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Serologic Follow-up of Middle East Respiratory Syndrome Coronavirus Cases and Contacts—Abu Dhabi, United Arab Emirates

Farida Ismail Al Hosani,[1,a] Lindsay Kim,[2,3,a] Ahmed Khudhair,[1] Huong Pham,[2] Mariam Al Mulla,[1] Zyad Al Bandar,[1] Krishna Pradeep,[1] Kheir Abou Elkheir,[1] Stefan Weber,[4] Mary Khoury,[4] George Donnelly,[4] Naima Younis,[1] Feda El Saleh,[1] Muna Abdalla,[1] Hala Imambaccus,[4] Lia M. Haynes,[2] Natalie J. Thornburg,[2] Jennifer L. Harcourt,[2] Congrong Miao,[2] Azaibi Tamin,[2] Aron J. Hall,[2] Elizabeth S. Russell,[5] Aaron M. Harris,[3,5] Craig Kiebler,[5] Roger A. Mir,[6] Kimberly Pringle,[2,5] Negar N. Alami,[5] Glen R. Abedi,[2] and Susan I. Gerber[2]

[1]Department of Health–Abu Dhabi, United Arab Emirates; [2]Division of Viral Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; [3]United States Public Health Service, Rockville, Maryland; [4]Sheikh Khalifa Medical Laboratory, Abu Dhabi, United Arab Emirates; and [5]Epidemic Intelligence Service and [6]Division of Health Informatics and Surveillance, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Although there is evidence of person-to-person transmission of Middle East respiratory syndrome coronavirus (MERS-CoV) in household and healthcare settings, more data are needed to describe and better understand the risk factors and transmission routes in both settings, as well as the extent to which disease severity affects transmission.

Methods. A seroepidemiological investigation was conducted among MERS-CoV case patients (cases) and their household contacts to investigate transmission risk in Abu Dhabi, United Arab Emirates. Cases diagnosed between 1 January 2013 and 9 May 2014 and their household contacts were approached for enrollment. Demographic, clinical, and exposure history data were collected. Sera were screened by MERS-CoV nucleocapsid protein enzyme-linked immunosorbent assay and indirect immunofluorescence, with results confirmed by microneutralization assay.

Results. Thirty-one of 34 (91%) case patients were asymptomatic or mildly symptomatic and did not require oxygen during hospitalization. MERS-CoV antibodies were detected in 13 of 24 (54%) case patients with available sera, including 1 severely symptomatic, 9 mildly symptomatic, and 3 asymptomatic case patients. No serologic evidence of MERS-CoV transmission was found among 105 household contacts with available sera.

Conclusions. Transmission of MERS-CoV was not documented in this investigation of mostly asymptomatic and mildly symptomatic cases and their household contacts. These results have implications for clinical management of cases and formulation of isolation policies to reduce the risk of transmission.

Keywords. Middle East respiratory syndrome coronavirus; asymptomatic infection; serology; transmission; United Arab Emirates.

Since its discovery in 2012 in the Kingdom of Saudi Arabia, Middle East respiratory syndrome coronavirus (MERS-CoV) continues to cause morbidity and mortality in the Arabian Peninsula and globally with 2143 laboratory-confirmed cases and 750 deaths as of 2 February 2018 [1]. Though most cases have occurred in the Kingdom of Saudi Arabia [2], the United Arab Emirates (UAE) has reported the third highest number of MERS cases since 2012 [3]. Documented individual risk factors for MERS-CoV include direct exposure to dromedary camels during the 2 weeks prior to illness onset and certain underlying conditions, including diabetes mellitus and heart disease [4].

The natural history of MERS-CoV continues to be investigated. In a large review of MERS-CoV cases from Abu Dhabi, authors found that 10 case patients with positive polymerase chain reaction (PCR) test results for >14 days duration were either asymptomatic or mildly symptomatic, highlighting the possibility of potential transmission from these persons [5]. Additionally, in a study of 9 healthcare workers in Saudi Arabia, antibodies have been found to persist at least 18 months after case patients experienced severe pneumonia, but more variability in antibody detection was documented among case patients with milder disease [6]. Similar findings were documented among case patients in South Korea [7]. A recently published study from Jordan found that antibodies persisted for 34 months in probable case patients [8]. Last, during the 2015 South Korean outbreak, investigators documented that weak antibody responses were associated with disease mortality [9].

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[a]F. I. A. H. and L. K. contributed equally to this work.

Correspondence: L. Kim, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS-A34, Atlanta, GA 30329 (lkim@cdc.gov).

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Although there is evidence of person-to-person transmission in household and healthcare settings [10–14], more data are needed to describe and better understand the risk factors and transmission routes in both settings, as well as the extent to which disease severity affects transmission. These data would be of importance to the public health response given that approximately 25% of confirmed MERS-CoV cases reported to the World Health Organization have been described as mildly symptomatic or asymptomatic [15].

