Middle East Respiratory Syndrome Coronavirus Transmission among Healthcare Workers: Implication for Infection Control

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Abstract:

Background:

Many outbreaks of the Middle East respiratory syndrome coronavirus (MERS-CoV) occurred in healthcare settings and involved health care workers (HCWs). We describe the occurrence of an outbreak among HCWs and attempt to characterize at risk exposures to improve future infection control interventions.

Materials and Methods: This study included an index case and all HCWs contacts. All contacts were screened for MERS using PCR.

Results: During the study period in 2015, the index case was a 30 year-old Filipino nurse who had a history of unprotected exposure to a MERS-CoV positive case on May 15, 2015 and had multiple negative tests for MERS. Weeks later, she was diagnosed with pulmonary tuberculosis and MERS-CoV infection. A total of 73 staff were quarantined for 14 days and nasopharyngeal swabs were taken on day 2, 5 and 12 post-exposure. Of those contacts three (4%) were confirmed positive for MERS-CoV. An additional 18 staff were quarantined and had MERS-CoV swabs. A 4th case was confirmed positive on day 12. Subsequent contact investigations revealed a four generation transmission. Only 7 (4.5%) of the total 153 contacts were positive for MERS-CoV.

Conclusion: The role of HCWs in MERS-CoV transmission is complex and although the majority of MERS-CoV infected HCWs are asymptomatic or have a mild disease, fatal infections can occur and HCWs can play a major role in propagating healthcare facility outbreaks. This investigation highlights the need to continuously review infection control guidance relating to the role of HCWs in MERS-CoV transmission in healthcare outbreaks.

Especially as it relates to the complex questions on definition of risky exposures, who to test and the frequency of MERS-CoV testing, criteria for who to quarantine and for how long, and clearance and return to active duty criteria.

Introduction:

Since the emergence of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in September 2012, the largest and most documented outbreaks to date had occurred in healthcare settings [1–6]. As of June 26, 2017, there were 2029 cases including a total of 704 deaths reported to World Health Organization [7]. The recent outbreaks of MERS-CoV infection highlight the importance of the emergency departments in being the initial site of the spread of this virus [8–12]. In addition, hemodialysis units were also highlighted as the focus of multiple documented and undocumented outbreaks in Al-Hasa and Taif, Saudi Arabia (SA) [5,13]. From April 2014 to November 2016, a total of 295 confirmed cases were admitted to Prince Mohamed Bin Abdulaziz Hospital (PMAH), Ministry of Health, Riyadh, SA. Of those cases, 98 (33%3) were diagnosed at PMAH, whereas the rest were transferred to PMAH from other Riyadh hospitals, being the reference corona center for the central region of SA. Here, we describe a detailed investigation of an outbreak of MERS-CoV among healthcare workers (HCWs) in a MERS-CoV referral hospital with key learning points to be highlighted.

Methods:

We describe the transmission pattern and contact tracing of a MERS-CoV infected HCW, resulting in an outbreak in PMAH in KSA. All suspected HCWs were tested for MERS-COV using real-time polymerase chain reaction (RT-PCR) [14]. The target upstream of the MERS-CoV envelope protein gene (*upE*) and the open reading frame 1a gene (*ORF1a*) [14].

The first case who initiated the outbreak was designated as the index case with all her positive contacts designated as primary transmissions. As described previously, subsequent cases

resulting from the first-generation cases were called second-generation transmission, and infected HCWs from those were designated as third-generation cases and so on [15].

Results:

The index Case: The case was confirmed on August 12, 2015 (from the first screening swab) and the patient was a 30-year-old Filipino nurse who had a history of unprotected exposure to a MERS-CoV positive case on May 15, 2015. She was not overweight (weight 58 kg). At that time and as per hospital protocol, she was quarantined for 14 days [16]. MERS-CoV swab was documented on day 2, 5 and 12 to be negative (May 17, 23 & 27). On June 26, she went on vacation to the Philippines. Two weeks after her arrival to the Philippines, she manifested symptoms of dry cough and shortness of breath. She self-medicated herself with amoxicillin with no significant improvement. On August 7, she came back to SA and on August 10, she was seen at the employee health clinic for evaluation. Given her recent arrival from a non-endemic country, screening for MERS-CoV was not considered. On August 11, she was allowed to resume work despite being symptomatic with dry cough and shortness of breath. On August 12, she was admitted as a suspected TB vs. MERS-CoV infection. On the following day, MERS-CoV test was positive (Ct values of EG35 and ORF 34), and she also tested positive for tuberculosis [17].

