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Where we missed? Middle East Respiratory Syndrome (MERS-CoV) epidemiology in Saudi Arabia; 2012–2019

Saman Khan, Rachida El Morabet, Roohul Abad Khan, Ahmad Bindajam, Saeed Alqadhi, Majed Alsubih, Nadeem Ahmad Khan

HIGHLIGHTS

• In overall MERS-CoV distribution most infected age group was 50–59 years.
• Male (%) > Female (%) in rate of infection, mortality and fatality.
• Female (69.35%) infection was > than male (40.65%) for Asymptomatic cases.
• In no comorbid and asymptomatic cases highest infected age group was 20–39 years.

GRAPHICAL ABSTRACT

ABSTRACT

MERS-CoV first case was reported on 23rd November 2012 in Saudi Arabia. Since, then MERS has remained on World Health Organization (WHO) Blueprint list and declared pandemic. This study was conducted on MERS lab confirmed cases reported to Ministry of Health, Saudi Arabia and WHO for year 2012–2019. The epidemiology was investigated based on infection rate, death rate, case fatality rate, Gender, Age group, and Medical conditions (Comorbid and Symptomatic). The overall median age of infected male was 58 years and of female was 45 years. While average mortality age in male was 60 years and of female was 65 years which is greater than the global average of 50 years. The results also report that specially after age of 40 years in both men and women, chances of infection are more while comorbidities increase the infection rate. The men are more susceptible to infection than women. In case of asymptomatic distribution trend was vice versa with 69.4% women and 30.6% in men. Second, most infected age group was reduced by 20 years in case of men with 47.37% infection for age group of 20–39 years. This was also observed in age-group of 20–39 years for no comorbid cases (men (50%) & women (79%)). This explains MERS-CoV prevalence in Saudi Arabia, as young and healthy population were infected, and acted as carrier and on coming in contact with vulnerable population (elderly, chronic and comorbid) transferred the infection. Hence, MERS-CoV outbreak kept on happening from time to time over past years. This finding might very well explain the exponential spread of Novel CoV-19 global pandemic.

Keywords:
MERS-CoV epidemiology
Gender
Age group
Comorbid
Symptomatic
1. Introduction

MERS-CoV was first reported in 2012, following death of a patient at hospital in Jeddah, Kingdom of Saudi Arabia (Poissy et al., 2014; Mohd et al., 2016; Wang et al., 2016; Elfan et al., 2017; Bawazir et al., 2018; Azhar et al., 2019). This incident acted as epicentre spreading in neighbouring countries then globally. (Alqahtani et al., 2017), alike Ebola or swine flu it became an alarming threat to global health security. The Middle East respiratory syndrome (MERS) is acute respiratory viral infection caused by novel extremely pathogenic coronavirus (Ahmadzadeh et al., 2020; Alosaimi et al., 2020). It is a single-stranded positive-sense RNA viruses (Dighe et al., 2019; Sohrab and Azhar, 2019) that turn up zoonotic (Ali-Omari et al., 2019) and pathogenic to human causing mild cold to severe acute respiratory syndrome (Alagaili et al., 2019). Other common symptoms are shortness of breath, cough, high temperature, diarrhoea, and eventually pneumonia (Degnah et al., 2020). Similar to beta coronavirus in bats (Letko et al., 2018; Sohrab and Azhar, 2019) which can outspread from bats to human (Terada et al., 2017) subsequently by camels and goats to human in Arabian Peninsula (Reusken et al., 2014). Its, human to human transmission especially among healthcare workers and within household contacts or by community transmission is also observed (Al-Tawfiq et al., 2018; Elkholy et al., 2019).

Between September 2012 and 30 April 2019, a total of 2428 laboratory-confirmed case and 839 associated deaths due to MERS-CoV infection were reported globally (World Health Organization, 2019). Most of published studies have assessed the epidemiological status of MERS-CoV infection in terms of transmission, among healthcare workers, healthy adult and also included gender-based prevalence. However, literature on MERS distribution based on Medical conditions is still lacking. Some studies have reported comorbidity and symptomatic distribution However, they have yet not analysed based on age and gender. Hence, objective of this study is to investigate MERS epidemiology distribution in Kingdom of Saudi Arabia based on various parameters including medical conditions. Also, to identify any parameter that has been overlooked and has led to passive action against its control globally.

