
Review

A Review of Asymptomatic and Subclinical Middle East Respiratory Syndrome Coronavirus Infections

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The epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) since 2012 has been largely characterized by recurrent zoonotic spillover from dromedary camels followed by limited human-to-human transmission, predominantly in health-care settings. The full extent of infection of MERS-CoV is not clear, nor is the extent and/or role of asymptomatic infections in transmission. We conducted a review of molecular and serological investigations through PubMed and EMBASE from September 2012 to November 15, 2018, to measure subclinical or asymptomatic MERS-CoV infection within and outside of health-care settings. We performed retrospective analysis of laboratory-confirmed MERS-CoV infections reported to the World Health Organization to November 27, 2018, to summarize what is known about asymptomatic infections identified through national surveillance systems. We identified 23 studies reporting evidence of MERS-CoV infection outside of health-care settings, mainly of camel workers, with seroprevalence ranges of 0%–67% depending on the study location. We identified 20 studies in health-care settings of health-care worker (HCW) and family contacts, of which 11 documented molecular evidence of MERS-CoV infection among asymptomatic contacts. Since 2012, 298 laboratory-confirmed cases were reported as asymptomatic to the World Health Organization, 164 of whom were HCWs. The potential to transmit MERS-CoV to others has been demonstrated in viral-shedding studies of asymptomatic MERS infections. Our results highlight the possibility for onward transmission of MERS-CoV from asymptomatic individuals. Screening of HCW contacts of patients with confirmed MERS-CoV is currently recommended, but systematic screening of non-HCW contacts outside of health-care facilities should be encouraged.

health-care workers; infection control; MERS-CoV; seroprevalence; subclinical infections

Abbreviations: HCW, health-care worker; MERS-CoV, Middle East respiratory syndrome coronavirus; PCR, polymerase chain reaction; WHO, World Health Organization.

INTRODUCTION

Since 2012, the epidemiology of cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection reported to the World Health Organization (WHO) has been characterized largely by recurrent zoonotic spillover from the known animal reservoir—dromedary camels—and human-to-human transmission in health-care settings (1). Outbreaks in health-care settings on occasion have resulted in large outbreaks (2–9). Of the 2,260 cases (including 803 deaths) reported to WHO, 83% of cases have been reported in the Kingdom of Saudi Arabia (10).

The clinical presentation of MERS-CoV infection ranges from asymptomatic to severe respiratory illness, with approximately 35.5% of cases resulting in death (1). The role of asymptomatic or subclinical infections in human-to-human transmission of MERS-CoV is not well understood, but there is evidence that laboratory-confirmed MERS-CoV infection in patients who are reported as asymptomatic may be transmitted to other individuals (11).

For many novel infectious pathogens, surveillance initially focuses on individuals with disease who seek care at health-care facilities, which undoubtedly underestimates the true prevalence of infection, because it will not account

for mild or asymptomatic infections not requiring medical care. Detailed outbreak investigations often include laboratory testing of close contacts and of health-care workers (HCWs), regardless of symptoms, and specialized serological investigations will include individuals thought to be at higher risk of infection, such as HCWs or those with occupational exposure to animal reservoirs. Estimates of the true prevalence of infection of high-risk pathogens are important to understand the populations required for vaccine candidates or specific therapeutic treatments as and when they become available. In addition, the role of subclinical or asymptomatic infection is critical in understanding chains of transmission missed by surveillance systems. For MERS-CoV, asymptomatic infection has been reported to WHO, but the possibility of transmission prior to symptom onset is critical for recommending effective infection prevention and control measures and for reducing secondary MERS-CoV transmission.

The role of asymptomatic infections in transmission of other respiratory viruses has been investigated previously. Highly pathogenic avian influenza H5N1 RNA, for example, has been detected by polymerase chain reaction (PCR) from asymptomatic family contacts of ill patients, suggesting the possibility for onward transmission, even in the absence of symptoms (12–15). For severe acute respiratory syndrome CoV, limited transmission to close contacts before symptom onset or hospitalization has been found in transmission-risk studies outside health-care settings, whereas human-to-human transmission within health-care settings was higher, likely due to higher viral load in hospitalized patients and more frequent exposure to the virus among HCWs (16–18).

Here, we have reviewed available evidence of the extent of subclinical and asymptomatic infection of MERS-CoV stratified by evaluating studies in which infection within and outside of health-care settings has been measured, and the potential role of onward human-to-human transmission from asymptomatic cases.

