BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011865
Article Type:	Research
Date Submitted by the Author:	12-Mar-2016
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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Global health, Public health
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE

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

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Abstract

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

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

Results: A total of 1250 patients (aged 0 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 ($p < 0.001$).

Conclusions: To date, nosocomial infections have fuelled 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.

Strengths and limitations of this study

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

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 transmission. However, MERS outbreaks of varying sizes have since occurred across Saudi

Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family clusters[12, 13] and healthcare facilities.[14, 15]

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

Materials and Methods

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

Data and Statistical Analyses

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

Results

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

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

Demographic Characteristics

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

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

Demographic characteristics (n)	Frequency	Percentage
Age in years (1244)		
0-10	41	3.30
11-25	63	8.36
26-39	292	31.83
40-109	848	68.17
Gender (1246)		
Female	439	35.23
Male	807	64.77
Occupational status (172)		
Employed	22	12.79
Unemployed	40	23.26
Retired	31	21.51
Private	37	18.02
Other	42	24.42
Main reason for testing (1247)		
Healthcare worker	249	19.97
Household	138	11.07
Suspect	860	68.97
Healthcare worker (1244)		
Yes	275	22.11
No	969	77.89
Does the patient raise camels? (205)		
Yes	29	14.15
No	176	85.85
During the 14 days before the patient became sick, did he/she travel outside or inside Saudi Arabia? (205)		
Yes	195	95.12
No	10	4.88
Was the patient 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 ($p < 0.001$).

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

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

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

	Outbreak cases *N = 485*		Non-outbreak cases *N = 765*		χ^2	p
	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%		

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

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

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

Discussion

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

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

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

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

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

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

Conclusions

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

Footnotes

Acknowledgments: We are grateful to the Ministry of Health staff who helped in data collection.

Contributors: FA is the study PI and wrote the manuscript. MM developed the study design and conducted the analyses. JH interpreted the results. JB reviewed the study design. DO performed the statistical analyses. HA, AA, and ABS acquired patient demographic and clinical data from the Saudi Ministry of Health database. MA participated in interpreting the clinical results and reviewed the manuscript. All authors participated in critical revision of the manuscript and approved the final version.

Funding: This study was supported in part by a grant from King Abdulaziz City for Science and Technology (15/3171).

Competing interests: None declared.

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

Data sharing: No additional data available.

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312 **Figure legends**

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

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

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

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

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

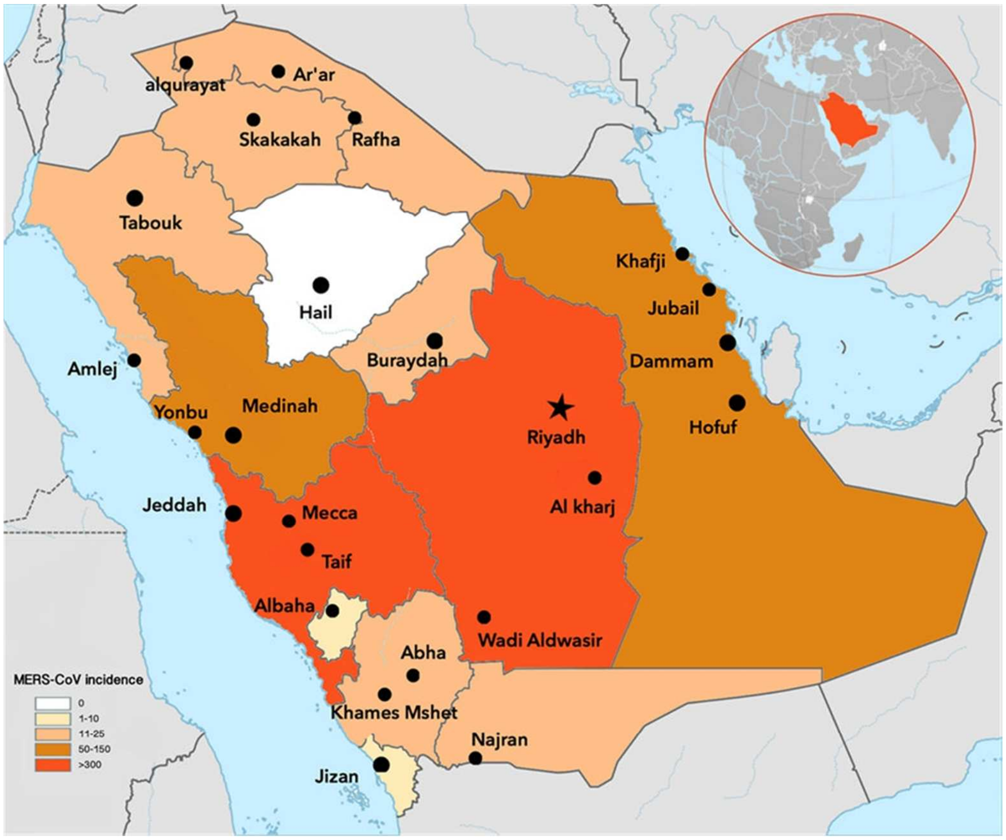
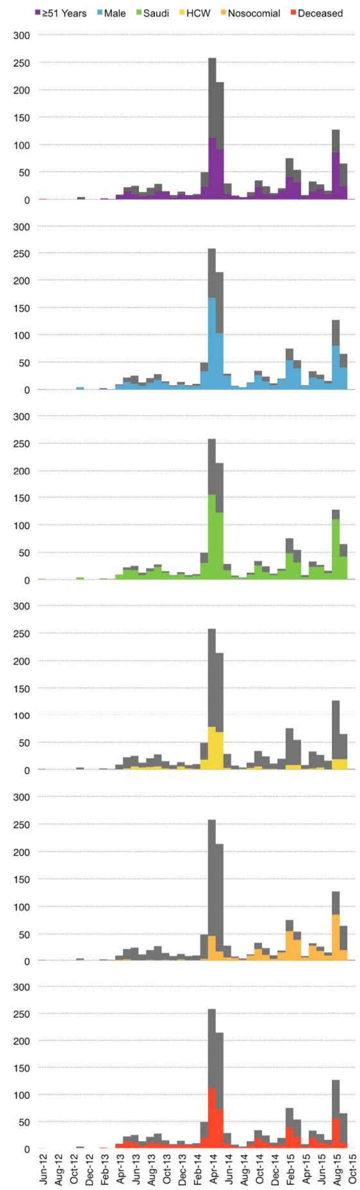


Figure 1. Incidence of MERS coronavirus infections (1250 confirmed cases) across the Kingdom of Saudi Arabia.

