Middle East respiratory syndrome coronavirus disease is rare in children: An update from Saudi Arabia

Jaffar A Al-Tawfiq, Rana F Kattan, Ziad A Memish

Abstract

AIM
To summarize the reported Middle East respiratory syndrome-coronavirus (MERS-CoV) cases, the associated clinical presentations and the outcomes.

METHODS
We searched the Saudi Ministry of Health website, the World Health Organization website, and the Flutracker website. We also searched MEDLINE and PubMed for the keywords: Middle East respiratory syndrome-coronavirus, MERS-CoV in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in 2012 to 2016. The retrieved articles were also read to further find other articles. Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary.

RESULTS
From June 2012 to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases. Of these cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. Twenty-five (80.6%) of the cases were reported from the Kingdom of Saudi Arabia. The most common source of infection was household contact (10 of 15 with reported source) and 5 patients acquired infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

CONCLUSION
Utilizing serology for MERS-CoV infection in Jordan and
Saudi Arabia did not reveal any positive patients. Thus, the number of the pediatric MERS-CoV is low; the exact reason for the low prevalence of the disease in children is not known.

**Key words:** Pediatric; Middle East respiratory syndrome-coronavirus; Children; Respiratory tract infection

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The number of the pediatric Middle East respiratory syndrome-coronavirus (MERS-CoV) is low and the exact reason for the low prevalence is not known. A total of 31 pediatric MERS-CoV cases were reported since June 2012. Of all the cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. The most common source of infection was household contact followed by infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

**INTRODUCTION**

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA)[1]. As more cases were reported, the case fatality rate changed to 40% from 60%[2-5]. In addition, initially there was a predominance of males; later this ratio decreased[2,6]. MERS-CoV is characterized by three different patterns of disease: Sporadic cases, intra-familial transmission[7-9] and health care associated infection[2,3,10-16]. Despite the increased number overtime and the multiple health care associated outbreaks[17], the number of pediatric cases remained low during the study period[18]. The initial description of 47 cases included only a 14-year-old child[1]. The first pediatric case was a 2-year-old child reported from Jeddah, KSA on June 28, 2013[19]. Later an additional three asymptomatic children were reported[4]. The largest report of childhood MERS-CoV cases included eleven, of which two patients were symptomatic and nine were asymptomatic[18]. The exact reason for this low prevalence of the disease in children is not known. In this study, we summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

**MATERIALS AND METHODS**

We searched the Saudi Ministry of Health website[20], the World Health Organization website[21], the Flutacker website[22], the medical literature and the retrieved published studies for any childhood MERS-CoV infections. We searched MEDLINE and PubMed for the keywords Middle East respiratory syndrome-coronavirus, MERS-CoV, in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in June 2012 until April 19, 2016. The retrieved articles were also read to find other relevant articles.

**Statistical analysis**

Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary, including mean and standard deviation when applicable and frequency. The statistical review of the study was performed by a biomedical statistician. Statistical review is performed before the submission of the manuscript.

**RESULTS**

**Summary of pediatric cases**

From June 2012, to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases as shown in Table 1. Of all the cases, thirteen (13) or 42% were asymptomatic, and there were 17 males, 10 females and 4 unreported (a male to female ratio of 1.7:1). The mean age of patients was 9.8 ± 5.4 (0.75-17) years. Twenty-five cases (80.6%) were reported from KSA; the other patients were in Jordan, United Arab Emirates and the Republic of Korea (Table 1). The most common source of the infection was household contact (10 of 15 with reported source), and 5 patients acquired the infection within a health care facility. About one half of the cases were reported in 2014, and 29% were reported in 2013 and 22.6% in 2015 (Table 2).

**Screening of pediatric patients for MERS-CoV**

Screening of pediatric patients for MERS-CoV infection using real time reverse transcriptase polymerase chain reaction showed that only 9 out of 552 (1.6%) were positive in KSA[23]. However, serologic testing of pediatric patients admitted with lower respiratory tract infection in Jordan and Saudi Arabia revealed no positive tests[24,25] (Table 3).

**Pregnancy associated MERS-COV**

The effect of MERS-CoV infection on the fetus was described in eight cases[26-29] as summarized in Table 4. The mean age of the mothers was 32.25 ± 3.4 years, and the mean gestational age was 28.4 ± 6.3 wk. Death of the fetus was observed in 3 (37.5%) of the 8 fetuses.

