
BRIEF OVERVIEW OF MERS: MIDDLE EAST RESPIRATORY SYNDROME

Ayesha Nadeem¹, Hafiza Arshi Saeed², Ambreen Talib³, Rabbya Rayan Shah⁴, Rameen Atique⁵, Abdul Samad⁶

^{12,3,4,5}Muhammad Nawaz Sharif University of Agriculture, Multan, Pakistan, ⁶Gyeongsang National University, Jinju, South Korea

buzdarabdulsamad@gmail.com

ABSTRACT

Middle East Respiratory Syndrome (MERS) is a zoonotic disease caused by MERS-CoV, a beta coronavirus with a mortality rate of approximately 35%. The disease exhibits a wide range of clinical symptoms, from mild respiratory issues to severe conditions like multi-organ failure and pneumonia. Person-to-person transmission has led to significant hospital and community outbreaks, underscoring the urgent need for effective infection control measures. This study explores MERS-CoV's epidemiology, pathogenesis, and transmission dynamics, aiming to enhance understanding of its replication, spread, and control strategies due to limited pharmaceutical interventions. A comprehensive review of current literature was conducted, focusing on epidemiological data, genetic characteristics, and transmission patterns across affected regions, including the Middle East, Asia, Africa, and North America. Findings indicate that MERS-CoV originated from recombination events in the spike protein of African dromedaries and spread to the Arabian Peninsula via camels. The virus affects not only humans but also domestic animals like sheep, cattle, horses, and pigs, with global transmission facilitated by travelers, resulting in outbreaks in Asia and North America. Despite extensive research, no effective vaccines, antiviral drugs, or immune therapies control MERS-CoV. The findings emphasize the high pandemic potential of MERS-CoV due to its mortality rate and lack of effective treatments, highlighting the need for strict infection control and further research into viable therapeutic options.

Keywords: coronavirus, dromedary camels, MERS, nucleocapsid protein, pandemic, respiratory illness

Corresponding Author: Abdul Samad
E-mail: buzdarabdulsamad@gmail.com

**INTRODUCTION**

Middle East Respiratory Syndrome, a fatal zoonotic disease, first emerged in Saudi Arabia and Jordan in 2012 (Elhazmi et al., 2021; Memish et al., 2020; Yang et al., 2022). It remains in the form of nosocomial outbursts, community clusters, and individual cases. From April 2012 to December 2019, 2499 verified cases of MERS-CoV were reported to the World Health Organization with a mortality rate of 34.3% (858 deaths) (Azhar et al., 2019). The majority of these cases (2106 cases, 780 deaths) were reported from Saudi Arabia. MERS-CoV remains a dangerous infection in various parts of the world (Abdullah Assiri et al., 2013; Babarinsa et al., 2021; Mahmood et al., 2022). Hospitalized patients possess a considerable mortality rate.

Middle East Respiratory Syndrome (MERS) can present with a broad spectrum of symptoms. In mild cases, it manifests as a simple respiratory illness with symptoms such as cough and sore throat (Biswas et al., 2024; Kandeel, 2022; Muhammad & Akram, 2024). However, in more severe instances, MERS can lead to significant complications, including pneumonia, multi-organ failure, and even death. Patients may experience additional symptoms affecting various systems in the body, such as fever, gastrointestinal symptoms like diarrhea, and neurological manifestations. The severity of symptoms varies significantly, often influenced by factors such as age, preexisting conditions, and immune status (Abdelfattah et al., 2023; Azhar et al., 2023; J. H. Lee et al., 2024).

Under the electron microscope, its structure is crown-like due to glycoprotein spikes. It consists of positive-sense single-stranded RNA as its genomic material (Rabaan et al., 2020). It consists of an outer envelope with a genomic size of 27 to 32 kb, which makes it a member of the most prominent RNA genome family, Coronaviridae (Shchelkanov et al., 2020). Other members of the Coronaviridae family include SARS-Cov and SARS-Cov-2 (Coronavirus). MERS-CoVs established a close relationship with two bat coronaviruses, HKU4 and HKU5, showcasing that MERS-CoV originated in bats (Corman et al., 2012).

