International Journal of Infectious Diseases 29 (2014) 307–308

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Middle East respiratory syndrome coronavirus (MERS-CoV) viral shedding in the respiratory tract: an observational analysis with infection control implications

Ziad A. Memish [a,*], Abdullah M. Assiri [b], Jaffar A. Al-Tawfiq [c,d]

[a] College of Medicine, Alfaisal University, Ministry of Health, Riyadh 11176, Kingdom of Saudi Arabia
[b] Ministry of Health, Riyadh, Kingdom of Saudi Arabia
[c] Johns Hopkins Aramco Healthcare, Dhahran, Kingdom of Saudi Arabia
[d] Indiana University School of Medicine, Indianapolis, Indiana, USA

ARTICLE INFO

Article history:
Received 20 October 2014
Accepted 20 October 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Middle East
MERS-CoV
RT-PCR
Coronavirus
Viral kinetics

SUMMARY

Background: Since the first description of Middle East respiratory syndrome coronavirus (MERS-CoV), it has not been known how long patients shed the virus in respiratory secretions. Thus, we analyzed the available data on time to negative MERS-CoV test in patients with confirmed MERS-CoV infection and asymptomatic positive contacts.
Methods: Data from repeated laboratory testing of respiratory samples received at the Saudi Arabian virology reference laboratory in Jeddah, Kingdom of Saudi Arabia from September 1, 2012 to September 31, 2013 were recorded. A real-time RT-PCR test for MERS-CoV was used. Data were analyzed by origin of sample, sample type, and MERS-CoV PCR test results.
Results: Twenty-six individuals (13 patients and 13 contacts) had repeated testing done until a negative test was obtained. Most samples from MERS-CoV cases were tracheal aspirate/sputum ($p = 0.0006$) and most samples from contacts were nose and throat swabs ($p = 0.0002$). Kaplan–Meier curve analysis showed that contacts cleared the virus at a much earlier time than patients. On day 12, 30% of contacts and 76% of cases were still positive for MERS-CoV by PCR.
Conclusions: Contacts cleared MERS-CoV earlier than ill patients. This finding could be related to the types of sample as well as the types of patient studied. More ill patients with significant comorbidities shed the virus for a significantly longer time. The results of this study could have critical implications for infection control guidance and its application in healthcare facilities handling positive cases.

1. Introduction

Since the emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, there have been 755 cases with a total 320 deaths in the Kingdom of Saudi Arabia.[1] The virus was initially thought to affect older adults and those with underlying medical conditions.[2] The reporting of asymptomatic and mildly symptomatic cases decreased the overall mortality rate and the mean age.[3] Data on viral kinetics in the respiratory tract and other body fluids are scarce. In a recent case study, MERS-CoV shedding from the respiratory tract was detected until day 24 of illness.[4] In this study we investigated the viral shedding of MERS-CoV in the respiratory secretions of patients who were ill and those with mild disease who underwent repeated testing.

2. Methods

Patients who underwent more than one virological test for MERS-CoV at least 1 day apart were included in the analysis. Repeat testing was done non-systematically using respiratory tract samples from September 1, 2012 to September 31, 2013.

The types of respiratory specimen collected from patients and contacts were sputum samples, nose and throat swabs, nasopharyngeal swabs, and endotracheal aspirate samples.

With regard to MERS-CoV screening, clinical samples were screened by real-time PCR (RT-PCR) amplification test, as described previously, with amplification targeting both the upstream E protein gene (upE) and ORF1a for confirmation; these are standard assays used in KSA for MERS-CoV testing.[2,5]

* Corresponding author.
E-mail address: zmemish@yahoo.com (Z.A. Memish).

http://dx.doi.org/10.1016/j.ijid.2014.10.002
1201-9712/

Table 1
Sample types based on the category of the patient (cases vs. contacts)

	Nasopharyngeal, *n* (%)	Nasal and throat, *n* (%)	Tracheal aspirate/ sputum, *n* (%)
Cases (*n* = 26)	8 (30.7)	2 (7.8)	16 (61.5)
Contacts (*n* = 20)	6 (30)	12 (60)	2 (10)
p-Value	1.0	0.0002	0.0006

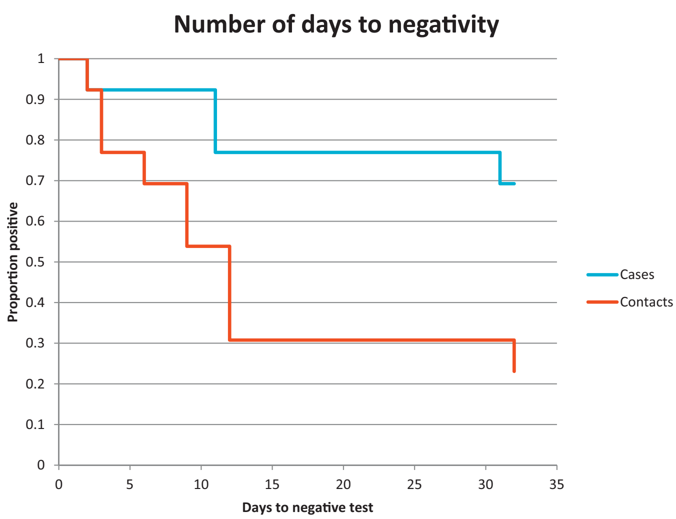

Figure 1. Kaplan–Meier curve showing time to negative test for cases and contacts.

