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MERS-CoV as an emerging respiratory illness: A review of prevention methods

Salim Baharoon[a,b,c], Ziad A. Memish[d,e,f,*]

[a] Infectious Disease Division, Department of Internal Medicine, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
[b] Department of Critical Care, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
[c] Professor of Critical Care, King Saud Bin Abdulaziz University for Health Science, Riyadh, Saudi Arabia
[d] Infectious Diseases Division, Department of Medicine and Research Department, Prince Mohamed Bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia
[e] College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[f] Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

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ABSTRACT

Introduction: Middle East Respiratory Coronavirus Virus (MERS-CoV) first emerged from Saudi Arabia in 2012 and has since been recognized as a significant human respiratory pathogen on a global level.
Methods: In this narrative review, we focus on the prevention of MERS-CoV. We searched PubMed, Embase, Cochrane, Scopus, and Google Scholar, using the following terms: 'MERS', 'MERS-CoV', 'Middle East respiratory syndrome' in combination with 'prevention' or 'infection control'. We also reviewed the references of each article to further include other studies or reports not identified by the search.
Results: As of Nov 2019, a total of 2468 laboratory-confirmed cases of MERS-CoV were diagnosed mostly from Middle Eastern regions with a mortality rate of at least 35%. A major outbreak that occurred outside the Middle East (in South Korea) and infections reported from 27 countries. MERS-CoV has gained recognition as a pathogen of global significance. Prevention of MERS-CoV infection is a global public health priority. Healthcare facility transmission and by extension community transmission, the main amplifier of persistent outbreaks, can be prevented through early identification and isolation of infected humans. While MERS-CoV vaccine studies were initially hindered by multiple challenges, recent vaccine development for MERS-CoV is showing promise.
Conclusions: The main factors leading to sustainability of MERS-CoV infection in high risk courtiers is healthcare facility transmission. MERS-CoV transmission in healthcare facility mainly results from laps in infection control measures and late isolation of suspected cases. Preventive measures for MERS-CoV include disease control in camels, prevention of camel to human transmission.

1. Introduction

Corona viruses are mostly zoonotic viruses and human corona strains usually cause mild respiratory and gastrointestinal syndromes and rarely lead to severe disease [1,2]. In the last decade two important corona viruses, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV), crossed animal to human barrier and emerged to become major human pathogens [3–7]. SARS-CoV and MERS-CoV caused disease outbreaks with significant morbidity and mortality changing our understanding of the pathogenic potentials of coronaviruses [8,9].

Although MERS-CoV has first been recognized as a human respiratory pathogen in Saudi Arabia only in 2012, MERS-CoV antibodies have been detected in dromedary camel from stored sera from Eastern Africa as early as 1990 [10,11]. Since 2012, human infection has been reported from 27 countries globally and as of November 2019, a total of 2468 laboratory-confirmed cases of MERS-CoV were reported [12].The majority of the cases are reported from the Arabian Peninsula with 85% of cases either originating or passed though Saudi Arabia [12–16]. After Saudi Arabia, South Korea reported the largest number of cases outside the Middle East due to a large outbreak in early 2015 resulting from a returning South Korean citizen who travelled in the Arabian Peninsula [17]. Since then, there has been about 80% reduction in the overall reported cases from Saudi Arabia and only few cases reported outside the Arabian Peninsula [12]. Despite this drop in reported cases, outbreaks continue to occur in Saudi Arabia and neighboring Gulf countries [12].

The most recent outbreak was reported from Wadi Aldawaser; 52

* Corresponding author. College of Medicine, Alfaisal University, P.O. Box 54146, Riyadh, 11514, Saudi Arabia.
E-mail address: zmemish@yahoo.com (Z.A. Memish).

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laboratory confirmed cases of which 31 cases were hospital acquired including 11 health care workers [12]. Until an effective preventative/therapeutic intervention becomes available, MERS-CoV will continue to be a major public health challenge and economic burden in the affected countries and the world [18].

1.1. Search strategy and classification of reviewed articles

We searched PubMed, Embase, Cochrane, Scopus, and Google Scholar using the following terms: 'MERS,' 'MERS-CoV,' 'Middle East respiratory syndrome' in combination with 'prevention' or 'infection control.' We also reviewed the references of each article to further include other studies or reports not identified by the search.

1.2. MERS-CoV infection: clinical presentation

The average incubation period for MERS-CoV is 5–7 days, but a range of 2 days–14 days have been reported [13,14,19–22].The clinical disease spectrum ranges from completely asymptomatic, mild disease and severe disease with multi-organ failure [13,14,19–26]. In a symptomatic patient, symptoms at presentation may include fever, chills, rigors, myalgia, malaise, cough and shortness of breath. Gastrointestinal symptoms of diarrhea, vomiting and abdominal pain may be present as part of the upper respiratory syndrome or as the main presenting complain [13]. Pneumonia is common at presentation [13,14,19–26]. Severe infection occurs specially among older patients with comorbidities and present with acute respiratory, renal failure and shock [24,25]. The crude fatality rate average is 35% among primary cases and 20% among secondary cases [3,25–27]. Predictors of poor outcome includes age above 60 years, male gender, diabetes mellitus, chronic lung disease and chronic renal disease, low albumin level and progressive lymphocytopenia [24–26]. Use of steroids and continuous renal replacement therapy have also been suggested as predictors of worse outcome [26]. MERS-CoV infections is noticeably infrequent in pediatric population and pediatric patients are usually asymptomatic or present with mild symptoms, infections frequently acquired from household contact and is associated with low morbidity and mortality [28–30].