The nucleocapsid protects the viral genome. The shape of the nucleocapsid alters according to its position: helical when relaxed and spherical when inside the virus (Mostafa et al., 2020). MERS-Cov genome encodes structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Each protein has its specific function. S protein helps assess the endoplasmic reticulum (ER) and attachment with receptors (Yan et al., 2020). M protein gives shape to virion. It helps bind to the nucleocapsid, E protein has a vital role in viral assembly and release, and N protein plays a role in packing the viral genome into viral particles, thus helping in viral assembly (Al-Tawfiq & Memish, 2016).

MERS-CoV transmits the disease by causing severe respiratory tract infections in patients (Corman et al., 2012). MERS-CoV antibodies in camels in the Middle East indicate that camels can act as intermediate hosts (Azhar et al., 2019). MERS-CoV infects humans and animals with direct contact with infected dromedary camels (Azhar et al., 2019). It causes various diseases in humans and animals, including upper respiratory tract, gastrointestinal, and neurological disorders (Oboho et al., 2015). MERS-CoV has become the second most pathogenic virus of the *coronaviridae* family. Its sporadic cases in the last 12 years require constant surveillance, proper handling of emergency cases, and international collaboration to tackle the disease (Hui et al., 2018).

While MERS-CoV shares characteristics with other coronaviruses, it presents unique challenges due to its high fatality rate and sporadic yet severe outbreaks, particularly in healthcare environments. Understanding MERS-CoV's transmission dynamics, clinical presentation, and control measures remain crucial for reducing its impact on public health. This study addresses these concerns by comprehensively analyzing MERS-CoV's epidemiology, transmission, and symptomatology, aiming to inform effective containment strategies.

This article seeks to enhance the understanding of MERS-CoV by exploring its transmission dynamics and comparing them with related coronaviruses. A novel aspect of this study is the focus on the distinct transmission behaviors observed in healthcare versus community settings and the varying clinical manifestations of the virus across different populations. By highlighting these unique perspectives, this study contributes new insights into MERS-CoV's public health implications and underscores the importance of context-specific preventive measures. The research aims to support

healthcare preparedness and inform targeted interventions to manage and mitigate MERS-CoV outbreaks effectively.

This epidemiological perspective provides critical insights into the ongoing risks posed by MERS-CoV, underscoring the importance of international collaboration, continuous surveillance, and effective public health measures to prevent future outbreaks. Understanding MERS-CoV's transmission patterns and comparing them to those of related coronaviruses can guide preventive strategies and enhance preparedness for emerging infectious diseases.

RESULTS AND DISCUSSION

Clinical Presentation and Symptomatology

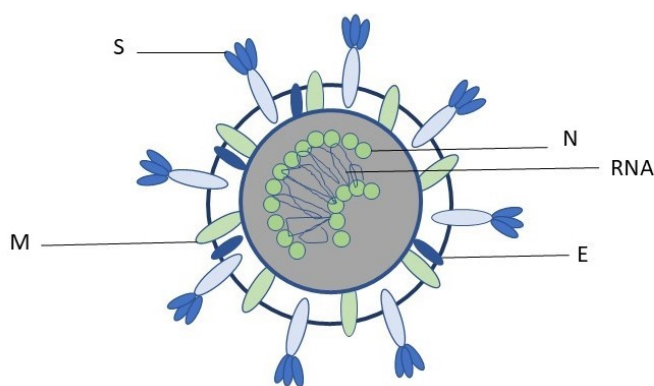


Figure 1.

Schematic Structure of MERS-Cov representing structural proteins, S (Spike protein), N (Nucleocapsid protein), E (Envelope protein), M (Membrane protein).

MERS-Cov belongs to the order Nidovirale, Coronaviridae family, and Coronavirinae subfamily, which have four further genera (alpha, beta, gamma, and delta coronaviruses). The glycoprotein spikes give a crown-like structure to the virus, hence named Corona (Corona meaning crown in Latin). SARS-Cov and SARS-Cov-2 are other members of the same family, mainly causing similar diseases in humans and animals like respiratory tract infection, gut infection, pneumonia, etc, and go along with human-to-human transmission. These are beta coronaviruses and, hence, are mostly similar. SARS-Cov first emerged in 2002 in Southeast Asia, MERS-Cov was found in 2012 in the Middle East, and SARS-Cov-2, Coronavirus, emerged in 2019 from Wuhan (Hubei province of China) (Shchelkanov et al., 2020).

