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## The first clusters of Middle East respiratory syndrome coronavirus in Oman: Time to act

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### ABSTRACT

**Introduction:** Middle East respiratory syndrome coronavirus (MERS-CoV), is an emerging infectious disease of growing global importance. This review describes the latest MERS-CoV clusters and the first cases of nosocomial transmission within health care facilities in Oman. We have highlighted lessons learned and proposed steps to prevent healthcare-associated infections.

**Methods:** A descriptive analysis of MERS-CoV cases was conducted between January 23 and February 16, 2019. The data from officials and other published sources used.

**Results:** Thirteen laboratory-confirmed cases of MERS-CoV were reported from three simultaneous clusters from two governorates without an epidemiological link between the clusters. Two clusters were reported from North Al Batinah Governorate, with nine cases (69%) and 1 cluster from South Ash Sharqiyah Governorate with four cases (31%). In total, four deaths were reported (case fatality rate 31%). Four cases (31%) reported were household contacts from the first cluster, 3 (23%) were nosocomial transmission in health care facilities (two for first and one from the second cluster) and 7 (54%) were community-acquired cases.

**Conclusions:** The first local clusters of MERS-CoV reported with evidence suggestive of healthcare and household-associated transmission. Early diagnosis and strict implementation of infection control measures remain fundamental in preventing and managing MERS-CoV infection.

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### Introduction

The Middle East respiratory syndrome (MERS) is caused by a zoonotic respiratory pathogen, coronavirus, which causes a non-specific respiratory illness that was first reported in Saudi Arabia in 2012 [1]. Following reports of MERS-CoV infections from the Ara-

bian Peninsula, cases were likewise reported from travelers visiting other continents [2]. Dromedary camels, in which the virus does not cause disease, are believed to be the major host reservoir [3,4]. The virus can spread from dromedary camels to humans through direct or indirect contact, causing significant morbidity and mortality [4]. The clinical spectrum ranges from asymptomatic illness to septic shock, multi-organ failure and death in severe cases [5]. Evidence suggests that the average incubation period in an infected human host is 5.5–6.5 days with a maximum of 10–14 days [6].

As of the end of December 2019, a total of 2499 laboratory-confirmed human cases of MERS-CoV from 27 countries have been reported, with 861 associated deaths (fatality rate of 34.2%). Ninety

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percent of the cases have been reported from countries of the Eastern Mediterranean Region (EMR) by WHO (2). Eighty-four percent (1106) of total global cases were reported from Saudi Arabia and resulted in at least 770 related deaths with a case fatality rate of close to 37.2% [2].

Limited human-to-human transmission of MERS-CoV has been described mostly in health care setting [2,6–13] and small household clusters of community-acquired cases, including a family cluster of mild disease [14–19]. Larger outbreaks have been reported in healthcare settings, which have led to multiple chains of limited transmission, as a result of contact with index cases or inadequate infection prevention and control measures causing excessive morbidity and mortality in several countries [2,5–11]. Currently, there is no evidence of sustained human-to-human transmission [2].

In Oman, the first laboratory-confirmed case of MERS-CoV was reported in June 2013 [6,8,20–22]. Sporadic cases were then reported until March 2018, with limited human-to-human transmission and secondary transmission. No secondary cases were reported among health care workers (HCWs).

In 2013, a countrywide MERS survey among dromedary camels showed MERS-CoV neutralising antibodies were detected in all (50) surveyed camels [23]. In addition, phylogenetic analysis and high MERS-CoV viral loads in dromedary camels suggested local zoonotic transmission through the respiratory route. However, MERS-CoV isolates from camels did not have sequences closely related to MERS-CoV strains recovered from human cases [24].

This review describes the latest MERS-CoV clusters and the first cases of nosocomial transmission within health care facilities in Oman. We have highlighted lessons learned and proposed steps to prevent future community and healthcare-associated infections.