The percentage of asymptomatic cases after a primary infection is variable and not precisely known. Earlier studies estimated that around 12.5–25% of MERS-CoV infections may be asymptomatic [31,32]. More recent studies suggested up to 50% may be asymptomatic [33]. Differences in the study setting, populations studied, and methods of screening may explain this variability [22,24,27,31,34,35]. Use of serologic testing can underestimate disease burden due to waning antibodies titer over time [15,16,22]. Most of asymptomatic cases reported have been detected following aggressive contact tracing [15,32,36,37]. Prolonged viral excretion from the respiratory tract for up to 4 weeks has been documented specially in patients with pneumonia at presentation [37,38]. Albeit in low loads, virus secretion was also reported for shorter periods in urine and stool [37,38]. Patients with mild symptoms can also have viral shedding for up to 10 days from symptoms onset [35,39].

2. Virology

MERS-CoV is an enveloped, single-stranded RNA virus of the family Coronaviridae subfamily Coronavirinae. There are four described coronavirus genera, alpha, beta, gamma and delta. Beta coronavirus genera includes two genetically related but distinct human pathogens of zoonotic origin, B lineage SARS-CoV origin and C lineage MERS-CoV of bat origin [1,8,9,40,41]. The C lineage is further divided to genetic sub lineages [clades] which includes at least two MERS-CoV strains with potential existence of additional clades. MERS-CoV is the first of this lineage known to infect humans. MERS-CoV genome encodes 10 proteins including four structural proteins (S, E, M and N). The surface spike glycoprotein (S protein) has gained the most attention because it confers receptor specificity and is the primary target for the humoral immune response during infection. It is currently the key focus of MERS-CoV vaccines and anti-viral therapeutics development efforts [42–44].

The S protein consists of S1 and S2 subunits. The Receptor Binding Domain (RBD) in S1 subunit is responsible for cellular receptor binding, while HR1 and HR2 regions in S2 mediate virus fusion and entry into the target cell. S-RBD contains a critical neutralizing domain which can induce potent neutralizing antibodies and S-RBD specific neutralizing antibodies titers correlated with protection from MERS-CoV infection. Dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2 or CD26 (cluster of differentiation 26) is a protein that is encoded by the DPP4 gene and is expressed on the surface of most cell types including non-ciliated bronchial cells including endothelial and alveolar epithelial cells (Type II pneumocytes), macrophages and fibroblasts. DPP4 is the functional receptor for MERS-CoV on the host cells surface and is utilized by the receptor-binding domain of the MERS-CoV spike [45,46].

2.1. Origin and reservoir

The primary origin of both human and camel MERS-CoV is probably the vesper bats in Southern Africa [47–49]. The first transfer from bat to camel has likely occurred in Africa after a recombination event leading to genetic divergence in the original bat virus [4,7,10,48,50–53]. MERS-CoV antibodies were detected in camel sera long before first human case reported [10,11]. MERS-CoV in camels causes only mild symptoms and traded infected camels from Africa has likely introduced the virus into the Arabian Peninsula dromedary camels and eventually camel to human transmission was first recognized in 2012 [3]. MERS-CoV infection is widespread among dromedary camels in the Arabian Peninsula [54,55].

2.2. Camel-to-human transmission

There is abundance of evidence that links dromedary camels to human infection [56–58],Identical genomic sequences of MERS-CoV from a camel owner and his symptomatic animal with identical MERS-CoV RNA fragments detected in the air at the same barn was reported [59]. Viral genomic sequences were similar in infected human and the one isolated from camels in outbreak site and many of the camel viruses can be classified into clades that correlate with human outbreaks [60]. There is a high seroprevalence of MERS-CoV infection among camel shepherds and slaughter-house workers [61]. Although dromedary camels are the only confirmed intermediate animal host for MERS-CoV Infection, other domestic livestock like sheep and goats in contact with MERS-CoV infected camels may be at risk of infection [62]. Other livestock role in human transmission is not yet clear. However, exposure to camels could not be documented in more than half of patients with primary MERS-CoV infections [20]. High MERS-CoV seroprevalence among those exposed to camels is not always consistent [63]. Human disease burden is not directly proportional to potential exposure to camels indicating that although camel-to-human transmission occurs it is not very efficient and occur relatively uncommonly.

Independent risk factors that increases risk of camel to human transmission includes direct close physical contact, involvement in animal training, milking camels, contact with camels' waste, poor hand hygiene before and after animal tasks and presence of host comorbidities. Infection is likely acquired via contact with camel respiratory droplets, saliva, and camel's respiratory organs during slaughtering and consumption of other camel products, such as milk, urine or undercooked camel meat. Nasal swabs and lung tissue were all positive for MERS-CoV especially among animals < 4 years of age. MERS-CoV added to unpasteurized camel milk stored at 4 °C remains infectious beyond 72 h [64].

2.3. Human-to-human transmission

2.3.1. Community transmission

Community transmission is not common and occurs sporadically after exposure to infected dromedary camel, through contact with a symptomatic human case within families can cause family clusters and travel associated infection has been reported if humans are incubating the virus [34,61,63,64]. Travel associated infection however contributed only modestly to community transmission [65,66]. MERS-CoV is a rare cause of community acquired pneumonia and most new human cases represent new introduction of the MERS-CoV from camels (zoonotic spillover) [31].

MERS-CoV is poorly suited for sustained human-to-human transmission, with an estimated R0 < 1 [27].Primary cases will not be sustainable if not for outbreak amplification via poor hygiene practices by individuals especially around camels. New MERS-CoV cases are predominantly restricted to the Arabian Peninsula and outbreaks outside that region are generally self-limited.