**DISCUSSION**

Despite the total number of MERS cases increasing, especially in KSA, the number of pediatric cases remained low during the study period. Initially, the
| Age | Gender | Country     | Sample source | Year of reporting | Symptoms                     | Co-morbidity | Signs                          | Sample type | Viral load ct value | Imaging                  | Intensive care | Death | Ref. |
|-----|--------|-------------|---------------|-------------------|------------------------------|--------------|--------------------------------|-------------|---------------------|--------------------------|----------------|--------|------|
| 2   | Male   | KSA         | Hospital inpatient | 2013              | Fever, respiratory distress  | Cystic fibrosis | Chest: Bilateral fine crepitation | NPS        | 36                  | Bilateral diffused infiltrate | +              | Yes    | [18] |
| 2   | Male   | KSA         | Hospital inpatient | 2013              | Fever                        | Down’s syndrome | NPS                            | 37          | Bilateral diffused infiltrate | No            | No    | [18] |
| 7   | Female | KSA         | Family contact | 2013              | Asymptomatic                 | None           | None                            | N + T       | 37                  | ND                       | No            | No    | [18] |
| 15  | Female | KSA         | Family contact | 2014              | Asymptomatic                 | None           | None                            | NPS        | 35                  | ND                       | No            | No    | [18] |
| 14  | Male   | KSA         | Family contact | 2014              | Asymptomatic                 | None           | None                            | NPS        | 34                  | ND                       | No            | No    | [18] |
| 12  | Female | KSA         | Family contact | 2014              | Asymptomatic                 | None           | None                            | NPS        | 35                  | ND                       | No            | No    | [18] |
| 16  | male   | KSA         | Family contact | 2013              | Asymptomatic                 | None           | None                            | NPS        | 36                  | ND                       | No            | No    | [18] |
| 7   | Female | KSA         | Family contact | 2014              | Asymptomatic                 | None           | none                            | NPS        | 37                  | ND                       | No            | No    | [18] |
| 3   | Female | KSA         | Family contact | 2013              | Asymptomatic                 | None           | None                            | NPS        | 38                  | ND                       | No            | No    | [18] |
| 0.75| Male   | KSA         | Family contact | 2013              | Asymptomatic                 | None           | none                            | NPS        | 34                  | ND                       | No            | No    | [18] |
| 14  | Female | KSA         | Family contact | 2013              | Asymptomatic                 | None           | none                            | NPS        | 36                  | ND                       | No            | No    | [18] |
| 4   | Male   | KSA         | NA             | 2014              | Mild respiratory symptoms   | None           | NPS                            | NA         | ND                  | Diffuse bilateral haziness | Yes           | Yes   | [35] |
| 8   | Male   | KSA         | NA             | 2013              | Mild respiratory symptoms   | None           | NPS                            | NA         | ND                  | None                     | NA            | NA    | [37] |
| 17  | Male   | KSA         | Contact        | 2014              | Asymptomatic                 | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [22] |
| 11  | Female | KSA         | Contact        | 2014              | Asymptomatic                 | NA             | NPS                            | NA         | NA                  | None                     | NA            | NA    | [22] |
| 16  | Female | KSA         | NA             | 2014              | Symptomatic                  | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [22] |
| 13  | Male   | KSA         | NA             | 2014              | Symptomatic                  | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [22] |
| 10  | Male   | KSA         | Hospital contact| 2014              | Symptomatic                  | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [20,22] |
| 2   | Male   | KSA         | NA             | 2014              | Symptomatic                  | Congenital anomalies | NPS                        | NA         | NA                  | NA                       | NA            | NA    | [20,22] |
| 11  | Female | KSA         | Hospital contact| 2014              | Symptomatic                  | Brain tumor    | NPS                           | NA         | NA                  | NA                       | NA            | NA    | [20,22] |
| 17  | Female | KSA         | NA             | 2014              | Symptomatic                  | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [20,22] |
| 16  | Male   | South Korea | Hospital contact| 2015              | Symptomatic                  | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [22] |
| 2   | Male   | KSA         | Hospital contact| 2015              | Symptomatic                  | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [20,22] |
| 16  | Male   | KSA         | contact       | 2015              | Symptomatic                  | NA             | NPS                            | NA         | NA                  | NA                       | NA            | NA    | [20,22] |
| 7   | Female | Jordan      | Contact        | 2015              | Asymptomatic                 | None           | NPS                            | NA         | NA                  | None                     | NA            | NA    | [22] |
| 0.8  | Female | Jordan      | Contact       | 2015              | Symptomatic                  | None           | NPS                            | NA         | NA                  | None                     | NA            | NA    | [22] |
| 14  | Female | KSA         | Contact       | 2015              | Symptomatic                  | None           | NPS                            | NA         | NA                  | None                     | NA            | NA    | [20,22] |
| 4   | Male   | UAE         | NA             | 2014              | NA                           | NA             | NPS                            | NA         | NA                  | None                     | NA            | NA    | [22] |
| 8   | Male   | UAE         | Family contact| 2013              | NA                           | NA             | NPS                            | NA         | NA                  | None                     | NA            | NA    | [22] |
| 11  | Male   | UAE         | Family contact| 2015              | Asymptomatic                 | None           | NPS                            | NA         | NA                  | None                     | NA            | NA    | [22] |

