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Chapter

Middle East Respiratory Syndrome Coronavirus Outbreaks

Abdulkarim F. Alhetheel and Faisal A. Alhetheel

Abstract

Middle East respiratory syndrome coronavirus (MERS-CoV) is a single-stranded RNA-enveloped virus that belongs to the Coronaviridae family. Initially reported in 2012 in Saudi Arabia, MERS-CoV is a zoonotic virus originating from bats and transmitted from camels to humans and among humans by contact. It causes both upper and lower respiratory tract infections and in some instances can lead to renal failure or death. This chapter provides an overview of the virologic aspects, outbreaks and risk factors, clinical symptoms, diagnostic methods, as well as prevention and management of MERS-CoV infection.

Keywords: MERS-CoV, outbreak, clinical symptoms, diagnosis, prevention

1. Introduction

The first case of the Middle East respiratory syndrome coronavirus (MERS-CoV) infection was reported in June 2012 in Saudi Arabia. MERS-CoV then spread to several neighboring countries, mainly Jordan and Qatar, and has since been reported in Asia, Africa, Europe, and America [1]. By October 16, 2018, 2260 confirmed cases and 803 deaths from MERS-CoV infection had been documented in 27 countries by the World Health Organization. The vast majority of cases (73%) were reported in Saudi Arabia, with only one widespread outbreak observed outside of the Arabian Peninsula in South Korea in 2015 [2]. Due to the high fatality rate (36%) [1], a lot of effort has been made to understand the origin and pathophysiology of this novel coronavirus strain to prevent it from becoming endemic in humans [3].

2. Middle East respiratory syndrome coronavirus

The first reported case of human MERS-CoV infection was in a 60-year-old man who was admitted to a private hospital in Jeddah, Saudi Arabia, on June 13, 2012. He presented with a 7-day history of fever, cough, expectoration, and dyspnea. He was a non-smoker, had no prior history of cardiopulmonary or renal disease, and was not maintained on any long-term medication. Vital sign examination showed a blood pressure of 140/80 mmHg, a pulse rate of 117 beats/minute, a temperature of 38.3°C, a respiration rate of 20 breaths/minute, and a body mass index of 35.1. Chest X-ray revealed low lung volume, bilateral enhanced pulmonary hilar vascular shadows more

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prominent on the left side, and accentuated bronchovascular lung markings. Multiple segmental, patchy, and veiling opacities were present in the middle and lower lung fields, and the costophrenic angles were mostly blunted. The cardiac silhouette was not enlarged, and the aorta was dilated and unfolded. Chest X-ray was repeated after 4 days, which showed that the opacities became denser and more confluent. Computed tomography performed 4 days after admission revealed few subcentimetric mediastinal and hilar lymph nodes, bilateral dependent airspace opacities with air bronchograms, scattered areas of ground-glass opacity, interstitial septal thickening, and nodularity in the upper lobes, with minimal bilateral pleural effusion. Collectively, these findings are suggestive of an infection. On the day of admission, oseltamivir, levofloxacin, piperacillin-tazobactam, and micafungin were started. Three days later, meropenem treatment was initiated, since meropenem-sensitive *Klebsiella pneumoniae* was identified in tracheal lavage sample collected on day 2. *Staphylococcus aureus* was detected in a sputum sample performed on admission. *Acinetobacter* was identified in tracheal aspirate collected on the day of death. No other pathogens were detected in respiratory specimens, and no bacterial growth was detected in blood samples.

The patient was transferred to the intensive care unit (ICU) for mechanical ventilation on the second day. Laboratory findings obtained on admission showed normal white blood cell counts except for a relatively high percentage of neutrophils (92.5%) and a low percentage of lymphocytes (4.3%). Liver enzymes, blood urea nitrogen, and creatinine levels were within the normal range. A small increase in the liver enzymes was noted from day 7 onward, with alanine aminotransferase levels of 20, 78, and 47 international unit (IU)/liter (l) on days 1, 7, and 8, respectively, and aspartate aminotransferase levels of 33 and 96 IU/l on days 1 and 8, respectively. The patient tested negative for the human immunodeficiency virus; however, testing for pneumocystis pneumonia was not performed. On the third day following admission, blood urea nitrogen and creatinine levels significantly elevated, and on the eighth day, white cell count began to rise and reached a peak of 23,800 cells per cubic millimeter by day 10, with neutrophilia, persistent lymphopenia, and progressive thrombocytopenia. Arterial oxygen saturation ranged from 78% to 98%. On day 11 (June 24, 2012), the patient died of progressive respiratory and renal failure [4].