86x72mm (300 x 300 DPI)



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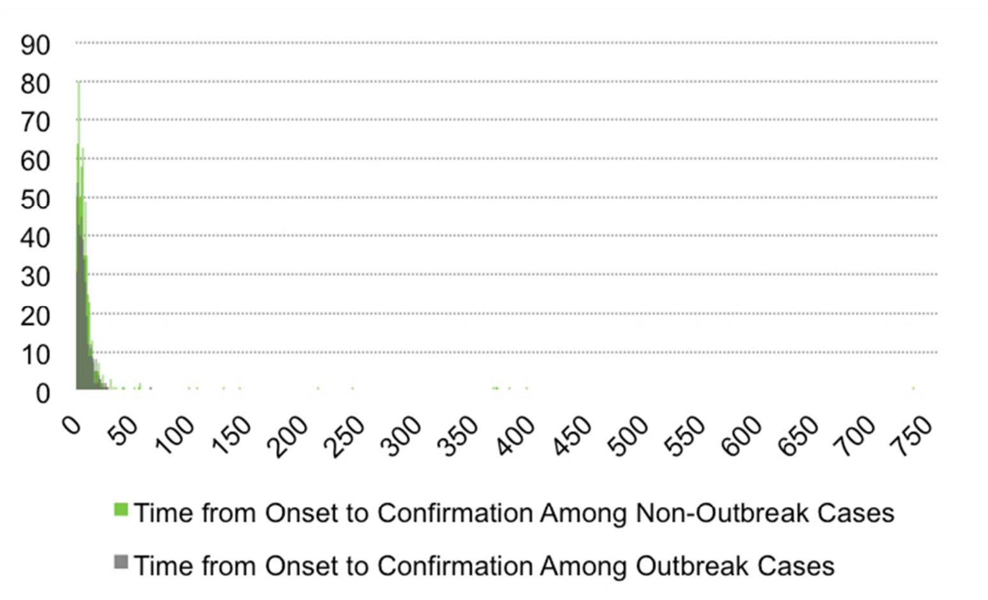

Figure 3. Histogram of the time from disease onset to MERS-CoV confirmation for outbreak and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases.

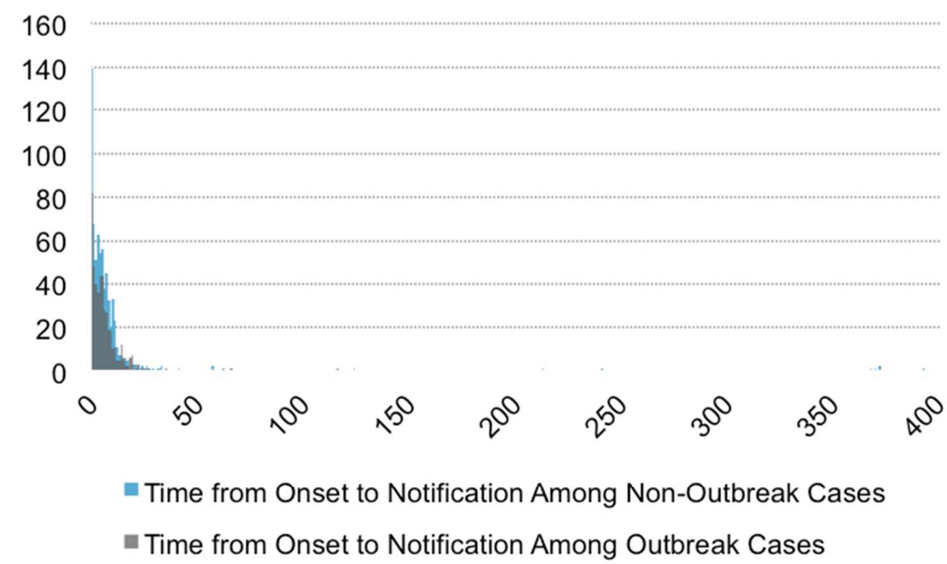

Figure 4. Histogram of time from disease onset to notification for outbreak and non-outbreak cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for non-outbreak cases.

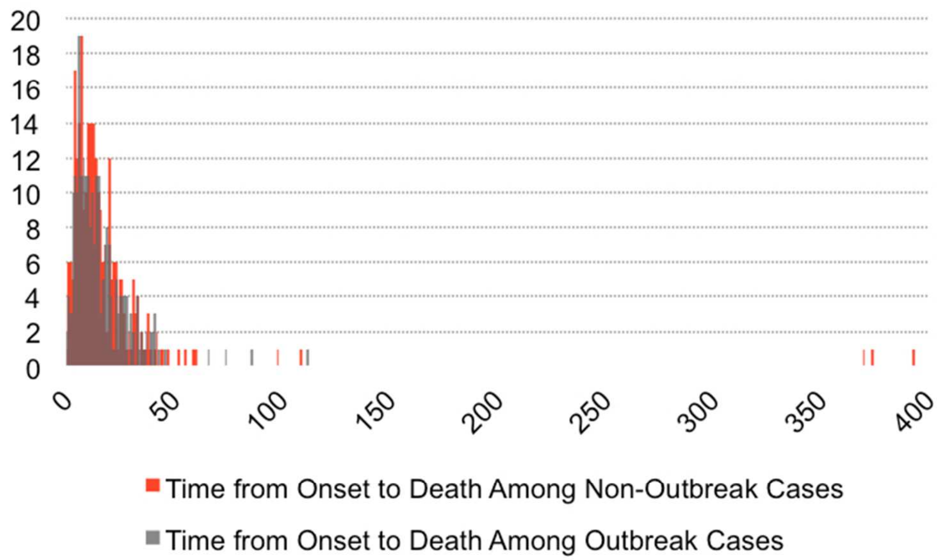

Figure 5. Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients that died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases

Supplementary Table1. 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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	

(*e*) Describe any sensitivity analyses

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*5-6*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011865.R1
Article Type:	Research
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.

