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Asymptomatic Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: Extent and implications for infection control: A systematic review

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ABSTRACT

Background: The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged in 2012 and attracted an international attention as the virus caused multiple healthcare associated outbreaks. There are reports of the role of asymptomatic individuals in the transmission of MERS-CoV, however, the exact role is not known.
Method: The MEDLINE/PubMed and Scopus databases were searched for relevant papers published till August 2018 describing asymptomatic MERS-CoV infection.
Results: A total of 10 papers were retrieved and included in the final analysis and review. The extent of asymptomatic MERS infection had increased with change in the policy of testing asymptomatic contacts. In early cases in April 2012–October 2013, 12.5% were asymptomatic among 144 PCR laboratory-confirmed MERS-CoV cases while in 2014 the proportion rose to 25.1% among 255 confirmed cases. The proportion of asymptomatic cases reported among pediatric confirmed MERS-CoV cases were higher (41.9%–81.8%). Overall, the detection rate of MERS infection among asymptomatic contacts was 1-3.9% in studies included in this review. Asymptomatic individuals were less likely to have underlying condition compared to fatal cases. Of particular interest is that most of the identified pediatric cases were asymptomatic with no clear explanation.
Conclusions: The proportion of asymptomatic MERS cases were detected with increasing frequency as the disease progressed overtime. Those patients were less likely to have comorbid disease and may contribute to the transmission of the virus.

1. Introduction

The emergence of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 had attracted an international attention as the virus had cause multiple healthcare associated outbreaks [1–21] within the Kingdom of Saudi Arabia [1,2,6,8,9,13] and outside Saudi Arabia [4,5,22,23]. As of December 7, 2018, the World Health Organization reported 2267 laboratory-confirmed cases worldwide and at least 804 related deaths in 27 countries [24]. Despite the increase in the number of cases, the actual incidence of MERS-CoV among hospitalized patients with community acquired pneumonia is low. In a longitudinal study from 2012 to 2016, a total of 2657 patients were screened for MERS-CoV and only 20 (0.74%) tested positive [25]. The study showed that MERS-CoV was rare in admitted patients with community acquired pneumonia and influenza was more common than MERS [25]. The explanation for the increased number of cases is the occurrence of multiple outbreaks as the hallmark of MERS-CoV transmission [26]. The main patterns of MERS-CoV transmissions are: sporadic community cases from presumed non-human exposure, family clusters resulting from contact with an infected family index case, and healthcare-acquired infections between patients and from patients to healthcare workers [5]. In addition, there were multiple occasions of transmission within the same family and that travel associated transmission of MERS-CoV poses a concern [27,28].

There are reports of the role of asymptomatic individuals in the transmission of MERS-CoV, however, the exact role is not known [26]. Many viral infections are associated with asymptomatic, subclinical, or very mild symptoms. In the case of poliomyelitis, 95% of those infected remain asymptomatic, yet they are still capable of spreading the virus (CDC). In one study, asymptomatic rhinovirus infection was four times