2.1 The source of MERS infections

In 2012, a new coronavirus strain was detected in patients from the Arabian Peninsula with severe respiratory symptoms known as MERS-CoV. Camels were identified as the source of the infections; however, the role of these animals in transmitting the infection is not well understood. Approximately 300 isolated MERS-CoV genomes had been sequenced from humans and camels during the epidemic. Previous attempts to understand the MERS-CoV epidemic relied on these data or reports of case numbers; however, this led to conflicting results at odds with other sources of evidence. Nevertheless, Dudas et al. [5] determined the relationship among MERS-CoV strains and reconstructed their family tree by analyzing their sequenced genomes.

2.2 Genome structure and function

MERS-CoV, a lineage C betacoronavirus (BCoV), has a positive-sense single-stranded RNA (ssRNA) genome of approximately 30 kb (**Figure 1A** and **B**) [6, 7]. As of 2016, phylogenetic analysis of MERS-CoV had been performed on 182 full-length

genomes and multiple concatenated genome fragments, including 94 from humans and 88 from dromedary camels [9, 10]. The MERS-CoV genomes share more than 99% sequence identity, indicating low mutation and variance rates. The MERS-CoV genome is divided into two clades: clade A, which contains only a few strains, and clade B, to which most strains belong [10].

Similar to other coronaviruses, approximately two-third of the 5′ end of the MERS-CoV genome consists of the replicase complexes open reading frame (ORF1a) and (ORF1b). The remaining one-third encodes the structural protein spike (S), envelope (E), membrane (M), and nucleocapsid (N) as well as five accessory non-replicating proteins (ORF3, ORF4a, ORF4b, ORF5, and ORF8b) likely involved in viral pathogenesis (**Figure 1B**) [6, 11–15]. Typical of coronaviruses, the MERS-CoV accessory proteins are not homologous with any known host or viral proteins other than those closely related to lineage C BCoV [10]. MERS-CoV structural and accessory protein-coding plasmids transiently transferred into cells showed that ORF4b is localized mostly in the nucleus, whereas all other proteins are localized in the cytoplasm (S, E, M, N, ORF3, ORF4a, and ORF5) [16]. In addition, MERS-CoV deletion mutations of ORFs 3–5 attenuate replication in human airway-derived (Calu-3) cells [17], while deletion mutations of ORFs 4a and 4b attenuate replication in hepatic carcinoma-derived (Huh-7) cells [14, 18]. This highlights the importance of MERS-CoV accessory proteins in viral replication *in vitro* [19].
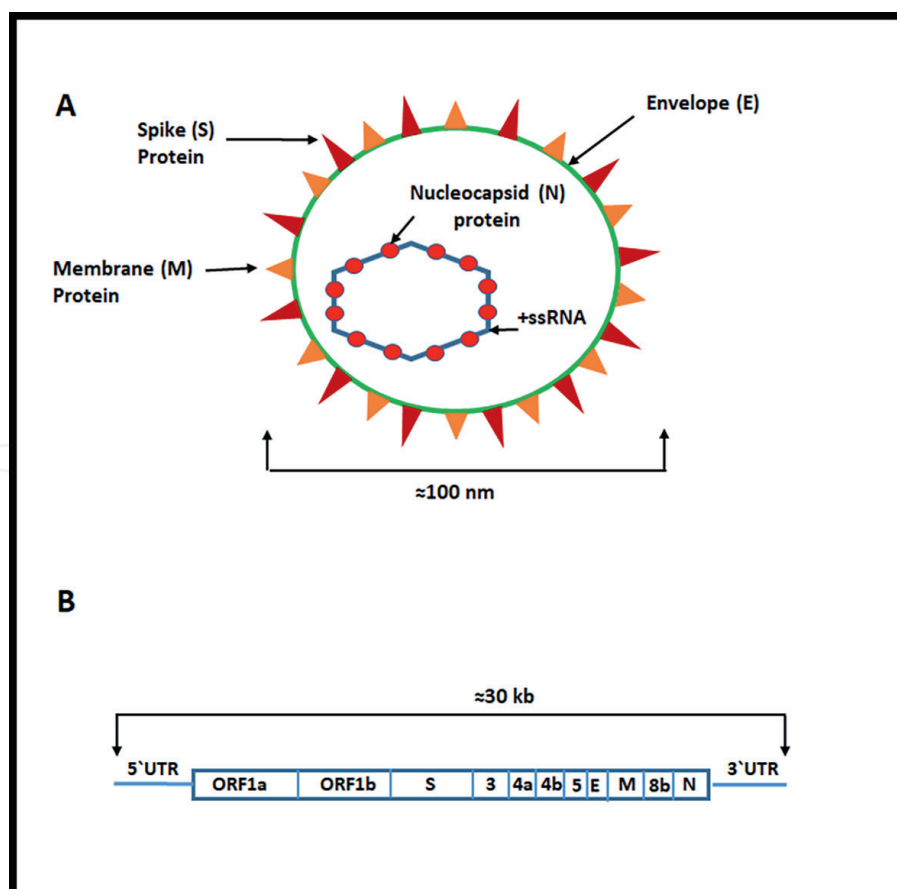