NPS: Nasopharyngeal swab; N + T: Nasal and tracheal aspirate; ND: Not done; KSA: Kingdom of Saudi Arabia; UAE: United Arab Emirates; ICU: Intensive care unit; NA: Not available.

MERS-CoV disease is rare in children. The definition includes those ≤ 14 years, meets the adult case definition and has either a history of exposure to a confirmed or suspected MERS-CoV in the proceeding 14 d or a history of contact with camels or camel products in the proceeding 14 d. The case definition also includes children with unexplained severe pneumonia. The 2015 change in the case definition does not account for the low rate of childhood MERS-CoV infection as 33% of the cases were reported in 2014 before the case definition was changed. One of the reasons for an increased number of cases in 2014 during the Jeddah outbreak was increased testing of asymptomatic and mildly symptomatic patients.
The pattern of MERS-CoV pediatric cases was similar to the 2003 SARS outbreak. Children were less affected than adults and children less than 2 years of age had milder disease[31]. In the largest screening of contacts, the rate of MERS-CoV positive children (1.6%, 9/552) compared to 2.2% (99/4440) in adults (P = 0.23)[23]. Thus, in this study utilizing MERS-CoV PCR the positivity rate did not differ in children and adults.

In adults with MERS-CoV infections, three patterns of transmissions were observed: Sporadic (primary) cases presumed to be due to animal exposure (mainly camels), household contacts or health care associated infections[23]. In KSA, the majority (45%) of cases were health care-associated infections, 38% were primary cases, and 13% were household contacts[23]. In contrast, in the majority of pediatric cases that reported source of acquisition (66.7% of the 15 with reported source), the disease was acquired through household contact. This pattern indicates a low exposure of children to animals and a higher rate of health care associated infections in adult wards. The male to female ratio (2.8:1 and 3:3:1) was initially high[3,4]. This apparent male predominance could be explained by the nature of hospital outbreaks[2]. Eventually the male to female ratio was reduced to 1.3:1 to 1.8:1[5,6]. Consistent with these studies, the male to female ratio in children with MERS-CoV was 1.7:1 and may indicate similar exposure of children to index cases in the household settings and differential host factors.

Possible explanations for the lower number of pediatric cases compared to adults include differential testing of adult patients and milder diseases in children; although, serologic testing of pediatric patients in KSA and Jordan did not reveal any positive cases[26,27,29]. In the largest sero-epidemiologic survey in KSA, the study did not include children and thus it is difficult to establish the rate of sero-positivity in children[31].

The MERS-CoV infection rate in children remains low and possible explanations include: A milder disease in children, asymptomatic infection, or the presence of yet to be identified factors. The development of a shorter duration of MERS in children is another possible explanation. If this is the case, it may limit the development of a positive serology. In one study, delayed antibody responses as measured with the neutralization test was associated with severe diseases[33]. The longevity of antibodies in MERS-CoV cases might be limited as was the case with SARS[33,34]. The only study of serology among children was done among hospitalized pediatric cases who presented with lower respiratory tract infections[25]. There is no systematic screening of exposed children using serologic testing; this limited the interpretation of available serologic studies.

Little data also exist regarding the effect and the likelihood of MERS-CoV in pregnancy. Eight cases were reported[26,27,29]. The outcome was favorable in the majority of cases. The exact prevalence of MERS-CoV in pregnancy. Eight cases were reported[26,27,29]. The outcome was favorable in the majority of cases. The exact prevalence of MERS-CoV cases might be limited as was the case with SARS[33,34]. The only study of serology among children was done among hospitalized pediatric cases who presented with lower respiratory tract infections[25]. There is no systematic screening of exposed children using serologic testing; this limited the interpretation of available serologic studies.

