genome, via the double capping of the 5' end of their genome through the catalysis of methyltransferase enzymes formed by the assembly of a few non-structural proteins encoded by the microbial genome, which prevents the cellular recognition of both Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), which in turn leads to the prevention of the activation of the signalling transduction responsible for the activation of Type I and Type III

Interferon-Encoding Genes (INGs); the active hijacking of the host, first-line immunity, via targeting transcription factors responsible for the activation of INGs, cleaving of mRNA that encodes Type I and Type III Interferons, targeting various components of the signalling transduction that is overall responsible for the activation of important Interferon-Stimulated Genes (ISGs), cleaving of the mRNA product of ISGs and lysis of ISG-encoded cytokine proteins, and the facilitation of the spread of both the microbial load and their protein products that support their process of immune evasion through inter-cellular channeling nanotubes. Throughout such an overall process, numerous infectious pathogens maintained a threshold level of adaptation via single-nucleotide polymorphisms that were proportional to the rate of immune adaptation to the pathogenic agent in cause. Likewise, despite the fact that major solutions against many infectious diseases as such may already exist, humanity may have reached a state of evolutionary context in which an update in prophylactic and early therapeutic-based immunotherapeutics and vaccinology is needed for both humans and animals to evolutionarily outcompete pathogenic agents with complex levels of displayed genetic polymorphism (Carp T., Metoudi M. and Ojha V., 2024).

It is well-known that the interferon system comprises major components of the cytokine system, which is contained by the innate immune system. Nonetheless, given the fact that an adequate synthesis of Type I and Type III Interferons is substantially responsible for the adequate synthesis of Type II Interferons by natural lymphocytes, it may be that Type I and Type III Interferons have major characteristics of pre-cytokine components, comprising the utmost foundational level of innate immunity and of the overall immune system. Such an aspect may explain the phenomenon in which human recombinant Type II Interferons, whilst bringing valid immunotherapeutic effects, they do bring a higher incidence of induced proinflammatory immune responses, compared to Type I and Type III Interferons, which modulates immune responses after they produce them in a more record amount of time. Nonetheless, it has been suggested that Natural Killer Cells, which are known as major factories of gamma-interferons, constitute a potential natural immunity-based vaccine candidate against COVID-19, which could further increase hopes that natural immunity-based vaccination is actually possible; not solely against COVID-19, but against several other infectious diseases induced by polymorphic microbes, as well as against various oncological diseases (Bossche G. V., 2017). In a nutshell, it may be more accurate to state that Type I and Type III Interferons represent part of first-line, innate immunity, whilst Type II Interferons represent part of second-line, innate immunity. Such an overall point of observation may indicate the fact that revolutionary immunostimulatory and immunomodulatory effects in the human and animal organisms may lead to results as far as the long-term slight increase of the average lifespan, due to the fact that a significantly lower extent of clinical disease would ultimately occur following exposure to various microbial agents, resulting in the metabolic system not to be exposed to more straining levels of activity - for example via excessive rates of oxidative stress - as frequently as before, which in turn could slightly decrease average rates of cellular and tissue-related aging. It may be more plausible for such effects to occur in the long run if there is a joint immunostimulatory and immunomodulatory approach, that perhaps would also include adaptive immunity-based and also specific live-attenuated microbial agent-derived vaccine candidates in more complex epidemiological contexts. Other approaches may involve a small-scale gene editing of live-attenuated pathogenic genomes, through the insertion of Type I and Type III Interferon-encoding genes into the pathogenic genome, during the process of live-attenuated pathogen-derived vaccine development. Furthermore, there may be a novel, experimental method in which circulating, relatively weak viruses like the Rhinovirus, would be isolated into a laboratory setting during the initial stages of a local outbreak of the seasonal flu - preferably at the beginning of the autumn season, when there may be a considerable opportunity for Type I and Type III Interferon-encoding genes to be distributed through natural viral replication- and perhaps have its pathogenicity decreased, before undergoing small-scale gene editing through the insertion of such Type I and Type III Interferon glycoprotein-encoding genes (INGs), before it is released back into the local environment. The implications of such a procedure would involve an automatic signalling to the immune system that a fault with an environmental

origin is present at the cellular level, leading to the lysis and disposal of the virus as soon as it undergoes receptor-mediated endocytosis into the first host cells and begins the process of viral gene expression. In other words, there may be a small window of opportunity for viruses to be turned into vaccines without the need of the utilisation of nasal or pharyngeal sprays; let alone traditional “needle” intervention. Interestingly, such a procedure would possibly reflect the Christian model of “God died and trampled upon death.” It is important to mention that all bioethical guidelines and the “First, do no harm” principle of medicine must be respected to the letter in any experimental research procedure. Likewise, it may be essential to clinically evaluate such a method “in small steps” and involving molecular agents that are not deemed as public health hazards. The key aspect of such a potential update in vaccine-based and immunotherapeutic approaches would be to induce an evolutionary shift that would involve faster rates of Type I and Type III Interferon-based signalling; ones that are promptly mounted once the first viral agent enters each host cell. The higher the delays of such interferon-based immune activation, the higher the discrepancies developed within the cytokine system and the higher the immune disruptions will overall be. There may be an existing relationship of proportion between the pre-symptomatic stage of an illness caused by a polymorphic virus and the probability that the induced clinical disease will significantly impact the health state of the patient due to the fact that the lower the rates of restriction against the viral load distribution makes the immune system more prone to become “overwhelmed” when it finally becomes activated, due to the need to rapidly produce a high quantity of Type I and Type III Interferons and also because such high concentrations of interferon glycoproteins will likely result in the development of excessive rates of pro-inflammatory cytokine-based immune responses. The majority of complementary, early therapeutic approaches aid in a faster and more proportional development of innate immune signals following cellular exposure to the pathogenic agent. Likewise, the key word in the present clinical context may be “timing”.