During 1 January 2013–9 May 2014, the Department of Health–Abu Dhabi (DOH) investigated 65 laboratory-confirmed cases and conducted extensive contact investigations in both household and healthcare settings [5]. Through these investigations, 72% of the laboratory-confirmed cases reported no symptoms or mild illness [5]. Contacts of case patients were tested by diagnostic PCR assays; however, results could include false negatives due to the 14-day incubation period.

In this investigation, we use serological detection of MERS-CoV antibodies to evaluate if asymptomatic or mildly ill case patients had detectable MERS-CoV antibodies, estimate transmission rates from known cases to their household contacts, and identify potential risk factors.

METHODS

Investigation Setting and Population

This investigation occurred in the Emirate of Abu Dhabi, which occupies >80% of the UAE's total area [16] and is comprised of 3 regions: Abu Dhabi (capital city), Al Ain Region, and Al Dhafra. The Emirate of Abu Dhabi has a population of 2.8 million (2015 estimate) [17]. The Al Ain Region borders Oman and Saudi Arabia and houses the second largest city in the Emirate, Al Ain City. While Al Ain City is an oasis, the rest of the region primarily consists of desert and mountains. The Al Dhafra Region is mainly desert and rural with approximately 285 000 residents and a population density of 8 residents/km^2 [18].

All laboratory-confirmed MERS-CoV cases (n = 65) in the Emirate of Abu Dhabi diagnosed between 1 January 2013 and 9 May 2014 and their household contacts (n = 452) were eligible for the investigation. These cases were a convenience sample during the ongoing MERS-CoV outbreak. Two of the 431 (0.5%) household contacts tested for MERS-CoV during initial contact investigations were PCR positive and eligible to be enrolled as cases for our investigation (Figure 1). The enrolled case was a healthcare worker who might have been exposed by another coworker, who also lived in the case's household; therefore, the enrolled case was a result of either household or healthcare transmission prior to this investigation's initiation. The case not enrolled in this investigation was exposed in the household. Household contacts were defined as any person who stayed at least 1 night at the same location as the case patient during the 14 days prior to the case patient's symptom onset or the date of first positive specimen if the case patient was asymptomatic. Excluded cases included palace workers and other high-level officials; their associated household contacts were also excluded.

For each MERS-CoV case identified in the investigation, clinical information, including symptoms, was collected using the International Severe Acute Respiratory and Emerging Infection

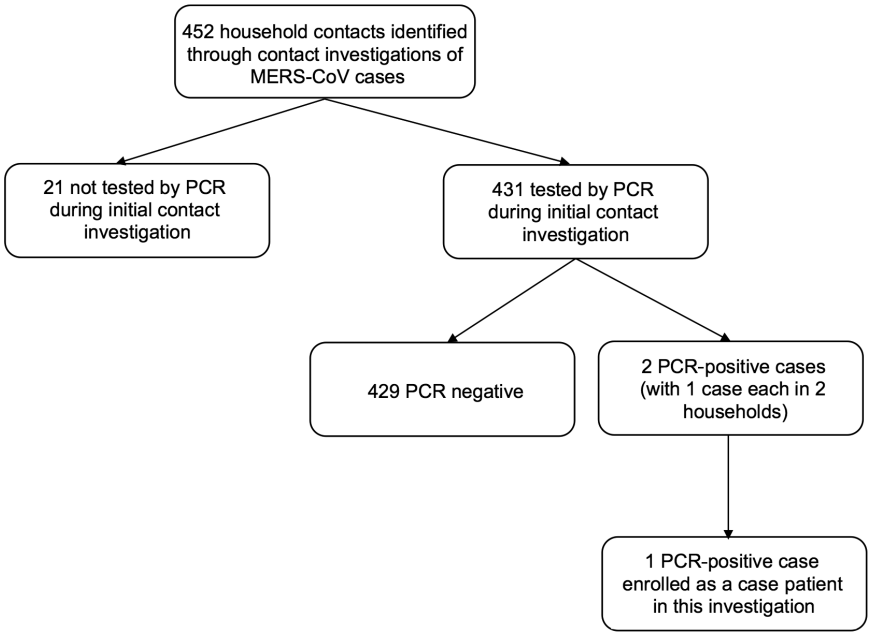

Figure 1. Flow diagram of Middle East respiratory syndrome coronavirus household contacts eligible for this serologic investigation. Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; PCR, polymerase chain reaction.

Consortium form, which was filled out in real time by healthcare providers and subsequently verified by retrospective chart review. In Abu Dhabi during this time period, all individuals who tested positive for MERS-CoV were admitted to a healthcare facility for observation and infection control regardless of symptom status.

The same definitions for case severity were used as in Al Hosani et al [5] including the following: asymptomatic cases reported no symptoms at the time of a positive test as recorded by a healthcare provider in the medical chart; mildly symptomatic cases reported symptoms, such as pharyngitis, rhinorrhea, or cough, and did not require oxygen during their hospitalization; and severely symptomatic cases required supplemental oxygenation during their hospitalization, ranging from nasal cannula to mechanical ventilation.