Population-based studies have showed low overall prevalence of MERS-CoV in general population ranging between 0.15 and 2% [16,37,67]. Male and camel-exposed individuals had higher MERS-CoV infection rate [37,67]. Although seasonal variation was not found in some studies, others noticed an increased rate between April and June [37,68–70]. The true community prevalence however may be underestimated due to antibodies waning over time [27,71].

Reports are suggestive of very limited human-to-human transmission within household and only a small number of contacts become infected. Some of the reported family clusters involve contacts with patients or relatives in the hospital setting, or infected animals in the community and are not truly community primary infections.

Transmission take place through air droplets produced during coughing or sneezing and indirectly through close contact with contaminated surfaces and devices [72,73].Transmission via other body fluids like urine, stool and vomitus is also theoretically possible because-MERS- CoV have been isolated from these secretions [23,38,74,75].

Recent evidence has clearly shown that MERS-CoV transmission from asymptomatic individuals can occur [34,35]. MERS-CoV was cultured from patients with mild symptoms and was detectable for up to 12 days in 30% of asymptomatic contacts and some asymptomatic health care workers had detectable MERS-CoV for over five weeks [73,76]. Given that transmission from asymptomatic individuals has occurred in SARS outbreak, it may also be possible with MERS-CoV [34,35,64,77,78].

Factors that facilitate community transmission include lack of knowledge on transmission mechanisms, poor general hygiene practices and exposure to camels. Primary MERS-CoV human cases are also more likely to occur when conditions are relatively cold and dry [79].

2.3.2. Prevention of community transmission

The key measure to prevent community transmission is disease control in camels and avoid camels contacts as much as possible. Community awareness of the disease is prudent though health education and health care facilities should remain vigilant especially around time of high disease activities.

Disease control in camels require effective camel vaccination. There is no current licensed camel vaccine. However 4 Viral Vector Vaccines, two MVA (Modified vaccinia virus Ankara) and two ChAdOx1 (Chimpanzee Adenovirus, Oxford University #1) MERS vaccines that incorporated DNA sequence encoding MERS-CoV's surface proteins have been tested in animal models [80]. MVA vaccine in dromedary camels led to significant reduction of MERS-CoV virus and viral RNA transcripts and detectable levels of both serum neutralizing MERS-CoV–specific antibody and MVA-vectored vaccine neutralizing antibodies [81].Although camel vaccination manages to reduce viral shedding, this response was not seen across all vaccinated animals [81]. The duration of protection also is not known. MERS-CoV is a disease that causes only mild symptoms in camels and acceptance of owners to vaccinate for such a mild disease may be a future challenge considering the widespread prevalence of MERS-CoV infection in camels.

Control of community transmission includes avoiding close contact with camels, camel's barn areas, and camel markets especially for high risk groups. It is also essential to practice good hygiene when around camels especially with symptomatic camels and during high disease activity which usually occur during April, May, June and July. This is the period when new camel generations become susceptible to MERS-CoV infection after the decline of their maternal protective antibodies [82–84].

Individuals screened for MERS-CoV who tests positive including asymptomatic and those with mild symptoms and who have no underlying comorbidities such as heart disease, renal failure, or immune-compromising conditions can be sent home for recovery. Those patients still remain at risk of rapid disease progression and need to be monitored during the first 2 weeks of illness [85].

Precautions to prevent transmission to household should be detailed to those individuals (Box 1). That include education on mechanism of MERS-CoV transmission and the importance of general hygiene especially hand and cough hygiene. Patients should be adequately separated from other persons in the house (separate rooms when possible or at least separate beds) and not share household items. Secretions like body fluids, sweats, saliva, sputum, vomitus and urine are all potential source of transmission and appropriate barriers should be used when dealing with these secretions. Such barriers should not be reused. Absorbent material, such as cotton, is preferred to non-absorptive material [86].

Household items should not be shared, and personal items and laundry should be washed thoroughly. Heat easily inactivate MERS-CoV. Surfaces such as counters, tabletops, doorknobs, bathroom fixtures, toilets, phones, keyboards, tablets, and bedside tables, should be disinfected every day using EPA-approved household disinfectant.

Only essential visitors should come and those with comorbidities should not have close contact with the infected person. Shared spaces in the home should have good air flow. Appropriate follow up with the healthcare system should be maintained till the full incubation period lapses, usually 14 days. Longer periods may be more appropriate for those who remain symptomatic and the immunocompromised patients who are more likely to shed virus for longer duration.

From a general public health perspective, increasing community awareness of the disease and transmission mechanism is important. Public knowledge was tested among two level of educated samples in Saudi Arabia, universities and high schools. Between 30% and 50% did not acknowledge fever and cough as manifestation of MERS-CoV infection. Only a minority thought camels, or its products are associated with higher risk of infection. Authors concluded that measures aimed at educating and improving public on preventive measures such as using tissues when sneezing and coughing and proper tissue disposal is needed [87].

In another study done in a female university in Saudi Arabia to assess awareness on MERS-CoV preventive strategies following an outbreak in the same city, 79% of the respondents recognized the typical symptoms of MERS-CoV but only 67.1% knew the recommended preventive hygiene practices. Overall knowledge score was 43%. Awareness of disease epidemiology, severity, fatality rate and treatment was very low [88].

These results highlight the importance of information sharing as this knowledge deficiency is occurring for important key measures most crucial in MERS-CoV transmission. The knowledge gap is expected to be even higher among less educated individuals.

2.3.3. Human transmission: health care facility

Given that 44%–100% of individual outbreaks were linked to hospitals, human to human transmission in healthcare setting appears to be more efficient than transmission within the community [32].

