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Major Article

Unusual presentation of Middle East respiratory syndrome coronavirus leading to a large outbreak in Riyadh during 2017

Hala Amer MD, MPH, PhD, CIC ^{a,b}, Abdulrahman S. Alqahtani MD ^c, Hind Alzoman MD ^a, Nawfal Algerian MD ^{d,e}, Ziad A. Memish MD, FRCPC, FACP ^{d,f,g,*}^a Infection Control Department, King Saud Medical City, Ministry of Health, Riyadh, Saudi Arabia^b Department of Community Medicine, National Research Center, Egypt^c Medical Affairs, King Saud Medical City, Ministry of Health, Riyadh, Saudi Arabia^d Department of Emergency Medicine, King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia^e College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia^f College of Medicine, Alfaisal University, Prince Mohammed Bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia^g Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA

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Background: The hallmark of Middle East respiratory syndrome coronavirus (MERS-CoV) disease is the ability to cause major health care-associated nosocomial outbreaks with superspreading events leading to massive numbers of cases and excessive morbidity and mortality. In this report, we describe a patient who presented with acute renal failure requiring hemodialysis and became a MERS-CoV superspreader, igniting a recent multihospital outbreak in Riyadh.

Material and Results: Between May 31 and June 15, 2017, 44 cases of MERS-CoV infection were reported from 3 simultaneous clusters from 3 health care facilities in Riyadh, Saudi Arabia, including 11 fatal cases. Out of the total reported cases, 29 cases were reported from King Saud Medical City. The cluster at King Saud Medical City was ignited by a single superspreader patient who presented with acute renal failure. After 14 hours in the open area of the emergency department and 2 hemodialysis sessions he was diagnosed with MERS-CoV. One hundred twenty contacts who had direct unprotected exposure were screened. Among those contacts, 9 out of 107 health care workers (5 nurses, 3 physicians, and 1 paramedic) and 7 out of 13 patients tested positive for MERS-CoV.

Conclusions: This hospital outbreak demonstrated the difficulties in diagnosing pneumonia in patients with renal and cardiac failure, which leads to delayed suspicion of MERS-CoV and hence delay in applying the proper infection control procedures. In MERS-CoV endemic countries there is an urgent need for developing rapid point-of-care testing that would assist emergency department staff in triaging suspected cases of MERS-CoV to ensure timely isolation and management of their primary illness and prevent major MERS-CoV outbreaks.

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Middle East respiratory syndrome Coronavirus (MERS-CoV) is a viral respiratory illness caused by a novel betacoronavirus that was first identified in the Kingdom of Saudi Arabia (KSA) in a businessman from Bisha who presented to Sulaiman Faqeeh Hospital in Jeddah with severe pneumonia and eventually died within 2 weeks

* Address correspondence to Ziad A. Memish, MD, FRCPC, FACP, College of Medicine, Alfaisal University, Infectious Diseases and Research Department, Prince Mohammed Bin Abdulaziz Hospital, Ministry of Health, P.O. Box 54146, Riyadh, 11514 Saudi Arabia.

E-mail address: zmemish@yahoo.com (Z.A. Memish).

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of admission during July 2012.¹ Since then, and as of January 28, 2018, the World Health Organization has been notified of 2,123 laboratory-confirmed cases of infection with MERS-CoV, with at least 740 deaths in 27 countries.² More than 85% of reported cases to date have been from countries of the Eastern Mediterranean region, with KSA carrying the major burden of outbreaks (n = 1,527 cases, including 624 deaths [40% of cases]).² The hallmark of this disease is the wide spectrum of presentation, ranging from completely asymptomatic to small family clusters of mild disease to major health care-associated nosocomial outbreaks with superspreading events leading to massive numbers of cases and excessive morbidity and mortality.³⁻⁵ Superspreading is a phenomenon well described in the

public health literature that refers to the ability of certain individuals to infect a disproportionately large number of secondary patients relative to a typical infectious individual. In MERS-CoV, previous reports have attributed this phenomenon to either a very high viral load in the upper airway secretions of the index case (usually related to exposure to patients in the later stage of disease; that is, the second week of illness), excessive cough or aerosol-generating procedures, or/and delayed diagnosis and improper isolation of the index case due to other illnesses known to mask MERS-CoV clinical presentation (eg, chronic renal failure and chronic heart disease).⁶⁻⁹ In this report, we describe a patient who presented with acute renal failure requiring hemodialysis and became a MERS-CoV superspreader igniting a recent multihospital outbreak in Riyadh. We describe the outbreak at King Saud Medical City (KSMC).

