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Middle East respiratory syndrome coronavirus (MERS Cov) outbreak so far exempted Sub Saharan Africa; is it good news or call for action?

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ABSTRACT

The reported cases of MERS Cov in Arabian Peninsula and sporadic cases elsewhere except in sub Saharan Africa at present is disquieting considering its initial clinical feature that mimic flu like symptoms caused by other viruses. However MERS Cov is associated with organ dysfunction and high mortality. Although the mode of transmission is still unclear, it is postulated that it spreads through close contact, possibly via respiratory route. High similarities of MERS CoV carried by humans and camels may suggest that the diseases are zoonotic. Furthermore, airborne nosocomial transmission can occur in the room shared by the patients in the hospitals. There is still the confusion of transmission through body fluids or clinical samples, including stools and a cross transmission with medical devices or hands. Currently, all known cases can be directly or indirectly linked to Middle East from where it derives its name. Cases reported outside the Middle East first developed infection in the Middle East and then were exported outside the region. Several hospital-acquired outbreaks that resulted in upsurge of MERS Cov cases in Jeddah revealed lack of systematic implementation of infection prevention and control measures to effectively control emerging infectious diseases. The causative agent is detected and identified using Enzyme Linked Immuunosorbent Assay (ELISA) and real-time polymerase chain reaction (RT-PCR) that is expensive and not readily available in hospitals located in resource poor settings such as sub Saharan Africa. Although, so far no case of MERS Cov has been reported from sub Saharan Africa, the devastating consequences of MERS epidemic will be more catastrophic if it emerges in developing nations especially in sub Saharan Africa where there are no up to date facilities for investigations and management of such cases. Against this backdrop, we review this hazardous and incurable disease believing that it would create the necessary awareness among stakeholders to prepare for 'alien'diseases like MERS Cov.

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Pilgrims all over the world visit Saudi Arabia for religious obligation (Hajj). This is a potential way this virus could be transmitted across the globe within a short span especially if an epidemic occurs during or towards the end of the hajj exercise.

INTRODUCTION

MERS is a respiratory illness caused by an emerging pathogenic viral strain belonging to group of coronaviruses. It causes a wide range of illness in humans from common cold to severe illness such as Severe Acute Respiratory Syndrome (SARS).[1] MERS first came to limelight in 2012 when a 60 year old patient presented with pneumonia, renal failure and other organs dysfunction in Saudi Arabia.[2] The causative agent was isolated and identified as a strain of coronavirus using Enzyme Linked Immunosorbent Assay (ELISA) and real-time polymerase chain reaction (RT-PCR).[3] The disease was then provisionally referred to as Middle East Respiratory

Syndrome (MERS), as most cases were reported from Saudi Arabia and other gulf states. Most of the cases reported elsewhere such as United States and Asia were traced to the Middle East.[1,4] Shortly after its characterization in 2012, the World Health Organization (WHO) "code named" the causative agent of MERS as " Novel Coronavirus 2012.[5] In May 2013, the Coronavirus study group of the International Committee on Taxonomy of Viruses adopted the official designation, the Middle East Respiratory Syndrome Coronavirus (MERS CoV).[6] As of June 19, 2015, cumulative confirmed cases of MERS stood at 1,338,with atleast 475 deaths and a case fatality of about 35.5%. Imported cases in Europe, North America, Africa, and Asia have been linked to travel to the Middle East.[7]

EPIDEMIOLOGY

Since the advent of the illness in 2012, MERS CoV out breaks occurred predominantly in the Middle East particularly in Saudi Arabia and other nations within the Arabian Peninsula. Most of the cases reported outside the region were from contacts that had either visited or worked in Middle East months or weeks preceding the illness. MERS has a high morbidity and mortality. As of April 2014 in Saudi Arabia 688 people got infected with the disease with 282 deaths and a case fatality rate of 41%.[1, 3, 7] The first confirmed case of MERS outside the shores of Middle East and Arabian Peninsula was reported on 2nd May 2014 by Centre for Disease Control and Prevention (CDC), in Indiana, United State involving a health care worker who returned a week prior to onset of his illness from Saudi Arabia in good clinical condition.[5, 7]