Healthcare associated outbreaks constitute the largest number of laboratory-confirmed MERS-CoV cases. The infection rate of MERS-CoV in healthcare facilities is more than four-fold the average estimated household transmission rate and hospital acquired MERS-CoV infection experience a significantly longer hospital stay and are more likely to die from the disease [15,74]. Transmission occur from patients to health care workers, visitors, within patients and among healthcare workers within the same facilities as well as between facilities. Episodic outbreaks in hospitals is the hallmark of MERS-CoV infection and is the main source of all new cases reported.

Risk factors for transmission of MERS-CoV in healthcare settings have been studied extensively. MERS-CoV is relatively stable in the hospital environment which can facilitate transmission. It was recoverable on surfaces after 48 h at 20 °C and 48% relative humidity and for at least 12 h at 30 °C with 30% humidity [89]. The virus is also recoverable from liquids after 2 h at 25 °C, patient's room environment including bed sheets and medical equipment for up to 5 days after patients MERS-CoV PCR turn negative. Unlike SARS-CoV, MERS-CoV titers in sputum samples of infected patients are high within the first 3 days after symptoms which make transmission very efficient during the early course of the disease [74].

Nosocomial outbreak of MERS-CoV can result in a large explosive cluster of cases, the so called "super-spreading events" which is defined as the ability of an infected patient to transmit the virus to 4–5 others [90]. Fever ≥38.5 °C and more extensive chest infiltrates with high viral load are identified as risk factors for more efficient spread. The most significant risk factor for hospital transmission however is delay in recognition, delay in initiation of isolation and use of proper PPE [76].

The number of non-isolated in-hospital days were the only parameter that is associated with super-spreaders events [90]. Even a 1-day delay in isolating patients led to secondary infections and early active quarantine is essential in reducing the size of an outbreak [91]. Inadequate or lapses of infection control measures in the inpatients and outpatient setting was observed in most of hospital outbreaks. Breaches in infection control measures varies, however those around high-risk aerosols generating procedures and in high risk areas like hemodialysis and respiratory intensive care units are frequently observed [14,92].

Overcrowding is also a significant risk factor in MERS-CoV transmission and outbreaks. During the two large MERS-CoV outbreaks in Saudi Arabia and South Korea, crowding in emergency room and hospital wards and lack of proper control over visitors played a significant role in increasing transmission [76,91] Box 2.

Airflow and ventilation were also implicated as a cause of more efficient spread within hospitals [93]. Although MERS-CoV is known to spread mainly by droplets via close contact, MERS-CoV air droplets can travel long distance significantly larger than 1–2 m if condition allows like a presence of an external airflow [93,94]. Among health care workers, nurses are the most commonly affected followed by physicians and respiratory therapist. Most of infections in healthy adult healthcare workers are mild and only discovered during contact tracing. Infection in healthcare workers however significantly amplify MERS-CoV infection outbreaks [73].

Only few cases have been reported among hospital laundry or maintenance workers with one case out of 1295 maintenance or housekeeping personnel screened in a major outbreak in Saudi Arabia in 2014. To date no clear evidence of sustained, person-to-person transmission has been reported [31].

Inadequate or lapses of infection control measures in the inpatients and outpatient setting was observed in most of hospital outbreaks. The most common breaches in infection control measures centered around high-risk aerosol generating procedures and in high risk areas like hemodialysis and respiratory intensive care units.

2.3.4. Prevention of healthcare facility transmission

The basic principles for MERS-CoV prevention relay on establishing administrative, environmental measures to ensure early recognition and use of personnel protective equipment to prevent cross transmission [95–97]. Healthcare facilities should not only create policy and procedures but invest heavily on the infrastructures of infection prevention and control to ensure efficient implementation of all administrate measures.It is crucial to allocate appropriate resources and training, support for all healthcare personnel as well as establishing a monitoring process for all policies [98].The sporadic nature of MERS-CoV outbreaks mandate continuous vigilance in maintaining a high level of awareness across the year. Environmental management is an essential domain for MERS-CoV prevention. Ensuring appropriate ventilation, patient's allocation and environmental disinfection along with an efficient mechanism to for monitoring [95–98].

Personnel Protective Equipment (PPE) is an essential tool to break transmission chain [95–98]. Healthcare facilities should provide adequate and sustainable supply of these items. They include gown, gloves, highly efficient masks, and goggles or face shield. The demands for PPE can increases dramatically and supply should remain adequate all the times. Protocols for how to use PPE and constant training and auditing is mandatory especially in places with high turnover rate of employee [95–98].

2.4. Prompt diagnosis and isolation of cases

Early identifications of suspected cases and strict implementation of infection control measures are crucial for prevention of transmission. Efficacy of strict implementation of infection control prevention measures in aborting hospital outbreaks has been well documented. Increase awareness and the reform in infection control policies and

Box 1
Recommendations for MERS-CoV positive cases managed at home

- Minimize contact with the MERS-CoV positive patient.
- Those attending the MERS-CoV positive patient should not be at increased risk of MERS-CoV complications (age > 60, immunocompromised, diabetics or with chronic illness like chronic respiratory or kidney disease).
- Ensure presence of a good ventilation at home specially in common areas like opening windows and air conditioners.
- Maintain a distant of at least 1.5 m from MERS-CoV positive patient, including sleeping in different beds or in different room.
- Hand hygiene with alcohol-based hand rub should be performed by both infected patient and caregiver following any contact with the patient or his/her environment.
- MERS-CoV positive patient should observe respiratory etiquette during sneezing or coughing.
- When in the room with the MERs-CoV positive patient, a regular mask should be used and touching the surfaces near the MERS-CoV infected person should be minimized.
- Use disposable gloves when in contact with body fluids like urine, stool, vomit and respiratory secretions.
- All waste generated in the room of a MERS-CoV positive patient should be bagged secularly and properly.
- Household items in the MERS-CoV positive patient room especially those within 1 m should be regularly cleaned with EPA approved commercial solution or diluted bleach (1part bleach to 99 parts water): includes bedside tables, bedframe, phones, keyboards, tablets & other bedroom furniture.