In conclusion, the number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add

Table 2 Summary of the demographic characteristics of pediatric Middle East respiratory syndrome-coronavirus

| Country | Testing method | Population | Positive n (%) | Yr | Ref. |
|---------|----------------|------------|----------------|----|------|
| KSA     | rRT-PCR        | Screening of children | 9/552 (1.6) | 2013 | [23] |
| KSA     | Neutralizing antibodies testing | Serum samples from children hospitalized for lower respiratory tract infections | 0/158 (0) | 2010-2011 | [25] |
| Jordan  | rRT-PCR        | Hospitalized children < 2 yr of age | 0/2427 (0) | 2013 | [24] |

rRT-PCR: Real time reverse transcriptase polymerase chain reaction; KSA: Kingdom of Saudi Arabia.
Background

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA). Despite the increased number of MERS-CoV cases overtime, the number of pediatric cases remained low. The exact reason for this low prevalence of the disease in children is not known. The aim of this study is to summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

Research frontiers

The first pediatric case was a two-year-old child reported from Jeddah, KSA on June 28, 2013. Later an additional three asymptomatic children were reported. The largest report of childhood MERS-CoV cases included eleven, including nine asymptomatic cases.

Innovations and breakthroughs

The number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add to the understanding of the low prevalence in this age group.

Applications

Despite the low number of pediatric MERS-CoV cases, it is important to continue to monitor the development of this disease in this age group and to understand the risk factors.

Terminology

MERS-CoV is a new emerging virus that was first isolated in 2012.

Peer-review

This complication of all known pediatric cases is a useful contribution to the medical literature, and knowing it is possible but rare is important.

REFERENCES

1. Zaki AM, van Boeckxmeer S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012; 367: 1814-1820 [PMID: 23075134 DOI: 10.1056/NEJMoa1211721]

2. Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus: epidemiology and disease control measures. Infect Drug Resist 2014; 7: 281-287 [PMID: 23595865 DOI: 10.2147/IDR.S51283]

3. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeelah AA, Cummings DA, Alabdullatif ZN, Assaad M, Almulhim A, Makhdoom H, Madani H, Alhakeem R, Al-Tawfiq JA, Cotten M, Watson SJ, Kellam P, Zumla AI, Memish ZA. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013; 369: 407-416 [PMID: 23782161 DOI: 10.1056/NEJMoa1306742]

4. Assiri A, Al-Tawfiq JA, Al-Rabeelah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, Flemhan B, Al-Nassir WN, Balkhy HY, Al-Hakeem RF, Makhdoom HQ, Zumla AI, Memish ZA. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013; 13: 752-761 [PMID: 23891402 DOI: 10.1016/S1473-3099(13)70204-4]

5. Penttinen PM, Kaaskis-Aaslav K, Friaux A, Donachie A, Sudre B, Amato-Gauci AJ, Memish ZA, Coulombier D. Taking stock of the first 133 MERS coronavirus cases globally—Is the epidemic changing? Euro Surveill 2013; 16: pii: 20596 [PMID: 24094061]
Al-Tawfiq JA et al. MERS-CoV Disease is Rare in Children

mers-cov/en/

22 Flutracker. 2012-2016 Case List of MoH/WHO Novel Coronavirus MERS nCoV Announced Cases. Available from: URL: https://flutrackers.com/forum/forum/novel-coronavirus-ncov-mers-2012-2014/146270-2012-2016-case-list-of-moh-who-novel-coronavirus-mers-ncoV-announced-cases

23 Memish ZA, Al-Tawfiq JA, Makhdoum HQ, Al-Rabeeah AA, Assiri A, Alhakeem RF, AlRabiah FA, Al Hajjar S, Albarrak A, Flenban H, Balkhy H, Barry M, Alhassan S, Alsubaie S, Zumla A. Screening for Middle East respiratory syndrome coronavirus infection in hospital patients and their healthcare worker and family contacts: a prospective descriptive study. Clin Microbiol Infect 2014; 20: 469-474 [PMID: 24460984 DOI: 10.1111/1469-0691.12562]