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 transmission. However, MERS outbreaks of varying sizes have since occurred across Saudi

Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family clusters [12,13] and healthcare facilities [14,15].

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

Materials and Methods

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

Data and Statistical Analyses

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

Results

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

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

Demographic Characteristics

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

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

Demographic characteristics (n)	Frequency	Percentage
Age in years (1244)		
0-10	41	3.30
11-25	63	8.36
26-39	292	31.83
40-109	848	68.17
Gender (1246)		
Female	439	35.23
Male	807	64.77
Occupational status (172)		
Employed	22	12.79
Unemployed	40	23.26
Retired	31	21.51
Private	37	18.02
Other	42	24.42
Main reason for testing (1247)		
Healthcare worker	249	19.97
Household	138	11.07
Suspect	860	68.97
Healthcare worker (1244)		
Yes	275	22.11
No	969	77.89
Does the patient raise camels? (205)		
Yes	29	14.15
No	176	85.85
During the 14 days before the patient became sick, did he/she travel outside or inside Saudi Arabia? (205)		
Yes	195	95.12
No	10	4.88
Was the patient 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 ($p < 0.001$).

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

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

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

	Outbreak cases *N = 485*		Non-outbreak cases *N = 765*		χ^2	p
	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%		

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

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

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

Discussion

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

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

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

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

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

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

Conclusions

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

Acknowledgments

We are grateful to the Ministry of Health staff who helped in data collection.

Funding: This study was supported in part by a grant from King Abdulaziz City for Science and Technology (15/3171).

Competing interests: None declared.

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

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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Figure legends

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

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.

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

Figure 5. 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

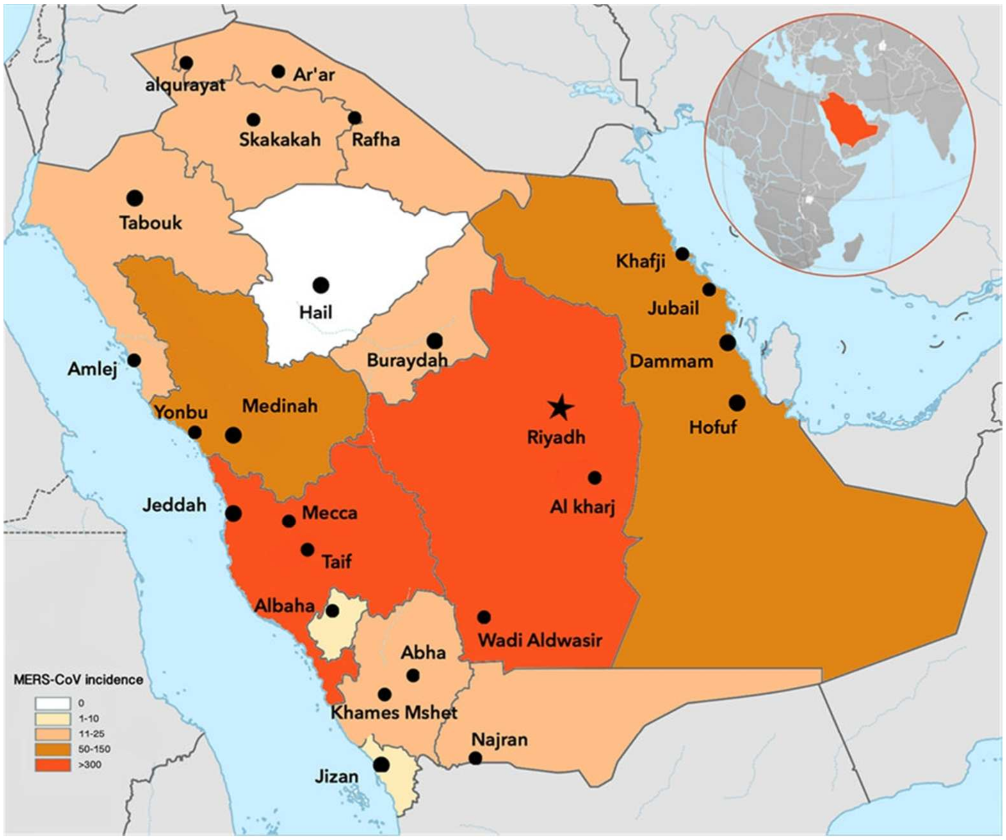

Figure 1. Incidence of MERS coronavirus infections (1250 confirmed cases) across the Kingdom of Saudi Arabia.

86x72mm (300 x 300 DPI)

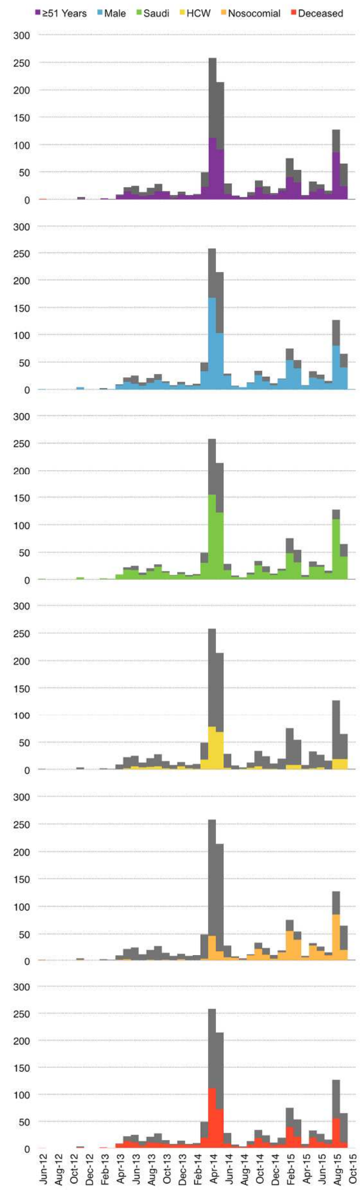

Figure 2. Epidemiologic curve showing the number of cases of MERS-CoV infection and various patient characteristics in the Kingdom of Saudi Arabia by month and year of confirmation. HCW, healthcare worker.

