

A Literature Review: Prevention of a Growing
Pandemic, Middle Eastern Respiratory Syndrome

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Abstract

Background: Middle Eastern Respiratory Syndrome is a viral respiratory syndrome caused by MERS-CoV. From its first identification in 2012 until today, 1,374 laboratory-confirmed cases of infection with MERS-CoV have been identified in 26 countries, with the majority of these cases (>80%) occurring in the Kingdom of Saudi Arabia (KSA). The rapid international spread of this virus suggests that it is crucial to review the current prevention & control strategies. It is also important to outline further recommendations to prevent the growth of a potential pandemic disease.

Methodology: This study was conducted as a targeted literature review and critical analysis of articles from multiple databases. An emphasis was put on the updates and archives posted by the WHO – coronavirus infections.

Prevention Strategies: Researchers have studied the rapid spread of MERS-CoV in KSA, focusing on viral spread in hospital settings, via dromedary camels, and religious mass gatherings as risk factors. Current advancements in the knowledge of camels as a potential MERS reservoir, guidelines for travelers to high-risk countries, and improvements in the surveillance have contributed to the reduction of the MERS incidence cases globally. Despite these prevention strategies, more outbreaks continue in KSA and major recent outbreaks have been reported in the Republic of Korea.

Conclusion: The remaining and ongoing MERS cases reported in KSA & Republic of Korea represent a global public health concern. As a result there is a need to further improve the management of MERS. Given the rapid spread of the virus and the gap in literature about the transmission of MERS, it is recommended that both high and low risk nations abide by the international MERS recommendations outlined by the WHO. Furthermore, collaboration between the animal and human public health organizations would serve as a progressive step to control the spread of this zoonotic disease.

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List of Abbreviations

CDC – Centre for Disease Control and Prevention

ELISA - Enzyme-linked immunosorbent assay

EUDC – European Centre for Disease Prevention and Control

KSA – Kingdom of Saudi Arabia

MERS – Middle Eastern Respiratory Syndrome

MERS-CoV - Middle Eastern Respiratory Syndrome Coronavirus

MOH – Ministry of Health

RT- PCR – Reverse transcription PCR

SARS – Severe Acute Respiratory Syndrome Coronavirus

SARS-CoV – Severe Acute Respiratory Syndrome Coronavirus

TB – Tuberculosis

UAE – United Arab Emirates

UK – United Kingdom

WHO – World Health Organization

Introduction & Summary

Middle Eastern Respiratory Syndrome (MERS) is a viral respiratory syndrome caused by MERS-CoV, a coronavirus which was first identified in March 2012. The clinical spectrum of MERS infection ranges from asymptomatic patients to those presented with acute severe respiratory disease and death (CDC, 2015).

Epidemiological statistics state that as of July 25th 2015, 1,374 laboratory-confirmed cases of infection with MERS-CoV, with a case fatality rate of at least 36%, have been reported in 26 countries (WHO, MERS-CoV Summary Updates, 2015). Many studies have been conducted to better understand the source and transmission of the virus, speculating that there is both a possible human-human (Assiri, *et al.*, 2013) along with animal-human (Gossner, *et al.* 2014) transmission of the virus, particularly dromedary camels. Given the quick global expansion of this virus, many organizations such as the World Health Organization (WHO) have highlighted MERS health related issues as an important public health priority in high-risk populations (i.e. those living in high endemic MERS regions like the Kingdom of Saudi Arabia (KSA)). However, there still remains a great gap in the background literature and transmission of this virus. The lack of background knowledge and the non-specific clinical symptoms have contributed and will continue to advance the spread of the virus, unless a more sustainable global prevention and control measure is implemented. This paper looks at the different factors in KSA (i.e. the nation with >80% of the MERS cases) that have exacerbated the viral spread. Moreover, the paper focuses on the current MERS prevention and control plan outlined by the Ministry of Health (MOH) in KSA and the WHO while providing some recommendations for both national and international surveillance.

Methodology

A targeted literature search approach was conducted of multiple databases including Global Health, PubMed, Google Scholar, Scopus, Medline, and Web of Science, using key words: 'Middle East* Respiratory Syndrome', 'MERS*-CoV', 'Saudi Arabia', 'risk factors', 'hospital setting', 'outbreak', 'dromedary camels', 'prevent*ion and control', 'KSA', 'Hajj', and 'Ministry of Health'. The exclusion criteria included articles that were posted before March 2012 (i.e. prior to the first reported MERS case), as well as, articles that were published in languages besides English and Arabic. A review was also carried out of other key reports and archives published by the MOH in Saudi Arabia, WHO, and the Centre for Disease Control and Prevention (CDC).

A compilation of MERS related documents was constructed based on the criteria. This was followed by a critical review of these documents with a focus on prevention and control strategies. Trends and outbreaks regarding MERS were analyzed and recommendations were recorded and compared with that of WHO, MOH and CDC.