Using data collected from DOH's surveillance of MERS-CoV cases, households with MERS-CoV case patients were approached. Household contacts who were eligible for the investigation included those that had been identified through contact investigations associated with the case patient performed by DOH officials within 24 hours' notification. Three attempts were made to contact each household. If no response was received after 3 attempts, the household was not enrolled. Households that agreed to be enrolled were given an appointment at the local Disease Prevention and Screening Center for questionnaire administration and serum collection. Questionnaires were administered in English, Arabic, or, if an interpreter was available, the participant's native language. Data collected included demographics; residence/household description; exposure history to other MERS-CoV cases, healthcare settings, and animals; travel history; and medical history, including any long-term effects reported by case patients. For deceased case patients, a proxy completed the case patient questionnaire using recall.

Laboratory Methods

The real-time reverse-transcription PCR (rRT-PCR) results were obtained from the DOH surveillance data. Upper (ie, nasopharyngeal, oropharyngeal) and lower respiratory tract specimens (ie, sputum, bronchoalveolar lavage fluid, tracheal aspirates) were analyzed using rRT-PCR in the Sheikh Khalifa Medical Center laboratory. Additional laboratory result verifications were performed in a random sample of 23 specimens using nucleocapsid-based rRT-PCR [5].

Serum samples were inactivated using 2×10^6 rads gamma irradiation and stored at ≤ −70°C until use. Screening of serum specimens by MERS-CoV nucleocapsid enzyme-linked immunosorbent assay (ELISA) was performed at the Sheik Khalifa Medical City in Abu Dhabi, UAE and the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. Titers of ≥1:400 were reported as positive. Recombinant full length MERS-CoV nucleocapsid protein indirect ELISA was used to screen serum specimens as described by Al-Abdallat et al [19].

Serum samples were tested for the presence of neutralizing antibodies to MERS-CoV using a microneutralization assay (MNT) [19]. The neutralization titer was measured as the reciprocal of the highest serum dilution that completely inhibited Vero cell lysis in at least 1 of the 3 triplicate wells. Positive and negative controls were included for each MNT performed and included back-titration and mock-infected cells. Titers of ≥1:20 were reported as positive. All work with live MERS-CoV was done in Biosafety Level 3 containment at the CDC. Immunofluorescence assays (IFAs) were performed by screening sera at a dilution of 1:50 and 1:100 on paraformaldehyde-fixed, acetone-methanol permeabilized MERS-CoV (strain MERS-CoV Hu/England-N1/2012) infected or uninfected control Vero cells. Antihuman immunoglobulin G, M, and A fluorescein isothiocyanate conjugate was used to detect anti–MERS-CoV antibodies in human serum, and nuclei were counterstained with 4′,6-diamidino-2-phenylindole to allow identification of individual MERS-CoV–infected cells. Fluorescence was detected using a Zeiss AxioImager fluorescence microscope. The positive control for the assay is a serum sample from a patient infected with MERS-CoV Hu/England-N1/2012. A positive result was scored when these 3 conditions were met: Cells were evenly stained (instead of punctate staining); fluorescence intensity was higher than that of the negative controls; and signal intensity declined with serial dilution. A minimum of 2 negative controls were included with each IFA. Approximately 10% of specimens negative by nucleocapsid ELISA were screened by both IFA and MNT to confirm the negative result.

MERS-CoV antibody positivity was defined as one of the following: (1) 2 of 3 tests (ie, MERS-CoV nucleocapsid ELISA, MERS-CoV MNT, and IFA) were positive; or (2) MERS Co-V MNT was the only positive test.

Data Management and Analysis

Household survey data were entered into electronic forms in Epi Info 7 version 7.1 (CDC). Quality control and assurance were performed through Epi Info 7 intelligent codes programmed into the forms. Household survey data were merged with the laboratory results, and descriptive analysis was completed. Differences in proportions were compared using the Mantel-Haenszel χ^2 test, while differences in continuous variables were compared using the Student t test. $P < .05$ was considered statistically significant. Data analysis of the merged dataset was conducted with SAS version 9.3 software (SAS Institute, Cary, North Carolina).

Ethical Considerations

Following local customs, informed consent was obtained from the head of the household, who provided consent for all members of a household; however, each individual was still able to decline participation. This investigation was determined

Table 1. Characteristics of Middle East Respiratory Syndrome Coronavirus Case Patients and Household Contacts

