Middle East Respiratory Syndrome (MERS): An Overview

36

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ABSTRACT

Middle East respiratory syndrome coronavirus (MERS-CoV) is a zoonotic disease that can cause mild pneumonia to severe respiratory infections in humans. The virus only produces a little infection in dromedary camels, but it transmits quickly amongst them. The behavior of the virus varies from person to person and between humans and dromedary camels, which emphasizes the part played by host variables in MERS-CoV pathogenesis and transmission. It results in a high temperature, cough, acute respiratory tract infection, and multiorgan dysfunction that may ultimately cause the infection victims to pass away In order to control MERS-CoV infection, no medication has yet received clinical approval. To avoid the negative effects of future epidemics like this one, a number of sensible precautions should be implemented. The development of efficient therapeutic and preventative anti-MERS-CoV infections, as well as further research into the epidemiology and pathogenesis of the virus, are all required.

Keywords: MERS-CoV, zoonotic importance, virus, respiratory disease

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1. INTRODUCTION

A virus is a microscopic organism that only reproduces within the living cells of plants, animals and humans. The Nucleic acid (DNA or RNA) and proteins constitute the viruses (Hyman and Abedon 2012). About 64% of identified human diseases come from vertebrate hosts apart from humans or zoonotic pathogens (Heeney 2006). Emerging infections are primarily caused by viruses of zoonotic importance.; These viruses include the Ebolavirus, human immunodeficiency virus (HIV), Hantavirus, Middle East Syndrome coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome (SARS), and Influenza A viruses (Mandl et al. 2015). Different infectious diseases arise and spread through a variety of environmental factors, including people, animals, and the environment (Wang and Crameri 2014). Animals are the primary source of the majority of respiratory diseases that infect humans. These zoonotic diseases are transmitted naturally from vertebrate animals to humans and from one individual to another (Rahman et al. 2020). One of the three zoonotic coronaviruses to infect people and cause severe pneumonia since 2002 is the MERS- CoV (Peiris and Perlman 2022). The infectious respiratory disease known as MERS was initially identified in the Kingdome of Saudi Arabia in September 2012 (Al-Tawfiq et al. 2014). MERS-CoV, known for its high pathogenicity, causes the disease in humans (Hui et al. 2021). People who have MERS-CoV infection maybe asymptomatic, or they may have mild, severe, or even fatal respiratory illness (Baharoon and Memish 2019). It is a new viral respiratory illness with a focus on the lungs and breathing airways (Durai et al. 2015). It is a novel, fatal, zoonotic human viral disease that resides entirely in the Middle East.

Patients with MERS-CoV caught this fatal disease from a variety of sources, including infected humans, camels, bats, other farmed animals, and pets (Ramadan and Shaib 2019). Clinical manifestation includes acute respiratory distress syndrome, influenza, pneumonia, and asymptomatic MERS. Occasionally, pneumonia develops, which advances to acute respiratory distress syndrome. Human coronavirus-EMC was the original name for the virus before it was universally agreed upon to be known as MERS-CoV (Kane and Gao 2023).

It was found in a pulmonary specimen from a patient who had died at the age of 60, from respiratory distress in Jeddah, Saudi Arabia, in 2012 (Abdel-Moneim 2014). Following, this respiratory distress in Jeddah, Saudi Arabia, MERS cases were found in other places throughout the globe. Travelling or residing in the Middle East countries played a role in the vast majority of these cases, either directly or indirectly (Fehr et al. 2017). The prevalence of these respiratory disorders are increasing in both adults and children, causing worldwide mortality and morbidity (Leung 2021). Respiratory conditions affect the lungs and airway, leading to difficult breathing and gas exchange. These airway systems leave the nose and proceed through the large and small windpipes before reaching the lungs (Lombardi et al. 2021). In general, respiratory conditions are often categorized as contagious (communicable) disorders like bronchitis and tuberculosis (Sencio et al. 2021). The morbidity and mortality caused by deadly viruses like MERS-CoV is significantly influenced by their epidemiology and transmission mechanism (Naz et al. 2023).

