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Middle East Respiratory Syndrome Coronavirus: Current Status and Future Implications

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Abstract

In September 2012, a novel coronavirus was recognized, later renamed Middle East Respiratory Syndrome Coronavirus. This novel coronavirus belong lineage C of the genus *Beta coronavirus* included virus isolates from bats and camels. Fever, cough and shortness of breath were the common initial symptoms. On the other hand, majority of Patients were rapidly progressed to severe pneumonia and renal failure. Dromedary camels are suspected the primary reservoir for MERS CoV infection; suggesting camels to human transmission via contact with their excretion and consuming their product. However, human to human transmission occurred via the respiratory droplet or close contact. There is no specific drug or vaccine available for illnesses caused by MERS-CoV infection. Currently this novel virus is the major emerging respiratory pathogen threats of the world and capable of lethal human infections. Still new cases have been reported around the world particularly Arabian Peninsula. It has been also emerged outside Middle East countries which have not occurred before in South Korea and China since 20 May, 2015.

Keywords: MERS CoV; Emerging pathogen; New cases

Abbreviations: BtCoV-HKU4: Bat Coronavirus HKU4; BtCoV-HKU5: Bat Coronavirus HKU5; DPP4: DiPeptidyl Peptidase 4; ECDC: European Centre for Disease Prevention and Control; HACE2: Human Angiotenssion Converting Enzyme 2; HCoV-229E: Human Coronavirus 229E; HCoV-HKU1: Human Coronavirus HKU1; HCoV-NL63: Human coronavirus NL63; HCoV-OC43: Human Coronavirus OC43; HCP: HealthCare Personnel; HCW: Health Care Workers; IFNα: Interferon alpha; IFNβ: Interferon beta; MERS CoV: Middle East Respiratory Syndrome Coronavirus; NCoV: Novel Coronavirus; ORF: Open Reading Frame; RT-PCR: Reverse-Transcriptase Polymerase Chain Reaction; RNA: Ribo Nucleic Acids; SARI: Sevier Acute Respiratory Illness; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; UAE: United Arab Emirates; UK: United Kingdom; WHO: World Health Organizations

Introduction

Coronaviruses are large enveloped positive single stranded Ribonucleic acids(RNA) viruses, family of *coronaviridae* that can infect and cause disease in humans, domestic and a wide variety of animal species [1]. This virus may causes enteric, hepatic, respiratory and neurological diseases with variable severity in their hosts. Up to 2003, only two coronaviruses were identified to infect humans. Human coronavirus-229E (HCoV-229E) and human coronavirus-OC43 (HCoV-OC43) were recognized in the 1960s [2]. From 2002 to 2003, Sevier Acute Respiratory Syndrome Coronavirus (SARS-CoV) affected more than 8000 people and caused about 800 deaths around the world [3-6]. After 2003, the SARS epidemic, two additional human coronaviruses-NL63 (HCoV-NL63) in 2004 and human coronavirus-HKU1 (HCoV-HKU1) in 2005 were discovered [7-9].

A novel coronavirus was recognized in September, 2012, later renamed Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in an individual who died with an acute respiratory distress syndrome in Saudi Arabia. This novel coronavirus belong lineage C of the genus *Beta coronavirus* included virus isolates from bats and somewhat close to bat coronavirus-HKU4 (BtCoV-HKU4) and bat coronavirus-HKU5 (BtCoV-HKU5) [10]. Since September 27, 2013, case clusters have been reported Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE). A small number of cases have been also reported from Germany, Greece, Iran, Italy, Malaysia, Netherlands, Philippines, Tunisia, Turkey, Algeria, Austria, Egypt, France, United Kingdom (UK), United States (US), South Korea, China and Thailand. A total of 1374 confirmed cases have been reported from different countries, of which over 490 individuals were died [11]. The majority of patients were develop initial symptoms including fever, cough and shortness of breath. Most of Patients rapidly progressed to severe pneumonia and renal failure [12,13].