All these viruses have a common ancestor, Bat, a natural reservoir, but intermediate hosts may vary for each virus. Traveling proved to be one of the primary reasons for the regional and global transmission of coronaviruses (De Wit et al., 2016). Studies revealed that these coronaviruses have structural similarities between them. SARS-Cov and SARS-Cov-2 are more similar in structure and pathogenicity than MERS-Cov (Abdelrahman et al., 2020). The main targets of these viruses are people with weaker immunity, such as newborns, older adults, and people with severe respiratory disorders

(Mostafa et al., 2020). Table 1 compares these coronaviruses that have caused terrible outbreaks in global history.

Table 1. Comparison between Coronaviruses (SARS-Cov, MERS-Cov, SARS-Cov-2) of Coronaviridae family

Epidemiology	SARS-CoV	MERS-CoV	SARS-CoV-2
Outbreak	November, 2002 ¹	April, 2012 ²	December, 2019 ³
Area	Guangdong, China ¹	Saudi Arabia ²	Wuhan, China ³
Intermediate Host	Live Animal Market ⁴	Camel ⁵	Wildlife Market ⁶
Number Of Cases	8096 ⁷	2622 ⁸	774 M ⁹
Mortality	10% ⁷	35% ⁸	0.94% ⁹
Cellular Receptor	ACE2 ¹⁰	DPP4, CD26 ¹¹	ACE2 ¹⁰
Effected Countries	29 ¹²	27 ¹³	229 ¹⁴
Transmitted Region	Globally ¹⁵	Regionally ¹³	Globally ¹⁶

Geographic distribution of Middle East Respiratory disease

Despite the first case of MERS-CoV happened in April 2012 in Jeddah, Saudi Arabia, it spread among people in September of the same year (Memish et al., 2020). Retrospective studies show that in April, the viral disease was found in only 13 patients, which increased in number and transmitted to the USA, Asia, Europe, Africa, and the Arabian Peninsula (Ahmed et al., 2017). The main reason for spreading MERS-CoV outside the Middle East was that the patients had recently visited the Arabian Peninsula or had close contact with the main case. The number of reported cases in Saudi Arabia in May 2015 was 1016 and 447 deaths (44% mortality), which made Saudi Arabia the country with the highest number of cases³⁸. Two thousand six hundred twenty-two laboratory-confirmed cases of MERS-Cov have been reported from all continents to the World Health Organization to date, with 918 deaths (~35% mortality rate) (Organization, 2018).

Several organizations from all over the world, including the World Health Organization, the European Center for Disease Prevention and Control, Public Health England, and the Saudi Ministry of Health, worked effortlessly and regularly update their guidelines for the treatment, control, and prevention of MERS (Tolentino et al., 2024). Middle Eastern countries that reported MERS-CoV cases include Saudi Arabia, United Arab Emirates, Jordan, Qatar, Oman, Kuwait, Iran, Yemen, Bahrain, and Lebanon. European countries with confirmed MERS patients are the United Kingdom, Germany, France, Italy, Netherlands, Turkey, Austria and Greece. Other countries are Tunisia, Thailand, the Republic of Korea, the Philippines, Malaysia, China, Egypt, Algeria, and the USA (Organization, 2019).

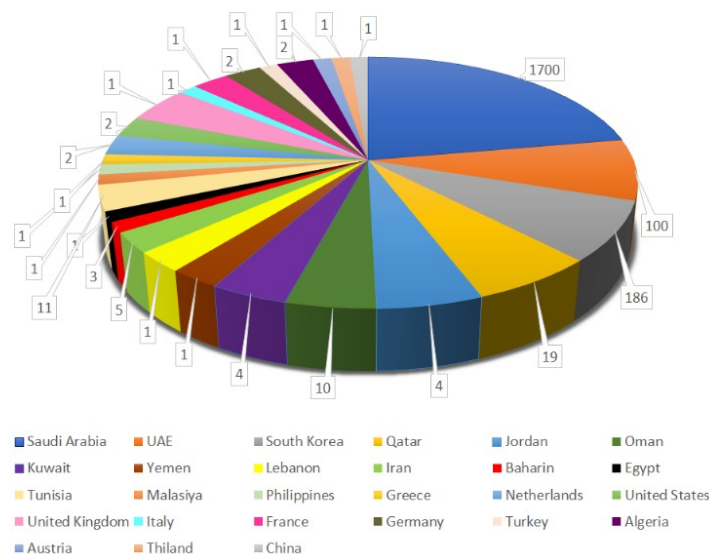


Figure 2.
Number of MERS cases in different countries.