According to the WHO, a primary MERS-CoV infection is one that occurred outside of a clinic or medical facility and was likely caused by contact with dromedary camels, which serve as a reservoir host (Durai et al. 2015). MERS-CoV infections exist in two types, primary MERS-CoV infections are those that have been confirmed in the lab and have no known direct epidemiological link to human infections (Goyal et al. 2022). Whereas, a secondary MERS-CoV infection is a lab-proven that has an apparent clinical interaction to a person who has a confirmed or likely MERS-CoV infection (Al-Ahmadi et al. 2019). Where and how MERS-CoV spreads to humans are both unknowns. Preliminary studies revealed that MERS-CoV originated in bats since MERS-related sequences have been identified in a number of bat species (Tai et al. 2022). MERS CoV was initially recognized in people in the Middle East in 2012 and then spread to many European countries (Azhar et al. 2023). Epidemiological research had specifically indicated that MERS was spreading from person to person and was on the verge of becoming a pandemic (Tai et al. 2022). CoV strains recovered from camels were nearly identical to human CoVs, dromedary camels were engaged in the MERS-CoV's emergence. Saudi Arabia, Jordan, Qatar, the United Arab Emirates, France, the United Kingdom, Germany, Tunisia, and Italy all reported cases of MERS-CoV that had been proven by lab testing (WHO 2022, Johari et al. 2023). The MERS-CoV is the most recent example to emerge from bats, and it is considered that all human CoVs originate from animal reservoirs (Alsafi 2022). This animal species is most likely to begin the zoonotic transmission, and it is predicted that it will do so for a very long time (Everard et al. 2020). MERS-CoV has not appeared to spread well from one individual to another, although reports of hospital outbreaks and individuals departing Middle Eastern countries and their close contacts have been made (Dawson et al. 2019). Currently, there are no medications available on the market that are specifically for treating MERS-CoV in humans (Bleibtreu et al. 2020). Currently, clinical management of MERS concentrates on symptoms, providing supportive care in addition to managing pain and fever, promoting the function of essential organs, and treating secondary or concomitant bacterial infections. The prevention of the transmission of zoonotic diseases depends on early detection, identification of potential and verified cases, and continuous monitoring. In most diagnostic laboratories, MERS-COV diagnosis remains a serious concern. Currently, the most common method employed for the diagnosis of MERS-CoV is the Real time Polymerase Chain Reaction (RT-PCR). Therefore, several intervention strategies, such as transmission control, are required to treat MERS patients (Mackay and Arden 2015). Since its emergence in 2012, researchers have been working on the development of a MERS vaccine (Zhang et al. 2014). To develop an efficient vaccine, extensive research is being done using multiple resources like viruses, antibodies, and protein. The MERS coronavirus spike (S) protein's receptor-bound area was discovered to be the focus for vaccine development in a prior investigation. The development of vaccine is being taken up by numerous organizations, some of which have demonstrated efficacy in animal models (Tai et al. 2022).

2. VIROLOGY of MERS

The β-coronavirus family includes MERS-CoV. It has four main surface proteins, including the envelope protein (E), spike protein (S), nucleocapsid protein (N), and membrane protein (M). These proteins help in the virus's ability to penetrate cells. The spike (S) protein is a transmembrane glycoprotein consisting of the S1 and S2 sub-units. According to recent research, these viral structural and nonstructural proteins can be used as potential therapeutic targets (Abdi and Javanshir 2022).

The MERS-CoV basic protein (S), (E), and (M), and (N) contaminated individuals' bronchial cells screened for MERS-CoV as a viral antigen (Durai et al. 2015) are shown in Fig. 1. MERS-CoV is an enveloped Nidovirus that enables entrance into host cells and is adorned with homotrimers of the spike (S) glycoprotein. The primary antigen at the viral surface, S, is the focus of vaccine development and the target of neutralizing antibodies during infection (Baharoon and Memish 2019). MERS-CoV binds to the dipeptidyl peptidase 4 receptor via receptor-binding domain (RBD) in spike (S) protein S1 subunit and then mediates virus entry into target cells via S2 subunit. Therefore, for merging of viruses as well as cells genomic RNA infusion into the cytol, protease cleavage of the S protein is necessary (Xia et al. 2014). The endoplasmic reticulum derived from double membrane compartments and additional membrane-like structures serve as the sites for the transcription and replication of viral RNA (Comar et al. 2022).

