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Review Article: Exploring the Impact of Human Metapneumovirus: A Red Global Alarm for 2025

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***Abstract*— Respiratory infections including Respiratory syncytial virus (RSV) and Human metapneumovirus (hMPV) are the most common worldwide infections, Respiratory syncytial virus's (RSV) and hMPV considers a public health concern among all countries since they are sharing same clinical presentation, these viruses have the potential to unleash as the global pandemic has already laid a strong foundation. While the similarities with RSV are clear, patient needs to follow a concrete approach including continuous administration of antibiotics or antivirals to fight these viruses. Mild to severe complications with hMPV demand more research covering both hMPV and RSV concurrently. This review attempts to improve knowledge of the pathogen and frequency of hMPV as a possible transmission vector by aggregating present data. Examining its possible effects and clinical differences among the human population will also help us to better understand hMPV and suggest ways of prevention. In conclusion, we seek to emphasize findings from prior research while generating empirical evidence to support our claims. Moreover, it is anticipated that by 2025, hMPV may present a global health risk.**

***Keywords*— Human Metapneumovirus (hMPV), global health risk, respiratory pathogenesis, global outbreak.**

I. INTRODUCTION

Human Metapneumovirus (hMPV) becomes an increasing concern in public health. However, despite its apparent significance and established threat, much remains to be better understood, including the identification and classification of the associated genotypes. This essay was conducted to explore hMPV and its potentially detrimental consequences for public health, particularly as it is foreseen to rise in importance by 2025. The current review aims to be informative by presenting numerous insights into hMPV and its significance. It calls for a broader sense of urgency and more widespread interest in this subject matter in order to bolster international research and policy-making efforts towards prevention and control measures. Human Metapneumovirus (hMPV) is a predisposing factor for a range of clinical illnesses, yet it is a pathogen mostly of growing, rather than present, impact [1].

It was first emphasized as a public health issue in 2001 when it was identified as the cause of community and household upper respiratory tract infections. At the first time, the virus was named Paramyxovirus but was subsequently renamed hMPV in 2002, which more precisely reflects its major viral structures [2]. Currently, at least five genotypes of group A and B hMPV have been identified, but research to further categorize other possible genotypes is yet to be carried out. Children in developing nations, in addition to adults in developed societies whose adaptive immune defenses are less active, are among the worst affected by this virus. The preferred peak ages of hMPV morbidity are deemed to be around three years of age and adult over ten years due to the phenomenon of immunosenescence, in inclusive order of precedence. Overall, hMPV appears to have an active predisposition to immunocompromised human cohorts [3]. This review came to elucidate the impact of the hMPV on the global public health that might be impact like COVID-19 pandemic or not.

II. UNDERSTANDING HUMAN METAPNEUMOVIRUS

Human Metapneumovirus (hMPV), a member of the Paramyxoviridae family, has an eccentric and pleiomorphic structure. The hMPV genome composed of non-segmented, negative-sense viral RNA, which encodes 10 genes, two of which encode multiple proteins. The hMPV surface is studded with the fusion glycoprotein (F) and the attachment glycoprotein (G), composed of both a globular head and a stalk. A ridge that stands upright on the G head distinguishes the protein among respiratory viruses

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and underlies the attachment of the virus to human airway epithelium. In the context of the epidemiology of respiratory viral infections, it is crucial to understand the distinct properties of the virus, including its replication and transmission mechanisms, to monitor outbreaks and contain the spread of the virus [4].

The virus shares symptoms with many others, causing acute respiratory tract infections (ARTI) across the globe. It is the most severely impact injury on case among respiratory viruses and leads in other regions or population socio-economic stratifications to lower respiratory tract infections (LRTI). HMPV is the second most prevalent pathogen of viral pneumonia in Asia, and also ranks second among children and elderly patients hospitalized due to viral infections. It affects diverse populations of different age groups and is associated with the cold weather season that has higher rates of outbreak of acute respiratory infections [5].