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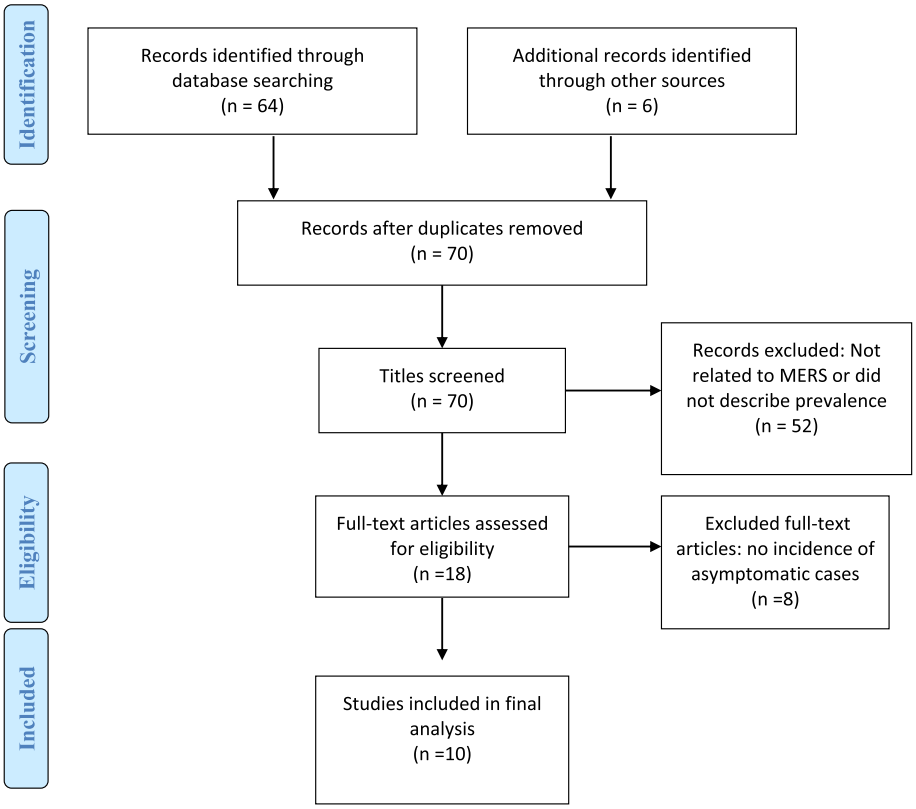

Fig. 1. A flow diagram of the search strategy according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32].

as common as symptomatic infection [29]. Another study found asymptomatic carriage of influenza virus to be 5.2–35.5% [30]. During the severe acute respiratory syndrome (SARS) outbreak, a study examined the rate of positive healthcare workers (HCWs) who were exposed to patients with SARS before infection control measures were applied [31]. Asymptomatic SARS based on serology was 13% compared to severe disease in 82% and 4% of mild symptoms [31]. In this article, we systematically review the available literature on the occurrence of asymptomatic MERS-CoV infection and shed light on the possible role of those in the transmission of the virus.

1.1. Search strategy

We searched MEDLINE and Scopus databases for articles in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prismastatement.org) [32]. We included the following terms:

#1: “Middle East Respiratory Syndrome Coronavirus” OR “MERS” OR “MERS-CoV” OR “Novel Coronavirus”
#2: “Asymptomatic”
3: “transmission”
#4: #1 AND #2 AND #3.

Early in the course of the MERS outbreak, the term MERS was not yet coined and the term Novel Coronavirus was used. Thus, we also conducted a focused search to identify any missed relevant publications.

We included articles describing transmission of MERS-CoV in animals and humans from asymptomatic infection.

2. Results

Initial screening of retrieved articles excluded articles which were: review articles, and those which did not include specific rates or cases of asymptomatic MERS-CoV infection. A total of 10 papers were retrieved and included in the final analysis and review (Fig. 1, Table 1) [6,33–41]. We included studies in humans describing the incidence of asymptomatic MERS [6,33–40] and two additional studies in animals [42,43].

2.1. Animal infection

In a rabbit model of MERS-CoV infection, MERS-CoV was detected in the lungs without significant histopathological changes and no symptoms [42]. In an evaluation of contacts of a positive dromedary camel, 2 (5.8%) of 34 dromedary contacts tested positive and were asymptomatic [43].

2.2. Extent of asymptomatic MERS in humans

The proportion of asymptomatic MERS probably remained unchanged, or even declined with implementation of personal protection measures; asymptomatic case identification increased by change in testing recommendations. This change had also resulted in the reduction of case-fatality rate from 65% mainly in severe cases to 44.5% in mixed population [44]. This reduction was partially related to an increase in the rate of asymptomatic individuals from 0% to 28.6% in early reports [44]. A summary of studies addressing asymptomatic MERS cases in Humans is shown in Table 1. In early cases from April 2012 to October 2013, there were 144 laboratory-confirmed MERS-CoV cases including 18 (12.5%) asymptomatic individuals [33]. In one study from Saudi Arabia, 4 (0.8%) of 520 asymptomatic HCWs screened were positive [35]. In South Korea, 3 (0.5%) of 591 asymptomatic HCWs were detected positive via PCR screening [34]. In a recent study from Saudi Arabia, 17 out of 879 HCWs tested positive for MERS-CoV and 53% of them were asymptomatic by PCR [41].

