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MERS-CoV infection among healthcare workers and risk factors for death: Retrospective analysis of all laboratory-confirmed cases reported to WHO from 2012 to 2 June 2018

Amgad A. Elkholy[a,1], Rebecca Grant[b,c,1], Abdullah Assiri[d], Mohamed Elhakim[a], Mamunur R. Malik[a], Maria D. Van Kerkhove[c,*]

[a] Infectious Hazard Management Unit, Department of Health Emergencies, World Health Organization Regional Office for the Eastern Mediterranean, Cairo, Egypt
[b] Centre for Global Health, Institut Pasteur, Paris, France
[c] Department of Infectious Hazard Management, WHO Health Emergencies Programme, World Health Organization, Geneva, Switzerland
[d] Ministry of Health, Riyadh, Saudi Arabia

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ABSTRACT

Background: Approximately half of the reported laboratory-confirmed infections of Middle East respiratory syndrome coronavirus (MERS-CoV) have occurred in healthcare settings, and healthcare workers constitute over one third of all secondary infections. This study aimed to describe secondary cases of MERS-CoV infection among healthcare workers and to identify risk factors for death.
Methods: A retrospective analysis was conducted on epidemiological data of laboratory-confirmed MERS-CoV cases reported to the World Health Organization from September 2012 to 2 June 2018. We compared all secondary cases among healthcare workers with secondary cases among non-healthcare workers. Multivariable logistic regression identified risk factors for death.
Results: Of the 2223 laboratory-confirmed MERS-CoV cases reported to WHO, 415 were healthcare workers and 1783 were non-healthcare workers. Compared with non-healthcare workers cases, healthcare workers cases were younger ($P < 0.001$), more likely to be female ($P < 0.001$), non-nationals ($P < 0.001$) and asymptomatic ($P < 0.001$), and have fewer comorbidities ($P < 0.001$) and higher rates of survival ($P < 0.001$). Year of infection (2013–2018) and having no comorbidities were independent protective factors against death among secondary healthcare workers cases.
Conclusion: Being able to protect healthcare workers from high threat respiratory pathogens, such as MERS-CoV is important for being able to reduce secondary transmission of MERS-CoV in healthcare-associated outbreaks. By extension, reducing infection in healthcare workers improves continuity of care for all patients within healthcare facilities.

Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) was first detected in a patient living in Saudi Arabia in September of 2012 [1]. Subsequent cases have included human infections across the Arabian Peninsula, occasional importation of cases outside the Arabian Peninsula and associated clusters in other regions of the world. Outbreaks of non-sustained, human-to-human transmission have occurred primarily in healthcare settings [2].

While MERS-CoV appears to be inefficient at transmitting between humans in the general community, about half of the reported MERS-CoV infections have occurred in healthcare settings [2]. Healthcare-associated transmission of MERS-CoV has been reported in France, Jordan, Saudi Arabia, United Arab Emirates, Republic of Korea and the United Kingdom and has on occasion resulted in large outbreaks [3–9]. Secondary transmission has occurred between patients, from patients to healthcare workers, and from patients to visitors of the hospital. To date, there has been limited evidence of transmission documented between healthcare

* Corresponding author at: Department of Infectious Hazard Management, WHO Health Emergencies Programme, World Health Organization, Avenue Appia 20, 1202 Geneva, Switzerland.
E-mail address: vankerkhovem@who.int (M.D. Van Kerkhove).
[1] Amgad A. Elkholy, Rebecca Grant contributed equally to this paper.

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workers in Saudi Arabia [10] and anecdotal evidence from healthcare workers to patients in Saudi Arabia [10]. Because HCW have not been consistently tested for MERS-CoV infection, nor has detailed outbreak investigations occurred within all hospital outbreaks, the role of healthcare workers in onward transmission remains unclear. Given the large number of HCWs infected to date, it is possible that HCW can propagate an outbreak within a healthcare facility. Among reported secondary MERS cases in such outbreaks, a substantial proportion have been healthcare workers [3,4,9–13].