Background

MERS is a viral respiratory syndrome caused by a newly identified coronavirus, named MERS-CoV. This strain of coronavirus was first detected in a case of a fatal respiratory disease in a previously healthy 60-year-old man in Jeddah, Saudi Arabia during March 2012 (Groot *et al.*, 2013). Since its initial discovery, isolates of the virus have been identified as a betacoronavirus and was described in the scientific literature, databases, and popular press under various names (e.g., human *betacoronavirus 2c* EMC, human *betacoronavirus 2c* England-Qatar, human *betacoronavirus 2C* Jordan-

N3, *betacoronavirus* England 1) with “novel coronavirus” as the one used most often (Groot *et al.*, 2013). Additional cases of infection with the novel betacoronavirus have been documented in the KSA, as well as, other countries in the Middle East, such as Qatar, Jordan, and the United Arab Emirates (UAE). Due to the prevalence of the virus in residents of the Middle East, researchers termed the novel coronavirus, MERS-CoV.

Symptoms and Clinical Features

Coronaviruses are known to cause the ‘common cold’. However, they have also been identified to cause more severe illnesses with flu-like symptoms, including the Severe Acute Respiratory Syndrome (SARS) pandemic observed in 2003-2004 (Peiris *et al.*, 2003). Most people who have been confirmed to have MERS-CoV infection presented similar clinical features to those seen in SARS; an initial phase of nonspecific fever and mild, nonproductive cough, which can last for several days before progressing to severe pneumonia (Annan *et al.*, 2013). Studies have shown that the median incubation period of MERS-CoV is 4.0 days, with 5% of cases developing within 1.8 days and 95% within 10.6 days (Lesser *et al.*, 2009). Although most MERS diagnosed patients were presented with fever, cough and dyspnea upon their hospital admission (WHO, MERS Summary Sheet, 2013), the clinical spectrum of MERS ranges from asymptomatic patients to severe acute respiratory disease and death. Other common presenting symptoms include renal failure, shortness of breath, chills, rigors, headache, myalgia (muscle pain) and malaise (CDC, FAQ, 2015). Similar to other betacoronaviruses, MERS-CoV has been recognized to infect the cell lines of the intestinal tract, leading to gastrointestinal symptoms such as diarrhea (Chan *et al.*, 2013).

Epidemiology

Globally, since September 2012, there have been 1,374 human laboratory-confirmed and reported cases of infection with MERS-CoV (WHO, Disease Outbreak News, 2015). Of these cases, there have been at least 490 related deaths, accounting for one of the highest case-fatality rates (35.7%) seen in infectious diseases.

Additionally, some physicians believe that MERS cases are underreported due to the non-specific symptoms of this disease, which could be misdiagnosed as a (chronic) respiratory illness, without being specifically tested for MERS-CoV.

During April-May 2014, there was a great increase in the numbers of reported MERS cases in KSA, particularly in Al-Ahsa region (Abdelmalik, 2015), and in Jeddah hospitals. These cases were mostly related to nosocomial outbreaks, poor hospital infection control measures, and improved screening (Abdelmalik, 2015). Today, MERS-CoV has spread to 26 countries (Appendix – Figure 1 & Figure 2): Algeria, Austria, China, Egypt, France, Germany, Greece, Iran, Italy, Jordan, KSA, Kuwait, Lebanon, Malaysia, the Netherlands, Oman, the Philippines, Qatar, Republic of Korea, Thailand, Tunisia, Turkey, UAE, the United Kingdom (UK), the United States of America (USA) and Yemen (WHO, MERS-CoV Update, 2015). A literature review has presented that the spread of MERS-CoV appears to be circulating widely throughout the Arabian Peninsula, with cases specifically originating from KSA. Furthermore, literature data reveal that all recent cases that have been reported outside the Middle East first developed the infection in the Middle East prior to the export of the case outside the region (WHO, MERS Summary, 2013). However, these travel-related cases do not appear to have infected others in their respective countries.

Source and Origin of MERS

Several studies have been conducted to explore the origin of MERS-CoV. Although the origins of the virus are not fully understood, according to the analysis of different viral genomes, it is proposed that the virus originated in bats and was then transmitted to camels (WHO, MERS-CoV Summary, 2015).

Phylogenetic analysis defined MERS-CoV as a novel lineage C, making this coronavirus a lineage c β -coronavirus that originates from the bat-associated clade 2c β -coronaviruses (Cotton *et al.*, 2013; Annan *et al.*, 2013). Despite the sequence similarity between the β -coronavirus found in bats and the one obtained from a MERS patient (Memish *et al.*, 2013), there has been limited evidence to support this hypothesis.

Studies about the source of this virus have shown that 95% of camels worldwide, known as the dromedary camels (*C. dromedarius*), are the only convincing evidence for a non-human MERS-CoV host species. Azhar *et al.* (2014) collected samples from dromedary camels in Qatar and KSA and analyzed them using reverse transcription PCR (RT-PCR) and full-genome sequencing of MERS-CoV RNA. The data gathered revealed that the camel MERS-CoV RNA sequence demonstrated a 100% concordance with humans' (Alagaili *et al.*, 2014). Moreover, serological studies in dromedary camels in the Arabian Peninsula and North Africa have shown high rates of antibodies against MERS-CoV, suggesting infection with the same virus (Alagaili *et al.*, 2014; Corman *et al.*, 2014). Other studies have detected MERS-CoV gene fragments in nasal swabs and feces samples taken from dromedary camels (Reusken *et al.* 2014; World Health

Organization for Animal Health, 2014).