METHODS

We conducted a literature search in PubMed and EMBASE databases for observational epidemiologic studies of laboratory-confirmed MERS-CoV infection using the following search terms: “MERS-CoV” or “MERS” AND “seroprevalence” or “prevalence” or “serological” or “infection” or “asymptomatic.” Additional studies were identified through consultation with the WHO MERS technical network and in the bibliography of a related recently published review (19). Publications in English dated before November 15, 2019, were considered, with no additional restrictions on year of publication. We assessed the titles and abstracts of identified studies to determine their eligibility for inclusion in the study. We stratified our analyses to evaluate subclinical and/or asymptomatic infection identified inside and outside health-care facilities. For descriptive analysis of WHO case-based data, we used the ggplot2 in R, version 3.4.2.0 (R Foundation for Statistical Computing, Vienna, Austria.).

For MERS-CoV infections studied outside health-care settings, we included studies in which evidence of MERS-CoV infection was reported, using molecular and/or serologic

methods in either individuals with occupational exposure to dromedary camels; familial, occupational, or social contacts of patients with confirmed MERS outside of health-care settings; the general population; or through national MERS surveillance records, when published. Eligible studies included reporting of the number of individuals tested and the number with molecular or serological evidence of MERS-CoV infection.

To evaluate MERS-CoV infections studied within health-care settings, we included studies in which the authors reported evidence of MERS-CoV infection, using molecular and/or serological methods among HCW and among non-HCW contacts (e.g., family contacts) of confirmed MERS cases treated in health care settings.

For each eligible study, we extracted information on the year of publication, the year biological samples were collected, the country in which the study was conducted, the number of individuals tested, characteristics of the individuals tested, and the total number of confirmed MERS-CoV infections by molecular or serological assay. Asymptomatic MERS-CoV infection was considered a laboratory-confirmed infection with no reported symptoms at the time of sampling.

In addition, we evaluated the symptomatic profile and place of reporting among laboratory-confirmed MERS-CoV infections reported to WHO from September 2012 to November 27, 2018. Within WHO databases, cases are classified as primary cases if they were reported as such by the reporting Member State; if direct or indirect contact with dromedary camels or dromedary products was reported in the case; and/or the exposures were under investigation without known contact with a patient with probable or confirmed MERS. Cases were classified as secondary cases due to human-to-human transmission if the patient reported recent direct contact with a patient known to have MERS-CoV infection and/or were identified as a household, occupational, or HCW contact of a patient known to have MERS-CoV infection.

RESULTS

In total, we identified 43 studies in which MERS-CoV infections measured by serology and/or molecular testing were reported; 23 focused on individuals with exposures outside of health-care settings (4, 7, 11, 20–39), and 20 focused on individuals with exposures inside health-care facilities (5, 7, 29, 32, 40–54). The selection of identified and included studies is shown in Figure 1.

The 23 studies in which MERS-CoV infections were measured by serology and/or molecular testing outside of health-care settings are described in Table 1. The majority of studies focused on measuring seroprevalence of MERS-CoV in individuals with occupational exposure to dromedaries in the Middle East and Africa (20–28).

In the largest seroprevalence study conducted to date, 0.1% seroprevalence was calculated among general population samples collected in 2012–2013, 2% seroprevalence among shepherds of dromedaries, and 4% seroprevalence among slaughterhouse workers (37). Additional estimates of seroprevalence among occupational high-risk populations