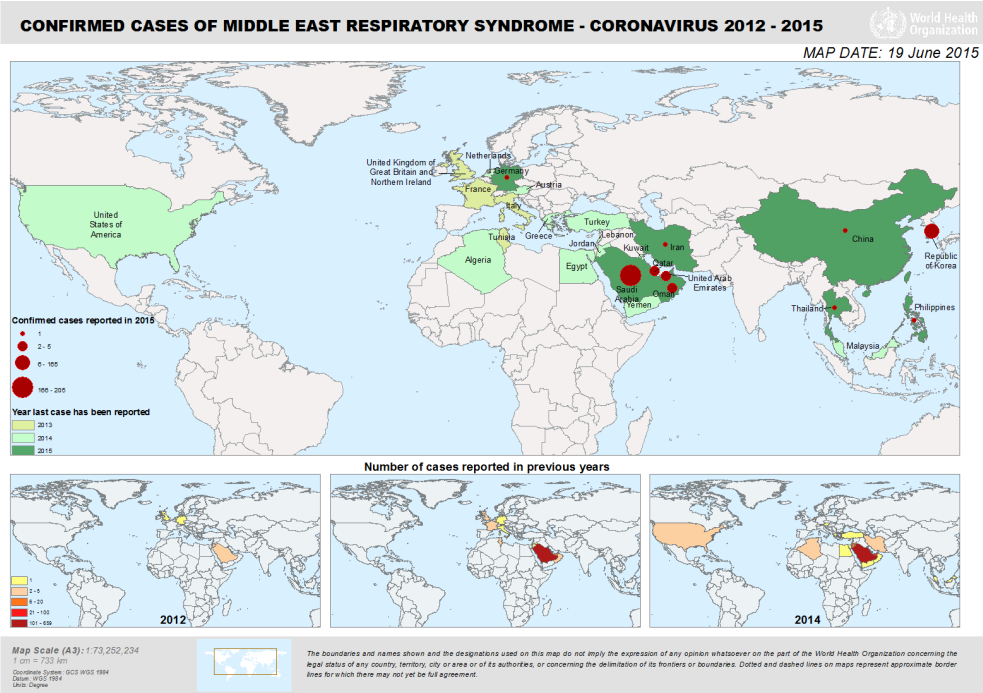

Figure 1 Location of laboratory confirmed cases of MERS-Cov infection by country of presumed exposure, March 2012 – 19th June 2015

MERS CoV disease was confirmed in May 2015 in Asia, in a South Korean National who visited Saudi Arabia not long before manifesting with features that was consistent with the disease. Although human infections are zoonotic in origin, clusters of human-to-human transmission have been reported, particularly within households or health care settings.[8-10] In an outbreak in Jeddah, Saudi Arabia, in 2014 involving multiple health care facilities, 255 laboratory-confirmed MERS cases were documented during a 2-month period, but intensified infection prevention measures in hospitals terminated that outbreak. [10, 11] Within a month of reported index case

in South Korea, 184 confirmed cases were documented with 19 deaths from the outbreak; as a result at least 6508 primary and secondary contacts of confirmed cases were quarantined to break the chain of transmission and bring the epidemic under control.[12] There were 896 laboratory-confirmed cases of MERS CoV reported to the public health authorities worldwide, which includes 357 deaths, as of 14 October 2014. MERS CoV not only affects humans but also infects animals like camels. The viruses has been isolated from Camels in Egypt and other African Countries.[13,14] The possible viral reservoirs[20] in Saudi Arabia[15,16], Qatar[17], Jordan[18], Oman[19] and UAE[20] is thought to be the Dromedaries Camel.

PEOPLE AT INCREASED RISK FOR MERS

Persons at risk includes residents of Arabian Peninsula or visitors in the region that develop fever and symptoms of respiratory illness, such as cough or shortness of breath, within 14 days after traveling from countries in or near the Arabian Peninsula.[21] The patient with fever and symptoms of respiratory illness, such as cough or shortness of breath, should be kept under surveillance for 14 days, starting from the day the contact was exposed. Patients under investigation should be quarantined, stay at home, from work or school and delay future travels to reduce the possibility of spreading the disease to others.[21-23] Close contacts of a confirmed case should be evaluated. These will include twice daily recording of temperature and documentation of symptoms such as cough and shortness of breath. Other early symptoms to watch for are chills, body aches, sore throat, headache, diarrhea, nausea/vomiting, and runny nose. Healthcare personnel who had close contact with a confirmed case while the case was ill, if not using recommended infection control precautions (e.g. appropriate use of personal protective equipment), are at increased risk of developing MERS CoV infection and should be evaluated and monitored.[21-24] Healthcare personnel should adhere to recommended infection control measures, including standard, contact, and airborne precautions, while managing symptomatic close contacts, patients under investigation, and patients who have probable or confirmed MERS CoV infections. Recommended infection control precautions should also be utilized when collecting specimens.[23,25]

