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Case characteristics among Middle East respiratory syndrome coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015

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ABSTRACT

Objectives: As of 1 November 2015, the Saudi Ministry of Health had reported 1273 cases of Middle East respiratory syndrome (MERS); among these cases, which included 9 outbreaks at several hospitals, 717 (56%) patients recovered, 14 (1%) remain hospitalised and 543 (43%) died. This study aimed to determine the epidemiological, demographic and clinical characteristics that distinguished cases of MERS contracted during outbreaks from those contracted sporadically (ie, non-outbreak) between 2012 and 2015 in Saudi Arabia.

Design: Data from the Saudi Ministry of Health of confirmed outbreak and non-outbreak cases of MERS coronavirus (CoV) infections from September 2012 through October 2015 were abstracted and analysed. Univariate and descriptive statistical analyses were conducted, and the time between disease onset and confirmation, onset and notification and onset and death were examined.

Results: A total of 1250 patients (aged 0–109 years; mean, 50.825 years) were reported infected with MERS-CoV. Approximately two-thirds of all MERS cases were diagnosed in men for outbreak and non-outbreak cases. Healthcare workers comprised 22% of all MERS cases for outbreak and non-outbreak cases. Nosocomial infections comprised one-third of all Saudi MERS cases; however, nosocomial infections occurred more frequently in outbreak than non-outbreak cases (p<0.001). Patients contracting MERS during an outbreak were significantly more likely to die of MERS (p<0.001).

Conclusions: To date, nosocomial infections have fuelled MERS outbreaks. Given that the Kingdom of Saudi Arabia is a worldwide religious travel destination, localised outbreaks may have massive global implications and effective outbreak preventive measures are needed.

Strengths and limitations of this study

- Confirmed outbreak and non-outbreak cases of Middle East respiratory syndrome (MERS) coronavirus infections in Saudi Arabia from September 2012 through October 2015 reported to the Saudi Ministry of Health (MOH) were abstracted and analysed.
- This is the first report to retrieve the epidemiological, demographic and clinical characteristics of MERS data from this database and analyse these data using univariate and descriptive statistical analyses.
- However, major leadership changes in the Saudi MOH during the study period led to alterations in the data collection forms as well as the surveillance system.
- These alterations caused some inconsistencies in the data acquired from the Saudi MOH database that may limit the interpretation of the study results.

INTRODUCTION

Following the isolation of a previously unknown coronavirus (CoV) from the sputum of a man aged 60 years in 2012,[1] 1618 laboratory-confirmed cases of Middle East respiratory syndrome (MERS) have been reported throughout 26 countries, with 579 cases resulting in death.[2] The vast majority of these 26 countries reported MERS cases after experiencing an exportation event from the Arabian Peninsula.[3 4] Most cases to date have occurred in Saudi Arabia, followed by South Korea, which experienced an outbreak of MERS after the return of an infected businessman who had been travelling in Middle East.[5]

The exact zoonotic source of MERS-CoV and its mode of transmission in humans remain unclear. Although related sequences have been detected in several bat species,[6] MERS-CoV has not been isolated from bats. However, MERS-CoV has been isolated from dromedary camels. A high rate of seropositivity has been confirmed in the camels of

Arabian Peninsula, with no evidence of MERS-CoV infection detected in cows, goats or sheep.[7–10] One study isolated the full MERS-CoV genome sequences from a dromedary camel and from a patient who died of laboratory-confirmed MERS-CoV infection after close contact with camels; the two isolates were identical. According to serological data, MERS-CoV had been circulating in the camel—but not in the patient—before human infection occurred, suggesting that MERS-CoV had been transmitted to the patient via the infected camel.[11]

Whether MERS-CoV is new to camel or human populations or whether it has been present but undetected for years remains unknown. Nonetheless, MERS-CoV was initially regarded primarily as a zoonotic pathogen, with only limited documentation of person-to-person transmission. However, MERS outbreaks of varying proportions have since occurred across Saudi Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family clusters[12 13] and healthcare facilities.[14 15]

Much remains unknown about MERS, including the risk factors associated with MERS-CoV transmissions in outbreak and non-outbreak settings. Here, we aimed to increase our understanding of the spread and mode of transmission of MERS-CoV by comparing the epidemiological, demographic and clinical characteristics of outbreak and non-outbreak MERS-CoV infections from September 2012 to October 2015 as reported to the Saudi Arabian Ministry of Health (MOH).