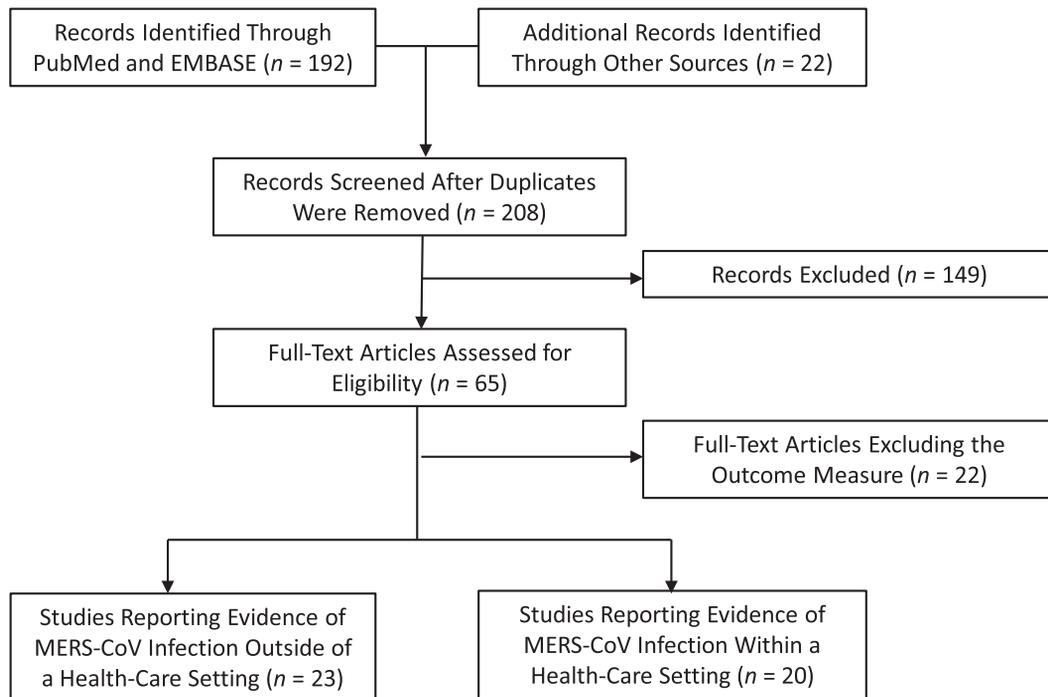


Figure 1. Flow diagram of selection of articles for the review of symptomatic and subclinical Middle East respiratory syndrome coronavirus (MERS-CoV) infections. Additional records identified through consultation with the World Health Organization MERS technical network and in the bibliography of a related review (19).

ranged from 0% to 67%, with seropositivity being detected in Kingdom of Saudi Arabia, Qatar, and Kenya, and from 0% to 54% among contacts of patients with confirmed MERS in household settings largely in countries of the Middle East. Within these studies, the majority of infections detected by serology appeared to be asymptomatic. Within these studies, a high proportion of seropositive camel workers reported no symptoms (80%–100% among seropositive individuals).

The 20 studies in which MERS-CoV infections were measured by serology and/or molecular testing within health-care settings are listed in Table 2 and include studies of HCWs and close contacts of patients with confirmed infection. The largest molecular and serological studies among HCWs were conducted among 1,695 and 1,169 HCWs in Kingdom of Saudi Arabia (32) and the Republic of Korea (40), respectively; the authors reported evidence of infection of 1% and 1.5%, respectively. Infection was more frequent among HCWs who did not use personal protective equipment when in contact with a patient with MERS (40).

Since 2012, 298 of the 2,274 laboratory-confirmed cases (13.1%) reported to WHO have been reported as asymptomatic at the time of reporting, 164 of these patients were HCWs. The demographic characteristics and clinical presentation of primary and secondary cases of MERS-CoV infection are listed in Table 3. There were significantly more asymptomatic cases reported among secondary cases ($n = 266$ of 1,094; 24.3%) than among primary cases ($n = 9$

of 642 (1.4%); $P < 0.001$). Overall, no deaths were reported among patients with asymptomatic infections. Figure 2 shows the epidemic curve of MERS-CoV infections reported to WHO stratified by HCWs and non-HCWs. Of the 414 MERS-CoV infections among HCWs that were reported to WHO, 164 (39.6%) were reported to be asymptomatic.

Evidence of human-to-human transmission from an asymptomatic infection

We found 4 studies that documented the duration of viral shedding from asymptomatic or mildly symptomatic individuals (55–58). Among asymptomatic, PCR-positive MERS-CoV infections, positive reverse transcriptase (RT)-PCR results were reported from the day of initial testing for as long as 28–42 days (55–58).

We found 1 study in which molecular and serological evidence of possible secondary transmission from asymptomatic individuals was reported (11). The study was conducted as part of an investigation of 12 household contacts, in whom upper respiratory tract samples from 7 were PCR positive and an additional 5 samples were seropositive using recombinant immunofluorescence or plaque reduction neutralization test (11). Eleven of these 12 individuals reported no symptoms at the time of sampling; this information, combined with epidemiologic data, indicated these people could have been involved in asymptomatic transmission within households.

Table 1. Evidence of Middle East Respiratory Syndrome Coronavirus Infection Outside Health-Care Settings, 2012–2018