OUTBREAK DETAILS

Between May 31 and June 15, 2017, 44 cases of MERS-CoV infection were reported in Riyadh, Saudi Arabia, including 11 fatal cases. Out of the total reported cases from the 3 simultaneous clusters from 3 health care facilities, 29 cases were reported from KSMC. The cluster at KSMC was ignited by a 46-year-old Yemeni man who presented to the emergency department (ED) through ambulance with cough, shortness of breath, and history of diarrhea for the past 2 days. He was afebrile with a temperature of 36.4°C. He denied any history of contact with camels or a MERS-CoV-positive patient. With this profile, his visual triage score was 5, which indicates the need for assessment for MERS-CoV suspicion. Visual triage scoring is a triaging system proposed by the Saudi Ministry of Health guidelines for management of patients with suspected MERS-CoV. It aims to filter patients who need to be assessed clinically, radiologically, for MERS-CoV suspicion and laboratory screening. The patient in this case had known diabetes and hypertension with a history of chronic bronchial asthma. Per the 5-level triaging system used at our ED, he was determined to be at level 2—in need of critical management (Canadian Triage and Acuity Scale¹⁰). On admission, his oxygen saturation was 93% on room air. His initial chest radiograph showed changes suggestive of pulmonary edema. The patient's initial bloodwork showed evidence of acute renal failure that required urgent hemodialysis. His clinical presentation and radiology findings were attributed to acute renal failure and the treating team did not consider MERS-CoV. The patient did not have any diarrhea symptoms throughout the course of his illness, but reported a 2-day history of diarrhea before admission. The patient spent more than 14 hours in the crowded open multibed ED where ventilation was neutral, through a central package air conditioning system (6 of 18 open recovery cubicles have a high-efficiency particulate air filter), after which he was shifted to a medical inpatient ward where he shared a normal pressure and ventilation parameters room with 4 other patients. Despite 2 hemodialysis sessions, his pulmonary edema decreased without remarkable improvement in his chest symptoms. After 2 days of admission, the patient experienced respiratory distress and hypoxia requiring intubation and admission to our intensive care unit where the team suspected MERS-CoV. The patient was then shifted to a negative pressure isolation critical care room with more than 12 air exchanges per hour. A nasopharyngeal swab was collected and tested at the Riyadh regional laboratory using real-time reverse-transcription polymerase chain reaction and found to be positive for MERS-CoV with positive results for both Orf1a and UP gene assays with cycle threshold (CT) value of 17 and the sample was negative for influenza. Mapping of the patient's journey inside the health care facility was carried out and dates and duration spent in different settings were documented (Fig 1). One hundred twenty contacts who had direct, unprotected exposure to the index patient were screened. Among those contacts, 107 were

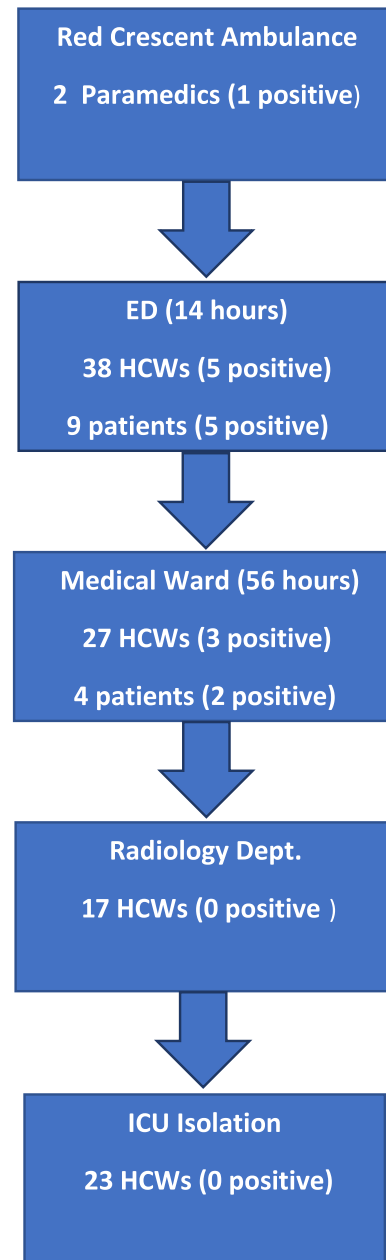


Fig 1. Mapping of the patient's journey with numbers of contacts. ED, emergency department; HCW, health care worker, ICU, intensive care unit.

