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Manuscripts

Case characteristics among Middle East Respiratory Syndrome

Coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015

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21 Abstract

22 **Objectives:** As of November 01, 2015, the Saudi Ministry of Health had reported 1273 cases of
23 MERS; among these cases, which included nine outbreaks at several hospitals, 717 (56%)
24 patients recovered, 14 (1%) remain hospitalized, and 543 (43%) died. This study aimed to
25 determine the epidemiologic, demographic, and clinical characteristics that distinguished cases
26 of MERS contracted during outbreaks from those contracted sporadically (i.e., non-outbreak)
27 between 2012 and 2015 in Saudi Arabia.

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

32 **Results:** A total of 1250 patients (aged 0 to 109 years; mean, 50.825 years) were reported
33 infected with MERS coronavirus (CoV). Approximately two-thirds of all MERS cases were
34 diagnosed in men for both outbreak and non-outbreak cases. Healthcare workers comprised 22%
35 of all MERS cases for both outbreak and non-outbreak cases. Nosocomial infections comprised
36 one-third of all Saudi MERS cases; however, nosocomial infections occurred more frequently in
37 outbreak than non-outbreak cases ($p < .001$). Patients contracting MERS during an outbreak
38 were significantly more likely to die of MERS ($p < 0.001$).

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

43 Strengths and limitations of this study

- 44 • Confirmed outbreak and non-outbreak cases of Middle East respiratory syndrome
45 (MERS) corona virus infections in Saudi Arabia from September 2012 through October
46 2015 reported to the Saudi Ministry of Health (MOH) were abstracted and analysed.
- 47 • This is the first report to retrieve the epidemiologic, demographic, and clinical
48 characteristics of MERS data from this database and analyse these data using univariate
49 and descriptive statistical analyses.
- 50 • However, major leadership changes in the Saudi MOH during the study period led to
51 alterations in the data collection forms as well as the surveillance system.
- 52 • These alterations caused some inconsistencies in the data acquired from the Saudi MOH
53 database.

54 Introduction

55 Following the isolation of a previously unknown coronavirus (CoV) from the sputum of a 60-
56 year-old man in 2012,¹ 1,618 laboratory-confirmed cases of Middle East respiratory syndrome
57 (MERS) have been reported throughout 26 countries, with 579 cases resulting in death.² The vast
58 majority of these 26 countries reported MERS cases after experiencing an exportation event from
59 the Arabian Peninsula.^{3,4} Most cases to date have occurred in Saudi Arabia, followed by South
60 Korea, which experienced an outbreak of MERS after the return of an infected businessman who
61 had been traveling in Middle East.⁵

62 The exact zoonotic source of MERS-CoV and its mode of transmission in humans remain
63 unclear. Although related sequences have been detected in several bat species,⁶ MERS-CoV has
64 not been isolated from bats. However, MERS-CoV has been isolated from dromedary camels. A
65 high rate of seropositivity has been confirmed in the camels of the Arabian Peninsula, with no
66 evidence of MERS-CoV infection detected in cows, goats, or sheep.⁷⁻¹⁰ One study isolated the
67 full MERS-CoV genome sequences from a dromedary camel and from a patient who died of
68 laboratory-confirmed MERS-CoV infection after close contact with camels; the two isolates
69 were identical. According to serologic data, MERS-CoV had been circulating in the camel—but
70 not in the patient—before human infection occurred, suggesting that MERS-CoV had been
71 transmitted to the patient via the infected camel.¹¹

72 Whether MERS-CoV is new to camel or human populations or whether it has been
73 present but undetected for years remains unknown. Nonetheless, MERS-CoV was initially
74 regarded primarily as a zoonotic pathogen, with only limited documentation of person-to-person
75 transmission. However, MERS outbreaks of varying sizes have since occurred across Saudi

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3 76 Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family
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5 77 clusters^{12, 13} and healthcare facilities.^{14, 15}
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8 Much remains unknown about MERS, including risk factors associated with MERS-CoV
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10 79 transmissions in both outbreak and non-outbreak settings. Here, we aimed to increase our
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12 80 understanding of the spread and mode of transmission of MERS-CoV by comparing the
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14 81 epidemiologic, demographic, and clinical characteristics of outbreak and non-outbreak MERS-
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16 82 CoV infections from September 2012 to October 2015 as reported to the Saudi Arabian Ministry
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18 83 of Health (MOH).
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23 24 85 **Materials and Methods**

25
26 86 Demographic and clinical data were obtained through the use of standardized contact tracing
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28 87 forms populated by the public health database maintained by the MOH Command & Control
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30 88 Center (CCC). According to the CCC, a confirmed MERS-CoV case is defined as a suspected
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32 89 case with laboratory confirmation of MERS-CoV infection. A suspected case of MERS-CoV in
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34 90 adults (>14 years) is defined as follows: (I) acute respiratory illness with clinical or radiological
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36 91 evidence of pneumonia or acute respiratory distress syndrome; (II) a hospitalized patient with
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38 92 healthcare-associated pneumonia based on clinical and radiological evidence; (III) upper or
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40 93 lower respiratory illness within 2 weeks of exposure to a confirmed or probable case of MERS-
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42 94 CoV infection; or (IV) unexplained acute febrile illness ($\geq 38^{\circ}\text{C}$) presenting with body aches,
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44 95 headache, diarrhoea, or nausea/vomiting, with or without respiratory symptoms, and with
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46 96 leucopenia.
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99 Data and Statistical Analyses

100 All data collected were stored and analysed using SAS (version 9.4) software. Univariate and
101 descriptive statistics were conducted to estimate proportions. Associations between age and two
102 variables (gender and death) were assessed using a χ^2 test. Chi-square analysis using Yates'
103 correction was performed on the dataset to compare case characteristics among outbreak and
104 non-outbreak cases. Distributions of time between onset and confirmation, onset and notification,
105 and onset and death (among patients that died) were also determined for both outbreak and non-
106 outbreak cases. All reported p values are two-tailed and were considered to be statistically
107 significant at $p < 0.05$.

109 Results

110 Distribution of Confirmed MERS-CoV Cases over Time in Saudi Arabia

111 The prevalence of MERS-CoV was highest in the Riyadh region with (46.91%) of the total
112 reported cases, followed by the Jeddah (21%), AlAhsa (5.69%), AlMadinah Almonowarah
113 (4.81%), Eastern (4.73%), AlTaif (4.33%), and Makkah (3.29%) regions. The remaining regions
114 comprised 9.14% of the total reported cases (Figure 1). More than 31% of all confirmed cases of
115 MERS-CoV in Saudi Arabia were reported in May and April of 2014. The highest number of
116 outbreaks was reported to have occurred in May and April of 2014, the second highest in
117 September 2015, and the third highest in February and March of 2015.

119 Demographic Characteristics

120 During the study period, a total of 1250 patients from 0 to 109 years old were reported as
121 infected with MERS-CoV in Saudi Arabia. MERS-CoV was prevalent among individuals who

122 were 30 years or older; by contrast, individuals who were 26 years or younger exhibited very low
 123 incidence. The distribution of age for all reported cases was approximately normal, with a mean
 124 of 50.825 years and a standard deviation of 19.494 years. MERS-CoV was more prevalent in
 125 males (64.77% of total reported cases) than in females. Females had an average age of 48 years
 126 (SD, 19 years), with a minimum of zero and maximum of 90 years. Males had an average age of
 127 52 years (SD, 19 years), with a minimum of zero and a maximum of 109 years (Table 1). We
 128 found a significant association between age and gender ($\chi^2 = 15.22$; $p < 0.01$) and between
 129 gender and death for patients diagnosed with MERS-CoV ($\chi^2 = 12.75$; $p < 0.01$).

130 **Table 1.** Patient characteristics in Middle East respiratory syndrome infection cases reported in
 131 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 hospitalized 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

Supplementary Table 1 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 fraction of outbreak than of non-outbreak cases ($p < 0.001$; Table 2). The prevalence of MERS-CoV infections among men was comparable for both outbreak and non-outbreak cases ($p = 0.239$; Table 2). Similarly, approximately two-thirds of all Saudi MERS diagnoses occurred among Saudi nationals for both outbreak and non-outbreak cases ($p = 0.558$; Table 2). Healthcare workers comprised 22% of all confirmed Saudi MERS cases for both 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 ($p < 0.001$).

149 Patients that became infected during outbreaks were more likely to die of MERS than those
 150 infected during non-outbreak conditions ($p < 0.001$).

151 Of the patients reporting data on camel exposure, 17% of the 123 non-outbreak cases and
 152 10% of the 81 outbreak cases indicated that they owned or raised camels; this difference was not
 153 statistically significant.

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

	Outbreak cases <i>N</i> = 485		Non-outbreak cases <i>N</i> = 765		χ^2	p
	n	%	n	%		
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 hospitalized 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%		

157 Yates' correction was used for all chi-square calculations.

158 **Distributions of Time between Onset and the Confirmation, Notification, and Death**

159 Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-
160 outbreak cases. For outbreak cases and non-outbreak cases, the average time from onset to
161 notification was 5.3 days and 9.2 days, respectively. Among patients that died, the average time
162 from onset to death was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases. All
163 three distributions were long-tailed, and non-outbreak cases were skewed further right (Figures
164 2–5).

166 **Discussion**

167 Using the Saudi MOH CCC public health dataset on MERS cases reported to have occurred from
168 September 2012 to September 2015, we found three factors distinguishing outbreak and non-
169 outbreak cases: (1) Patients older than the mean age of 51 years represented a larger than
170 expected fraction of outbreak than of non-outbreak cases, (2) nosocomial infections occurred
171 much more frequently among outbreak cases than among non-outbreak cases, and (3) patients
172 infected during outbreaks were more likely to die of MERS-CoV infection than those infected
173 during non-outbreak conditions (Table 2).

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

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3 180 Our results also showed that healthcare workers comprised 22% of all Saudi MERS cases
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6 181 diagnosed up to October 2015 (Table 2). This percentage is in agreement with a 2014 World
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8 182 Health Organization (WHO) report stating that 109 of the 402 (approximately 25%) reported
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10 183 MERS-CoV infections in the Jeddah (Saudi Arabia) 2014 outbreak occurred in healthcare
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12 184 workers.¹⁶ Areas neighbouring Saudi Arabia, including the city of Al-Ain in the United Arab
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14 185 Emirates, also reported MERS-CoV infections in 16 healthcare workers out of 23 total cases.¹⁷
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17 186 Additionally, during the large South Korean outbreak in 2015, 14% of the infected cases were in
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19 187 healthcare workers.⁵

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22 188 Another 2014 WHO report stated that most person-to-person MERS-CoV infections
23
24 189 likely occurred in healthcare settings.¹⁸ We found that nosocomial transmissions comprised one-
25
26 190 third of all Saudi MERS-CoV cases reported to date. Importantly, these nosocomial infections
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28 191 occurred more frequently in outbreak cases than in non-outbreak cases, suggesting that
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30 192 nosocomial infections fuelled outbreaks (Table 2). The first outbreak in Al-Hasa, Saudi Arabia,
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32 193 (2013) provided valuable information about MERS-CoV transmission in a healthcare setting.
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34 194 The outbreak started in a haemodialysis unit of a private hospital in Al-Hasa, but subsequently
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36 195 spread to three other hospitals. Phylogenetic analysis of the outbreak showed that only eight of
37
38 196 the epidemiologic transmissions were related, indicating multiple zoonotic introductions of
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40 197 MERS-CoV.¹⁸

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43 198 To date, MERS-CoV has been detected in camels from Saudi Arabia, Oman, Qatar,
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45 199 Jordan, and Kenya,^{7, 8, 10, 19, 20} and it has been shown that humans can acquire MERS-CoV
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47 200 directly from dromedary camels.²¹ Because camel exposure data (i.e., whether the patient owned
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49 201 or raised camels) were gathered for only 204 of the 1250 cases in the database used by this study,
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51 202 we did not include this information in Table 2. Nonetheless, we found that 17% of the 123 non-
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3 203 outbreak cases and 10% of the 81 outbreak cases reporting data on camel exposure indicated that
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5 204 the patients owned or raised camels. Although this difference was not statistically significant,
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8 205 this result suggested that camel exposure, and thus zoonotic transmission, might be more
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10 206 common among sporadic, non-outbreak cases than among outbreak cases. A full analysis of this
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12 207 relationship will require more vigilant collection of camel exposure data.

