G Model
JIPH-970; No. of Pages 7
ARTICLE IN PRESS
Journal of Infection and Public Health xxx (2018) xxx–xxx
Contents lists available at ScienceDirect
Journal of Infection and Public Health
journal homepage: http://www.elsevier.com/locate/jiph

Individual and network characteristic associated with hospital-acquired Middle East Respiratory Syndrome coronavirus

Oyelola Adegboye [a,*], Timor Saffary [b], Majeed Adegboye [c], Faiz Elfaki [d]

[a] Australian Institute of Tropical Health & Medicine, James Cook University, Townsville, QLD 4811, Australia
[b] Independent Researcher, MD 20876, USA
[c] American University of Nigeria, 640001 Yola, Nigeria
[d] Department of Mathematics, Statistics and Physics, Qatar University, 2713 Doha, Qatar

ARTICLE INFO

Article history:
Received 16 July 2018
Received in revised form 31 October 2018
Accepted 5 December 2018

Keywords:
Hospital-acquired infections
MERS
Healthcare workers
Network analysis

ABSTRACT

Background: During outbreaks of infectious diseases, transmission of the pathogen can form networks of infected individuals connected either directly or indirectly.
Methods: Network centrality metrics were used to characterize hospital-acquired Middle East Respiratory Syndrome Coronavirus (HA-MERS) outbreaks in the Kingdom of Saudi Arabia between 2012 and 2016. Covariate-adjusted multivariable logistic regression models were applied to assess the effect of individual level risk factors and network level metrics associated with increase in length of hospital stay and risk of deaths from MERS.
Results: About 27% of MERS cases were hospital acquired during the study period. The median age of healthcare workers and hospitalized patients were 35 years and 63 years, respectively, Although HA-MERS were more connected, we found no significant difference in degree centrality metrics between HA-MERS and non-HA-MERS cases. Pre-existing medical conditions (adjusted Odds ratio (aOR) = 2.43, 95% confidence interval: (CI) [1.11–5.33]) and hospitalized patients (aOR = 29.99, 95% CI [1.80–48.65]) were the strongest risk predictors of death from MERS. The risk of death associated with 1-day increased length of stay was significantly higher for patients with comorbidities.
Conclusion: Our investigation also revealed that patients with an HA-MERS infection experienced a significantly longer hospital stay and were more likely to die from the disease. Healthcare worker should be reminded of their potential role as hubs for pathogens because of their proximity to and regular interaction with infected patients. On the other hand, this study has shown that while healthcare workers acted as epidemic attenuators, hospitalized patients played the role of an epidemic amplifier.

Introduction

Middle East Respiratory Syndrome Coronavirus (MERS) is transmitted via interactions among individuals. The danger of infection is highest for groups of individuals living in close proximity. From the intermittent transmission that occurred in animal-to-human, many human-to-human cases of MERS have also been documented within family and healthcare facilities [1–3]. Transmission of MERS pathogen can form networks of infected individuals that were connected either directly or indirectly. One should expect in such environments the formation of large clusters of infections as observed during the outbreak in the Kingdom of Saudi Arabia (KSA) [4] and South Korea (SK) [5]. Cluster size of human-to-human transmissions of MERS has been shown to vary and a high variability and heterogeneity in the transmission potential have been underscored [6,7].

The first case of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was reported in 2012. By February 2018, a total of 2182 laboratory-confirmed MERS-CoV infections had been reported to the World Health Organization (WHO) [8]. The disease has now spread to over 27 countries with most index patients either residing or recently traveling to areas neighboring the Arabian Peninsula [9,10]. Similarly, the vast majority of the total cases (82%) occurred in KSA [8]. The global mortality rate was highest

* Corresponding author.
E-mail address: oyelola.adegboye@jcu.edu.au (O. Adegboye).

https://doi.org/10.1016/j.jiph.2018.12.002

(58%) at the beginning of the epidemics (September 2012–February 2013) and it dropped continuously to an absolute low of 23% during September 2015–February 2016. As of February 2018, these infections has led to 779 documented deaths (a mortality rate of 36%) [8]. People within the age-group 50–59 years are at the highest risk of being infected as primary cases and have the highest mortality rate [8]. Forty-five day survival rate was lowest in patients older than 65 years (44.86%) [11]. Also, healthcare workers (HCW) are regularly exposed to MERS due to their regular contacts with MERS patients and are at greater risk of being infected; however, they are less likely to die of the disease [10,12–14].

Strong links between healthcare facilities and the spread of the MERS disease have been found in KSA, where the majority of patients were in contact with other patients at healthcare facilities [15–18]. Unfortunately, this phenomenon is widespread and well-known as nosocomial infections (hospital-acquired infections) which occur frequently with surgical-site infections (SSIs), pneumonia and gastrointestinal infections among the top hospital-acquired infections (HAIs) [19,20].