The Kaplan–Meier method was used to calculate the time to negative repeat MERS-CoV RT-PCR test. 'Positive test' curves were drawn for patients and contacts who had repeated testing. The statistical significance of the difference between the curves was assessed using a log-rank test. SPSS software (SPSS for Windows, Version 11. Chicago, IL: SPSS Inc.; 2002) was used for the analysis.

3. Results

Twenty-six individuals (13 patients and 13 contacts) underwent repeat respiratory sample testing until a negative test result was obtained. Table 1 shows the specimen type by category. Most samples from MERS-CoV cases were tracheal aspirate/sputum ($p = 0.0006$) and most samples from contacts were nose and throat swabs ($p = 0.0002$). The Kaplan–Meier curve showed that contacts cleared the virus at a much earlier time than patients (Figure 1). On day 12, 30% of contacts and 76% of cases were still positive for MERS-CoV by PCR.

4. Discussion

The viral kinetics and the time of shedding of MERS-CoV in the respiratory tract are not known. In previous case reports, MERS-CoV was isolated from the respiratory tract secretions up to day 24 in one patient,[4] and day 18 in another.[6] In this large retrospective analysis, cases had more prolonged viral shedding from the respiratory tract than contacts. The difference is related to the severity of the disease and the significant underlying comorbidities among the cases. However, the study did not examine viral shedding systematically and thus patients with more severe disease may have been selected for repeat testing rather than those who had milder disease. A systematic and prospective study is required to further delineate the kinetics of MERS-CoV, not only in respiratory secretions but also in other body fluids (blood, urine, and stool). The reporting of these data is important to further characterize the pathogenesis of this disease and for better application of the infection prevention and control measures required. The need to quantify the viral load is also very important for any recommendations regarding the need for isolation of those who continue to have positive MERS-CoV by PCR. The presence of viral RNA in respiratory secretions may indicate a replicating or a dead virus.

Although the data showed a difference between cases and contacts – contacts had more upper respiratory tract swabs tested, while cases had lower respiratory tract samples tested – the difference could be attributed to the sample type rather than the exposure type. We have previously shown that lower respiratory tract samples yield higher MERS-CoV viral loads and genome fractions than upper respiratory tract samples.[7] Since cases had lower respiratory tract samples collected more often than upper respiratory tract samples, this indicates that cases were more ill and probably shed virus much longer. This finding, if confirmed by the prospective systematic collection of respiratory samples, would highlight the importance of applying prolonged infection control measures in severely ill patients with MERS-CoV in the healthcare setting. The pattern of transmission of MERS-CoV is well characterized as sporadic, intra-familial, and healthcare-associated.[8–10] The transmission of MERS-CoV within healthcare facilities was noted in the Al-Hasa outbreak,[11] and of 95 cases in one report, 63.2% were healthcare-associated and 13.7% were intra-familial transmission.[12] In support of the low infectivity of asymptomatic and mildly symptomatic cases is the finding of a low transmission rate within family contacts.[13]

Conflict of interest: No conflict of interest to declare.

Acknowledgments

This study was part of a public health investigation of retrospective data analysis under the authority of the Ministry of Health of the Kingdom of Saudi Arabia.

References

1. Saudi Ministry of Health. Command and Control Center. Statistics. Kingdom of Saudi Arabia: Ministry of Health; 2014. Available at: http://www.moh.gov.sa/en/CCC/PressReleases/Pages/default.aspx [accessed July 15, 2014].
2. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis* 2013;**13**:752–61.
3. Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus: epidemiology and disease control measures. *Infect Drug Res* 2014 (in press).
4. Spanakis N, Tsiodras S, Haagmans BL, Raj VS, Pontikis K, Koutsoukou A, et al. Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regimen. *Int J Antimicrob Agents* 2014 Sep 18 [Epub ahead of print].
5. Al-Tawfiq JA, Hinedi K, Ghandour J, Khairalla H, Musleh S, Ujayli A, et al. Middle East respiratory syndrome coronavirus: a case–control study of hospitalized patients. *Clin Infect Dis* 2014;**59**:160–5.
6. Drosten C, Seilmaier M, Corman VM, Hartmann W, Scheible G, Sack S, et al. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. *Lancet Infect Dis* 2013;**13**:745–51.
7. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, Assiri A, Alhakeem RF, Albarrak A, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. *J Infect Dis* 2014 May 15. pii: jiu292. [Epub ahead of print].
8. Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus: transmission and phylogenetic evolution. *Trends Microbiol* 2014;**22**:573–9.
9. Al-Tawfiq JA, Zumla A, Memish ZA. Travel implications of emerging coronaviruses: SARS and MERS-CoV. *Travel Med Infect Dis* 2014;**12**:422–8.
10. Al-Tawfiq JA, Zumla A, Memish ZA. Coronaviruses: severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus in travelers. *Curr Opin Infect Dis* 2014;**27**:411–7.
11. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al., KSA MERS-CoV Investigation Team. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med* 2013;**369**:407–16.
12. The WHO MERS-CoV Research Group. State of knowledge and data gaps of Middle East respiratory syndrome coronavirus (MERSCoV) in humans. PLoS Curr 2013 Nov 12;5. pii: ecurrents.outbreaks.0bf719e352e7478f8ad85fa30127ddb8
13. Drosten C, Meyer B, Müller MA, Corman VM, Al-Masri M, Hossain R, et al. Transmission of MERS-coronavirus in household contacts. *N Engl J Med* 2014;**371**:828–35.