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14
15 208 This study was limited by the information available in the Saudi MOH CCC public health
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17 209 dataset on MERS-CoV infections that were reported to have occurred between September 2012
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19 210 and October 2015. The surveillance system and data collection forms were inconsistent over the
20
21 211 years during which these data were acquired, likely due to major leadership changes in the
22
23 212 MOH. The outbreak cases have thus far been confirmed faster than non-outbreak cases,
24
25 213 indicating that improved future surveillance may allow for faster identification of sporadic cases
26
27 214 (Figure 5).

215 216 **Conclusions**

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

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3 226 **Footnotes**
4

5 227 **Acknowledgments:** We are grateful to the Ministry of Health staff who helped in data
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7
8 228 collection.

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10 229 **Contributors:** FA is the study PI and wrote the manuscript. MM developed the study design and
11
12 230 conducted the analyses. JH interpreted the results. JB reviewed the study design. DO performed
13
14 231 the statistical analyses. HA, AA, and ABS acquired patient demographic and clinical data from
15
16 232 the Saudi Ministry of Health database. MA participated in interpreting the clinical results and
17
18 233 reviewed the manuscript. All authors participated in critical revision of the manuscript and
19
20 234 approved the final version.

21
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25
26 237 **Competing interests:** None declared.

27
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29
30 239 Specialist Hospital and Research Centre (KFSH&RC; RAC #2130 033) and the Ministry of
31
32 240 Health in Riyadh, Saudi Arabia, and included a waiver of informed consent. Informed consent
33
34 241 was waived because this study involved a retrospective evaluation of publicly available data, the
35
36 242 data collection was anonymous, and no patient identity was revealed.

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38 243 **Data sharing:** No additional data available.
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3 312 **Figure legends**
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6 313 **Figure 1.** Incidence of MERS coronavirus infections (1250 confirmed cases) across the
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8 314 Kingdom of Saudi Arabia.

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11 315 **Figure 2.** Epidemiologic curve showing the number of cases of MERS-CoV infection and
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13 316 various patient characteristics in the Kingdom of Saudi Arabia by month and year of
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15 317 confirmation. HCW, healthcare worker.
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20 318 **Figure 3.** Histogram of the time from disease onset to MERS-CoV confirmation for outbreak
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22 319 and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak
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24 320 cases and 11.9 days for non-outbreak cases.
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28 321 **Figure 4.** Histogram of time from disease onset to notification for outbreak and non-outbreak
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30 322 cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for
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32 323 non-outbreak cases.
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36 324 **Figure 5.** Histogram of time from onset to death for outbreak and non-outbreak in those cases
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38 325 ending in death. Average time from onset to death among patients that died was 15.6 days for
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40 326 outbreak cases and 19.5 days for non-outbreak cases
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Figure 1. Incidence of MERS coronavirus infections (1250 confirmed cases) across the Kingdom of Saudi Arabia.

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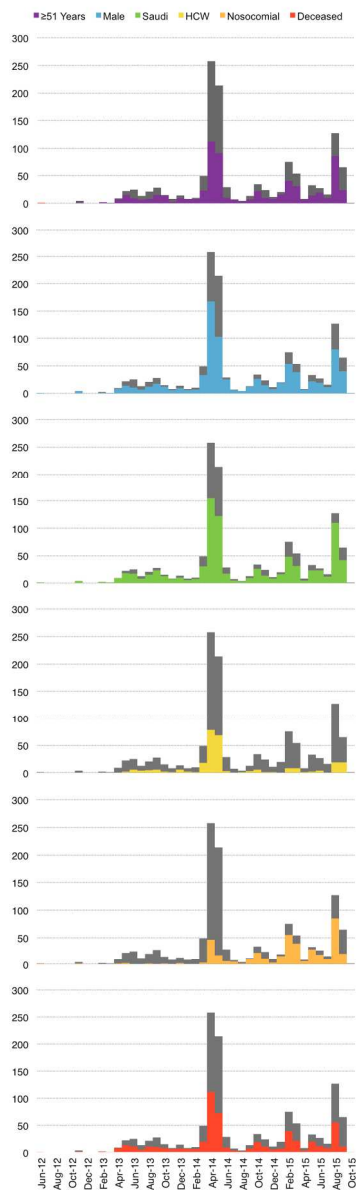


Figure 2. Epidemiologic curve showing the number of cases of MERS-CoV infection and various patient characteristics in the Kingdom of Saudi Arabia by month and year of confirmation. HCW, healthcare worker.

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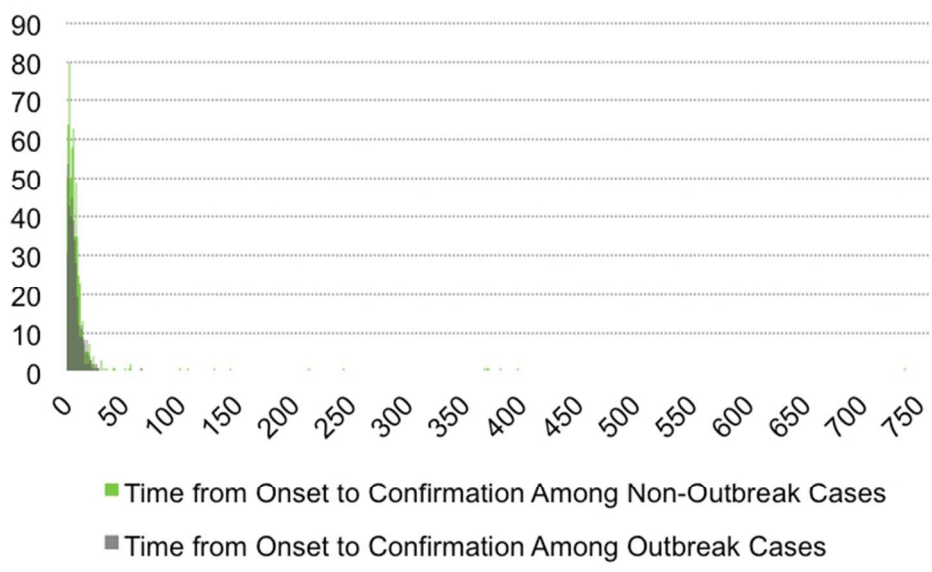


Figure 3. Histogram of the time from disease onset to MERS-CoV confirmation for outbreak and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases.

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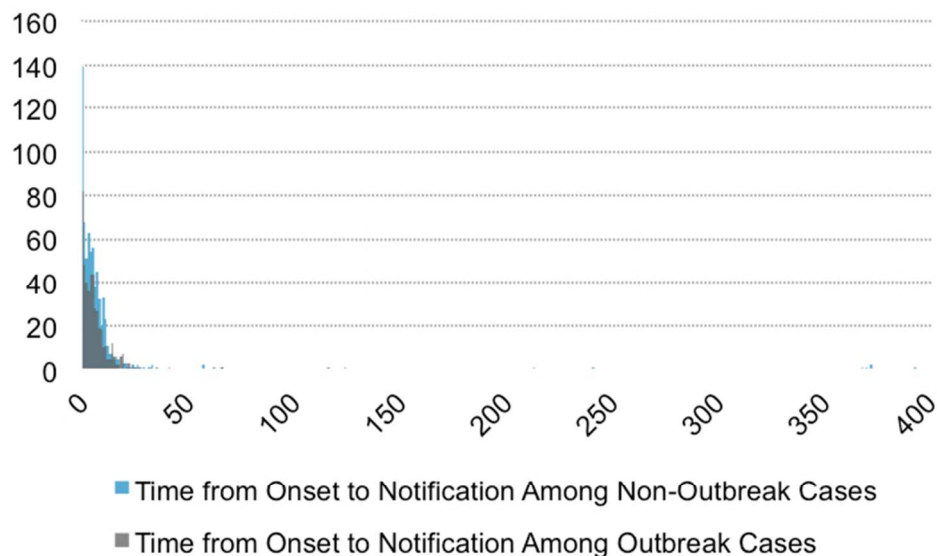


Figure 4. Histogram of time from disease onset to notification for outbreak and non-outbreak cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for non-outbreak cases.

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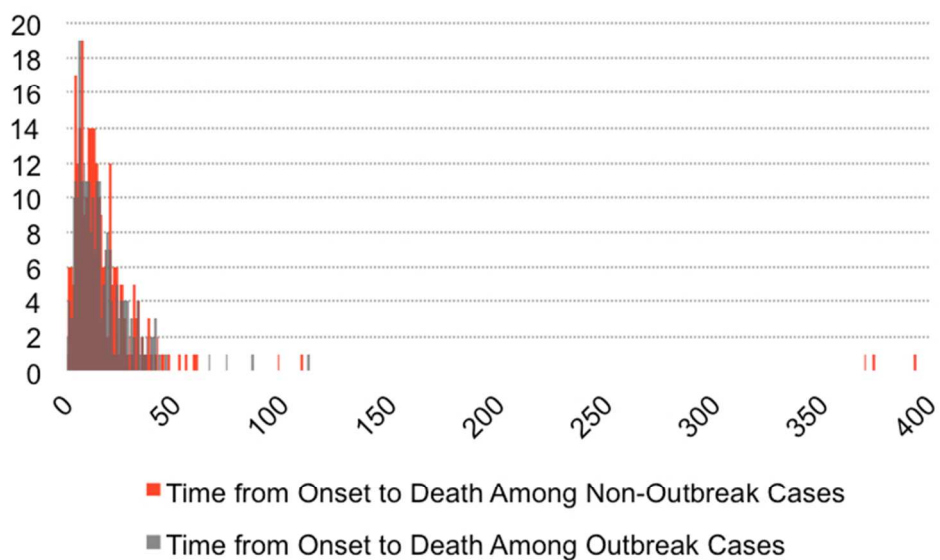


Figure 5. Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients that died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases

Review only

Supplementary Table 1. Nationalities for patients who were diagnosed with MERS-CoV virus in Saudi Arabia

Nationality				
Nationality	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Australia	1	0.08	1	0.08
Azerbaijan	1	0.08	2	0.17
Bangladesh	19	1.59	21	1.76
Chad	1	0.08	22	1.85
Egypt	33	2.77	55	4.61
Eritrea	3	0.25	58	4.87
Ethiopia	1	0.08	59	4.95
India	47	3.94	106	8.89
Indonesia	6	0.50	112	9.40
Jordan	7	0.59	119	9.98
Kuwait	1	0.08	120	10.07
Lebanon	4	0.34	124	10.40
Malaysia	6	0.50	130	10.91
Morocco	1	0.08	131	10.99
Myanmar	5	0.42	136	11.41
Pakistan	18	1.51	154	12.92
Palestine	18	1.51	172	14.43
Philippines	131	10.99	303	25.42
Saudi Arabia	788	66.11	1091	91.53
Somalia	2	0.17	1093	91.69
South Africa	3	0.25	1096	91.95
Sri Lanka	1	0.08	1097	92.03
Sudan	22	1.85	1119	93.88
Syrian Arab Republic	24	2.01	1143	95.89
Tunisia	1	0.08	1144	95.97
Turkey	1	0.08	1145	96.06
United Kingdom	1	0.08	1146	96.14
United States	2	0.17	1148	96.31
Yemen	44	3.69	1192	100.00
Frequency Missing = 68				

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	4-5

(g) Describe any sensitivity analyses

Continued on next page

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Results			Page #
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	5-6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Case characteristics among Middle East Respiratory Syndrome Coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-011865.R1
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Date Submitted by the Author:	29-May-2016
Complete List of Authors:	Alhamlan, fatimah; King Faisal Specialist Hospital and Research Center, Department of Infection and Immunity Majumder , Maimuna; Massachusetts Institute of Technology, Engineering Systems Division Brownstein, John; Children's Hospital Boston, CHIP Hawkins, Jared; Children's Hospital Boston, HealthMap Alabdely , Hail; Ministry of Health , Public Health Alzahrani, Abdulaziz; Ministry of Health , Public Health Obeid, Dalia; King Faisal Specialist Hospital and Research Center, Department of Infection and Immunity Al-Ahdal, Mohammed; King Faisal Specialist Hospital, Department of Infection and Immunity BinSaeed, Abdulaziz; Ministry of Health, Public Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Global health, Public health
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE

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Case characteristics among Middle East Respiratory Syndrome

**Coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to
2015**

Running Title: MERS outbreak/non-outbreak cases in Saudi Arabia

Keywords: Middle East Respiratory Syndrome, MERS-CoV, Emerging Infectious Disease,
Saudi Arabia

Word Count: 1908

Abstract**Background:**

As of November 01, 2015, the Saudi Ministry of Health has reported 1273 cases of MERS; among these cases, which include nine outbreaks at different hospitals, 717 (56%) patients have recovered, 14 (1%) remain hospitalized, and 543 (43%) have died. Here, we determine the epidemiologic, demographic, and clinical characteristics that distinguish cases of MERS contracted during outbreaks from those contracted sporadically (i.e. non-outbreak) between 2012 and 2015 in Saudi Arabia.

