Middle East Respiratory Syndrome Coronavirus Could be a Priority Pathogen to Cause Public Health Emergency: Noticeable Features and Counteractive Measures

Environmental Health Insights
Volume 18: 1–7

DOI: 10.1177/11786302241271545

Deepak Chandran[1], Sandip Chakraborty[2], Diljith Chandran[3], Deepak Subedi[4], Ankitha Indu Jisha[5], Hitesh Chopra[6], Ali A Rabaan[7,8,9], Jaffar A Al-Tawfiq[10,11,12], Md. Rabiul Islam[13] and Kuldeep Dhama[14]

[1]Department of Animal Husbandry, Government of Kerala, Kerala, India. [2]State Disease Investigation Laboratory, ARDD, Abhoynagar, Agartala, West Tripura, India. [3]KVG Dental College & Hospital, Kurunjibhag, Sullia, Karnataka, India. [4]Department of Poultry Science, University of Georgia, Athens, Georgia, USA. [5]Amrita School of Agricultural Sciences, Amrita Vishwa Vidyapeetham University, Coimbatore, Tamil Nadu, India. [6]Department of Biosciences, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India. [7]Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia. [8]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia. [9]Department of Public Health and Nutrition, The University of Haripur, Haripur, Pakistan. [10]Specialty Internal Medicine and Quality Patient Safety Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia. [11]Infectious Diseases Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA. [12]Infectious Diseases Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [13]School of Pharmacy, BRAC University, Merul Badda, Dhaka, Bangladesh. [14]Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Izatnagar, Uttar Pradesh, India.

ABSTRACT: Middle East respiratory syndrome (MERS) is caused by a specific strain of the 6 types of human coronaviruses (HCoV). MERS-CoV has spread unchecked since it was first discovered in Saudi Arabia in 2012. The virus most likely spreads through nosocomial and zoonotic channels. Genetic analyses suggest that bats were the initial hosts and that the disease spread to camels. Person-to-person transmission occurs with varying frequency, being most prevalent in clinical settings and the least common among the general population and among close relatives. Due to the severity of the illness, high fatality rate, potential for epidemic spread, and lack of adequate medical countermeasures, the World Health Organization (WHO) continues to list MERS-CoV as a priority pathogen. While no specific antiviral medicines exist, a combination of antivirals has shown promise in recent clinical trials. Vaccines against MERS-CoV are critically needed and are currently being developed. Early diagnosis and implementing appropriate infection control measures are keys to preventing hospital-associated outbreaks. Preventive measures include avoiding raw or undercooked meats and other animal products, ensuring proper hand hygiene in healthcare settings and around dromedaries, educating the public and healthcare personnel about the disease, and adhering to other recommended practices. Countries with a high prevalence of MERS should adhere to regulations designed to limit the transmission of the virus. The recent spread of MERS-CoV highlights the importance of public awareness regarding the significance of reporting symptoms so that appropriate control measures can be adopted. The narrative review discusses the incidence of MERS, its clinical presentation, potential transmission routes, recent reports, preventative and control measures, and current therapeutic options.

KEYWORDS: MERS-CoV, coronavirus, respiratory illness, transmission, recent reports, infection control, management

RECEIVED: January 31, 2024. **ACCEPTED:** July 2, 2024.

TYPE: Perspective

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHORS: Md. Rabiul Islam, School of Pharmacy, BRAC University, Kha 224 Bir Uttam Rafiqul Islam Avenue, Merul Badda, Dhaka 1212, Bangladesh. Email: robi.ayaan@gmail.com

Kuldeep Dhama, Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Izatnagar, Uttar Pradesh 243122, India. Email: kdhama@rediffmail.com

Introduction

Historically, the threat posed by emerging illnesses has always been present. Over the past century, significant changes in human behavior and the environment have accelerated the spread of new diseases to the human population.[1] The coronavirus responsible for Middle East respiratory syndrome (MERS-CoV) is an RNA coronavirus that produces a respiratory illness of the same name. Following viral genome decoding, MERS-CoV enters host cells via the receptor dipeptidyl peptidase 4 (DPP4), also known as CD26.[2-5] According to the World Health Organization (WHO), the recommended case definitions for MERS rely on laboratory confirmation of infection.[6,7] Testing for viral nucleic acid or acute and convalescent serology are 2 methods the WHO

recommends for laboratory confirmation. Various assay probes and sets of primers that target the open reading frame (ORF)1a and upstream of the gene E usually display the highest sensitivity and are the most extensively used targets for detecting MERS-CoV. Additionally, a single positive assay result confirmed by gene sequencing can also be considered a positive result. WHO mandates that all cases, both suspected and confirmed, be reported to the Regional Contact Point for International Health Regulations in the appropriate WHO Regional Office.[7-9]