## Methodology

Between January 23 and February 16, 2019, a review of the MERS-CoV data were collected from the following sources: the MOH Communicable Diseases Weekly Surveillance Updates, WHO/EMRO Weekly Epidemiological Monitor for MERS cluster in Oman [25]. The information collected included baseline demographic characteristics (time, place, gender, age, residency and nationality), risk factors including history of previous exposure to camels, co-morbidities, laboratory investigations, clinical management and outcomes including mortality rates. A comprehensive investigation of close contacts, including health care personnel who may have been exposed to patients infected with MERS-CoV was conducted. Close contacts were defined as any person who provided care for the patient, including a healthcare worker or family member, or had another similarly close physical contact, for example, someone with whom the patient had resided or visited [26]. Close contacts of confirmed or probable cases were identified and monitored for the appearance of respiratory symptoms for 14 days after their last exposure to the confirmed or suspected case, while the index case remained symptomatic. Any contact that became ill during that period of time was tested for MERS-CoV using real-time polymerase chain reaction (RT-PCR) [27] to detect viral RNA from patient blood samples. RT-PCR was also used to test the camels, starting with RNA extracted from nasal and conjunctive swabs. The ethical approval was obtained based on Ministry of Health regulation.

## Results

### Cluster description

Between January 23 and February 16, 2019, a total of 13 human cases of laboratory-confirmed MERS-CoV were reported in Oman

[Fig. 1]. Nine cases (69%) were residents of North Al Batinah, and four cases (31%) were from South Ash Sharqiyah Governorates (23) [Fig. 2]. Eleven cases (85%) were Omani nationals.

The first cluster of five females (Four from the same family), reported on January 23 and 28, 2019, were residents of North Al Batinah (Fig. 2). Their median age was  $42 \pm$  SD 10.8 years (range: 30–59 years). Three of the five cases were probably secondary cases, exposed to the index case who reported a history of direct contact with camels [28]. These secondary cases had neither a recent history of travel outside of Oman nor a history of a recent hospitalization or direct contact with camels. There is also a history of sleeping in an index case-patient's room and spending time in the same room and assisting the possible index case during his illness. Three cases (60%) were admitted to ICU [Table 1]. Two of the five cases died (Case fatality rate: 40%).

The second and third clusters were reported between January 27 and February 12, 2019, from North Al Batinah and South Ash Sharqiyah Governorates each reported 4 additional cases (Eight totals). These two additional clustered cases had no epidemiological link to the previous cluster. The median age was  $55 \pm$  SD 17.5 years (range: 30–77 years), with an equal number of males and females. Two cases (50%) from South Ash Sharqiyah and one case (25%) from North Al Batinah were admitted to ICU [Table 1]. In total, uncontrolled diabetes mellitus (Five cases, 38%), hypertension (Six cases, 46%) and ischemic heart diseases (Two cases, 15%) were the most common co-morbidities and were reported in all clusters. Three of the four cases (75%) had septic shock, and bronchopneumonia was the most common cause of death. The overall case-fatality rate was 4 (31%) [Table 1].

Eleven cases (85%) presented with the typical MERS-CoV symptoms, including fever, cough, and shortness of breath. Four cases (31%) presented with gastrointestinal symptoms and diarrhoea. A total of 2 cases (15%) were asymptomatic and 4 (30%) had a mild illness. The two asymptomatic cases were health care workers detected by contact screening. The median time from symptom onset to hospitalization was 4 days (range 1–13 days) and from hospitalization to case notification was 12 days (range 1–22 days).

The two index cases (15%) from North Al Batinah and South Ash Sharqiyah Governorates had a history of contact with camels, and 6 of the 13 cases (46%) had a history of contact with MERS-CoV patients either within the household or nosocomial [Fig. 3]. Community-acquired cases were reported during the winter month of January with a peak number of cases (46%) reported on January 11 [Fig. 2].

Laboratory investigations revealed that 5 cases (38%) presented with anaemia, and 2 cases and 1 case (15% and 8%) with leukopenia and thrombocytopenia, respectively. C-reactive protein was high in all except 1 patient. Alanine aminotransferase was elevated in 3 cases (23%). Hyponatremia was observed in 8 cases (61%) and creatinine was elevated in 4 cases (31%) [Table 1]. Three cases (23%) had co-infection with other respiratory viruses and 6 cases (46%) had bacterial infections. The antibiotics and antiviral drugs used to manage the patients during hospitalization has been shown in [Table 2].

