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Research Article

# Outbreak of Middle East Respiratory Syndrome in the Emergency Room of a Large Tertiary Hospital in Riyadh, Saudi Arabia, 2015: Lessons Learnt

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## Abstract

**Background:** An outbreak of Middle East respiratory syndrome (MERS) occurred in the emergency room of a large tertiary hospital in Riyadh City, Saudi Arabia in 2015. This study describes the outbreak and the factors that led to its continuation.

Methods: We collected epidemiological data for all laboratory-confirmed cases diagnosed at the hospital during the outbreak from hospital surveillance data and electronic and paper medical records of the patients visiting or admitted to the hospital. We calculated the incubation period, duration of stay in different emergency room units and hospital wards before and after the onset of symptoms, the time between admission and collection of biological specimens, receipt of laboratory tests and duration of virus shedding.

**Results:** The outbreak continued for eight weeks, with 130 MERS cases, including 20 primary cases and 110 secondary cases, of which 43 were healthcare workers. There were 51 deaths (case fatality rate = 58.6%, 95% CI: 48.1 - 68.4). The incubation period was 7 days. The time between exposure to a known MERS case and onset of symptoms of MERS was constant throughout the outbreak: mean 6.3 - 7.5 days (range 2 - 12 days). Mean times between onset of symptoms and laboratory confirmation of MERS at the start of the outbreak were 23 (SD 9) days and 6 (SD 3.5) days for primary and secondary cases respectively. The mean (SD) duration of shedding of MERS-CoV was 23.7 (12.2) days, range 5.5 - 67.5 days. The mean (SD) length of stay in the emergency room was 167 (146) hours, range 7 - 747 hours. Three of seven emergency room units were associated with MERS-CoV infection: adult care expansion (OR = 26.0, 95% CI: 4.5 - 566), resuscitation (OR = 5.8, 95% CI: 2.1 - 18.3) and hydration (OR = 4.4, 95% CI: 1.4 - 16.5).

**Conclusion:** This is the largest outbreak of MERS reported to date in a single health facility in Saudi Arabia. Contributory factors included prolonged stay of patients in an overcrowded emergency room, inadequate implementation of infection control and prevention measures, and delayed detection and reporting of MERS cases. Delays could have been reduced if a respiratory triaging system existed in the emergency room, healthcare workers had been better trained, infection prevention and control measures had been implemented, and test requests had been monitored.

***Keywords:*** *Outbreak; Middle East Respiratory Syndrome; Tertiary Care Centre; Infection Control; Saudi Arabia*

## Introduction

Middle East respiratory syndrome (MERS) is a zoonotic viral respiratory disease caused by a new coronavirus (MERS-CoV) that was first identified in Saudi Arabia in 2012 [1]. The virus causes more severe disease in the elderly, the immunocompromised, and people with chronic illnesses [2,3]. There is growing evidence that humans are infected with MERS-CoV through direct and indirect exposure to infected calves of dromedary camels [4-11]. To date, no sustained human-to-human transmission has been documented [2,12-14]. The clinical spectrum of MERS-CoV infection ranges from asymptomatic or mild respiratory symptoms to severe acute respiratory disease and death [2,15]. The disease has a high case-fatality rate of about 40% in Saudi Arabia among laboratory-confirmed symptomatic cases [15-18]. Community-acquired primary cases of MERS have been associated with small family clusters while more extensive and prolonged outbreaks have occurred in major health facilities [19]. Since the emergence of MERS, a total of 1800 cases have been reported from 27 countries around the world, predominantly from the Arabian Peninsula [20]. More than 80% of all cases have been reported from Saudi Arabia [21]. In Saudi Arabia, the first large MERS outbreak occurred in four health facilities in the eastern region of the country in 2013 [22]. This was followed by some more family clusters and other notable outbreaks within health facilities in Jeddah, Taif, Riyadh and Al-Ahssa [23-25]. Outbreaks of MERS in Saudi Arabia have been brought to an end within 18 - 35 days. The outbreaks in major health facilities were attributed to a break down in infection prevention and control measures major outbreaks tend to occur in large hospitals, mainly because of inadequate implementation of infection prevention and control measures [12-14,24,26,27]. However, an unusually prolonged outbreak occurred in a large tertiary hospital in Riyadh between 28 June 2015 and 8 September 2015 [27]. The hospital administration screened 1310 patients and healthcare workers for MERS-CoV during the course of the outbreak. It had to close the emergency rooms, which included seven sections with 150 beds and a staff of more than 1000 [28] and suspend elective surgeries on 18 August 2015.

## Aim of the Study

The aim of this study is to describe an outbreak of MERS in an emergency department of a large tertiary care hospital and some of the factors that led to its continuation for a relatively long time.

## Materials and Methods

The outbreak of MERS occurred in a 12 000-bed, non-Ministry of Health governmental tertiary hospital in Riyadh City [29]. The emergency room (ER) of the hospital has a 150 beds and seven units: rapid assessment unit of the general condition of patients visiting the ER, urgent care centre, resuscitation unit, observation unit, hydration unit and an adult care unit. The adult care unit is subdivided into four areas, including an area for patients with pulmonary complaints, especially chronic obstructive pulmonary disease and asthma. In addition, there is a section (adult care expansion) to accommodate ER patients until an appropriate hospital bed is made available for them. Patients can be moved from one bed to another within and between different ER units according to their condition, stability and bed availability. More than 1000 healthcare workers work in the ER of the hospital.