297x984mm (300 x 300 DPI)

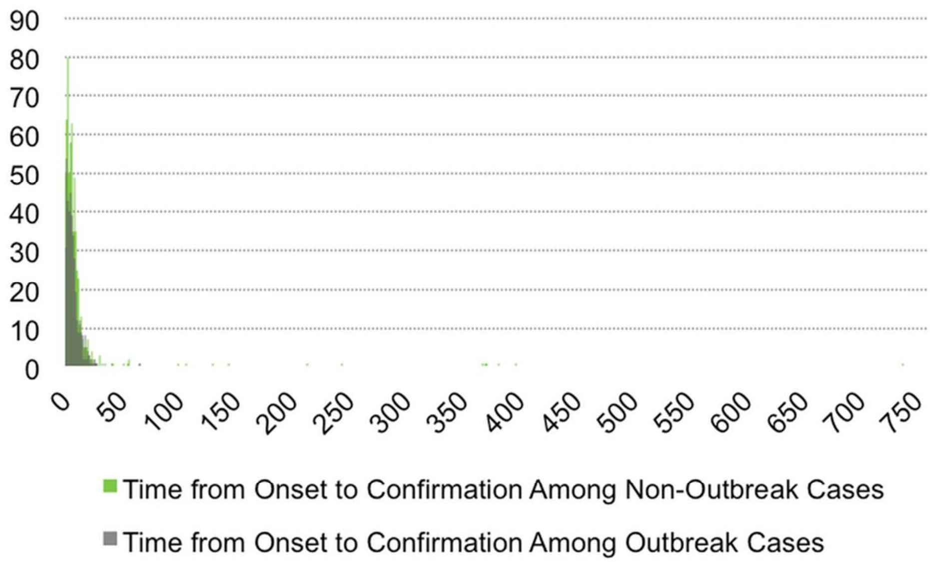

Figure 3. Histogram of the time from disease onset to MERS-CoV confirmation for outbreak and non-outbreak cases. Average time from onset to confirmation was 6.6 days for outbreak cases and 11.9 days for non-outbreak cases.

90x54mm (300 x 300 DPI)

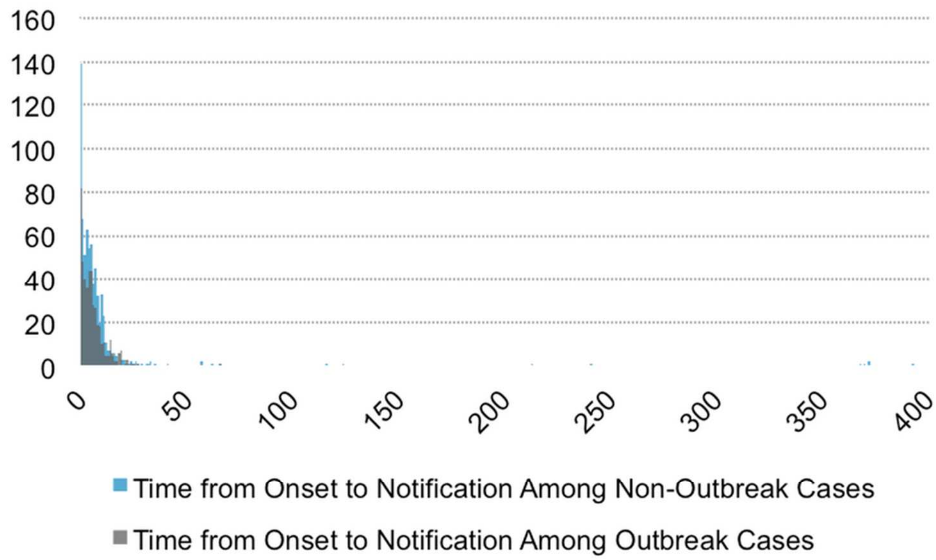

Figure 4. Histogram of time from disease onset to notification for outbreak and non-outbreak cases. Average time from onset to notification was 5.3 days for outbreak cases and 9.2 days for non-outbreak cases.

90x54mm (300 x 300 DPI)

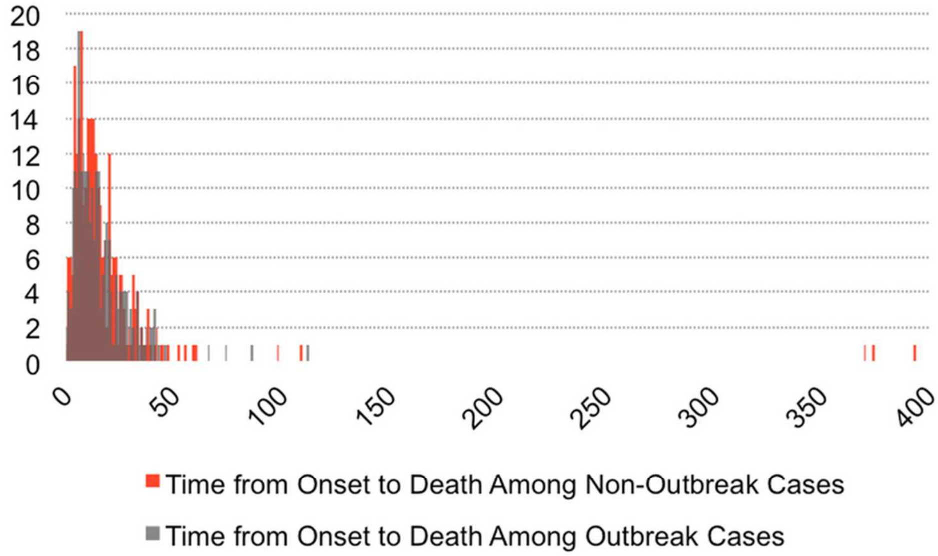

Figure 5. Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients that died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases

90x54mm (300 x 300 DPI)

Supplementary Table1. 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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	

(*e*) Describe any sensitivity analyses

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*5-6*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011865.R2
Article Type:	Research
Date Submitted by the Author:	08-Jul-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

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

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Abstract

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

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

Results: A total of 1250 patients (aged 0 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 ($p < 0.001$).