SARS-CoV caused a respiratory disease with high morbidity and mortality. However, it was not easily transmissible between human to human. Because it utilizes the receptor called human angiotensin converting enzyme 2 (hACE2), is most abundant in the lungs and less so in the upper airway [14]. Dipeptidyl peptidase 4 (DPP4) was recently identified as a MERS CoV receptor [15], highly abundant in the upper respiratory tract unlike that of SARS CoV. Therefore, MERS CoV can infect human, bat and pig cells, making it much more infectious and obviously transmittable between humans and animals [14].

The number of cases enlarged intensely in March to April, 2014 then declined dramatically in mid-May, 2014. Still new cases and deaths have been reported from Arabian Peninsula and South Korea. Therefore, the aim of this review is to compile available data on current epidemiology (morbidity and mortality, mode of transmissions, origins), clinical features, risk factors, diagnostic test, prevention and controls of MERS CoV infection.

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Epidemiology

Since April 2012, 1374 laboratory-confirmed cases of human infection with MERS-CoV have been reported to world health organization (WHO), case clusters have been reported in Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, and the UAE. A small number of cases have also been reported from Germany, Greece, Iran, Italy, Malaysia, Netherlands, Philippines, Tunisia, Turkey, Algeria, Austria, Egypt, France, UK, US, South Korean, China and Thailand. Over 490 individuals were died as shown in (Table 1). Over 85% have been documented in Saudi Arabia, including some case clusters [11]. Still new cases and deaths have been reported in Saudi Arabia, After a slow April, MERS-CoV cases in Saudi Arabia has risen [16,17]. Saudi officials have expressed great concern that when the Hajj, or pilgrimage to Mecca, these mass gatherings may have potential for imminent to amplify MERS-CoV cases and contributes to its international disseminations [18]. Since 20 May, 2015, total 172 MERS-CoV cases were reported from South Korean [19]. Most patients presented with severe acute respiratory disease requiring hospitalization and eventually required mechanical ventilation or other advanced respiratory support. The median age of the cases with known age is 48years (range, 9 month to 94 years), and 64 % of cases were male [20]. The original source of infection and mode of transmission to humans were unclear till October, 2013, whether the MERS CoV was transmitted to humans by a direct interspecies jump or it involved another intermediary animal. Van Boheemen et al and Kathryn et al have reported that this novel coronavirus (NCoV) genome closely related to bat coronavirus [10,21], indicates that it might have originated from bats, jump to humans. Another studies revealed bats considered to be a reservoir of MERS-CoV. However, it is implausible that they are the immediate source for most human cases because human contact with bats is unusual [22]. Moreover, This virus belongs lineage C of the genus *Beta coronavirus* included virus isolates from bats, most closely related to bat coronaviruses and somewhat close to BtCoV-HKU4, BtCoV-HKU5 and BtCoV/VM314/2008 in Netherland and South Africa [23-25]. Recent studies have shown dromedary camels are considered as the primary reservoir for MERS-CoV [26]. Azhar et al revealed MERS-CoV was isolated from a man from one of his camels; the full-genome sequencing confirmed that the viruses isolated from the man and his camel were identical [27]. On the other hand, Reusken et al reported Omani camels and Spanish camels had protein specific antibodies against MERS Cov spike, 100% and 14% respectively [28]. They have also identified serologic evidence for MERS CoV among dromedary camels in Ethiopia, Nigeria and Tunisia [29]. In Qatar, 2014 Antibodies to MERS-CoV were identified in serum and milk collected from 33 camels. They revealed that active virus shedding in nasal secretions and feces from camels was observed [30]. Moreover, Chu et al identified MERS-CoV in 3.6% apparently healthy dromedary camels in a slaughterhouse in Egypt. They have also detected MERS-CoV in 92% of camels from 52 of the camels out of 179 slaughterhouse workers. However, none of the workers were detected. The all positive tasted camels were imported from Sudan and Ethiopia [31].