Methods:

We abstracted and analyzed the data of confirmed outbreak and non-outbreak cases of MERS-CoV infections from September 2012 through October 2015 using data acquired from the Saudi Ministry of Health. Univariate and descriptive statistical analyses were conducted, and time between disease onset and confirmation, onset and notification, and onset and death were examined.

Results:

We determined that 1250 patients (aged 0 to 109 years; mean, 50.825 years) were reported infected with MERS coronavirus (CoV). Approximately two-thirds of all MERS cases were diagnosed in men for both outbreak and non-outbreak cases. Healthcare workers comprised 22% of all MERS cases for both 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 ($p < .001$). Patients contracting MERS during an outbreak were significantly more likely to die of MERS ($p < 0.001$).

Conclusion:

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

48 Introduction

49 Following the isolation of a previously unknown coronavirus (CoV) from the sputum of a 60-
50 year-old man in 2012 [1], 1,618 laboratory-confirmed cases of Middle East respiratory syndrome
51 (MERS) have been reported throughout 26 countries, with 579 cases resulting in death [2]. The
52 vast majority of these 26 countries reported MERS cases after experiencing an exportation event
53 from the Arabian Peninsula [3,4]. Most cases to date have occurred in Saudi Arabia, followed by
54 South Korea, which experienced an outbreak of MERS after the return of an infected
55 businessman who had been traveling in Middle East [5].

56 The exact zoonotic source of MERS-CoV and its mode of transmission in humans remain
57 unclear. Although related sequences have been detected in several bat species [6], MERS-CoV
58 has not been isolated from bats. However, MERS-CoV has been isolated from dromedary
59 camels. A high rate of seropositivity has been confirmed in the camels of the Arabian Peninsula,
60 with no evidence of MERS-CoV infection detected in cows, goats, or sheep [7-10]. One study
61 isolated the full MERS-CoV genome sequences from a dromedary camel and from a patient who
62 died of laboratory-confirmed MERS-CoV infection after close contact with camels; the two
63 isolates were identical. According to serologic data, MERS-CoV had been circulating in the
64 camel—but not in the patient—before human infection occurred, suggesting that MERS-CoV
65 had been transmitted to the patient via the infected camel [11].

66 Whether MERS-CoV is new to camel or human populations or whether it has been
67 present but undetected for years remains unknown. Nonetheless, MERS-CoV was initially
68 regarded primarily as a zoonotic pathogen, with only limited documentation of person-to-person
69 transmission. However, MERS outbreaks of varying sizes have since occurred across Saudi

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3 70 Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family
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5 71 clusters [12,13] and healthcare facilities [14,15].
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8 72 Much remains unknown about MERS, including risk factors associated with MERS-CoV
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10 73 transmissions in both outbreak and non-outbreak settings. Here, we aimed to increase our
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12 74 understanding of the spread and mode of transmission of MERS-CoV by comparing the
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14 75 epidemiologic, demographic, and clinical characteristics of outbreak and non-outbreak MERS-
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16 76 CoV infections from September 2012 to October 2015 as reported to the Saudi Arabian Ministry
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18 77 of Health (MOH).
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24 79 **Materials and Methods**

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27 80 Demographic and clinical data were obtained through the use of standardized contact tracing
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29 81 forms populated by the public health database maintained by the MOH Command & Control
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31 82 Center (CCC). According to the CCC, a confirmed MERS-CoV case is defined as a suspected
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33 83 case with laboratory confirmation of MERS-CoV infection. A suspected case of MERS-CoV in
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35 84 adults (>14 years) is defined as follows: (I) acute respiratory illness with clinical or radiological
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37 85 evidence of pneumonia or acute respiratory distress syndrome; (II) a hospitalized patient with
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39 86 healthcare-associated pneumonia based on clinical and radiological evidence; (III) upper or
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41 87 lower respiratory illness within 2 weeks of exposure to a confirmed or probable case of MERS-
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43 88 CoV infection; or (IV) unexplained acute febrile illness ($\geq 38^{\circ}\text{C}$) presenting with body aches,
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45 89 headache, diarrhea, or nausea/vomiting, with or without respiratory symptoms, and with
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93 Data and Statistical Analyses

94 All data collected were stored and analyzed using SAS (version 9.4) software. Univariate and
95 descriptive statistics were conducted to estimate proportions. Associations between age and two
96 variables (gender and death) were assessed using a χ^2 test. Chi-square analysis using Yates'
97 correction was performed on the dataset to compare case characteristics among outbreak and
98 non-outbreak cases. Distributions of time between onset and confirmation, onset and notification,
99 and onset and death (among patients that died) were also determined for both outbreak and non-
100 outbreak cases. All reported p values are two-tailed and were considered to be statistically
101 significant at $p < 0.05$.

103 Results

104 Distribution of Confirmed MERS-CoV Cases over Time in Saudi Arabia

105 The prevalence of MERS-CoV was highest in the Riyadh region with (46.91%) of the total
106 reported cases, followed by the Jeddah (21%), AlAhsa (5.69%), AlMadinah Almonowarah
107 (4.81%), Eastern (4.73%), AlTaif (4.33%), and Makkah (3.29%) regions. The remaining regions
108 comprised 9.14% of the total reported cases (Figure 1). More than 31% of all confirmed cases of
109 MERS-CoV in Saudi Arabia were reported in May and April of 2014. The highest number of
110 outbreaks was reported to have occurred in May and April of 2014, the second highest in
111 September 2015, and the third highest in February and March of 2015.

113 Demographic Characteristics

114 During the study period, a total of 1250 patients from 0 to 109 years old were reported as
115 infected with MERS-CoV in Saudi Arabia. MERS-CoV was prevalent among individuals who

116 were 30 years or older; by contrast, individuals who were 26 years or younger exhibited very low
 117 incidence. The distribution of age for all reported cases was approximately normal, with a mean
 118 of 50.825 years and a standard deviation of 19.494 years. MERS-CoV was more prevalent in
 119 males (64.77% of total reported cases) than in females. Females had an average age of 48 years
 120 (SD, 19 years), with a minimum of zero and maximum of 90 years. Males had an average age of
 121 52 years (SD, 19 years), with a minimum of zero and a maximum of 109 years (Table 1). We
 122 found a significant association between age and gender ($\chi^2 = 15.22$; $p < 0.01$) and between
 123 gender and death for patients diagnosed with MERS-CoV ($\chi^2 = 12.75$; $p < 0.01$).

124 **Table 1.** Patient characteristics in Middle East respiratory syndrome infection cases reported in
 125 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 hospitalized 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

Supplementary Table 1 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 fraction of outbreak than of non-outbreak cases ($p < 0.001$; Table 2). The prevalence of MERS-CoV infections among men was comparable for both outbreak and non-outbreak cases ($p = 0.239$; Table 2). Similarly, approximately two-thirds of all Saudi MERS diagnoses occurred among Saudi nationals for both outbreak and non-outbreak cases ($p = 0.558$; Table 2). Healthcare workers comprised 22% of all confirmed Saudi MERS cases for both 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 ($p < 0.001$).

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8 145 Of the patients reporting data on camel exposure, 17% of the 123 non-outbreak cases and
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10 146 10% of the 81 outbreak cases indicated that they owned or raised camels; this difference was not
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12 147 statistically significant.
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17 149 **Table 2.** Characteristics of patients with confirmed Middle East respiratory syndrome
18
19 coronavirus infection in the Kingdom of Saudi Arabia from 2012 to 2015 evaluated by outbreak
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21 versus non-outbreak conditions
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	Outbreak cases <i>N</i> = 485		Non-outbreak cases <i>N</i> = 765		χ^2	<i>p</i>
	<i>n</i>	%	<i>n</i>	%		
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 hospitalized 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%		

152 Yates' correction was used for all chi-square calculations.

153

154

155 **Distributions of Time between Onset and the Confirmation, Notification, and Death**

156 Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-
 157 outbreak cases. For outbreak cases and non-outbreak cases, the average time from onset to
 158 notification was 5.3 days and 9.2 days, respectively. Among patients that died, the average time
 159 from onset to death was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases. All
 160 three distributions were long-tailed, and non-outbreak cases were skewed further right (Figures
 161 2–5).

162

163 **Discussion**

164 Using the Saudi MOH CCC public health dataset on MERS cases reported to have occurred from
 165 September 2012 to September 2015, we found three factors distinguishing outbreak and non-
 166 outbreak cases: (1) Patients older than the mean age of 51 years represented a larger than
 167 expected fraction of outbreak than of non-outbreak cases, (2) nosocomial infections occurred
 168 much more frequently among outbreak cases than among non-outbreak cases, and (3) patients
 169 infected during outbreaks were more likely to die of MERS-CoV infection than those infected
 170 during non-outbreak conditions (Table 2).

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3 171 Given that age was associated with death, it is worth noting that the third factor may be
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5 172 explained in part by the over-representation of older individuals among the outbreak cases.
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8 173 Although age was also associated with gender, we found that the proportion of male MERS-CoV
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10 174 infections was approximately two-thirds for both outbreak and non-outbreak cases (Table 2).
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12 175 However, the general over-representation of men is consistent with many previous studies
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15 176 showing predominantly male MERS-CoV patients [3,16,17].
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18 177 Our results also showed that healthcare workers comprised 22% of all Saudi MERS cases
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20 178 diagnosed up to October 2015 (Table 2). This percentage is in agreement with a 2014 World
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22 179 Health Organization (WHO) report stating that 109 of the 402 (approximately 25%) reported
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24 180 MERS-CoV infections in the Jeddah (Saudi Arabia) 2014 outbreak occurred in healthcare
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27 181 workers [16]. Areas neighboring Saudi Arabia, including the city of Al-Ain in the United Arab
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29 182 Emirates, also reported MERS-CoV infections in 16 healthcare workers out of 23 total cases
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31 183 [17]. Additionally, during the large South Korean outbreak in 2015, 14% of the infected cases
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34 184 were in healthcare workers [5].
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37 185 Another 2014 WHO report stated that most person-to-person MERS-CoV infections
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39 186 likely occurred in healthcare settings [18]. We found that nosocomial transmissions comprised
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41 187 one-third of all Saudi MERS-CoV cases reported to date. Importantly, these nosocomial
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43 188 infections occurred more frequently in outbreak cases than in non-outbreak cases, suggesting that
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46 189 nosocomial infections fueled outbreaks (Table 2). The first outbreak in Al-Hasa, Saudi Arabia,
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48 190 (2013) provided valuable information about MERS-CoV transmission in a healthcare setting.
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50 191 The outbreak started in a hemodialysis unit of a private hospital in Al-Hasa, but subsequently
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53 192 spread to three other hospitals. Phylogenetic analysis of the outbreak showed that only eight of
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3 193 the epidemiologic transmissions were related, indicating multiple zoonotic introductions of
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5 194 MERS-CoV [18].
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8 195 To date, MERS-CoV has been detected in camels from Saudi Arabia, Oman, Qatar,
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10 196 Jordan, and Kenya [7,8,10,19,20], and it has been shown that humans can acquire MERS-CoV
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12 197 directly from dromedary camels [21]. Because camel exposure data (i.e., whether the patient
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14 198 owned or raised camels) were gathered for only 204 of the 1250 cases in the database used by
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16 199 this study, we did not include this information in Table 2. Nonetheless, we found that 17% of the
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18 200 123 non-outbreak cases and 10% of the 81 outbreak cases reporting data on camel exposure
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20 201 indicated that the patients owned or raised camels. Although this difference was not statistically
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22 202 significant, this result suggested that camel exposure, and thus zoonotic transmission, might be
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24 203 more common among sporadic, non-outbreak cases than among outbreak cases. A full analysis
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26 204 of this relationship will require more vigilant collection of camel exposure data.
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31 205 This study was limited by the information available in the Saudi MOH CCC public health
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33 206 dataset on MERS-CoV infections that were reported to have occurred between September 2012
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35 207 and October 2015. The surveillance system and data collection forms were inconsistent over the
36
37 208 years during which these data were acquired, likely due to major leadership changes in the
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39 209 MOH. The outbreak cases have thus far been confirmed faster than non-outbreak cases,
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41 210 indicating that improved future surveillance may allow for faster identification of sporadic cases
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43 211 (Figure 5).
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50 213 **Conclusions**

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52 214 Although it has been three years since MERS-CoV was first identified in humans, cases continue
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54 215 to occur in household and healthcare settings, though our results indicated that most person-to-
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3 216 person transmissions involved healthcare-associated infections. Nosocomial outbreaks likely
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6 217 begin when a primary patient seeks care and then escalate due to insufficient implementation of
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8 218 scalable infection control measures. Our results indicate that the best way to control MERS-CoV
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10 219 infections may be to block its spread by practicing rigorous infection control measures in
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12 220 hospitals. Therefore, strengthening of infection control measures in healthcare settings will be
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14 221 critical to the prevention of future outbreaks.
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24 226 Technology (15/3171).