On 6 August 2015, the hospital was notified by the Ministry of Health of an unusual increase in the number of cases of MERS at its ER. On 11 August the Ministry of Health rapid response team was allowed to join the activities of the hospital's infection control and prevention team. On 18 August 2015, the hospital management decided to close the ER, suspend elective surgeries, and postpone all outpatient appointments and visits for three weeks; complete evacuation of the emergency department was achieved on 22 August [29].

We collected epidemiological data for all laboratory-confirmed cases diagnosed at the hospital during the outbreak period. The hospital used case definitions of MERS recommended by the Ministry of Health for adults (> 14 years). Briefly the Ministry of Health defines a case of MERS as an acute respiratory illness with clinical and/or radiological evidence of pulmonary parenchymal disease (pneumonia or acute respiratory distress syndrome; or a hospitalized patient with healthcare-associated pneumonia based on clinical and radiological evidence; or upper or lower respiratory illness within two weeks of exposure to a confirmed or probable case of MERS infection; or unexplained acute febrile (≥ 38°C) illness and body aches, headache, diarrhoea, or nausea/vomiting, with or without respiratory symptoms, and leukopenia (white blood cell count $< 3.5 \times 10^9$/L) [30].

A primary case of MERS was defined as a patient who came to the hospital ER with a clinical presentation suggestive of MERS that started before his/her visit to the ER and with no history of a visit or admission to the hospital within a month of his/her presentation, and subsequent laboratory investigation confirmed the diagnosis of MERS. A secondary case of MERS was defined as a confirmed case that developed symptoms suggestive of MERS at least 48 hours after admission to the ER or the hospital. An infected healthcare worker was any worker in the hospital who was symptomatic and tested positive for MERS or was asymptomatic and was detected through MERS screening.

We obtained the complete surveillance data of all cases of MERS from the health electronic surveillance network of the Ministry of Health. The network data covered a five-month period (1 June to 31 October 2015) for Riyadh region. We obtained temporary access to the electronic and paper medical records of the patients visiting or admitted to different departments of the hospital (ER, intensive care unit and medical wards). Using the medical record numbers of the patients, we were able to abstract demographic details of all patients with MERS (name, sex, date of birth), address and contact numbers, and history of visits to the ER and clinics, and admissions. The dates of onset of symptoms suggestive of MERS were ascertained by recording the exact dates and times of patients' complaints, their vital signs, and laboratory (nasopharyngeal swabs or endotracheal tube aspirates) and radiological requests indicative or suggestive of MERS. We reviewed doctors' and nurses' follow-up notes in the medical records for all laboratory-confirmed MERS cases. A pre-designed data collection form was used to record the data abstracted from medical records. All laboratory tests used to confirm MERS diagnosis using real-time polymerase chain reaction (RT-PCR) from nasopharyngeal, endotracheal or sputum were obtained and reviewed.

We collected data from the electronic medical record system at the hospital which documents the exact time and date of all movements of patients, including MERS patients admitted to the ER, within and between ER units, collection of biological specimens and receipt of results of laboratory tests, other bedside investigations and clinical procedures throughout the admission of the patients. The data were entered in a spreadsheet (Excel, version 2013) to construct two detailed time lines for each patient using three-hour and 24-hour intervals to illustrate the dynamics of movements and outcome of patients during their stay in the hospital. We used the time lines to determine links between patients. Patients were considered to be epidemiologically linked if they were the same gender, and/or shared the same room at the same time and their beds were next to each other. MERS patients, who were admitted to the hospital, including the ER, with symptoms and signs not related to MERS for periods exceeding 14 days-the longest incubation period for MERS-were considered to have acquired MERS infection inside the hospital. If a secondary case could be linked to more than one symptomatic laboratory-confirmed case, the first patient with a MERS diagnosis was considered to be the source for the second case. If more than one possible link could be determined, we chose the earliest in time and/or with the closest bed proximity in the ER unit. We tracked the electronic medical records of all primary cases for at least one month before their admission with a MERS diagnosis to find out whether or not they were exposed to a known MERS case at the hospital.

The minimum stay for cases of MERS in any of the emergency room stations was estimated to be one hour if there was no registration in the medical record of the exact timing of the patient's visit to the emergency room. The time of onset of symptoms, specimen collection, receipt of the results of laboratory investigations and discharge was set at 12:00 if not recorded.

We divided the outbreak period into three phases based on the awareness of healthcare workers and the hospital of control measures. The first phase included the period between 11 and 26 July 2015 when the healthcare workers at the hospital were not fully aware of the emergence of an outbreak of MERS in the hospital. The second phase included the period between 27 July and 9 August 2015 when the hospital administration became aware of the increased number of MERS cases, but inadequate infection control and prevention measures were put in place. The third phase from 10 to 18 August 2015 was when strict infection control and prevention measures were implemented. In the first phase, 6402 patients visited the ER, and 6190 and 3239 visited during the second and third phases respectively. The hospital screened 1310 healthcare workers and inpatients for MERS-CoV during the outbreak period; screening started on 19 June 2015 and increased gradually to a peak on 26 August 2015.

A list of all ER visitors to the hospital between 30 June and 18 August 2015 (the date of ER closure) was obtained (n = 22,320). The ER visits were sorted by date and time and systematic random sampling was used to select 200 patients as controls. Of these controls, 35 were excluded because the medical records of 10 could not be accessed, and two were healthcare workers and 23 were women who visited a specialized gynaecological ER which is in a separate building from the adult ER where the outbreak occurred. Therefore 165 controls were included in the analysis.