First Author, Year (Reference No.)	Years of Study	Location of Study	No. of Subjects	Description of Subjects	Laboratory Results	Evidence of Asymptomatic MERS-CoV Infection Among PCR/Serologically Positive Subjects
<i>Occupational Exposure to Dromedaries</i>						
Aburizaiza, 2014 (20)	2012	KSA	226	Slaughterhouse workers	0 (0%) had specific antibodies against MERS-CoV (immunofluorescence assay and neutralization)	
Chu, 2014 (21)	2013	Egypt	179	Camel abattoir workers	0 (0%) had serological evidence of MERS-CoV infection	
Hemida, 2015 (22)	2013–2014	KSA	191	Occupational exposure to dromedary camels	0 (0%) had specific antibodies against MERS-CoV (ppNT)	
Memish, 2015 (23)	2012	KSA	75	Direct contact with domestic animals, including camels	0 (0%) had specific antibodies against MERS-CoV (ppNT)	
Reusken, 2015 (24)	2013–2014	Qatar	294	Daily occupational contact with dromedary camels	10 (3.4%) had specific neutralizing antibodies against MERS-CoV (ELISA and PRNT ₉₀)	10 (100%) reported no severe health problems
Liljander, 2016 (25)	2013–2014	Kenya	1,222	Livestock handlers in Kenya	2 (0.2%) had confirmed serological evidence of MERS-CoV infection (recombinant ELISA, PRNT ₅₀ and PRNT ₉₀)	2 (100%) reported no recent clinical symptoms, indication mild or subclinical infection
So, 2018 (26)	2016	Nigeria	261	Abattoir workers with exposure to dromedaries	0 (0%) had specific neutralizing antibodies against MERS-CoV (ELISA and ppNT)	
Aishukairi, 2018 (27)	2018	KSA	30	Camel herders, truck drivers, and handlers	20 (67%) seropositive for MERS-CoV infection (ELISA, PRNT ₅₀ and MERS-CoV-specific T-cell response)	6 (20%) reported fever or cold in the previous 4 months
Zohaib, 2018 (28)	2016–2017	Pakistan	840	Camel herders	0 (0%) had serological evidence of MERS-CoV infection (ELISA, PRNT ₅₀)	
<i>Contacts of Patients Outside Health-Care Settings Who Had Confirmed MERS</i>						
Health Protection Agency, 2013 (29)	2013	United Kingdom	33	Close contacts of a confirmed case	2 (6%) had molecular evidence of MERS-CoV infection (RT-PCR)	0 (0%) were asymptomatic
Assiri, 2013 (4)	2013	KSA	217	Household contacts of confirmed cases	5 (2%) had confirmed MERS-CoV infection (RT-PCR and viral load)	Not reported
Omrani, 2013 (30)	2013	KSA	10	Household contacts of confirmed cases	0 (0%) had molecular evidence of MERS-CoV infection (RT-PCR)	

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Years of Study	Location of Study	No. of Subjects	Description of Subjects	Laboratory Results	Evidence of Asymptomatic MERS-CoV Infection Among PCR/Serologically Positive Subjects
Mailles, 2013 (31)	2013	France	162	Contacts of a confirmed case	1 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	0 (0%) were asymptomatic
Memish, 2014 (32)	2012–2014	KSA	462	Family contacts of confirmed cases	10 (2%) had molecular evidence of MERS-CoV infection (RT-PCR)	Not reported
Drosten, 2014 (11)	2013	KSA	280	Household contacts of confirmed cases	12 (4%) had laboratory evidence of secondary MERS transmission (RT-PCR, ELISA, recombinant immunofluorescence assay, PRNT ₅₀ , PRNT ₉₀)	11 (92%) were asymptomatic
Arwady, 2016 (33)	2014	KSA	79	Relatives of patients infected with MERS-CoV	11 (14%) had molecular evidence of MERS-CoV infection (RT-PCR); 8 (10%) additional contacts had serological evidence of MERS-CoV infection (ELISA)	2 (11%) reported mild symptoms and 3 (16%) were asymptomatic
Pilpat, 2017 (34)	2015	Thailand	48	High-risk contacts of a confirmed case	0 (0%) had molecular evidence of MERS-CoV infection (RT-PCR)	
Al Hosani, 2019 (35)	2013–2018	United Arab Emirates	124	Case patients and household contacts of patients with MERS-CoV	13 (54%) cases had MERS-CoV antibodies; 0 (0%) household contacts had serological evidence of MERS-CoV infection (ELISA and microneutralization)	3 of 13 case patients (23%) were asymptomatic
Gierer, 2013 (36)	2010–2012	KSA	268	<i>General Population</i> Children hospitalized for lower respiratory tract infection and male blood donors	0 (0%) had specific neutralizing antibodies against MERS-CoV (lentiviral vector system)	
Müller, 2015 (37)	2012–2013	KSA	10,009	Healthy individuals across all 13 provinces of KSA	15 (0.1%) had anti-MERS-CoV antibodies (recombinant ELISA, recombinant immunofluorescence assay, PRNT ₅₀ and PRNT ₉₀)	Not reported
Munyua, 2017 (38)	2013	Kenya	760	Households exposed to seropositive camels	0 (0%) had specific neutralizing antibodies against MERS-CoV (ELISA and PRNT ₅₀)	