Characteristic	MERS-CoV Case Patients (N = 34)	Household Contacts (N = 124)
Demographics		
Sex		
Male	10 (29.4)	58 (46.8)
Female	24 (70.6)	66 (53.2)
Age, y		
0–19	1 (2.9)	45 (36.3)
20–29	4 (11.8)	16 (12.9)
30–59	25 (73.5)	62 (50.0)
≥60	4 (11.8)	1 (0.8)
Nationality		
United Arab Emirates	4 (11.8)	47 (37.9)
Kingdom of Saudi Arabia	0 (0)	0 (0)
Oman	2 (5.9)	6 (4.8)
Bangladesh	1 (2.9)	9 (7.3)
India	4 (11.8)	12 (9.7)
Pakistan	2 (5.9)	13 (10.5)
Jordan	1 (2.9)	1 (0.8)
Philippines	12 (35.3)	13 (10.5)
Other	8 (23.5)	23 (18.5)
Region of residence		
Al Ain	30 (88.2)	86 (69.4)
Al Dhafra	2 (5.9)	36 (29)
Abu Dhabi	2 (5.9)	2 (1.6)
Exposure history		
Contact with MERS-CoV–positive household member		
Care	3 (8.8)	31 (25.0)
Housecleaning	2 (5.9)	28 (22.6)
Prepared food	3 (8.8)	18 (14.5)
Shared meals	4 (11.8)	61 (49.2)
Shared utensils	3 (8.8)	14 (11.3)
Eat with hands from same dish	1 (2.9)	37 (29.8)
Use same bathroom	0 (0)	63 (50.8)
Sleep overnight in same room	1 (2.9)	45 (36.3)
Sleep in same bed	0 (0)	15 (12.1)
Hug	2 (5.9)	67 (54.0)
Kiss/nose-kiss	2 (5.9)	60 (48.4)
Contact with others in community with respiratory symptoms 30 d prior to MERS-CoV diagnosis	1 (2.9)	20 (16.1)
Worked in a healthcare setting 14 d prior to diagnosis	24 (70.6)	30 (24.2)
Visited healthcare setting	9 (26.5)	15 (12.1)
Animal exposures		
Own or visit farm	4 (11.8)	17 (13.7)
Camel	4 (11.8)	9 (7.3)
Travel 30 d prior to diagnosis/illness	5 (14.7)	8 (6.5)
Clinical characteristics		
Underlying medical conditions		
Diabetes	6 (17.6)	6 (4.8)
Asthma	3 (8.8)	11 (8.9)
Hypertension	9 (26.5)	8 (6.5)
Kidney failure	2 (5.9)	2 (1.6)
Heart failure	2 (5.9)	0 (0)
Chronic anemia	0 (0)	2 (1.6)
Cancer	0 (0)	1 (0.8)
Take medications for any illness	13 (38.2)	21 (16.9)
Limitations to activities due to illness	3 (8.8)	NA
Days, median (IQR)	5 (4–24)	NA
Days until able to resume normal activities, median (IQR)	5 (3–7)	NA

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; MERS-CoV, Middle East respiratory syndrome coronavirus; NA, not applicable.

by DOH and CDC to be part of a public health response, not research, and therefore not subject to institutional review board review.

RESULTS

Description of Households

Thirty-four case patients' households were included (Supplementary Table 1). Household residences ranged in size from 7 m^2 to 1100 m^2 (interquartile range [IQR], 70–200 m^2). A median of 4 individuals (range, 1–30) lived in the households 14 days prior to the diagnosis of a MERS-CoV household case patient. More than half of MERS-CoV case patients shared a bathroom with others in the household. All households reported having air conditioning.

Description of MERS-CoV Cases and Household Contacts

Thirty-four cases of 65 (52%) and 124 household contacts of 452 (27%) participated (Table 1). Females comprised a higher proportion of case patients compared with household contacts (70.6% vs 53.2%), and case patients were older compared with household contacts (median, 42 years vs 31 years). Most case patients and contacts were from the Al Ain Region of the Abu Dhabi Emirate.

Seventy-one percent (n = 24) of case patients reported working in a healthcare setting 14 days prior to diagnosis, with nurses being most represented (24%, n = 8) (Table 1); only 24% (n = 30) of household contacts worked in a healthcare setting 14 days prior to a case patient's diagnosis. Compared with household contacts, case patients less frequently reported visiting or owning a farm (12% vs 14%), but reported camel exposure more frequently (12% vs 7%).

Household contacts reported the following frequent exposures to MERS-CoV case patients: hugging (54%, n = 67), using the same bathroom (51%, n = 63), sharing meals (49%, n = 61), and kissing or nose-kissing (ie, rubbing tips of noses against one another) (48%, n = 60).

Table 2. Characteristics of Middle East Respiratory Syndrome Coronavirus Case Patients, by Symptom Severity