Box 2
Risk factors for MERS-CoV transmission & super spreading events

Fever ≥ 38.5 °C *
Symptoms of Cough, Sputum production and Dyspnea.
Longer interval from symptom onset to isolation.
Diagnosis of pneumonia.
Pulmonary infiltration of ≥3 lung zones*
Mechanical ventilation.
CRP ≥ 3.0 mg/dL.
Symptom onset to negative conversion, day, median.
Primary case as opposed to secondary or tertiary in the chain of transmission.
More non-isolated in-hospital days**
Non isolated in-hospital days ≥2 day.
Hospitalization or emergency room visits before isolation.
Patients with more visitor & HCWs involved in their care.
More frequent pre-isolation pneumonia diagnoses.
Lower cycle thresholds for the upE and ORF1a genes *
Patients outcome (deceased vs recovered) *
Presence of comorbidities.

* Significant in multivariate analysis.
** Super spreading.

Box 3A
Saudi Ministry of Health MERS-CoV infection case definition

Confirmed Case

A suspected case with laboratory confirmation of MERS-CoV infection.

Suspected Case

I. Severe pneumonia (severity score ≥3 points) (Severity Scores for Community-Acquired Pneumonia (CURB 65)) or ARDS (based on clinical or radiological evidence). No epidemiological link required.

II. Unexplained deterioration of a chronic condition of patients with congestive heart failure or chronic kidney disease on hemodialysis. No epidemiological link required.

III. Acute febrile illness (T ≥380 C) with/without respiratory symptoms. Epidemiological link required.

OR

IV.Gastrointestinal symptoms (diarrhea or vomiting), AND leukopenia (WBC ≤ 3.5x109/L) or thrombocytopenia (platelets < 150x109/L). Epidemiological link required.

epidemiological link:

1. Exposure to a confirmed case of MERS-CoV infection OR
2. Visit to a healthcare facility where MERS-CoV patients(s) has recently (within 2 weeks) been identified/treated OR
3. Contact with dromedary camels or consumption of camel products (e.g. raw meat, unpasteurized milk, urine) Within 14 days before symptom onset.

implementation is likely contributing to the 80% reduction in the number of MERS-CoV cases reported in Saudi Arabia. Although sporadic outbreaks still occur, however they are contained more efficiently. Physicians should have high index of suspicion of all febrile syndromes in endemic areas even in the absence of history of contacts with camels. All febrile syndromes with history of travel to or work in the Middle East especially the Arabian Gulf countries should also be considered as possible cases. (Box 3 A&B).

Clinical predictors of MERS-CoV pneumonia presenting in ER includes overweight, diabetes mellitus, end-stage renal disease, respiratory distress on admission, normal WBC and interstitial infiltrates on chest x ray [21].

A risk prediction model for MERS-CoV pneumonia was developed and incorporated gender, contact with a sick patient or camel, diabetes, pneumonia severity at presentation, low white blood cell (WBC) count, low alanine aminotransferase (ALT), and high aspartate aminotransferase (AST) [99].

2.5. Diagnosis

Molecular testing is currently the standard method for diagnosis of MERS-CoV infection and are based on detecting viral RNA in clinical samples by Real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays. A positive rRT-PCR for two specific genomic targets or a single positive target with sequencing of a second target. Both an upper respiratory sample (nasopharyngeal swab) and a lower respiratory specimen need to be obtained. Lower respiratory samples have better yield due to higher viral load [23,38,75].

Nasopharyngeal and oropharyngeal specimens can be an acceptable alternative in patients with mild symptoms if deep respiratory samples is not practical. All patients who have initial negative upper respiratory sample and subsequently intubated would require a repeat deep respiratory sample after intubation. Multiple samples may be needed especially in highly suspected cases before diagnosis is ruled out, due to intermittent shedding. To discontinue isolation at least 2 negative

Box 3B
WHO MERS-CoV infection case definition

Confirmed case.

A person with laboratory confirmation of MERS-CoV infection irrespective of clinical signs and symptoms.

Probable case.

I A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome) AND Direct epidemiologic link with a laboratory-confirmed MERS-CoV case AND Testing for MERS-CoV is unavailable, negative on a single inadequate specimen or inconclusive
II A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome) that cannot be explained fully by any other etiology AND The person resides or travelled in the Middle East, or in countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred AND Testing for MERS-CoV is inconclusive
III An acute febrile respiratory illness of any severity AND Direct epidemiologic link with a confirmed MERS-CoV case AND Testing for MERS-CoV is inconclusive.

A direct epidemiological link with a confirmed MERS-CoV patient may include:

I Health care associated exposure, including providing direct care for MERS-CoV patients, working with health care workers infected with MERS-CoV, visiting patients or staying in the same close environment of individuals infected with MERS-CoV.
II Working together in close proximity or sharing the same environment with individuals infected with MERS-CoV.
III Traveling together with individuals infected with MERS-CoV in any kind of conveyance
IV Living in the same household as individuals infected with MERS-CoV.
V The epidemiological link may have occurred within a 14-day period before or after the onset of illness in the case under consideration.

samples that are 48 h apart with clinical improvement are needed.