### Statistical analysis

We used Excel 2013 for data entry, and Epi Info 7 and SPSS version 22 for data analysis. We calculated the mean, standard deviation (SD), inter-quartile range (IQR) for the incubation period, duration of stay in different ER units and hospitalization wards before and after the onset of symptoms, the time between admission and collection of biological specimens, receipt of laboratory tests and the duration of virus shedding. The t-test was used to assess the difference between means where appropriate. We estimated the risk (odds ratio (OR) and 95% confidence interval (CI)) of acquiring MERS infection in different units of the ER of the hospital using the rapid assessment unit as the reference group. We compared the case fatality rate with the national cumulative data for MERS from 2012 to 31 August 2016, with (1286 MERS cases including 559 deaths) and the rate without inclusion of the MERS cases and fatalities in the hospital reported during the current outbreak (1416 MERS cases including 610 deaths). Statistical analysis was stratified by phases of the outbreak.

## Results

During the period between 28 June and 8 September 2015, 130 cases of MERS were diagnosed at the hospital, 43 of which were healthcare workers. Of the 87 cases who were not healthcare workers, 57 (65.5%) were males; the male-female sex ratio = 1.9:1. The mean age (SD) was 65.4 (17.2) years and 62.1 (20.1) years for males and females respectively ($P = 0.42$). Of the 130 cases, 20 (15%) were primary cases and 110 (85%) were secondary cases. Proportionately, more males were primary cases than secondary cases (70% vs 64.2%, $P < 0.05$). Table 1 summarizes the characteristics of non-healthcare worker cases.

| Characteristic | Primary (n = 20) | Secondary (n = 67) | Total (n = 87) |
|---|---|---|---|
| | No. (%) | No. (%) | No. (%) |
| Sex: males | 14 (70.0) | 43 (64.2) | 57 (65.5) |
| **Age (years)** | | | |
| Mean (SD) | 63.5 (18.3) | 64.5 (18.3) | 64.3 (18.2) |
| Median | 63 | 68 | 66 |
| **Clinical presentation** | | | |
| Fever | 14 (70.0) | 42 (62.7) | 56 (64.4) |
| Shortness of breath | 9 (45.0) | 30 (44.8) | 39 (44.8) |
| Cough | 6 (30.0) | 17 (25.4) | 23 (26.4) |
| Chest pain | 2 (10.0) | 10 (14.9) | 12 (13.8) |
| Vomiting | 2 (10.0) | 6 (9.0) | 8 (9.2) |
| Abdominal pain | 2 (10.0) | 5 (7.5) | 7 (8.0) |
| Headache | 2 (10.0) | 4 (6.0) | 6 (6.9) |
| Dizziness | 1 (5.0) | 4 (6.0) | 5 (5.7) |
| Body aches | 2 (10.0) | 1 (1.5) | 3 (3.4) |
| Diarrhoea | 1 (5.0) | 2 (3.0) | 3 (3.4) |
| Sore throat | 0 (0.0) | 2 (3.0) | 2 (2.3) |
| Runny nose | 0 (0.0) | 1 (1.5) | 1 (1.1) |
| **No. of laboratory tests needed to confirm MERS diagnosis** | | | |
| 1 | 2 (10.0) | 12 (17.9) | 14 (16.1) |
| 2 | 11 (55.0) | 32 (47.8) | 43 (49.4) |
| 3 | 2 (10.0) | 13 (19.4) | 15 (17.2) |
| > 3 | 5 (25.0) | 10 (14.9) | 15 (17.2) |

***Table 1:*** *Characteristics and clinical presentation of MERS cases at the tertiary care hospital, Riyadh, 2015[a].*
*SD: Standard Deviation.*
*[a]: Healthcare workers not included.*

The stratified epidemic curve for the outbreak (Figure 1) shows the sequence of events throughout the outbreak. The date of onset of the first MERS primary case was on 17 June; he visited the ER on 21 June 2015. The link between primary and all secondary cases (excluding healthcare workers) across different generations of the secondary cases was ascertained except for two secondary cases that occurred during phase two of the outbreak. There was no epidemiological or laboratory evidence that linked the first primary case to subsequent secondary cases. The second primary case came three weeks after the first one and he visited the ER two days after the onset of symptoms (9 July 2015). Subsequently, primary cases continued to visit the ER and there was progressive increase in the number of secondary cases thereafter. On average, one to two primary cases of MERS were admitted to the ER every two days. The date of onset of symptoms of the first secondary MERS case was 19 July (about 8 days after exposure to the second MERS primary case). Of the 110 secondary cases, 43 (39.1%) were healthcare workers. The first healthcare worker with MERS was identified on 23 July. Of the 43 healthcare workers infected, 25 (58%) had symptomatic MERS. Repeated screening detected 18 asymptomatic infections with MERS-CoV among healthcare workers. One of the infection control and prevention practitioners (an infectious disease consultant) had severe MERS and was admitted to the intensive care unit.