Countries	Cases	Deaths	Case fatality rate
Saudi Arabia	1055	466	44%
Italy	1	0	0
Jordan	19	6	32%
Qatar	13	5	60%
Tunisia	3	1	33%
UK	4	3	75%
UAE	78	10	14%
Oman	5	3	60%
Iran	5	2	40%
Germany	3	1	33%
Kuwait	3	1	33%
Algeria	2	1	50%
Spain	2	0	0%
Netherland	2	0	0%
Philippines	2	0	0%
United states	2	0	0%
Greece	1	1	100%
Malaysia	1	1	100%
Turkey	1	1	100%
Yemen	1	1	100%
Austria	1	0	0%
Egypt	1	0	0%
Lebanon	1	0	0%
South Korea	186	36	18.13%%
China	1	0	0%
Thailand	1	0	0%

Table 1: MERS Cases and Deaths, April 2012 – 27 July, 2015 [CDC, 2015.]

Clustered cases in different Arabian and European countries strongly suggest that human-to-human transmission possible. In the family cluster, 3 members had contracted this infections [12]. In UK the two laboratory confirmed cases were reported, also had no contact with animals or any history of travel to the Middle East. Both appear to have contracted the infection from a family member who had recently returned from Saudi Arabia [32]. Drosten et al revealed human to human transmission during the outbreak of MERS Cov in Jeddah, Saudi Arabia. They have reported also virus shedding and virus functions did not change significantly during the outbreak. They suggested the outbreaks to have been caused by biologically unchanged viruses in association with nosocomial transmission [33]. On the other hand Assiri et al have reported that over 200 HCW contacts were identified among 217 household contacts [34]. Together, these suggest that human to- human transmission is very likely, droplet and contact transmission, is highly plausible. SARS-CoV mostly transmitted by respiratory droplets over a relatively close distance. However, direct and indirect contact with respiratory secretions, feces or animal vectors could also lead to transmission, at least under some circumstances [35,36].

Risk Factors

This novel virus can cause severe acute respiratory disease, mainly in patient with immunosuppression condition and underlying disease including diabetes, heart disease, renal failure, chronic lung disease. Moreover, history of travel in at risk countries and smoking might have considered as a risk factors of severe disease. A 45-year old Saudi man was a heavy smoker with a number of underlying chronic conditions, including a history of ischemic heart disease, type 2 diabetes, and an atrophied right kidney [25]. A 64-year-old man, also had a history of hypertension and diabetes, and had undergone renal transplantation [13]. In the family clusters one of the four members had history with hypertension, type 2 diabetes and ischemic heart disease, and two members were long term smokers[12]. The second case was in a 49-year old Qatari patient had a history of travel to Saudi Arabia [37]. A 60-year old UK resident, had travelled to Pakistan and Saudi Arabia Prior to his illness [37], and his family member had pre-existing medical condition and he died from his illness [38]. The list of at-risk countries, as defined in European Centre for Disease Prevention and Control (ECDC) rapid

risk assessment included Iraq, Israel, Jordan, Qatar, Saudi Arabia, Syria, Kuwait, Lebanon, Palestine, Oman, UAE, Yemen, Bahrain and Iran [39]. The French case definitions for possible cases were including severe febrile clinical signs or febrile diarrhea in immune-compromised persons or in those with chronic underlying conditions, returning from an at-risk country [40].

Health care workers and Patients in hospital might have considered higher risk of infection [41,42]. In spite of the recognition of few infections since September 2012, MERS- CoV has demonstrated a real potential for nosocomial transmission, and strict recommendations have to be implemented around possible cases as soon as MERS-CoV infection is suspected [43]. In May 2013, MERS-CoV infection was diagnosed in an adult male in France, who had travelled to the UAE before symptom onset. Contact tracing recognized a secondary case in 51-year-old male patient in the same hospital room [43]. Two Qatari patients were treated under strict isolation measures in the UK, no secondary cases occurred. 10 HCW who had cared for the patient were investigated and afterward developed mild respiratory disease yielded no evidence of infection [44].