25 227 Competing interests: None declared.

26 228 Ethical approval: This study was approved by the Office of Research Affairs of King Faisal
27 229 Specialist Hospital and Research Centre (KFSH&RC; RAC #2130 033) and the Ministry of
28 230 Health in Riyadh, Saudi Arabia, and included a waiver of informed consent. Informed consent
29 231 was waived because this study involved a retrospective evaluation of publicly available data, the
30 232 data collection was anonymous, and no patient identity was revealed.
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What is already known on this subject?

Middle East respiratory syndrome (MERS) has a firm foothold in the Kingdom of Saudi Arabia. As of November 01, 2015, the Saudi Ministry of Health has reported 1273 cases of MERS; among these cases, which include nine outbreaks at different hospitals, 717 (56%) patients have recovered, 14 (1%) remain hospitalized, and 543 (43%) have died.

What does this study add?

This is the first report to retrieve the epidemiologic, demographic, and clinical characteristics of Middle East respiratory syndrome (MERS) data in Saudi Arabia from September 2012 through October 2015 using univariate and descriptive statistical analyses. We determined that of 1250 patients nosocomial infections comprised one-third of all cases, but they occurred more frequently in outbreak than non-outbreak cases ($p < 0.001$), suggesting that nosocomial infections fueled MERS outbreaks.

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6 308 **Figure 1.** Incidence of MERS coronavirus infections (1250 confirmed cases) across the
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9 309 Kingdom of Saudi Arabia.

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12 310 **Figure 2.** Epidemiologic curve showing the number of cases of MERS-CoV infection and
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14 311 various patient characteristics in the Kingdom of Saudi Arabia by month and year of
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16 312 confirmation. HCW, healthcare worker.

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20 313 **Figure 3.** Histogram of the time from disease onset to MERS-CoV confirmation for outbreak
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22 314 and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak
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24 315 cases and 11.9 days for non-outbreak cases.

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28 316 **Figure 4.** Histogram of time from disease onset to notification for outbreak and non-outbreak
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30 317 cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for
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32 318 non-outbreak cases.

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36 319 **Figure 5.** Histogram of time from onset to death for outbreak and non-outbreak in those cases
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38 320 ending in death. Average time from onset to death among patients that died was 15.6 days for
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40 321 outbreak cases and 19.5 days for non-outbreak cases
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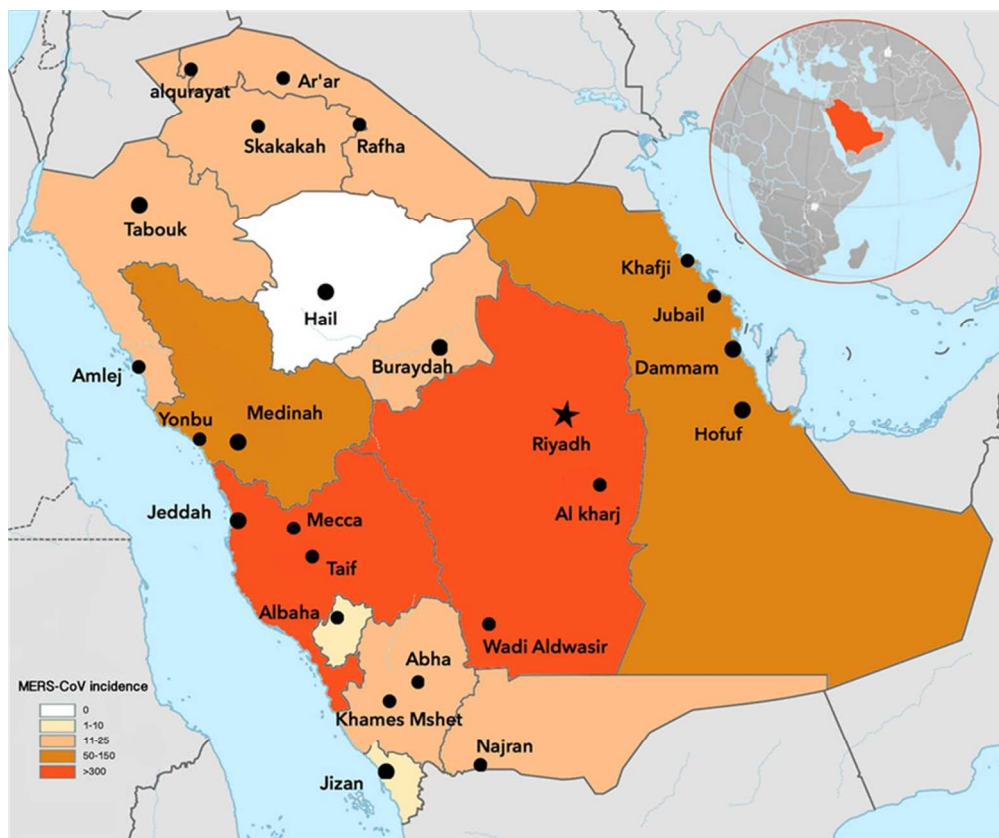


Figure 1. Incidence of MERS coronavirus infections (1250 confirmed cases) across the Kingdom of Saudi Arabia.

86x72mm (300 x 300 DPI)

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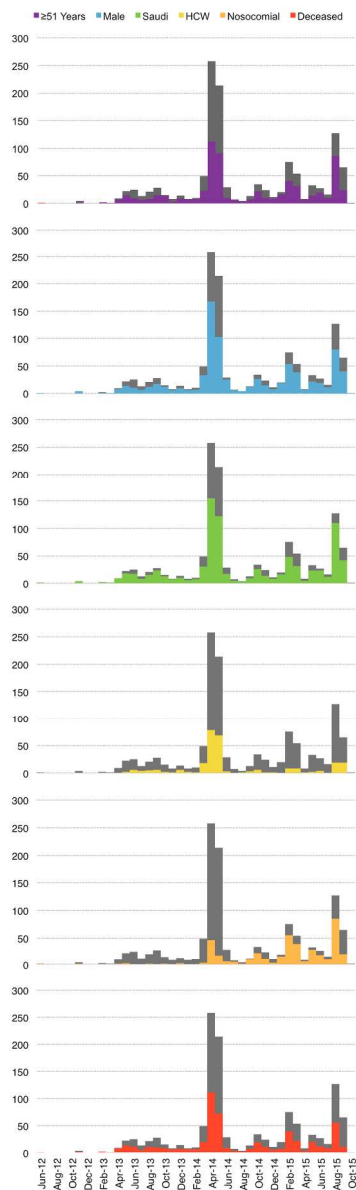


Figure 2. Epidemiologic curve showing the number of cases of MERS-CoV infection and various patient characteristics in the Kingdom of Saudi Arabia by month and year of confirmation. HCW, healthcare worker.

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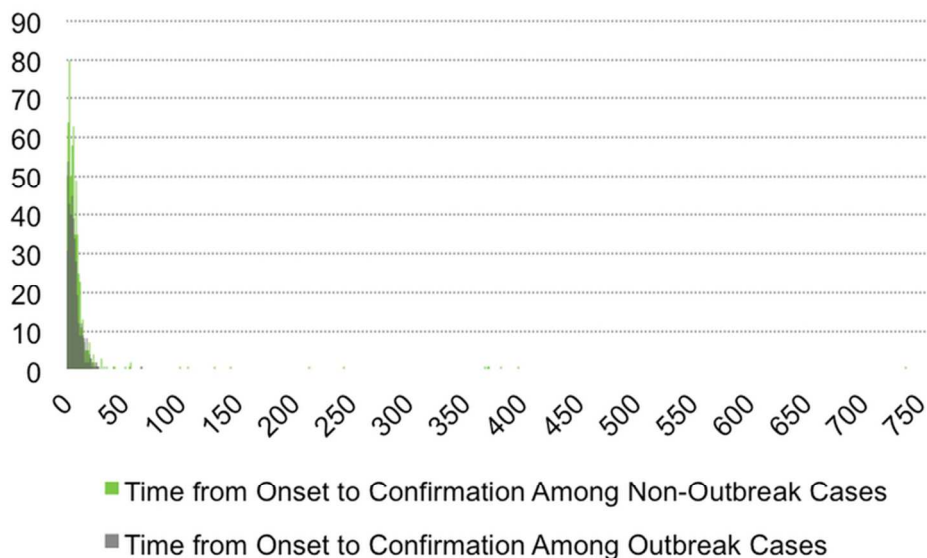


Figure 3. Histogram of the time from disease onset to MERS-CoV confirmation for outbreak and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases.

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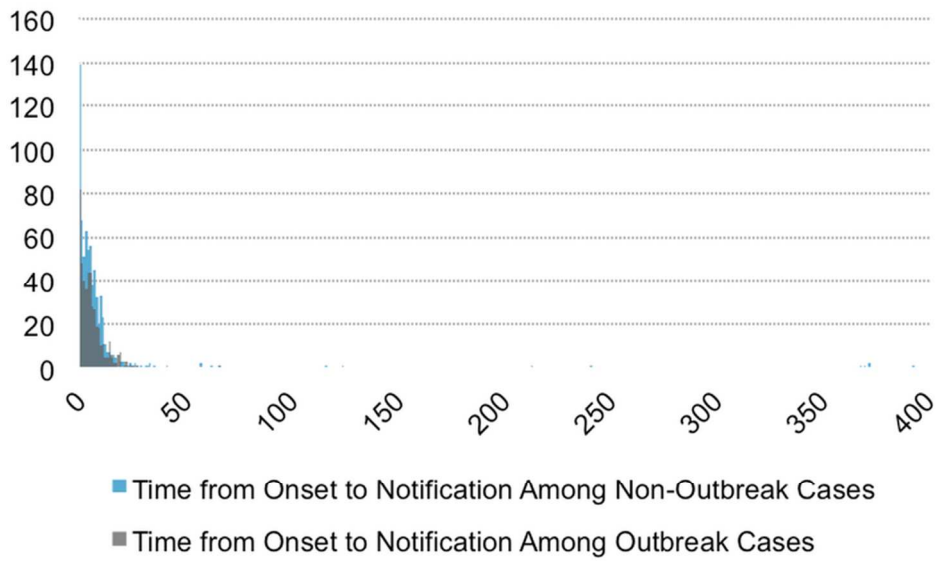


Figure 4. Histogram of time from disease onset to notification for outbreak and non-outbreak cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for non-outbreak cases.