MATERIALS AND METHODS

Demographic and clinical data were obtained through the use of standardised contact tracing forms populated by the public health database maintained by the MOH Command & Control Center (CCC). According to the CCC, a confirmed MERS-CoV case is defined as a suspected case with laboratory confirmation of MERS-CoV infection. A suspected case of MERS-CoV in adults (>14 years) is defined as follows: (1) acute respiratory illness with clinical or radiological evidence of pneumonia or acute respiratory distress syndrome; (2) a hospitalised patient with healthcare-associated pneumonia based on clinical and radiological evidence; (3) upper or lower respiratory tract illness within 2 weeks of exposure to a confirmed or probable case of MERS-CoV infection; or (4) unexplained acute febrile illness ($\geq 38°C$) presenting with body aches, headache, diarrhoea or nausea/vomiting, with or without respiratory symptoms, and with leucopoenia.

Data and statistical analyses

All data collected were stored and analysed using SAS (V.9.4) software. Univariate and descriptive statistics were conducted to estimate proportions. Associations between

Figure 1 Incidence of Middle East respiratory syndrome coronavirus infections (1250 confirmed cases) across the Kingdom of Saudi Arabia.

age and two variables (gender and death) were assessed using a χ^2 test. χ^2 analysis using Yates' correction was performed on the data set to compare case characteristics among outbreak and non-outbreak cases. Distributions of time between onset and confirmation, onset and notification and onset and death (among patients that died) were also determined for outbreak and non-outbreak cases. All reported p values are two-tailed and were considered to be statistically significant at p<0.05.

RESULTS

Distribution of confirmed MERS-CoV cases over time in Saudi Arabia

The prevalence of MERS-CoV was highest in the Riyadh region with 46.91% of the total reported cases, followed by the Jeddah (21%), AlAhsa (5.69%), AlMadinah Almonowarah (4.81%), Eastern (4.73%), AlTaif (4.33%) and Makkah (3.29%) regions. The remaining regions comprised 9.14% of the total reported cases (figure 1). More than 31% of all confirmed cases of MERS-CoV in Saudi Arabia were reported in April and May 2014. The highest number of outbreaks was reported to have occurred in April and May 2014, the second highest in September 2015 and the third highest in February and March 2015.

Demographic characteristics

During the study period, a total of 1250 patients from 0 to 109 years old were reported as infected with MERS-CoV in Saudi Arabia. MERS-CoV was prevalent among individuals who were 30 years or older; in contrast, individuals who were 26 years or younger exhibited very low incidence. The distribution of age for all reported cases was almost normal, with a mean of 50.825 years and an SD of 19.494 years. MERS-CoV was more prevalent in men (64.77% of total reported cases) than in women. Women had an average age of 48 years (SD, 19 years), with a minimum of zero and maximum of 90 years. Men had an average age of 52 years (SD, 19 years), with a minimum of zero and a maximum of 109 years (table 1). We found a significant association between age and gender (χ^2=15.22; p<0.01) and between gender and death for patients diagnosed with MERS-CoV (χ^2=12.75; p<0.01).

Online supplementary table S1 presents the nationalities of patients diagnosed with MERS-CoV in Saudi Arabia. Most patients were Saudi (66%), followed by Filipino (10.99%), Indian (3.99%) and Yemeni (3.69%) nationalities.

Univariate analysis for outbreak versus non-outbreak cases

Univariate analysis revealed that older individuals—namely, those older than the mean age of 50.825 years—represented a larger than expected proportion of outbreak than of non-outbreak cases (p<0.001; table 2).

Table 1 Patient characteristics in Middle East respiratory syndrome infection cases reported in the Kingdom of Saudi Arabia from 2012 to 2015