Clinical Features

Most patients were experienced flu-like syndrome at the prodrome including fever, cough, chills, rigors, headache, myalgia and shortness of breath. The majority Patients rapidly progressed to severe pneumonia and renal failure. However, majority of secondary cases were asymptomatic or showed mild respiratory symptoms [12,13,34,45]. The incubation period has been extended to 2-14 days [37,41]. Most cases have required mechanical ventilation and extracorporeal membrane oxygenation. Gastrointestinal symptoms also have been reported including anorexia, nausea, vomiting, abdominal pain, and diarrhea [12,37,46].

The first reported case was in a 60-year old Saudi man. He was admitted to hospital with a 7-day history of fever, shortness of breath and cough. He died 11-days later of progressive respiratory and renal failure [45], and the fourth reported case a 70 years old Saudi man also died from acute renal failure [13,40]has reported the prodorme of two patients were included fever, chills, and myalgia in both patients, and for one member of patient, diarrhea. Both patients developed acute renal failure [13]. However, no one in the Jordanian cluster had renal failure [47]. In the family cluster, all four patients had similar symptoms at the onset of infection, included high fever, rigors, and malaise, followed by cough, myalgia, and headache. Productive cough with purulent, blood-streaked sputum and exertion dyspnea appeared early in the course of illness for two Patients, whereas it developed later in one of the four Patient. Among them one Patient progressed rapidly to severe pneumonia and hypoxia and the need for mechanical ventilation. Two of the four patients had progressed acute renal failure. Three of the four patients had gastrointestinal symptoms: anorexia, abdominal pain, and diarrhea [12]. Even though this novel coronavirus does not appear to a common cause of gastrointestinal symptoms, those complex of symptoms was also shared by patients with SARs [48,49]. Similarly SARs, Hematologic abnormalities, in particular lymphocytopenia, had been identified in patient with MERS Cov [50].

Laboratory Diagnosis

Types of specimens for testing for the presence of novel coronavirus are natural produced sputum from lower respiratory tract, nasopharyngeal aspirate, combined nose/throat swab, whole blood for virus detection, particularly in the first week of illness. Nasopharyngeal swab, tissue from biopsy or autopsy including from lung, serum for serology or virus detection: always collect paired samples if possible acute – first week of illness. Lower respiratory tract specimens (such as tracheal aspirates and Broncho alveolar lavage) appear to have the highest virus titre. Upper respiratory tract specimens are also recommended, especially when lower respiratory tract specimens cannot be collected [12,13,51].

Rapid verification of cases of novel coronavirus infection will be based on detection of unique sequences of viral RNA by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and immunofluorescence. However, antibodies against beta coronaviruses are identified to cross-react within the genus. Therefore immunofluorescence effectively limits their use to confirmatory applications [52-54].

Preventions and Controls

Currently, there is adequate information that would be needed to inform on how to prevent and control MERS CoV infection; interrupt any human to human and reservoir to human transmission. However, still inadequate information how to manage and treat human infections.

Hospital Setting

Person-to-person via respiratory route, aerosol-generating procedures were associated with "super-spreading events were considered as mode of transmissions. Therefore, droplet precautions should be added to standard precautions for any patient known or suspected to have an acute respiratory infection, including patients with suspected or confirmed infection with novel coronavirus. Airborne precautions should be used for aerosol-generating procedures, which have been consistently associated with an increased risk of pathogen transmission [55-57]. MERS-CoV has demonstrated a real potential for nosocomial transmission, and strict recommendations have to be implemented around possible cases as soon as MERS-CoV infection is suspected [43]. Recommended Personal Protective Equipment (gloves, gowns, eye and respiratory protection) should be worn by healthcare personnel upon entry into patient rooms or care areas. Upon exit from the patient room or care area, personnel protective equipment should be removed and either discarded, or for re-useable, cleaned and disinfected according to the manufacturer's reprocessing instructions. Follow standard procedures, per manufacturers' instructions or hospital policy, for disinfection and/or cleaning of environmental surfaces and equipment (textiles, laundry food utensils) are useful for controlling environmental infection [57].