Conclusions: To date, nosocomial infections have fuelled 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.

Strengths and limitations of this study

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

- These alterations caused some inconsistencies in the data acquired from the Saudi MOH database.

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 transmission. However, MERS outbreaks of varying sizes have since occurred across Saudi Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family clusters[12, 13] and healthcare facilities.[14, 15]

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

Materials and Methods

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

Data and Statistical Analyses

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

Results

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

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

Demographic Characteristics

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

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

Demographic characteristics (n)	Frequency	Percentage
Age in years (1244)		
0-10	41	3.30
11-25	63	8.36
26-39	292	31.83
40-109	848	68.17
Gender (1246)		
Female	439	35.23
Male	807	64.77
Occupational status (172)		
Employed	22	12.79
Unemployed	40	23.26
Retired	31	21.51
Private	37	18.02
Other	42	24.42
Main reason for testing (1247)		
Healthcare worker	249	19.97
Household	138	11.07
Suspect	860	68.97
Healthcare worker (1244)		
Yes	275	22.11
No	969	77.89
Does the patient raise camels? (205)		
Yes	29	14.15
No	176	85.85
During the 14 days before the patient became sick, did he/she travel outside or inside Saudi Arabia? (205)		
Yes	195	95.12
No	10	4.88

Was the patient 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 ($p < 0.001$).

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

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

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

	Outbreak cases *N = 485*		Non-outbreak cases *N = 765*		χ^2	p
	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%		

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

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

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

Discussion

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

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

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

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

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

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

Conclusions

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

Footnotes

Acknowledgments: We are grateful to the Ministry of Health staff who helped in data collection.

Contributors: FA is the study PI and wrote the manuscript. MM developed the study design and conducted the analyses. JH interpreted the results. JB reviewed the study design. DO performed the statistical analyses. HA, AA, and ABS acquired patient demographic and clinical data from the Saudi Ministry of Health database. MA participated in interpreting the clinical results and reviewed the manuscript. All authors participated in critical revision of the manuscript and approved the final version.

Funding: This study was supported in part by a grant from King Abdulaziz City for Science and Technology (15/3171).

Competing interests: None declared.

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

Data sharing: No additional data available.

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Figure legends

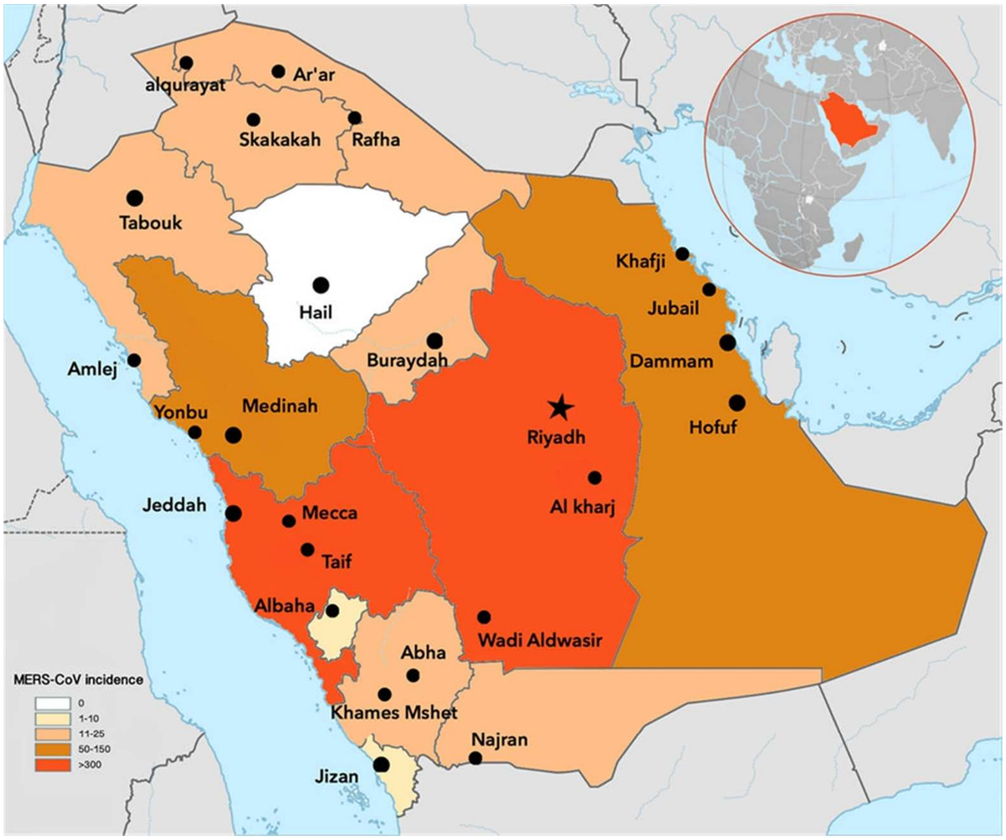
Figure 1. Incidence of MERS coronavirus infections (1250 confirmed cases) across the Kingdom of Saudi Arabia.

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.