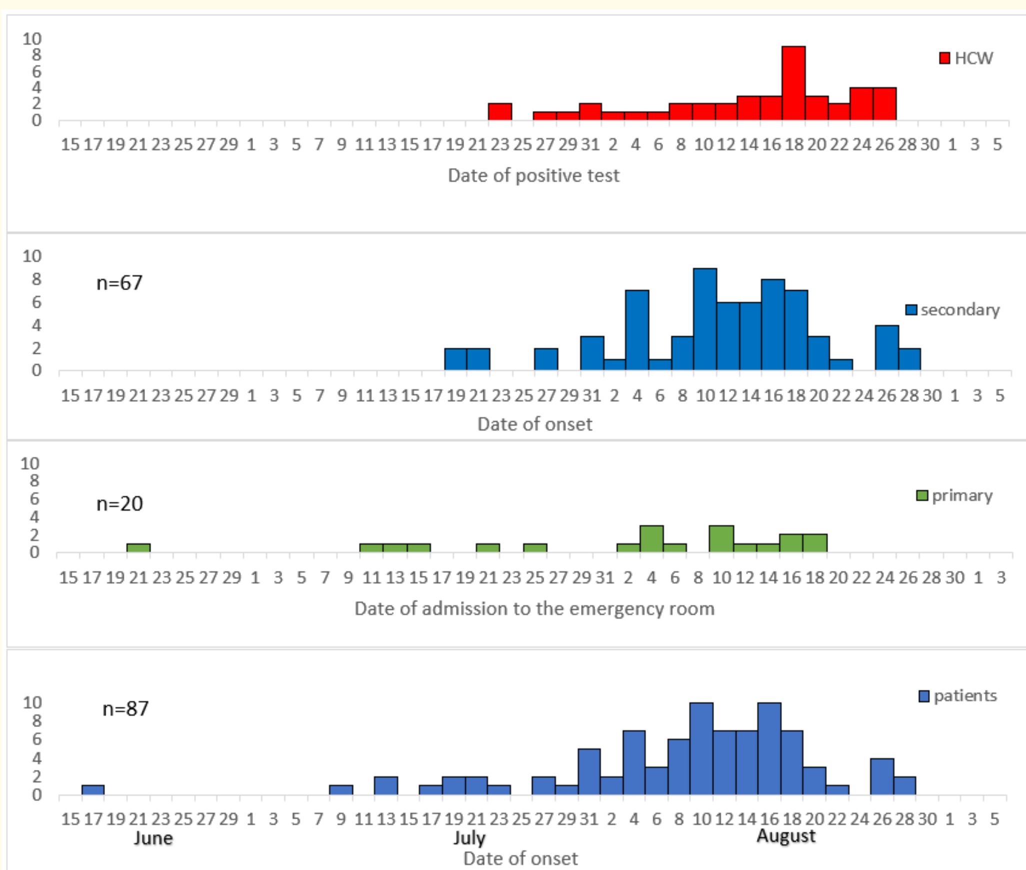


***Figure 1:*** *Epidemiological curve of MERS cases at the tertiary care hospital, Riyadh, 2015. Primary cases are plotted by date of admission to the emergency room and secondary cases are plotted by date of onset of symptoms.*

The epidemic curve indicated that the incubation period was 6 - 8 days. The mean (SD) duration of shedding of MERS-CoV in 30 cases was 23.7 (12.2) days and the range was 5.5 - 67.5 days. The three most common clinical presentations among the 87 cases who were not healthcare workers were fever (n = 56, 64%), shortness of breath (n = 39, 45%) and cough (n = 23, 26%). The first symptoms of MERS reported by the patients were fever (48.3%) and shortness of breath and cough (20.7%), the three clinical presentations combined (18.4%), and pulmonary radiological changes consistent with chest infection (8.0%). All secondary cases who were not healthcare workers were symptomatic except one; this asymptomatic secondary case was detected by screening of ER patients exposed to a known MERS case during phase three of the outbreak. Almost half of the MERS cases (49.4%) needed to repeat the RT-PCR test twice to confirm MERS diagnosis. Three primary cases were diagnosed during their second visit to the ER as they were missed during the first visit.

The mean (SD) of stay of cases of MERS in the emergency room was 7 days (6.1 days) (range 7 hours - 31.1 days). The mean (SD) duration of shedding of MERS-CoV was 23.7 (12.2) days (range 5.5 - 67.5 days). Patients admitted to the emergency room were moved between units and within units (changing beds) several times. A primary cases visited a mean (SD) of 4.5 (1.9) stations (range 2 - 9 stations) and some primary cases changed beds during their stay in the emergency room up to 9 times, mean (SD) 3.4 (1.8) times. Secondary cases visited a mean (SD) of 6.7 (2.7) stations (range 2 - 12 stations). Secondary cases changed beds in the emergency room up to 13 times, mean (SD) 3.9 (2.1) times, during their stay in the emergency room before developing symptoms. The mean (SD) number of stations visited in the emergency room by secondary cases before onset of symptoms was 2.9 (1.5) (range 1 - 7) and 3.4 (1.8) after developing symptoms. Table 2 gives a summary of the time taken to perform a series of actions or procedures related to suspected cases of MERS. The time taken was consistently shorter in phase 3 of the outbreak. The mean times between onset of symptoms suggestive of MERS and collection of biological specimens for confirmation of the diagnosis and between onset of symptoms and confirmation of the diagnosis were shorter for secondary cases. The time between exposure and onset of symptoms for the secondary cases was almost constant in the three phases of the outbreak at a mean of 6.3 - 7.5 days (range 2 - 12 days). For primary cases, the time between the onset of symptoms and getting the first negative laboratory result ranged between 14 days in phase 3 and 68 days in phase 1. The mean times between confirmation of diagnosis and discharge from the emergency room, and onset of symptoms and discharge from the emergency room were shorter for primary cases diagnosed in phase 3.