A. Structure and Genome

Human Metapneumovirus (hMPV) belongs to the Metapneumovirus genus in the Paramyxoviridae family. The virus possesses antigenic as well as established pathogenic similarities with respiratory syncytial virus (RSV), displaying a genome that shares common configurations and mechanisms. Structurally, hMPV displays a pleomorphic envelope and two glycoproteins inserted in the lipid bilayers, F and G. The RNA genome of hMPV possesses a negative and single-stranded configuration, composed of 13.3–13.5 kilobases that undergo replication inside the cytoplasm of the host cell. The heterogeneity in the length of genetic material occurs because of the addition of non-templated nucleotides on the genome ends, post-transcription, influenced by the P protein cofactor. The extra nucleotides negatively impact the processivity of replication and consequently the virulence [6].

The genome can express a total of eight proteins in the respective order of nucleoprotein (N), phosphoprotein (P), matrix (M), fusion (F), small hydrophobic (SH), attachment protein (G), matrix-2 (M2-2), and polymerase (L), which are involved in the virus life cycle. It was that SH has structural contributions to the viral RNA genome [7]. Variations in the mRNA transcript organization have been reported concerning the SH-G gene, which impacts the genetic composition of hMPV genomes. A correlation has been established with SH deletion and potential immunocompromised individuals, who may have prolonged the incubation period of the virus [8]. Sequence variations of hMPV genomes can introduce conformational changes in the attachment protein and, consequently, escape the immune system directly targeting the F attachment glycoprotein. Structural shapes on the L DNA sequence between MPV A and MPV B provide distinct attachment sites that may influence the tropism of the virus. Gene sequences and gene arrangement from the entire genome, when compared with the known ERSV, are completely distinct, influencing drug and vaccination potential targets. Genomic studies from human hosts, sampling hMPV for a period of 14 years starting in 2002, classified the virus to be a single, continuous, large population. Loss of gene polymorphism over contiguous sites influenced evolutionary studies [9, 10]. The same gene sampling's G glycoprotein verified a maximum mutation rate of roughly 1.191 x 10 to the power of -3, which closes to the previously established 10-point amplification. In particular, there is now more variance at position 2612 (WDNK), a crucial target for hMPV treatment drugs. Immune escape that the virus has caused medication resistance in addition to other general global health issues. In Germany, strain F was the most prevalent viral strain found [10] (figure -1) [11].

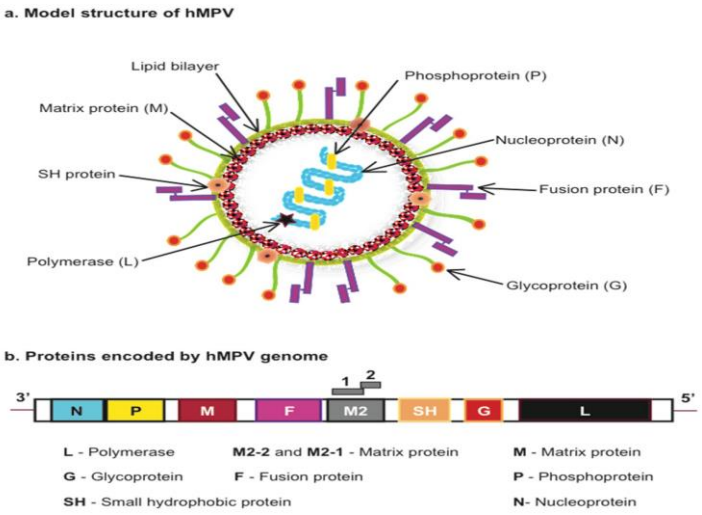

Fig.1: Illustrates human metapneumovirus **A-** Model structure of hMPV. **B-** Proteins encoded by hMPV genome [11]

B. Human Metapneumovirus genotyping

Human metapneumovirus (hMPV) is a negative-sense RNA virus in the family Paramyxoviridae that was first isolated from respiratory secretions of Dutch children in 2001. It is one of key pathogens in respiratory infections in all ages. HMPV is divided into two major genotypes, A and B, which are further divided into subgroups (A1, A2, B1, B2) and sub-genotypes (A2a, A2b, A2c). There are efforts to more deeply classify genotypes as 'the G protein, which facilitates viral attachment, has approximately 55.9 to 87.4% homology between genotypes. The amino acid identity of the G protein lies between 31% and 53.3% and evades clonal immune protection. High nucleotide sequence heterogeneity of G proteins results from variations in threonine and isoretinic acid repeats, adenosine addition clusters, and other substitutions. The nucleotide variation of the G protein gene among hMPV genotypes is about 45%–53% with the sequence identities being 45.5%–52.6% (nucleotide) and 22%–27.6% (amino acids). The G gene's sequence is one of the most variable regions with respect to hMPV identification and genetic analysis. The latest data suggests the pattern of behavior is endemic indicating influence by diversity of the virus genotypes.