Contacts of the index case: A comprehensive contact tracing was done with a total of 73 staff were quarantined for 14 days and nasopharyngeal swabs were taken on day 2, 5 and 12 post-exposure. All quarantined HCWs contacts had daily monitoring for fever and respiratory symptom. Of those contacts three (4%) were asymptomatic and confirmed positive for MERS-CoV by nasopharyngeal swabs (on first swab). An additional 18 new HCWs contacts were

quarantined and had MERS-CoV swabs as indicated above. A 4th case was asymptomatic and tested negative on day 2 and day 5 but was confirmed positive on day 12. Thus, an additional 7 staff were quarantined (the 4th case flat mates). A 5th staff had fever and sore throat and was confirmed positive on first swab and she came into contact with 15 additional staff. A 6th case had cough and sore throat and was confirmed positive on 3rd swab. This 6th case had 21 additional contacts. Of those, one nurse was diagnosed with MERS-CoV (the 7th case). The staff was asymptomatic and was positive on the first swab. The 7th case had an additional 22 exposed staff but none of them were positive (figure 1). Thus, only 7 (4.5%) of the total 153 contacts were positive for MERS-CoV.

All confirmed cases were nurses and two of the seven subsequent cases were thought to acquire the infection through an exposure within the housing compound. Detailed questioning on the significance of the contact with the positive cases revealed the following. Three (43%) had a contact less than 1.5 meters, four (57%) had a contact for less than 10 minutes, 3 (43%) had a contact < 1.5 meters, and > 10 minutes and the remaining had a contact > 1.5 meters and < 10 minutes (table 1). Only the index case had an abnormal chest x-ray and the laboratory evaluations of all positive cases are shown in table 2. All the positive cases were positive on the first swab except for two who were positive on the 2th and 3rd swab. The mean time to negative swab was 4.8 days (range 2-14 days).

Discussion:

In this outbreak investigation, we report four generation of transmission of MERS-CoV among HCWs. The transmission dynamics suggests that the transmission occurred within the setting of the hospital as well as the in the housing environment. These findings highlight the importance

of continued vigilance and detailed systematic screening of exposed HCWs whether they are symptomatic or not. Such an activity is very complex and often it is difficult to elucidate the exact contact pattern between HCWs due to the extensive social interaction within the hospital and housing among different healthcare workers from different units. In addition there are difficulties in relying on the HCWs memory of exact contacts and infection control precautions taken during that contact.

The index case was initially identified as a contact of a MERS-CoV patients, she had multiple swabs that were negative. She then went to the Philippine and started to have symptoms. Later, she was diagnosed with both MERS-CoV and pulmonary tuberculosis. Since, the diagnosis of MERS had occurred many weeks after several negative MERS swabs, the exact source of the infection could not be determined. In the South Korea MERS-CoV outbreak, five patients with MERS-CoV had unclear infection sources [15]. During the outbreak investigation, there were four spreaders (transmitting MERS to $\geq$ 1 individuals) and one possibly was a super-spreader (transmitted the virus to four HCWs). In the South Korea outbreak, super-spreader was arbitrarily defined as a transmission of MERS-CoV to $\geq$ 5 cases [15]. However, the exact definition of super-spreader is not well established [18]. The characteristics of the index case of an infectious disease outbreak potentially influence the transmission dynamics. These dynamics may also depend on the traits of the individuals with whom the index case interacts.