There has been a number of documented outbreaks of MERS infection within clusters of healthcare facilities among hospitalized patients and healthcare worker [15,17,18]. In 2015, cases of MERS were reported in SK when the index patient returned from his trip to the Arabian Peninsula where he had contracted MERS [18]. The disease spread out across various cities in SK within two months, expanding from one to 17 hospitals and infecting a total of 186 people. Similarly, a major MERS outbreak was registered at a tertiary-care hospital in Riyadh in 2015 [4,17,21,22]. The escalation of the Riyadh outbreak was linked to extended healthcare-related human-to-human transmissions [4,17,21,22]. These outbreaks were attributed to few index cases and the level of their spreading depended on interactions between individuals. For example, 82 out of the 186 infected patients in SK were traced back to one index patient alone due to the overcrowded emergency room with patients, visitors and healthcare worker [23].

This study focused on cases of hospital-acquired MERS (HA-MERS) in Saudi Arabia. The objectives of this study were to explore the structure of transmission networks formed by these outbreaks in order to describe its routes and the relationship between patients' characteristics and the disease network metrics. Specifically, we will investigate the effects of place of exposure in the transmission mechanisms of MERS, whether outbreaks in the hospital vs. outbreaks elsewhere in the community have significant differences in the length of hospital stay (LOS). Similarly, we estimate the risk of death associated with MERS diseases between HA-MERS and non HA-MERS.

Materials and methods

Data source

The data for this study was based on laboratory confirmed and probable cases of MERS-CoV infection in the KSA between 2012 and 2016 from various sources such as WHO bulletins, media reports and Kingdom of Saudi Arabia Ministry of Health (MoH), and obtained from the case-by-case list compiled and maintained by Dr. Andrew Rambaut [24]. The data sets were also assessed for accuracy with those reported by Flu Trackers, KSA MoH and WHO. The data contains information on patient demographics, clinical outcome, whether the patient was a healthcare worker (HCW), comorbidity status of the patient, and place of exposure to known risk factors. We used the following approaches to estimate length of hospital stay (LOS): (1) we restricted our analysis to those patients who are still alive and those that died within 60 days for short-time risk of death analysis (2) LOS was calculated as the difference between the date of onset of disease (or date reported whenever date of onset was not available) and date of death/discharged.

Study population and definitions

The study population consisted of patients with confirmed MERS infection. The cases were confirmed via real-time RNA-positive using Reverse transcription polymerase chain reaction (RT-PCR) showing positive PCR on at least two specific genomic targets upstream E protein (upE) and ORF1a or a single positive target (upE) with sequencing of a second target (RdRpSeq assay) or N gene (NSeq assay) [25]. Overall, 787 patients with known contact history to identify the place of exposure which was classified as HA-MERS or non HA-MERS were included in this study. A MERS infection is described as hospital acquired (HA-MERS) if the patient has contact with confirmed patients (alive or deceased) or healthcare workers, or healthcare facilities which had MERS-CoV outbreak while non HA-MERS were those acquired elsewhere such as community, household/family [26].

Statistical analysis

The data was analysed in three stages. First, descriptive statistics were presented as medians and interquartile range for continuous variables, and frequencies and percentages for categorical variables. Odds ratios (OR) together with their 95% confidence interval were also used for categorical variables. The chi-square test was used to compare patient's attributes (categorical variables) for those infections acquired in the hospital and those acquired elsewhere in the community while the Mann-Whitney U-test was used to compare continuous attributes (continuous variables).

In the second stage, the unit of analysis for the networked data were the nodes representing individuals infected with MERS. In network analysis, the nodes (individual patients) have distinguishable attributes such as age, gender, etc., while interactions or relationships between nodes are called edges or links [27]. A network can be defined as a collection of nodes connected by edges where nodes and/or edges have attributes [28]. Each patient (node) was assigned a unique identification number and his/her contact history was tracked within 14 days of the onset of the disease. MERS patients who were in contact with other laboratory-confirmed MERS patients were identified and a list of each patient-contact pair (dyad) was prepared. A dyad is a linked pair of patients (nodes) in the network that is the fundamental unit for deriving network metrics. The outbreak network visualization and network analysis were conducted in UCINET 6.0 Version 1.00 [29]. The following centrality metrics were used to measure the structural importance of patients (nodes) in a network. "Degree centrality" was used to reveal the most active nodes in the network and how well a node is connected with its neighbours — a node degree is the number of edge incidents on a node; the "betweenness centrality" was used to measure how many pairs of nodes a node can be connected to through a shortest path while "eigenvector centrality" was used to measure the importance of a node depending on the importance of its neighbours [27,29].

In the final analysis, a covariate-adjusted multivariable logistic regression model was used to assess the effects of individual level risk factors and network level metrics (patients nested within networks) on risk of deaths from MERS between HA-MERS and non-HA-MERS patients. Similarly, we used a generalized linear model to identify disease-risk factors associated with the increase in the length of stay (LOS) between HA-MERS and non-HA-MERS patients.

We used stepwise selection to select the variables for inclusion in the regression models. All statistical analyses were conducted in

Table 1
Characteristics of HAI-MERS and non-HAI-MERS cases in Saudi Arabia between June 2012 and September 2016. Number of cases (%) or median (IQR).