Serology can also be used to confirm the diagnosis but requires demonstration of sero-conversion in 2 samples taken 14 days apart by a screening (ELISA, IFA) and confirmation by neutralization assay [100].

2.6. Efficient screening

Health care facilities should implement an efficient screening process at point of entry to the hospital and medical care areas especially in high risk areas like emergency, hemodialysis, critical care, and respiratory care units. This has proved to be a huge challenge since data on efficacy of triage screening applied by Saudi Ministry of Health (MOH) have failed to prevent outbreaks. Screening alone is not expected to be the sole factor in preventing outbreaks. Our better understanding of the spectrum of disease at presentation may enhance screening efficacy. Monitoring of compliance of screening procedures and strict vigilance especially during high MERS-CoV activity is prudent. In the absence of an efficient, reliable and cost-effective point of care testing to be applied in the hot areas mentioned above, optimization and auditing of screening may be a valuable component of minimizing outbreak potentials.

During outbreaks and in corona heavy season, patients should be screened for fever and symptoms of respiratory infection using a screening template and then triaged to dedicated areas for prompt diagnostic work up and isolation when indicated [101].

Screening has proved effective in controlling ongoing transmission during outbreak control measures [101]. One Saudi hospital implemented a two-step screening process by creating a drive through at the Emergency entrance to initially triage patients either to dedicated respiratory unit or the main Emergency areas. Similarly, health care workers (HCW) working in critical area like isolation wards ICUs and hemodialysis units and visitors to these areas can also be screened for fever and respiratory symptoms.

2.7. Placement and infection control measures

In countries with ongoing risk of transmission a dedicated respiratory clinic could be set as a separate quarantine area within the main emergency areas or as a distinct separate physical area with a clear pathway for patient and staff to follow. These clinics must be designed to reduce potential of transmission. Exit and entry to such units must be well controlled. The patients waiting area should be spacious, well ventilated and with a space between patients of at least 1–2 m. Patient's rooms should be single and if feasible with negative pressure or have HEPA filters especially if aerosol generating symptoms or procedures are needed. All patients with respiratory symptoms need to be given surgical masks to reduce aerosolization and educational materials in the unit can be utilized to increase community awareness of MERS-CoV infection and proper cough etiquette.

Dedicated ward and critical care units need to be allocated for admitted patients from emergency room or admitted from any other hospital areas until MERS-CoV is reliably excluded. Care should be observed during transfer from emergency room (ER) to designated areas to reduce transmission. This may include measures to contain patient's secretion. Patients should be admitted to single rooms and if feasible with negative pressure. Critical care units ideally should be single room and if not possible adequate distance between patients should be observed. Every person entering patient's room should use designated PPE equipment's (droplet and airborne isolation) with proper protocol.

All suspected and confirmed cases should be placed under standard, contact, and droplet precautions with airborne precautions for patients requiring aerosol-generating medical procedures, such as mechanical ventilation, endotracheal intubation, and endotracheal aspiration. Due to the well documented prolonged MERS-CoV shedding, Infection control precautions should be applied until two consecutive lower respiratory tract samples (sputum or tracheal aspirates) 48hrs apart become RNA negative and patient becomes asymptomatic [78]. Strict infection control measures should be observed during sample collection including use of approved collection methods and equipment and transporting samples according to appropriate protocols. Samples are preferably collected in negative pressure rooms especially deep respiratory samples by trained healthcare professionals.

Traffic control and eliminating overcrowding in the emergency department and in clinical areas is essential. Reducing ER time, restricting visitors in ER, educating visitors and sitters to wear mask and observe basic infection control measures like hand hygiene, providing posters and educational materials and creating a visitor log to allow for rapid identification and assessment of contact risk levels are all measures that were utilized during outbreaks in Saudi Arabia and South Korea.

HCWs should be educated and trained in infection prevention and control tools and emerging infections and should refresh these skills regularly. Although HCWs seem to understand the importance of infection control practices like hand hygiene they fail to properly implement protocol-driven hand hygiene applications. The use of PPE was inconsistent among these HCWs. Even though MERS-CoV has been identified since 2012, outbreaks continue to occur in Saudi Arabia and continue to involve substantial number of HCWs in each outbreak. Vigilant observation to infection control practices among HCWs to ensure readiness is prudent.

2.8. Outbreak management

Early detection, isolation of patients and exposed high-risk contacts, minimizing patient load are imperative to control an outbreak of MERS-CoV [101]. In an outbreak setting, early quarantining of all exposed individuals followed by an assessment and monitoring of their contact significance as opposed to quarantining after assessing them for close contact, is less labor-intensive and time-consuming and likely shorten the delay in isolating MERS-CoV patients in healthcare settings. During an outbreak many individuals can be exposed, and identification of all exposed individuals may be difficult. Indeed, 43.2% of the patients in Korea during the 2015 outbreak had not been identified as exposed individuals and were not monitored [90].

During an outbreak, healthcare facilities especially those with limited infection control infrastructure can be strained and even totally paralyzed with huge incremental increase in costs and resources utilization [102–104]. Measures needs to be in place to eliminate cross infection that may include increasing manpower, budgets and other resources reallocation [104]. During MERS-CoV outbreak in Saudi Arabia, implementation of an intensified goal oriented educational programs for healthcare providers especially for those working in critical areas with emphasis on the rule of nurses educators impacted positively on the cross infection and staff confidence [105].