Over the past 2 decades, 3 different zoonotic coronaviruses have caused human mortality: severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), MERS-CoV, and SARS-CoV-2.[10] It is believed bats serve as natural reservoirs for MERS-CoV. Bats may have been the initial hosts, and the virus may have moved to camels or some other intermediate host species.[11] MERS-CoV transmission between camels in Africa and the Arabian Peninsula has a long history.[1,12] Nosocomial epidemics, where the disease is spread among hospital staff and patients, have occurred before, notably in Riyadh and Jeddah, Saudi Arabia, in the 2014, and South Korea in 2015.[4,13] Between 29 December 2021 and 31 October 2022, Saudi Arabia reported 4 laboratory confirmed cases of MERS-CoV to WHO, with no fatalities. No secondary cases were identified during the follow-up of household contacts.[14] To date there have been 2600 confirmed cases of MERS-CoV in 27 countries, resulting in 935 deaths across all 6 WHO regions. The majority of these deaths (approximately 35%) have occurred in the Middle Eastern regions.[14] Recent MERS cases reported from Qatar and Saudi Arabia have renewed attention to this pandemic threat but do not change the overall risk assessment.[15]

From 22 March and 3 April 2022, Qatar reported 2 laboratory-confirmed cases of MERS-CoV to WHO, 1 of which resulted in death. Both patients had close contact with dromedary camels and had consumed raw milk from these animals in the 14 days before developing MERS symptoms.[16] A recent study recorded a total of 28 MERS cases in Qatar, with an incidence rate of 1.7 per 1 000 000 population and no healthcare outbreaks.[17,18] The Camel Mzayen Club's camel beauty pageant festival coincided with the FIFA World Cup 2022 in Qatar. WHO and Qatari authorities issued detailed health warnings to visitors to curb the spread of MERS-CoV. Visitors to both events were likely to encounter imported and local dromedary camels, owners of camels, and camel dairy products, which are popular in Qatar.[19,20] There was always a risk that MERS-CoV could spread from travelers in Qatar to their home countries. Public health authorities and healthcare workers worldwide were alerted to the risk of MERS-CoV infection, not just in the Middle East but in all countries to which event attendees to either event have traveled. Hospitals and clinics were advised to be on high alert, particularly in the month following the 2 outbreaks, even though the WHO did not recommend MERS-CoV screening at entry points. Returning travelers who were felt ill were advised to seek medical attention immediately and inform their healthcare providers about their recent trip to Qatar.[19]

Since the initial reporting of MERS from Saudi Arabia 2012, most patients with the disease have had geographical links to the Arabian Peninsula. However, the disease has also been reported in other parts of the world. A significant cluster of MERS cases occurred in South Korea in 2015. MERS-CoV infections occurs sporadically, with intrafamilial and healthcare-associated infections observed. Symptoms of the disease vary widely, ranging from asymptomatic cases to death outcomes. Despite the high mortality rate associated with the infection, there is a lack of specific antiviral therapy, particularly for patients with comorbidities. Several studies have assessed the risk factors and severity of MERS, but there is variation in the indices presented by these studies. For instance, the case fatality rate in the Middle East was 25.9%, compared to 20.4% in South Korea. The incubation period was determined to be 5.2 days across different locations in Saudi Arabia but 6.83 to 7 days in South Korea. Accurate risk assessment of MERS is critical for predicting and preventing the disease.[21,22]

On January 5, 2023, the Oman National IHR Focal Point reported a case of MERS to WHO from the North Batinah Governorate. Investigation revealed that camel racing activities near the patient's home were a potential exposure risk in the 14 days before the onset of symptoms. The patient, a driving instructor, denied direct contact with camels, goats, sheep, or their products (including milk and urine). Oman reported its first laboratory-confirmed case of MERS-CoV in June 2013. Since then, Oman has documented 26 cases of MERS-CoV, resulting in 7 fatalities.[23]

Modes of Transmission and Pathogenesis

Several transmission mechanisms between camels and humans are conceivable. Droplet, contact, and airborne transmission may play roles in the spread of MERS-CoV. Secondary cases linked to exposure have an incubation period of 2 to 14 days.[24] Patients with symptoms typically have the virus in their lower respiratory tract. Shedding of the virus may continue for up to 2 weeks or longer, suggesting that persistent shedding may contribute to the transmission of the disease during hospital outbreaks.[5,25] Transmission occurs in 3 distinct ways: isolated incidents in the community from what is thought to be non-human exposure, clusters of illness within a family after interaction with an infected family member, and disease acquired by patient and healthcare in clinical settings. Healthcare settings can be significant sites for the spread of MERS.[26] The primary causes of healthcare-associated epidemics include substandard practices such as inadequate infection control, poor triage and isolation of patients suspected of having MERS or other respiratory infections, overcrowding, and patients staying in the emergency room for extended periods.[27,28]