Community and Personal Setting

Surveillance for cases or doubtful clusters of severe disease, with appropriate diagnostic testing; strict adherence to infection control precautions and early isolation; vigilance monitoring of contacts and rapid identification; in some instances, Consideration of quarantine to reduce movement of exposed persons [43].

Air travel and movement of infected patients between hospitals are important for dissemination of the MERS Cov, especially the former for international spread and the latter for local spread [45,58]. However, WHO has not recommended that any travel restrictions are applied with respect to this event [59]. Delay or postpone travelling when persons with febrile respiratory illnesses; Exit screening is useful for febrile respiratory illness for those leaving a country where transmission was taking place commonly; preventing or minimizing in transfer and movement of certain patients. All traveller to Arabian Peninsula

should avoid contact with dromedary camels and their secretions, and avoid drinking raw camel milk. All travellers should practise safe food and water, and personal hygiene, mainly where reservoir are present [60]. Testing should be considered for: a history of recent travel to, or residence in, the Arabian Peninsula or neighboring countries, and those with Sevier Acute Respiratory Illness (SARI) or neighboring countries; those with acute respiratory infection and a history of contact with a confirmed or probable case; HCW with SARI, who have been caring for patients with similar infections, particularly patients with travel, residence or contact history [59].

Treatments and Vaccines

Currently, there is no specific drug or vaccine available for illnesses caused by MERS-CoV. Therefore medical care is supportive and symptomatic management [61]. Several studies have shown that a variety of therapeutics inhibit MERS-CoV replication in cell culture. In part due to the lack of a small animal model, none have been tested *in vivo*. Interferon alpha (IFNα) was shown in various models to protect against SARS-CoV induced disease. MERS-CoV is also sensitive to interferon beta (IFNβ) treatment *in vitro.* Ribavirin has also been demonstrated to inhibit MERS-Cov replication [10,62,63]. On the other hand, De Wilde et al., observed FDA-approved drugs for anti-MERS CoV activity in cell culture and identified compounds such as chloroquine, chlorpromazine, loperamide, and lopinavir able to inhibit MERS-CoV [64,65].

There is no licensed vaccine to tackle MERS-CoV infection. However, one company has developed an experimental candidate MERS-CoV vaccine which is based on the major surface spike protein [66]. Almazán et al developed other candidate vaccines that are being studied a full-length infectious cDNA clone of the MERS-CoV genome in a bacterial artificial chromosome [67]. On the other hand, Song et al observed a recombinant modified vaccine Ankara vaccine expressing full-length MERS-CoV spike protein [68].

Conclusion and Recommendations

Globally, as of 30 May, 2015, 1374 MERS CoV confirmed cases and over 490 deaths were identified since the beginning of the worldwide outbreak. The numbers of cases in SAU and UAE have sharply declined since mid-May, 2014. However, both cases and deaths continue to be reported from SAU and UAE. Since 20 may, 2015 this novel virus outbreak occurred in South Korea, and they have reported total 173 cases. WHO expects that additional cases of MERS CoV infection will be reported from Arabian Peninsula and it is likely that cases will continue to be exported to other countries by tourists, travelers and migrant workers. Moreover, it is probably that cases will be emerged and cause outbreak in other countries which have not occurred before. The outbreak of MERS CoV is more limited as compared to SARS. However, the future adaptations of this novel virus in humans may potentially rise human-to-human transmission. Moreover, it may alter the virulence of the virus, causing more severe disease.

Therefore, urgent epidemiologic investigations through surveillance on environmental, animal and testing around sporadic unexplained cases are needed to find another animal reservoirs. Reviewing the outcome of the case finding around the identified cases especially new cases and HCW. Moreover, through laboratory research and applied epidemiological studies in a number of countries testing patients with unexplained severe lower respiratory tract infection; serological surveys to established protocols are significant to determining the level of global threats.

Competing Interests

The authors declare no commercial or other associations that might pose a conflict of interest.

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