| Action | Phase | Primary cases (n = 20) | | | Secondary cases (n = 67) | | |
|---|---|---|---|---|---|---|---|
| | | No. | Mean (SD)[a] | Min-Max | No. | Mean (SD)[a] | Min-Max |
| Admission to sample collection | 1 | 6 | 414 (266) | 20 - 755 | 12 | 587 (203) | 240 - 762 |
| | 2 | 8 | 66 (36) | 23 - 119 | 35 | 215 (153) | 1 - 519 |
| | 3 | 6 | 25 (16) | 1 - 42 | 20 | 47 (46) | 1 - 131 |
| Onset of symptoms to collection of biological specimen[b] | 1 | 6 | 468 (48) | 96 - 816 | 9 | 132 (98) | 24 - 336 |
| | 2 | 8 | 129 (54) | 24 - 216 | 30 | 114 (86) | 1 - 384 |
| | 3 | 6 | 96 (59) | 24 - 192 | 16 | 66 (87) | 1 - 336 |
| Sampling to receipt of laboratory confirmation of diagnosis of MERS | 1 | 6 | 88 (69) | 24 - 216 | 12 | 100 (142) | 12 - 504 |
| | 2 | 8 | 138 (169) | 12 - 528 | 35 | 122 (148) | 12 - 648 |
| | 3 | 6 | 46 (33) | 12 - 96 | 20 | 165 (300) | 12 - 1296 |
| Exposure to a known MERS patient to onset of symptoms | 1 | NA | NA | NA | 12 | 151 (65) | 48 - 264 |
| | 2 | NA | NA | NA | 35 | 162 (86) | 48 - 384 |
| | 3 | NA | NA | NA | 20 | 180 (68) | 48 - 288 |
| Onset of symptoms to laboratory confirmation of MERS | 1 | 6 | 556 (226) | 312 - 912 | 12 | 152 (84) | 72 - 360 |
| | 2 | 8 | 264 (107) | 168 - 456 | 35 | 188 (134) | 12 - 720 |
| | 3 | 6 | 140 (62) | 96 - 264 | 20 | 116 (103) | 12 - 360 |
| Onset of symptoms to first negative laboratory result for MERS[b] | 1 | 4 | 1071 (490) | 468 - 1620 | 3 | 564 (83) | 516 - 660 |
| | 2 | 2 | 516 (170) | 396 - 636 | 11 | 552 (140) | 348 - 732 |
| | 3 | 3 | 436 (132) | 348 - 588 | 7 | 386 (174) | 132 - 636 |
| Laboratory confirmation of diagnosis of MERS to ER discharge[b] | 1 | 1 | 50 (NC) | 50 | 2 | 1.4 (0.9) | 1 - 2 |
| | 2 | 3 | 42 (40) | 11 - 88 | 1 | 198 (NC) | 198 - 198 |
| | 3 | 2 | 6 (31.3) | 1 - 11 | 8 | 41 (57) | 2 - 159 |
| Onset of symptoms of MERS to ER discharge | 1 | 6 | 261 (177) | 119 - 567 | 7 | 71 (137) | 1 - 374 |
| | 2 | 8 | 223 (176) | 35 - 484 | 21 | 129 (89) | 1 - 377 |
| | 3 | 6 | 122 (82) | 34 - 261 | 17 | 113 (80) | 4 - 286 |
| Number of tests repeated for diagnosis of MERS[c] | 1 | 6 | 3.17 (1.6) | 2 - 6 | 12 | 2 (0.6) | |
| | 2 | 8 | 3.13 (1.4) | 2 - 5 | 35 | 2.7 (1.3) | |
| | 3 | 6 | 2.7 (1.4) | 1 - 2 | 20 | 2.2 (1.6) | |

***Table 2:*** *Time taken to perform actions or procedures related to suspected primary and secondary cases of Middle East Respiratory Syndrome (MERS).*

*[a]: Durations in hours.*

*[b]: Some data were missing and total is not equal to 20 or 67.*

*[c]: Not a duration.*

*ER: Emergency Room, SD: Standard Deviation, NA: Not Applicable, NC: Not Calculated.*

All primary cases and secondary cases who were not healthcare workers were admitted to the ER during the outbreak period, except six patients who were admitted directly to the hospital. These included two patients who were already hospitalized for more than three months before the date of onset of symptoms. The mean (SD) stay in the ER was 167 (146) hours (range 7 - 747 hours). MERS patients and controls were moved frequently during their stay at the hospital. Patients were moved within ER units (changing beds within one unit), between ER units (moving to different ER units) or to other hospital wards (proper admission to the hospital) for variable durations (Table 3). Table 4 shows the duration of stay in hours for MERS cases and controls at different ER units. Primary cases of MERS stayed a mean of 180 hours at the adult care expansion area, 25.7 hours at the resuscitation unit and 7 hours at the rapid assessment unit. Secondary cases of MERS stayed two-three times longer in the ER before the onset of MERS than controls, especially at the adult care expansion, hydration and observation units. The mean (SD) stays of secondary cases before the onset of MERS symptoms and controls were 128 (136) hours and 10.5 (27) hours respectively (P < 0.01). None of the primary and secondary cases was admitted to the urgent care centre, whereas controls were admitted to this centre for a mean period of 3.6 hours.