Variables	Hospital-acquired	Acquired elsewhere	p-value	Odds-ratio (95% C.I.)
	N = 378	N = 409		
Age	47 (33–64)	46 (31–60)	<0.0860	1.01 (1.00, 1.02)
Length of stay[a]	19 (13–29)	14 (10–19)	<0.0001	1.02 (1.00, 1.03)
Gender				
Male	200 (52.9%)	287 (70.2%)	<0.0001	2.04 (1.53, 2.74)
Female	176 (46.6%)	121 (29.6%)		Ref
Unknown	2 (0.5%)	1 (0.2%)		
Comorbidity				
Presence	225 (69.5%)	204 (48.8%)	<0.0001	1.88 (1.43, 2.48)
Absence	94 (24.9%)	77 (18.8%)		Ref
Unknown	59 (15.6%)	128 (31.3%)		
Outcome				
Fatal	125 (33.1%)	100 (24.4%)	<0.0001	1.53 (1.12–2.08)
Non-fatal	253 (66.9%)	309 (75.6%)		Ref
Healthcare worker (HCW)	166 (43.9%)			

[a] The length of stay was calculated as difference between: date of onset of symptoms and date discharged or date of death.

Table 2
Descriptive summaries (and unadjusted odds ratio) for cases of hospital acquired MERS infection among different groups. Number of cases (%) or median (IQR).

Risk factors	Place of infection			Total (N = 378)		
	Healthcare workers	Hospitalized patient	Hospital visitor	Fatal	Non-fatal	Odds-ratio (95% C.I.)
	N = 166 (43.9%)	N = 194 (51.3%)	N = 18 (4.8%)	N = 125 (33.1%)	N = 253 (66.9%)	
Age	35 (28–44)	63 (51–75)	44 (38–60)	68 (54–77)	39 (30–54.5)	1.06 (1.05, 1.08)
Length of stay	16 (12–25)	39 (17.75–7.75)	12 (9–16)	18 (10.3–28)	17 (12.5–26)	1.02 (1.00–1.03)
Gender						
Male	102 (61.5%)	127 (65.5%)	11 (61.1%)	83 (66.4%)	117 (46.3%)	2.26 (1.46, 3.56)
Female	62 (37.3%)	67 (34.5%)	7 (39.95%)	42 (33.6%)	134 (53%)	
Unknown	2 (1.2%)	0	0		2 (0.8%)	
Comorbidity						
Presence	32 (45.8%)	182 (93.8%)	11 (61.11)	117 (93.6%)	108 (42.7%)	19.28 (8.30, 56.29)
Absence	76 (45.7%)	11 (5,67%)	7 (38.9)	5 (4.0%)	89 (35.1%)	
Unknown	58	1 (0.51)	0	23(2.4%)	56 (22.1%)	
Mortality N (%)						
Fatal	5 (3%)	119 (61.3%)	1 (5.6%)			
Non-fatal	161 (97%)	75 (38.7%)	17 (94.4%)			
OR (95%CI)	Ref	31.1 (22.05, 48.95)	1.89 (0.09,12.68)			

SAS 9.3 Software Version 6 of the SAS System for Windows [30] and inference was at 5% level of significance.

Results

Overall 787 cases were included in this study. There were 378 (48%) cases of HA-MERS infection while 409 (52%) cases occurred elsewhere in the community, for instance within households (Table 1). Three different HA-MERS groups were defined based on their type of exposure: (1) Healthcare worker, (2) Hospital visitors, (3) Hospitalized patients. The demographic characteristics of the infected patients are presented in Table 1. Patients with HA-MERS had significantly longer stays in the hospital (Median (Med) LOS = 19 days, Interquartile range (IQR) = 13–29) compared to non-HA-MERS (Med. LOS = 14 days, IQR = 10–19). One hundred and twenty-five (33.1%) of the HA-MERS cases died during their hospital stay while 100 (22.4%) of the non-HA-MERS cases died during their treatment in the hospital. There was no significant difference between the median age of HA-MERS and that of non-HA-MERS, 47 years (33.0–64) vs. 46 years (31–60) in Table 1; however, age among healthcare workers, hospitalized patients and hospital visitors differed significantly (Table 2). The overall crude fatality rate (CFR) was 32%, with significantly higher CFR in HA-MERS cases (33.1%) than among non HA-MERS (24.4%) (Table 1). Similarly, 69.5% of HA-MERS patients had comorbidities against 48.8% of non-HA-MERS patients (Fig. 1).

Male patients were more likely to have HA-MERS infection compared to females (unadjusted odds ratio (OR) = 2.04, 95% confidence interval (CI), [1.53–2.74]). There were slightly more patients with comorbidities among HA-MERS (69.5%) than non-HA-MERS (48.8%) (P-value <0.0001). Patients with comorbidities were twice likely to have HA-MERS than patients without comorbidities (OR = 1.88, 95% CI [1.43–2.48]). Similarly, being a healthcare worker and of older age significantly increased the odds of having a HA-MERS infection (Table 1). Patients with longer hospital stays were significantly more likely to have an HA-MERS than non-HA-MERS (OR = 1.02, 95% CI [1.00–1.03]).