Demographic characteristics (n)	Frequency	Percentage
Age in years (1244)		
0–10	41	3.30
11–25	63	8.36
26–39	292	31.83
40–109	848	68.17
Gender (1246)		
Female	439	35.23
Male	807	64.77
Occupational status (172)		
Employed	22	12.79
Unemployed	40	23.26
Retired	31	21.51
Private	37	18.02
Other	42	24.42
Main reason for testing (1247)		
Healthcare worker	249	19.97
Household	138	11.07
Suspect	860	68.97
Healthcare worker (1244)		
Yes	275	22.11
No	969	77.89
Does the patient raise camels? (205)		
Yes	29	14.15
No	176	85.85
During the 14 days before the patient became sick, did he/she travel outside or inside Saudi Arabia? (205)		
Yes	195	95.12
No	10	4.88
Was the patient hospitalised when a positive result was obtained? (450)		
Yes	413	91.78
No	37	8.22
Did the patient visit any healthcare facilities during the 14 days before onset of symptoms? (245)		
Yes	98	40
No	109	44.49
Unknown	38	15.51
Does the patient smoke? (205)		
Yes	36	17.56
No	169	82.44
Is the patient diabetic? (278)		
Yes	220	79.14
No	58	20.86
Did the patient die before October 2015? (1250)		
Yes	535	42.80
No	715	57.20

The prevalence of MERS-CoV infections among men was comparable for outbreak and non-outbreak cases (p=0.239; table 2). Similarly, approximately two-thirds of all Saudi MERS diagnoses occurred among Saudi nationals for outbreak and non-outbreak cases (p=0.558; table 2). Healthcare workers comprised 22% of all confirmed Saudi MERS cases for outbreak and non-outbreak cases (p=0.920; table 2). However, nosocomial

infections, which comprised one-third of all confirmed Saudi MERS cases, occurred much more frequently among outbreak cases than among non-outbreak cases (p<0.001). Patients who became infected during outbreaks were more likely to die of MERS than those infected during non-outbreak conditions (p<0.001).

Of the patients reporting data on camel exposure, 17% of the 123 non-outbreak cases and 10% of the 81 outbreak cases indicated that they owned or raised camels; this difference was not statistically significant.

Distributions of time between onset and the confirmation, notification and death

The average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases. For outbreak cases and non-outbreak cases, the average time from onset to notification was 5.3 and 9.2 days, respectively. Among patients who died, the average time from onset to death was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases. All three distributions were long-tailed, and non-outbreak cases were skewed further right (figures 2–5).

DISCUSSION

Using the Saudi MOH CCC public health data set on MERS cases reported to have occurred from September 2012 to September 2015, we found three factors distinguishing outbreak and non-outbreak cases: (1) patients older than the mean age of 51 years represented a larger than expected fraction of outbreak than of non-outbreak cases, (2) nosocomial infections occurred much more frequently among outbreak cases than

Table 2 Characteristics of patients with confirmed Middle East respiratory syndrome coronavirus infection in the Kingdom of Saudi Arabia from 2012 to 2015 evaluated by outbreak versus non-outbreak conditions

	Outbreak cases N=485		Non-outbreak cases N=765		χ^2	p Value
	n	Per cent	n	Per cent		
Age (years)						
≥51	281	58	362	47	12.66	<0.001
<51	204	42	401	52		
Unknown (UNK)	0		2			
Sex						
Male	323	67	484	63	1.39	0.239
Female	160	33	279	36		
UNK	2		2			
Nationality						
Saudi	331	68	509	67	0.34	0.558
Non-Saudi	153	32	255	33		
UNK	1		1			
Healthcare worker (HCW)						
Yes	108	22	167	22	0.01	0.920
No	375	77	594	77		
UNK	2		4			
Patient hospitalised prior to onset of MERS symptoms (nosocomial infection)						
Yes	193	40	220	29	15.84	<0.001
No	292	60	545	71		
Reason for testing (mode of transmission)						
Suspect	357	74	503	66	22.85	<0.001
HCW	99	20	150	20		
Household	27	6	110	14		
UNK	2		2			
Reason for testing (symptoms presented)						
Group 1	107	22	288	28	100.84	<0.001
Group 2	96	20	65	8		
Group 3	11	2	35	5		
Group 4	140	29	288	28		
Group 5	128	26	85	11		
Group 6	1	0	3	0		
UNK	2		1			
Outcome						
Deceased	245	51	290	38	18.76	<0.001
Alive	240	49	475	6%		