In a seroepidemiologic survey conducted in South Korea, of 1610

Table 1
A summary of studies addressing asymptomatic MERS cases in Humans.

Study	Year	Setting	Method of diagnosis	Total number of confirmed MERS cases	Proportion of asymptomatic cases among confirmed cases (%)	Number of confirmed cases among asymptomatic screened contacts	Reference
1	April 2012 to October 2013	Laboratory-confirmed and probable MERS-CoV symptomatic cases from 9 countries	PCR	144	18 (12.5%)	–	[33]
2	December 2012 and August 2013	Asymptomatic Saudi Arabian HCWs contacts (n = 520 screened)	PCR	4	–	4/520 (0.8%)	[35]
3	2015	Asymptomatic South Korea HCWs contacts (n = 591 screened)	PCR	3	–	3/591 (0.5%)	[34]
4	2015	South Korea HCWs (n = 574 screened) and non-HCWs contacts (n = 307 screened)	Serology (ELISA/IFA/PRNT)	1	–	0/574 HCWs 1/307 non-HCWs (0.3%) 1/1610 (0.06%)	[36]
5	January 1 through May 16, 2014	Laboratory-confirmed cases reported to the Saudi Arabian Ministry of Health during the Jeddah Outbreak	PCR	255	64 (25.1%) including 41 HCWs and 23 non-HCWs		[6]
6	June 4, 2013, to November 5, 2013	Saudi Arabian household contacts (N = 280 screened)	PCR or serology	12	11 (91.7%)	Not available	[37]
7	September 1, 2012, to December 2, 2013	Laboratory-confirmed pediatric cases reported to the Saudi Arabian Ministry of Health	PCR	11	9 (81.8%)	–	[38]
8	June 2012, to April 19, 2016	Laboratory-confirmed pediatric cases reported to the Saudi Arabian Ministry of Health	PCR	31	13 (41.9%)	–	[39]
9	April 2014 to November 2016	Laboratory-confirmed pediatric cases admitted to one Saudi Arabian Hospital	PCR	7	3 (42.8%)	–	[40]
10	June 2017 Outbreak	Healthcare workers contacts at one hospital in Saudi Arabia	PCR	879	15 (53%)	–	[41]

asymptomatic HCWs and non-HCWs contacts only 1 non-HCW (0.06%) tested positive [36]. Asymptomatic persons were identified in the Jeddah outbreak. There were 64 (25%) asymptomatic of 255 individual tested including 41 HCWs and 23 non-HCWs [6]. In a total of 280 household contacts, 12 individuals were identified by PCR or serology of whom 11 (3.9%) were asymptomatic [37]. Asymptomatic individuals were less likely to have underlying condition (42%) compared to 86% of fatal cases [45]. However, serologic evaluation of contacts and patients may underestimate the extent of the disease as antibodies wane over time and is related to disease severity [46]. Of particular interest is that most of the identified pediatric cases were asymptomatic with no clear explanation [38–40,47].

Overall, the detection rate of MERS cases among asymptomatic contacts when screened was less than 1% in the available studies included in this review (Table 1). The proportion of asymptomatic cases among all confirmed cases, widely differed in the available reports. The differences between the study setting and the populations studied did not allow any reliable comparison. According to the last WHO update 21% of the 2228 cases confirmed MERS-CoV cases were reported to have no or mild symptoms while 46% had severe disease or died [48].

2.3. Asymptomatic travelers

Imported MERS-CoV cases were treated in healthcare settings. More than 20 travel-related MERS-CoV had occurred as summarized previously [28]. However, there were no reported asymptomatic cases. Travel related MERS-CoV occurred infrequently among pilgrims performing Umrah [28,49].