Transmission of MERS

Although there have been many studies revealing that dromedary camels could be a potential reservoir for the virus, there still remains limited epidemiological evidence regarding the role these camels play in the zoonotic transmission of the virus. Further evidence and transmission studies are required to identify the exact mode of transmission. By identifying the transmission mechanism, we could conclude that camels in fact are reservoirs for the virus rather than a functional vector in the transmission (Gossner, 2014). To date, we have identified cases of human-human and non-human-human transmissions, particularly through dromedary camels.

Since 2012, many MERS outbreaks have been reported in various hospitals within in KSA (Assiri *et al.*, 2013; Memish *et al.*, 2013). By studying the disease outbreaks in the health care-facilities of an eastern province in Saudi Arabia, Assiri *et al.* (2013) note that there appears to be a clear heterogeneity in the virus transmission; where some infected patients did not transmit the disease at all, while others transmitted the disease to up to seven other patients in the same healthcare facility. Similarly, numerous healthcare facilities in different regions of Saudi Arabia have reported clusters of cases where human-to-human transmission appears to be more probable, especially when infection prevention and control practices are inadequate (MOH Saudi Arabia, 2014). Together these literature findings propose that the virus follows a human-human route of transmission (WHO, MERS-CoV Summary, 2015). However, a sustained community transmission of the virus has not been documented

and there is little verified data about the transmission characteristics of this virus.

Therefore, person-to-person transmission can only be proposed as potential risk factor of the disease.

Based on findings that infected dromedary camels accumulate very high virus concentrations in their nasal sections, researchers proposed that droplet spread of the virus is a likely route of its transmission. Findings from this study were further validated by the detection of airborne MERS-CoV droplets in the environment the infected dromedary camels encompassed (Azhar *et al.* 2014). Moreover, strains of MERS-CoV that are identical to human strains have been isolated from camels in several countries, including Egypt, Oman, Qatar, and KSA (Chu *et al.*, 2014; Nowotny *et al.*, 2014). Although the route of transmission from animals-humans is not fully understood, researchers concluded that dromedary camels are likely to be a major reservoir for MERS-CoV and an animal source of infection in humans.

MERS in the Kingdom of Saudi Arabia and Risk Factors

About 80% of global MERS cases have been reported in KSA, with the remaining majority in the Middle East (WHO, MERS Summary Update, 2015). For the few cases that have been reported outside the Middle East, studies revealed that these infections were most likely first acquired in the Middle East, particularly KSA, and then exported outside the region (Hui and Zumla, 2014). Given that KSA serves for a majority of the MERS cases, it is of crucial importance to investigate these cases in order to identify what is considered a MERS-related risk factor. Similar to many infectious diseases, the spread of coronaviruses are common in areas of high viral concentrations and densely populated areas. In order to better manage the epidemiology of the virus, there is a

need to enhance our understanding of the underlying factors that allow this virus to spread widely in KSA.

Camels, particularly dromedary camels, have been long known to play a role in the culture and traditions in KSA along with other nations in the Arabian Peninsula. For example many of Saudi Arabian residents have reported direct contact with camels, participating in camel racing as a popular traditional sport, camel farm work, butchering, and raising camels as pets. Several serological studies conducted in humans in KSA, Qatar, and UAE have found higher levels of prevalence of antibodies against MERS-CoV among those populations in close, regular occupational contact with dromedary camels when compared to the general population (Reusken *et al.*, 2013), positioning camel contact as a risk factor. Although there have yet been any studies proving that eating camel meat can transmit MERS-CoV to humans, public health officials recognize these traditions as risky practices. As raw camel meat may contain the virus, it is recommended that general health prevention approaches be taken, such as ensuring that the meat is not undercooked prior to consumption (WHO, Summary Update, 2015). Some researchers studying contact with dromedary camels added that religious traditions also play a role as a confounding risk factor. During one of the major Muslim festivals called *Eid al-Adha* or “Feast of the Sacrifice”, many families sacrifice a camel as part of a religious ritual followed by eating and distributing the sacrificed camel’s meat to a population in need. Therefore, if ‘undercooked’ camel meat does in fact act as a transmission route for the virus, this religious tradition can be perceived to contribute to the ongoing spread of the virus.

Moreover, the use of camel extracts such as urine or milk as cosmetic products is another risky but common practice in the Arabian Peninsula (Faye *et al.* 2014). In Saudi Arabia, 78% of the camel milk products, including dromedary camel milk, are sold as unpasteurized fresh or fermented milk to consumers, which further put the public at risk (Faye *et al.* 2014). Another traditional and cultural custom amongst Bedouins and camel-herding peoples in KSA, along with other countries in the Arabian Peninsula and East Africa is drinking and washing ones hands, face and hair in camel urine. Camel urine has also ben used as a component in skin creams, as well as, part of the traditional pharmacopeia; where it is believed to have therapeutic properties in strengthening the immune system (Drosten *et al.* 2013). Although there is yet any documentation of MERS-CoV detection in camel urine, there has been a reported case of the virus in human urine samples (Drosten *et al.* 2013), which puts dromedary camel urine along with other camel extracts as other potential risk factors for virus transfer. However, since there still remains a gap in the exact route of transmission of the virus from camels to human, the Ministry of Health (MOH) in Saudi Arabia along with international health organizations such as WHO and CDC, have situated camels and people who have direct contact with camels as a high risk population. This population should familiarize themselves with the appropriate public health recommendation strategies to avoid disease transmission.