2. Method and data used

2.1. Data collection

Our study focused MERS-CoV epidemiology based on number of cases and related deaths from 2012 to 2019 in Kingdom of Saudi Arabia. The data was obtained from global epidemiological electronic database viz WHO (World Health Organization, 2019) and MOH (Ministry of Health, Saudi Arabia). The MERS-CoV distribution was assessed based on age, gender, characteristics, infection, death, mortality, risk factor and case fatality associated with MERS-CoV patient. The death rate, mortality rate and infection rate were calculated based on the data for year 2012–2019. However, for epidemiology prevalence based on Gender, Age group and Medical conditions it was carried out for year 2013–2016 owing to non-availability of detailed data in other years. Medical conditions were further divided in comorbid and symptomatic conditions, which were further classified for analysis into comorbid – no comorbid and symptomatic - asymptomatic category.

2.2. Statistical analysis

Descriptive analysis was carried out for all laboratory confirmed-CoV cases reported to WHO for Kingdom of Saudi Arabia for 2012–2019 using SPSS version 25 (IBM). Mean and Standard Deviation were used to express quantitative measurements. Absolute frequency and percentage were the units to express qualitative measurement. The relationship between risk factors and their final outcome for Laboratory confirmed cases of MERS CoV was assessed through logistic regression.

3. Results

3.1. Epidemiology distribution based on infection rate

Total number of confirmed cases and deaths due to MERS-CoV reported all over the world are 2428 and 839 respectively out of which within the Kingdom of Saudi Arabia there are 1396 confirmed cases and 266 deaths from 2012 to 2019. (WHO report 17 May 2019). Among the confirmed cases all over world KSA itself comprise of 55.35% infection rate which is greater than average. This makes Saudi Arabia, most MERS infected country worldwide.

From year 2012 to 2019 (Fig. 1a and b), the most infectious year was 2015 (owing to multiple outbreaks) where 452 cases were reported followed by 32.4% infection rate. The least infectious year was outbreak year 2012 in KSA where 9 confirmed cases were reported followed by the 0.7% infection rate (First case on November 23rd, 2012). In year 2013 and 2014 the infection rate was 6.1% and 6.7% respectively. By spreading awareness, proper diagnosis and treatment to the contagious infection, attributed to Ministry of Health, KSA, greatly reduced cases in preceding years (Faridi, 2018). Also, during period 2016 to 2019 shows significant decline in infection ratio. This can be validated against, respective infection ratio for year 2016 to 2019 as 16.9%, 14.3%, 10.5% and 12.4%.

3.2. Epidemiology distribution based on death rate

Among 839 deaths all over the world there were 266 deaths within KSA from 2012 to 2019 which shows the death ratio of 31.70%. Out of 2012 to 2019, most deaths were observed in year 2015 (Fig. 1c and d) where 70 deaths were followed by 26.32% death rate. Least death rate was in the outbreak year that is 2012 in KSA where 4 deaths were reported followed by the 1.5% death rate. In year 2013 and 2014, respective death rate was 12.03% and 3.38%. The study reported that delay in diagnosis was responsible for death rate increment while required early and proper diagnosis counterparts the better clinical management which attribute to infection control and epidemiologic death rate due to MERS infection (Azhar et al., 2019). The respective death ratio for the year 2016–2019 are 9.77%, 14.29%, 18.05% and 14.66%.

The overall mortality rate from 2012 to 2019 in KSA was 19.1%. The highest mortality rate was reported in the outbreak year 2012 with 44.4%. And the least mortality was reported in 2016 with 11%. The mortality rate was higher in male (70.07%) than female (29.93%). The median age of death in male and female was 60 years and 65 years respectively. So, women with MERS death tended to be aged than men. The study shows that on an average, median mortality age was 63 years and patients were likely to die above 60 years (45.5% mortality) due to infection with respect to younger patient (19.7% mortality). Pre-
existing diseases like cancer or diabetes boosts the infection in MERS patient which then subject to more acute disease and higher mortality rates.