3. Discussion

3.1. Role of asymptomatic individuals in MERS-CoV infection

The role of asymptomatic individuals was evaluated in a family cluster [50]. The index case in that study was thought to have acquired MERS infection from an unrecognized mild or asymptomatic case [50]. However, the link was not established in this case. One study suggested the possible transmission of MERS from an asymptomatic individual. The index case of a family cluster acquired infection 14 days after hospitalization suggesting that the infection occurred from an asymptomatic person [50]. This is based on an incubation period of 7–10 days. In the South Korea outbreak, 82 contacts of an asymptomatic or mild MERS-CoV infection were tested by RT-PCR and serology and all of them were negative [51]. In a study from Abu Dhabi, of 34 case-patients, 91% were asymptomatic with no evidence of transmission [52]. In another study, most of the cases were either asymptomatic or mildly symptomatic [53]. MERS-CoV was cultured from a patient with mild respiratory symptoms confirming the ability of such patients to transmit MERS-CoV [54].

The role of asymptomatic travelers in the potential transmission of the infection to household contacts is a concern. However, so far no such event had been reported. The risk of MERS-CoV infection seems to be low in travelers [49], and there were multiple cases described in travelers [28]. The risk of MERS-CoV was evaluated in a mathematical study and the model included all Middle East countries with reported locally acquired cases, and 41% of the travel-imported cases outside the Middle East were in the top ten countries [55]. Although, India was the most at-risk country, there had been no reported cases from this country.

The initial 2012 Hajj season started few weeks after the first case of MERS-CoV infection was reported [56]. However, there were no reported cases among pilgrims in 2012 [57–60]. Thus, the Saudi Ministry of Health utilized the MERS-CoV case definition for monitoring any occurrence of the disease during Hajj for early detection of cases among pilgrims [61]. An enhanced surveillance system was established for the detection of MERS-CoV cases. The disease remains limited to the Middle

East with the exception of sporadic travel associated infections and the large outbreak in South Korea [22,28,62,63]. In one study conducted September 2012–October 2013, 77 travelers from the Middle East met the possible case definition for MERS and two of them tested positive for MERS [28]. In a small study of 14 retuning Pilgrims, all patients were hospitalized for respiratory symptoms and none of them tested positive for MERS-CoV in Marseille France in October 2013 [64]. Furthermore, nasopharyngeal swabs were collected from suspected cases and all samples tested negative for MERS-COV [56]. Another small study of 7 Pilgrims in 2014 in Austria, none had MERS-CoV [65].

Mathematical models estimated the risk of MERS-CoV among pilgrims to be 1–7 cases per Hajj, and 3–10 per Umrah per year [66]. It was estimated that 6.2 pilgrims may develop MERS-CoV symptoms during the Hajj, and 4 pilgrims may become infected and return home before symptoms development [67]. However, systematic screening of pilgrims for MERS-CoV showed no positive cases [59,65,68–81]. Systematic surveillance of returning Pilgrims was done in several studies in Egypt, Iran, France, Ghana, Iran and Saudi Arabia [64,68,71,72]. Few studies examined MERS-CoV among symptomatic pilgrims and none was positive for MERS-CoV) [56,59,65,81]. There had been an extensive surveillance of MERS-CoV among pilgrims and only 4 cases have been linked to Umrah (Mini-Hajj) [82–86].

3.2. Infection control implications

The occurrence of asymptomatic infection of MERS and the possibility of transmission to other individuals is of particular importance for healthcare settings and for travelers. These RT-PCR positive persons with mild or no symptoms are usually identified when conducting laboratory screening tests as part of active case monitoring or contact investigations. Asymptomatic health care workers may contribute to healthcare associated transmission and asymptomatic travelers may potentially transmit the infection to household contacts. The WHO recommends the isolation of asymptomatic PCR-positive individuals and daily follow up for the occurrence of symptoms. Those individuals should be tested at least weekly and HCWs should not return to work until two consecutive upper respiratory tract samples are RT-PCR negative [87]. In a study of severe cases and those with mild disease, the latter group cleared MERS-CoV at an earlier time than patients with severe disease whereby on day 12, 30% of mild cases and 76% of severe cases were positive for MERS-CoV by PCR [88]. Another study reported prolonged nasal virus RNA detection (more than 5 weeks) from one asymptomatic RT-PCR positive health-care worker [89].

In conclusion, the proportion of asymptomatic MERS cases were detected with increasing frequency as the disease progressed overtime. Those patients were less likely to have comorbid disease and may contribute to the transmission of the virus.

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Conflicts of interest

All authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2018.12.003.

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