health care workers among whom 9 tested positive for MERS-CoV. Five were nurses, 3 were physicians and 1 was a Saudi Red Crescent Authority paramedic who transferred the patient in the ambulance to the ED of KSMC. The other 13 contacts were patients, among whom 7 tested positive for MERS-CoV. One of those positive patients were reported in other health care facilities and linked to exposure history at KSMC. The spider chart in (Fig 2) represents the MERS-CoV outbreak; this reported superspreader patient (labeled "MA" in the center of the chart) was the index case for the outbreak.

The patient was transferred in stable condition to the allocated MERS-CoV regional reference center Prince Mohammed Bin Abdulaziz Hospital on the second day of his confirmed positive MERS-CoV status. During his stay at Prince Mohammed Bin Abdulaziz Hospital, screening for MERS-CoV was repeated twice, 1 week apart

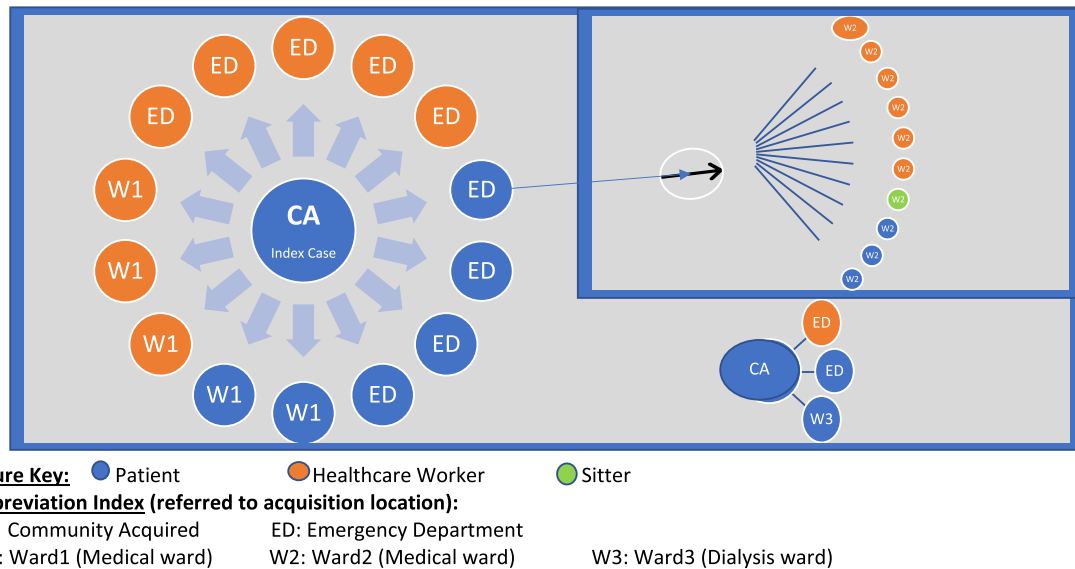


Fig 2. Spider chart of Middle East respiratory syndrome coronavirus outbreak.

Table 1

Middle East respiratory syndrome coronavirus testing follow-up for the reported index case

Date of report	Result	ORF gene value
May 31, 2017	Positive	17
June 8, 2017	Positive	15
June 16, 2017	Positive	28

(results are shown in Table 1). The patient died after 22 days of hospitalization.

DISCUSSION

The outbreak at KSMC required 30 full days to be brought under control. The infection control measures applied included decreasing patient load (through downsizing the acceptance in the ED, maintaining low elective services, minimizing outpatient visit rates, limiting inpatient admissions, encouraging patients' discharge, not allowing visitors after visiting hours, and minimizing visiting hours). High vigilance by infection control staff focusing on early detection and quarantining of any suspected cases (through extensive contact tracing, properly triaging all patients upon admission, consistent monitoring of any emerging acute respiratory illness among inpatients and health care workers, allocation of more single rooms inside the facility and the staff dormitory, and extending the services of the virology laboratory to get timely results). Lastly, extensive education on infection control practices and monitoring health care workers' adherence and considering public and health care worker reassurance by keeping transparency of published reports and launching the hotline telephone number to receive health care worker's inquiries and provide needed advice by infection control professionals in the facility. Moreover, applying travel restriction during the 2-week monitoring period for any person—health care worker or patient—with a history of exposure to a confirmed MERS-CoV case.