Characteristic	Asymptomatic (n = 17)		Mildly Symptomatic (n = 14)		Severely Symptomatic (n = 3)		All (N = 34)	
Demographics								
Sex								
Female	3	(17.6)	7	(50.0)	0	(0)	10	(29.4)
Male	14	(82.4)	7	(50.0)	3	(100.0)	24	(70.6)
Age, y								
Median (IQR)	37	(30–45)	42	(38–48)	59	(40–65)	42	(32–48)
0–19	0	(0)	1	(7.1)	0	(0)	1	(2.9)
20–29	4	(23.5)	0	(0)	0	(0)	4	(11.8)
30–59	10	(58.8)	13	(92.9)	2	(66.7)	25	(73.5)
≥60	3	(17.6)	0	(0)	1	(33.3)	4	(11.8)
Nationality								
Bangladesh	1	(5.9)	0	(0)	0	(0)	1	(2.9)
United Arab Emirates	2	(11.8)	1	(7.1)	1	(33.3)	4	(11.8)
India	1	(5.9)	2	(14.3)	1	(33.3)	4	(11.8)
Jordan	1	(5.9)	0	(0)	0	(0)	1	(2.9)
Oman	0	(0)	1	(7.1)	1	(33.3)	2	(5.9)
Pakistan	2	(11.8)	0	(0)	0	(0)	2	(5.9)
Philippines	5	(29.4)	7	(50.0)	0	(0)	12	(35.3)
Other	5	(29.4)	3	(21.4)	0	(0)	8	(23.5)
Region								
Al Ain	16	(94.1)	12	(85.7)	2	(66.7)	30	(88.2)
Al Dhafra	1	(5.9)	0	(0)	1	(33.3)	2	(5.9)
Abu Dhabi	0	(0)	2	(14.3)	0	(0)	2	(5.9)
Exposure history								
Contact with MERS-CoV–positive household member								
Care	1	(5.9)	2	(14.3)	…	…	3	(8.8)
Clean house	0	(0.0)	2	(14.3)	…	…	2	(5.9)
Prepare food	0	(0.0)	3	(21.4)	…	…	3	(8.8)
Eat meal	0	(0.0)	4	(28.6)	…	…	4	(11.8)
Shared utensils	0	(0.0)	3	(21.4)	…	…	3	(8.8)
Eat with hands from same dish	0	(0.0)	1	(7.1)	…	…	1	(2.9)
Used the same bathroom	0	(0.0)	0	(0.0)	…	…	0	(0.0)
Sleep overnight	1	(5.9)	0	(0.0)	…	…	1	(2.9)
Sleep in the same bed	0	(0.0)	0	(0.0)	…	…	0	(0.0)
Hug	1	(5.9)	1	(7.1)	…	…	2	(5.9)
Kiss/nose-kiss	1	(5.9)	1	(7.1)	…	…	2	(5.9)
Contact with person with respiratory symptoms past 14 d	0	(0.0)	1	(7.1)	0	(0.0)	1	(2.9)
Work at healthcare 14 d prior to diagnosis	12	(70.6)	12	(85.7)	0	(0.0)	24	(70.6)
Visited healthcare facilities	3	(17.6)	5	(35.7)	1	(33.3)	9	(26.5)
Visited farm	3	(17.6)	0	(0.0)	1	(33.3)	4	(11.8)
Camel exposure	2	(11.8)	1	(7.1)	1	(33.3)	4	(11.8)
Traveled 30 d before diagnosis	3	(17.6)	1	(7.1)	1	(33.3)	4	(11.8)
Clinical characteristics								
Underlying medical conditions								
Diabetes	3	(17.6)	1	(7.1)	2	(66.7)	6	(17.6)
Asthma	1	(5.9)	2	(14.3)	0	(0.0)	3	(8.8)
Hypertension	5	(29.4)	2	(14.3)	2	(66.7)	9	(26.5)
Heart failure	0	(0.0)	1	(7.1)	1	(33.3)	2	(5.9)
Kidney failure	1	(5.9)	0	(0.0)	1	(33.3)	2	(5.9)
Chronic medications	6	(35.3)	4	(28.6)	3	(100.0)	13	(38.2)
ICU care	1	(5.9)	0	(0)	3	(100.0)	4	(11.8)
Intubated	0	(0)	0	(0)	2	(66.7)	2	(5.9)
Days hospitalized, median (IQR)	9	(6–12)	19	(18–24)	26	(5–35)	19	(12–26)
Duration since positive PCR test								
Days, median (IQR)	51	(47–56)	56	(54–66)	80	(49–87)	55	(49–58)
1 mo	1	(5.9)	0	(0)	0	(0)	1	(2.9)

Table 2. *Continued*

Characteristic	Asymptomatic (n = 17)		Mildly Symptomatic (n = 14)		Severely Symptomatic (n = 3)		All (N = 34)	
2 mo	15	(88.2)	10	(71.4)	1	(33.3)	26	(76.5)
3 mo	0	(0)	2	(14.3)	2	(66.7)	4	(11.8)
1 y	1	(5.9)	2	(14.3)	0	(0)	3	(8.8)
Days of PCR positivity, median (IQR)	4	(1–8)	11	(2–16)	1	(1–23)	5	(1–14)
Serology testing available	10	(58.8)	13	(92.9)	1	(33.3)	24	(70.6)
Seroconversion[a]	3	(30.0)	9	(69.2)	1	(100.0)	13	(54.2)
Symptoms at 30 d[b]	1	(5.9)	2	(14.3)	0	(0)	3	(8.8)
Limitation of activities	2	(11.8)	0	(0)	1	(33.3)	3	(8.8)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MERS-CoV, Middle East respiratory syndrome coronavirus; PCR, polymerase chain reaction; …, unknown.

[a]Denominator = serology testing available.

[b]Asymptomatic patient had cough at 30 days; mildly symptomatic: cough (n = 1), muscle aches (n = 1).