Figure 1.
MERS-CoV genome and schematic structure of viral proteins. (A) Schematic structure of major MERS-CoV structure proteins. (B) The MERS-CoV genome consists of two partially overlapping replicase open reading frames (ORF1a and 1b) and several ORFs that encode viral functional structural proteins and other proteins with unknown functions [8]. Abbreviation: MERS-CoV, Middle East respiratory syndrome coronavirus.

In response to viral infection, mammalian cells activate the type I interferon (IFN)-mediated innate immune response by producing type I IFNs (IFN-α and IFN-β). In contrast, evasion of host innate immunity through IFN antagonism, mediated by virus-encoded IFN antagonist proteins, is critical to viral pathogenesis. Each protein blocks key signaling proteins in the IFN and nuclear factor kappa B (NF-κB) pathways to enhance viral replication and pathogenesis [20–23]. Coronaviruses have evolved similar mechanisms to impede or bypass the innate immunity of their host at various levels, which ultimately contribute to viral virulence. Moreover, various coronavirus proteins disrupt signal transduction events required for the IFN response [24], often by interfering with host type I IFN induction.

MERS-CoV weakly induces type I IFN late during infection. In addition, MERS-CoV M, ORF4a, ORF4b, and ORF5 proteins are strong INF antagonists [16]. Studies using transient overexpression of the MERS-CoV accessory proteins ORF4a, ORFb, and ORF5 showed that they inhibit both IFN induction [16, 25, 26] and NF-κB signaling pathways [26]. MERS-CoV ORF4a, a double-stranded RNA (dsRNA) binding protein [25], potentially antagonizes antiviral IFN activity by inhibiting interferon production (IFN-beta promoter activity, IRF-3/7, and NF-kB activation) and the ISRE promoter element signaling pathway [16]. On the contrary, MERS-CoV ORF4b belongs to the 2H-phosphoestras (2H-PE) family and possesses phosphodiesterase (PDE) activity. Although MERS-CoV ORF4b is detected primarily in the nucleus of both infected and transfected cells [16, 25, 26], cytoplasmic expression levels are sufficient to inhibit activation of RNase L, a potent interferon-induced antiviral protein [16, 26]. MERS-CoV ORF4b was the first identified RNase L antagonist expressed by human or bat coronaviruses. It inhibits type I IFN NF-κB signaling pathways, providing a mechanism through which MERS-CoV can evade innate immunity [14, 26]. In addition, the MERS-CoV replicase nonstructural proteins (nsp1, nsp3, and nsp14) have been shown to interfere with innate immune signaling pathways through differing mechanisms [19, 27, 28]. In short, MERS-CoV has developed various mechanisms to evade the host immune system [29].