24 Khuri-Bulos N, Payne DC, Lu X, Erdman D, Wang L, Faouri S, Shehabi A, Johnson M, Becker MM, Denison MR, Williams JV, Halasa NB. Middle East respiratory syndrome coronavirus not detected in children hospitalized with acute respiratory illness in Amman, Jordan, March 2010 to September 2012. Clin Microbiol Infect 2014; 20: 678-682 [PMID: 24313317 DOI: 10.1111/1469-0691.12438]

25 Gierer S, Hofmann-Winkler H, Albuali WH, Bertram S, Al-Rubaish AM, Yousef AA, Al-Nafaa AN, Al-Ali AK, Obeid OE, Alkharshah KR, Pöhlmann S. Lack of MERS coronavirus neutralizing antibodies in humans, eastern province, Saudi Arabia. Emerg Infect Dis 2013; 19: 2034-2036 [PMID: 24274664 DOI: 10.3201/eid1912.130701]

26 Payne DC, Iblan I, Alqasrawi S, Al Nsour M, Rha B, Tohme RA, Abedi GR, Farag NH, Haddadin A, Al Sanhouri T, Jarour N, Swerdlov DL, Jamieson DJ, Pallansch MA, Haynes LM, Gerber SI, Al Abdallat MM. Stillbirth during infection with Middle East respiratory syndrome coronavirus. J Infect Dis 2014; 209: 1870-1872 [PMID: 24474813 DOI: 10.1093/infdis/jiu068]

27 Alserehi H, Wali G, Alshukairi A, Alraddadi B. Impact of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) on pregnancy and perinatal outcome. BMC Infect Dis 2016; 16: 105 [PMID: 26936356 DOI: 10.1186/s12879-016-1437-y]

28 Malik A, El Masry KM, Ravi M, Sayed F. Middle East Respiratory Syndrome Coronavirus during Pregnancy, Abu Dhabi, United Arab Emirates, 2013. Emerg Infect Dis 2016; 22: 515-517 [PMID: 26890615 DOI: 10.3201/eid2203.151049]

29 Assiri A, Abedi GR, Almasry M, Bin Saeed A, Gerber SI, Watson JT. Middle East Respiratory Syndrome Coronavirus Infection During Pregnancy: A Report of 5 Cases From Saudi Arabia. Clin Infect Dis 2016; 63: 951-953 [PMID: 27358348 DOI: 10.1093/cid/ciw412]

30 Madani TA, Althaqafi AO, Alraddadi BM. Infection prevention and control guidelines for patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection. Saudi Med J 2014; 35: 897-913 [PMID: 25129197]

31 Denison MR. Severe acute respiratory syndrome coronavirus pathogenesis, disease and vaccines: an update. Pediatr Infect Dis J 2004; 23: S207-S214 [PMID: 1557755]

32 Al-Tawfiq JA, Memish ZA. Drivers of MERS-CoV transmission: what do we know? Expert Rev Respir Med 2016; 10: 331-338 [PMID: 26848513 DOI: 10.1586/17476348.2016.1150784]

33 Park WB, Perera RA, Choe PG, Lau EH, Choi SJ, Chun YJ, Oh HS, Song KH, Bang JH, Kim ES, Kim HB, Park SW, Kim NJ, Man Poon LL, Peiris M, Oh MD. Kinetics of Serologic Responses to MERS Coronavirus Infection in Humans, South Korea. Emerg Infect Dis 2015; 21: 2186-2189 [PMID: 26583829 DOI: 10.3201/eid2112.151421]

34 Cao WC, Liu W, Zhang PH, Zhang F, Richardus JH. Disappearance of antibodies to SARS-associated coronavirus after recovery. N Engl J Med 2007; 357: 1162-1163 [PMID: 17855683 DOI: 10.1056/NEJMoa070348]

35 Thabet F, Chehab M, Bafaqih H, Al-Mohammeed S. Middle East respiratory syndrome coronavirus in children. Saudi Med J 2015; 36: 484-486 [PMID: 25828287 DOI: 10.15537/smj.2015.4.10243]

36 WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) update. Disease Outbreak News. [updated 2014 Apr 26]. Available from: URL: http://www.who.int/csr/don/2014_04_26_mers/en/

37 WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) update. Disease Outbreak News. [updated 2013 Dec 2]. Available from: URL: http://www.who.int/csr/don/2013_12_02/en/

P- Reviewer: Chen XL, Striker R  S- Editor: Ji FF  L- Editor: A E- Editor: Li D