Case patients reported a higher proportion of underlying medical conditions than household contacts, including diabetes (18% vs 5%, $P = .01$), hypertension (27% vs 7%, $P < .001$), kidney failure (6% vs 2%, $P = .03$), and heart failure (6% vs 0%, $P < .01$) (Table 1). Case patients also reported taking medications for any illness more frequently than contacts (38% vs 17%).

Three case patients (9%) reported limitation to activities due to MERS-CoV with a median duration of 5 days (IQR, 4–24 days) (Table 1). Normal activities were resumed at a median of 5 days (IQR, 3–7 days).

MERS-CoV Case Patients by Symptom Severity

Of 34 case patients, 17 (50%) reported being asymptomatic, 14 (41%) reported being mildly symptomatic, and 3 (9%) were severely symptomatic. Age and proportion having underlying medical conditions increased with symptom severity (Table 2). Symptom duration did not have any noticeable trend with symptom severity (data not shown). All severe case patients were treated in the intensive care unit, as well as 1 asymptomatic case, who had underlying diabetes, hypertension, and kidney disease. The median days hospitalized increased with symptom severity (Table 2).

Serology Results

Sera were obtained from 24 of 34 (71%) case patients and 105 of 124 (85%) household contacts. Among the 24 case patients with available sera (Table 3), 13 (54%) had detectable MERS-CoV antibodies 45–348 days after the first PCR-positive result (Supplementary Figure 1*A* and 1*B*; median, 55 days [IQR, 53–58 days]), including 3 asymptomatic, 9 mildly symptomatic, and 1 severely symptomatic case patient. A mildly symptomatic case patient had detectable MERS-CoV antibodies almost 1 year after the first positive PCR result. There were no positive serology results among the household contacts.

Among the 13 case patients with detectable antibodies against MERS-CoV, all of them were aged <60 years, with a median age of 43 years, compared to a median of 32 years for case patients without detectable antibodies (Table 4, $P = .04$). Number of days of PCR positivity was notably higher among those who had detectable antibodies compared to those who did not (median, 15 days vs 2 days, $P = .01$).

DISCUSSION

We describe the results of follow-up of 34 MERS-CoV case patients and 124 of their household contacts from the Emirate of Abu Dhabi during 2013–2014. Notably, serologic testing did not find any evidence of MERS-CoV transmission in the households of MERS-CoV case patients in our investigation, suggesting that viral transmission from asymptomatic or mildly symptomatic individuals to household contacts does not readily occur. Sera were tested with a combination of 3 different laboratory assays (nucleocapsid ELISA, IFA, and MNT); we feel confident that individuals identified as "negative" did not seroconvert. Although there was clear evidence of household transmission in 1 household not enrolled in this investigation, our investigation's results did not show evidence of additional household transmission. Overall, our findings support current recommendations that home isolation may be appropriate for asymptomatic cases and close contacts who are ill and do not require hospitalization in consultation with local public health departments [20, 21].

Because this investigation occurred during May–June 2014, many case patients were recruited from the April 2014 healthcare-associated outbreak at an Al Ain Region hospital [22]. A Kingdom of Saudi Arabia study found that while healthcare personnel were at high risk for infection, most illness was relatively mild and could be unrecognized, highlighting potential undetected transmission of the virus to others [23]. In our investigation, case patients tended to be younger (30–59 years), and most reported working in a healthcare setting 14 days prior to their diagnosis where they were exposed to a

Table 3. Available Serology Results for Middle East Respiratory Syndrome Coronavirus Case Patients (n = 24)