### Contact and active case tracing

A total of 761 close contacts from the clusters were identified and screened. In South Ash Sharqia, 294 contacts were screened, of which 151 (51%) were HCWs and 24 (8%) were close household contacts. In North Al Batinah, 467 contacts, 234 (50%) HCWs, and 114 (24%) household contacts were screened. Contacts were monitored for 14 days from their final date of exposure. MERS-CoV was not detected by RT-PCR, except in two HCWs, one from each Governorate. These HCWs were a female nurse and a female

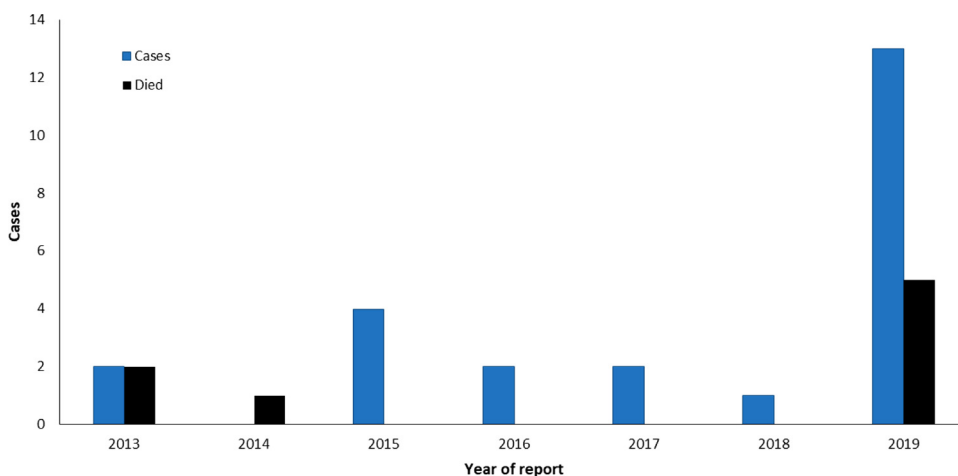


Fig. 1. MERS-CoV notified cases and death by year of report, Oman, 2013-2019.

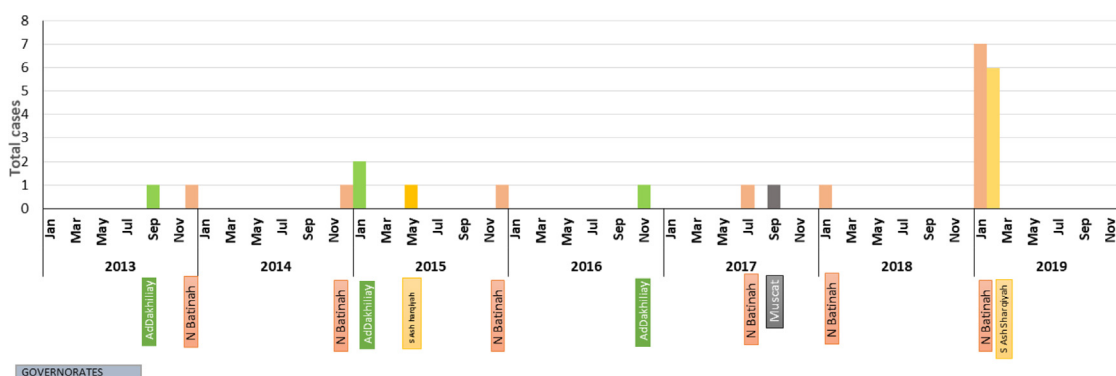


Fig. 2. MERS-CoV cases, by month of report and Governorate (province), Oman, 2013-2019.