Although the transmission and clinical manifestations differ significantly between infected humans and camels (dromedary), the viruses isolated from these species have high similarity. This indicates play a significant role in the transmission and pathogenesis of MERS-CoV. However, the identities of these host factors and the mechanism for MERS-CoV transmission and pathogenesis are often poorly understood. The potential host factors critically affect in vitro infection are the receptor for MERS-CoV, DPP4, sialic acids, interferons, and proteases.[29-31]

Both human and dromedary camels are susceptible to acquiring MERS-CoV infection and can transmit the virus. However, current data indicate that dromedary camels are more efficient at spreading the virus than humans. This variation in transmissibility can be due to variations in the tropism of the virus in these species. In dromedaries, MERS-CoV replicates in the epithelium of the nasal cavity when experimentally infected in vivo. In contrast, in humans, the virus is replicated in the lower part of the respiratory tract, particularly in the epithelium of the bronchi and alveoli. Higher levels of RNA of the virus have been detected in the lavage and sputum samples of the patients compared to the throat and nasal swabs, aligning with the virus tropism in humans. The differential tropism of MERS-CoV between humans and dromedary camels corresponds with the distinct tissue distribution of the receptor DPP4 in their respiratory systems. DPP4 is not present in the human nasal epithelium but is abundant in type II pneumocytes and the epithelium of the lower respiratory tract. Interestingly, in dromedary camels, DPP4 is expressed in the nasal epithelium. These findings suggest that DPP4 is critical determinant of MERS-CoV tropism.[31-33]

Crucially, epidemiological data indicate that individuals with certain risk factors are at greater risk of developing MERS-CoV infection. Specific host factors can influence the infection outcome. It has been found that there is upregulation of the expression of DPP4 in the human lungs in association with 2 risk factors: smoking and chronic obstructive pulmonary disease (COPD). This suggests that DPP4 may contribute to variation observed among patients infected with MERS-CoV. In healthy human lungs, DPP4 is expressed almost exclusively in type II pneumocytes. However, in smokers and patients suffering from COPD, DPP4 is expressed in both in the type I and II pneumocytes, indicating upregulation of DPP4 in type I pneumocytes. Therefore, type I pneumocytes expressing DPP4 play a crucial role in the pathogenesis of MERS-CoV. Studies have shown that there is heightened replication of the virus in immunocompromised rhesus macaques, consistent with the observation that immunocompromised patients struggle to clear MERS-CoV upon infection. Moreover, the replication of the virus is inhibited in the cells susceptible to type I interferon, partially by inhibition of double-membrane vesicles formation. Clinical manifestations and histopathological lesions are more severe in mice lacking type I interferon, suggesting its protective role. Age related decline in type I interferon response upon infection is also noted. Making advanced age a well-known risk factor for MERS-CoV infection-induced fatality. Therefore, from the perspective of MERS-CoV pathogenesis, crucial determinants include the upregulation of DPP4 in type I pneumocytes and an insufficiency in the type I interferon-mediated response.[31,34-37]

Clinical Manifestation and Diagnosis

People without known medical conditions often have flu-like symptoms, including a high temperature, cough, chills, sore throat, muscle and joint pain, and fatigue. Within a week, some patients develop severe dyspnea and a life-threatening case of pneumonia, necessitating mechanical ventilation and sometimes additional support measures like hemodialysis.[38-40] In addition, some individuals may report gastrointestinal issues such as nausea, loss of appetite, abdominal pain, and diarrhea. These patients frequently experience a combination of respiratory viruses, nosocomial bacteria, and fungal infections.[41,42] Symptoms can be particularly severe in people with compromised immune systems due to immunosuppression or preexisting conditions such as, obesity, diabetes, heart disease, lung disease, or acute renal failure (ARF).[38] Overexpression of DPP4 in the kidney may contribute to the increased incidence of kidney infection in these patients.[5]

Elevated creatinine, lactate dehydrogenase, abnormal liver enzyme values, leukopenia, and consumptive coagulopathy are common laboratory findings in MERS. In some cases of MERS, chest X-rays reveal signs of viral pneumonitis and acute respiratory distress syndrome. Small pleural effusions and bilateral hilar and patchy infiltrates are also observed.[3,4] It is essential to promptly collect samples from the lower respiratory tract and analyze them with a real-time reverse-transcriptase polymerase chain reaction (RT-PCR). If respiratory samples are unavailable, the virus can be detected in urine or stool specimens, although at a much lower concentration. However, isolating the virus from urine or stool is challenging and the risk of virus transmission via these routes is considered low due to the difficulty of isolation.[1,2,43] Several serologic approaches have been established for detecting MERS-CoV antibodies, including immunofluorescence, protein microarray, and ELISA (enzyme-linked immunosorbent assay) testing.[44]