Other groups of researchers have focused solely on the human-human transmission of the virus (Assiri, 2013). In doing so, there has been a shift in focus from dromedary camels to transmission through densely populated atmospheres. Two 'risk factors' that have gathered a fair amount of attention in KSA are religious mass

gatherings and overly populated healthcare settings. These risk factors were identified as contributors to the spread of MERS along with other past infectious diseases in KSA (Assiri, 2013; Tomasulo, 2011). Human-to-human transmission in healthcare settings have added to the majority of the current human reported MERS cases (WHO, MERS-CoV Summary Update, 2015).

Tracking the trends of infectious diseases, most notably MERS and SARS, reveals a consistent annual trend with a peak increase after the Muslim religious pilgrimage, *Hajj*. *Hajj* is an Islamic religious duty that every able-bodied Muslim must perform, which lasts for a period of a week. Every year over three million Muslims travel to Mecca, Saudi Arabia, to perform this annual pilgrimage. Being one of the largest mass gatherings in the world, millions of people share crowded spaces and experience extreme exhaustion and heat (Tomasulo, 2011). These factors create a favorable environment for communicable disease transmission such as the spread of SARS (Tomasulo, 2011), tuberculosis (TB), and now MERS. Figure 3 (Appendix) demonstrates the total number of MERS cases since 2012, revealing annual rises in MERS cases after the annual pilgrimage, *Hajj*.

Past studies have shown that mass gatherings such as the annual *Hajj* or more frequent *Umrah* (i.e. non-annual visit to Mecca, Saudi Arabia) have greatly contributed to the spread of the respiratory disease SARS (Pieris *et al.*, 2003). With this background knowledge epidemiologists studied and tracked the spread of communicable diseases such as MERS during the annual pilgrimage (Figure 3 – Appendix). Such trends do in fact reveal a correlation between the mass gatherings and the proliferation of MERS.

Under this clause, religious mass gatherings are perceived as another risk factor in KSA and should be appropriately controlled for disease transmission. Additionally, knowing that *Hajj* hosts these three million international Muslims from 180 countries raises the possibility of a pandemic. One hypothesis is that with these mass gatherings acting as a risk factor, Mecca, Saudi Arabia could be perceived as an international hub for the proliferation and cross-transmission of MERS-CoV followed by the export of the virus by the returning pilgrims to their countries. In fact, some researchers suggest that the reported cases in France, Greece, Malaysia, Philippines and Oman might have been a result of this hypothesis. With this assumption the MOH in Saudi Arabia collaborated with the WHO to outline some international guidelines for travelers to KSA, particularly the pilgrims visiting to attend *Hajj*. Reviewing the annual MERS trends, Figure 3, demonstrates that there still remains a persistent increase in reported cases of MERS after the religious ceremonies (2013 versus 2014 versus 2015), which brings to question: Are the prevention and control strategies taken to manage the spread of the virus sufficient?

Prevention and Management of MERS

The ability for the virus to spread rapidly and infect individuals in close contact with infected individuals, such as physicians, other healthcare workers, or the patients' family suggests that MERS may represent a global health threat (Zumla *et al.* 2015). Moreover, the disease has a high mortality rate signifying the need for a sustainable treatment discovery. Currently, there are no (prophylactic/prevention) vaccines or specific antiviral agents that are effective in the prevention and/or treatment of MERS

(WHO, MERS-CoV Summary, 2015). Researchers have argued that this has been partly due to the limited amount of attention MERS has received and lack of research done on this topic (Zumla *et al.* 2015). Furthermore, as Zumla *et al.* (2015) argues, the primary focus and funding directed to research involving Ebola (vaccination development, containment measures) has had an overshadowing effect on research revolving around MERS. As a result, there remains a big gap in the background information regarding the spread and transmission route of the virus. Unless these topics are better understood, developing evidence-based and sustainable treatments or prevention plans will continue to be a daunting task. To date, general public health precautions seem to be the center of primary preventive strategy. These measures focus on alleviating those possible non-human-human and human-human risk factors.

Controlling non-human-human transmission

Until more evidence is gathered, it is crucial for camel farm workers, butchers, and individuals handling or visiting dromedary camels to practice good personal hygiene. According to WHO (2013) and CDC (2014), personal hygiene precautions to be taken include: washing one's hands with soap and water or alcohol gel before and after contact with animal flesh; avoiding contact with camels that may appear sick, wearing facial protection where feasible and protective clothing that should be removed after work (followed by hand hygiene) and washed daily. It is also advised that employees working with camels avoid exposing family members to soiled work clothing, shoes, or other items that may have come into contact with camel secretions and excretions.