According to recent scientific evidence, the human metapneumovirus is among the viral agents that cause signals of natural immunity to be poorer than the threshold level of response, and it may be that this phenomenon leads to the production of a domino effect of decreased quality of an overall immune response, as the production of cytokine is affected, causing natural lymphocytes not to be recruited in a significant manner, the levels of gamma-interferon synthesis to be deficient and consequently, adaptive lymphocytes not to undergo an effective level of polarisation, which is crucially required for an overall qualitative immune response to occur (J. A. Soto et al., 2018). Moreover, the recent HIV-1-induced AIDS pandemic involved a direct infection and lysis of both helper CD4<sup>+</sup> and cytotoxic CD8<sup>+</sup> T-Lymphocytes, and they had their interferon system hijacked in the first stages of their infection as well. Likewise, clinicians may suggest a treatment of such adaptive lymphocytes with a low dosage of Type I and Type III Interferons, perhaps alongside a low dose of protollin, which confers similar interferon-sensitising effects and which is known to represent an immune system-based vaccine candidate against Alzheimer’s Disease (Frenkel D. et al., 2005). A similar application may be deemed as successful for the Retinitis Pigmentosa proteinopathy, which involves a progressive loss of vision to the point of patients reaching a state of complete, clinical blindness, usually by their mid-ages (Carp T., 2024). Such a context may not have been more relevant than in today’s situation of unprecedented lack of certainty and even security with regards to potential public health threats in the near future. Perhaps there is also a unique opportunity for clinical researchers to implement various models of Artificial Intelligence to increase the accuracy and speed of projecting specific single-nucleotide polymorphic mutations in specific microbial agents, as well as of the projection of prophylactic and early therapeutic approaches against such induced infectious diseases (Carp T., 2024). The ideal rates of IFN I and III-based activation in both temporal and quantitative planes bring a balanced ratio between pro-inflammatory and anti-inflammatory cytokines, which is a result of an adequate expression rate of Interferon-Stimulated Genes (ISGs). Such a balance is highly responsible for the adequate recruitment and polarisation of adaptive lymphocytes, which in turn rapidly decrease the viral load and prevents the immune system from building responses that may be too straining for the host tissues and organs.

## Conclusion

The continuous emergence of novel epidemic outbreaks in various parts of the world should not concern humankind as much as stimulate clinical researchers worldwide to innovate revolutionary approaches in immunological therapy and possibly in vaccine-based research and innovation. With recent local outbreaks of Monkeypox, Marburg, Avian Influenza and now Human Metapneumovirus, it has become increasingly clear that the principal target of polymorphic viruses is the host interferon system, and particularly Type I and Type III Interferon glycoprotein-encoding genes (INGs), which are often silenced in direct and indirect ways, ultimately resulting in the development of an overall phenomenon of “immune confusion”. It may be that the primary solution to the evolutionary dilemma of both direct and indirect methods of microbial self-camouflaging implicates the development of a broader and firmer bridge between first-line and third-line immune activation, according to the novel “United Immune System” concept, which in turn would decrease the extent of time between such two immune activation events. As a result, it may be that the shorter the duration of the pre-symptomatic stage of the infectious disease, the more statistically probable it is for the immune system to successfully lyse and dispose of the pathogen without undergoing significant complications. Apprehending the evolutionary abilities of numerous microbial agents to profoundly hijack the host immune system may aid in the innovation of proportional public health and medical solutions. Based on the current pattern of public health events worldwide, it may be important to precautionary build a scientific hypothesis in which the emergence of a new, life-threatening pandemic illness may occur as soon as the year 2035, particularly if there is no significant update in immunological prophylaxis and therapeutic pathways. Change represents a key term in the entirety of the evolutionary process, and progress may only occur if specific gears are eventually changed into a more evolved version. Likewise, scientific updates and progress are as real as the theory of evolution, and this certainly includes the domains of human and animal immunology and vaccinology. The burdens that mankind bore during the SARS-CoV-2-induced COVID-19 pandemic places a major pressure onto scientific researchers to innovate novel methods of immunotherapy and possibly vaccination to at least attenuate the burden of following public health crises. An overall update of immunotherapy and vaccinology may lead to a Golden Age of human and animal health and overall quality of life if performed in thorough accordance with all principles of qualitative scientific and clinical research, as well as to biological and medical ethics.

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