Infection Control and Preventive Measures

Due to the limited infectivity of MERS-CoV in the community settings and the enormous cost and time commitment required to develop a vaccine, few vaccines have been developed. Among these, vaccines based on ChAdOx1 and MVA viral vectors are notable.[45-47] Patients infected with MERS-CoV are generally treated with palliative care. However, there is evidence to suggest that specific therapy, including the use of convalescent patient sera, interferon, and

lopinavir should be further investigated. Currently both monoclonal and polyclonal antibodies, are being developed. There is no evidence that other therapies, particularly antiviral medicines, are effective against MERS-CoV.[1] Efforts have been made to develop therapeutics for treating MERS. The most promising treatment is a combination of recombinant interferon beta-1b and lopinavir-ritonavir.[44,48]

According to WHO forecasts, more instances of MERS-CoV infection are expected to be reported and exported from the Middle East and other regions where dromedaries serve as a reservoir for the virus. WHO monitors the epidemiological situation and evaluates risk using the most recent data.[1,17] Since the beginning of the current COVID-19 outbreak, WHO has observed a significant decline in the number MERS-CoV cases. This decrease is likely because COVID-19 monitoring activities have taken precedence over testing and identifying MERS-CoV cases.[49,50] Efforts to contain the SARS-CoV-2 pandemic (such as mask, hand washing, physical distancing, improved ventilation of indoor spaces, respiratory etiquette, home quarantines, and movement restrictions) are also likely to be effective against the spread of MERS-CoV. However, there is limited evidence that these interventions reduced MERS-CoV transmission in dromedary camels. The decline in the number of verified secondary MERS cases does not diminish the risk of zoonotic transmission.[10,51]

People with impaired immune systems, diabetes, chronic lung illness, or kidney disease are strongly encouraged by the WHO to avoid areas populated by. The WHO has made no recommendations on screening visitors or quarantining goods entering certain areas, or limiting trade and travel to these regions. However, non-affected nations should be on high alert, especially those with significant numbers of travelers or guest workers returning from the Middle East.[1,4,52-54] Additionally, mass gathering events such as the FIFA World Cup 2022 pose risks of transmission and spread of infectious pathogens, including MERS-CoV. We must learn from the COVID-19 pandemic and global monkeypox public health emergency and adopt appropriate disease monitoring and surveillance and adequate infection prevention and control measures.[55-59] Furthermore, more research is needed to determine why there are no reports of zoonotic disease in Africa or Asia despite a high density of MERS-CoV-infected camels in these regions.[18] Human disease has only been reported from the Arabian Peninsula, although it has been suggested that MERS-CoV may have spread from camels to humans in Kenya.[60]

Dromedary camels with MERS-CoV have been found in various countries across Africa, the Middle East, and Asia. While MERS-CoV primarily affects the respiratory system, it can causes a range of symptoms.[1,10,15] No specific antiviral medicines are available, although combination antivirals have shown promise in recent clinical trials for severely ill patients.[61] Early diagnosing of MERS-CoV infection in humans, timely isolation, and implementation of adequate infection control measures are critical to preventing hospital-associated outbreaks and the spread of the virus within healthcare facilities.[5,58,62]

Humanity remains vulnerable to emerging diseases and viruses, despite significant advancements in medical research in recent decades. Although MERS-CoV infections are relatively rare, they can still occur on a regional or national scale. Many aspects of MERS, including its epidemiology, pathogenesis, transmission, and management remain unresolved despite the disease's potential to cause a pandemic. There is a need for a greater global focus on MERS awareness and MERS-CoV to prevent future outbreaks. Key preventative measures include voiding raw or undercooked meats and other animal products, practicing proper hand hygiene in healthcare settings and around dromedaries, educating the public and healthcare professionals about the disease, and implementing other recommended precautions. Individual at higher risk of severe MERS should avoid contact with dromedary camels, drinking raw milk or urine from a camel, or eating undercooked meat. These actions are critical to mitigating the risk of infection.[56]

Due to its potential to cause severe disease with a high fatality rate, pandemic potential, and a lack of adequate medical countermeasures, MERS-CoV continues to be on WHO's list of priority infectious diseases. Strengthening adherence to internationally recognized infection control standards and rapidly implement control measures in the event of a MERS-CoV epidemic are critical. It is essential to Prioritize research, preparedness, response, and control efforts, as well as to build robust public health infrastructures and successful global consortia. These measures are crucial for the early and effective identification, characterization, and surveillance of novel infectious disease threats. Despite a decade since MERS-CoV was first identified, many questions about the virus remain unanswered. Given the lack of effective drugs and vaccines, the high fatality rates associate with MERS-CoV infections, and potential to cause a public health emergency, there is an urgent need to accelerate research and development. Establishing and strengthening surveillance partnerships to also necessary to counteract MERS. The recent MERS cases reported by Qatar and Saudi Arabia in 2022 underscore the need to expand global awareness of this important pathogen and to be prepared with proactive control measures and preparedness plans to tackle MERS. Metadichol, a non-cytotoxic product with significant margin of safety and no side effects, made from renewable sources like sugar cane and rice, has been used effectively as an immunomodulator for preventing SARS-CoV-2. It could potentially be tried for MERS-CoV infection as well.[63,64] The development of an effective vaccine against MERS-COV is urgently needed but has not yet been completed.[65] Figure 1 provides an n overview of various aspects of MERS and key counteracting strategies.