The clinical spectrum of MERS-CoV infection ranges from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and other life-threatening complications [13–16]. Mild symptoms are non-specific and can include headache, tiredness, fever, mild cough, sore throat and runny nose. Some patients may present with gastrointestinal symptoms, including diarrhoea. The non-specificity of MERS signs and symptoms poses several challenges, not only for the timely identification and isolation of infected patients, but also for reducing secondary transmission within the healthcare facility, particularly to healthcare workers and between patients.

Preventing MERS-CoV infection in healthcare workers is critical because of their role in the clinical management of patients and in ensuring adequate infection prevention and control measures are implemented in healthcare facilities. Unnecessarily exposing healthcare workers to MERS-CoV affects the safety of both the healthcare workers and other patients in the healthcare facility, potentially propagating secondary transmission in healthcare-associated outbreaks. Understanding MERS-CoV infection in healthcare workers to date and the risk factors for adverse outcomes is important for preventing future infection of healthcare workers, for informing and updating infection prevention and control measures in healthcare facilities and for reducing secondary MERS-CoV transmission within healthcare settings.

The International Health Regulations [17] require all laboratory-confirmed cases of MERS-CoV to be reported to the World Health Organization (WHO) within 24 h of laboratory confirmation [18]. In this study, we use the epidemiological data of all MERS cases reported to date to WHO to describe secondary cases of MERS-CoV infection among healthcare workers and to identify the risk factors for death among healthcare workers with secondary infection.

Methods

Study design and participants

A retrospective analysis was conducted on epidemiological data of laboratory-confirmed MERS-CoV cases reported to WHO [18] from September 2012 to 2 June 2018. We looked specifically at healthcare workers involved in the delivery of health care to patients within the same healthcare facility as a confirmed or suspected MERS-CoV case. Primary cases were defined as cases with laboratory confirmation of MERS-CoV infection with no epidemiological link to a suspected or confirmed human MERS case. Secondary cases were defined as those with laboratory confirmation of MERS-CoV infection and with a direct epidemiological link with a confirmed or probable MERS-CoV case.

Prior to 2015, data from individual cases including occupation, signs/symptoms, exposures and risk factors for infection, etc. was not collected systematically. Following the large MERS outbreak in Jeddah and Riyadh in 2014, case report forms and policies related to the investigation of cases and contacts became more systematic from 2015 onwards. Given the inconsistencies in the collection and reporting of epidemiologic data from MERS-CoV cases to WHO prior to 2015, we performed a secondary analysis with data reported only from 1 January 2015 to 2 June 2018.

Statistical analysis

Descriptive analysis was performed for all MERS-CoV cases reported to WHO from 2012 to 2018. For all statistical analyses, $P < 0.05$ was considered statistically significant and all analyses were performed using the Epidemiological Data Display Package in R, version 3.2.2.0 (https://CRAN.R-project.org/package=epiDisplay).

We compared all secondary cases in healthcare workers with all secondary cases among non-healthcare workers, using the Student t-tests for continuous variables and chi-squared tests for categorical variables. We also aggregated survival outcomes of healthcare workers with MERS-CoV infection by year of infection.

To identify risk factors for adverse outcomes in healthcare workers with secondary infection, we performed multivariable logistic regression analysis on all healthcare worker secondary cases. Variables considered were dichotomous (sex, residency, symptomatic clinical presentation, presence of any comorbidities), categorical (year of infection) or continuous (age). The final multivariable model, constructed using the backward, stepwise elimination method, included all variables with an adjusted $P < 0.10$.

Results

Our analysis considered all 2223 cases of MERS-CoV reported to WHO up to 2 June 2018. Among these cases, 462 were primary cases, 989 secondary cases, 380 cases for which the information reported was insufficient to be able to determine whether it was a primary or secondary case, and 392 cases with missing case information. Among all cases, 790 (35.5%) deaths occurred.