International recommendations note that the population should be vigilant about the consumption of raw or undercooked animal products, including camel milk and meat (WHO, MERS-CoV Risk Assessment, 2015). Animal products (i.e. meat or milk) that have been processed appropriately through cooking or pasteurizations are safe for consumption, but should still be handled with care to avoid cross contamination with uncooked foods (WHO, MERS-CoV Risk Assessment, 2015). Furthermore, people at high risk of developing severe disease, the immune-compromised people and those with comorbidities such as diabetes, renal failure, and chronic lung disease, should take the aforementioned precautions when visiting farms and markets where dromedary camels are present, particularly in the Middle East and Africa (WHO, MERS-CoV Risk Assessment, 2015).

Controlling human-human transmission

The other set of recommendations listed in international documents (CDC and WHO in compliance with the MOH in Saudi Arabia) center around the human transmission for the virus in hospital settings and mass gatherings, such as the annual pilgrimage in Mecca, Saudi Arabia. Preventing the transmission of respiratory pathogens, such as SARS-CoV and MERS-CoV, in healthcare settings requires operative infection control procedures and protocols that consider environmental and engineering controls, administrative controls, safer work practices, and personal protective equipment (CDC, Prevention & Control, 2015). It is advised that a high risk population such as those in contact with camels, or a population living in high risk nations like Saudi Arabia should consult a health worker if they have a fever (38°C or

higher), cough or difficulty breathing (WHO, MERS-CoV Summary, 2015). This additional precautionary measure can help with the early detection of the virus in individuals to prevent future spread of the disease. WHO (MERS-CoV Summary, 2015) also encourages health care facilities providing care for MERS (suspected) patients to outline clear administrative policies and take appropriate measures in order to decrease the risk of transmission of the virus from an infected patient. These measures include interventions at the patient-carer interface and other general hygiene measures such as waste management, linen management, cleaning and disinfection (WHO, MERS-CoV Summary, 2015). Healthcare workers should take contact precautions and eye protection should also be added when caring for probable or confirmed cases of MERS. Furthermore, airborne precautions should be applied when performing aerosol-generating procedures (MERS-CoV Summary, 2015).

One problem that has attributed to the proliferation of MERS in healthcare facilities is patient misdiagnosis. Due to the ambiguous and non-specific clinical symptoms of the disease, physicians often have trouble providing an accurate and confident MERS diagnosis (Assiri, 2013). For this reason, it is crucial that all health care facilities in high-risk regions, particularly KSA, establish and implement clear triage policies for rapid screening and assessment of potential MERS cases and all cases with acute respiratory symptoms (WHO, 2014). It is also important that workers apply standard precautions consistently with all patients, regardless of their diagnosis, in all work practices all the time. Failures in hospital infection prevention and control have resulted in large numbers of secondary cases, as was seen in KSA in April-May 2014

(WHO, Outbreak News, 2015) and Republic of Korea in May-July 2015 (EUDC, Rapid Risk Assessment, 2015).

MERS and travelers

Due to the July 2015 outbreak in the Republic of Korea, a few steps were recommended by a WHO mission to stop further cases of MERS CoV in the high prevalence nations, including Republic of Korea and KSA. These include a need of early and complete identification of all contacts, quarantine or isolation and monitoring of all contacts and suspected cases, a full implementation of infection, prevention and control measures, and prevention of travel, especially internationally, for infected persons and contacts (WHO, Republic of Korea, 2015). WHO does not recommend travel restrictions with regards to MERS-CoV, but rather to raise awareness among travellers to and from affected countries (WHO, Republic of Korea, 2015). For example, citizens of the European Union travelling to a high-risk nation are made aware through EUDC guidelines that MERS-CoV is circulating in these areas and reminded of general travel advice of good hand and food hygiene (EUDC, Rapid Risk Assessment, 2015). Additionally, travellers returning from the high-prevalence areas should be made aware to both report their travel history and seek medical attention if they develop respiratory symptoms or diarrhoea either during the travel or up to two weeks after their return.

MERS and Hajj

Researchers studying the transmission of communicable diseases during mass gatherings supported the importance of a control and risk management plan to prevent

the spread of the newly identified virus at the time – MERS. Travel and health recommendations were disseminated through WHO (Travel Advice, 2013) during July 2013, prior to the annual Muslim pilgrimage, *Hajj* (October 13-15 2013). These guidelines advised travelers on actions to take before, during, and after the mass gatherings (WHO, Travel Advice, 2013). However, as observed in Figure 3 (Appendix), the Hajj ceremony was followed by a great increase in the prevalence of MERS globally. Many researchers and epidemiologists speculated that this increase was mostly a result of inadequate and subjective MERS guidelines developed for Hajj 2013, where contact precautionary measures such as the facemask were not mandated (Gautret *et al.*, 2013). As a result, global health officials advocated for a more comprehensive risk management plan that was particular to mass gatherings such as *Hajj* and *Ummrah*. These regulations include an emphasis on good hand hygiene¹ and respiratory hygiene² practice along with the responsibility of countries to distribute WHO guidelines to travels heading to KSA, particularly before *Hajj* (WHO, Risk Assessment, 2015).