TRANSMISSION

MERS CoV is transmitted through sustained contact with secretions from symptomatic person to uninfected person both in household as well as in hospital settings. Most transmission has occurred "in the circumstance of closed contact with severely ill persons in healthcare or household settings" and there is no evidence of transmission from asymptomatic patients.[26,27] Cluster size have ranged from 1 to 26 people, with an average of 2.7. MERS CoV may as well be a zoonotic disease as a study revealed high titres of neutralizing antibodies to MERS CoV in the blood serum of dromedary camels. Further study validated that the viral strain was identical to previously sequenced human isolate. It is however still unclear how the virus is transmitted from camels to humans.[20,28,29]

VIRAL TAXONOMY

MERS CoV, is a single-stranded RNA belonging to the genus beta-coronavirus which is distinct from SARS Coronavirus and the Common Cold Coronavirus. Its genome are phylogenetically classified into two clades, Clades A and B.[30-32] Initial reported causes cases of MERS were of Clade A Cluster (EMC/2012 and Jordan NZ/2012) while new cases are genetically different in general (Clade B). Coronavirus tend to be highly species-specific. Little is known about the pathogenesis of Coronavirus diseases in humans.[31,32] Infection is primarily zoonotic in nature but can be spread from human to human. Most of the known animal Coronavirus displays a tropism for epithelial cells of the respiratory or gastrointestinal tract. Coronavirus infection in humans usually remains limited to the upper respiratory tract. In contrast, the outbreak of SARS in 2003 was characterized by serious respiratory illness, including pneumonia and progressive respiratory failure. The virus can also be detected in other organs, including kidney, liver, small intestine and stool.[30,31,33]

CASE DEFINITIONS[34]

Patient under Investigation (PUI)

A person who has both clinical features and an epidemiologic risk should be considered a patient

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under investigation (PUI) based on one of the following scenarios:

Table 1 Scenarios considered as a Patient Under Investigation (PUI)

Clinical Case	Epidemiological Risk
Mild Case	
Fever and symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath)	A history of being in a healthcare facility (as a patient, worker, or visitor) within 14 days before onset of symptom in a country or territory in or near the Arabian Peninsula in which recent healthcare-associated cases of MERS have been identified.
Moderate Case	
Fever or symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath)	Close contact with a confirmed MERS case while the case was ill.
Severe Illness	
Fever *and* pneumonia or acute respiratory distress syndrome (based on clinical or radiological evidence)	A history of travel from countries in or near the Arabian Peninsula within 14 days before onset of symptom *or* close contact with a symptomatic traveler who developed fever and acute respiratory illness (not necessarily pneumonia) within 14 days after traveling from countries in or near the Arabian Peninsula – *or* – A history of being in a healthcare facility (as a patient, worker, or visitor) in the Republic of Korea within 14 days before symptom

The risk stratification and criteria can serve as guidance for testing; however, patients should be evaluated on a case-by-case based on the pattern of clinical presentation or exposure.

Confirmed Case

A confirmed case is a person with laboratory confirmation of MERS CoV infection. Confirmatory laboratory testing requires a positive Polymerase chain reaction on at least two specific genomic targets or a single positive target with sequencing on a second.[34]

Probabale Case

A probable case is a PUI with absent or inconclusive laboratory results for MERS CoV infection, but an established close contact of a laboratory-confirmed MERS CoV case. Laboratory results considered inconclusive include a positive test on a single PCR target, a positive test with an assay, or a negative test on an inadequate specimen.[34]

LABORATORY TESTING FOR MERS CoV

CDC advocates a two-phase approach for serology testing, using ELIZA and IFA assay and/or microneutralization assay.[35] Serology tests detect antibodies to MERS-CoV in those that have been exposed to the virus. The presence of antibodies to MERS-CoV indicates previous infection with the virus and an immune response. Evidence to date suggests there may be a broader range of MERS disease than was initially thought.[35] Reports have shown PCR-positive cohorts without MERS symptoms; it is however yet to be determined if such individuals can spread MERS-CoV.[36] Voluntary testing of blood samples from close contacts of people known to have MERS is therefore advocated.[36,37] MERS-CoV serology tests are useful for surveillance or investigational purposes but limited for diagnostic purposes they are tools developed in response to the MERS-CoV outbreak.[35,37] IFA assay and/or micro neutralization assay increases the sensitivity of serological test. Immunofluorescence assay (IFA), detects specific antibodies against MERS-CoV, if present in the person's blood, attach to virus-infected cells fixed on a glass slide. The micro neutralization assay is a highly specific test that measures neutralizing antibodies or antibodies that can neutralize virus.[38] This method is considered the gold standard for detection of specific antibodies in serum samples.