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Years of Study	Location of Study	No. of Subjects	Description of Subjects	Laboratory Results	Evidence of Asymptomatic MERS-CoV Infection Among PCR/Serologically Positive Subjects
<i>Retrospective Review of National Surveillance Records</i>						
Al Hosani, 2016 (7)	2013–2014	United Arab Emirates	1,586	Case patients from surveillance records who were suspected to have MERS	65 (4%) had molecular evidence of MERS-CoV infection (RT-PCR)	23 (35%) were asymptomatic
Saeed, 2017 (39)	2015–2016	KSA	57,363	Case patients suspected to have MERS	384 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	19 (5%) were asymptomatic

Abbreviations: ELISA, enzyme-linked immunoassay; KSA, Kingdom of Saudi Arabia; MERS-CoV, Middle East respiratory syndrome coronavirus; PCR, polymerase chain reaction; ppNT, pseudoparticle neutralization test; PRNT₅₀, 50% plaque reduction neutralization test; PRNT₉₀, 90% plaque reduction neutralization test; RT-PCR, reverse transcriptase polymerase chain reaction.

We found 9 studies that described molecular evidence of MERS-CoV infection among asymptomatic individuals in health-care settings (7, 32, 42, 43, 45, 46, 50, 51, 53). Infectivity of an asymptomatic HCW infected with MERS-CoV was investigated in 1 study, but no evidence was found of secondary transmission to 82 HCWs with contact to the HCW with MERS-CoV infection (44).

DISCUSSION

In this review, we found 43 studies in which molecular and/or serological evidence of MERS-CoV infection was reported. Outside of health-care settings, the evidence of MERS-CoV infection has largely been focused on individuals with occupational exposure to dromedaries. The results to date are heterogenous, and although attempts have been made to evaluate MERS-CoV genetic diversity (59, 60), the differences in seroprevalence results to date likely reflect differences in the selection and characteristics of dromedary herds and humans tested. The available evidence of the MERS-CoV epidemiologic and genetic characteristics does not suggest there are differences in the virus's ability to infect humans. Evidence supports that individuals with occupational exposure to dromedaries have higher rates of seroprevalence compared with household contacts of patients with confirmed MERS-CoV infection, likely reflecting more intense, unprotected exposures to MERS-CoV through dromedary secretions (61). That these individuals have subclinical infection and do not develop disease is likely because those with occupational exposure tend to be younger and healthier, without underlying high-risk conditions such as hypertension, diabetes, and renal failure. Variations in the seroprevalence rates by study are also likely due to variations in methodologies, including the timing of sample collection, serologic assays used, and interpretation of assay results.

Although the majority of human MERS-CoV infections have been reported to WHO from countries in the Arabian Peninsula, particularly Kingdom of Saudi Arabia, there is increasing evidence of infection in dromedary camels in herds throughout Africa and South Asia (62). Additional serological and molecular epidemiology studies at the dromedary-human interface using a standardized approach and consistent methodology, in the Arabian Peninsula and in Africa and South Asia, are needed to further understand this observed heterogeneity—that is, whether the observed differences in evidence of infection outside health-care settings may be attributable to genetic variation of the virus across different geographic regions and/or to factors and behaviors in human populations in these regions, which may change the susceptibility to infection. WHO is currently supporting studies underway in several countries in the Middle East, Africa, and South Asia in which the extent of infection in occupationally exposed persons is being evaluated. The results of such studies can contribute to better understanding the geographic reach of MERS-CoV in dromedaries and humans.

Within health-care settings, the detection of asymptomatic, PCR-positive infection has been reported to WHO from affected member states and also documented in 10

Table 2. Evidence of Middle East Respiratory Syndrome Coronavirus Infection in Health-Care Settings, 2012–2018