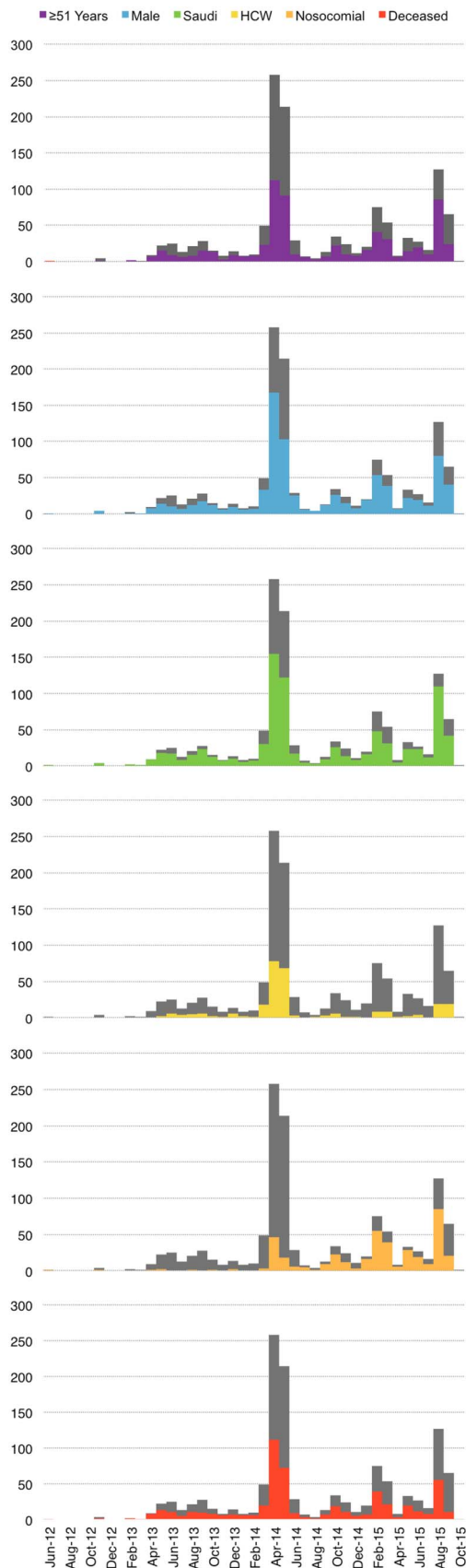Yates' correction was used for all χ^2 calculations.

Figure 2 Epidemiological curve showing the number of cases of MERS-CoV infection and various patient characteristics in the Kingdom of Saudi Arabia by month and year of confirmation. HCW, healthcare worker.
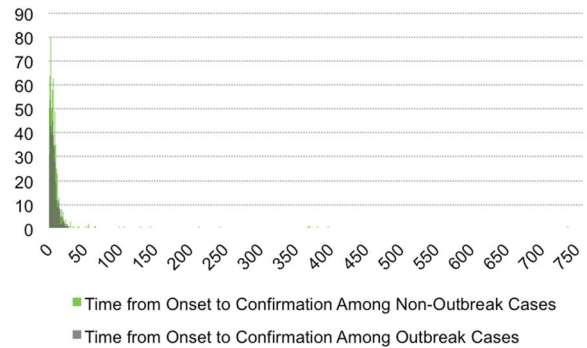

Figure 3 Histogram of the time from disease onset to MERS-CoV confirmation for outbreak and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases.

among non-outbreak cases and (3) patients infected during outbreaks were more likely to die of MERS-CoV infection than those infected during non-outbreak conditions (table 2).

Given that age was associated with death, it is worth noting that the third factor may be explained in part by the over-representation of older individuals among the outbreak cases. Although age was also associated with gender, we found that the proportion of MERS-CoV infections in men was approximately two-thirds for outbreak and non-outbreak cases (table 2). However, the general over-representation of men is consistent with many previous studies showing predominantly male patients with MERS-CoV.[3 16 17]

Our results also showed that healthcare workers comprised 22% of all Saudi MERS cases diagnosed up to October 2015 (table 2). This percentage is in agreement with a 2014 WHO report stating that 109 of the 402 (~25%) reported MERS-CoV infections in the Jeddah (Saudi Arabia) 2014 outbreak occurred in healthcare workers.[16] Areas neighbouring Saudi Arabia, including the city of Al-Ain in the United Arab Emirates, also reported MERS-CoV infections in 16 healthcare workers out of 23 total cases.[17] Additionally, during the large
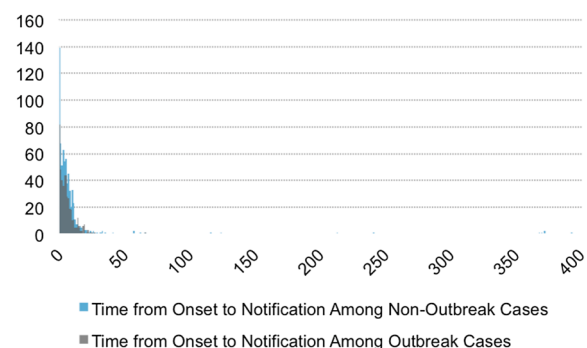