| Variable | Secondary cases (n = 67) | | | | | | | | Primary cases (n = 20) | | | | Controls (n = 165) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before onset of symptoms | | | | After onset of symptoms | | | | After onset of symptoms | | | | All | | | |
| | No. | Mean (SD) | Min. | Max. | No. | Mean (SD) | Min. | Max. | No. | Mean (SD) | Min. | Max. | No. | Mean (SD) | Min. | Max. |
| ER units[a] | 61 | 2.9 (1.5) | 1 | 7 | - | - | - | - | 20 | 2.3 (1.4) | 1 | 6 | 162 | 1.2 (0.6) | 1 | 4 |
| Total hospital stations[b] | 67 | 6.7 (2.7) | 2 | 12 | - | - | - | - | 20 | 4.6 (1.9) | 2 | 9 | 165 | 1.3 (0.9) | 1 | 8 |
| ER bed changes[c] | 61 | 3.9 (2.1) | 1 | 13 | 35 | 3.4 (1.8) | 1 | 7 | 20 | 4.0 (2.7) | 1 | 9 | 162 | 1.4 (0.9) | 1 | 6 |
| Total hospital bed changes[d] | 67 | 8.2 (3.3) | 2 | 16 | - | - | - | - | 20 | 6.4 (2.9) | 2 | 12 | 165 | 1.5 (1.3) | 1 | 10 |

***Table 3:*** *Number of emergency room (ER) units, hospital stations and bed changes patients with Middle East respiratory syndrome experienced during hospitalization at the tertiary care hospital, Riyadh, 2015.*

*SD: standard deviation.*

*[a]: The number of ER units that patients passed through during ER admission.*

*[b]: Total stations including ER units and hospital wards.*

*[c]: Bed changes within and between ER units.*

*[d]: Total bed changes in the ER and hospital wards.*

| ER unit | Secondary cases (n = 67) | | | | | | | | | | Primary cases (n = 20) | | | | | Controls (n = 165) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Duration of stay before onset of symptoms (hours)[a] | | | | | Duration of stay after onset of symptoms (hours) | | | | | Duration of stay after onset of symptoms (hours)[b] | | | | | Duration of stay at the ER (hours)[c] | | | | |
| | No.[d] | Mean | SD | Min | Max | No. | Mean | SD | Min | Max | No. | Mean | SD | Min | Max | No. | Mean | SD | Min | Max |
| ACE | 21 | 121.4 | 164.1 | 4 | 681.0 | 10 | 110.3 | 86.1 | 5.0 | 248.0 | 5 | 180.2 | 110.8 | 51.0 | 290.0 | 1 | 42.5 | NC‡ | 42.5 | 42.5 |
| HYD | 14 | 65.5 | 90.5 | 10.0 | 366.0 | 10 | 57.5 | 51.2 | 2.0 | 154.0 | 5 | 76.4 | 47.3 | 4.0 | 131.0 | 4 | 39.5 | 28.6 | 17.0 | 80.0 |
| OU | 7 | 57.0 | 31.5 | 17.0 | 113.0 | 1 | 21.8 | NC | 22.0 | 22.0 | 0 | 0.0 | 0.0 | 0.0 | 0.0 | 4 | 51.8 | 32.6 | 6.0 | 80.0 |
| AC | 35 | 49.5 | 49.3 | 2.0 | 201.0 | 20 | 53.4 | 46.4 | 5.0 | 189.0 | 14 | 68.9 | 93.0 | 2.0 | 286.0 | 24 | 19.6 | 35.9 | 1.0 | 150.0 |
| RU | 23 | 47.8 | 43.8 | 5.0 | 183.0 | 24 | 41.3 | 37.5 | 2.0 | 143.0 | 9 | 25.7 | 16.9 | 7.0 | 57.0 | 5 | 14.6 | 18.4 | 3.0 | 47.0 |
| RAZ | 41 | 21.4 | 62.9 | 1.0 | 411.0 | 13 | 12.4 | 10.9 | 3.0 | 38.0 | 12 | 7.3 | 5.9 | 3.0 | 25.0 | 52 | 7.7 | 18.5 | 1.0 | 136.0 |
| UCC | 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0 | 0.0 | 0.0 | 0.0 | 0.0 | 93 | 3.7 | 9.0 | 1.0 | 49.0 |

***Table 4:*** *Duration of stay of cases of Middle East respiratory syndrome and controls in different emergency room (ER) units at the tertiary care hospital, Riyadh, 2015.*

*ACE: Adult Care Expansion, AC: Adult Care, HYD: Hydration, OU: Observation Unit, RU: Resuscitation Unit, RAZ: Rapid Assessment Zone, UCC: Urgent Care Centre, SD: Standard Deviation.*

*[a]: A patient could stay as short as one hour in an ER unit but this does not reflect the total duration of stay of that patient in the ER as a patient could be admitted to different units for different periods of time.*

*[b]: Duration of stay of primary cases before onset of symptoms was not calculated because they presented to the ER with symptoms.*

*[c]: The whole duration of stay in the ER was calculated.*

*[d]: This is the number of patients visiting the respective ER unit. The total number is more than the number of secondary cases because patients visited more than one ER unit.*

Table 5 summarizes the estimated risk for acquiring MERS-CoV infection at different units of the ER. Secondary cases were more likely to have contracted MERS-CoV infection in the adult care expansion (OR = 26.0, 95% CI: 4.5 - 566), resuscitation unit (OR = 5.8, 95% CI: 2.1 - 18.3) and hydration unit (OR = 4.4, 95% CI: 1.4 - 16.5). The risk of infection with MERS-CoV infection in the urgent care centre was lower (OR = 0.014, 95% CI: 0.001-0.08). Of the 43 infected healthcare workers, 12 (30%) were hospitalized and 31 (72%) were isolated at home for about two weeks until two consecutive nasopharyngeal swabs were negative for MERS-CoV.