Case	Age, y	Sex	Severity	First Specimen Collection Date	N ELISA Titer	IFA	MNT Titer	Final Interpretation	Second Specimen Collection Date	N ELISA Titer	IFA	MNT Titer	Final Interpretation	Third Specimen Collection Date	N ELISA Titer	IFA	MNT Titer	Final Interpretation
1	31	F	Asymp	9 Aug 2013	<400	ND	ND	Neg	15 Jun 2014	<400	ND	<20	Neg					
2	44	M	Asymp	10 Apr 2014	<400	ND	ND	Neg	30 Apr 2014	1600	Pos	<20	Pos	4 Jun 2014	400	Pos	<20	Pos
3	22	M	Asymp	13 Apr 2014	<400	ND	ND	Neg	29 May 2014	<400	ND	<20	Neg					
4	30	M	Asymp	13 Apr 2014	<400	ND	ND	Neg	5 Jun 2014	400	Neg	<20	Neg					
5	45	M	Asymp	13 Apr 2014	<400	ND	ND	Neg	4 Jun 2014	400	Neg	<20	Neg					
6	29	M	Asymp	14 Apr 2014	<400	ND	ND	Neg	11 Jun 2014	<400	ND	<20	Neg					
7	42	M	Asymp	17 Apr 2014	<400	ND	ND	Neg	4 Jun 2014	>6400	Pos	<20	Pos					
8	32	M	Asymp	21 Apr 2014	<400	ND	ND	Neg	9 Jun 2014	<400	ND	<20	Neg					
9	26	M	Asymp	7 May 2014	1600	Pos	20	Pos	22 Jun 2014	1600	Pos	<20	Pos					
10	38	F	Mild	13 Jul 2013	<400	ND	ND	Neg	8 Mar 2014	<400	Neg	<20	Neg	26 Jun 2014	<400	ND	ND	Neg
11	40	F	Mild	16 Jul 2013	400	Neg	<20	Neg	20 Jul 2013	<400	Neg	<20	Neg	26 Jun 2014	<400	ND	40	Pos
12	34	M	Mild	9 Apr 2014	<400	ND	ND	Neg	30 Apr 2014	1600	Pos	80	Pos	9 Jun 2014	400	Pos	320	Pos
13	38	F	Mild	9 Apr 2014	<400	ND	ND	Neg	9 Jun 2014	<400	ND	20	Pos					
14	41	M	Mild	9 Apr 2014	<400	ND	ND	Neg	9 Jun 2014	1600	Pos	<20	Pos					
15	44	F	Mild	9 Apr 2014	<400	ND	ND	Neg	30 Apr 2014	>6400	Pos	80	Pos	9 Jun 2014	400	Neg	<20	Neg
16	48	M	Mild	9 Apr 2014	<400	Neg	<20	Neg	4 Jun 2014	<400	ND	20	Pos					
17	43	M	Mild	10 Apr 2014	<400	ND	ND	Neg	30 Apr 2014	1600	Pos	20	Pos	9 Jun 2014	400	Neg	<20	Neg
18	52	F	Mild	10 Apr 2014	1600	Pos	<20	Pos	30 Apr 2014	400	Pos	<20	Pos	19 Jun 2014	<400	ND	<20	Neg
19	55	F	Mild	12 Apr 2014	<400	ND	ND	Neg	19 Jun 2014	<400	ND	<20	Neg					
20	44	M	Mild	20 Apr 2014	<400	ND	ND	Neg	5 Jun 2014	<400	ND	<20	Neg					
21	5	M	Mild	[a]	[a]	ND	ND	Neg	5 Jun 2014	<400	ND	<20	Neg					
22	51	M	Mild	19 Jun 2014	>6400	Pos	160	Pos										
23	59	M	Required oxygen	13 Apr 2014	>6400	Pos	40	Pos	11 Jun 2014	>1:6400	Pos	80	Pos					
24	36	M	Asymp	22 Jun 2014	<400	ND	<20	Neg										

Definitions: MERS-CoV N ELISA: <400 titer is considered negative. MERS-CoV IFA positive: Positive IFA at 1:50 and/or 1:100 serum dilution. MERS Co-V IFA negative: Negative IFA at 1:50. MERS-COV MNT: <20 titer is considered negative.

Two criteria constituted a positive test result: a positive ELISA test and confirmation by IFA and/or MNT or a >20 microneutralization titer. (1) If a specimen was positive by both ELISA and IFA, the specimen was determined to be positive. (2) If a specimen was positive by MNT, then regardless of IFA and ELISA results, the specimen was determined to be positive. (3) If a specimen was positive by ELISA, indeterminate or negative by IFA, the Centers for Disease Control and Prevention then performed additional confirmatory testing (ie, MNT). (4) If a specimen was positive by ELISA, indeterminate by IFA, and positive by MNT, the specimen was determined to be positive. (5) If a specimen was positive by ELISA, indeterminate or negative by IFA, and negative by MNT, the specimen was determined to be negative.

Abbreviations: Asymp, asymptomatic; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; MNT, microneutralization assay; N, nucleocapsid protein; ND, not determined; Neg, negative; Pos, positive.

[a]Specimen collection date and N ELISA titer not available for this case patient.

Table 4. Characteristics of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Case Patients With Available Serology, by Status of MERS-CoV Detectable Antibodies