Of the 2223 cases, 415 were reported as healthcare workers. The mean age of healthcare workers was 39.3 (interquartile range 30.0–46.0) years and 54.9% were women. Five were primary cases, 338 were secondary cases, 54 cases had insufficient information to be able to determine whether it was a primary or secondary case and 18 cases had missing case information. Fig. 1 shows the epidemic curve of cases of MERS-CoV among healthcare workers and non-healthcare workers reported from 2012 to 2 June 2018. Table 1 provides further description of the 415 healthcare worker cases, as well as the 178 healthcare worker cases reported to WHO from 1 January 2015 to 2018.

Table 2 compares all secondary healthcare worker cases and all secondary non-healthcare worker cases. Compared with secondary non-healthcare worker cases, secondary healthcare worker cases were younger ($P < 0.001$), had a higher proportion of women ($P < 0.001$), were non-national residents ($P < 0.001$), and had asymptomatic infection ($P < 0.001$), fewer comorbidities ($P < 0.001$) and higher survival ($P < 0.001$).

Further comparison between laboratory-confirmed MERS-CoV cases in healthcare workers and non-healthcare workers are shown in the Supplementary material.

Tables 3a and 3b shows the survival outcomes of all infections by year of infection. Tables 3a shows outcomes of all infections by year of infection for healthcare workers, while Table 3b shows outcomes of all infections by year of infection for non-healthcare workers. There have been no fatal MERS infections among healthcare workers since 2015.

Table 4 shows the regression coefficients and adjusted odds ratios (95% confidence interval) for the two variables retained in the final multivariable risk model for death in secondary cases among healthcare worker. Year of infection and having no comorbid conditions were found to be independent protective factors against death in healthcare workers with secondary MERS-CoV infection.

Healthcare workers include, but are not restricted to: doctors, nurses, pharmacists, physiotherapists, radiologists, rehabilitation

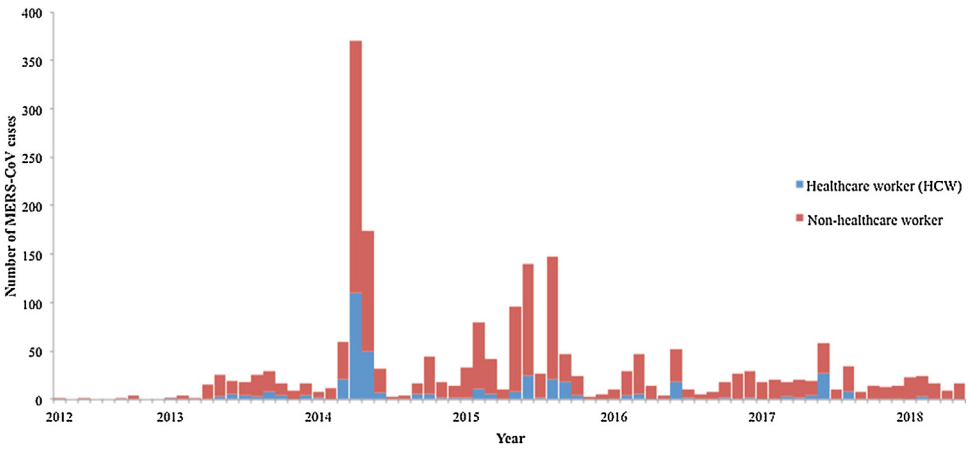

Fig. 1. Epidemic curve of laboratory-confirmed cases of MERS-CoV among healthcare workers and non-healthcare workers reported to WHO between September 2012 and 2 June 2018.

staff, infection prevention and control staff, intensive care staff, ambulance staff, respiratory therapists, auxiliary healthcare workers, attendants, laboratory, X-ray and ultrasound technicians, and healthcare administrators. A lack of consistency in reporting specific job titles prohibited subgroup analysis by different roles of healthcare worker.