The necessity of elucidating the epidemic state and molecular features of hMPV in certain parts of the world reinforces the need to comprehend the transmission control and disease prevention measures associated with hMPV genotypes [12,13,14,15].

C. Subgenotypes in the Middle East

There are six different types of hMPV that have been found. When phylogenetic Middle Eastern data is used, each

of these types seems to be very different from those found on other continents. Within this specific region, a new cluster A2b along with sub-genotypes B1, B2, A2c, and A2d were found to be dominant. In stark contrast, areas like North America and Asia reported dominantly 2 or 3 sub-genotypes only [16]. The implication of this hMPV variation is important since it requires close monitoring and study on the effects of hMPV infection on immunocompromised patients, who sadly experience a host of complications leading to increase the length of stay and greater levels of resources used. This was further augmented by the recent findings of other countries that had previously gone unmonitored in the region. One of the initial detections of hMPV in the most western Asian countries, like Jordan, Palestine, Lebanon & Syria, as well as the UAE, was in 2006. The study brings out an intriguing fact of note: the common hMPV sub-genotypes found in North America and Asia were noticed 1-2 years earlier as opposed to in the Middle East or Australia [17].

D. Transmission and Epidemiology

The mode of hMPV transmission was quickly inferred when the virus was discovered, with direct and close person-to-person contact identified as its main pathway of spread. This transmission pattern was observed during several outbreak investigations, with the virus responsible for both household, school, and health care transmission following close contact. Airborne transmission of hMPV is likely, leading to a contagious virus able to jump to susceptible subjects through respiratory droplets emitted when coughing or sneezing and through the virus-contaminated environment. Fecal-oral transmission was also discussed without being clearly proven [18]. The efficiency of the human immune response to hMPV and the wide range of viral loads produced in infected subjects lead to differences in susceptibility between populations. Very high viral loads can be reached in the nasopharynx of individuals infected with hMPV. In addition, viral antigen can be detected up to six days before symptom onset. Even when the viral load decreases, detected virus shedding is extended. Given the high transmission of hMPV, a median basic reproduction number ranging from 1.2 to 5.3 has been determined under various health care settings [19].

Several groups have described and discussed the seasonality of hMPV around the globe, characterized by epidemic periods during the colder seasons. An analysis of hospital laboratory records suggested peak occurrences in February and March. More global epidemiological studies conducted generally confirmed a clear winter peak in hMPV detection [20]. In the majority of tropical zones, hMPV activity peaks between January and May, between November and May in African temperate zones, and between November and March in Asian and South American temperate zones. This distribution differs from the autumn and spring peaks determined for respiratory syncytial virus, the other major cause of bronchiolitis and pneumonia; both viruses thus contribute differentially to the occurrence of winter viral bronchiolitis. In summary, hMPV generally induces a wintertime epidemic peak in temperate climates, and its spread may be enhanced by dry air factors resulting from inside/outside differences in terms of temperature and humidity. Several studies reported a higher incidence of hMPV infection in people with other co-infections with various viruses, but they were not conclusive [21]. Table -1 and figurer-2 show the prevalence rate of the virus around the world. Also figure-3 show the studies that have conducted and published about hMPV over time starting from 2002 – 2003[22].

Table.1 show the prevalence of the hMPV on different countries correlated with the lower respiratory infection.