Structural proteins of MERS-CoV, their stability, function, or effect on the host is shown in Table 1. The genomic structure of MERS-CoV also consists of accessory proteins like ORF3 and ORF4a that help in replication of virus (Joshi et al. 2023).

3. EPIDEMIOLOGY of MERS

The epidemiology and transmission method of MERS-CoV significantly impact the morbidity and mortality caused by these viruses. There are numerous established methods that spread MERS-CoV. Cattle to man, dogs to man, cats to man, bats to man, dromedary camel to the human method, bats to camels, among camels, cattle to man, and lastly man to man transmission are included (Xie and Chen 2020). In close quarters and congested environments, human-to-human transmission is very effective and frequent. In addition, nosocomial infection has also been reported (Assiri et al. 2013). There have been instances where patients have transferred diseases to healthcare professionals. Dromedary camels are crucial to the epidemiology of MERS-CoV because they serve as reservoir hosts. Additionally, dromedary camels serve as "gene mixing vessels". A new subtype of MERS-CoV develops when two distinct MERS-CoV strains from two different sources infect dromedary camels. This happens because the two genetically distinct MERS-CoV swap their ssRNA. These unique virulence genes and novel antigens are the striking characteristics of these new MERS-CoV subtypes. Possible incidences of human transmission via consuming camel milk have been reported in Saudi Arabia. However, no incidences of transmission to humans by consumption of camel flesh have been reported (Widagdo et al. 2019).

Table 1: Structural proteins of MERS-CoV, their functions, and stability

Protein	Function and effect on host	Stability	References
PL protease	Viral replication, membrane proliferation	Stable	(Naz et al. 2023)
3CL protease	Survival of viruses	Stable	(Li et al. 2019)
Helicase	Viral replication, effect tropism	Stable	(Li et al. 2019)
Spike	Receptor binding, virus entry	Stable	(Li et al. 2019)
ORF3	Pathogenesis and replication	Stable	(Naz et al. 2023)
ORF4a	Viral replication and IFN antagonism	Unstable	(Li et al. 2019)
sssORF5	Mediated inflammation	Unstable	(Naz et al. 2023)
Envelope	Virion assemblage	Stable	(Li et al. 2019)
Membrane	IFN antagonism, virion assembly	Unstable	(Naz et al. 2023)
Nucleocapsid	Replication and assembly	Unstable	(Li et al. 2019)

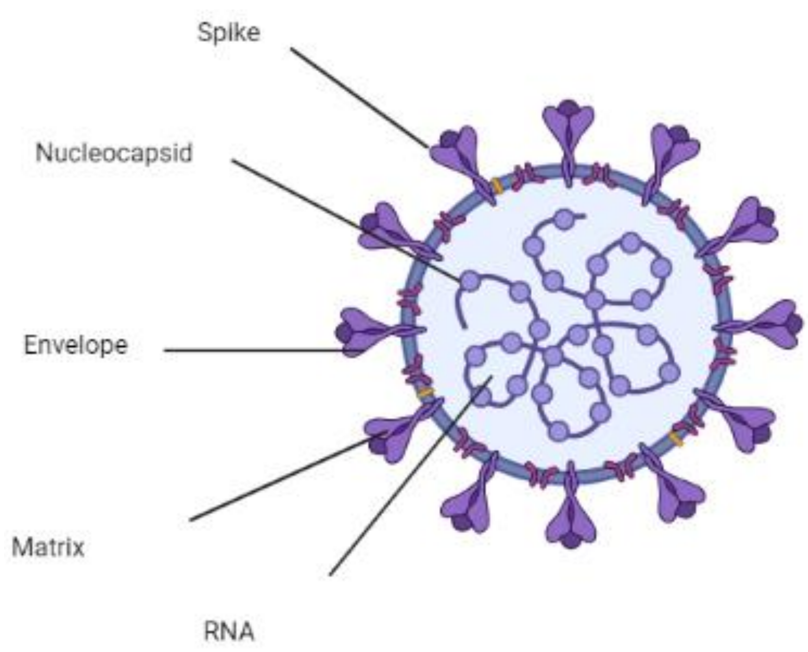

Fig. 1: Genomic structure of MERS-CoV (Retrieved from biorender)