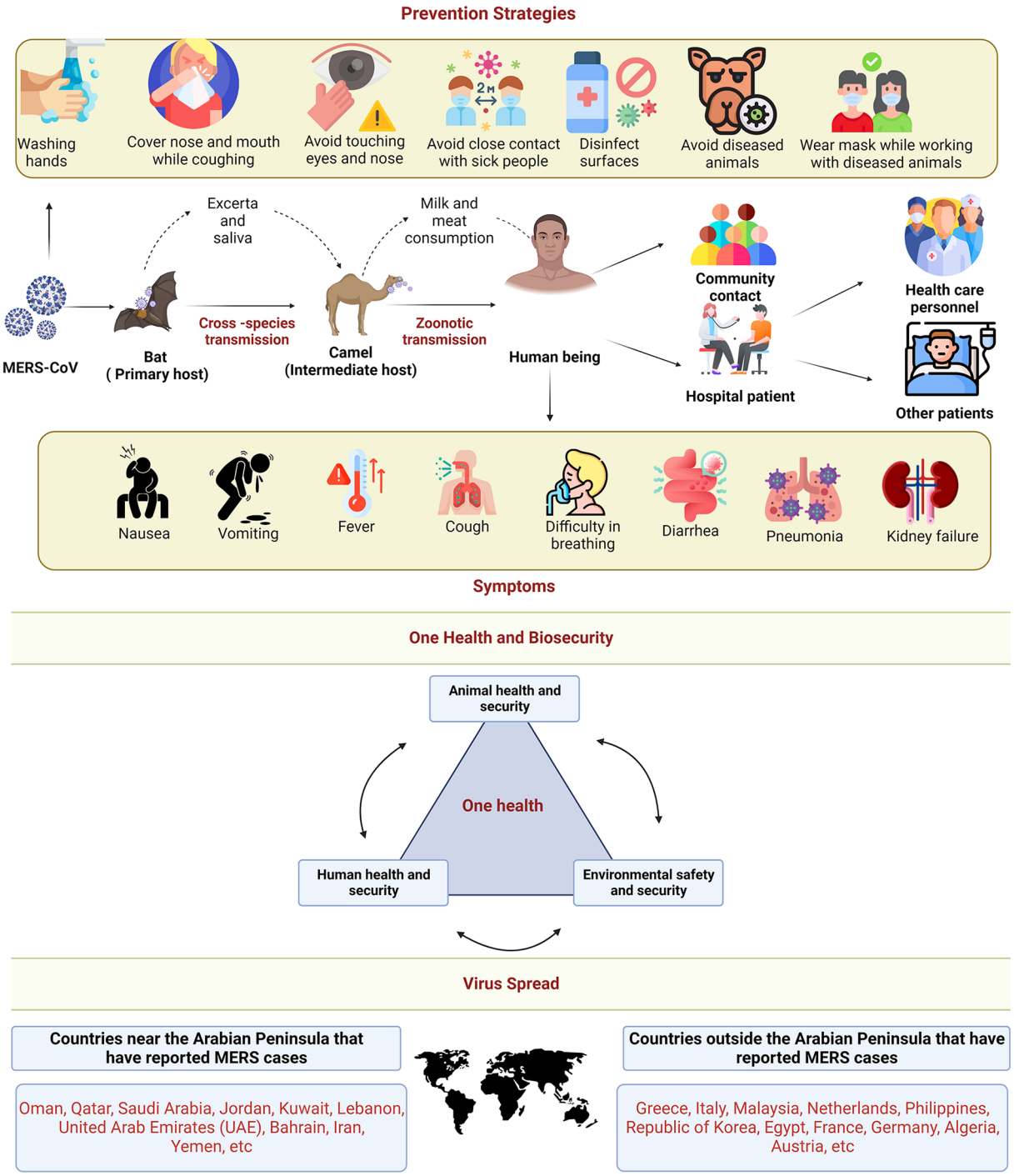

Figure 1. Various aspects of transmission, disease manifestations, and mitigation strategies of MERS-CoV.

Conclusion and Future Prospects

It is now widely recognized that MERS, a zoonotic disease that causes severe lower respiratory infection, poses a threat to public health on a global scale. Unfortunately, several epidemiological and clinical features of the virus remain unclear. Although the camel-to-human transmission of MERS-CoV has been extensively investigated, the reverse transmission from humans to camels is still speculative, complicating effective monitoring.

There is a potential for further outbreaks, particularly in countries where no cases have been reported, likely due to the unknown precise transmission mode, including the possible involvement of other intermediary hosts. Although MERS-CoV is less infectious to human than SARS-CoV, the risk of it mutating to become highly contagious cannot be ruled out.