Replication of MERS-CoV

Viral replication is aided by respiratory epithelial cells, which have been proven highly susceptible to MERS-CoV ((Zhou et al., 2015). The replication of the MERS-CoV virus starts when the virus binds with the host's plasma membrane. This attachment is facilitated by the S protein, which blends the plasma membrane and finally discharges the RNA in the nucleocapsid, and then genome transcription takes place. The virus is entered through membrane fusion or endocytosis. In genome transcription, the virus mutates to make itself more accessible from person to person, significantly raising disease prevalence (Fehr et al., 2017). After entry, the virus replicates its RNA and proteins. As it is a positive sense, it does not require RNA polymerase enzyme for transcription. The MERS-CoV genome contains about 30,000 nucleotides and ten predicted open reading frames (Pan et al., 2021). The newly synthesized viral RNA and proteins amalgamate together to form progeny virions. These virions assemble in cytoplasm inside the host cell.

At last, the newly synthesized virions are transported to the Endoplasmic Reticulum and Golgi apparatus, which help them release through exocytosis, infecting further hosts and continuing the cycle (Song et al., 2019). Upon invasion of pathogens, human epithelial cells produce antiviral cytokines and chemokines. The induction of antiviral interferons is lessened by the viral antagonistic effect (Vigant et al., 2015). Many MERS-CoV proteins, including membrane protein and accessory proteins 4a, 4b, and 5, are proven to muzzle interferon production (Aleebrahim-Dehkordi et al., 2021).

Host Risk factors

The main target of MERS is adults above 50 years of age who are taking immunosuppressive treatment or with comorbidities including diabetes, high blood pressure, heart disease, obesity, acute and chronic respiratory disease, renal disease, or cancer (Dyall et al., 2017). So, deaths among infected patients are linked to older age and respiratory problems (Haagmans et al., 2015). Among healthcare providers and young people, infections are mild and asymptomatic (Oboho et al., 2015). Infections among children are infrequent (Memish et al., 2020). Genetic impact on MERS-CoV infection is not recorded. People with direct or indirect contact with dromedary camels are at high risk of getting infected (Park, 2020). Healthcare providers are also at risk of MERS-CoV infection due to continuous contact with infected patients (Majumder et al., 2017). One study shows that males are at higher risk than females (Nam et al., 2017).

Transmission

In healthcare settings, transmission is often amplified due to close contact with infected patients, especially in environments with inadequate infection control practices. Factors contributing to healthcare-associated outbreaks include prolonged patient stays, invasive procedures, and the presence of immunocompromised individuals who are more susceptible to infection. For example, a significant outbreak in South Korea in 2015 spread rapidly among healthcare workers and patients due to delayed diagnosis and overcrowded facilities. The super-spreader phenomenon, where one individual transmits the virus to a disproportionately large number of secondary cases, has been documented in these settings, highlighting the critical need for stringent infection control measures.

Transmission of MERS-CoV in humans is reported through both animals and humans. Animals and humans play significant roles in transmitting the virus to other people. Viruses, hosts, and environmental factors, like pollution, play a significant role in MERS-CoV transmission.

Transmission From Animals to Humans

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) transmission occurs through animal-to-human and human-to-human interactions. In human-to-human transmission, the virus spreads primarily via respiratory droplets, close contact, and potential airborne transmission in specific settings. MERS-CoV outbreaks have demonstrated different transmission dynamics in healthcare settings compared to community outbreaks. As MERS-CoV spreads from one individual to another, the infection can manifest with a variety of symptoms, affecting multiple body systems and leading to complications ranging from mild respiratory issues to severe systemic illnesses.