Table 2 presents the descriptive summaries of the HA-MERS cases and unadjusted odds ratio for mortality due to MERS. Although those patients who died of MERS disease were significantly less likely to have HA-MERS infection than those with non-fatal health outcome (Table 1), place of infection significantly influenced mortality from MERS disease among HA-MERS patients with greater risk for hospitalized patients (OR = 31.1, 95% CI [22.05–48.95[).

In the unadjusted analysis in Table 2, the likelihood of fatality from MERS disease increased proportionally with age by a factor of 6% for every unit increase, fatal cases in male HA-MERS patients were more likely than fatal cases in female HA-MERS patients (OR = 2.26, 95% CI [1.46–3.56]). Among the 378 HA-MERS cases, comorbidities were recorded in 225 (69.5%) cases out of which 117 cases were fatal. HA-MERS patients with comorbidities were at a significantly higher risk of death from MERS

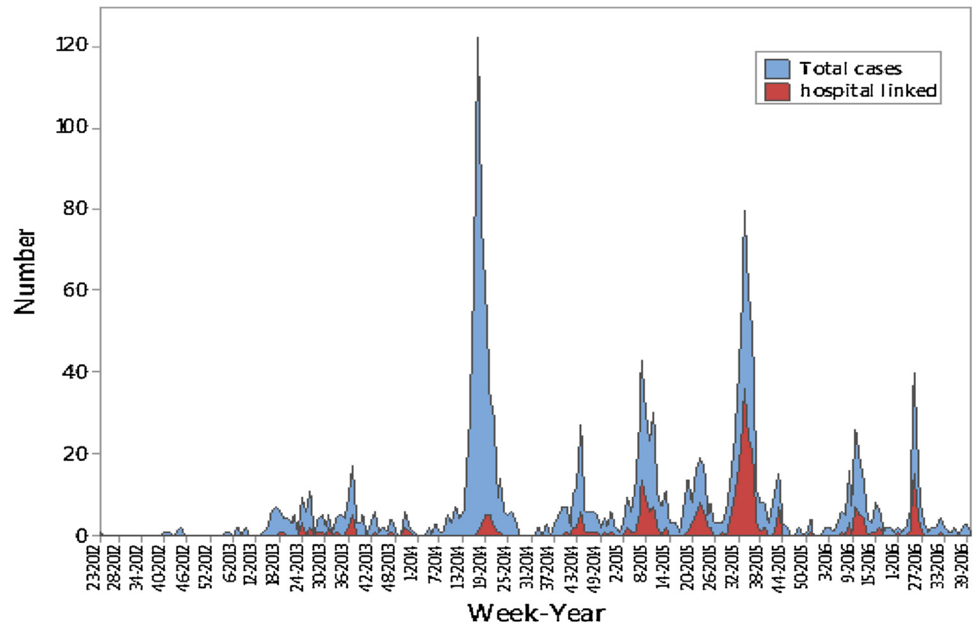

Fig. 1. Distribution of weekly number of MERS cases by week of symptom onset and the number of HA-MERS in KSA. Wherever the date of onset is not available, the date hospitalized or date the disease is reported was used (whichever comes first).

disease than patients with no comorbidity (OR = 19.28, 95% CI [8.30–56.29]).

Transmission network

The network structure of HA-MERS infection is presented in Fig. 2 together with the degree centrality metrics. Because these network centrality metrics were highly correlated, we shall limit our focus to degree centrality. The network density of HA-MERS was 0.019 (1.9%) with an average degree of 1.8 contacts. Greater degree centrality was associated with increased risk of death from MERS. Our results suggest that healthcare workers have on average significantly lower degree centrality scores than non-healthcare workers. Although HA-MERS were more connected, we have found no significant difference in degree centrality between HA-MERS and non HA-MERS cases. Patient's transmission degree centrality was significantly negatively correlated with age. As depicted in Fig. 2, the larger node size represents the prioritized patients (1664, 124, 1025, 133, 897, 898) based on the degree centrality metrics because they have the most ties to other patients within the network.

Length of stay and risk of death

On the basis of unadjusted analysis, HA-MERS, hospitalized patients, older patients and patients with comorbidities were positively associated with length of hospital stay while being HWC has a negative association. Results from further investigation of the associated risk factors for increased LOS among MERS patients after controlling for other risk factors revealed that only patients with comorbidities significantly increased the length of hospital stay (Table 3).

Table 4 shows the estimated risk of death associated with each patient's characteristics used in this study. The adjusted analysis indicates that comorbidity, HCW, hospitalized patient, hospital visitor, age and LOS were significantly associated with risk of mortality from MERS.

In the model, patients with comorbidities (OR = 2.43, 95% CI [1.11–5.33[) and hospitalized patients (OR = 29.93, 95% CI [1.80–48.65]) were the strongest risk predictors of mortality from MERS.

Between HA-MERS infections and non HA-MERS infections, the effect of one-day increase in LOS on risk of death after adjusting for several predictors is illustrated in Table 5. We have found that when age alone was in the model, there was a significant increase in risk of death between HA-MERS and non HA-MERS. After controlling for age and comorbidities, we found that risk of MERS mortality were significantly higher in patients with HA-MERS compared with patients without HA-MERS (OR = 4.41, 95% CI [1.29–14.98]).