In retrospect, 2 key issues led to this hospital outbreak. The difficulties in diagnosing pneumonia in a patient with renal failure without fever, which is often diagnosed as volume overload, led to delayed suspicion of MERS-CoV and not applying the proper infection control procedures, including the isolation of a patient who had very high viral load of the virus in his respiratory secretions (low

cycle threshold value). Similar incidents among renal and cardiac patients have led to several outbreaks, including the Alhassa cluster in 2013,³ the King Fahad hospital outbreak in Jeddah in 2014,¹¹ and the most recent clusters in King Abdulaziz Medical City in Riyadh and South Korea in 2015.^{12,13} Similarly, in a major outbreak of severe acute respiratory syndrome (SARS) coronavirus infection in Hong Kong, a patient with renal failure on hemodialysis was responsible for a superspreading event at the Amoy Garden through diarrhea with very high viral load and prolonged viral shedding.¹⁴⁻¹⁶ Our index patient in this report had a 2-day history of diarrhea before presentation but had no diarrhea during his course of illness and we could not document prolonged viral shedding due to his early death. EDs have been implicated in the initiation of most of the reported outbreaks and many unreported ones. More attention is needed to address the triage system in EDs to make them impervious to MERS-CoV until a preventative vaccine or effective therapeutic agents are found for MERS-CoV.¹⁷ Until then, early suspicion and rapid identification of patients at high risk for MERS-CoV can only be achieved using effective, highly sensitive and specific point-of-care testing in EDs.¹⁸⁻²¹

Superspreading, which was the hallmark of SARS, is defined as a single index case infecting ≥ 5 cases.^{22,23} Although higher viral load was always suspected to be a contributing factor, most of the studies focused on host factors referring to the severity of systemic symptoms and the susceptibility of the host, the virus, and its infectiousness and the environment, including the number of contacts and poor infection control practices.²⁴ Higher virus load for SARS and MERS have been reported to be associated with lower oxygen saturation, diarrhea, hepatic dysfunction, and the need for mechanical ventilation.²² Other infectious diseases like Ebola virus disease, measles, tuberculosis, and influenza have superspreading potential, as well.²²

Some weaknesses of this investigation include the lack of viral sequences on the cluster to ensure lack of viral mutation, which would make the virus more infectious. In addition, no viral sequences of MERS-CoV have been published during the past 2 years from KSA or abroad. Although the number of large health care facility outbreaks have declined over the years in KSA, in every large outbreak of MERS-CoV over the past 5 years, including the large outbreak in Alhassa in 2013, King Fahad Hospital in Jeddah in 2014, and the South Korea outbreak and King Abdulaziz Medical City

Hospital in Riyadh in 2016, no data demonstrated that the virus has become more virulent. In this outbreak, like all the previously mentioned outbreaks, a clear breach of infection control standards was the source of the outbreak and rapid application of the known infection control standards led to the resolution of the cluster, which makes virus transformation very unlikely. Although many outbreaks occurred in KSA and elsewhere, the link to CT value and superspreading has not been clearly identified to be a statistically significant risk factor.⁹ In addition, over the past 5 years, many smaller outbreaks have not been reported in peer-reviewed journals, highlighting the simple fact the patients presenting with MERS-CoV who have underlying chronic renal failure and heart disease are too often missed by health care workers early in their presentation. Continuing education and training of the large, rapidly changing expatriate health care worker population in KSA is needed to stop future outbreaks. Therefore, this report is to remind and stress to health care workers in KSA and globally the importance of applying simple infection control measures to prevent the spread of MERS-CoV.

Special high vigilance and a low level of suspicion for MERS-CoV among patients presenting with congestive heart failure among cardiac and renal failure patients has been suggested and this report confirms the need to rule out MERS-CoV in such patients when indicated.^{25,26} A high level of suspicion in the large population in KSA with this disease will add extra burden on ED physicians in their challenging task of deciphering MERS-CoV from other viral etiologies, in addition to delaying the usually urgent care needed in such a population due to the need for isolation and awaiting testing results, which sometimes takes up to 72 hours. There is no question that in countries like KSA where MERS-CoV is considered endemic, there is an urgent need for investing in research and validation of rapid point-of-care testing that would be easily used by ED triage teams to ensure timely isolation and management of a patient's primary illness and prevent major MERS-CoV outbreaks.

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