| Emergency room unit | Exposed | | Controls | | Odds ratio (95% confidence interval) |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| RAZ (Reference) | 41 | 28.0 | 52 | 28.4 | 1 |
| ACE | 21 | 15.2 | 1 | 0.5 | 26.0 (4.5 - 566) |
| RU | 23 | 16.7 | 5 | 2.7 | 5.8 (2.1 - 18.3) |
| HYD | 14 | 9.1 | 4 | 2.2 | 4.4 (1.4 - 16.5) |
| AC | 35 | 25.8 | 24 | 13.1 | 1.8 (0.95 - 3.6) |
| OU | 7 | 5.3 | 4 | 2.2 | 2.4 (0.6 - 9.1) |
| UCC | 0 | 0.0 | 93 | 50.8 | 0.014 (0.001 - 0.08) |
| Total[a] | 135 | 100 | 183 | 100 | |

***Table 5:*** *Risk of secondary MERS-CoV infection in the different units of the emergency room at the tertiary care hospital, Jeddah, 2015.*

*RAZ: Rapid Assessment Zone, ACE: Adult Care Expansion, RU: Resuscitation Unit, HYD: Hydration, AC: Adult Care, OU: Observation Unit, UCC: Urgent Care Unit.*

*[a]: Some patients and controls visited more than one section.*

Of the 67 secondary cases, 34 visited the ER at least once within two weeks of the date of onset of symptoms: 23 visited once, eight twice and three visited three times. Fifty-one cases of MERS died, eight primary and 43 secondary cases. No deaths occurred among healthcare workers. The case fatality rate for MERS varied from 39.2% (95% CI: 31.3 - 47.8%) to 58.6% (95% CI: 48.1 - 68.4%). The case fatality rate during this outbreak was significantly higher than the national figure for Saudi Arabia which is around 40%.

## Discussion

The results of our study showed that three out of the seven units of the ER were more likely to be associated with MERS-CoV infections- the adult care expansion, resuscitation and hydration units. This may be because of the nature of the activities and duration of stay in these ER units. Resuscitation is where risky aerosol-generating procedures, such as intubation, suction and resuscitation, take place [31]. On the other hand, the data clearly demonstrated that primary and secondary cases were kept for long periods in the adult care expansion and hydration units before and after developing symptoms of MERS compared with other ER units; a similar finding was reported from the outbreak that occurred in South Korea [32]. These ER units as well as the observation unit are generally used to keep patients when no beds are available for hospitalization in wards.

The policy to admit in the ER is probably dictated by the shortage of beds in the hospital; some in-patients with chronic illnesses are hospitalized for long periods. Patients can be kept in the ER for longer periods under observation to prevent premature discharge and minimize unnecessary costly hospitalizations [33]. The shorter stays at adult care and rapid assessment areas could explain why these units were relatively less risky. No primary case was admitted to the observation unit. The urgent care unit was protective against MERS infection because ER visitors stayed for very short periods in this unit because it provides only ambulatory consultation for patients with urgent but less serious conditions. These patients usually do not mix with patients visiting other ER units.

The ER of this hospital has an unusually large number of beds and healthcare workers. Our study showed that during their stay in the ER, primary and secondary cases of MERS and the controls were moved within 1 - 7 ER units and stayed in 1 - 13, 1 - 9 and 1 - 6 ER beds respectively. MERS cases were moved from one bed to another within and between ER units for variable periods which could have increased the risk of being exposed to MERS cases.

About one third of MERS cases were healthcare workers; more than half of them were symptomatic and 20 worked in the ER. Such a large number of cases among healthcare workers indicates that they were not aware of the case definitions of MERS. As a result, some cases of MERS were missed at the beginning of the outbreak and healthcare workers did not adhere adequately to infection prevention and control guidelines. Healthcare workers might not have been using personal protective equipment, and there was no triaging of patients with respiratory illnesses in the ER at the beginning of the outbreak. It was also observed that many infection prevention and control practitioners were on leave at the beginning of the outbreak.

The study showed that the intervals between the time of onset of symptoms suggestive of MERS and suspecting and confirming the diagnosis of MERS at the hospital were undesirably long. Similar findings were reported from outbreaks in other main hospitals [33,34]. Delays in confirming the diagnosis of MERS increases the risk of passing MERS-CoV infection to other patients visiting the emergency room, particularly among people with a compromised immune system. Likewise; the risk to HCWs to be infected increases; especially if they are not aware of the diagnosis and or are not using personal protective equipment. The time taken to confirm the diagnosis was almost constant during phases 1 and 2 but was shorter in phase 3, which is consistent with better implementation of infection prevention and control measures in phase 3. According to Ministry of Health guidelines, the time between suspicion and confirmation should be 18 hours in cities, 24 hours within a region and 36 hours between regions. Public health laboratories usually do two runs of polymerase chain reaction testing a day. The Ministry of Health has a systematic tracking system monitored by a well-equipped national situation room which operates 24 hours a day every day. Ministry of Health guidelines state that the transportation of specimens to the public health reference laboratory in Riyadh city should not exceed 24 hours. The national situation room monitors the time taken to complete different actions and the performance of the courier company responsible for handling and transporting the biological specimens.

The hospital used to run provisional diagnostic tests for MERS within the hospital and only specimens that tested positive for MERS-CoV would be sent to the Ministry of Health public health laboratory for confirmation of the diagnosis. This policy itself caused some delay. The Ministry of Health does the laboratory diagnostic tests in selected public health laboratories in the country to ensure quality.