3. MERS-CoV infections and outbreaks

Between September 2014 and January 2015, a MERS-CoV outbreak resulting in 38 cases and 21 deaths was reported in Taif, Saudi Arabia. Clinical and public health records showed that 13 patients were healthcare personnel (HCP) and 15 patients, including 4 HCP, were associated with 1 dialysis unit. Serological studies done on three additional HCP in the same dialysis unit showed a positive report for MERS-CoV infection. Viral RNA was then measured from serum specimens of 15 patients in the acute phase, and full spike gene-coding sequencing was obtained from 10 patients, forming an unrelated cluster where sequences from 9 patients were closely related. Contrastingly, similar gene sequences among patients not linked by time or location suggest unidentified route of viral transmission. In short, circulation persists in multiple healthcare settings over an extended period, underscoring the importance of strengthening MERS-CoV surveillance and infection control practices [30].

Between May and July 2015, a large outbreak of MERS-CoV infection occurred in South Korea, which resulted from a traveler returning from the Middle East. This outbreak led to 186 confirmed cases in the country due to a primary case [31]. Patient 1 was diagnosed at Samsung Medical Center after transmitting the virus to several healthcare facilities. Patient 14 was exposed to Patient 1 outside the hospital

and sought medical attention at the institution without knowing his infection status. Therefore, the experience gained from South Korea's first MERS-CoV case and a case following single-patient exposure in an emergency room showed the importance of investigating the epidemiology of MERS-CoV infection in a crowded areas such as an emergency room for the potential presence of super-spreaders [2].

4. MERS-CoV clinical features

MERS-CoV affects both upper and lower respiratory tracts in humans and may lead to complications ranging from renal failure to death. The symptoms in a patient with MERS-CoV are fever, sore throat, runny nose, and muscle ache. Some of the cases have developed to severe diseases by progression to acute respiratory distress syndrome. In severely ill patients, X-rays and other scans showed multilobar airspace disease [32].

Extra-pulmonary manifestations are common in severe cases; 30% of critical cases had gastrointestinal symptoms like nausea, vomiting, and diarrhea. Kidney disease has been reported for about 50% of critical MERS-CoV cases. Laboratory results showed leukopenia, lymphopenia, anima, and thrombocytopenia. Also, partial to moderate increase in amino transferase level is usual in MERS-CoV infection [32].

Herein we present the cases of two immunocompromised patients with MERS-CoV. In April 2013, two MERS-CoV cases were reported following nosocomial transmission from one patient to the other in a French hospital. Patient 1 visited Dubai, while patient 2 lived in France and had not traveled abroad. Both patients presented with fever, chills, and myalgia; however, patient 1 also complained of diarrhea. Respiratory status deteriorated, leading to acute respiratory failure requiring mechanical ventilation and extracorporeal membrane oxygenation (ECMO), and both patients experienced acute renal failure. MERS-CoV RNA was detected in lower tract specimens from both patients using reverse transcriptase polymerase chain reaction (RT-PCR) (e.g., cycle threshold [CT] values of 22.9 for upE and 24 for Orf1a from patient 1; CT values of 22.5 for upE and 23.9 for Orf1a from patient 2), whereas nasopharyngeal swab specimens were weakly positive or indeterminate. The patients shared a room for 3 days, and the incubation period was estimated to be 9–12 days for the second case. Patient 1 died on May 28 due to refractory multiple organ failure [33].

Another MERS-CoV case was presented in an old man with multiple myeloma. On March 8, a 73-year-old patient from Abu Dhabi developed flu-like symptoms with fever and a non-productive cough. He was admitted to the Mafraq Hospital in Abu Dhabi and was diagnosed with pneumonia. He was then intubated on day 9 due to progressive hypoxia and acute respiratory distress syndrome (fraction of inspired oxygen, 60%; positive end-expiratory pressure, 10 cm H_2O). The patient received intensive antimicrobial treatment with meropenem, levofloxacin, vancomycin, caspofungin, acyclovir, and oseltamivir during his stay in the ICU without major improvement of his pulmonary function. The patient was then transferred to the Klinikum Schwabing on March 19, 2013. Of note, relatives reported that the patients owned camels. He was diagnosed with multiple myeloma in 2008 and received several lines of treatment in the past few years, including high-dose chemotherapy with autologous stem cell transplantation in 2009. In November 2012, the patient had a relapse of multiple myeloma and was treated with lenalidomide and dexamethasone. During his stay in Munich, thrombocytopenia was observed. Interestingly, thrombocytopenia was also reported in early cases of MERS-CoV infection [4] including two of the four patients from a family cluster in Saudi Arabia [34] and two cases reported

in France [33]. The patient then developed renal insufficiency on day 14 requiring dialysis. Despite continuous invasive ventilation and antibiotic treatment, the health status of the patient worsened, and he died on day 18 due to septic shock with signs of hemolysis and acute coagulation disorder [35].