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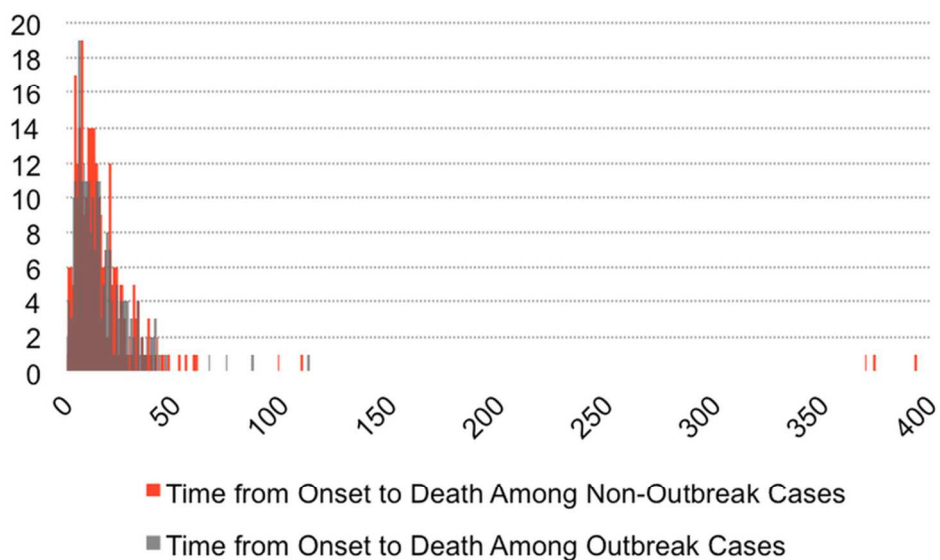


Figure 5. Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients that died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases

90x54mm (300 x 300 DPI)

Supplementary Table 1. Nationalities for patients who were diagnosed with MERS-CoV virus in Saudi Arabia

Nationality				
Nationality	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Australia	1	0.08	1	0.08
Azerbaijan	1	0.08	2	0.17
Bangladesh	19	1.59	21	1.76
Chad	1	0.08	22	1.85
Egypt	33	2.77	55	4.61
Eritrea	3	0.25	58	4.87
Ethiopia	1	0.08	59	4.95
India	47	3.94	106	8.89
Indonesia	6	0.50	112	9.40
Jordan	7	0.59	119	9.98
Kuwait	1	0.08	120	10.07
Lebanon	4	0.34	124	10.40
Malaysia	6	0.50	130	10.91
Morocco	1	0.08	131	10.99
Myanmar	5	0.42	136	11.41
Pakistan	18	1.51	154	12.92
Palestine	18	1.51	172	14.43
Philippines	131	10.99	303	25.42
Saudi Arabia	788	66.11	1091	91.53
Somalia	2	0.17	1093	91.69
South Africa	3	0.25	1096	91.95
Sri Lanka	1	0.08	1097	92.03
Sudan	22	1.85	1119	93.88
Syrian Arab Republic	24	2.01	1143	95.89
Tunisia	1	0.08	1144	95.97
Turkey	1	0.08	1145	96.06
United Kingdom	1	0.08	1146	96.14
United States	2	0.17	1148	96.31
Yemen	44	3.69	1192	100.00
Frequency Missing = 68				

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4-5
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	

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(e) Describe any sensitivity analyses

Continued on next page

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Results			Page #
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	5-6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Case characteristics among Middle East Respiratory Syndrome Coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015

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Secondary Subject Heading:	Epidemiology, Global health, Public health
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE

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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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Running Title: MERS outbreak/non-outbreak cases in Saudi Arabia

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21 Abstract

22 **Objectives:** As of November 01, 2015, the Saudi Ministry of Health had reported 1273 cases of
23 MERS; among these cases, which included nine outbreaks at several hospitals, 717 (56%)
24 patients recovered, 14 (1%) remain hospitalized, and 543 (43%) died. This study aimed to
25 determine the epidemiologic, demographic, and clinical characteristics that distinguished cases
26 of MERS contracted during outbreaks from those contracted sporadically (i.e., non-outbreak)
27 between 2012 and 2015 in Saudi Arabia.

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

32 **Results:** A total of 1250 patients (aged 0 to 109 years; mean, 50.825 years) were reported
33 infected with MERS coronavirus (CoV). Approximately two-thirds of all MERS cases were
34 diagnosed in men for both outbreak and non-outbreak cases. Healthcare workers comprised 22%
35 of all MERS cases for both outbreak and non-outbreak cases. Nosocomial infections comprised
36 one-third of all Saudi MERS cases; however, nosocomial infections occurred more frequently in
37 outbreak than non-outbreak cases ($p < .001$). Patients contracting MERS during an outbreak
38 were significantly more likely to die of MERS ($p < 0.001$).

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

42 Strengths and limitations of this study

- 44 • Confirmed outbreak and non-outbreak cases of Middle East respiratory syndrome
45 (MERS) corona virus infections in Saudi Arabia from September 2012 through
46 November 2015 reported to the Saudi Ministry of Health (MOH) were abstracted and
47 analysed.
- 48 • This is the first report to retrieve the epidemiologic, demographic, and clinical
49 characteristics of MERS data from this database and analyse these data using univariate
50 and descriptive statistical analyses.
- 51 • However, major leadership changes in the Saudi MOH during the study period led to
52 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.

Introduction

Following the isolation of a previously unknown coronavirus (CoV) from the sputum of a 60-year-old man in 2012,¹ 1,618 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 traveling 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 the 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 serologic 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

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101 **Data and Statistical Analyses**

102 All data collected were stored and analysed using SAS (version 9.4) software. Univariate and
103 descriptive statistics were conducted to estimate proportions. Associations between age and two
104 variables (gender and death) were assessed using a χ^2 test. Chi-square analysis using Yates'
105 correction was performed on the dataset to compare case characteristics among outbreak and
106 non-outbreak cases. Distributions of time between onset and confirmation, onset and notification,
107 and onset and death (among patients that died) were also determined for both outbreak and non-
108 outbreak cases. All reported p values are two-tailed and were considered to be statistically
109 significant at $p < 0.05$.

110

111 **Results**

112 **Distribution of Confirmed MERS-CoV Cases over Time in Saudi Arabia**

113 The prevalence of MERS-CoV was highest in the Riyadh region with (46.91%) of the total
114 reported cases, followed by the Jeddah (21%), AlAhsa (5.69%), AlMadinah Almonowarah
115 (4.81%), Eastern (4.73%), AlTaif (4.33%), and Makkah (3.29%) regions. The remaining regions
116 comprised 9.14% of the total reported cases (Figure 1). More than 31% of all confirmed cases of
117 MERS-CoV in Saudi Arabia were reported in May and April of 2014. The highest number of
118 outbreaks was reported to have occurred in May and April of 2014, the second highest in
119 September 2015, and the third highest in February and March of 2015.

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121 **Demographic Characteristics**

122 During the study period, a total of 1250 patients from 0 to 109 years old were reported as

123 infected with MERS-CoV in Saudi Arabia. MERS-CoV was prevalent among individuals who
 124 were 30 years or older; by contrast, individuals who were 26 years or younger exhibited very low
 125 incidence. The distribution of age for all reported cases was approximately normal, with a mean
 126 of 50.825 years and a standard deviation of 19.494 years. MERS-CoV was more prevalent in
 127 males (64.77% of total reported cases) than in females. Females had an average age of 48 years
 128 (SD, 19 years), with a minimum of zero and maximum of 90 years. Males had an average age of
 129 52 years (SD, 19 years), with a minimum of zero and a maximum of 109 years (Table 1). We
 130 found a significant association between age and gender ($\chi^2 = 15.22$; $p < 0.01$) and between
 131 gender and death for patients diagnosed with MERS-CoV ($\chi^2 = 12.75$; $p < 0.01$).

132 **Table 1.** Patient characteristics in Middle East respiratory syndrome infection cases reported in
 133 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 hospitalized 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

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Supplementary Table 1 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.

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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 fraction of outbreak than of non-outbreak cases ($p < 0.001$; Table 2). The prevalence of MERS-CoV infections among men was comparable for both outbreak and non-outbreak cases ($p = 0.239$; Table 2). Similarly, approximately two-thirds of all Saudi MERS diagnoses occurred among Saudi nationals for both outbreak and non-outbreak cases ($p = 0.558$; Table 2). Healthcare workers comprised 22% of all confirmed Saudi MERS cases for both 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 ($p < 0.001$).

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151 Patients that became infected during outbreaks were more likely to die of MERS than those
 152 infected during non-outbreak conditions ($p < 0.001$).

153 Of the patients reporting data on camel exposure, 17% of the 123 non-outbreak cases and
 154 10% of the 81 outbreak cases indicated that they owned or raised camels; this difference was not
 155 statistically significant.

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

	Outbreak cases <i>N</i> = 485		Non-outbreak cases <i>N</i> = 765		χ^2	p
	n	%	n	%		
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 hospitalized 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%		

159 Yates' correction was used for all chi-square calculations.

160 **Distributions of Time between Onset and the Confirmation, Notification, and Death**

161 Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-
162 outbreak cases. For outbreak cases and non-outbreak cases, the average time from onset to
163 notification was 5.3 days and 9.2 days, respectively. Among patients that died, the average time
164 from onset to death was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases. All
165 three distributions were long-tailed, and non-outbreak cases were skewed further right (Figures
166 2–5).

168 **Discussion**

169 Using the Saudi MOH CCC public health dataset on MERS cases reported to have occurred from
170 September 2012 to September 2015, we found three factors distinguishing outbreak and non-
171 outbreak cases: (1) Patients older than the mean age of 51 years represented a larger than
172 expected fraction of outbreak than of non-outbreak cases, (2) nosocomial infections occurred
173 much more frequently among outbreak cases than among non-outbreak cases, and (3) patients
174 infected during outbreaks were more likely to die of MERS-CoV infection than those infected
175 during non-outbreak conditions (Table 2).

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

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4 182 Our results also showed that healthcare workers comprised 22% of all Saudi MERS cases
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6 183 diagnosed up to October 2015 (Table 2). This percentage is in agreement with a 2014 World
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8 184 Health Organization (WHO) report stating that 109 of the 402 (approximately 25%) reported
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0 185 MERS-CoV infections in the Jeddah (Saudi Arabia) 2014 outbreak occurred in healthcare
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2 186 workers.¹⁶ Areas neighbouring Saudi Arabia, including the city of Al-Ain in the United Arab
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4 187 Emirates, also reported MERS-CoV infections in 16 healthcare workers out of 23 total cases.¹⁷
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6 188 Additionally, during the large South Korean outbreak in 2015, 14% of the infected cases were in
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8 189 healthcare workers.⁵

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3 190 Another 2014 WHO report stated that most person-to-person MERS-CoV infections
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5 191 likely occurred in healthcare settings.¹⁸ We found that nosocomial transmissions comprised one-
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7 192 third of all Saudi MERS-CoV cases reported to date. Importantly, these nosocomial infections
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9 193 occurred more frequently in outbreak cases than in non-outbreak cases, suggesting that
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1 194 nosocomial infections fuelled outbreaks (Table 2). The first outbreak in Al-Hasa, Saudi Arabia,
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3 195 (2013) provided valuable information about MERS-CoV transmission in a healthcare setting.
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5 196 The outbreak started in a haemodialysis unit of a private hospital in Al-Hasa, but subsequently
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7 197 spread to three other hospitals. Phylogenetic analysis of the outbreak showed that only eight of
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9 198 the epidemiologic transmissions were related, indicating multiple zoonotic introductions of
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1 199 MERS-CoV.¹⁸

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3 200 To date, MERS-CoV has been detected in camels from Saudi Arabia, Oman, Qatar,
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5 201 Jordan, and Kenya,^{7, 8, 10, 19, 20} and it has been shown that humans can acquire MERS-CoV
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7 202 directly from dromedary camels.²¹ Because camel exposure data (i.e., whether the patient owned
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9 203 or raised camels) were gathered for only 204 of the 1250 cases in the database used by this study,
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1 204 we did not include this information in Table 2. Nonetheless, we found that 17% of the 123 non-

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3 205 outbreak cases and 10% of the 81 outbreak cases reporting data on camel exposure indicated that
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5 206 the patients owned or raised camels. Although this difference was not statistically significant,
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8 207 this result suggested that camel exposure, and thus zoonotic transmission, might be more
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1 208 common among sporadic, non-outbreak cases than among outbreak cases. A full analysis of this
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3 209 relationship will require more vigilant collection of camel exposure data.
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5 210 This study was limited by the information available in the Saudi MOH CCC public health
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7 211 dataset on MERS-CoV infections that were reported to have occurred between September 2012
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9 212 and October 2015. The surveillance system and data collection forms were inconsistent over the
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1 213 years during which these data were acquired, likely due to major leadership changes in the
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3 214 MOH. The outbreak cases have thus far been confirmed faster than non-outbreak cases,
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5 215 indicating that improved future surveillance may allow for faster identification of sporadic cases
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7 216 (Figure 5).
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218 **Conclusions**

219 Although it has been three years since MERS-CoV was first identified in humans, cases continue
220 to occur in household and healthcare settings, though our results indicated that most person-to-
221 person transmissions involved healthcare-associated infections. Nosocomial outbreaks likely
222 begin when a primary patient seeks care and then escalate due to insufficient implementation of
223 scalable infection control measures. Our results indicate that the best way to control MERS-CoV
224 infections may be to block its spread by practicing rigorous infection control measures in
225 hospitals. Therefore, strengthening of infection control measures in healthcare settings will be
226 critical to the prevention of future outbreaks.
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3 228 **Footnotes**
4

5 229 **Acknowledgments:** We are grateful to the Ministry of Health staff who helped in data
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7
8 230 collection.