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

Figure 5. 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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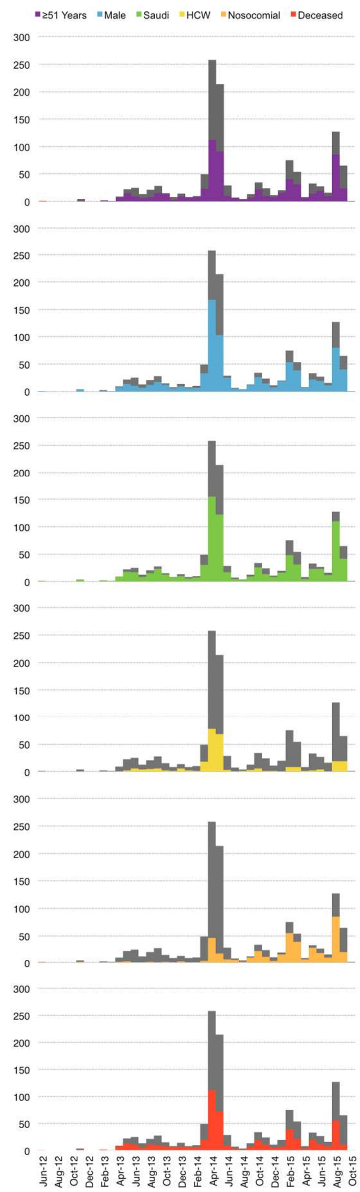

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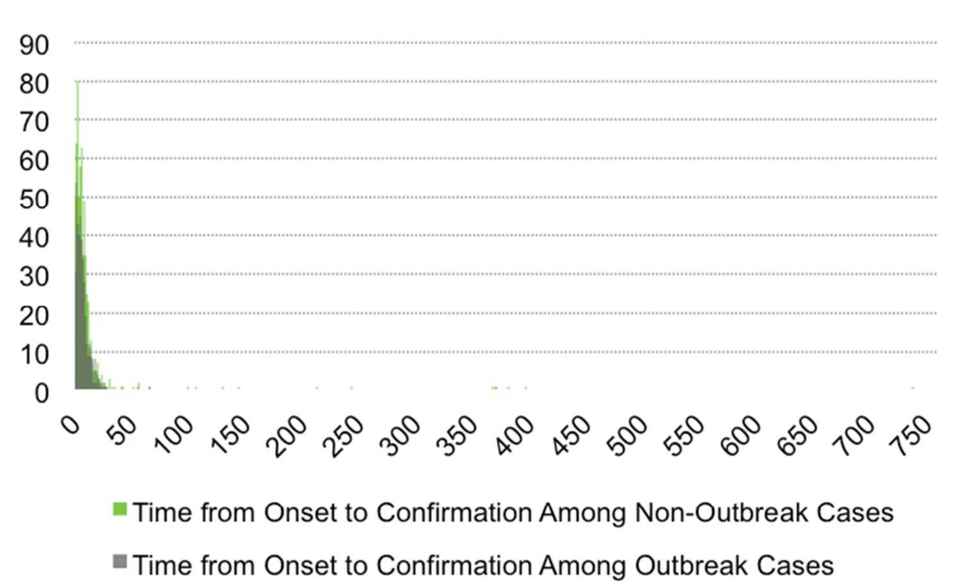

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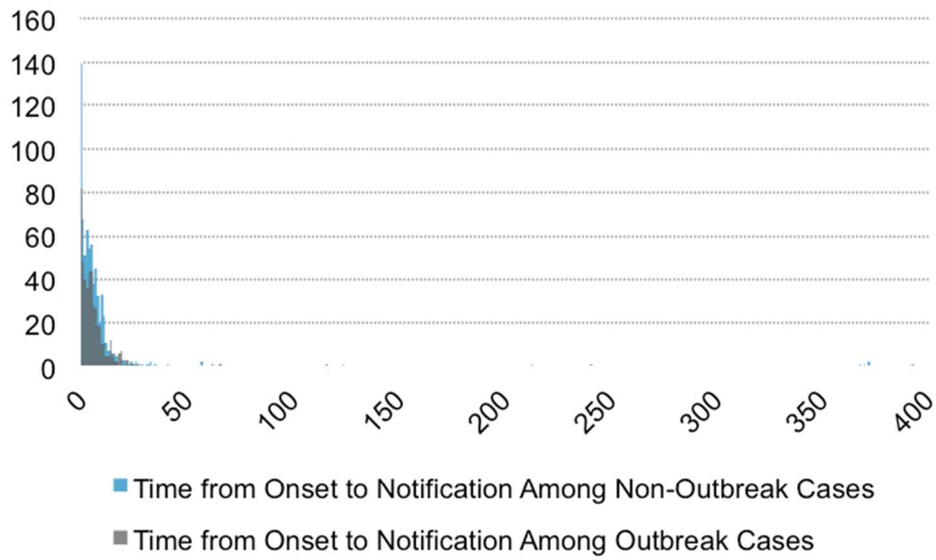

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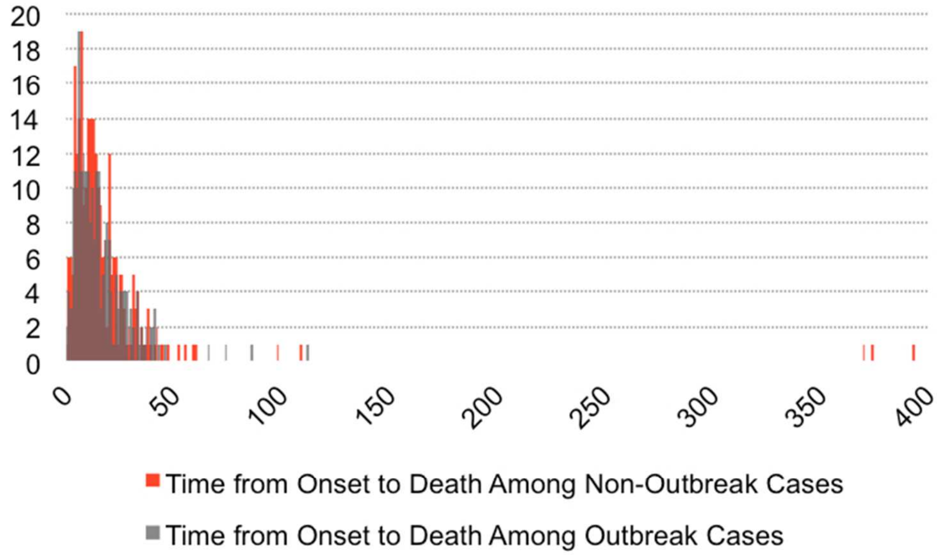

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Supplementary Table 1

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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	

(*e*) Describe any sensitivity analyses

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*5-6*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011865.R3
Article Type:	Research
Date Submitted by the Author:	14-Sep-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

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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

Abstract

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

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

Results: A total of 1250 patients (aged 0 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 ($p < 0.001$).