On September 14, 2012, the United Kingdom Health Protection Agency (HPA) Imported Fever Service was notified of a case of unexplained severe respiratory illness in an ICU in London. The patient was a 49-year-old man who had recently been transferred from Qatar and had a travel history to Saudi Arabia. He developed mild undiagnosed respiratory illness while visiting Saudi Arabia in August 2012, which was fully resolved. On September 3, he presented to a physician in Qatar with cough, myalgia, and arthralgia and was prescribed oral antibiotics. Five days later, he was admitted to Qatar Hospital with a fever of 38.4°C and hypoxia (saturation of 91% in room air). Chest X-ray revealed bilateral lower-zone consolidation, and the patient required intubation and ventilation and was then transferred to London via air ambulance. The patient was clinically unstable and required manual ventilation during the transfer. On admission to the ICU in London, he remained severely hypoxic with arterial oxygen partial pressure of 6.5 kPA on 100% oxygen with optimized pressure ventilation. He required low-dose norepinephrine to maintain blood pressure. C-reactive protein was high (350 mg/L), and creatinine was high (353 μmol/L), with normal liver function and coagulation. The patient was treated with corticosteroids and broad-spectrum antibiotics, including meropenem, clarithromycin, and teicoplanin. Colistin and liposomal amphotericin B were later added. The patient's condition deteriorated with progressive hypoxia between September 11 and 20. His C-reactive protein level peaked at 440 mg/L and procalcitonin level at 68 ng/ml. His renal function also worsened, and hemofiltration was initiated on September 14. He was then transferred to a specialist ICU, and ECMO was initiated on September 20 (day 17 of illness). On October 2, he remained stable but was fully dependent on ECMO after 13 days (day 30 of illness) [36].

5. Diagnostic tests for MERS-CoV

MERS-CoV identification by diagnostic testing is crucial for tracking down cases of MERS-CoV, selecting appropriate treatment modalities to improve patient health, and lowering MERS-CoV symptoms and mortality rate. To date, RT-PCR is the mainstay test to diagnose MERS-CoV. However, like other tests, it has some limitations, including a long turnaround time and a lack of common measurements and correlations with viral load (VL). Most laboratories determine only CT values—which are inversely related to VL—to predict the viral concentration and disease progression as well as serve as a cut-off marker for diagnosis. However, few studies have evaluated the relationship between CT values and clinical severity [37]. Nevertheless, screening for MERS-CoV by RT-PCR upstream of the envelope gene (upE) is recommended, followed by confirming the presence of one of the following genes: open reading frame 1A, 1B genes, or nucleocapsid (N) [38]. Serology testing is another method to diagnose MERS-CoV.

Similar to other viruses, detecting antibodies and antigens by molecular methods may sometimes lag behind detecting the viral genome. To date, kinetics of antigen production in nasopharyngeal samples have not been studied. Moreover, viral antibodies usually appear 10 days after illness onset and are further delayed in severely ill patients requiring mechanical ventilation [39].

An enzyme-linked immunosorbent assay (ELISA) capture assay that can detect NP antigens of MERS-CoV virus in nasopharyngeal samples has been recently developed [40]. The assay is highly sensitive (detecting MERS-CoV-NP of less than 1 ng/mL) and specific (specificity of 100%) for MERS-CoV and can also be used in animals. Song et al. developed a rapid immunochromatographic assay to detect MERS-CoV nucleocapsid protein from camel nasal swabs, with a sensitivity of 93.9% and specificity of 100%. This assay is promising and worthy of replication in both camels and humans; however, antigen detection assays are not widely available. Nevertheless, this type of assay is valuable for ruling infections in or out.