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0 231 **Contributors:** FA is the study PI and wrote the manuscript. MM developed the study design and
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2
3 232 conducted the analyses. JH interpreted the results. JB reviewed the study design. DO performed
4
5 233 the statistical analyses. HA, AA, and ABS acquired patient demographic and clinical data from
6
7
8 234 the Saudi Ministry of Health database. MA participated in interpreting the clinical results and
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0 235 reviewed the manuscript. All authors participated in critical revision of the manuscript and
1
2 236 approved the final version.

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4
5
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7 239 **Competing interests:** None declared.

8 240 **Ethical approval:** This study was approved by the Office of Research Affairs of King Faisal
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0 241 Specialist Hospital and Research Centre (KFSH&RC; RAC #2130 033) and the Ministry of
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2 242 Health in Riyadh, Saudi Arabia, and included a waiver of informed consent. Informed consent
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4 243 was waived because this study involved a retrospective evaluation of publicly available data, the
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6 244 data collection was anonymous, and no patient identity was revealed.

7 245 **Data sharing:** No additional data available.
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314 **Figure legends**

315 **Figure 1.** Incidence of MERS coronavirus infections (1250 confirmed cases) across the
316 Kingdom of Saudi Arabia.

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

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

323 **Figure 4.** Histogram of time from disease onset to notification for outbreak and non-outbreak
324 cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for
325 non-outbreak cases.

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

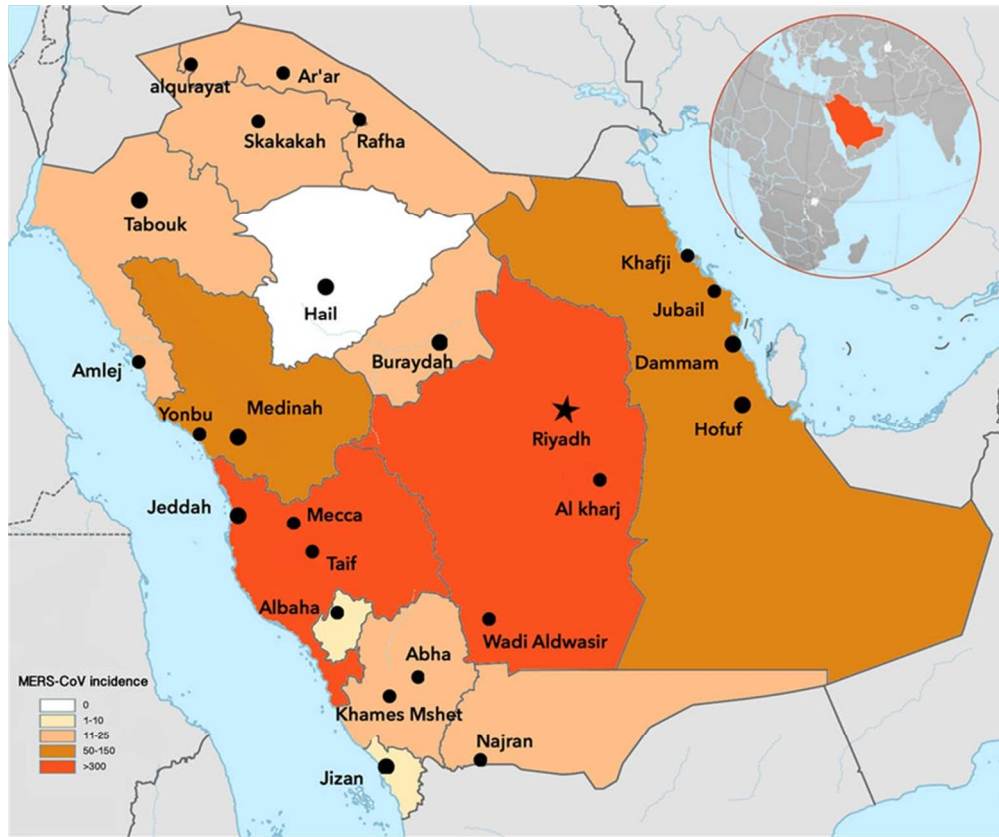


Figure 1. Incidence of MERS coronavirus infections (1283 confirmed cases) across the Kingdom of Saudi Arabia.

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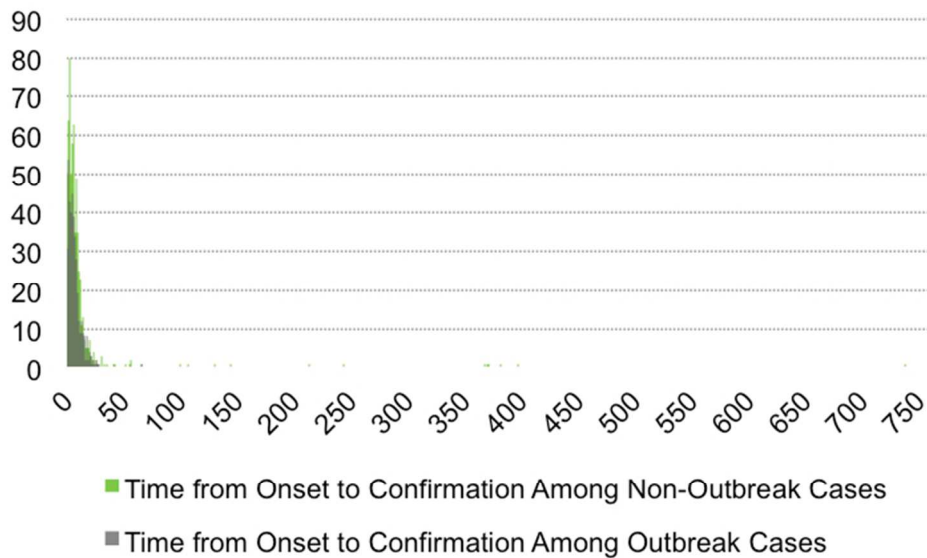


Figure 3. Histogram of the time from disease onset to MERS-CoV confirmation for outbreak and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases.

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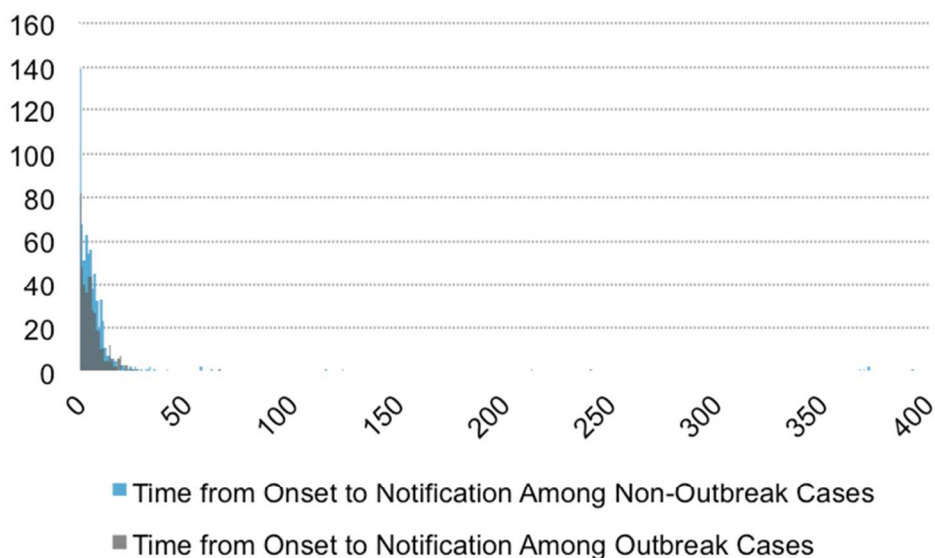


Figure 4. Histogram of time from disease onset to notification for outbreak and non-outbreak cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for non-outbreak cases.

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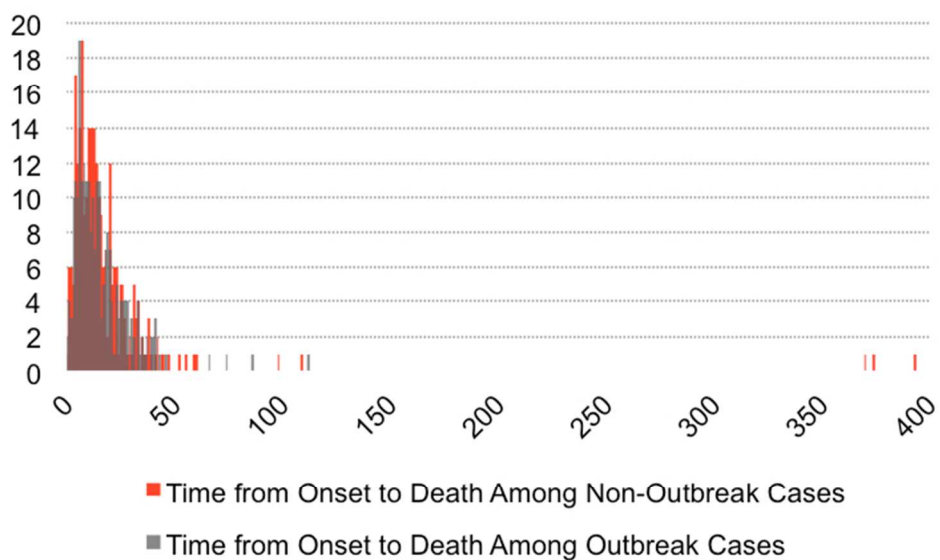


Figure 5. Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients that died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases

Review only

Supplementary Table 1

Nationality	Frequency	Percent
Saudi Arabia	793	66.25
Philippines	131	10.94
India	47	3.93
Yemen	44	3.68
Egypt	33	2.76
Syrian Arab Republic	24	2.01
Sudan	22	1.84
Bangladesh	19	1.59
Pakistan	18	1.50
Palestine	18	1.50
Jordan	7	0.58
Indonesia	6	0.50
Malaysia	6	0.50
Myanmar	5	0.42
Lebanon	4	0.33
Eritrea	3	0.25
South Africa	3	0.25
Somalia	2	0.17
United States	2	0.17
Australia	1	0.08
Azerbaijan	1	0.08
Chad	1	0.08
Ethiopia	1	0.08
Kuwait	1	0.08
Morocco	1	0.08
Sri Lanka	1	0.08
Tunisia	1	0.08
Turkey	1	0.08
United Kingdom	1	0.08

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4-5
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	

(e) Describe any sensitivity analyses

Continued on next page

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Results		Page #	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	5-6
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-9
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Case characteristics among Middle East Respiratory Syndrome Coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015

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Manuscripts

Case characteristics among Middle East Respiratory Syndrome

Coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015

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Running Title: MERS outbreak/non-outbreak cases in Saudi Arabia

Keywords: Middle East Respiratory Syndrome, MERS-CoV, Emerging Infectious Disease, Saudi Arabia

Word Count: 1908

22 Abstract

23 **Objectives:** As of November 01, 2015, the Saudi Ministry of Health had reported 1273 cases of
24 MERS; among these cases, which included nine outbreaks at several hospitals, 717 (56%)
25 patients recovered, 14 (1%) remain hospitalized, and 543 (43%) died. This study aimed to
26 determine the epidemiologic, demographic, and clinical characteristics that distinguished cases
27 of MERS contracted during outbreaks from those contracted sporadically (i.e., non-outbreak)
28 between 2012 and 2015 in Saudi Arabia.