3.3. Epidemiology distribution based on case fatality rate

Based on epidemiological characteristics the overall global case fatality rate due to MERS was 34.56% [2428 confirmed cases and 839 deaths], which is substantially higher than 19.1% [with 1396 confirmed cases and 266 deaths] in KSA from 2012 to 2019 (WHO report 17 May 2019). While the Peterson et al. found overall case fatality rate of 40% in KSA (Petersen et al., 2014). Although our findings report lower fatality rate as compared to the largest MERS outbreak in South Korea with 21% case fatality rate (Cowling et al., 2015). However, our research is larger than the overall global SARS-CoV case fatality rate of 10% (8273 confirmed cases and 775 deaths) (Al-Hazmi, 2016). Among years from
2012 to 2019 in Kingdom of Saudi Arabia, highest case fatality rate years was the MERS outbreak year that is 2012 with the case fatality rate of 44.44% (9 confirmed case and 4 deaths). While least case fatality rate year was 2014 that was 9.6% with the decline of 34.9% compared to year 2012. In year 2013 and 2016, respective case fatality rate was 37.6% and 11%. The highest MERS outbreak year of Saudi Arabia was 2015 with case fatality rate of 15.5% (452 confirmed cases and 70 deaths) followed by decline of 28.9% in case fatality rate if compared to year 2012. The respective case fatality rate for the year 2017 to 2019 are 19%, 32.7% and 22.5%.

3.4. Epidemiology distribution based on age group

On an average, most affected age group was 50–59 years (22.6% of all the cases) followed by 40–49 years (15.9%), 60–69 years (15.2%) and 70–80 years (14.2%) as presented in Fig. 3. While, least infected age group was below 20 years (1.5%). Also, age group of 20–29 years, 30–39 years & above 80 years contribute to 10.5%, 11.9% and 8.2% of respective infection rate. The median age in KSA was 30 years while the study reported that chances of infection were more at and above age of 40 years. The median age of MERS infection was 54.5 years. There was enhancement of 22.2% by the age of 50–59 years followed by the decline infection rate of 14.4% by the age of Above 80 years.

3.5. Epidemiology distribution based on gender

From 2013 to 2016 in KSA, out of 867 confirmed MERS-CoV cases 599 (69.1%) were males and 268 (30.9%) were females (Fig. 4). Men are primarily responsible for outdoor activities (livelihood, socialization, businesses, etc.) which renders them highly susceptible to infection. On the other hand women are primarily homemakers and are less susceptible to infection. The most infected year for male was 2014 (80.9%) followed by 2016 (74.2%), 2015 (66.6%) and 2013 (55.3%). For female most infected year was 2013 with 44.7% infection followed by 2015 (33.4%), 2016 (25.8%) and 2014 (19.1%). The overall median age of infected male and female was 54.5 years. Overall Male are 38.2% more infected with the infection ratio of 69.1% [599/867] than female 30.9% [268/867] from the year 2013 to 2016 in KSA. Also, in both men and women the most infected age range was 50–59 years with respective infection ratio of 22.4% & 23.1% while the least infected range is Below 20 years with infection ratio of 1.2% (Male) & 2.2% (Female).

3.6. Epidemiology distribution based on medical conditions

Most of the MERS cases have medical conditions like some have co-morbidity, symptomatic but rare are asymptomatic. Based on analysis 70.6% of cases were comorbid, while 21.9% cases were no comorbid and 7.5% cases are unknown. In cases of symptoms, 90.6% were symptomatic and 6.7% were asymptomatic and 2.7% were unknown (Table 3).