Camel products such as milk, meat, blood, urine, and other birth products contain MERS-CoV. However, genetic research still does not justify the presence of viral particles in these products (Arabi et al., 2017). People having direct contact with dromedary camels are at high risk of getting infected (Fehr et al., 2017). Genetic studies showed that isolates obtained from patients are the same as those obtained from infected camels having frequent nasal discharge (Azhar et al., 2014). Preventive measures should be taken to avoid contact with infected camels, treat the infection, and regularly check and monitor dromedary camels (Azhar et al., 2019).

Transmission From Human to Human

Two main factors play a significant role in transmitting MERS-CoV from human to human. These include transmission due to an infected person in the same house, household transmission, and transmission among the community, including friends, colleagues, and healthcare providers. These are discussed below in detail.

Household Transmission

In human-to-human transmission, one of the primary sources is close residence, living within the same house. Household transmission is the primary factor for virus transmission (Abdullah Assiri et al., 2013). One survey shows that 24% family members of family were infected with MERS-CoV due to intimate residence with infected patients and inhaling the same infected air with respiratory secretions of patients (Azhar et al., 2019). In human-to-human transmission, asymptomatic infections may have an underrated but notable role (Guarner, 2020). Advanced technology and enhanced techniques have enabled us to identify asymptomatic cases more precisely with every dealing (Mackay & Arden, 2015). Nasal discharge and drops from the lungs are primary sources of transmission among humans having intimate contact (Baharoon & Memish, 2019). Environmental conditions like surface contamination and lack of desirable protections in the infected person's room are also a source of transmission of infection (Bin et al., 2016).

Community Transmission

The outbreak of MERS-CoV in several countries happened due to community virus transmission. In community transmission, transmission among healthcare providers is most common. In healthcare settings, factors like cramped places, lack of infection control practices, undistinguished infection cases, super infector phenomenon, and poor classification of severity of infection (Al-Tawfiq & Memish, 2016). The contact of infected persons with the community, either with close contact, such as relatives and friends, or with healthcare providers and other non-infected patients in the hospital, causes the transmission of MERS-CoV. Lack of diagnostic techniques and asymptomatic cases were significant reasons for viral transmission. The risk factors of MERS-CoV need to be adequately understood for its control.

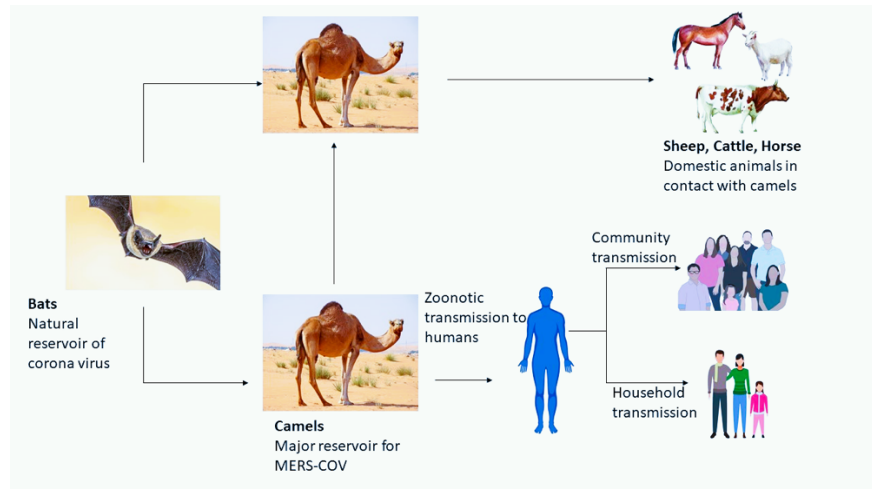


Figure 3.

MERS is transmitted from bats, a natural reservoir of coronavirus, to camels, the primary reservoirs.