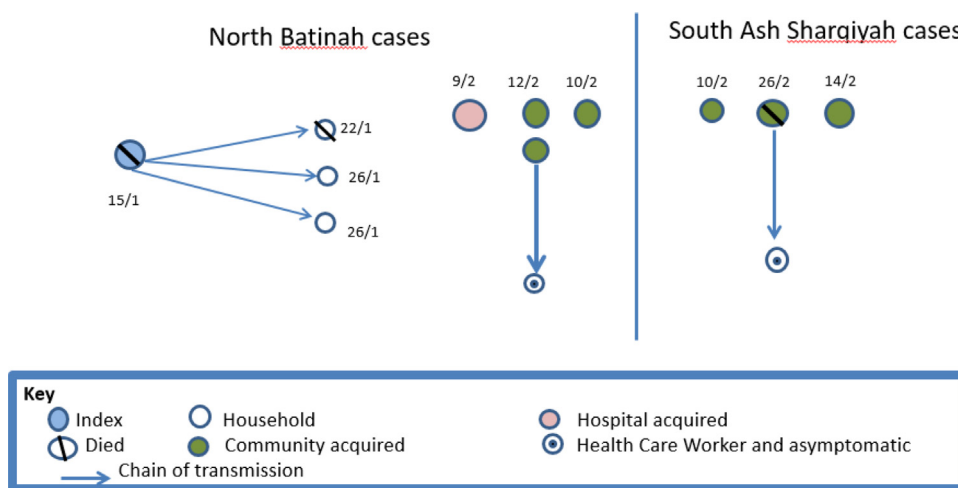


Fig. 3. MERS-CoV confirmed cases by date of onset of symptoms, type of case, and Governorate, Oman, 2019.

physician. One had a single encounter with the patient during intubation, and the other was involved in providing care for a patient for over a week in a high-dependency ward. Both were asymptomatic. Screening for MERS-CoV was not repeated if the first sample tested negative. Almost all other HCWs who attended the MERS-CoV patients were females, aged between 30 and 40 years. None of these HCWs exhibited co-morbidities.

Two cases (15%) from South Ash Sharqia rapidly progressed to acute respiratory distress syndrome (ARDS), with a median of 3 days from hospitalization to ICU admission. At the time of submit-

ting this manuscript, there are no epidemiological data to suggest further propagation of the outbreak.

The index cases' source of exposure was investigated by the Oman Ministry of Agriculture (MOA) less than a week after case notification and a total of 86 camels were tested (nasal and conjunctival swabs) in the vicinity and found to be negative for the virus. None of the camels in North Al Batinah Governorate tested positive for the virus and only one camel in South Ash Sharqiyah Governorate tested positive.

**Table 1**  
Demographic and clinical characteristics of clusters MERS-CoV cases, Oman, 2019.

Characteristics	SouthAsh Sharquia (1 cluster) (n = 4)	North Al Batinah (2 clusters) (n = 9)	Total, n (%) (n = 13)
Age (years)			
30–40	1	3	4 (30)
40–50	1	1	2 (15)
50–60	0	1	1 (8)
≥60	2	4	6 (46)
Gender			
Male	2	7	9 (69)
Female	2	2	4 (31)
Health Care Workers infected with MERS-CoV	1	1	2 (15)
Patients admitted to ICU			
Yes	3	4	7 (53)
No	1	5	6 (47)
Average number of days admitted	15 days (Range 1–99days)		
Clinical outcome			
Survived	2	7	9 (69)
Died	2	2	4 (31)
Possible cause of death			
Bronchopneumonia with Septic shock	1		1/4* (25)
Septic shock	1		1/4* (25)
Bronchopeumonia		2	2/4* (50)
Multi-organ failure		1	1/4* (25)
Heart failure	1		1/4* (25)
Comorbidities			
DM	2	3	5 (38)
HTN	1	5	6 (46)
IHD	1	1	2 (15)
Chronic Kidney disease	1	1	2 (15)
Chronic lung disease			
Others	Cardiomyopathy CVA, Dementia, Alzheimer, Asthma		7 (53)
Exposure to:			
Camels	1	1	2 (15)
MERS-CoV cases (Household)	3		3 (23)
Hospital-acquired	2	1	3 (23)
Community-acquired	3	2	5 (38)
General clinical characteristics			
Fever >38 °C	2	2	4 (31)
Malaise	1	2	3 (23)
Confusion	1		1 (7)
Rhinorrhea	1		1 (7)
Sore throat	1		1 (7)
Haemoptysis	1		1 (7)
Pulmonary clinical characteristics			
Cough	1	7	8 (62)
Shortness of breath	1	2	3 (23)
Pneumonia	1	1	2 (15)
Extra-pulmonary clinical characteristics			
Abdominal pain		3	3 (23)
Nausea and vomiting	2	3	5 (38)
Diarrhea		1	1 (7)
Acute renal failure		1	1 (7)
Blood analysis			
Leukopenia	2 (15)		
Thrombocytopenia	1 (7)		
Anaemia	2 (15)		
c-reactive protein	12 (92)		
Alanine Aminotrasferase	3 (23)		
Elevetaed creatinine	4 (31)		
Hyponatremia	8 (61)		

\* Total deaths.