It is apparent that physicians and other healthcare workers were not aware of the case definitions of MERS. Consequently, the screening of healthcare workers, which was conducted towards the end of the outbreak, detected a large number of healthcare workers infected with MERS. This lack of awareness of the case definitions is probably because only a few sporadic cases of MERS had been diagnosed in the hospital in the six months before the start of the outbreak. During the first phase of the outbreak, the start of the outbreak probably passed unnoticed.

The continual movement of primary and secondary cases between and within emergency room units created a favourable environment for the continuing spread of MERS-CoV in the emergency room. The occurrence of super-spreading events was not investigated and hence could not be ruled out [35,36]. Improved case ascertainment following concerted efforts to trace contacts could help detect cases early and allow appropriate control measures to be started [37]. The duration between exposure to onset for the secondary cases remained almost constant throughout the three phases of the outbreak as it represents the incubation period for the disease the median incubation period for MERS was 7 days, which is consistent with other studies [37]. The slightly longer incubation period during phase 3 could be explained by the precise way the investigators calculated the incubation period, which was based on the exact date and time of exposure and recording of symptoms. However, the minimum and maximum incubation periods are consistent with previous studies, except for one case that had a 15-day of incubation. This patient developed symptoms after he was discharged from the emergency room and came back to the emergency room 15 days later with MERS symptoms.

Surprisingly, more time than the standard time given in the Ministry of Health guidelines [37] was needed to confirm the diagnosis of MERS probably because the laboratory was overburdened with increased numbers of new laboratory requests or repeat tests and also the screening of healthcare workers. The need to repeat a laboratory test for diagnosing MERS illustrates the importance of collecting of a proper sample for testing [3]. The time taken to confirm the diagnosis for the secondary cases was shorter but still long enough to allow the outbreak to propagate. The time between onset of symptoms and receipt of the first negative laboratory result for MERS for primary cases ranged from 14 to 68 days and probably indicates the time for shedding MERS-CoV.

The length of the delays could have been significantly shorter if the hospital had had a functioning respiratory triaging system at the emergency room. Implementation of a proper respiratory triaging system in the emergency room of large hospitals, training of healthcare workers, improved case ascertainment after contact tracing, implementation of infection prevention and control measures and continuous monitoring of the flow of patients would together be an excellent operational performance indicator to guard against the occurrence of secondary cases of MERS and could have changed the course of the outbreak.

These factors could have contributed to the infection of a large number of healthcare workers during the outbreak. None of the infected healthcare workers died; this could be attributed to active detection of cases and selection bias as healthcare workers were younger and healthier than other patients with MERS. No deaths among infected healthcare workers is consistent with other MERS outbreaks [18,31]. The need to implement proper infection prevention and control measures in such settings cannot be overemphasized [26,27].

We found a preponderance of males among MERS cases who were not healthcare workers, and fever, shortness of breath and cough were the commonest clinical presentations. These results corroborate the findings reported elsewhere [38]. The median incubation period for MERS was 7 days, which is slightly longer than reported in the literature, 5.5 - 6 days [5,17]. The longer incubation period could be explained by the way we calculated it, which was based on the exact date and time of exposure and recording of symptoms. On the other hand, during identification of epidemiological links between cases, we chose to link secondary cases to the first patient with a MERS diagnosis as the source of the secondary case if there was more than one symptomatic laboratory-confirmed case implicated.

The case fatality rate for MERS was 45.5% for symptomatic cases that presented to the hospital during the outbreak. The case fatality rate increased to 51.5% when we counted only MERS patients admitted to the hospital. The case fatality rate during the outbreak among admitted cases and excluding healthcare workers was 58.6% which was significantly higher than the national rate (43.5%) (559 deaths out of 1286 MERS cases without inclusion of MERS cases that occurred during this outbreak).

The outbreak at the hospital continued for almost eight weeks and was brought to an end by closing the ER and all elective services. This is twice as long as the second largest outbreak that took place in a major health facility in Jeddah in 2014 [26]. The long duration of the outbreak could be attributed to delays in detecting and reporting MERS cases to the Ministry of Health and in accepting the technical support provided by the Ministry of Health rapid response team at the beginning of the outbreak.

## Conclusion

This is the largest outbreak of MERS reported to date in a single health facility in Saudi Arabia. Contributory factors included prolonged stay of patients in an overcrowded ER, inadequate implementation of infection control and prevention measures, and delayed detection and reporting of MERS cases. Delays in confirming the diagnosis of MERS mean that the risk of passing the MERS infection to healthcare workers and other patients visiting the ER increases, particularly to immune-compromised people. The risk to HCWs of acquiring MERS-CoV infection increases; especially, if they were not aware of the diagnosis and were not using personal protective equipment. The occurrence of a long outbreak in a very busy emergency room visited by more than 22,320 visitors during the course of the outbreak and the limited number of cases throughout the outbreak suggests that MERS-CoV is not highly infectious. Except for super-spreading events, the transmission potential of MERS-CoV seems to be low [39].

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## Competing Interests

None declared.

## Ethical Approval

Not required as this was investigation of an outbreak.

## Author Contributions

HEB, MM, MNA, OA, HAA, ZKM and MM carried out the fieldwork, active surveillance data collection, abstraction of medical records, and data cleaning and management. HA, MBFA, AAS, HEB, HAA, RSMN, OA and MM discussed and interpreted the results. HEB, MNA and HAA did the statistical analysis. HEB, HAA, OA and MM prepared the manuscript. All authors reviewed the manuscript and approved the final version.

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