4. PATHOGENESIS AND TRANSMISSION

According to the host, MERS-CoV manifests to a different extent of pathogenicity. Particularly in humans, it stimulates the highest level of pathogenic potential. This because the bronchial non-ciliated epithelia exhibit significant MERS-CoV tropism (Killerby et al. 2020). MERS-CoV infects and replicates in the human airway epithelial cells and suppresses the production of interferons. MERS virus interacts with the host DPP4 receptor through its spike (S) protein after entering the respiratory tract. DPP4 receptors are present on the epithelial surface of various human organs such as, the lungs, kidneys, liver, bone marrow, thymus and intestines. The systemic distribution of DPP4 facilitates the dissemination of virus in the human body (Choudhry et al. 2019).

4.1. ANIMALS TO HUMAN TRANSMISSION

The MERS-CoV transmission mechanism and route continue to be a mystery. The most likely method of camel to human transmission may be droplet transmission or direct contact with infected camels shown in Fig. 2 (Hemida et al. 2017). Other potential pathways include ingestion of unpasteurized camel milk, close contact with intermediate hosts, urinalysis for medical purposes, or intake of raw meat. Foodborne transmission via uncooked meat or unpasteurized camel milk is also a possibility (Widagdo et al. 2019).

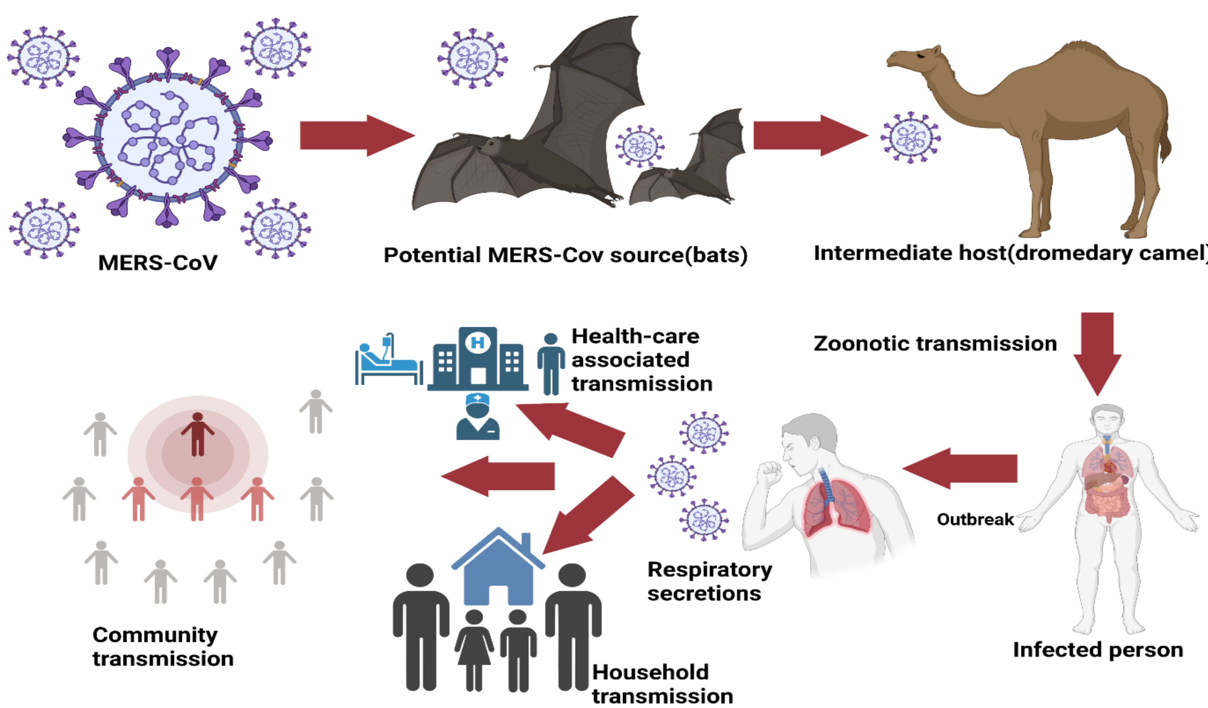

Fig. 2: Potential routes of emergence and transmission of MERS-CoV

4.2. HUMAN-HUMAN TRANSMISSION

MERS-CoV is mostly spread from person to person by nosocomial transmission. Despite the possibilities of airborne or fomite transmission, it was considered that transmission would primarily occur by contact and big droplets. Since MERS- CoV have been isolated from such excretions, transmission by other bodily fluids such as diarrhea, the stool, and vomit are also potentially probable. The majority of infections were passed from person to person, highlighting the significance of taking the proper protection for aerosols and communication to stop spreading to additional affected persons, healthcare professionals, as well as relatives (Raj et al. 2014). Communities, homes, and, most dramatically, hospital settings are all places where human to human transmission occurs (De Wit et al. 2016).

4.3. TRANSMISSION FROM BATS

Numerous viruses, including Henipaviruses, Lyssaviruses, and SARS-CoVs, have been identified to be reservoir hosts in bats. Although it was just recently discovered, the virus may have been spread to humans in antiquity. Therefore, limiting initial and ongoing interaction among bats and individuals, would be one potential future strategy to prevent infection. Knowing these methods of spreading can aid us stop prospective occurrences of recognized and possibly undiscovered diseases that spread from bats to people either directly or through intermediary animals. MERS-CoV significant sequence similarity to viruses found in bats suggests that bats may have been the virus's source, even though its natural reservoir has not yet been identified (Mohd et al. 2016).

5. CLINICAL FEATURES