Characteristic	MERS-CoV Detectable Antibodies				Total (n = 24)		*P* Value
	No (n = 11)		Yes (n = 13)				
Sex							.85
Female	3	(27.3)	4	(30.8)	7	(29.2)	
Male	8	(72.7)	9	(69.2)	17	(70.8)	
Age, y							
Median (IQR)	32	(29–44)	43	(40–48)	41	(32–45)	.04
0–19	1	(9.1)	0	(0.0)	1	(4.2)	.17
20–29	2	(18.2)	1	(7.7)	3	(12.5)	
30–59	8	(72.7)	12	(92.3)	20	(83.3)	
Nationality							.79
Bangladesh	1	(9.1)	0	(0.0)	1	(4.2)	
United Arab Emirates	2	(18.2)	0	(0.0)	2	(8.3)	
India	0	(0.0)	3	(23.1)	3	(12.5)	
Oman	0	(0.0)	1	(7.7)	1	(4.2)	
Pakistan	1	(9.1)	1	(7.7)	2	(8.3)	
Philippines	5	(45.5)	5	(38.5)	10	(41.7)	
Other[a]	2	(18.2)	3	(23.1)	5	(20.8)	
Region							1.00
Al Ain	9	(81.8)	11	(84.6)	20	(83.3)	
Al Dhafra	1	(9.1)	1	(7.7)	2	(8.3)	
Abu Dhabi	1	(9.1)	1	(7.7)	2	(8.3)	
Duration of stay in same house as a MERS-CoV case, d							.07
1	4	(36.4)	0	(0.0)	4	(16.7)	
2–7	6	(54.5)	6	(46.2)	12	(50.0)	
8–14	0	(0.0)	4	(30.8)	4	(16.7)	
15–21	1	(9.1)	2	(15.4)	3	(12.5)	
≥22	0	(0.0)	1	(7.7)	1	(4.2)	
Days of PCR positivity, median (IQR)	2	(1–8)	15	(4–21)	8	(2–16)	.005
No. of days being PCR positive							.008
<7	8	(72.7)	4	(30.8)	12	(50.0)	
7–14	2	(18.2)	2	(15.4)	4	(16.7)	
15–21	1	(9.1)	4	(30.8)	5	(20.8)	
≥22	0	(0.0)	3	(23.1)	3	(12.5)	
Duration since last PCR-positive test							.45
1 mo	1	(9.1)	0	(0.0)	1	(4.2)	
2 mo	7	(63.6)	11	(84.6)	18	(75.0)	
3 mo	1	(9.1)	1	(7.7)	2	(8.3)	
1 y	2	(18.2)	1	(7.7)	3	(12.5)	
Severity							.04
Asymptomatic	7	(63.6)	3	(23.1)	10	(41.7)	
Mild symptoms	4	(36.4)	9	(69.2)	13	(54.2)	
Required oxygen	0	(0.0)	1	(7.7)	1	(4.2)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; MERS-CoV, Middle East respiratory syndrome coronavirus; PCR, polymerase chain reaction.

[a]For case patients with no detectable antibodies, "other" includes Syria (n = 1) and Turkey (n = 1). For case patients with detectable antibodies, "other" includes Nepal (n = 1), Sudan (n = 1), and Tunisia (n = 1).

MERS-CoV case. Because most of these case patients did not have severe underlying illnesses and reported being asymptomatic or mildly symptomatic, it is possible that these patients may have had a relatively low viral load, decreasing the likelihood of transmission.

Similar to previous studies, case patients with severe disease had higher frequency of comorbid conditions and required intensive care, including intubation [24–26]. In a recent investigation from South Korea, patients with a higher host infectivity, which included evaluation of PCR cycle threshold values, along with higher numbers of contacts, were more likely to transmit MERS-CoV [27]. It is likely that most of the primary case patients in this investigation had lower host infectivity.

While our investigation found that some asymptomatic or mildly symptomatic case patients had detectable antibodies, we did not find any detectable antibodies in 11 asymptomatic and mildly symptomatic case patients. Other studies also did not find detectable antibodies in some asymptomatic and mildly ill cases [6, 28]. If seroconversion is to occur in case patients, studies have demonstrated that this usually occurs within the first month of illness [28–30]. For the majority of case patients with detectable antibodies, we found persistence of antibody response for several months after the initial diagnosis, even close to a year. Additionally, these case patients had a longer duration of MERS-CoV PCR positivity than those who did not have detectable antibodies, indicating a potential relationship between longer viral shedding and seroconversion.

Previous studies have demonstrated that asymptomatic and mildly symptomatic case patients can test PCR positive >2 weeks from lower respiratory tract specimens [5, 31]. Our investigation's serology results do not provide additional evidence of transmission to household contacts, though there is evidence from other settings to suggest limited household transmission [11]. Also, very low rates of household transmission have been reported during hospital-based outbreaks [19, 32]. More robust transmission studies involving larger numbers of case patients representing a range of clinical and demographic characteristics and their contacts are needed to further investigate risk exposures.

There are several limitations to this investigation. First, serum samples were collected at varying intervals after illness onset for each case patient, potentially affecting serology results. The duration of antibody response is unknown. Second, recall bias might have led to the misclassification of symptom severity among household contacts; however, for case patients, to minimize this bias, we relied upon retrospective medical chart review, though this also might not be as complete since it depended on the initial healthcare provider's history and physical. Third, these case patients were immediately isolated in hospitals after PCR-positive results were discovered. The removal from the household setting might have reduced exposure to household contacts although the case patients were residing with household contacts at the time of the contact investigations. Last, because our investigation did not detect household transmission, we cannot comment on any behaviors or exposures that would increase risk among household contacts of case patients.

In summary, we did not document additional household transmission in this investigation that included a preponderance of asymptomatic and mildly symptomatic confirmed MERS-CoV case patients. Our investigation findings support the recommendation to consider home isolation for asymptomatic and mildly ill cases that do not require hospitalization while using proper precautions, including face masks, frequent hand washing, and minimizing exposure to the case patient in the household [20, 21, 33]. While no vaccines or antivirals against MERS-CoV are currently available, reducing transmission through effective infection control management remains a major priority. Understanding transmission risk for different MERS-CoV–infected patients who live in different settings will be important data that must be factored into prevention strategies. Further studies on human-to-human transmission in different settings should be conducted to inform MERS-CoV prevention and control guidelines.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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