3.6.1. Epidemiology distribution based on comorbidity

The epidemiology distribution based on comorbidity is presented in Fig. 5. Among 70.6%[652/924] Comorbid MERS cases, highest comorbidity year was 2013 with 74.1% [63/85] comorbidity followed by 2015, 2014 & 2016 with 73.5% [332/452], 68.9 [104/151] & 64.8 [153/236] respectively. It was also reported that patients have one or more pre-existing illness like cardio vascular disease, nausea, fever, wet or dry cough, shortness of breath, mild or acute injury, diabetes mellitus. The chances of no comorbidity are 21.9% [203/924]. Some comorbid are smokers or ex-smokers or shisha tobacco consumers. Men are more comorbid 69.8% [455/652] than women 25.6% [167/652] while 4.6% [30/652] are unknown. The least comorbid age range in both men and women was <20 years and most comorbid age range was 40–59 years with 41.3% (in men) & 60–79 years with 44.9% (in women) comorbidity. Hence, women were found to be stronger in immune with respect to men but both of 40 years or above age have one or more illness or
susceptible to attract infection. In no comorbid men and women age range of 20–39 years was found to be highest in infection with 50% and 70% respectively. However, Above or below 20 years getting infected have higher chances of recovery owing to stronger immunity. The median age of comorbid male and female was 55 years and 54.5 years respectively. The median age of male and female with no comorbidity was 35 years & 39.5 years respectively. The details of comorbid and no comorbid cases along with distribution among male and female is presented in Table 1.

3.6.2 Epidemiology distribution based on symptoms

Fig. 6 presents MERS-CoV epidemiology based on symptoms. The symptom-based analysis was divided as symptomatic and asymptomatic. 90.6% [837/924] cases are symptomatic while 6.7% [62/924] are asymptomatic and 2.7% [25/924] are unknown. Asymptomatic MERS case are those who have healthcare, outside healthcare and household contacts and identified by contact tracing history without the symptoms of Corona Virus. Symptomatic cases 69.3% [580/837] in men were more than women 26.9% [225/837] while 3.8% [32/837] are unknown. Asymptomatic cases 69.4% than Men 30.7%. The most symptomatic age range is 40–59 years with 41.4% (Male) & 34.7% (Female). Women are more asymptomatic than Men 30.7%. The most asymptomatic age range in male was 20–39 years (47.1%) while in female was 40–59 years (51.16%). The median symptomatic and asymptomatic age in male was 55 years and 49.5 years respectively. The median symptomatic and asymptomatic age in female was 54.5 years and 45 years respectively. The details of symptomatic and asymptomatic cases are presented in Table 2.

4. Discussion

The MERS-CoV epidemiology was studied in this study for Kingdom of Saudi Arabia for year 2012–2019. The recognized age group of 40–59 years as highest infected group in terms of Infection rate, death rate and fatality rate. This trend was also reflected in comorbid and symptomatic cases where highest infection was for age group 40–59 years and above. This group of age also lies in coherence with WHO identifying group range of 50–59 years with highest susceptibility of acquiring primary infection. Nevertheless, most unique finding of this study was that in all aspect of distribution men were prevailing in infection than women, however, in case of asymptomatic distribution the trend was vice versa with 69.4% women and 30.6% in men. Also, the age group reduction of 20 years was observed in men 20–39 (47.37%) while it remained same for women 40–59 (51.56%) as compared to symptomatic cases. Even though the number of asymptomatic cases is low. Additionally, in no-comorbid cases also the most infected group was 20–39 years of age with men reporting 50% and women reporting 70%. This major finding was overlooked owing to the fact that asymptomatic cases comprise only 6.71% while no comorbid cases were upto 21%. These two categories comprise of lower percentage especially asymptomatic category, primarily due to non-testing of infected person owing to no sign of infection. However, the low percentage doesn't mean that infection was not prevalent, these cases were detected on tracing contact history and thereby testing the identified contact, hence statistics obtained does not depicts real time scenario, as there was no mass testing to detect infection among masses. Thus, this criterion was not analysed in depth in majority of studies. Nevertheless, this finding has revealed
one of the primary factors that was overlooked worldwide. This is a startling revelation as until now age group with older age was considered to be highest susceptible. The younger people 20–39 years of age group went out for daily activities thinking they will be safer as 50–59 years of age group is mostly infected. However, they brought the infection back with them showing no symptoms but infected the elder population. This very well explains why MERS-CoV never stopped in Saudi Arabia, as younger group of population was infected and acted as carrier. When this group of population visited vulnerable population (Elderly, chronic and comorbid) they transferred the virus causing the infection to restart. Hence the MERS-CoV incident kept on happening from time to time over past years. This finding might very well explain the exponential spread of Novel CoV-19 globally, as initial control measures required older people to stay indoors while younger generation brought the infection from outside. Also, since the strain was new the human body adaption was too slow causing widespread of the virus globally. Hence, CoV-19 is more infectious than MERS and SARS as the world is experiencing now. Additionally, initial transmission of MERS-CoV has been linked to camels so the spread of virus was restricted to selective cluster of people who had direct or indirect contacts with animals. However, the CoV-19 transmission is yet to be established, Hence, this may be one of the factors responsible for exponential growth rate of infection rate.