Any infection has specific symptoms that help with diagnosis and differential diagnosis with other viral infections. However, this effort is quite difficult due to the lack of distinct clinical characteristics for MERS-CoV infection. This causes delays in implementing the safety measures necessary to avoid subsequent contamination. Additionally, it may lead to improper patient management and medical ambiguity. MERS has no defined signs or symptoms; however, it typically manifests as respiratory symptoms. Through asymptomatic manifestations to moderate to severe illness including ARDS, multi organ dysfunction, and mortality, clinical presentation might vary. In the beginning, these individuals only exhibit minor symptoms such as shivers, headache, fatigue, a stuffy nose, coughing, throat discomfort, drowsiness and a mild fever. MERS-CoV might manifest clinically as anything from asymptomatic infections to severe respiratory conditions. Patients who are infected frequently display hemoptysis; a difficulty of breath, coughing, throat discomfort, a high body temperature and additional symptoms of digestion like vomiting and diarrhea (Mann et al.2020).

6. TREATMENT

Currently, there is no MERS-CoV vaccine or medication available (Ramadan and Shaib 2019). Clinical treatment for mild cases of MERS focuses mostly on symptom relief and supportive care, including pain and fever-relieving drugs, plus resting at home. Severe instances necessitate hospital inpatient care for supportive therapy with the goal of lowering the risk of consequences like organ failure and subsequent infections. Additionally, pharmaceutical companies have little incentive to develop the MERS-CoV vaccine because clinical trials are exceedingly expensive and it can take at least 10 years for the vaccine to be authorized for use (Ying et al. 2015).

Patients primarily get supportive treatment, which is frequently augmented by various medication combinations as given in Table 2, in the absence of an antiviral therapy against MERS-CoV that has been clinically demonstrated to be successful. Supportive care is required to maintain renal and hepatic function, assist the respiratory and circulatory systems, and to avoid subsequent infections (Li et al. 2019).

Table 2: Potential therapeutics for MERS-CoV

Treatments	Stage of development	References
Host protease inhibitors	In-vitro inhibition	(Alyami et al. 2020)
Viral protease inhibitors	In-vitro inhibition	(Alyami et al. 2020)
Repurposed FDA-approved drugs	In-vitro inhibition	(De Wit et al. 2016)
Monoclonal and polyclonal antibodies	Efficient in nonhuman primate, mice, and rabbit models.	(Memish et al. 2020)
Convalescent plasma	Efficient in a mice model; clinical study approved	(Alyami et al. 2020)
Interferons	Excellent in nonhuman primate studies; illegally used in patients	(Memish et al. 2020)
Ribavirin	Excellent in nonhuman primate studies; illegally used in patients	(Memish et al. 2020)
Mycophenolic acid	In the nonhuman primate model, protection was ineffective	(Azhar et al. 2019)
Lopinavir and ritonavir	Excellent in nonhuman primate studies; illegally used in patients	(Azhar et al. 2019)