Figure 4 Histogram of time from disease onset to notification for outbreak and non-outbreak cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for non-outbreak cases.
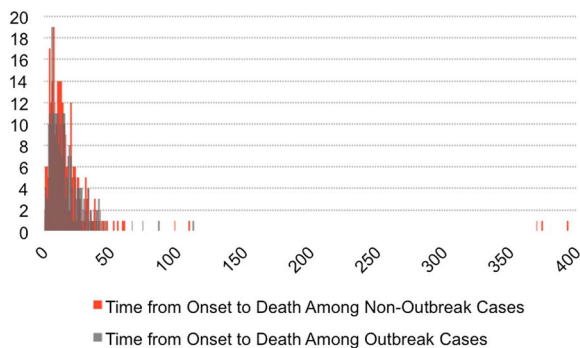
Figure 5 shows a histogram with y-axis values: 20, 18, 16, 14, 12, 10, 8, 6, 4, 2, 0 and x-axis values: 0, 50, 100, 150, 200, 250, 300, 350, 400.

■ Time from Onset to Death Among Non-Outbreak Cases
■ Time from Onset to Death Among Outbreak Cases

Figure 5 Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients who died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases.

South Korean outbreak in 2015, 14% of the infected cases were in healthcare workers.[5]

Another 2014 WHO report stated that most person-to-person MERS-CoV infections likely occurred in healthcare settings.[18] We found that nosocomial transmissions comprised one-third of all Saudi MERS-CoV cases reported to date. Importantly, these nosocomial infections occurred more frequently in outbreak cases than in non-outbreak cases, suggesting that nosocomial infections fuelled outbreaks (table 2). The first outbreak in Al-Hasa, Saudi Arabia, (2013) provided valuable information about MERS-CoV transmission in a healthcare setting. The outbreak started in a haemodialysis unit of a private hospital in Al-Hasa, but subsequently spread to three other hospitals. Phylogenetic analysis of the outbreak showed that only eight of the epidemiological transmissions were related, indicating multiple zoonotic introductions of MERS-CoV.[18]

To date, MERS-CoV has been detected in camels from Saudi Arabia, Oman, Qatar, Jordan and Kenya,[7 8 10 19 20] and it has been shown that humans can acquire MERS-CoV directly from dromedary camels.[21] Since camel exposure data (ie, whether the patient owned or raised camels) were gathered for only 204 of the 1250 cases in the database used by this study, we did not include this information in table 2. Nonetheless, we found that 17% of the 123 non-outbreak cases and 10% of the 81 outbreak cases reporting data on camel exposure indicated that the patients owned or raised camels. Although this difference was not statistically significant, this result suggested that camel exposure, and thus zoonotic transmission, might be more common among sporadic, non-outbreak cases than among outbreak cases. A full analysis of this relationship will require more vigilant collection of camel exposure data.

This study was limited by the information available in the Saudi MOH CCC public health data set on MERS-CoV infections that were reported to have occurred between September 2012 and October 2015. The surveillance system and data collection forms were inconsistent over the years during which these data were acquired, likely due to major leadership changes in the MOH. The outbreak cases have thus far been confirmed faster than non-outbreak cases, indicating that improved future surveillance may allow for faster identification of sporadic cases (figure 5).

CONCLUSIONS

Although it has been 3 years since MERS-CoV was first identified in humans, cases continue to occur in household and healthcare settings, though our results indicated that most person-to-person transmissions involved healthcare-associated infections. Nosocomial outbreaks likely begin when a primary patient seeks care and then escalates due to insufficient implementation of scalable infection control measures. Our results indicate that the best way to control MERS-CoV infections may be to block its spread by practicing rigorous infection control measures in hospitals. Therefore, strengthening of infection control measures in healthcare settings will be critical to the prevention of future outbreaks.

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