2.9. Environmental cleaning and disinfectants to use

Environmental cleaning is crucial. Housekeepers should receive dedicated training and should be wearing PPE all times during cleaning. All surfaces should be thoroughly cleaned and disinfected at least daily and more frequently if needed using an EPA-registered disinfectant. Cleaning and disinfectant of surfaces around patient is also prudent after aerosol generating procedures. The virus is not hardy and in-vitro data has shown that different concentrations of povidone iodine were sufficient to kill the virus.

2.10. Travelers

Although the total number of MERS-CoV cases reported is relatively small but the major outbreak in South Korea highlight the risk travelers pose to their countries healthcare system. Travel-associated MERS-CoV cases have been reported in at least 17 countries and all of them were related to travelers incubating MERS-CoV during their travel. No transmission on airplanes has been documented to date.

Saudi Arabia hosts two large religious mass gathering annually where millions of Muslims of diverse ethnic groups visit. Though very limited in numbers, MERS-CoV cases amongst pilgrimage travelers returning from Saudi Arabia have been observed [106,107]. Some related to contact with the large dromedary camel present in Makkah area.

The Saudi Ministry of Health recommendations include that elderly people, above 65 years of age, and those with chronic diseases e.g. heart disease, kidney disease, respiratory disease and diabetes and pilgrims with immune deficiency such as congenital and acquired, malignancies and terminal illnesses, pregnant women and children (under 12), should postpone the performance of the Hajj and Umrah for their own safety. It is also prudent for people coming for Hajj and Umrah to avoid contact with camels.

Employment related migration is a common reason for travel to the Middle Eastern countries that host large foreign-born populations of migrant workers. Many business travelers who visited tropical and subtropical areas travel through the Middle East [108]. Travel associated MERS-CoV cases included business travelers, expatriates residing in the Middle East including healthcare providers. Few cases among travelers had history of contact with dromedary camels.

Travelers to countries within the Arabian Peninsula especially high-risk groups like those with diabetes, immunosuppression, chronic lung disease and pre-existing renal failure should be advised of risk. Such travellers need to avoid visiting farms, barn areas or market environments where camels are present. In addition, avoiding contact with camels, camel slaughter house, drinking unpasteurized milk in general and camel milk in specific, consuming other camel raw products, eating food that may be contaminated with animal secretions or products unless they are properly washed, peeled, or cooked and always be vigilant with personal hygiene measures. If it will be mandatory to be around camels, extreme cautions to avoid sick animals or their sick owners and be very vigilant with hand hygiene practices. Travelers who have respiratory symptoms during their stay in Arabian Peninsula countries should seek medical attention, always practice cough etiquette (covers coughs and sneezes with disposable tissues, maintain distance, and wash hands) and to postpone their return travel until they are no longer symptomatic when possible. Those who develop respiratory symptoms within 14 days after their return should seek medical attention and provide history about their recent trip and type of exposures to animals.

2.10.1. Efficient communication and education

Risk of MERS-CoV infection is a significant public health concern. An efficient communication network is essential. Transparency and sharing of real-time information help in gaining trust and increase awareness and readiness in community and healthcare facilities in the battle against MERS-CoV [109–111]. Coordinated efforts will minimize barriers in implementing appropriate and efficient healthcare strategies to control MERS-CoV infection especially in the most heavily affected countries [111].

A reliable and updated source of information for all healthcare providers and healthcare institutions should be established at a national level. Similar reliable and trustable source of MERS-CoV infection information should also be established for the public in order to minimize panic yet to increase awareness. Although internet is powerful tool for spreading information, methods of disseminating information should respect the variability in education level and accessibility of information to the end-user [110].

2.11. Vaccines

Development of an effective, safe, affordable and long-lasting human vaccine for MERS-CoV will be the most efficient cost-effective medical countermeasure to block animal to human transmission and prevent infection. These vaccines can target high risk groups like HCWs and those with close contact to dromedary camels. Vaccine studies were initially hindered by multiple challenges including absence of economic incentive since MERS-CoV infection occurs only sporadically in humans and mostly contained in one geographical area [12]. There were also no suitable animal models of MERS-CoV disease for testing [112]. Another challenge was that neutralizing antibodies titers waned rapidly overtime in humans recovered from MERS- CoV infection leaving uncertainty on duration of protection [113].

Coalition for Epidemic Preparedness Innovations (CEPI) is an innovative partnership between public, private, philanthropic and civil organizations founded in Davos in 2017 to develop vaccines to stop future epidemics. Development of MERS-CoV vaccine has been set as a priority by CEPI due to its continual threat to global public health and high mortality. This step has led to significant expedite in peruse of vaccine development for MERS-CoV moving them to large-scale development and beginning clinical trials.

There are multiple candidate vaccines that are at different phases of trials. Some were tested in animals and human clinical trials are ongoing. There are 5 types of vaccine platforms namely, subunit vaccines, DNA vaccines, viral vector vaccines, live attenuated and inactivated vaccines [114]. Majority of vaccines under development or set for clinical trial are based on viral S protein and its fragments which are the key vaccine targets in MERS-CoV and are aimed to stimulate the host immune response [115]. Immunogens based on full-length S protein or its subunits led to strong antibody and/or cellular immune responses in mice, rabbits and non-human primates protecting or reducing the severity of MERS-CoV infection in these animals. Adjuvanted MERS-CoV Spike protein subunit vaccine results in reduced and delayed viral shedding in the upper airways of dromedary camels although Lower titers of serum neutralizing antibodies was observed [116].