Country (year)	No of cases	References
Germany (2002)	11	[23]
USA (2006-2007)	11	[24]
Spain (2006)	24	[25]
Spain (2006)	101	[26]
Kenya (2007-2016)	274	[27]
Seoul (2007-2016)	1275	[28]
Guatemala (2007-2012)	596	[29]
Iran (2008-2009)	20	[30]
China (2008-2010)	49	[31]
China (2009)	20	[32]
Japan (2009-2011)	18	[33]
Canada (2009-2012)	195	[34]
Jordon (2010-2013)	273	[35]
Kuwait (2010-2013)	15	[36]
China (2010-2019)	524	[37]
Thailand (2011)	75	[38]
Argentina (2011-2013)	161	[39]
China (2013-2017)	76	[40]
Taiwan (2013-2023)	114	[41]
Colombia (2015-2017)	420	[42]
China (2016-2020)	56	[43]
Bulgaria (2016-2019)	83	[44]
India (2016-2018)	20	[45]
China (2017-2018)	52	[46]
China (2017-2021)	189	[47]
China (2017-2023)	167	[48]
Australia (2018)	12	[49]
India (2021-2024)	113	[50]
India (2022)	4	[51]
India (2021-2024)	113	[52]
Slovenia (2022-2023)	78	[53]
China (2023)	96	[54]
USA (2023)	107	[55]

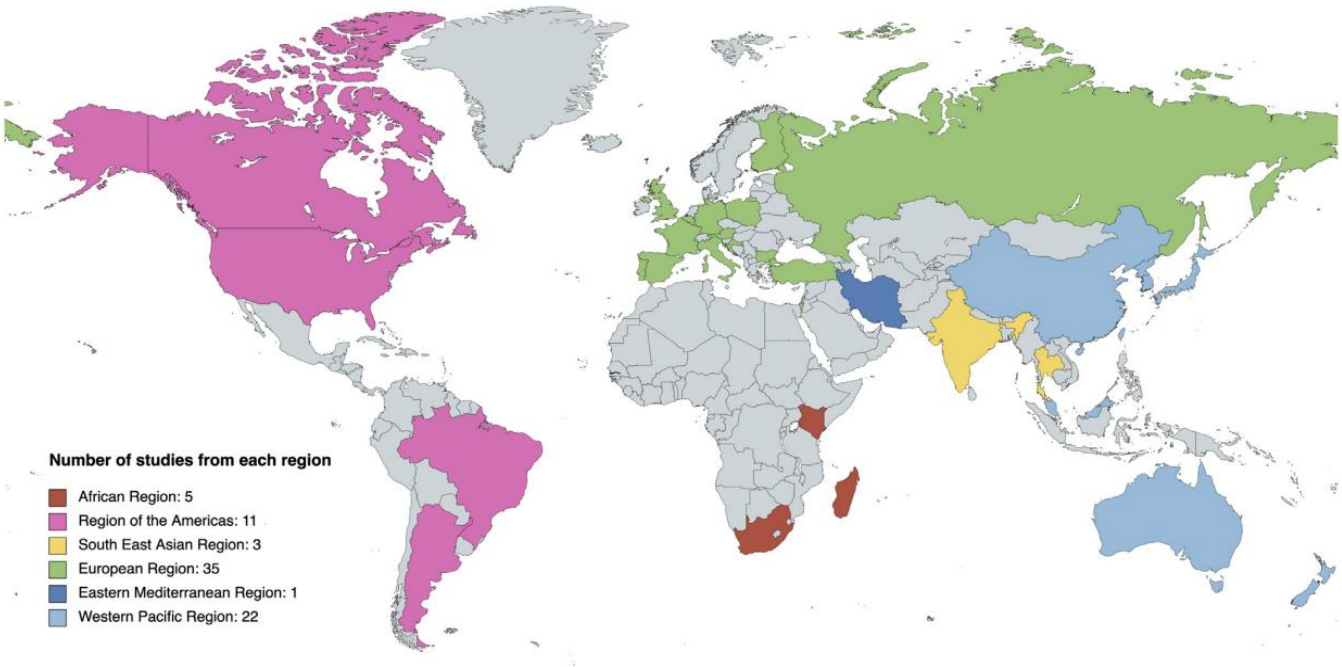

Fig.2: Global map show studies that were conducted regarding the prevalence of the hMPV around the world [56].