First Author, Year (Reference No.)	Years of Study	Location of Study	No. of Individuals Tested	Description of Subjects	Laboratory Results	Evidence of Asymptomatic MERS-CoV Infection Among PCR/Serologically Positive Subjects
Health Protection Agency, 2013 (29)	2013	United Kingdom	59	HCW	0 transmission (RT-PCR)	
Memish, 2014 (32)	2012–2013	KSA	1,695	HCW	19 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	2 (11%) were asymptomatic; 5 (26%) had mild infection
Kim, 2016 (40)	2015	ROK	1,169	HCW	17 (1%) had evidence of MERS-CoV infection, higher among HCWs who did not use PPE (ELISA and indirect immunofluorescence test)	
Cho, 2016 (41)	2015	ROK	218	HCW	8 (4%) had molecular evidence of MERS-CoV infection (RT-PCR)	
Park, 2016 (42)	2015	ROK	519	HCW	3 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	3 (100%) were asymptomatic
Hastings, 2016 (43)	2014	KSA	16	HCW	14 (88%) had molecular evidence of MERS-CoV infection (RT-PCR)	13 (81%) were asymptomatic
Moon, 2017 (44)	2015	ROK	82	HCW	0 transmission from asymptomatic HCWs (RT-PCR and ELISA)	
Alfaraj, 2019 (45)	2015	KSA	153	HCW	7 (5%) had molecular evidence of MERS-CoV infection (RT-PCR)	5 (71%) were asymptomatic
Amer, 2018 (46)	2017	KSA	879	HCW	17 (2%) had molecular evidence of MERS-CoV infection (RT-PCR)	17 (100%) were asymptomatic or had mild disease
Amer, 2018 (47)	2017	KSA	107	HCW	9 (8%) positive for MERS-CoV (RT-PCR)	
Alshukairi, 2016 (48)	2014–2016	KSA	NR	HCW	18 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA)	6 (33%) were asymptomatic
Assiri, 2016 (49)	2014–2015	KSA	NR	HCW	7 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA, MT)	4 (57%) were asymptomatic
Balkhy, 2016 (50)	2015	KSA	NR	HCW	43 had molecular evidence of MERS-CoV infection (RT-PCR)	25 (58%) were asymptomatic

Table continues

Table 2. Continued

First Author, Year (Reference No.)	Years of Study	Location of Study	No. of Individuals Tested	Description of Subjects	Laboratory Results	Evidence of Asymptomatic MERS-CoV Infection Among PCR/Serologically Positive Subjects
Al Hosani, 2016 (7)	2013–2014	United Arab Emirates	NR	HCW	31 had molecular evidence of MERS-CoV infection (RT-PCR)	12 (39%) were asymptomatic
Alenazi, 2017 (51)	2015	KSA	NR	HCW	43 had molecular evidence of MERS-CoV infection (RT-PCR)	18 (42%) were asymptomatic
2018 ^a	2012–2018	Global	NR	HCW	389 had laboratory-confirmed MERS-CoV infection	94 (24%) were asymptomatic
Al-Abdallat, 2014 (5)	2012–2013	Jordan	124	Contacts identified during MERS outbreak	<i>MERS-CoV Infection in Health-Care Settings Among Non-HCWs</i> 9 (7%) had serological evidence of MERS-CoV infection (ELISA, IFA, MT)	0 (0%) were asymptomatic
Cho, 2016 (41)	2015	ROK	675	Patients in hospital, contacts of patients infected with MERS-CoV	33 (5%) had molecular evidence of MERS-CoV infection (RT-PCR)	
Oboho, 2015 (52)	2014	KSA	NR	Confirmed MERS-CoV infection	<i>Extent of Asymptomatic Infection Among Laboratory-Confirmed MERS Cases</i> 255 had molecular evidence of MERS-CoV infection (RT-PCR)	64 (25%) patients were asymptomatic, although 26 patients interviewed reported at least 1 symptom consistent with respiratory illness
Assiri, 2016 (49)	2014–2015	KSA	NR	Confirmed MERS-CoV infection	38 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA, MT)	2 (5%) were asymptomatic
Alenazi, 2017 (51)	2015	KSA	NR	Patient contacts in hospital	61 had molecular evidence of MERS-CoV infection (RT-PCR)	3 (5%) were asymptomatic
Zhao, 2017 (53)	2015	KSA	NR	MERS survivors	18 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA, MT, PRNT ₅₀ , and MERS-CoV-specific T-cell response)	3 (17%) were asymptomatic; patients with higher PRNT ₅₀ and T-cell responses had longer stays in the intensive care unit
Payne, 2018 (54)	2015–2016	Jordan	NR	Patient-contacts in hospital	16 had laboratory-confirmed MERS-CoV infection (RT-PCR, ELISA, MT)	3 (19%) were asymptomatic

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HCW, health-care worker; IFA, immunofluorescence assay; KSA, Kingdom of Saudi Arabia; MERS-CoV, Middle East respiratory syndrome coronavirus; MT, microneutralization assay; NR, not reported; PPE, personal protective equipment; PRNT, plaque reduction neutralization test; ROK, Republic of Korea; RT-PCR, reverse transcriptase polymerase chain reaction.

^a World Health Organization, unpublished data, 2018.