Discussion

Healthcare workers continue to constitute a substantial proportion of secondary MERS-CoV infections. That is, among all cases of MERS-CoV reported to WHO as of 2 June 2018, healthcare workers accounted for 18.6% of all MERS-CoV cases and 34.2% of secondary MERS-CoV cases. This is similar to other respiratory pathogens: in the 2003 outbreak of severe acute respiratory syndrome, 23% of cases in Hong Kong, 40% in Canada and 41% in Singapore were healthcare workers [19]. Protecting health care workers from infectious hazards is paramount to ensuring their safety in delivering health care. In addition, being able to protect healthcare workers, constituting the front line response against high-threat respiratory pathogens, such as MERS-CoV, is important for reducing secondary transmission in healthcare-associated outbreaks. Reducing infection in healthcare workers, even if their infection does not cause morbidity or mortality, will improve the continuity of care for all patients in the same healthcare facility.

We also found that the demographic and clinical profile of secondary infections in healthcare workers was different from secondary infections among non-healthcare workers. Healthcare workers infected with MERS-CoV were younger, more were female and non-national residents, and had fewer comorbidities, more asymptomatic infections and higher survival. Importantly, no deaths have occurred among healthcare workers with secondary MERS infection since the end of 2015.

These results are similar to the findings in individual outbreaks reports [4,5,7–12,14]. The highest burden of MERS cases to date is in Saudi Arabia where healthcare workers are more likely to be female, a large proportion of whom are expatriates. The younger age and fewer comorbidities may partly explain the higher survival observed among healthcare workers, as well as the possibility of earlier identification or suspicion of MERS among healthcare workers. Indeed, the case fatality rate among all healthcare workers was 5.8% compared with 42.8% among all non-healthcare workers.

This is the first study to perform multivariable logistic regression to identify risk factors for death among 338 healthcare workers with secondary infections reported to date. The analysis showed that year of infection (2013–2018) and having no comorbidities were independent protective factors against death. The decline in risk of death since 2013 may reflect the substantial improvements in surveillance and the infection prevention and control measures that have been introduced in affected countries in recent years. In Saudi Arabia, for example, the Ministry of Health regularly review and update national infection prevention and control guidelines, according to which, healthcare workers who had unprotected "high-risk exposure" (within 1.5 m of the patient) or have suggestive symptoms regardless of exposure type are required to stop performing their duties immediately; to have a nasopharyngeal swab tested for MERS-CoV; to not resume their duties until cleared by the infection control team and to delay travel until cleared by infection control team [20]. Any healthcare worker who tests positive for MERS, any healthcare worker who develops MERS suggestive symptoms and any healthcare worker who had unprotected high-risk exposure are considered clear and able to resume work if they meet all of the following criteria: asymptomatic for at least 48 h, and the 14-day observation period is over, and they have at least one negative RT-PCR [20].

The enhanced infection prevention and control (IPC) efforts which have been introduced since 2015 include regular training of healthcare workers on IPC, auditing of IPC in healthcare facilities, improved case notification and isolation within emergency departments, and comprehensive contact-tracing and testing of all contacts, including healthcare workers, regardless of the development of symptoms. Guidelines on contact tracing were revised after 2015 to include the testing of all contacts of confirmed MERS cases (including healthcare workers) for MERS-CoV. Prior to 2015, contacts were only tested if they developed symptoms. This has increased the detection of asymptomatic or mildly symptomatic cases, which in turn, may have decreased the case fatality rate.

Specific IPC measures which may have contributed to the decreased case fatality rate include more systematic use of appropriate personal protective equipment and increased testing of asymptomatic personnel which effectively increases the detection of asymptomatic healthcare workers who are less likely to die, therefore increasing the denominator of healthcare worker cases and decreasing the case fatality rate. In addition, earlier detection of cases, and more efficient contact tracing have likely identified MERS-CoV infections in healthcare workers at an earlier stage of infection, enabling more timely treatment and clinical management, and, as a result, a reduction in the case fatality rate.