Symptoms of MERS

Various body systems, such as the respiratory, gastrointestinal, and digestive systems, can be involved in the signs and symptoms of MERS. Common symptoms include fever, vomiting, diarrhea, abdominal pain, chills, shivering, headache, sore throat, arthritis, fatigue, and asthma (Guarner, 2020). Gastrointestinal tract infection is followed by pneumonia (Li & Du, 2019). Other viruses that infect MERS-CoV patients include Enteroviruses, parainfluenza viruses, rhinoviruses, and influenza A&B viruses ((Azhar et al., 2019). In immunodeficient patients, MERS is more severe (Chan et al., 2015). A few cases of children under 5 are also reported (Aleebrahim-Dehkordi et al., 2021). Mild symptoms and uncommon demonstrations of diarrhea have also been recorded in MERS cases (De Wit et al., 2016). MERS may lead to severe illness and even fatal consequences, including abortion (Alserehi et al., 2016). Severe diseases caused by MERS are cystic fibrosis, lung diseases, multi-organ failure, lymphocytosis, thrombocytopenia, and even cancer (Nassar et al., 2018).

Clinical samples for Laboratory Testing

According to the WHO suggestion, upper respiratory tract specimens (nasopharyngeal and oropharyngeal) and lower respiratory tract specimens (sputum, tracheal aspirate, or lavage) are collected for laboratory testing (Organization, 2019). Lower respiratory tract specimens are prioritized over upper respiratory tract specimens as they are diagnostically valuable (Organization, 2018). It is advised to repeat the collection and testing of samples, as a single negative test result does not rule out the diagnosis. To confirm the eradication of the virus from the patient's body, consecutive respiratory samples should be taken (every 2-4 days) and tested as soon as two consecutive negative results appear in a clinically recovered person (Ahmed et al., 2017).

Diagnosis of MERS

Clinical Spectrum

Transmission from dromedary camels to humans poses a potential pandemic threat (Hemida et al., 2017). Clinical radiology tests and MRI findings show neurological symptoms in MERS patients. MERS

infection documents other common viruses and bacteria like E.coli (Sarathy et al., 2022). Fever, cough, joint pain, sore throat, and elevated body temperature are common symptoms of MERS that are clinically diagnosed (Jolly, 2016). In worsened cases, severe inflammation, lung tissue swelling, and kidney failure are also diagnosed (Yan et al., 2020). A study shows that regular initial chest X-rays are done on 42% of observed patients. Bilateral diffuse involvement increases over time, commonly obtained from follow-up X-rays, and is linked to higher mortality. The importance of chest X-ray progression in MERS-CoV patients is determined by the fact that understanding specific radiographic patterns is critical for outcome analysis (Ajlan et al., 2022).

Laboratory Findings

Diagnostics have always been essential in handling Middle Eastern Respiratory Syndrome outbreaks. This highlights the importance of molecular and serological tests for detecting, monitoring, and surveillance MERS-CoV in humans and camels. It is recommended that testing procedures be improved, including upgrading sample collection and using various serological assays to successfully maintain and control the spread of the virus (Kelly-Cirino et al., 2019). However, healthcare providers face many challenges, including optimizing infection kinetics, documenting test results, and accessing clinical materials for new tests. For effective monitoring and international control of viruses, we must standardize laboratory methods and conduct routine quality assessments (Pormohammad et al., 2020).

Table 2. Different assays that can be used to identify and amplify MER-CoV

Assays	Types	Target gene (region)	Genome target	Result	References
Screening RT-PCR		Upstream of Envelope gene (upE)	Non-coding region upstream of the envelope gene		(Corman et al., 2012)
		Nucleocapsid gene (N2)	Nucleocapsid gene		(Li & Du, 2019)
Confirmatory RT-PCR		Open reading frame (ORF) 1a gene	Transcriptase-replicase complex		(Corman et al., 2012)
		Open reading frame (ORF) 1b gene	Transcriptase-replicase gene		(Corman et al., 2012)
		Nucleocapsid gene (N3)	Nucleocapsid gene		(Li & Du, 2019)

Confirmatory assays by sequencing		RNA-dependent-RNA polymerase (RdRp)	Transcriptase-replicase complex	(Corman et al., 2012)
		Nucleocapsid gene	Nucleocapsid gene	(Corman et al., 2012)
Antibody detection assays	Conventional IFA Rapid IFA		Better cell morphology Biosafety requirements for shipment	(Corman et al., 2012)
RT-RPA		Nucleocapsid gene	Nucleocapsid gene	(Abd El Wahed et al., 2013)
RT-LAMP		Nucleocapsid gene	Nucleocapsid gene	(Shirato et al., 2018)