Conclusion and Recommendations

Going forward, the WHO identified that the most effective way to control the spread of the virus is to improve the current surveillance and expand the available literature on MERS. By improving the surveillance one can detect early, sustained human-to-human transmission as well as determine the geographic risk area for

¹ Washing hands often with soap and water. When hands are not visibly dirty, a hand rub can be used.

² Covering mouth and nose when coughing or sneezing, washing hands after contact with respiratory secretions, and keeping a distance of one metre with other persons when having acute febrile respiratory symptoms.

infection with the virus (WHO, Surveillance for MERS-CoV, 2015). Furthermore, more research studies should be developed to expand the clinical and epidemiological knowledge of the disease (WHO, Risk Assessment, 2015). Additional clinical and epidemiological investigations would help in defining key clinical characteristics, such as spectrum of disease, incubation period, and clinical course of disease. Future research should focus on determining the additional risk factors, modes of transmission, and secondary attack rates (WHO, Surveillance for MERS-CoV, 2015).

Advancements in surveillance

The rise in current cases can be perceived as improved MERS detection through diagnostic tools and improvements in proactive surveillance. Lab tests directly conducted by CDC involve both molecular tests³, which look for evidence of active infection, and serology tests⁴, which serve for surveillance or investigational purposes rather than diagnostic purposes. Serological tests particularly look for previous infections by detecting MERS-CoV specific antibodies (CDC, Prevention & Control, 2015). There has also been a greater understanding on how improved sample collection can lead to better diagnostic results. For example, the CDC (Prevention & Control, 2015) recommends that multiple specimens should be collected, including lower (e.g. sputum, endotracheal aspirate, or bronchoalveolar lavage) and upper respiratory samples (e.g. nasal swabs), serum and stool specimens. This is because in early

³ Molecular tests detect the presence of MERS-CoV in patients with a suspected infection with MERS-CoV based on their clinical symptoms and having links to places where MERS has been reported. These tests primarily use real-time RT-PCR assays.

⁴ Serology tests are carried as a two-phase approach using once screening test, enzyme-linked immunosorbent assay (ELISA), and two confirmatory tests, immunofluorescence assay and microneutralization assay, to detect MERS-CoV antibodies.

stages of the disease, the virus may be more difficult to detect in the upper respiratory track. Moreover, in some circumstances upper respiratory system samples can provide false negative test results compared to a correct detection by lower respiratory samples (WHO, Surveillance guidance, 2015). Although lower viral titers are demonstrated in body fluids (e.g. blood, urine, and stool) than in the respiratory tract, it is advised for such specimens to be collected when good quality respiratory tract specimens are unavailable (WHO, Surveillance guidance, 2015).

Future prevention and control steps

Despite these advancements in the surveillance of MERS, there still remains a great area for improvement in the prevention and management of this virus.

Epidemiological trends reveal that the virus continues to rapidly spread internationally during 2015: smaller but more frequent hospital outbreaks in KSA continue and the largest outbreak outside KSA, in the Republic of Korea, has been recently reported (WHO, Outbreak News, 2015). These repeated and ongoing hospital outbreaks are of concern, indicating that there is still a need for more work to better understand the reasons behind these outbreaks.

Today, updated international guidelines through CDC and WHO continue to abide by the previously listed public health regulations regarding MERS. However, these global recommendations are beginning to experience shift towards more strict regulations, particularly in high-risk nations. For example, the latest WHO set of MERS recommendations outline strict infection control measures. These enforcements include mandating the use of personal protection equipment by the hospital staff during

healthcare delivery. Moreover, both probable and confirmed cases should be reported within a 24-hour period (WHO, Investigation of cases of MERS, 2015). In addition to strengthening the guideless, there have also been some advancements in the *Knowledge Sharing* strategies to raise MERS awareness amongst both the high and low risk nations (WHO, Summary Updates, 2015).

A major lesson learned from the June 2015 MERS outbreak in Republic of Korea is the need to expand the current *Knowledge Sharing and Translation* measures to safeguard the health of both high and low risk nations. This could be done by conducting informational videos about MERS and disseminating this data through popular television channels and social media. The large and complex outbreak in Korea has followed similar epidemiological patterns to previous hospital-associated MERS transmission in the Middle East (WHO, Republic of Korea, 2015). Which brings to question, how did a previously managed virus spread once again occur in such a short time? Experts in epidemiology, risk communications, virology, clinical management, infection prevention and control, as well as public health specialists, identified several reasons why the virus, which arrived in the Republic of Korea with a single infected traveller, was able to go on to infect large numbers of people in a relatively short time (WHO, Republic of Korea, 2015). These perspectives included that MERS-CoV was unexpected and unfamiliar to most physicians in the Republic of Korea, thus was overlooked in nosomical settings, hospital emergency rooms were overcrowded with sub-optimal prevention and control measures, and the role of the Korean culture where hospitalized patients are visited by very many friends and family members (WHO, Risk Assessment, 2015). Another recommendation to the Korea outbreak was the need to

include increased negative-pressure isolation rooms. Moreover, droplet precautions should be added to the standard precautions in health-care setting when providing care to any patient with symptoms of acute respiratory infection (WHO, Surveillance guidance, 2015).