Based on these findings, we propose the following broad and narrow guidelines:

1. **Immediate Epidemiological Investigations:** Conduct environmental and animal investigations, and surveillance testing around isolated, unexplained cases to identify more animal reservoirs and understand the transmission dynamics better.
2. **Accelerated Development of Treatments and Vaccines:** Prioritize efforts to develop and distribute effective treatments and vaccines for MERS-CoV.
3. **Food Safety:** Avoid consuming camel milk and meat unless cooked or pasteurized, particularly in pastoral areas where camels may transmit the virus.
4. **Healthcare Precautions**: Healthcare personnel caring for patients under investigation for MERS-CoV or confirmed cases should follow standard measures, including hand hygiene and contact or airborne precautions.

MERS-CoV is a coronavirus with the potential to spread internationally. Countries with high MERS-CoV infection rate should develop and implement comprehensive guidelines. The use of personal protective equipment (PPE) must be rigorously enforced to prevent hospital-acquired infections and transmission. Travelers to MERS-CoV-affected areas should be informed about the disease's symptoms and encouraged to seek medical attention immediately if they experience any of sign of illness.

Acknowledgements

The authors appreciate the editors and the reviewers for their insightful and helpful comments and remarks.

Author Contributions

DeC, SC, DiC, DS and AIJ conceived and designed this paper. **DS, HC, AAR, and JAAT** wrote the manuscript. **DS, MRI and KD** revised the manuscript. All authors contributed significantly in drafting, writing, reviewing the manuscript and approved the revised final version.

Transparency Statement

The lead author, Deepak Chandran, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

ORCID iD

Deepak Subedi https://orcid.org/0000-0002-0677-7094

Data Availability Statement

The data in this correspondence article is not sensitive and is accessible in the public domain. Therefore, it is available and not confidential.

REFERENCES

1. Te N, Ciurkiewicz M, van den Brand JMA, et al. Middle East respiratory syndrome coronavirus infection in camelids. *Vet Pathol*. 2022;59:546-555.
2. McFee RB. Middle East respiratory syndrome (MERS) coronavirus. *Dis Mon*. 2020;66(9):101053.
3. Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus. *Semin Respir Crit Care Med*. 2020;41:568-578.
4. Al-Tawfiq JA, Azhar EI, Memish ZA, Zumla A. Middle East respiratory syndrome coronavirus. *Semin Respir Crit Care Med*. 2021;42:828-838.
5. Alnuqaydan AM, Almutary AG, Sukamaran A, et al. Middle East respiratory syndrome (MERS) virus-pathophysiological axis and the current treatment strategies. *AAPS PharmSciTech*. 2021;22:173.
6. Fehr AR, Channappanavar R, Perlman S. Middle East respiratory syndrome: emergence of a pathogenic human coronavirus. *Annu Rev Med*. 2017;68:387-399.
7. Chafekar A, Fielding BC. MERS-CoV: understanding the latest human coronavirus threat. *Viruses*. 2018;10:93.
8. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet*. 2015;386:995-1007.
9. Okba NMA, Widjaja I, Li W, et al. Serologic detection of Middle East respiratory syndrome coronavirus functional antibodies. *Emerg Infect Dis*. 2020;26:1024-1027.
10. Rabaan AA, Mutair AA, Alawi ZA, et al. Comparative pathology, molecular pathogenicity, immunological features, and genetic characterization of three highly pathogenic human coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-2). *Eur Rev Med Pharmacol Sci*. 2021;25:7162-7184.
11. Hu B, Ge X, Wang LF, Shi Z. Bat origin of human coronaviruses. *Virol J*. 2015;12:221.
12. Corman VM, Muth D, Niemeyer D, Drosten C. Hosts and sources of endemic human coronaviruses. *Adv Virus Res*. 2018;100:163-188.
13. Bleibtreu A, Bertine M, Bertin C, Houhou-Fidouh N, Visseaux B. Focus on Middle East respiratory syndrome coronavirus (MERS-CoV). *Med Mal Infect*. 2020;50:243-251.
14. ECDC. MERS-CoV worldwide overview. 2022. Accessed December 10, 2022. https://www.ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus-mers-cov-situation-update
15. WHO. Middle East Respiratory Syndrome Coronavirus- Saudi Arabia. 2022. Accessed December 10, 2022. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON422
16. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) – Qatar. 2022. Accessed December 10, 2022. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON370
17. Ben Abid F, El-Maki N, Alsoub H, et al. Middle East respiratory syndrome coronavirus infection profile in Qatar: an 8-year experience. *IDCases*. 2021;24:e01161.
18. Peiris M, Perlman S. Unresolved questions in the zoonotic transmission of MERS. *Curr Opin Virol*. 2022;52:258-264.
19. Azhar EI, Hui DS, McCloskey B, et al. The Qatar FIFA World cup 2022 and camel pageant championships increase risk of MERS-CoV transmission and global spread. *Lancet Glob Health*. 2023;11:e189-e190.
20. WHO. Healthy FIFA World Cup Qatar 2022. 2022. Accessed December 10, 2022. https://www.who.int/initiatives/sports-and-health/healthy-2022-world-cup
21. Cho SY, Kang JM, Ha YE, et al. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. *Lancet*. 2016;388:994-1001.
22. Park JE, Jung S, Kim A, Park JE. MERS transmission and risk factors: a systematic review. *BMC Public Health*. 2018;18:574.
23. Nowotny N, Kolodziejek J. Middle East respiratory syndrome coronavirus (MERS-CoV) in dromedary camels, Oman, 2013. *Euro Surveill*. 2014;19(16):20781.
24. Killerby ME, Biggs HM, Midgley CM, Gerber SI, Watson JT. Middle East respiratory syndrome coronavirus transmission. *Emerg Infect Dis*. 2020;26:191-198.
25. Adney DR, Clancy CS, Bowen RA, Munster VJ. Camelid inoculation with Middle East respiratory syndrome coronavirus: experimental models of reservoir host infection. *Viruses*. 2020;12:1370.
26. Moniri A, Marjani M, Tabarsi P, Yadegarynia D, Nadji SA. Health care associated Middle East respiratory syndrome (MERS): a case from Iran. *Tanaffos*. 2015;14:262-267.
27. Al-Tawfiq JA, Auwaerter PG. Healthcare-associated infections: the hallmark of Middle East respiratory syndrome coronavirus with review of the literature. *J Hosp Infect*. 2019;101:20-29.
28. Ahmad T. Global research trends in MERS-CoV: a comprehensive bibliometric analysis from 2012 to 2021. *Front Public Health*. 2022;10:933333.
29. Dudas G, Carvalho LM, Rambaut A, Bedford T. MERS-CoV spillover at the camel-human interface. *eLife*. 2018;7:e37324.
30. Iwata-Yoshikawa N, Okamura T, Shimizu Y, et al. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *J Virol*. 2019;93:e01815-e01818.
31. Widagdo W, Sooksawasdi Na Ayudhya S, Hundie GB, Haagmans BL. Host determinants of MERS-CoV transmission and pathogenesis. *Viruses*. 2019;11:280.