Treatment

Antiviral antibiotic treatment is usually recommended for 10-14 days in patients infected with MERS-CoV (Chong et al., 2015). A research study shows that using ribavirin or interferon alpha 2b reduces the improvement and development of MERS (Cheng et al., 2013). Nevertheless, the inhibition of MERS-CoV multiplication was not detected by the use of viral vaccines but by the number of vaccines that show mortality and virulency among people (Falzarano et al., 2013). If patients regain the viral infection, the duration of the administration of antiviral drugs should be reduced. Issues concerning side effects are also traced (Vigant et al., 2015). Long-term usage of pharmaceutical drugs is recommended in case of a weak immune system (Ko et al., 2021). Ribavirin drugs are preferred in MERS outbreaks in collaboration with or without interferon or steroid therapy (Dyall et al., 2017).

Another appealing method of drug discovery in the case of MERS-CoV is drug reuse, which has been accepted as pharmaceutical healthcare in the last 10 years (Ford et al., 2020). A study comparing the therapy and non-therapy groups revealed that using ritonavir decreased the MERS-CoV colonies in the pulmonary system. Combining interferon alpha and interferon beta can improve the treatment of MERS-Cov in case of severe infection (Momattin et al., 2019). Drug therapies used for MERS-CoV treatment include cyclosporine, chloroquine, chlorpromazine, and mycophenolic acid—these work by inhibiting viral replication (Ko et al., 2021). Recovered samples from treated patients and antibodies or antigens are helpful in the treatment process (Ford et al., 2020). Corticosteroids are experimentally proven to lessen the host's reaction to infection (K. H. Lee et al., 2020). Steroids are used along with precautionary measures. Properly understanding of procedures and treatment facilities generally enhances the medical treatment of MERS-CoV. This also contributes to reducing the side effects of treatment (Momattin et al., 2019).

Control or Prevention of MERS

International organizations like the World Health Organization, the US Centers for Disease Control and Prevention, and the Middle East Ministry of Health provide all the directions for controlling and preventing MERS-CoV. While visiting a patient or during an interaction with the patient, wearing a mask, gown, and gloves and taking them off after a visit are primary steps for preventing and controlling the infection (Corman et al., 2012). Precautions must be applied while treating the infected person. While caring for suspected or confirmed patients, healthcare providers must wear eye protection as a precaution (Almutairi et al., 2016). Disposable N95 filtering facepiece respirators certified by the National Institute for Occupational Safety and Health and essential personal protective equipment are recommended while managing the known or suspected MERS-CoV infection (Tolentino et al., 2024). Precautionary measures related to treating MERS-CoV patients demand the presence of HEPA filters (high-efficiency particulate absorbing filters) in the patient's room, or the patient should be kept under negative pressure. Air must be filtered, and at least six air exchangers should be installed in the treatment room (Licina et al., 2020). These recommendations are given based on experimental results and are effective in hospitals. To prevent a severe MERS-CoV outbreak, effective disease surveillance and monitoring and control strategies are required during extensive gatherings (Abolfotouh et al., 2017).

CONCLUSION

This review concludes that MERS-CoV is a viral particle that can cause occasional human disease, which causes upper and lower respiratory tract infections and extrapulmonary manifestations such as renal failure, hepatic dysfunction, and diarrhea. The global spasmodic outbreaks of MERS-CoV notify the constant spread of the virus. It remains a priority for WHO due to its high rate of deaths. In the geographic regions of the Middle East and Africa, MERS-CoV is an endemic disease. These viral outbreaks will keep emerging because the genetic and evolutionary changes are inexorable—the re-emerging cases of MERS-CoV demand continuous research for its treatment and control. One of the main goals of endemic and endangered regions for controlling and treating MERS-CoV is to develop human and dromedary camel vaccines. Monitoring, medical therapies, and public health research programs are other priorities for controlling and preventing MERS-CoV. The transmission of MERS-CoV in dromedary camels and among people at high risk of healthcare and community infection can be prevented by developing effective vaccines. By understanding the molecular process of the viral life cycle and pathogenicity, we can make an effective treatment for the disease.

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