Discussion

Preventing the spread of emerging infectious diseases within healthcare settings is of utmost importance [31]. Early warning systems and infection control mechanisms were essential for an efficient global public health response. In 2013, Assiri et al. [2] warned that human-to-human outbreaks of MERS can occur in healthcare settings which could be associated with considerable morbidity. Recent studies have documented and investigated the outbreaks of MERS in hospitals [4,17,18,22,32]. This study sets out to estimate the risk of death associated with MERS diseases between HA-MERS and non HA-MERS, to explore the structures of transmission networks formed by MERS patients and to investigate the effects of place of exposure on the risk of deaths from MERS, whether hospital outbreaks significantly increase length of hospital stay (LOS). Similarly, we also tested if infected individuals become super-spreaders because they were exposed in a specific area or not.

Several studies have reported hospital outbreak of MERS cases in KSA [2,4,17,32–34], United Arab Emirates [35] and South Korea [18,23,34]. In this study, we have identified that, about 48% of MERS patients with known contact history can be linked to healthcare settings through person-to-person transmission and a large number of those infected were healthcare workers. The role of the patient's characteristics was explored with network analysis, since the propagation of the pathogen varies among patients, visitors and healthcare workers [17]. Some nodes may amplify the intensity of disease transmission while others might attenuate the spread [36].

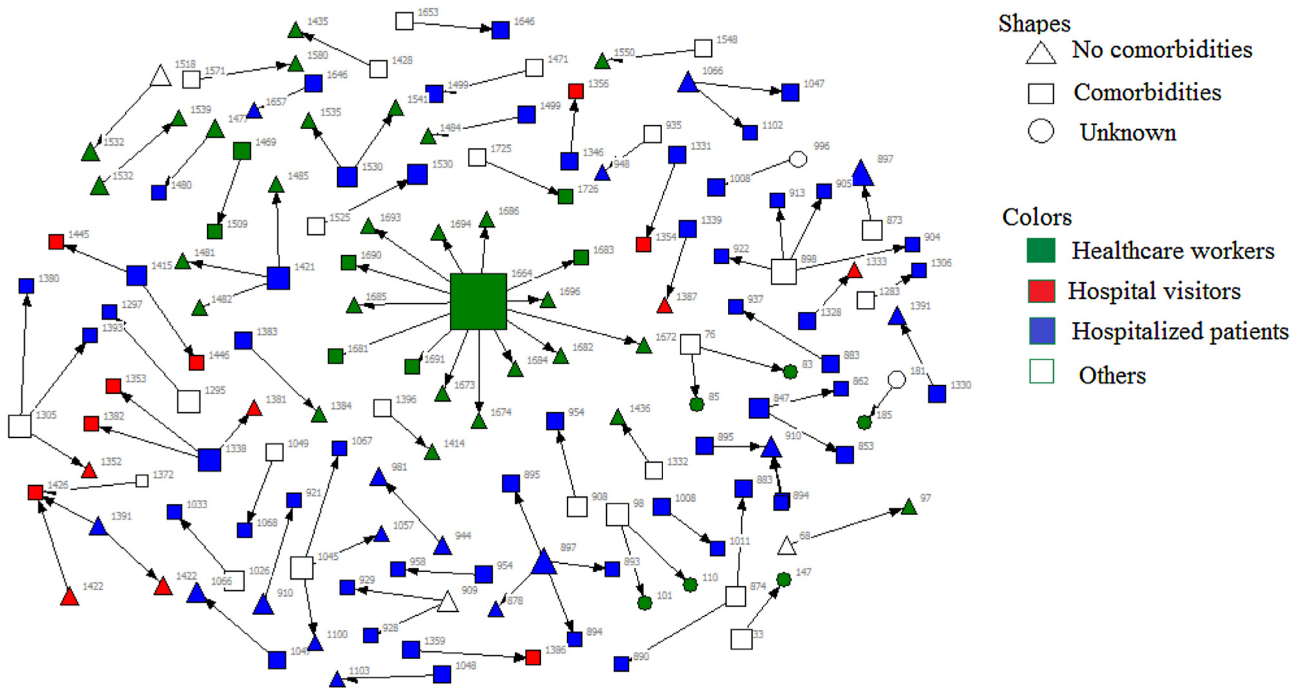

Fig. 2. Visualization of MERS-CoV cases during the outbreak. Isolated cased were not included in the figure. The size of the node represents the degree centrality, increasing node sizes implies the more important the patient is.

Table 3
Factors associated (95% confidence limits) with length of hospital stay after the onset of MERS (N = 787).

Risk factors	Effect	95% confidence limits		P-value
		Lower	Upper	
Age[a]	−0.045	−0.135	0.061	0.4241
Gender (male)	−1.801	−5.118	1.692	0.2878
HA-MERS (yes)	6.133	−0.626	14.724	0.0725
Comorbidity (true)	4.976[b]	0.294	9.247	0.0306
HCW (yes)	−3.322	−8.222	2.499	0.1844
Hospitalized patients	−0.258	−7.336	6.819	0.943
Hospital visitors	−6.9332	−8.475	9.065	0.9474
Degree centrality[c]	−1.033	−3.010	1.008	0.3061
Betweenness centrality[c]	0.899	−2.833	1.904	0.6368
Eigenvector centrality[c]	9.548	−21.116	15.645	0.5421

[a] A 1-year increase in age.
[b] Statistical significant at 5% level.
[c] A unit increase in centrality metrics.