7. PREVENTION AND CONTROL

From the SARS epidemic, the primary infection prevention and management techniques for treating MERS affected individuals are well established. The prevention of nosocomial spread requires continual observation, early detection of suspected or confirmed infections, and isolation of those people. It is necessary to use higher levels of personal protective equipment (a greater protection, stronger types of respiratory immunity), air circulation (more oxygen changes, more ventilation,), and more intensive efforts to stop airflow from spreading past the origination point (enclosure, capture ventilation). In order to prevent MERS infection in hospitals an adequate room air circulation efficiency of twelve air turnovers every hour within one room or a minimum of 161L/s per receptive in establishments via ventilation from the outdoors is recommended to minimize room contaminants in the healthcare environment while taking care for patients obtaining ventilatory therapy along with aerosol-generating processes (Subbaram and Gatasheh 2017). Other preventive strategies included;

7.1. PHYSICAL DISTANCING

An effective and powerful strategy to reduce viral transmission among people and the number of people dying from sickness during the pandemic is to engage in forceful physical distance-creating activities to reduce direct interaction between persons. Absolute containment was used in several countries around the world and showed positive results, most notably reducing the increase in the number of cases. Activities that isolate affected people, quarantine close connections, allow people to work for virtually, close schools, and prohibit large gatherings have all proven effective social distancing measures (Zinn 2021).

7.2. DECREASING THE RISK OF TRANSMISSION

To stop transmission, especially in hospitals, proper infection control measures must be put in place as soon as the diagnosis is taken into account. Primary instances of people with MERS-CoV infection are challenging to diagnose because the symptoms and indications are nonspecific (Ezhilan et al. 2021). It's crucial to take actions for preventing infection and management to stop the transmission of MERS-CoV in homes, communities, and healthcare facilities (Alslamah and Abalkhail 2022).

7.3. PREVENTION OF HEALTHCARE FACILITY TRANSMISSION

The fundamental tenets of MERS-CoV prevention revolve around implementing organizational and environmental events to guarantee initial detection and use of personal protective equipment to avoid cross transmission. To ensure the effective implementation of all administrative measures, healthcare facilities should actively invest in infrastructure for infection prevention and control in addition to developing policies and procedures. All healthcare workers must receive assistance, adequate resources, and training, and all policies must be subject to regular inspection (Behnke et al. 2021). Healthcare institutions must have a sufficient and reliable supply of these supplies. They consist of a robe, gloves, a mask that is very effective, goggles, or a face shield. Demand for PPE may expand significantly, but supply should always be sufficient. PPE use protocols, ongoing training, and auditing are required, especially in settings with significant personnel turnover rates (Kim et al. 2015).

7.4. HEALTH CARE WORKERS AND COMMUNITY EDUCATION

Education about MERS-CoV and MERS preventive strategies may lessen the potential for spreading within the home and avoid community cases in MERS-CoV endemic areas wherever MERS-CoV cases can arise within communities and homes. It is advisable to regularly wash your hands before and after handling camels and to stay away from ill ones (Aleebrahim-Dehkordi et al. 2021). It is not recommended for people to consume uncooked camel meat or to drink raw camel milk or urine. People who suffer from illnesses such as diabetes, cancer, persistent lung condition, or renal illness, who suffer from illnesses such as diabetes, melanoma, persistent lung condition, or renal illness, or who are receiving immunosuppressant therapy must keep distance from bats and camels because they run a significant threat of acquiring severe MERS-CoV illness (Aldohyan et al. 2019).

7.5. GUIDANCE FOR TRAVEL

Travelers should be warned not to go to areas where MERS has been found, per the WHO and CDC's recommendations, in order to avoid MERS infections (Errett et al. 2020). The suggestion is to provide travelers with up-to-date information about MERS coupled with advice on how to prevent illnesses, particularly respiratory illnesses (Alnuqaydan et al. 2021).