Further efforts to prevent and manage emerging respiratory disease infections, including MERS among healthcare workers, still need to be made. These include improving identification and rapid diagnosis of MERS, further understanding of the mecha-

Table 1
Descriptive analysis of laboratory-confirmed MERS-CoV HCW reported to WHO as of 2 June 2018 (N = 415).

Variable	All cases No. (%) (N = 415)	January 2015 onwards No. (%) (N = 178)
Age (years)		
Mean	39.3	38.3
Interquartile range	30.0–46.0	29.3–46.0
Sex		
Female	228 (54.9)	104 (58.4)
Male	187 (45.1)	74 (41.6)
Country of nationality		
Philippines	123 (29.6)	53 (29.8)
Kingdom of Saudi Arabia	99 (23.9)	22 (12.4)
India	44 (10.6)	24 (13.5)
Egypt	22 (5.3)	9 (5.1)
Bangladesh	15 (3.6)	7 (3.9)
Jordan	7 (1.7)	4 (2.2)
Sudan	6 (1.4)	2 (1.1)
Malaysia	5 (1.2)	2 (1.1)
Pakistan	5 (1.2)	3 (1.7)
Republic of Korea	5 (1.2)	5 (2.8)
Syrian Arab Republic	5 (1.2)	2 (1.1)
Myanmar	2 (0.5)	0 (0)
Bosnia and Herzegovina	1 (0.2)	1 (0.6)
Indonesia	1 (0.2)	0 (0)
Islamic Republic of Iran	1 (0.2)	0 (0)
Lebanon	1 (0.2)	1 (0.6)
South Africa	1 (0.2)	0 (0)
United Kingdom	1 (0.2)	0 (0)
United States of America	1 (0.2)	0 (0)
Yemen	1 (0.2)	1 (0.6)
Missing data	70 (16.9)	42 (23.6)
Year of infection (total infections)		
2012 (N = 9)	0 (0)	–
2013 (N = 186)	37 (19.9)	–
2014 (N = 756)	200 (26.5)	–
2015 (N = 677)	95 (14.0)	95 (1.0)
2016 (N = 259)	34 (13.1)	34 (13.1)
2017 (N = 248)	45 (18.1)	45 (18.1)
2018 (N = 88)	4 (4.5)	4 (4.5)
Type of case (total infections)		
Primary case (N = 462)	5 (1.1)	2 (0.4)
Secondary case (N = 989)	338 (34.2)	147 (14.9)
Unknown (N = 380)	54 (14.2)	14 (3.7)
Missing data (N = 392)	18 (4.6)	15 (3.8)
Comorbidities		
Any	38 (9.2)	20 (11.2)
None	377 (90.8)	158 (88.8)
Clinical manifestation		
Symptomatic	321 (77.3)	118 (66.3)
Asymptomatic	94 (22.7)	60 (33.7)
Outcome		
Survived	391 (94.2)	177 (99.4)
Died	24 (5.8)	1 (0.6)

nisms of transmission in healthcare settings, optimizing the layout of emergency departments for better triage of patients with respiratory symptoms, standardization of infection prevention and control practices and (re)training at facilities with high hospital staff turnover, and auditing of healthcare facilities for adherence to infection prevention and control measures. These will be critical to minimizing transmission in healthcare facilities, particularly until interventions are introduced to stop the virus entering the human population from the dromedary camel reservoir. The role of environmental contamination was evaluated in a number of hospitals following the 2015 MERS outbreak in the Republic of Korea and collaborative, experimental studies were conducted to evaluate the viability and persistence of MERS-CoV on surfaces and in the air [21–23]. The role of mild or asymptomatic cases in transmission chains, however, remains unclear [24–27]. Further epidemiological and environmental studies to determine route(s) of secondary transmission will also be critical.