Another important suggestion put forth by public health experts is a collaboration between human and animal health sectors in affected countries. An alliance between both fields is essential to understand the risk of transmission of MERS-CoV between animals and humans, whether there is any seasonal variation in the circulation of the virus in animals, and the natural reservoir(s) of MERS- CoV (WHO, Risk Assessment, 2015). In order to successfully control the spread of MERS on both a national and global scale, there is a need to understand: how easily does human-human transmission occur? What exposures result in infection? What are the clinical appearances and course of illness? And what is the source of MERS-CoV? These questions could be answered by enhancing the current available literature on MERS by surveying healthcare providers, case-study reports, retrospective testing of clinical specimens, reviewing surveillance data, following epidemiological trends, and collecting more samples for research (WHO, Surveillance guidance, 2015).

In conclusion, there have been great advancements and contributions done to both understand and prevent the spread of MERS. However, as new public health concerns seem to arise there is a need for ongoing research and collaboration from different health sectors. Moreover, there is a need for an organization such as WHO to take high priority in the knowledge sharing and dissemination of available literature on

MERS to both high and low risk nations to avoid future outbreaks and a growth of what has a potential to become a pandemic.

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Appendix

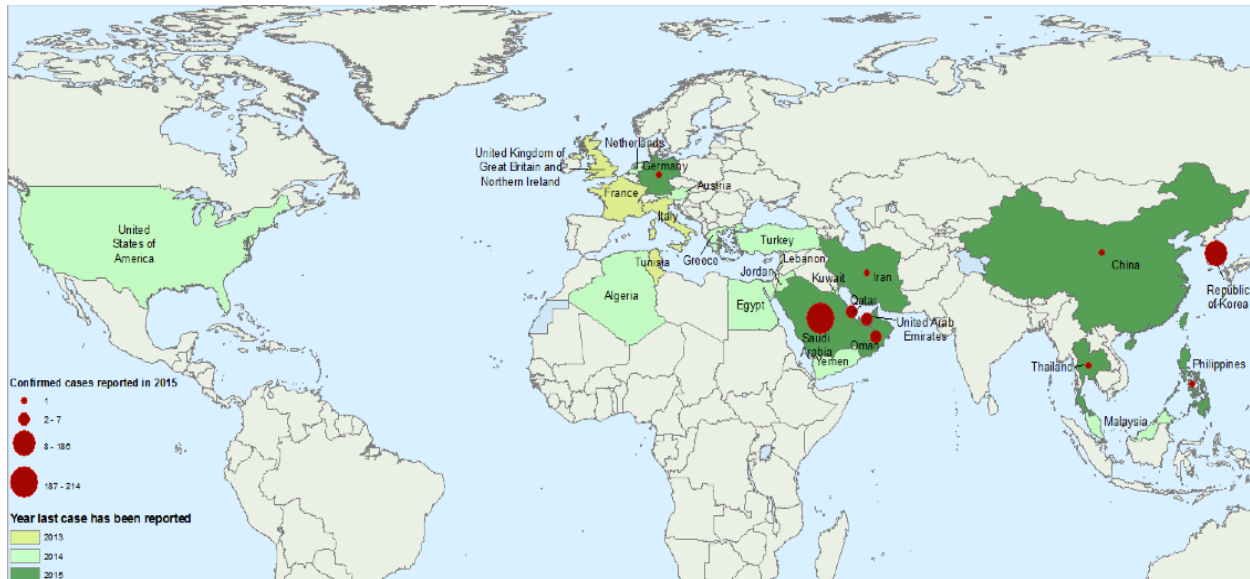


Figure 1 - World map demonstrating the regions with confirmed MERS cases. A total of 26 countries have reported MERS cases to the WHO. Nations shaded yellow-green, light green, and dark green represent cases that have last been reported 2015, 2014, and 2013 respectively. Figure developed from WHO MERS-CoV Summary Report, updated as of 7 July 2015.