Perera et al. [41] produced and optimized a microneutralization test to detect specific antibodies for MERS-CoV. Serial dilutions of serum sample were incubated with the Vero cells/MERS-CoV virus, and after 3-day incubation at 37°C, the antibody titers were scored based on virus cytopathic effect (CPE). Also, they developed a MERS-CoV spike pseudoparticle neutralization test [41], in which HIV/MERS spike pseudoparticles were used to infect Vero E6 cells. After 2 days, infected cells were lysed and antibodies that resulted in 90% luciferase reduction were reported as the ppNA antibody titer. As opposed to virus neutralization test, the pseudoparticle neutralization assay does not require biosafety level-3 (BSL3) containment.

An indirect immunofluorescent antibody assay to detect MERS-CoV antibodies was carried out using either whole virus in Vero cells [42, 43] or Vero cells transfected with MERS-CoV spike or nucleocapsid proteins [42]. ELISA utilizing S1 protein was also used to investigate the epidemiology of viral exposure [44]. To date, no studies have compared ELISA to either immunofluorescences assay (IFA) or neutralization assays.

Western blotting has been previously used to confirm antibody specificity to other viruses, such as SARS-CoV [45]. In addition, western blotting assays are needed to confirm antibody specificity in MERS-CoV, which can be in the form of genetically engineered specific MERS-CoV antigens blotted on the membrane.

Overall, MERS-CoV diagnostic testing and molecular techniques are the first-line methods used to confirm MERS-CoV infections. RT-PCR or sequencing of lower respiratory samples (tracheal aspirates and bronchoalveolar lavage samples) are recommended for viral detection. Thus, serological testing is a valuable tool to confirm suspected MERS-CoV cases; however, the virus cannot be detected in respiratory samples [46].

6. Prevention and treatment of MERS-CoV

Documenting the source of infection is key to preventing viral spread of MERS-CoV. Outbreaks are caused by viral transmission within healthcare settings facilitated by overcrowding, poor compliance with basic infection control measures, unrecognized infections, super-spreaders, and poor triage. However, actual contributing factors leading to MERS-CoV infection have not yet been systematically studied, but viral, host, and environmental factors are suggested to play major roles.

MERS vaccines can induce humoral and cellular immune responses. Specifically, a suitable MERS vaccine must induce a strong humoral immune response and, depending on the immunization route, activate B cells to produce systemic IgG and secretory IgA antibodies that bind to the virus and mediate systemic and mucosal responses [47–49], respectively. Serum IgA is also induced upon vaccination, particularly through the mucosal or intranasal routes [48]. The antibodies then neutralize MERS-CoV infection by blocking viral binding of the cell via the cellular receptor dipeptidyl-peptidase 4 (DPP4) and thus inhibiting cell entry [50, 51]. B cells can become

antigen-specific memory B cells that can further boost immunization and induce rapid recall antibody responses [52]. However, this outcome has not been extensively studied in MERS-CoV vaccines.

Non-human primate (NHP) models were initially established as effective vehicles for MERS-CoV infection and vaccine evaluation; however, no vaccine against MERS-CoV is currently available for human use. Nevertheless, progress has been made since the emergence of the MERS-CoV in 2012. Unlike the SARS vaccines, which are developed based on attenuated or inactivated SARS-CoV and can potentially recover virulence factors [53–57], recombinant MERS-CoV vaccines can be developed based on recombinant viral particles using reverse genetics. For instance, a recombinant MERS-CoV with specific mutations is produced using a panel of contiguous cDNAs covering the whole viral genome and propagated to high titers in different tissue types. Additionally, an engineered mutant MERS-CoV that lacks the structural protein E was rescued and replicated in cells expressing the viral E protein [17, 18]. Using reverse genetics, developing replication-competent and propagation-defective MERS-CoV candidate vaccines that can provide a platform for designing live-attenuated MERS-CoV vaccines becomes possible. However, as recombinant MERS viruses contain major viral components and virulence factors, safety concerns need to be addressed, and their efficacy requires further assessment in appropriate animal models.

6.1 Viral-vector-based MERS vaccines

MERS vaccines can also be developed using viral vectors that express main MERS-CoV proteins, including the S proteins. As such, several MERS vaccine candidates have been produced and evaluated for immunogenicity in hDPP4-expressing mouse models and camels [47, 58–60].