Although most of the patients in this study had comorbidity, they did not significantly amplify the spread of the disease. On the contrary, hospitalized patients with comorbidity had a higher risk of spreading the disease.

Older patients were more likely to have a hospital-acquired MERS infection than non-hospital-acquired MERS infections. Older people seem to have been statistically more exposed to the disease at healthcare facilities than at other places which might be the result of a combination of senior people been admitted to the hospital more frequently due to their advanced age and having less active social interactions than younger people. This is consistent with previous findings that the chances of dying from the MERS grew with increasing age beyond 25 years [10]. It also confirms the common assumption that the danger of infection is greater for senior patients and, therefore, special attention needs to be paid to them.

Table 4
Odds ratio and the 95% confidence limits of risk of death associated with MERS disease (including patients who died during hospital stay) (N = 787).

Risk factors	Odds ratio	95% confidence limits		P-value
		Lower	Upper	
Gender: male vs. female	1.413	0.832	2.401	0.2317
Comorbidity true vs. false	2.432[f]	1.110	5.332	0.0068
Healthcare worker true vs. false	0.085[f]	0.018	0.395	<0.0001
Hospitalized patient yes vs. no	29.93[f]	1.804	48.653	0.0177
Hospital visitors yes vs. no	0.095[f]	0.005	1.787	0.0357
HA-MERS (yes vs. no)	2.392	0.3	19.059	0.168
Age[a]	1.028[f]	1.013	1.044	0.0002
Length of stay 1-day[b]	0.981[f]	0.971	0.991	0.0002
Length of stay 7-day[c]	0.873[f]	0.814	0.937	0.0002
Length of stay 14-day[d]	0.763[f]	0.662	0.878	0.0002
Degree centrality[e]	0.882	0.639	1.22	0.4488

[a] 1-year increase in age.
[b] 1-day increase in length of hospital stay.
[c] 7-day increase in length of hospital stay.
[d] 14-day increase in length of hospital stay.
[e] Unit increase in degree centrality metric.
[f] Statistical significant at 5% level.

Table 5
Odds ratio and the 95% confidence limits of risk of death associated with MERS disease for a 1-day increase in length of hospital stay (N = 787).

Model	Risk factors	Odds ratio	95% confidence limits	
		HA-MERS vs. non HA-MERS	Lower	Upper
1	Adjusted for age	1.0239	1.0010	1.0475
2	Adjusted for age + comorbidity	4.4106	1.2986	14.9797
3	Model 2 + Healthcare worker	0.0704	0.0235	0.2114

The risk of death associated with increased length of stay was significantly higher for patients with comorbidities and hospital-acquired MERS infections. The impact of MERS infection together with another disease or condition was investigated earlier. Such a combination was much more likely to be fatal [10,37]. This result is insofar important as it applies to a large portion of the population given the fact that many were affected by non-communicable diseases of affluence such as diabetes, obesity, heart diseases, etc. For instance, more than half of the population of Saudi Arabia with the age of at least 50 years has diabetes [38].

Our analysis has revealed that patients with a hospital-acquired MERS infection experienced a significantly longer hospital stay and were associated with a higher risk of death from the disease. This might be closely linked to the second outcome, because the group of hospital-acquired infections included patients who had already been hospitalized for other health issues. The length of hospital stay has been investigated from various perspectives both medical and economical [39–42]. Our result is in accordance with Glance et al. [43], who showed that the length of hospital stay, associated costs and mortality rate of hospital-acquired infections were significantly higher for trauma patients. We tested the correlation of centrality metrics with each other and other patient's level characteristics. All but the eigenvector and betweenness showed significant association, a property which might be less evident for complicated networks [44].

Many studies indicate that healthcare workers are at greater risk of MERS infection [10,12–14,33]. However, we found healthcare workers who were at the receiving end of MERS infections to act as epidemic attenuator. Health care workers are often in compliance with risk management approaches to reduce and control transmission of MERS by wearing protective gears and are aware of other hygienic measures, to reduce the dose of infectious agents preventing further spread of the disease. In the same vein, hospitalized patients played the role of an epidemic amplifier, i.e. they played more the role of transmitters. This complements an earlier publication showing that the vast majority of documented MERS patients had contacts with other patients in healthcare facilities and that nosocomial infections occurred more often in outbreak than non-outbreak cases [15,16].