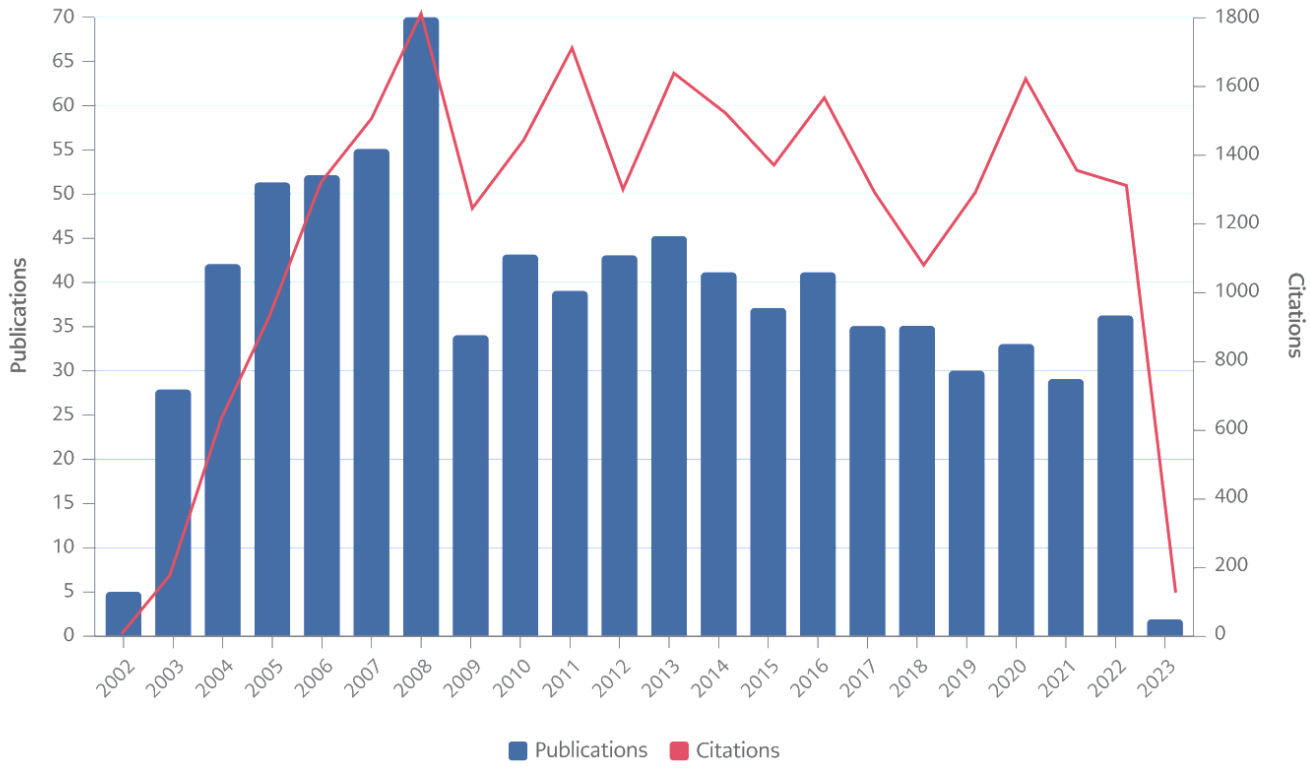

Fig.3: Publication and citation of hMPV overtime from 2002 -2023 [22]

III. RISK FACTORS

Different risk factors such as environmental risks, socioeconomic risks and health-related variables can affect the prevalence of human metapneumovirus (hMPV) genotypes and sub-genotypes in the Middle East. The virus impacted by climate and population density within healthcare accessible regions. Therefore, reducing physical interaction among people can promote the spread of the disease. With no control measures, these practices in conjunction with high population density areas and cause a rapid increase in the spread of diseases. Recognizing these elements is paramount in framing sound public health measures to diminish the effect of human metapneumovirus in exposed populations. This permits the determination of at-risk populations and the application of much more effective vaccination campaigns, educational activities, and surveillance strategies to significantly lower the probability of spreading infection. Addressing the epidemiological

determinants of human metapneumovirus (hMPV) focuses on public health vulnerabilities. These can include age, underlying health issues, and even geographic regions. Young children and the elderly tend to become severely ill which is why this understanding helps highlight vulnerable risk groups. Furthermore, the spread of hMPV is influenced by healthcare access, and living conditions which are considered socio-economic factors [57,58].

IV. Clinical Manifestations

Human metapneumovirus (hMPV) has the propensity of primarily affecting the respiratory tract of a person, cause myriads of symptoms which may include, but is not limited to, upper respiratory tract infections and severe lower respiratory tract diseases. The most vulnerable population includes infants, elderly, and unwell individuals. The incubation period usually lasts from three to six days [59].