## Discussion

To the best of our knowledge, this is the first healthcare and household-associated transmission cluster of MERS-CoV infection in the country. The current three clusters are different than what has been previously reported: the total number of cases in a single month exceeds the total number of cases from the previous 6 years [3]. It would have been advantageous in order to confirm the household transmission to perform a whole-genome sequencing of the virus isolated from individuals and analyze the sera from close

contacts to cluster cases at 3–4 weeks after contact with index case [29].

In Oman, sporadic MERS-CoV cases have been reported [21–23,30,31] with limited human-to-human transmission until the time of this clustered outbreak. Most of the community-acquired cases were reported during the winter month of January 2019, which is consistent with data from other countries in the EMR [32]. No healthcare-associated MERS-CoV infections have been previously reported. This has been mainly attributed to an effective triage system and HCWs awareness [33].

**Table 2**  
Characteristic of confirmed MERs-CoV Cases, Oman, 2019.

No	Sex	Age	Nationality	Symptoms	Co-morbidities	Exposure camels/ Camel products Y/N	Type of contact	Date of onset of symptoms	Date of admission	Date of Isolation	Duration of hospitalization	Intubation Y/N	Antibiotics received on admission	Antibiotics received during hospitalization	Organisms grown during hospitalization	Outcome
1	F	43	Omani	Headaches, Nausea abdominal pain	HTN	N	Index case	15/1/19	18/1/19	23/1/19	16 days	Y	CRO CRL OTV	TZP LVX TGC CS	BC: <i>A.baumannii</i>	Died Septic shock
2	F	30	Omani	Cough Nausea abdominal pain	DKA	N	Household of index case	22/1/19	25/1/19	25/1/19	8 days	Y	CRO CRL	TZP MEM LVX TGC	No growth	Died Septic shock
3	F	39	Omani	Fever	cardiomyopathy	N	Household of index case	26/1/19	26/1/19	29/1/19	19 days	N	CRO CRL OTV	TZP	No growth	Alive
4	F	59	Omani	Severe respiratory distress	CKD DM, HTN IHD Hypothyroidism	N	Nosocomial	26/1/19	26/1/19	28/1/19	48 days	Y	CIP OTV	TZP MEM LZD AN	UC: <i>E.coli</i> BC: <i>Candida</i> spps.	Alive
5	F	37	Omani	Nausea Abdominal pain		N	Household of index case	26/1/19	29/1/19	1/2/19	16 days	N	CRO CRL OTV		No growth	Alive
6	F	77	Omani	Asymptomatic	CVA DM HTN Alzheimer	N	Unknown	Unknown	27/1/19	13/2/19	17 days		CRO CRL	TZP LZD	BC: <i>Enterococcus</i> spps.	Alive
7	F	65	Omani	SOB	DM HTN CVA	N	Nosocomial	9/2/19	12/2/19	12/2/19	99 days	Y	AMP	CIP, GEN, CAZ, MEM, TZP	BC: <i>P mirabilis</i> <i>A. baumannii</i>	Alive
8	F	61	Omani	Fever Cough	DM HTN CVA Dementia	N	Nosocomial	12/2/19	12/2/19	15/2/19	12 days	N	TZP CRL OTV	TGC	UC: ESBL <i>E. coli</i> , <i>A. baumannii</i> ESBL <i>K. pneumonia</i>	Alive
9	F	31	Indian	Asymptomatic	N	N	HCW Nurse	16/2/19	16/2/19	16/2/19	7 days	N	OTV		No growth	Alive
10	M	63	Omani	Fever cough	DM IHD CKD	Y	Index case	26/1/2019	29/1/2019	No isolation	10 days	Y	TZP CLR	MEM, CS, LZD, LVX	UC: <i>CRE</i> <i>K. pneumonia</i>	Died Septic shock Broncho Pneumonia
11	M	68	Omani	SOB	DM HTN CKD	No	Nosocomial	9/2/19	9/2/19	9/2/19	3 days	Y	TZP OTV	VAN, MEM, CS	No growth	Died Broncho Pneumonia
12	M	30	Sudanese	Runny nose sore throat	Asthma	No	Nosocomial-Physician	10/2/19	13/2/19	13/2/19	1 day	N	No		13/2 Rhinovirus positive	Alive
13	M	48	Bangladeshi	Fever hemoptysis	Cardiomyopathy	No	Nosocomial	14/2/19	14/2/19	18/2/19	10 days	N	TZP OTV		No growth	Died Cardiomyo pathy

In the current report, we observed three distinct clusters occurring at the same time without any epidemiological link between them (two clusters from North Al Batinah and 1 cluster from South Ash Sharqiyah Governorates).