Conclusions: To date, nosocomial infections have fuelled 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.

Strengths and limitations of this study

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

- These alterations caused some inconsistencies in the data acquired from the Saudi MOH database that may limit the interpretation of the study results.

Introduction

Following the isolation of a previously unknown coronavirus (CoV) from the sputum of a 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 transmission. However, MERS outbreaks of varying sizes have since occurred across Saudi Arabia; additionally, apparent cases of sustained secondary transmission have occurred in family clusters[12, 13] and healthcare facilities.[14, 15]

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

Materials and Methods

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

Data and Statistical Analyses

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

Results

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

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

Demographic Characteristics

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

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

Demographic characteristics (n)	Frequency	Percentage
Age in years (1244)		
0-10	41	3.30
11-25	63	8.36
26-39	292	31.83
40-109	848	68.17
Gender (1246)		
Female	439	35.23
Male	807	64.77
Occupational status (172)		
Employed	22	12.79
Unemployed	40	23.26
Retired	31	21.51
Private	37	18.02
Other	42	24.42
Main reason for testing (1247)		
Healthcare worker	249	19.97
Household	138	11.07
Suspect	860	68.97
Healthcare worker (1244)		
Yes	275	22.11
No	969	77.89
Does the patient raise camels? (205)		
Yes	29	14.15
No	176	85.85
During the 14 days before the patient became sick, did he/she travel outside or inside Saudi Arabia? (205)		
Yes	195	95.12
No	10	4.88

Was the patient 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 ($p < 0.001$).

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

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

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

	Outbreak cases *N = 485*		Non-outbreak cases *N = 765*		χ^2	p
	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%		

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

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

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

Discussion

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

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

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

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

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

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

Conclusions

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

Footnotes

Footnotes

Acknowledgments: We are grateful to the Ministry of Health staff who helped in data collection.

Contributors: FA is the study PI and wrote the manuscript. MM developed the study design and conducted the analyses. JH interpreted the results. JB reviewed the study design. DO performed the statistical analyses. HA, AA, and ABS acquired patient demographic and clinical data from the Saudi Ministry of Health database. MA participated in interpreting the clinical results and reviewed the manuscript. All authors participated in critical revision of the manuscript and approved the final version.

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

Competing interests: None declared.

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

Data sharing: No additional data available.

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Figure legends

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

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.

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

Figure 5. 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

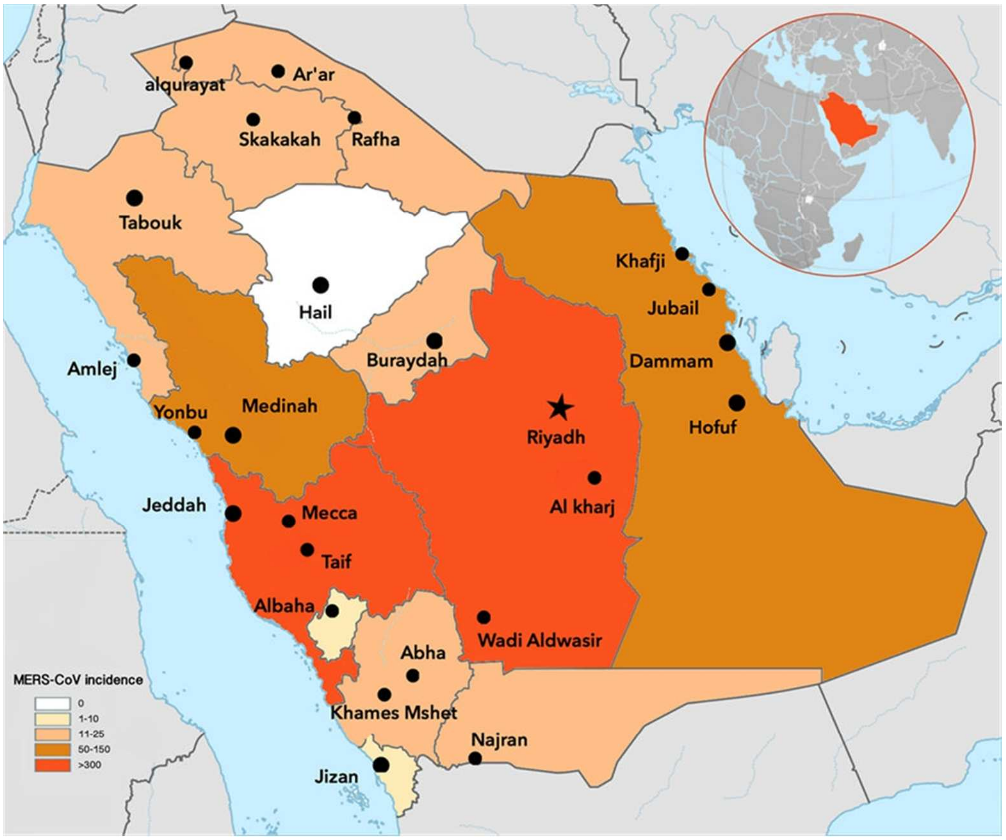
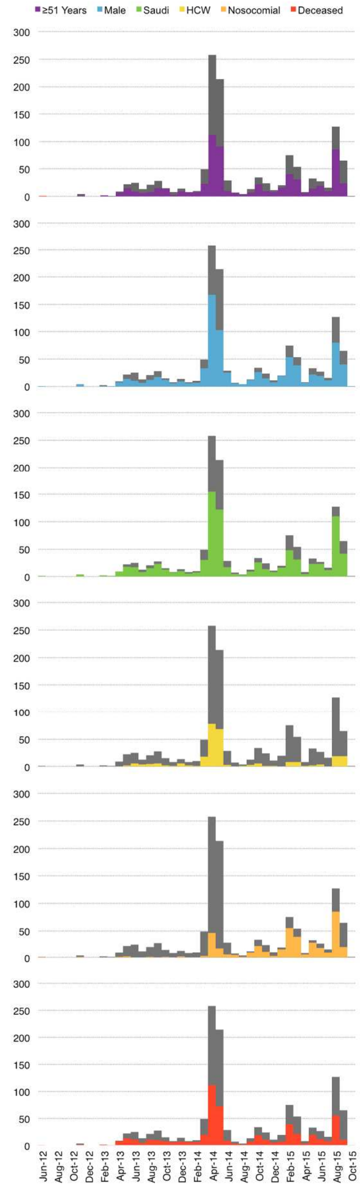


Figure 1. Incidence of MERS coronavirus infections (1283 confirmed cases) across the Kingdom of Saudi Arabia.