A. Upper respiratory tract infections (URTI)

Other infections may be considered more drastic, a well-nourished individual may consider hMPV infections less severe as they are comparable to common cold infections. These symptoms that might be less sever involving nasal blockade retainment, runny nose, and pain in throat, sore cough, oropharyngeal inflammation, pleasantly low fevers, and sickness [60].

B. Lower respiratory tract infections (LRTI)

Ninety five percent of the population suffers from wheezy bronchitis and asthmatic wheeze. Other cases may involve severe infections of Pneumonia as well. Their symptomology consists of low-grade fever, cough, and rest of the aforementioned abnormal lung sounds such as rales or wheezing [61].

C. Severe complications

Along with those extreme symptoms mentioned in the previous section, there remain extremely drastic and life-threatening complications as well. Some of them involve respiratory disorders, for instance or even in dire cases leading to lung failure and requiring oxygen or a breathing machine to aid. Further side effects would result of this viruses like lower pulse rate and blood pressure at critical levels [62].

D. Atypical presentations

An additional febrile seizure in an infant or child seems to break the fundamental rule described earlier, and is treatable as it does not involve altering the core of infant's pre-development state. Gastrointestinal issues, such as vomiting and diarrhea, may occur alongside respiratory infections, particularly in younger children [63, 64].

V. Diagnosis and Treatment

A. How to identify hMPV

Because it is distinct from other respiratory viruses, Human Metapneumovirus (hMPV) identification requires high-tech laboratory equipment. RT-PCR, was used to detect hMPV RNA in collected samples from the respiratory tract very specifically and sensitively. Virus proteins and antibodies can be detected using immunofluorescence and enzyme-linked immunosorbent tests; however, not all of these results were reported in a routine clinical practice. Another alternative method is virus culture, which is less sensitive and takes a long period. Genomic mapping and viral mutation surveillance are two more applications of Next-Generation Sequencing (NGS). For the sake of optimal therapy, infection control, and epidemiological management of hMPV, a rapid and accurate diagnosis is essential [65].

B. Treatment of hMPV

Since Human Metapneumovirus (hMPV) vaccines and antiviral drugs are not yet available, supportive care is the mainstay of treatment, particularly in vulnerable groups including elderly, children, and individuals with compromised immune systems. The goal of management is to alleviate symptoms while simultaneously lowering the risk of consequences. People with trouble breathing are given oxygen therapy, and those who are really sick are given intravenous fluids to keep them from becoming dehydrated. Pain relievers and fever reducers like ibuprofen and acetaminophen are known as antipyretics. While bronchodilators such as albuterol may help patients with wheezing or blockage. Their usages in cases of viral bronchiolitis are a still up for debate. Patients with chronic obstructive pulmonary disease (COPD) or persistent asthma utilize corticosteroids like prednisone or dexamethasone to manage inflammation in their airways. Mechanical ventilation or non-invasive ventilation (CPAP or BiPAP) may be necessary for patients with severe respiratory insufficiency. Ribavirin, along with a small number of monoclonal antibodies targeting the viral fusion (F) protein and a few fusion inhibitors, are still undergoing clinical trials. Nevertheless, no antiviral drugs have been licensed for usage at this time. Inhibitors of viral RNA polymerase, which try to stop replication, are also being explored. Since there is currently no vaccine for hMPV, the best way to protect yourself from contracting the virus is to practice good hand hygiene, covering mouth and nose after coughing or sneezing, wearing a mask as necessary, and staying away from sick people. A dramatic improvement in treatment choices is being pursued by continuous research into the development of antiviral medicines and vaccines [66, 67].

VI. Preparedness and Most Important Public Health Strategies

A. Monitoring and detection procedures

Design and carry out periodic surveillance activities geared toward ascertaining the progression and seasonal activity of hMPV in the high-risk demographic (children, elderly, and immunocompromised patients). Employ RT-PCR molecular diagnosis for the swift and precise confirmation of hMPV in cases that are clinically suspicious. Establish sentinel surveillance units in hospitals and community outpatient clinics to facilitate timely detection and control of significant outbreaks [68].