Induction of robust neutralizing humoral immune and/or cellular immune responses by vaccination would prevent human infection and in animals reduces viral shedding and diminish the risk of zoonotic transmission. Vaccines with multiple immunogenic epitopes will be ideal against virus escape phenomenon and hopefully provide cross-protection against future heterologous strains within lineage.

Inducing harmful immune response is an inherited risk of vaccination. Their safety profile and potential immunopathological consequences must be vigorously demonstrated in clinical trials. Pre-clinical testing of any future MERS-CoV vaccine needs to consider heterologous models to show efficacy and safety [117]. Previous studies on SARS have shown different effects between young and old animals Successful vaccine have to be balanced to achieve protection and yet do not cause excessive immune activation.

2.12. Post-exposure prophylaxis

There is one report that suggested ribavirin and lopinavir/ritonavir for 14 days after high risk exposure to patients with severe MERS-CoV pre-isolation pneumonia resulted in a 40% decrease in the risk of infection. Only mild adverse effects were observed during treatment [118].This report includes few patients and has not been replicated to confirm its effectiveness.

2.13. Other therapeutics

Antibody-based therapies for MERS-CoV is one therapeutic intervention that is been extensively studied [119]. There is no current anti-MERS-CoV antibody approved for human use yet however both human and animal antibodies are being investigated [120]. As in vaccine development specific targets in the S protein are key in these antibodies. Most of Neutralizing human monoclonal antibodies under investigation target MERS-CoV S receptor binding domain (RBD) and few tested in cell culture and animal models conferring variable levels of protection [119,121–124].Lung viral loads reminded high with some of these mAbs despite symptoms control. Target epitopes and targets other than S receptor binding domain were also used including anti-DPP4 mAbs, DPP4 antagonists, peptide fusion inhibitors, protease inhibitors and short interfering RNA (siRNA). Anti-MERS-CoV polyclonal immunoglobulin produced from S protein nanoparticle-immunized transchromosomic (Tc) cattle immunized with a Middle East Respiratory Syndrome (MERS) coronavirus vaccine demonstrates safety and tolerability in human Phase I trials [125].

Successful use of antibodies in treatment of MERS-CoV infection will require combinations targeting different neutralizing epitopes on the functional regions in MERS-CoV S protein. Combination antibodies with diverse targets and mechanism of action will avoid generation of escape mutant virus strains and improve antiviral activity against divergent virus strains. Human antibodies are also preferred over those of animal origin to avoid immune reaction [126].

2.13.1. Key issues

- MERS-CoV is primarily a zoonotic infection that was first recognized as a human pathogen in 2012 in Saudi Arabia.
- Camels are the only known animal reservoir for MERS-CoV and animal to human transmission occurs when viral infection in camels reach a threshold and episodic human transmission occurs.
- Camel vaccination is an ideal way to block the camel to human transmission or at least to significantly reduce transmission risk.
- Community transmission is not very efficient but does occur.
- The main factors leading to sustainability of MERS-CoV infection in high risk courtiers is healthcare facility transmission.
- MERS-CoV transmission in healthcare facility mainly results from laps in infection control measures and late isolation of suspected cases
- Although no current human vaccine is available, significant progress has been made.
- Successful vaccine must be balanced to achieve protection and yet do not cause excessive immune activation.
- Both vaccination and antiviral therapeutics would ideally have different mechanism of action to avoid generation of escape mutant virus strains and improve activity against divergent virus strains.

3. Expert opinion section

Preventive measures for MERS-CoV include disease control in camels to prevent camel to human transmission. Key measure to prevent community transmission include avoid close contact with camels, barn area, and camel markets specially for high risk groups, monitoring disease activity in camels and good hygiene practice when around camels. MERS-CoV is poorly suited for human-to-human transmission and most of primary cases represent animal spillover that are not sustainable outside healthcare facilities. Number of vaccine candidates have been developed but yet tested on large scales. Current studies suggest that candidate vaccines in development can only reduce viral shedding which may not be enough to prevent human transmission. The duration of protection also is not known. MERS-CoV is a disease that causes only mild symptoms in camels and acceptance of owners to vaccinate for such a mild disease may n e future challenge.

Prevention of healthcare facility transmission which is the main amplifier of persistent outbreaks and control community transmission. Prevention of infection at healthcare facilities is essential too, since healthcare transmission is more efficient than community transmission and represent 44%–100% of all individual outbreaks. Inadequate or lapses of infection control measures in the inpatients and outpatient sitting is the most important risk factor for transmission. Late identification of cases and delay in isolation of patients is by far the most preventive strategy that can be adopted. Effective screening, prompt diagnostic methods and crowding control are other important interventions.

All suspected and confirmed cases should be placed under standard, contact, and droplet precautions with airborne precautions for patients requiring aerosol-generating medical procedures, such as mechanical ventilation, endotracheal intubation, and endotracheal aspiration. Due to the well documented prolonged MERS-CoV shedding, Infection control precautions should be applied until two consecutive lower respiratory tract samples (sputum or tracheal aspirates) 48hrs apart become RNA negative and patient becomes asymptomatic. Strict infection control measures should be observed during sample collection including use of approved collection methods and equipment and transporting samples according to appropriate protocols. Samples are preferably collected in negative pressure rooms especially deep respiratory samples by trained healthcare professionals.

Symptomatic individuals exposed to MERS-CoV who do not require hospital admission can be cared for and isolated at their home. They should be wearing surgical mask, observing cough etiquettes and remain restricted in their activities. Asymptomatic HCWs with MERS-CoV exposure under quarantine should remain vigilance for fever and development of respiratory symptoms and keep infection control office informed. They are tested weekly and would only return to work if two respiratory samples are negative.

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