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However, unlike ELISA and IFA, the micro neutralization assay is not a rapid test, it is labor-intensive and time-consuming. A clinical sample is determined positive if it is reactive by ELISA, indeterminate by IFA, and positive by micro neutralization. Conversely a clinical sample is negative if it is positive by ELISA, indeterminate or negative by IFA, and negative by microneutralization.[3, 38] Molecular tests are used to diagnose active infection (presence of MERS-CoV) in those thought to be infected with MERS-CoV based on their clinical symptoms and established links to places where MERS has been reported. Real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays are molecular tests that detect viral RNA in clinical samples.[3, 37, 38]

CDC's current case definition for laboratory confirmation of MERS-CoV infection requires either a positive rRT-PCR result for at least two specific genomic targets, or a single positive target with sequencing of a second target. The success of rR T-PCR testing depends on several factors, including the experience and expertise of laboratory personnel, laboratory environment (e.g., avoidance of contamination), and the type and condition of specimens being tested. For rRT-PCR assay, CDC recommends collecting multiple specimens, including lower (broncho-alveolar lavage, sputum and tracheal aspirates) and upper (e.g., nasopharyngeal and oropharyngeal swabs) respiratory samples, serum, and stool specimens. Patient under investigation are considered negative for active MERS-CoV infection if rRT-PCR test is negative on the recommended specimens. Since a single negative result does not completely rule out MERS-CoV infection, in some circumstances additional specimens may be tested. CDC considers a known MERS patient to be negative for active MERS-CoV infection following two consecutive negative rRT-PCR tests on all specimens. Information is limited about MERS-CoV and how the virus is spread. As research into molecular biology of MERS-CoV advances, the approach to conducting these types of laboratory tests might change.[3, 35-38]

TREATMENT

Currently there is no effective treatment against MERS-CoV .However, conservative management has helped in reducing morbidity and mortality. Combination of interferon (IFN)-alpha-2b and ribavirin appears to limit viral replication in cell culture and animal experiments.[39] Other experimental therapies include the use of convalescent plasma, monoclonal antibodies, and inhibition of the viral protease.[40]

VACCINES

There are candidate's vaccines that may be effective against MERS-CoV infection, although they are still at experimental stages. A vaccine based on the major surface spike protein developed through recombinant nanoparticle technology appears promising.[41] Other candidate vaccines studied include a full-length infectious cDNAclone of the MERS-CoVgenome in a bacterial artificial chromosome[42] and a recombinant Modified Vaccine Ankara (MVA) vaccine expressing full-length MERS-CoVspike protein.[43]

PREVENTION

The CDC routinely advises protections from respiratory illnesses through basic personal hygiene and preventive actions such as: [44]

1) Washing of hands often with soap and water for 20 seconds, and help young children do the same, alternatively where there is no soap, use an alcohol-based hand sanitizer.
2) Covering of nose and mouth with a tissue when coughing or sneezing, then disposing the tissue in the trash or waste basket.
3) Avoid touching eyes, nose and mouth with unwashed hands.
4) Avoid personal contact, such as kissing, or sharing cups or eating utensils, with ill people.
5) Clean and disinfect frequently touched surfaces and objects, such as doorknobs.

CONCLUSION AND RECOMMENDATIONS

Although Middle East is believed to be the hub of MERS-CoV infection, it has shown potential of being exported to other countries by tourists, travelers, guest workers or pilgrims who might acquire infection following exposure to an animal or human

source. Given the deadly and virulent nature of MERS-CoV infection, further research into its transmission pattern among humans, animals to humans and vice versa, environmental exposure especially in health care setting is imperative. Other measure will include systemic implementation of infection prevention and prevention measures, international collaboration and surveillance. Until the aforementioned measures are strengthened especially in sub Saharan Africa with dearth of both expertise and facilities for infection prevention and control, the region may not fortunate from being exempted from future outbreak of this infection.

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