Ad5 or Ad41 vectors expressing full-length S or S1 protein of MERS-CoV induce S-specific antibody and/or T-cell response in a mouse model via the intramuscular (IM) or intragastric route, effectively neutralizing MERS-CoV infection in vitro [58, 61]. In addition, IM or subcutaneous vaccination of mice with an MVA-based full-length S vaccine elicited the MERS-CoV challenge. Intranasally or intramuscularly administered MVA-S vaccine also induced mucosal immunity in camels, causing a significant decrease of excreted infectious viral RNA transcripts after MERS-CoV challenge. Similarly, a recombinant MV-based MERS vaccine expressing full-length or truncated S protein of MERS-CoV induced significant MERS-CoV, neutralizing antibodies and T-cell response, protecting mouse transducers with hDPP4 from the MERS-CoV challenge [62]. Although viral-vector-based vaccines can produce strong immune responses and/or protection, they may have unwanted safety and potency limitations.

6.2 Nanoparticle-based MERS vaccines

Nanoparticles can be used as delivery vehicles for MERS vaccines. The MERS-CoV full-length S protein can be prepared and purified from pellets of infected baculovirus insect cells. In the absence of adjuvants, nanoparticles induce a low level of MERS-CoV neutralizing antibodies in mice. However, by adding adjuvants such as aluminum hydroxide (Alum) or matrix M1, neutralizing antibodies become significantly increased and maintained. In addition, matrix M1 promotes increased production of neutralizing antibodies compared to alum [63]. Thus, adjuvants are required for MERS nanoparticle vaccines to promote immunogenicity. However, the efficacy and protection of this vaccine type have not yet been evaluated in MERS-CoV challenge models.

6.3 DNA prime/protein-boosted MERS vaccines

DNA priming followed by protein boosting could be used to develop MERS vaccines and subsequently expand DNA immunogenicity and efficacy. In this combined vaccination plan, DNA was constructed to encode the full-length MERS-CoV S protein, while the protein was expressed as the viral S1 subunit [64]. Studies have demonstrated that IM/electroporation priming of full-length S DNA and IM boosting of S1 protein of MERS-CoV with Ribi or alum (aluminum phosphate, AlPO4) adjuvant in mice and rhesus macaques induced robust neutralizing antibodies against MERS-CoV infection, conferring the protection of NHPs against MERS-CoV-induced radiographic pneumonia. However, the potential for vaccine-induced immune pathology needs to be investigated further.

6.4 Subunit MERS vaccines

Protein-based subunit vaccines against MERS-CoV have also been developed [49, 50, 65, 66]. While some subunit vaccines are designed based on the full-length S1 protein [64], most are based on viral RBD [49, 50, 65–67]. RBD-based vaccines have been evaluated for immunogenicity and protection in several MERS-CoV animal models, including hDPP4-transduced and hDPP4-Tg mice, as well as in NHPs [65–70]. The antigenicity and functionality of RBD proteins have also been extensively investigated.

Subunit vaccines do not induce the immune system as strongly as the other previously mentioned vaccines. However, the immunogenicity of subunit vaccines can be significantly enhanced by adding an ideal adjuvant via the appropriate route [48, 69]. In addition, maintaining a suitable conformation of the protein antigens in the vaccine, such as MERS-CoV RBD proteins [49, 50], is essential.

Subunit vaccines are the safest vaccine type since they do not contain viral genetic material. They are composed of antigens essential for developing protective immune responses, thus excluding the possibility of recovering virulence or inducing adverse reactions [71–73]. In contrast to vaccines based on the full-length S or S1 protein, RBD-based MERS subunit vaccines contain major neutralizing epitopes and lack non-neutralizing immunodominant domains; thus, they possess minimal risk of inducing non-neutralizing antibodies that can potentially lead to harmful immune responses or enhancement of virus infection [49, 74, 75]. This review aimed to provide guidelines for the development of effective and safe MERS vaccines.

7. Conclusion

With every passing years, our knowledge of MERS-CoV virus is improving; fewer cases of MERS-CoV have been reported as more studies improve our understanding of the virus. Appropriate diagnostic testing such as RT-PCR, documenting causes of viral outbreaks, and developing infection control units in every hospital have played key roles in hindering viral spread and preventing MERS-CoV from becoming endemic in humans, also lowering the risk of human infection by controlling animal-to-human transmission of the virus by vaccinating animals to prevent any transmission. There are studies that support developing potential therapies and vaccines to prevent infections [32].

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