B. Measures to control and prevent infection

Promote effective handwashing with soap and water or the use of alcohol sanitizers, particularly in the healthcare environment and other populated areas. Encourage respiratory etiquette like the use of tissues or an elbow to cover a cough or a sneeze to limit the spread of viruses. Put

infected persons under protective isolation, especially in hospitals and long-term care facilities, to avoid the incidence of nosocomial infection [69].

C. Development of vaccines and antivirals

Support the development of effective vaccines even in the absence of a licensed one for hMPV. Explore the use of monoclonal antibodies and broad-spectrum antivirals for treatment of severe cases of hMPV.
Foster collaboration between research scientists and pharmaceutical companies at a global level to facilitate faster processes for vaccine trials and the approval of antiviral medications [70].

D. Dissemination of information and mobilization of the community

Constantly educate and sensitize the population on the symptoms of hMPV, how it is transmitted, and how to prevent it. Creating and distributing pamphlets to schools, daycares, and clinics to promote awareness, provide guidance, and ensure compliance with prevention measures. Collaborate with community stakeholders and leaders in medicine to strengthen prevention education and promote early intervention for respiratory conditions [66, 71].

E. Enhancing healthcare systems

Educate medical personnel on the appropriate procedures for diagnosing and treating hMPV infections.
Provision of sufficient hospital resources: ICU beds, ventilators, PPE (especially during outbreak situations). Create hMPV outbreak management teams that respond rapidly and collaborate with domestic and foreign health institutions [72].

F. Health security at the border and on travel

Control the movement of people by instituting borders and air travel hMPV checks, especially during its outbreak periods. Intelligently issue guides on travel destination together with health-related information on respiratory infections and the necessary precautionary measures that should be taken while traveling [73].

G. Development of policies and research

Facilitate new research on understanding how the virus evolves, its transmission, and risk factors that need to be better understood. Lobbying at member states and health organizations, the WHO, and CDC urging evidence-based policy formulation for hMPV prevention and response. Shifting funds to new diagnostic tools and therapeutic vaccine development within the biotechnology sector [73].

VII. CONCLUSIONS

The Human Metapneumovirus (hMPV) signifies as a major global concern that requires immediate attention concerning its impact, epidemiology, clinical approach, and even its pattern of transmission. While its similarity to the Respiratory Syncytial Virus: (RSV) is noted, hMPV suffers a deficit of understanding as to its pathogenesis, immune evasion, and possible pandemic threats. In any case, this serves to shed light to the inadequate attention Surveillance and diagnostic techniques as well as therapeutic endeavors which must be specifically directed towards its respiratory diseases.

Evidence suggests that hMPV possess a possibility of causing respiratory infections in large quantification especially towards the very elderly, very young children and even the debilitated sick. With the seasonal attacks and hibernation precision, hMPV poses a very obvious threat to health care systems worldwide. Like most issues, this one is no different from the rest since it needs undivided attention and further research like anti-viral therapy and vaccine precision medicine. This issue in regard to treatment present actually supportive strategies throughout all conditions.
Along with these identified and current issues, policymakers must also shift their focuses to aid with the early recognition, prevention, as well as hMPV containment. Here, we witness how collaborative efforts of researchers and healthcare professional are needed. This can help formulate an approach that is potent enough to eliminate the uncanny problem which, if undiagnosed will become another major threat to overcome like the previous viral pandemics.

In closing, with the information hMPV has provided thus far, steps to know its impact have been taken. However, more detailed plans must be researched and executed on a global level. Broadening the engagement of research, improving medical technology, and strengthening public health policies are actions which can be taken to lower potential risk hMPV brings forth and protect countries from future occurrences.

VIII. RECOMMENDATIONS

1) Developing and evaluating effective hMPV vaccines:

The most important of which is to develop safe and effective vaccines and to evaluate their impacts on hMPV associated illness in older adults, pregnant women, and very young infants.

Decreasing maternal hMPV illness and transplacental or through breast milk-mediated antibody transfer from capable offspring.

2) Expanded studies of naturally occurring hMPV in animal models:

It will be essential to define comparative virulence between hMPV subtypes and between hMPV and RSV. These studies will provide insights into the resilience of hMPV in the lungs, duration of infectivity, shedding, and outcomes of lower and upper respiratory tract symptoms. This detailed information is key for the development of any therapy for severe disease associated with hMPV.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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