Table 2
Comparison of laboratory-confirmed secondary MERS-CoV cases among healthcare workers (HCW) (N = 338) and non-healthcare workers (N = 642) reported to WHO as of 2 June 2018.

Variable	Secondary cases in HCWs No. (%) (N = 338)	Secondary cases in non-HCWs No. (%) (N = 642)	P-value
Age			<0.001
Mean (years)	39.2	51.6	
Sex			<0.001
Female	191 (56.5)	212 (33.0)	
Male	147 (43.5)	430 (67.0)	
Residence			<0.001
National	82 (24.3)	395 (61.5)	
Non-national	200 (59.2)	93 (14.5)	
Comorbidities			<0.001
Any	29 (8.6)	217 (33.8)	
None	309 (91.4)	425 (66.2)	
Clinical manifestation			<0.001
Symptomatic	249 (73.7)	607 (94.5)	
Asymptomatic	89 (26.3)	35 (5.5)	
Outcome			<0.001
Survived	322 (95.3)	408 (63.6)	
Died	16 (4.7)	234 (36.4)	

Table 3a
Outcomes of laboratory-confirmed MERS-CoV infection among healthcare workers (N = 415) reported to WHO as of 2 June 2018 by year of infection.

Year of MERS-CoV infection	Survived	Died	Case fatality rate (%)
2013	30	7	18.9
2014	184	16	8.0
2015	94	1	1.1
2016	34	0	0
2017	45	0	0
2018	4	0	0

Table 3b
Outcomes of laboratory-confirmed MERS-CoV infection among non-healthcare workers (N = 1808) reported to WHO as of 2 June 2018 by year of infection.

Year of MERS-CoV infection	Survived	Died	Case fatality rate (%)
2012	3	6	66.7
2013	57	91	61.5
2014	284	272	48.9
2015	338	224	39.9
2016	142	79	35.7
2017	136	67	33.0
2018	59	25	29.8

Table 4
Multivariable logistic regression model predicting risk of death in all laboratory-confirmed secondary MERS-CoV infections among healthcare workers (N = 338) reported to WHO as of 2 June 2018.

Variable	Regression coefficient	Adjusted OR (95% CI)	P-value
Year of infection (2013–2018)	−1.75	0.17 (0.07–0.45)	<0.001
Comorbidity (none vs any)	−1.52	0.22 (0.05–0.92)	0.04

OR: odds ratio; CI: confidence interval.

The results of our study are strengthened by the size of the study, which included all cases reported to WHO since the first case was notified in 2012. Our database has cases from all 27 countries reporting cases globally. However, since 2012, some inconsistencies have occurred in the way data have been collected and reported to WHO, for example in the use of a systematic data collection tool

and in reporting the outcome of all cases. Challenges also exist in classifying cases based on the available information at the time of reporting. For example, thorough outbreak investigations, which include full genome sequencing to clarify the transmission chains within the outbreak or separate introductions from outside, may find that cases that were initially classified as secondary case are in fact primary cases [4,11], but this information is not systematically relayed to WHO. Efforts are currently being made to retrospectively review and update the epidemiological data for all 2223 cases reported to WHO to date, particularly before 2015.

Conclusion

Healthcare workers still make up a significant proportion of secondary MERS-CoV infections. Understanding transmission to healthcare workers, preventing infection and improving clinical management of infected healthcare workers will all be critical to further reducing the incidence of secondary infections in healthcare settings.

Authors' contributions

All authors contributed to the study design, and reviewed and edited the manuscript. AAE, RG and ME performed the statistical analysis. All authors were involved in the interpretation of the findings.

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Competing interests

None declared.

Ethical approval

The case-patient data reported to WHO is anonymized, thus neither informed consent, nor approval from an institutional review board were required by WHO or countries providing this data to WHO under the International Health Regulations (2005).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2019.04.011.

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