Nevertheless, MERS-CoV was always existing in KSA, however with early detection and proper treatment available in the country it was controlled efficiently and effectively. The major challenge faced in this study is lack of details based on gender age group and medical conditions being reported from the year 2016–2019 which may have provided more in-depth knowledge of the prevalence of the epidemiology. Further studies are required for epidemiology analysis based on clusters, travel history and specific comorbidity related mortality to provide better understanding and developing mitigation policies for the prevailing pandemic worldwide.

| Item | Symptomatic | p-Value | Symptomatic cases | p-Value | Asymptomatic cases | p-Value |
|------|-------------|---------|-------------------|---------|-------------------|---------|
| Category | Yes | No | Unknown | | Male | Female | Unknown | | Male | Female | Unknown | |
| Total number | 837 | 62 | 25 | 0.001 | 580 | 225 | 32 | | 0.001 | 19 | 43 | 25 | 0.001 |
| 2013 | 67 | 18 | 0 | | 43 | 24 | 0 | | 4 | 14 | 0 | |
| 2014 | 123 | 3 | 25 | | 73 | 18 | 32 | | 3 | 0 | 25 | |
| 2015 | 448 | 4 | 0 | | 300 | 148 | 0 | | 2 | 2 | 0 | |
| 2016 | 199 | 37 | 0 | | 164 | 35 | 0 | | 10 | 27 | 0 | |

| Medical conditions | Comorbid | No comorbid | Unknown | Symptomatic | Asymptomatic | Unknown |
|------------------|----------|-------------|---------|------------|-------------|---------|
| 70.56 | 21.97 | 7.47 | 90.58 | 6.71 | 2.71 |

| Gender | Comorbid | No comorbid | Unknown | Symptomatic | Asymptomatic | Unknown |
|--------|----------|-------------|---------|------------|-------------|---------|
| Male | 69.79 | Female | 25.61 | Female | 63.05 | Female | 28.88 | Female | 69.35 |
| Unknown | 4.60 | Unknown | 3.94 | Unknown | 3.82 | Unknown | - |

| Age | Comorbid cases | No comorbid | Symptomatic | Asymptomatic |
|-----|----------------|-------------|------------|-------------|
| Male (%) | Female (%) | Male (%) | Female (%) | Male (%) | Female (%) |
| 0–19 years | 0.66 | 0.60 | 2.34 | 0.00 | 1.03 | 0.44 |
| 20–39 years | 9.23 | 7.19 | 50.00 | 79.10 | 17.76 | 25.33 |
| 40–59 years | 41.32 | 39.52 | 42.97 | 20.90 | 41.38 | 34.67 |
| 60–79 years | 36.04 | 44.91 | 4.69 | 0.00 | 30.34 | 33.33 |
| 80 & Above | 12.75 | 7.78 | 0.00 | 0.00 | 9.48 | 6.22 |

Fig. 6. Epidemiology based on symptomatic, asymptomatic, gender and age group cases in Saudi Arabia 2013–2016.
CRediT authorship contribution statement

Saman Khan: Data curation, Formal analysis, Writing - original draft, Methodology. Rachida El Morabat: Project administration, Supervision, Visualization. Roohul Abad Khan: Conceptualization, Writing - original draft, Investigation. Ahmad Bindajam: Resources, Software. Saeed Alqadhi: Writing - review & editing. Majed Alsubih: Writing - review & editing. Nadeem Ahmad Khan: Writing - review & editing.

Declaration of competing interest

All the Authors hereby declare that there is no conflict of interest in any context.

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