In the first cluster, we suspect that 3 out of 5 patients in the household-associated transmission acquired infection secondarily. Though the family lived on a camel farm and the index case reported a history of contact with camels, these 3 family members reported no direct contact with camels or camel products, neither a history of travel outside Oman nor recent hospitalizations. Risk factor for the household-associated cluster infection was direct contact with a confirmed case. The three secondary cases were caring for or sharing a room with a confirmed case. Therefore the possible source of their infection is the index case. In addition, the date of onset of illness of the three cases suggested that they are secondary cases with a link to the index case [Fig. 3, Table 2].

The clustered cases showed three remarkable features. Firstly, the cases reported from the North Al Batinah cluster were household contacts, indicating that for the first time in the country human-to-human transmission occurred at the household level. Similar family clusters were reported in Saudi Arabia [14,15,17,34–39], Tunisia [40] and the UK [39]. Secondly, the epidemiological characteristics of these 13 cases are different from what has been observed in cases reported from other countries [5,10,11,39,40]. The age is skewed towards younger age groups while the reported global median age of MERS-CoV cases acquired through community transmission is 55 and above [5,10,11,39,40]. Thirdly, most of the cases are females (69%) and not males, as reported elsewhere [2,32]. The reason for the strong female predominance of the outbreak remains unexplained.

The season of dromedary camel breeding and racing is from January to March in these governorates and the camel farms may become a source of MERS-CoV circulation and transmission during this time [32]. Two of the index cases had a history of contact with dromedary camels. At this time, evidence suggests that dromedary camels (*Camelus dromedarius*) are the main source of transmission of MERS-CoV to humans [24]. It is known that individuals in close contact with dromedary camels are at an increased risk of acquiring MERS-CoV infection compared to the general population [41]. The transmission from camels to humans can be via direct contact with respiratory secretions or indirect contact through the use of camel products [41].

In these clustered outbreaks, we observed non-linked clusters and sporadic cases, in addition to nosocomial transmission in health care facilities with neither evidence of sustained human-to-human transmission nor community transmission. A similar situation was observed in Saudi Arabia, where up to 50% of MERS-CoV cases were classified as secondary, due to possible human-to-human transmission through contact with asymptomatic or symptomatic individuals infected with MERS-CoV [42]. Furthermore, limited human-to-human transmission of MERS-CoV was observed in several other clusters in other countries, including family members [14–19] and patients in health care facilities [39,40,42–44].

The current outbreak highlights the significant challenges associated with suspecting and diagnosing MERS-CoV infection. The median time from hospitalization to case notification was 12 days, which is relatively long, reflecting the need for increased awareness among health care workers and the community. However, a study conducted in Saudi Arabia showed the median time to notification was 2 days [45].

The general clinical characteristics of the MERS-CoV clustered cases observed in this study were consistent with data from other countries in the EMR [39,40,42–45]. Healthcare-associated MERS-CoV outbreaks have been reported in several countries, with the largest outbreaks in Saudi Arabia, the United Arab Emirates and the Republic of Korea [2–5,7–9,32–44]. Although most MERS-CoV-

infected HCWs were asymptomatic [42], serious infections have occurred, and HCWs might have played a critical role in spreading the virus [43]. Several factors could have contributed to transmission in the current outbreak within the healthcare facilities, including delays in suspicion and case detection, delays in timely index case isolation and most importantly, lack of adherence to optimal infection control measures such as: using proper personal protective equipment (PPE) while providing care to the infected patients, proper hand hygiene and lack of proper isolation facilities like negative pressure rooms.