32. Widagdo W, Raj VS, Schipper D, et al. Differential expression of the Middle East respiratory syndrome coronavirus receptor in the upper respiratory tracts of humans and dromedary camels. *J Virol*. 2016;90:4838-4842.
33. Paden CR, Yusof MFBM, Al Hammadi ZM, et al. Zoonotic origin and transmission of Middle East respiratory syndrome coronavirus in the UAE. *Zoonoses Public Health*. 2018;65:322-333.
34. Algaissi A, Agrawal AS, Han S, et al. Elevated human dipeptidyl peptidase 4 expression reduces the susceptibility of hDPP4 transgenic mice to Middle East respiratory syndrome coronavirus infection and disease. *J Infect Dis*. 2019;219:829-835.
35. Alsaad KO, Hajeer AH, Al Balwi M, et al. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection - clinicopathological and ultrastructural study. *Histopathology*. 2018;72:516-524.
36. Prescott J, Falzarano D, de Wit E, et al. Pathogenicity and viral shedding of MERS-CoV in immunocompromised rhesus macaques. *Front Immunol*. 2018;9:205.
37. Seys LJM, Widagdo W, Verhamme FM, et al. DPP4, the Middle East respiratory syndrome coronavirus receptor, is upregulated in lungs of smokers and chronic obstructive pulmonary disease patients. *Clin Infect Dis*. 2018;66:45-53.
38. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis*. 2013;13:752-761.
39. Al-Tawfiq JA, Hinedi K, Ghandour J, et al. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. *Clin Infect Dis*. 2014;59:160-165.
40. Al-Tawfiq JA, Rabaan AA, Hinedi K. Influenza is more common than Middle East respiratory syndrome coronavirus (MERS-CoV) among hospitalized adult Saudi patients. *Travel Med Infect Dis*. 2017;20:56-60.
41. Hui DS, Azhar EI, Kim YJ, et al. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis*. 2018;18:e217-e227.
42. Shokri S, Mahmoudvand S, Taherkhani R, Farshadpour F. Modulation of the immune response by Middle East respiratory syndrome coronavirus. *J Cell Physiol*. 2019;234:2143-2151.
43. Kim JM, Kim HM, Lee EJ, et al. Detection and isolation of SARS-CoV-2 in serum, urine, and stool specimens of COVID-19 patients from the Republic of Korea. *Osong Public Health Res Perspect*. 2020;11:112-117.
44. Tian L, Pang Z, Li M, et al. Molnupiravir and its antiviral activity against COVID-19. *Front Immunol*. 2022;13:855496.
45. Alharbi NK, Padron-Regalado E, Thompson CP, et al. ChAdOx1 and MVA based vaccine candidates against MERS-CoV elicit neutralising antibodies and cellular immune responses in mice. *Vaccine*. 2017;35:3780-3788.
46. Alharbi NK, Qasim I, Almasoud A, et al. Humoral immunogenicity and efficacy of a single dose of ChAdOx1 MERS vaccine candidate in Dromedary Camels. *Sci Rep*. 2019;9:16292.
47. Alharbi NK, Aljamaan F, Aljami HA, et al. Immunogenicity of high-dose MVA-based MERS vaccine candidate in mice and camels. *Vaccines*. 2022;10:1330.
48. Arabi YM, Asiri AY, Assiri AM, et al. Interferon beta-1b and lopinavir–Ritonavir for Middle East respiratory syndrome. *New Engl J Med*. 2020; 383:1645-1656.
49. Kumar V. Emerging Human coronavirus infections (SARS, MERS, and COVID-19): where they are leading us. *Int Rev Immunol*. 2021;40:5-53.