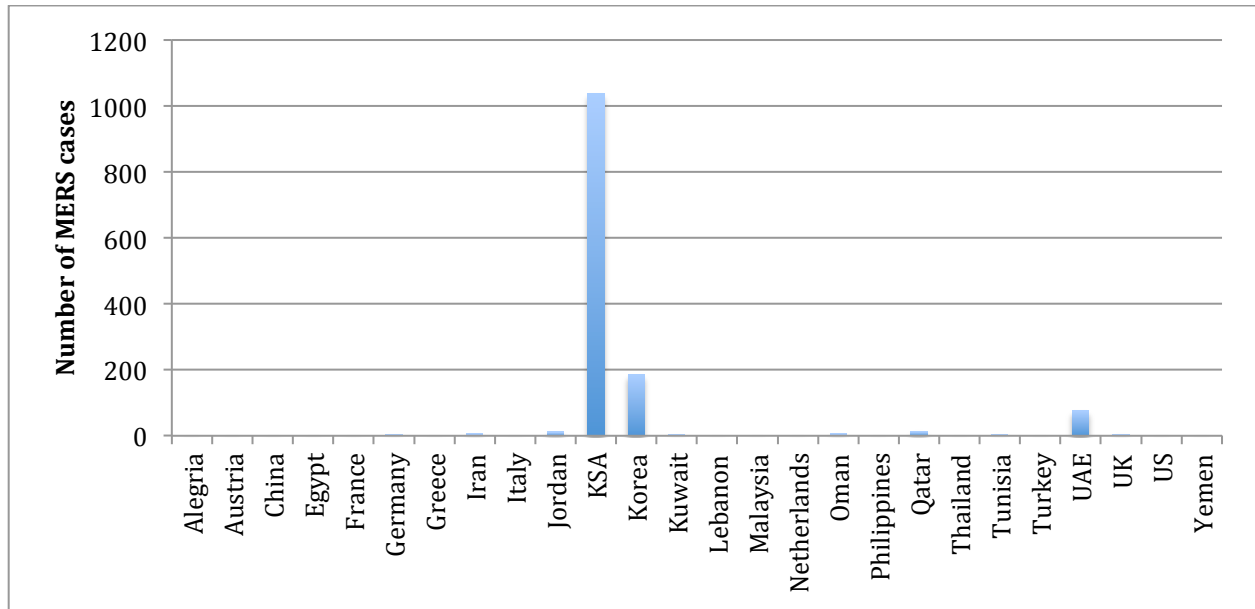


Figure 2 – Reveals the number of MERS confirmed cases documented from 2012 till July 7th 2015 across the 26 affected countries. Countries with the highest prevalence are KSA, Korea, and UAE. As of July 2015, 1,374 MERS cases have been confirmed and reported to the WHO. Data obtained from WHO MERS-CoV Summary Updates.

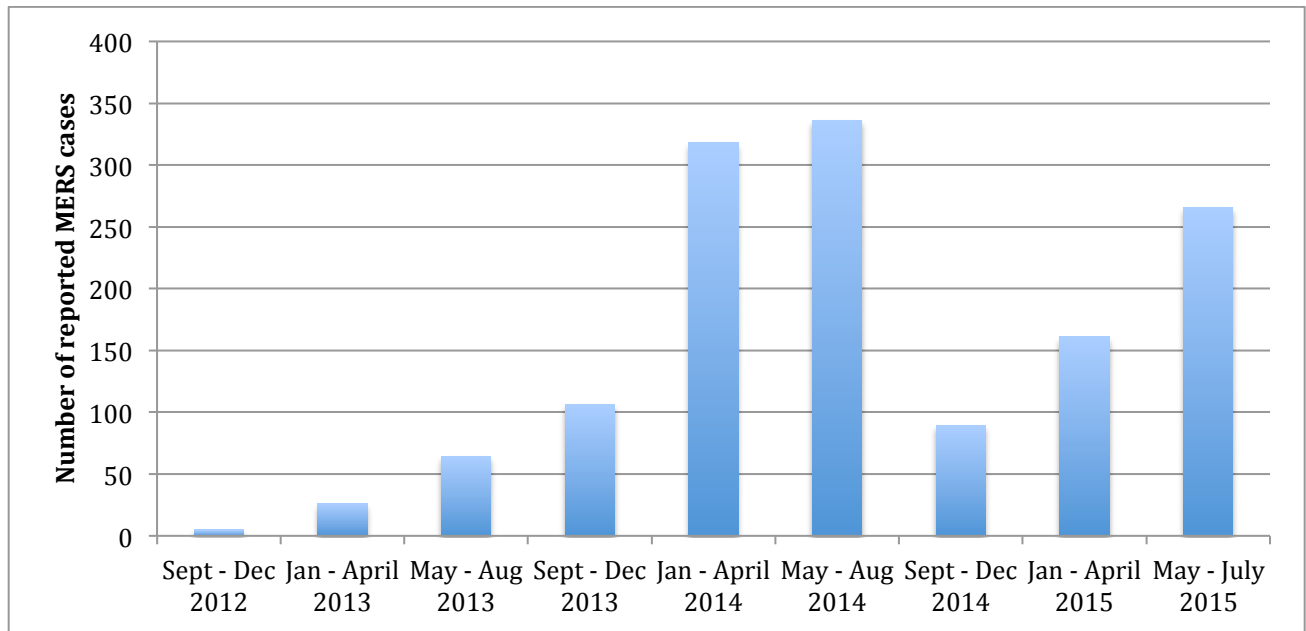


Figure 3 – Between 2012 and 25 July 2015, 1374 laboratory-confirmed cases of human infection with MERS-CoV have been reported. Overall, 65% of the gender reported cases are male and the median age is 50 years, ranging 9 months- 99 years (WHO, MERS-CoV update). The annual pilgrimage, *Hajj*, occurred during October 13-17 in 2013 and October 2-7th in 2014. As illustrated in this figure, there is a great increase in the prevalence of MERS, particularly in KSA, in the months after Hajj. In 2013-2014 this increase was almost a 6-fold increase, while during 2014-2015 this increase was nearly a 3-fold increase.