7.6. INTENSIVE CARE MANAGEMENT

To lower the risk of consequences like organ failure and subsequent infections, hospital inpatient care is necessary for serious patients. In infected individuals acute hypoxemic respiratory distress brought on by MERS-CoV infection, invasive-free airflow is linked to a high failure rate i.e. 92% (Al-Dorzi et al. 2016). It may be necessary to manage patients with severe symptoms in a hospital's surgical unit, where lung protecting ventilatory methods for acute respiratory distress syndrome, inotropic provision, antibiotic therapy for concurrent infections, and replacement of renal function treatment for acute kidney dysfunction can be offered (Aleebrahim-Dehkordi et al. 2021).

8. DIAGNOSIS

Rapid diagnostic tests are needed to control epidemics of virus because there isn't a particular, dependable antiviral medication or vaccine authorized for clinical use in MERS-CoV infections. A thorough contact and travel history as well as exact laboratory tests are used to make the diagnosis of MERS. Molecular techniques, serology, and viral culture are currently used as diagnostic tools (Al Johani and Hajeer 2016).

8.1. MOLECULAR DIAGNOSTIC

The most popular diagnostic technique uses molecular detection, such as RT-PCR (reverse transcription Polymerase chain reaction), with RNA isolated from samples of the respiratory tract, such as nasopharyngeal swabs, sputum, deep tracheal aspirates, or bronchoalveolar lavage (Skariyachan et al. 2019). Nucleic acid amplification tests (NAAT) are advised by the WHO laboratory recommendations for diagnosis specimens of the lowest pulmonary system's sputum, bronchial aspirates, or lavage of the bronchoalveolar, where MERS-CoV multiplication takes place at faster and longer heights of MERS-CoV RNA, provide the highest NAAT test sensitivity (Mustafa Hellou et al. 2021).

8.2. SEROLOGICAL ASSAYS

Serology is not frequently used to diagnose acute MERS-CoV infection, but it has been a valuable technique to assess the level of infection in the vicinity of clusters and in sero-epidemiological research within people and in animals. Neutralization tests, IIFT, and ELISA are several serological techniques for detecting antibodies against MERS-CoV. As capture agents, commercial reagents or exclusive monoclonal antibodies may be used in MERS-CoV serological testing (Chan et al. 2017).

8.3. MULTIPLEX PANEL

Early MERS-CoV infection symptoms may resemble those of other respiratory infections, such as SARS, pneumonia, influenza, or pneumonia (Liya et al. 2020). A syndromic technique includes assessing infections in response to a condition like fever or acute respiratory distress; moving multiplexing arrays from individual evaluations may swiftly recognize or rule out potential solitary sample of germs. Microbead based multiplexed immune assays have been utilized for circulating reservoir analysis to find IgG antibodies for various infections (Banik et al. 2015).

9. CONCLUSION

Continually posing a threat to human life, MERS-CoV is responsible for the Middle East respiratory syndrome, which is rapidly spreading in the Middle East and around the world. MERS has become a widespread epidemic as a result of the coronavirus rapid evolution. The precise intermediate host for MERS-CoV and its geographic distribution remains unknown despite the studies that have been done to date. Despite being a zoonotic origin for the virus is utmost probable, direct or indirect contact, as well as ingestion of tainted food or food products, could also result in virus transmission. Further research is needed to determine whether or if the virus is boosting the host's involvement is transferred from bats to camels and then to humans, or whether there are other amplifying hosts implicated in the transmission of the MERS-CoV to humans. Given the nosocomial patterns of transmission within healthcare institutions, MERS-CoV continues to pose a significant risk to the public's health, and any additional international spread could have negative effects that are potentially life-threatening. Since MERS-CoV tends to be largely persistent in dromedaries across geographically extensive regions of the Middle East and Africa, zoonotic transmission and the associated danger of human disease outbreaks will very certainly persist for many years. New MERS-CoV cases are still being reported despite significant improvements in diagnosis and public health interventions. Explosive MERS-CoV outbreaks are a severe threat to the world's public health and highlight the additional investigations are required into the epidemiology and pathophysiology of this virus. They also highlight the need for the development of efficient therapeutic and preventive MERS-CoV infection medications. To discover the viral and host variables that are crucial in the emergence of MERS in humans, it is necessary to better understand the pathophysiology of MERS-CoV that could lead to the development of potentially novel treatment and intervention options. In addition, efforts to create vaccinations against this lethal virus have been steadily expanding, which has resulted in the creation of potential therapies.

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