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

33 **Results:** A total of 1250 patients (aged 0 to 109 years; mean, 50.825 years) were reported
34 infected with MERS coronavirus (CoV). Approximately two-thirds of all MERS cases were
35 diagnosed in men for both outbreak and non-outbreak cases. Healthcare workers comprised 22%
36 of all MERS cases for both outbreak and non-outbreak cases. Nosocomial infections comprised
37 one-third of all Saudi MERS cases; however, nosocomial infections occurred more frequently in
38 outbreak than non-outbreak cases ($p < .001$). Patients contracting MERS during an outbreak
39 were significantly more likely to die of MERS ($p < 0.001$).

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

44 Strengths and limitations of this study

- 45 • Confirmed outbreak and non-outbreak cases of Middle East respiratory syndrome
46 (MERS) corona virus infections in Saudi Arabia from September 2012 through October
47 2015 reported to the Saudi Ministry of Health (MOH) were abstracted and analysed.
- 48 • This is the first report to retrieve the epidemiologic, demographic, and clinical
49 characteristics of MERS data from this database and analyse these data using univariate
50 and descriptive statistical analyses.
- 51 • However, major leadership changes in the Saudi MOH during the study period led to
52 alterations in the data collection forms as well as the surveillance system.

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4 53 • These alterations caused some inconsistencies in the data acquired from the Saudi MOH
5 54 database that may limit the interpretation of the study results.
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1 56 **Introduction**

2 57 Following the isolation of a previously unknown coronavirus (CoV) from the sputum of a 60-
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4 58 year-old man in 2012,¹ 1,618 laboratory-confirmed cases of Middle East respiratory syndrome
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6 59 (MERS) have been reported throughout 26 countries, with 579 cases resulting in death.² The vast
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8 60 majority of these 26 countries reported MERS cases after experiencing an exportation event from
9
0 61 the Arabian Peninsula.^{3,4} Most cases to date have occurred in Saudi Arabia, followed by South
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2 62 Korea, which experienced an outbreak of MERS after the return of an infected businessman who
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4 63 had been traveling in Middle East.⁵

5 64 The exact zoonotic source of MERS-CoV and its mode of transmission in humans remain
6
7 65 unclear. Although related sequences have been detected in several bat species,⁶ MERS-CoV has
8
9 66 not been isolated from bats. However, MERS-CoV has been isolated from dromedary camels. A
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1 67 high rate of seropositivity has been confirmed in the camels of the Arabian Peninsula, with no
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3 68 evidence of MERS-CoV infection detected in cows, goats, or sheep.⁷⁻¹⁰ One study isolated the
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5 69 full MERS-CoV genome sequences from a dromedary camel and from a patient who died of
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7 70 laboratory-confirmed MERS-CoV infection after close contact with camels; the two isolates
8
9 71 were identical. According to serologic data, MERS-CoV had been circulating in the camel—but
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1 72 not in the patient—before human infection occurred, suggesting that MERS-CoV had been
2
3 73 transmitted to the patient via the infected camel.¹¹

4 74 Whether MERS-CoV is new to camel or human populations or whether it has been
5
6 75 present but undetected for years remains unknown. Nonetheless, MERS-CoV was initially
7
8 76 regarded primarily as a zoonotic pathogen, with only limited documentation of person-to-person

77 transmission. However, MERS outbreaks of varying sizes have since occurred across Saudi
 78 Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family
 79 clusters^{12, 13} and healthcare facilities.^{14, 15}

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

87 **Materials and Methods**

88 Demographic and clinical data were obtained through the use of standardized contact tracing
 89 forms populated by the public health database maintained by the MOH Command & Control
 90 Center (CCC). According to the CCC, a confirmed MERS-CoV case is defined as a suspected
 91 case with laboratory confirmation of MERS-CoV infection. A suspected case of MERS-CoV in
 92 adults (>14 years) is defined as follows: (I) acute respiratory illness with clinical or radiological
 93 evidence of pneumonia or acute respiratory distress syndrome; (II) a hospitalized patient with
 94 healthcare-associated pneumonia based on clinical and radiological evidence; (III) upper or
 95 lower respiratory illness within 2 weeks of exposure to a confirmed or probable case of MERS-
 96 CoV infection; or (IV) unexplained acute febrile illness ($\geq 38^{\circ}\text{C}$) presenting with body aches,
 97 headache, diarrhoea, or nausea/vomiting, with or without respiratory symptoms, and with
 98 leucopenia.

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101 **Data and Statistical Analyses**

102 All data collected were stored and analysed using SAS (version 9.4) software. Univariate and
103 descriptive statistics were conducted to estimate proportions. Associations between age and two
104 variables (gender and death) were assessed using a χ^2 test. Chi-square analysis using Yates'
105 correction was performed on the dataset to compare case characteristics among outbreak and
106 non-outbreak cases. Distributions of time between onset and confirmation, onset and notification,
107 and onset and death (among patients that died) were also determined for both outbreak and non-
108 outbreak cases. All reported p values are two-tailed and were considered to be statistically
109 significant at $p < 0.05$.

110

111 **Results**

112 **Distribution of Confirmed MERS-CoV Cases over Time in Saudi Arabia**

113 The prevalence of MERS-CoV was highest in the Riyadh region with (46.91%) of the total
114 reported cases, followed by the Jeddah (21%), AlAhsa (5.69%), AlMadinah Almonowarah
115 (4.81%), Eastern (4.73%), AlTaif (4.33%), and Makkah (3.29%) regions. The remaining regions
116 comprised 9.14% of the total reported cases (Figure 1). More than 31% of all confirmed cases of
117 MERS-CoV in Saudi Arabia were reported in May and April of 2014. The highest number of
118 outbreaks was reported to have occurred in May and April of 2014, the second highest in
119 September 2015, and the third highest in February and March of 2015.

120

121 **Demographic Characteristics**

122 During the study period, a total of 1250 patients from 0 to 109 years old were reported as

123 infected with MERS-CoV in Saudi Arabia. MERS-CoV was prevalent among individuals who
 124 were 30 years or older; by contrast, individuals who were 26 years or younger exhibited very low
 125 incidence. The distribution of age for all reported cases was approximately normal, with a mean
 126 of 50.825 years and a standard deviation of 19.494 years. MERS-CoV was more prevalent in
 127 males (64.77% of total reported cases) than in females. Females had an average age of 48 years
 128 (SD, 19 years), with a minimum of zero and maximum of 90 years. Males had an average age of
 129 52 years (SD, 19 years), with a minimum of zero and a maximum of 109 years (Table 1). We
 130 found a significant association between age and gender ($\chi^2 = 15.22$; $p < 0.01$) and between
 131 gender and death for patients diagnosed with MERS-CoV ($\chi^2 = 12.75$; $p < 0.01$).

132 **Table 1.** Patient characteristics in Middle East respiratory syndrome infection cases reported in
 133 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 hospitalized 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

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Supplementary Table 1 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.

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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 fraction of outbreak than of non-outbreak cases ($p < 0.001$; Table 2). The prevalence of MERS-CoV infections among men was comparable for both outbreak and non-outbreak cases ($p = 0.239$; Table 2). Similarly, approximately two-thirds of all Saudi MERS diagnoses occurred among Saudi nationals for both outbreak and non-outbreak cases ($p = 0.558$; Table 2). Healthcare workers comprised 22% of all confirmed Saudi MERS cases for both 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 ($p < 0.001$).

151 Patients that became infected during outbreaks were more likely to die of MERS than those
 152 infected during non-outbreak conditions ($p < 0.001$).

153 Of the patients reporting data on camel exposure, 17% of the 123 non-outbreak cases and
 154 10% of the 81 outbreak cases indicated that they owned or raised camels; this difference was not
 155 statistically significant.

156
 157 **Table 2.** Characteristics of patients with confirmed Middle East respiratory syndrome
 158 coronavirus infection in the Kingdom of Saudi Arabia from 2012 to 2015 evaluated by outbreak
 159 versus non-outbreak conditions

	Outbreak cases <i>N</i> = 485		Non-outbreak cases <i>N</i> = 765		χ^2	p
	n	%	n	%		
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 hospitalized 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%		

160 Yates' correction was used for all chi-square calculations.

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163 **Distributions of Time between Onset and the Confirmation, Notification, and Death**

164 Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-
 165 outbreak cases. For outbreak cases and non-outbreak cases, the average time from onset to
 166 notification was 5.3 days and 9.2 days, respectively. Among patients that died, the average time
 167 from onset to death was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases. All
 168 three distributions were long-tailed, and non-outbreak cases were skewed further right (Figures
 169 2–5).

170

171 **Discussion**

172 Using the Saudi MOH CCC public health dataset on MERS cases reported to have occurred from
 173 September 2012 to September 2015, we found three factors distinguishing outbreak and non-
 174 outbreak cases: (1) Patients older than the mean age of 51 years represented a larger than
 175 expected fraction of outbreak than of non-outbreak cases, (2) nosocomial infections occurred
 176 much more frequently among outbreak cases than among non-outbreak cases, and (3) patients
 177 infected during outbreaks were more likely to die of MERS-CoV infection than those infected
 178 during non-outbreak conditions (Table 2).

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4 179 Given that age was associated with death, it is worth noting that the third factor may be
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6 180 explained in part by the over-representation of older individuals among the outbreak cases.
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8 181 Although age was also associated with gender, we found that the proportion of male MERS-CoV
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0 182 infections was approximately two-thirds for both outbreak and non-outbreak cases (Table 2).
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2 183 However, the general over-representation of men is consistent with many previous studies
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4 184 showing predominantly male MERS-CoV patients.^{3, 16, 17}

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6 185 Our results also showed that healthcare workers comprised 22% of all Saudi MERS cases
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8 186 diagnosed up to October 2015 (Table 2). This percentage is in agreement with a 2014 World
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0 187 Health Organization (WHO) report stating that 109 of the 402 (approximately 25%) reported
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2 188 MERS-CoV infections in the Jeddah (Saudi Arabia) 2014 outbreak occurred in healthcare
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4 189 workers.¹⁶ Areas neighbouring Saudi Arabia, including the city of Al-Ain in the United Arab
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6 190 Emirates, also reported MERS-CoV infections in 16 healthcare workers out of 23 total cases.¹⁷
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8 191 Additionally, during the large South Korean outbreak in 2015, 14% of the infected cases were in
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0 192 healthcare workers.⁵

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2 193 Another 2014 WHO report stated that most person-to-person MERS-CoV infections
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4 194 likely occurred in healthcare settings.¹⁸ We found that nosocomial transmissions comprised one-
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6 195 third of all Saudi MERS-CoV cases reported to date. Importantly, these nosocomial infections
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8 196 occurred more frequently in outbreak cases than in non-outbreak cases, suggesting that
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0 197 nosocomial infections fuelled outbreaks (Table 2). The first outbreak in Al-Hasa, Saudi Arabia,
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2 198 (2013) provided valuable information about MERS-CoV transmission in a healthcare setting.
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4 199 The outbreak started in a haemodialysis unit of a private hospital in Al-Hasa, but subsequently
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6 200 spread to three other hospitals. Phylogenetic analysis of the outbreak showed that only eight of

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3 201 the epidemiologic transmissions were related, indicating multiple zoonotic introductions of
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5 202 MERS-CoV.¹⁸
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8 203 To date, MERS-CoV has been detected in camels from Saudi Arabia, Oman, Qatar,
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0 204 Jordan, and Kenya,^{7, 8, 10, 19, 20} and it has been shown that humans can acquire MERS-CoV
1 205 directly from dromedary camels.²¹ Because camel exposure data (i.e., whether the patient owned
2 206 or raised camels) were gathered for only 204 of the 1250 cases in the database used by this study,
3 207 we did not include this information in Table 2. Nonetheless, we found that 17% of the 123 non-
4 208 outbreak cases and 10% of the 81 outbreak cases reporting data on camel exposure indicated that
5 209 the patients owned or raised camels. Although this difference was not statistically significant,
6 210 this result suggested that camel exposure, and thus zoonotic transmission, might be more
7 211 common among sporadic, non-outbreak cases than among outbreak cases. A full analysis of this
8 212 relationship will require more vigilant collection of camel exposure data.