In this investigation, we found that all HCWs were nursing staff. In a previous outbreak study, none of a neurology unit workers contracted MERS, but 15 medical ICU workers (11.7%) and 5 emergency department workers (4.1%) did contract MERS [19]. The seropositivity of HCWs after a contact with MERS-CoV patients is variable. In this study, the PCR positivity rate was 4.5% among the exposed staff and no serological testing was conducted. In a previous study of 1169 HCWs, 15 were

positive by PCR and 5 of 737 HCWs were positive by serology testing [20]. In a second study from Thailand, none of 38 HCWs tested positive by serology [21]. Using serology, none of 48 contacts were positive for MERS-CoV infection [22]. In Korea, 36 (19.9%) of 181 confirmed MERS-CoV cases were HCWs [23].

Although MERS-CoV among HCWs is usually asymptomatic or presents as a mild disease, fatal cases had been reported. Comparing MERS-CoV with SARS, the majority of HCWs with SARS had symptomatic infection with an associated high case fatality rate. In one study, the case fatality rate was 7% among MERS infected HCWs vs. 12% in SARS among HCWs [24]. The current study showed that most of the MERS-CoV positive HCWs had asymptomatic or mild disease consistent with previous observations [25]. What is surprising in our report was the fact that asymptomatic HCWs were able to transmit the virus to other HCWs despite being asymptomatic. This is in sharp contrast to the recent report from South Korea were none of 82 contacts of asymptomatic patients turned to be positive [26]. Although, the Ct value of the index case was high, the index case was able to infect additional four cases. The relationship between Ct value and transmission dynamics was not studied. However, a lower Ct of 31 for E gene was significantly lower than the median of 33 of survivors [27].

Systematic thorough screening for MERS-CoV among contacts is needed for effective infection control of outbreaks. The current guidelines from the Saudi Ministry of Health does not advocate routine MERS-CoV testing of asymptomatic contacts and advocate the return to normal duty. However, the guidelines stress the need for testing of all those HCWs involved in high-risk unprotected exposure. High-risk exposure was defined as “contact with confirmed MERS-CoV case within 1.5 meters for > 10 minutes”. And those who are asymptomatic should have only

one test [28]. The CDC recommends that asymptomatic HCWs do not get routine MERS-CoV testing [29]. During an outbreak investigation, HCWs with no symptoms were allowed to work with active monitoring and to be excluded from work if they develop MERS-like symptoms developed [30]. The index case acquired MERS from the community and she had a concomitant TB with MERS-CoV. The co-infection might have contributed to increase infectiveness because of coughing and damaged lung tissue. The WHO recommends testing of all contacts in health-care associated outbreaks regardless of the development of symptoms [31]. In addition, WHO recommends that asymptomatic HCWs with positive MERS-CoV by PCR should be isolated. Those HCWs can return to work when two consecutive upper respiratory tract samples taken at least 24 hours apart are negative on RT-PCR [32].n this study, 43% had a contact < 1.5 meters, 57% had a contact < 10 minutes, and 43% had a high-risk contact (< 1.5 meters and > 10 minutes contact). [33]. Thus, of those positive only 43% had a high-risk exposure and thus this definition alone may not be sufficient to exclude HCWs from testing. In a study of nine HCWs who had a contact within 3–6 feet of a MERS-CoV patient revealed that only one of them was positive for MERS-CoV [34]. In another study, all HCWs contacts reported 100 % compliance with personal protective equipment and none were positive In a study of 48 HCWs contacts, none had serologic evidence of MERS-CoV infection [22]. However, the largest screening of MERS-CoV among HCWs showed a positive rate of 1.1% among 1695 HCWs [35]. In the SARS era, asymptomatic patients were culture negative for SARS [36]. Thus, it is not clear if asymptomatic MERS behave similar to SARS patients.

In conclusion, all HCWs in contact with confirmed MERS-CoVpatients need to be quarantined for 14 days no matter how significant the contact is; if the full compliance with PPE cant be assured with certainty. One and two sampling might not be adequate and a third sampling is

advisable prior to HCW clearance. The current detailed investigation identified contacts of asymptomatic positive MERS-CoV HCWs who tested positive which highlights the possibility of being infectious even if symptoms are lacking, a question which has been debated by scientists for years.