50. Motavalli R, Abdelbasset WK, Rahman HS, et al. The lethal internal face of the coronaviruses: Kidney tropism of the SARS, MERS, and COVID19 viruses. *IUBMB Life*. 2021;73:1005-1015. Erratum in: IUBMB Life. 2022 Mar;74(3):272. Erratum in: IUBMB Life. 2022 Jun;74(6):554.
51. Kandeel M. Meta-analysis of seroprevalence and zoonotic infections of Middle East respiratory syndrome coronavirus (MERS-CoV): a one-health perspective. *One Health*. 2022;15:100436.
52. Pavli A, Tsiodras S, Maltezou HC. Middle East respiratory syndrome coronavirus (MERS-CoV): prevention in travelers. *Travel Med Infect Dis*. 2014; 12:602-608.
53. Almaghrabi RS, Omrani AS. Middle East respiratory syndrome coronavirus (MERS-CoV) infection. *Br J Hosp Med*. 2017;78:23-26.
54. Al-Omari A, Rabaan AA, Salih S, Al-Tawfiq JA, Memish ZA. MERS coronavirus outbreak: implications for emerging viral infections. *Diagn Microbiol Infect Dis*. 2019;93:265-285.
55. Zumla A, Alagaili AN, Cotten M, Azhar EI. Infectious diseases epidemic threats and mass gatherings: refocusing global attention on the continuing spread of the Middle East respiratory syndrome coronavirus (MERS-CoV). *BMC Med*. 2016;14:132.
56. Al-Tawfiq JA, Gautret P, Schlagenhauf P. Infection risks associated with the 2022 FIFA World cup in Qatar. *New Microbes New Infect*. 2022;49-50:101055.
57. Chamari K, Dergaa I, Mujika I, et al. Football in times of COVID-19: a recapitulation of preventive measures and infection control policies aiming at a safe game environment. *Int J Sports Physiol Perform*. 2022;17: 1448-1451.
58. Mohapatra RK, Padhi BK, Kandi V, et al. Camel virus (MERS) reported from Qatar: a threat to the FIFA-2022 and Middle East. *QJM*. 2023;116:152.
59. Sah R, Alshahrani NZ, Shah P, et al. FIFA World cup 2022 in Qatar: mitigating the risk of imported infections amid the COVID-19 pandemic, monkeypox outbreak and other emerging diseases. *Travel Med Infect Dis*. 2022;50:102450.
60. Ngere I, Hunsperger EA, Tong S, et al. Outbreak of Middle East respiratory syndrome coronavirus in camels and probable spillover infection to humans in Kenya. *Viruses*. 2022;14:1743.
61. Rabaan AA, Al-Ahmed SH, Sah R, et al. MERS-CoV: epidemiology, molecular dynamics, therapeutics, and future challenges. *Ann Clin Microbiol Antimicrob*. 2021;20:8.
62. Baharoon S, Memish ZA. MERS-CoV as an emerging respiratory illness: a review of prevention methods. *Travel Med Infect Dis*. 2019;32:101520.
63. Raghavan PR. Metadichol®: a novel nanolipid formulation that inhibits SARS-CoV-2 and a multitude of pathological viruses in vitro. *Biomed Res Int*. 2022;2022:14.
64. Raghavan PR. Metadichol®: A Novel Nanolipid Formulation That Inhibits SARS-CoV-2 and a Multitude of Pathological Viruses In Vitro. *Biomed Res Int*. 2022;2022:1558860. Published 2022 Jan 15. doi:10.1155/2022/1558860
65. Rahman A, Sarkar A. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: analyses of risk factors and literature review of knowledge, attitude and practices. *Zoonoses Public Health*. 2022;69:635-642.