Limitations

We acknowledge the following limitations in our study. Firstly, this analysis was based on retrospective study of publicly available data collected from multiple sources; the accuracy of some of the information provided by the patient may not be verifiable especially during the early outbreaks. However, the reporting has been improved upon over the years with coordination between Saudi government agencies and WHO. The data sets were also assessed for accuracies with those reported by Flu Trackers, Saudi MOH and WHO. Secondly, the network analysis considered in this study was solely based on confirmed MERS cases with strict directionality; therefore, unconfirmed cases will be missed. Similarly, we restricted our analysis to those with known contact history to be able to differentiate the source of infection and construct the transmission network. In spite of these limitations, analysis based on network analysis offers very interesting findings on the distribution of secondary cases caused by each primary case. Lastly, lack of information on hospitals prevented us from exploring the spread of MERS between hospitals.

Conclusions

During infectious disease outbreaks, networks of infected individuals may be formed depending on the nature of the pathogen's transmission. The mechanisms of the transmission and the structure of the networks need to be well-understood in order to optimize preventive measures, and have reliable early warning systems as well as effective treatment methods. The outcomes of our research emphasize the importance of putting patients with communicable diseases, especially life-threatening diseases, immediately under quarantine and minimizing the access of healthcare workers to such patients. Such precautionary measures could be lifesaving, in particular for patients with comorbidities and/or of senior age who need to be observed closer during their entire hospital stay. Moreover, healthcare workers should be advised on their potential role as hubs for pathogens due to the nature of their occupation. Loose adherences to preventive and protective measures by the health care workers should be identified and immediately corrected in order to avoid the negative role they may play in transmitting the agent.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Chowell G, Abdirizak F, Lee S, Lee J, Jung E, Nishiura H, et al. Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study. BMC Med 2015;13(1):210.
[2] Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013;369(5):407–16.
[3] Mackay IM, Arden KE. MERS coronavirus: diagnostics, epidemiology and transmission. Virol J 2015;12(1):222.
[4] Al-Dorzi HM, Aldawood AS, Khan R, Baharoon S, Alchin JD, Matroud AA, et al. The critical care response to a hospital outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection: an observational study. Ann Intensive Care 2016;6(1):101.
[5] Kucharski AJ, Althaus C. The role of superspreading in Middle East respiratory syndrome coronavirus (MERS-CoV) transmission. Eurosurveillance 2015;20(25):21167.
[6] Nishiura H, Miyamatsu Y, Chowell G, Saitoh M. Assessing the risk of observing multiple generations of Middle East respiratory syndrome (MERS) cases given an imported case. Eurosurveillance 2015;20(27):21181.
[7] Fisman DN, Leung GM, Lipsitch M. Nuanced risk assessment for emerging infectious diseases. Lancet 2014;383(9913):189–90.
[8] World Health Organization. MERS situation update, February 2018; 2018. Available from: http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-february-2018.html. [Cited 18 April 2018].