Table 3. Description of Characteristics of Middle East Respiratory Syndrome Coronavirus Infection Reported to World Health Organization from September 2012 to November 27, 2018

MERS Case Characteristic	Reported Source of Infection					
	Outside Health-Care Setting		Within in Health-Care Setting		Not Known at the Time of Reporting to WHO	
	No.	%	No.	%	No.	%
Case classification	764		826		681	
Primary case ^a	561	73.4	2	0.2	79	11.6
Secondary case ^b	193	25.3	816	98.8	85	12.5
Unknown at the time of reporting	10	1.3	8	1.0	517	75.9
Primary MERS-CoV infection ^a						
Age, years ^c	55.9 (45.0–69.0)		47.0 (39.0–55.0)		57.8 (46.0–72.0)	
Sex						
Male	459	81.8	2	100	72	91.1
Female	102	18.2	0	0	5	6.3
Comorbidity						
Any	316	56.3	1	50	17	21.5
None	62	11.1	0	0	3	3.8
Not reported	183	32.6	1	50	59	74.7
Clinical presentation						
Asymptomatic	7	1.2	0	0	2	2.5
Symptomatic	521	92.9	2	100	65	82.3
Not reported	33	5.9	0	0	12	15.2
Outcome						
Survived	167	29.8	1	50	14	17.7
Died	277	49.4	0	0	32	40.5
Not reported	117	20.8	1	50	33	41.8
Secondary MERS-CoV infection ^b						
Age, years ^c	40.7 (27.0–54.0)		49.3 (34.0–62.0)		42.7 (28.0–54.0)	
Sex						
Male	124	64.2	451	55.3	51	60
Female	69	35.8	365	44.7	34	40
Comorbidity						
Any	47	24.4	281	34.4	13	15.3
None	43	22.3	104	12.7	10	11.8
Not reported	103	53.4	431	52.8	62	72.9
Clinical presentation						
Asymptomatic	74	38.3	180	22.1	12	14.1
Symptomatic	103	53.4	482	59.1	51	60
Not reported	16	8.3	154	18.9	22	25.9
Outcome						
Survived	127	65.8	337	41.3	28	32.9
Died	27	14.0	248	30.4	20	23.5
Not reported	39	20.2	231	28.3	37	43.5

Abbreviations: IQR, interquartile range; MERS-CoV, Middle East respiratory syndrome coronavirus; WHO, World Health Organization.

^a Primary infection: reported direct or indirect contact with dromedary camels, no contact with a probable or confirmed MERS-CoV infected human case, no prior health care facility contact ($n = 642$).

^b Secondary infection: direct epidemiologic link to a human MERS infection ($n = 1,094$).

^c Values are expressed as mean (interquartile range).