The execution of basic infection control measures must be continuous and the efforts should be sustained whether there is an outbreak or not. The majority of the responsibility lies with the staff and the leadership of a healthcare facility to ensure adherence to existing infection control practices at all times.

Three patients (27%) exhibited noticeable gastrointestinal symptoms, including abdominal pain and diarrhoea. Two of these 3 patients (75%) occurred in persons with underlying chronic medical conditions. Several other countries have reported similar co-morbidities (7–10). Fifteen percent (2) of our MERS-CoV patients had severe pneumonia, complicated by ARDS, septic shock, or multi-organ failure leading to death. A similar situation was observed in a number of countries [7,44]. These patients had several underlying comorbidities including diabetes, hypertension, chronic heart disease, and chronic kidney disease. Individuals with comorbidities and on immunosuppressive treatments are at high risk of severe disease [46]. The high fatality rates (31%) observed in our patients with these co-morbidities are in line with what has been reported globally (approximately 35%) [47]. The high fatality rate may also be attributed to a delay in seeking medical care, as the mean date of the onset of symptoms to hospitalization was 4 days, and a delay was seen mostly in those with underlying chronic medical conditions.

The current outbreak highlights the need for increased awareness among the public as well, particularly in individuals with co-morbidities, who are at higher risk of complications and death. Awareness among this group should focus on avoiding close contact with camels or camel products, particularly in camel race festivals and breeding areas. Encouraging regular hand washing, especially following contact with camels [41] and early presentation to health care facilities when feeling unwell are also important messages. Practicing safe hygiene habits around dromedaries could reduce further transmission and prevent community clustered outbreaks.

Many patients received multiple courses of antimicrobials and may have developed resistance during therapy. The present MERS-CoV management approach, with regards to antimicrobial use, is not standardized. There is an urgent need to develop regional and national treatment guidelines addressing MERS-CoV antiviral drugs and certain adjunct treatments including antibiotics among patients infected with MERS-CoV according to current WHO guidelines [48].

In order to better understand future MERS-CoV transmission dynamics, we recommend a series of clinical steps. a) Perform whole-genome sequencing of the virus isolated from individuals. Also, conduct a serological investigation in order to see if silent transmission had occurred at the household level and to determine the extent of infection, i.e., sub-clinical or asymptomatic amongst high and low risk contacts of the cases. b) Sera collection should be repeated in close contacts 3–4 weeks after contact with the index case, regardless of whether close contacts have developed symptoms [26]. Close contacts include family members and health care worker contacts of the infected patients, including family member contacts that previously tested negative as per the WHO guideline [26]. c) It would have been advantageous to consider implementation of a study design using inferential methods, from which evidence-based conclusions can be drawn as the review limitation.

The timing of this investigation is critical and should be initiated as soon as the first patient with MERS-CoV (the index case) is identified. MERS-CoV-specific antibodies take 14–21 days to develop in infected individuals [26]. Therefore, it is ideal to wait 21 days from the day the index case was reported to be sure that anti-MERS-CoV IgG is not missed in the serum of the contact cases as many mild or asymptomatic cases of MERS-CoV do not seroconvert.

The agenda to address existing knowledge gaps in relation to MERS-CoV infection should include the following technical areas: virus origin and characteristics, epidemiology and transmission and infection prevention and control [47]. Oman can contribute to the research agenda by addressing key fundamental issues associated with public and animal health. We should focus on the primary source of MERS-CoV infections, which remains unclear, as does the transmission pattern from dromedary camels to humans. Special attention should be particularly paid to the types of behaviour or exposure that result in human infections, even asymptomatic infections that elicit immune responses.

Efforts are required to improve infection prevention and control in order to minimize nosocomial transmission. Institutional monitoring and evaluation and training of HCWs remain the mainstays of disease prevention in healthcare facilities. Furthermore, the urgent adoption of a “One Health” strategic approach, including the establishment of a robust, timely, integrated surveillance system and strengthening the governorates’ capabilities for rapid and efficient investigation of the disease is critical for minimizing the spread of disease. This is the first local clusters of MERS-CoV ever reported in Oman with evidence suggestive of healthcare transmission and limited household-associated transmission. Early diagnosis and strict implementation of infection control measures remain fundamental in preventing and managing MERS-CoV infection.

### Conflicts of interest

All authors declare no conflicts of interest.

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