86x72mm (300 x 300 DPI)



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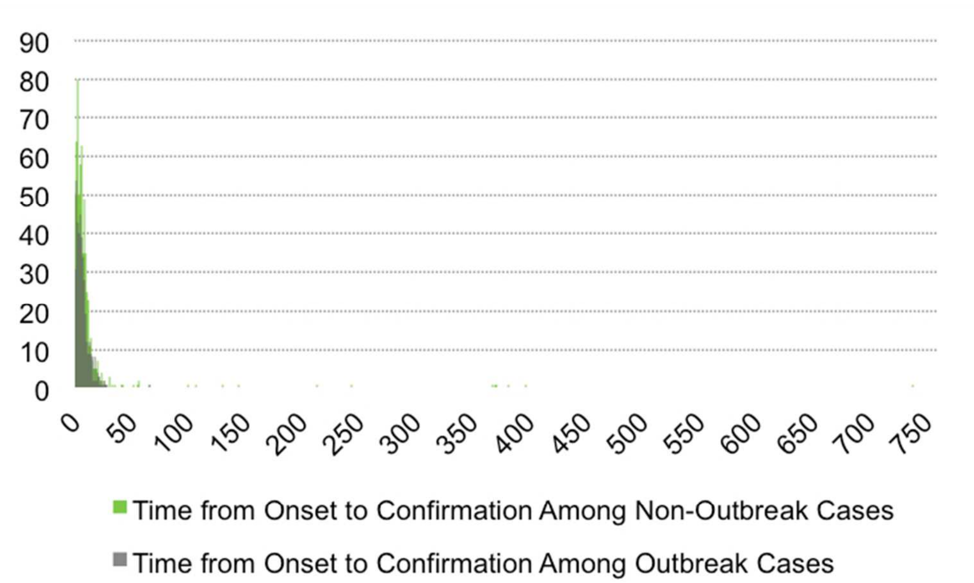

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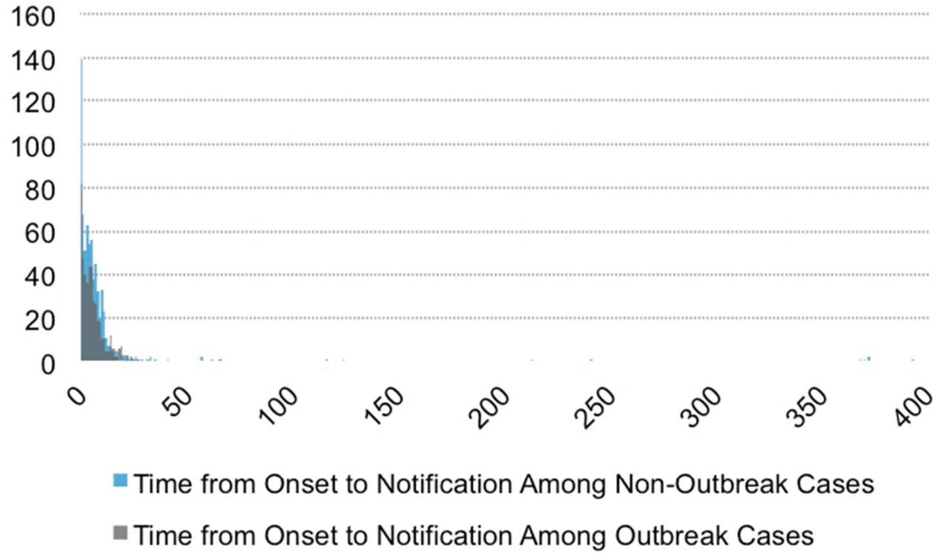

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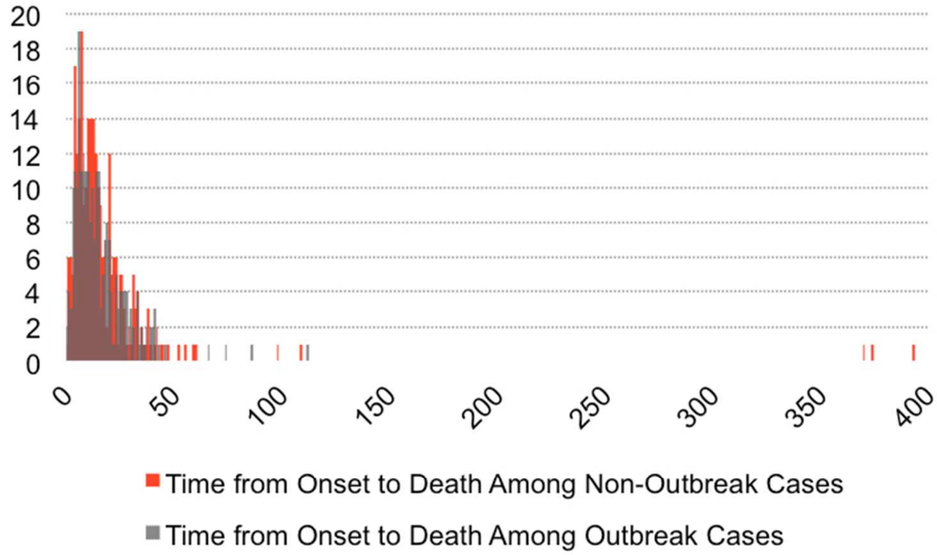

Figure 5. Histogram of time from onset to death for outbreak and non-outbreak in those cases ending in death. Average time from onset to death among patients that died was 15.6 days for outbreak cases and 19.5 days for non-outbreak cases

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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	

(*e*) Describe any sensitivity analyses

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*5-6*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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.

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'.

BMJ Open 2019;**9**:e011865corr1. doi:10.1136/bmjopen-2016-011865corr1