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Figure 1: Graphical Representation of the Evolution of the Outbreak

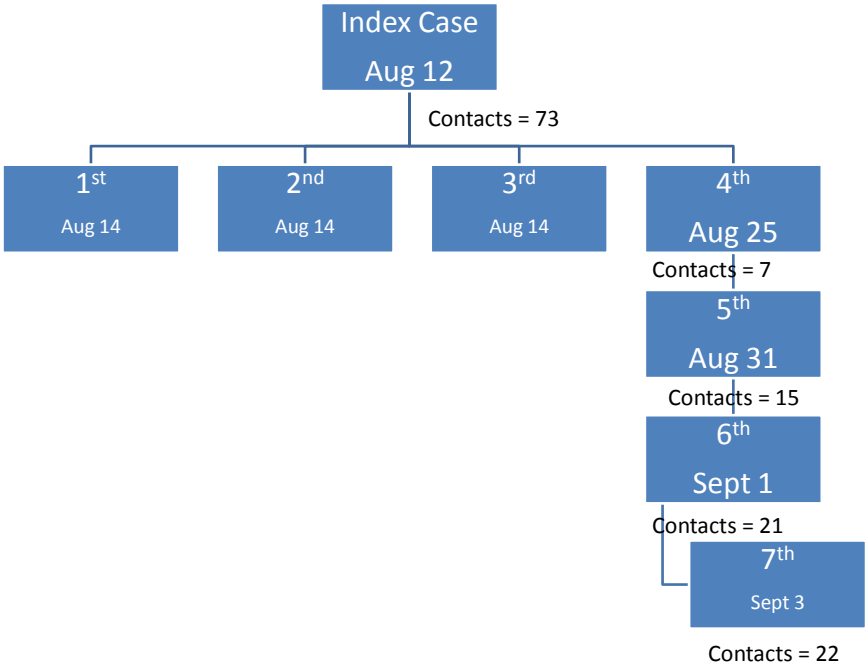

Table 1: Characteristics of Confirmed MERS-CoV cases

NO	SEX	AGE	Nationality	Symptoms	Days to negative	NUMBER OF CONTACT	DISTANCE OF CONTACT (meters)	DURATION (min)	department	LOS
Index	F	30	Filipino	cough, SOB	2	79	> 1.5	< 10	ICU	32
1	F	37	Filipino	Asymptomatic	4	5	< 1.5	> 10	ICU	10
2	F	28	Filipino	Asymptomatic	4	7	> 1.5	< 10	ICU	10
3	F	28	Indian	Asymptomatic	4	6	> 1.5	< 10	ICU	12
4	F	26	Filipino	Asymptomatic	2	0	< 1.5	> 10	ICU	14
5	F	27	Filipino	fever, sore throat	3	21	> 1.5	< 10	WARD 24	16
6	F	29	Filipino	cough, Sore throat	14	15	> 1.5	< 10	WARD 12	14
7	M	30	Jordanian	Asymptomatic	6	20	< 1.5	> 10	WARD 24	12

Table 2: Laboratory Data of Confirmed MERS-CoV cases

NO	WBCS X 10^9/L	Hgb g/L	PLAT X 10^9/L	NEUT # X 10^9/L	NEUT %	CK 100 U/L	ALT 13 U/L	AST 29 U/L	Creatinine umol/L	Albumin 33g/L
Index	6.8	133	330	4.7	69	NA	NA	NA	61	NA
1	8	140	205	5.37	70	131	53	32	63.9	43
2	10	156	360	NA	NA	NA	14	20	67.1	49
3	12.2	119	206	NA	NA	NA	28	21	48.3	34
4	9	150	301	6.35	71	NA	23	32	50.2	45
5	17.7	146	166	15.3	86	NA	19	20	68.1	45
6	13	153	439	8.26	64	NA	NA	NA	NA	NA
7	5.2	159	181	2.89	55	NA	20	21	71.8	44