9 213 This study was limited by the information available in the Saudi MOH CCC public health
0 214 dataset on MERS-CoV infections that were reported to have occurred between September 2012
1 215 and October 2015. The surveillance system and data collection forms were inconsistent over the
2 216 years during which these data were acquired, likely due to major leadership changes in the
3 217 MOH. The outbreak cases have thus far been confirmed faster than non-outbreak cases,
4 218 indicating that improved future surveillance may allow for faster identification of sporadic cases
5 219 (Figure 5).
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9 221 **Conclusions**

0 222 Although it has been three years since MERS-CoV was first identified in humans, cases continue
1 223 to occur in household and healthcare settings, though our results indicated that most person-to-

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3 224 person transmissions involved healthcare-associated infections. Nosocomial outbreaks likely
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5 225 begin when a primary patient seeks care and then escalate due to insufficient implementation of
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8 226 scalable infection control measures. Our results indicate that the best way to control MERS-CoV
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1 227 infections may be to block its spread by practicing rigorous infection control measures in
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3 228 hospitals. Therefore, strengthening of infection control measures in healthcare settings will be
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5 229 critical to the prevention of future outbreaks.
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2 231 **Footnotes**

2 232 **Footnotes**

3 233 **Acknowledgments:** We are grateful to the Ministry of Health staff who helped in data
4
5 234 collection.

6 235 **Contributors:** FA is the study PI and wrote the manuscript. MM developed the study design and
7
8 236 conducted the analyses. JH interpreted the results. JB reviewed the study design. DO performed
9
0
1 237 the statistical analyses. HA, AA, and ABS acquired patient demographic and clinical data from
2
3 238 the Saudi Ministry of Health database. MA participated in interpreting the clinical results and
4
5 239 reviewed the manuscript. All authors participated in critical revision of the manuscript and
6
7 240 approved the final version.

8 241 **Funding:** This study was partially supported by a summer grant from King Abdulaziz City for
9
0 242 Science and Technology (15/3171).

1 243 **Competing interests:** None declared.

2 244 **Ethical approval:** This study was approved by the Office of Research Affairs of King Faisal
3
4 245 Specialist Hospital and Research Centre (KFSH&RC; RAC #2130 033) and the Ministry of
5
6 246 Health in Riyadh, Saudi Arabia, and included a waiver of informed consent. Informed consent

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247 was waived because this study involved a retrospective evaluation of publicly available data, the
248 data collection was anonymous, and no patient identity was revealed.

249 **Data sharing:** No additional data available.

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6 321 **Figure 1.** Incidence of MERS coronavirus infections (1250 confirmed cases) across the
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8 322 Kingdom of Saudi Arabia.

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1 323 **Figure 2.** Epidemiologic curve showing the number of cases of MERS-CoV infection and
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3 324 various patient characteristics in the Kingdom of Saudi Arabia by month and year of
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5 325 confirmation. HCW, healthcare worker.

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8 326 **Figure 3.** Histogram of the time from disease onset to MERS-CoV confirmation for outbreak
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0 327 and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak
1 328 cases and 11.9 days for non-outbreak cases.

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4 329 **Figure 4.** Histogram of time from disease onset to notification for outbreak and non-outbreak
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6 330 cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for
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8 331 non-outbreak cases.

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1 332 **Figure 5.** Histogram of time from onset to death for outbreak and non-outbreak in those cases
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3 333 ending in death. Average time from onset to death among patients that died was 15.6 days for
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5 334 outbreak cases and 19.5 days for non-outbreak cases



Figure 1. Incidence of MERS coronavirus infections (1283 confirmed cases) across the Kingdom of Saudi Arabia.

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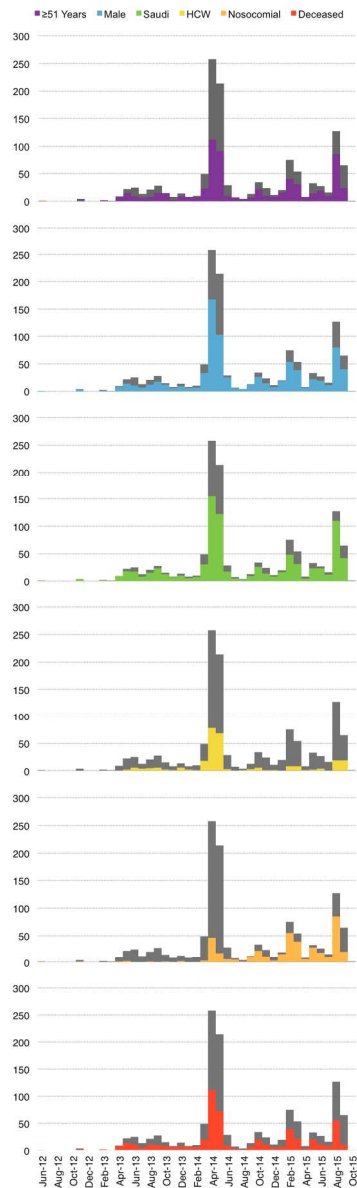


Figure 2. Epidemiologic curve showing the number of cases of MERS-CoV infection and various patient characteristics in the Kingdom of Saudi Arabia by month and year of confirmation. HCW, healthcare worker.

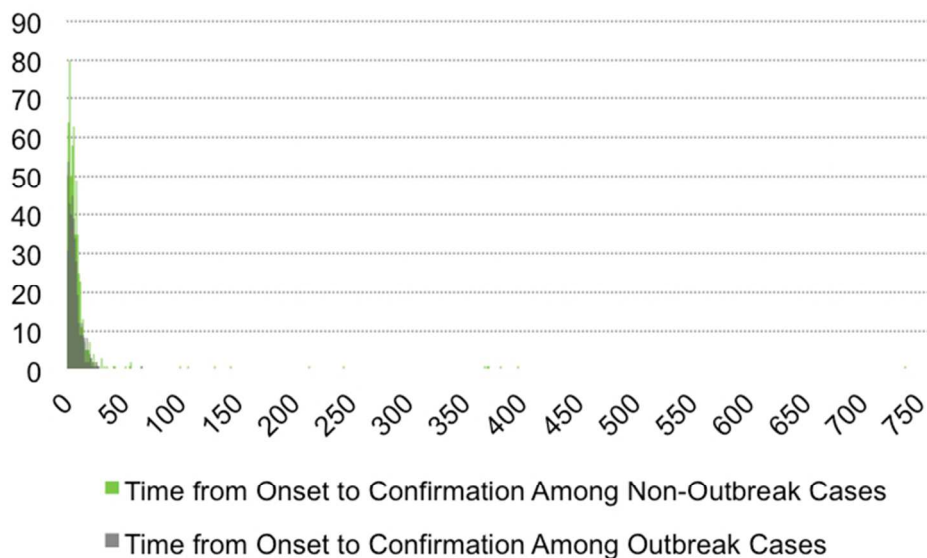


Figure 3. Histogram of the time from disease onset to MERS-CoV confirmation for outbreak and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases.

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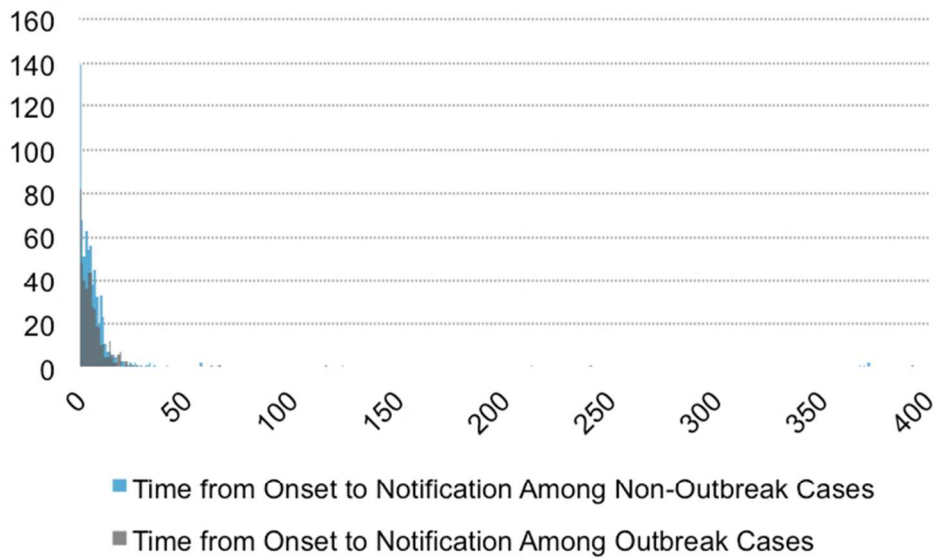


Figure 4. Histogram of time from disease onset to notification for outbreak and non-outbreak cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for non-outbreak cases.

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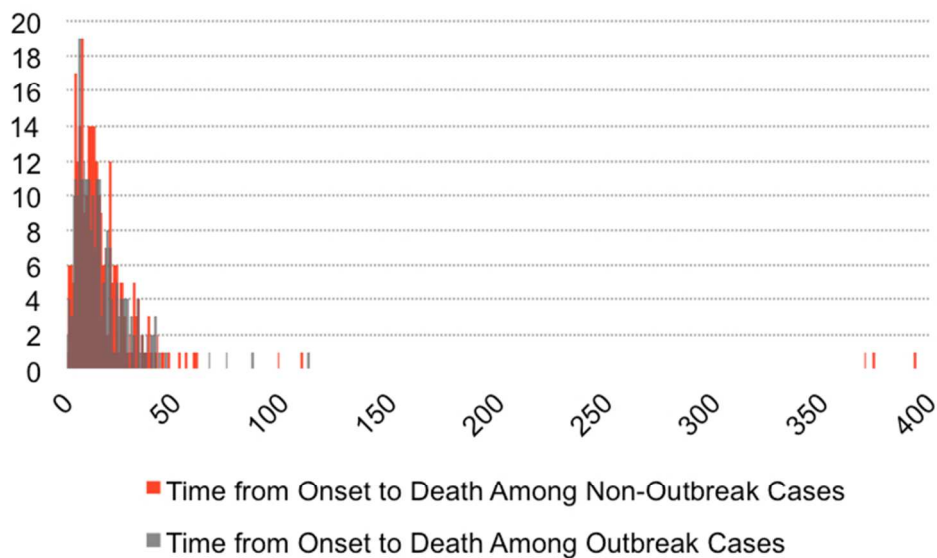


Figure 5. Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients that died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases

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Supplementary Table 1

Nationality	Frequency	Percent
Saudi Arabia	793	66.25
Philippines	131	10.94
India	47	3.93
Yemen	44	3.68
Egypt	33	2.76
Syrian Arab Republic	24	2.01
Sudan	22	1.84
Bangladesh	19	1.59
Pakistan	18	1.50
Palestine	18	1.50
Jordan	7	0.58
Indonesia	6	0.50
Malaysia	6	0.50
Myanmar	5	0.42
Lebanon	4	0.33
Eritrea	3	0.25
South Africa	3	0.25
Somalia	2	0.17
United States	2	0.17
Australia	1	0.08
Azerbaijan	1	0.08
Chad	1	0.08
Ethiopia	1	0.08
Kuwait	1	0.08
Morocco	1	0.08
Sri Lanka	1	0.08
Tunisia	1	0.08
Turkey	1	0.08
United Kingdom	1	0.08

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4-5
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	

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(e) Describe any sensitivity analyses

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Results		Page #	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	5-6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

Alhamlan FS, Majumder MS, Brownstein JS, *et al.* Case characteristics among Middle East respiratory syndrome coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015. *BMJ Open* 2017;7:e011865. doi: 10.1136/bmjopen-2016-011865.

There was an error in the affiliation of A BinSaeed.

The correct affiliation for A BinSaeed is 'Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia'.

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