[9] Zumla A, Alagaili AN, Cotten M, Azhar EL. Infectious diseases epidemic threats and mass gatherings: refocusing global attention on the continuing spread of the Middle East Respiratory syndrome coronavirus (MERS-CoV). BMC Med 2016;14(1):132.
[10] Adegboye O, Gayawan E, Hanna F. Spatial modelling of contribution of individual level risk factors for mortality from Middle East respiratory syndrome coronavirus in the Arabian Peninsula. PloS One 2017;12(7):e0181215.
[11] Ahmed AE. Estimating survival rates in MERS-CoV patients 14 and 45 days after experiencing symptoms and determining the differences in survival rates by demographic data, disease characteristics and regions: a worldwide study. Epidemiol Infect 2018;146(4):489–95.
[12] Adegboye O. Spatial covariate adjusted survival rates for Middle East Respiratory Syndrome (MERS) Coronavirus in the Arabian Peninsula. In: Qatar Foundation Annual Research Conference Proceedings 2016 Mar 21 (Vol. 2016, No. 1, p. HBPP1764). 2018.
[13] Adegboye O, Elfaki F. Network analysis of MERS coronavirus within households, communities, and hospitals to identify most centralized and super-spreading in the Arabian Peninsula, 2012–2016. Can J Infect Dis Med Microbiol 2018;2018:1–9.
[14] Al-Turaiki I, Alshahrani M, Almutairi T. Building predictive models for MERS-CoV infections using data mining techniques. J Infect Public Health 2016;9(6):744–8.
[15] Oboho IK, Tomczyk SM, Al-Asmari AM, Banjar AA, Al-Mugti H, Aloraini MS, et al. 2014 MERS-CoV outbreak in Jeddah—a link to health care facilities. N Engl J Med 2015;372(9):846–54.
[16] Alhamlan F, Majumder M, Brownstein J, Hawkins J, Al-Abdely H, Alzahrani A, 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(1):e011865.
[17] Balkhy HH, Alenazi TH, Alshamrani MM, Baffoe-Bonnie H, Arabi Y, Hijazi R, et al. Description of a hospital outbreak of Middle East respiratory syndrome in a large tertiary care hospital in Saudi Arabia. Infect Control Hosp Epidemiol 2016;37(10):1147–55.
[18] Ki M. 2015 MERS outbreak in Korea: hospital-to-hospital transmission. Epidemiol Health 2015;37.
[19] Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370(13):1198–208.
[20] Friedman ND, Bull AL, Russo PL, Gurrin L, Richards M. Performance of the national nosocomial infections surveillance risk index in predicting surgical site infection in Australia. Infect Control Hosp Epidemiol 2007;28(1):55–9.
[21] Centers for Disease Control and Prevention. Nosocomial outbreak of Middle East Respiratory Syndrome in a large tertiary care hospital. In: Morbidity and mortality weekly report; 2016. p. 163–4.
[22 Almutairi AF, Adlan AA, Balkhy HH, Abbas OA, Clark AM. "It feels like I'm the dirtiest person in the world.": exploring the experiences of healthcare providers who survived MERS-CoV in Saudi Arabia. J Infect Public Health 2018;11(2):187–91.
[23] Cho SY, Kang J-M, Ha YE, Park GE, Lee JY, Ko J-H, et al. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. Lancet 2016;388(10048):994–1001.
[24] A. Rambaut, MERS-CoV spatial, temporal and epidemiological information; 2013.
[25] Ministry of Health Saudi Arabia. Infection prevention/control and management guidelines for patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection; 2014. Available from: http://www.moh.gov.sa/en/CCC/StaffRegulations/Corona/Documents/GuidelinesforCoronaPatients.pdf. [Cited 18 April 2018].
[26] Chen X, Chughtai AA, Dyda A, MacIntyre CR. Comparative epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia and South Korea. Emerg Microbes Infect 2017;6(6):e51.
[27] Borgatti SP, Everett MG, Johnson JC. Analyzing social networks. Sage; 2018.
[28] Das S. Handbook of research on computational methodologies in gene regulatory networks. IGI Global; 2009.
[29] Borgatti SP, Everett MG, Freeman LC. Ucinet for Windows: software for social network analysis; 2002.
[30] SAS Institute Inc. SAS 9.3 software version 6 of the SAS system for Windows. Cary, NC: SAS Institute Inc.; 2012.
[31] Al-Tawfiq JA, Rothwell S, Mcgregor HA, Khouri ZA. A multi-faceted approach of a nursing led education in response to MERS-CoV infection. J Infect Public Health 2018;11(2):260–4.
[32] Al-Abdallat MM, Payne DC, Alqasrawi S, Rha B, Tohme RA, Abedi GR, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clin Infect Dis 2014;59(9):1225–33.
[33] Balkhy HH, Perl TM, Arabi YM. Preventing healthcare-associated transmission of the Middle East Respiratory Syndrome (MERS): our Achilles heel. Elsevier; 2016.
[34] Arabi YM, Fowler R, Balkhy HH. Proceedings of the Middle East Respiratory Syndrome (MERS) Coronavirus research initiative workshop, September 9–10 2015 in Riyadh, KSA. J Infect Public Health 2016;9(3):205–7.
[35] Hunter JC, Nguyen D, Aden B, Al Bandar Z, Al Dhaheri W, Elkheir KA, et al. Transmission of Middle East respiratory syndrome coronavirus infections in healthcare settings, Abu Dhabi. Emerg Infect Dis 2016;22(4):647.
[36] Lee T, Lee HR, Hwang K. Identifying superspreaders for epidemics using R0-adjusted network centrality. In: Simulation Conference (WSC). IEEE; 2013. Winter 2013 Dec 8 (pp. 2239–2249).
[37] Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, et al. Risk factors for primary Middle East respiratory syndrome coronavirus illness in humans, Saudi Arabia, 2014. Emerg Infectious Dis 2016;22(1):49.
[38] Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. Ann Saudi Med 2011;31(1):19.
[39] Taylor SL, Sen S, Greenhalgh DG, Lawless M, Curri T, Palmieri TL. A competing risk analysis for hospital length of stay in patients with burns. JAMA Surg 2015;150(5):450–6.
[40] Li JZ, Willke RJ, Rittenhouse BE, Glick HA. Approaches to analysis of length of hospital stay related to antibiotic therapy in a randomized clinical trial: linezolid versus vancomycin for treatment of known or suspected methicillin-resistant staphylococcus species infections. Pharmacother J Hum Pharmacol Drug Ther 2002;22(2P2):45S–54S.
[41] Nordström P, Gustafson Y, Michaëlsson K, Nordström A. Length of hospital stay after hip fracture and short term risk of death after discharge: a total cohort study in Sweden. BMJ 2015;350:h696.
[42] Moran JL, Solomon PJ. A review of statistical estimators for risk-adjusted length of stay: analysis of the Australian and New Zealand intensive care adult patient data-base, 2008–2009. BMC Med Res Methodol 2012;12(1):68.
[43] Glance LG, Stone PW, Mukamel DB, Dick AW. Increases in mortality, length of stay, and cost associated with hospital-acquired infections in trauma patients. Arch Surgery 2011;146(7):794–801.
[44] Christley RM, Pinchbeck G, Bowers R, Clancy D, French N, Bennett R, et al. Infection in social networks: using network analysis to identify high-risk individuals. Am J Epidemiol 2005;162(10):1024–31.

Please cite this article in press as: Adegboye O, et al. Individual and network characteristic associated with hospital-acquired Middle East Respiratory Syndrome coronavirus. J Infect Public Health (2018), https://doi.org/10.1016/j.jiph.2018.12.002