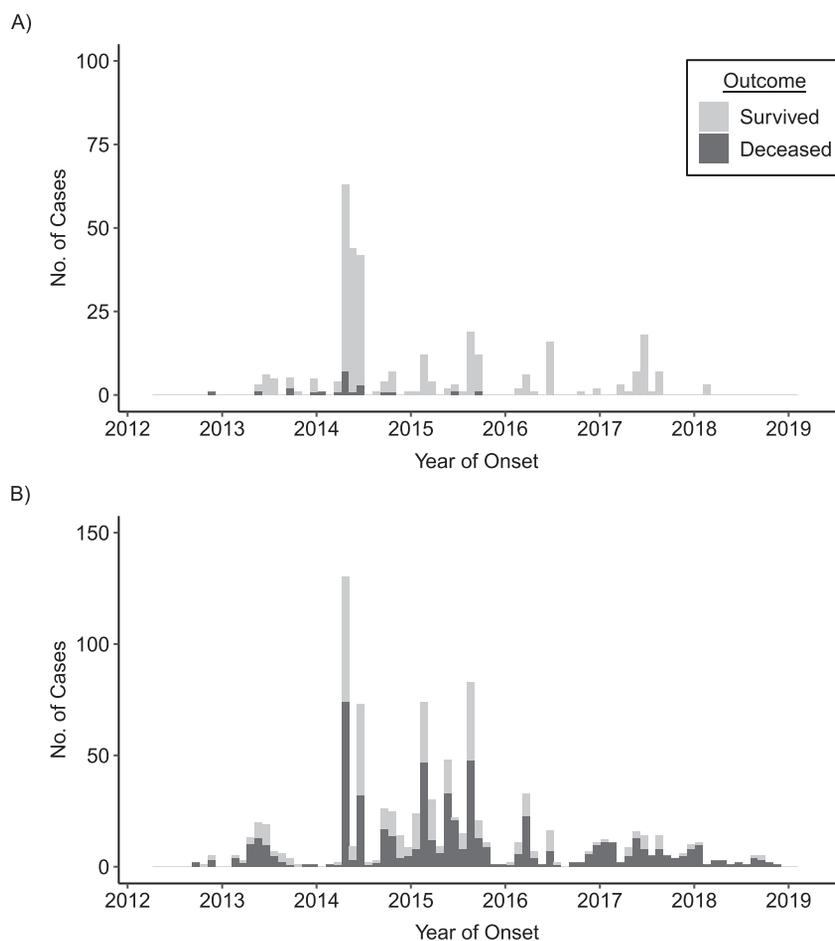


Figure 2. Epidemic curve of laboratory-confirmed Middle East respiratory syndrome coronavirus infections among A) health-care workers and B) non-health-care workers and outcome reported to the World Health Organization from 2012 to November 27, 2018.

published studies. Although onward transmission was not investigated in those studies, the researchers did capture evidence of RNA shedding, which suggests human-to-human transmission is possible from individuals with no signs or symptoms of infection. This is supported by evidence documenting duration of viral shedding beyond 3 weeks in patients with subclinical MERS-CoV infection (55–58).

At the same time, the evidence for acute, asymptomatic MERS-CoV infection described in this review does not represent the full extent of subclinical infection. Asymptomatic contacts clear the virus more quickly than do symptomatic patients (58) and antibody titers in the former are likely to be lower, if they seroconvert at all, than in infected patients exhibiting symptoms (63). Timely and repeated biological specimen collection is needed to capture viral shedding and antibody kinetics of symptomatic and asymptomatic contacts (11). This can be achieved if all high-risk contacts of patients with confirmed MERS-CoV infection are identified during an outbreak and then tested using molecular and serologic laboratory assays, regardless of whether the individual exhibits symptoms. In outbreak settings, without

the inclusion of testing of all contacts, the identification of chains of transmission may be incomplete.

Indeed, the latest WHO surveillance guidelines recommend that all contacts of patients with laboratory-confirmed MERS outside of health care facilities should be placed under active surveillance for 14 days after the last exposure to the confirmed case and that any contacts with symptoms of respiratory illness should be tested for MERS-CoV infection (64). If feasible, we recommend that follow-up should include molecular testing, regardless of the development of symptoms. In addition, studies conducted of high-risk workers, which have typically only included serologic testing, should also include molecular testing of upper respiratory samples in an attempt to capture viral carriage.

Despite these limitations in our current knowledge, the findings of our review reinforce the evidence that HCWs are more likely to be at risk of MERS-CoV infection due to close unprotected contact with patients with MERS patients prior to their diagnosis, particularly when aerosolizing procedures are performed. Because HCWs tend to be younger and healthier than patients in whom severe MERS develops,

HCWs have fewer symptoms, if any, and present a silent risk of human-to-human transmission to others. Among HCW contacts, detailed studies of viral shedding and immune response of asymptomatic, PCR-positive MERS-CoV infections are urgently needed and should be conducted when outbreaks occur and enhanced surveillance is put in place by government and hospital officials.

Surveillance and testing for MERS-CoV have improved substantially since the virus was first discovered in 2012. In affected countries, visual respiratory triage systems before a patient enters the emergency department have been introduced; some emergency departments in affected countries have been restructured for enhanced triage of patients with respiratory symptoms; trainings specific to infection prevention and control of respiratory pathogens have been introduced and reintroduced in high-risk areas and hospitals with high turnover of HCWs; and audits of hospitals for compliance to specific infection prevention and control measures are regularly performed (6). In addition, the systematic testing of HCWs, extending beyond nurses and doctors to include reception staff, cleaners, technicians, and so forth, regardless of the development of symptoms, as required by the latest infection prevention and control guidelines for HCWs by WHO and Kingdom of Saudi Arabia, for example, has detected subclinical and asymptomatic infections that likely would have gone undetected in past outbreaks. Asymptomatic infections may have played a role in extensive secondary transmission in health-care settings before the latest guidelines were introduced, and the impact of such policies may be reflected in the lower peaks on the global MERS-CoV epidemic curve since 2016. Without this level of contact follow-up in community settings, the extent of asymptomatic infections in the community will remain unknown.

Screening of HCWs with exposure to patients infected with MERS-CoV may be feasible for preventing human-to-human transmission in health-care settings, and appears to be effective in Kingdom of Saudi Arabia and other affected countries in which this infection prevention and control measure has been introduced. Screening of non-HCW contacts in health-care settings should also be encouraged. Outside health-care settings, the feasibility of screening may be reduced, particularly given the difficulty in detecting asymptomatic infections. Therefore, transmission of MERS-CoV outside health-care settings should be expected to continue until zoonotic spillover from dromedaries can be interrupted.

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