

# Follow-up of Contacts of Middle East Respiratory Syndrome Coronavirus–Infected Returning Travelers, the Netherlands, 2014

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Notification of 2 imported cases of infection with Middle East respiratory syndrome coronavirus in the Netherlands triggered comprehensive monitoring of contacts. Observed low rates of virus transmission and the psychological effect of contact monitoring indicate that thoughtful assessment of close contacts is prudent and must be guided by clinical and epidemiologic risk factors.

During April 2012–May 2015, the World Health Organization received 1,110 notifications of confirmed cases of infection with Middle East respiratory syndrome coronavirus (MERS-CoV), including at least 422 deaths (1,2), mostly from countries in the Arabian Peninsula. Travel-related cases have been reported in Europe, Asia, and the United States, with limited, local, person-to-person secondary transmission (3).

Although dromedary camels are considered to be the probable source for zoonotic infections in humans, the mode of transmission from animals to humans is not understood (4). In 2014, Saudi Arabia experienced an outbreak due to increased zoonotic transmission and amplification by health care–related human-to-human transmission (3); the risk for secondary transmission from patients to household contacts was estimated at  $\approx 5\%$  (5). To prevent secondary cases and

local transmission, the World Health Organization recommends monitoring all contacts of confirmed patients (6).

On May 13 and 14, 2014, MERS-CoV infection was confirmed in 2 residents of the Netherlands who had taken pilgrimages to Medina and Mecca, Saudi Arabia (7). We undertook comprehensive monitoring of contacts of these patients and evaluated the risk for secondary transmission and the effects of the monitoring on the contacts.

## The Study

Formal ethical approval from a medical ethical committee was not required for this research because it was carried out as part of the public health monitoring and evaluation of contacts and did not entail subjecting participants to medical treatment. From the onset of symptoms in the 2 MERS-CoV patients (May 1) until their discharge from the hospital (June 5), they came into contact with 131 persons. Of these, 78 had unprotected exposure (defined as  $>15$  min of face-to-face contact without wearing personal protective equipment) and 53 had protected exposure (defined as providing care while wearing adequate personal protection at all times). Of the unprotected contacts, 29 were members of the patients' travel group, 17 were aircraft contacts, and 32 were contacts in the Netherlands before hospital admission (28 relatives plus 4 persons at a general medical practice and the hospital emergency department, including 1 health care worker). The travel group had traveled with the 2 confirmed case-patients through Saudi Arabia during April 26–May 10 and had direct contact with them. Four travelers reported direct contact with dromedary camels, 11 consumed unpasteurized camel milk, and 4 visited a local hospital. One traveler accompanied 1 case-patient to 4 different hospitals and shared a hotel room with both case-patients (7). The aircraft contacts had been seated within 3 rows of the case-patients on the return flight.

All contacts were asked to take their temperature twice a day and report any episode of fever (temperature  $\geq 38^\circ\text{C}$ ), cough, diarrhea, or dyspnea for 14 days following their last possible exposure to the case-patients. Unprotected contacts were asked to remain in the country during the monitoring period. Throat swabs were obtained from contacts on days 7 and 14 postexposure, and serum samples were drawn on days 7 and 21 postexposure (online Technical Appendix, <http://wwwnc.cdc.gov/EID/article/21/8/>)

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**Table 1.** Laboratory results and compliance of follow-up among 131 unprotected and protected contacts of 2 patients with imported MERS-CoV infections, the Netherlands, 2014\*

Type of contact	No. persons	Male sex, %	Median age, y (range)	No. (%) contacts				
				First throat swab sample	Paired throat swab sample	First serum sample	Paired serum sample	Symptomatic
Unprotected contacts	78	40	45 (1–78)	77 (99)	77 (99)	77 (99)	67 (86)	7 (9)
Travel group	29	45	52 (9–70)	29 (100)	29 (100)	29 (100)	28 (97)	2 (7)
Aircraft contacts	17	47	39 (7–78)	17 (100)	17 (100)	17 (100)	14 (82)	2 (12)
Other contacts†	32	32	44 (1–64)	31 (97)	31 (97)	31 (97)	25 (78)	3 (9)
Protected contacts	53	34	36 (18–63)	44 (83)	29 (55)	53 (100)	32 (60)	1 (2)
Total contacts	131	37	41 (1–78)	121 (92)	106 (81)	130 (99)	99 (76)	8 (6)

\*MERS-CoV, Middle East respiratory syndrome coronavirus.

†Other contacts were those who had contact with the case-patients after their return to the Netherlands: 28 relatives, plus 4 persons at a general medical practice and the hospital emergency department, including 1 health care worker.

15-0560-Techapp1.pdf). Throat swab samples from 1 relative contact were unavailable; a second serum sample was missing from 7 relatives, 3 aircraft contacts, and 1 travel contact (a woman who had had no contact with animals, had not visited a hospital, and had no concurrent conditions). Eight contacts who reported symptoms (7 unprotected and 1 protected) were sampled immediately after onset of symptoms. MERS-CoV reverse transcription PCR (RT-PCR) was performed on paired throat swabs from 106 (81%) and serologic analysis on paired serum samples from 99 (76%) of the 131 contacts (Table 1). PCR did not detect MERS-CoV RNA from any throat swab or serum samples, and MERS-CoV-specific IgG responses were absent in serum samples tested (8) (Table 1). All specimens obtained from the symptomatic contacts tested negative by RT-PCR and analysis of paired serum samples for MERS-CoV.

All contacts also received an online questionnaire containing questions about demographics, type of contact, quality of information received, perceived severity and vulnerability, feelings of anxiety, interference of the measures with daily life, and knowledge of the measures and travel advice (online Technical Appendix). To evaluate the effect of monitoring, we used the Revised Impact of Event Scale (IES-R), a validated questionnaire designed to assess current subjective distress for a specific traumatic life event (9). The IES-R contains 22 items divided into 3 subscales: avoidance (e.g., avoidance of feelings), intrusion (e.g., nightmares) and hyperarousal (e.g., anger). The mean score on 3 subscale domains indicates the level of distress experienced (9). Mean scores of unprotected contacts were compared with those of protected contacts by a Wilcoxon rank-sum test or *t*-test. Significance was determined at the 5% level (*p* value  $\leq 0.05$ ). A

total subjective stress IES-R score with a maximum score of 88 (Likert scale of 0–4 [0, never; 1, seldom; 2, sometimes; 3, often; 4, very often]) can be calculated. We considered a score  $\geq 20$  to be an indicator of posttraumatic stress disorder to enable comparison with previous studies (10,11).

Of 131 contacts, 72 (55%, 48 unprotected and 24 protected) filled out the questionnaire. The median age was 39 years (range 9–77 years); 53% were female, and 51% had at least a college education. Protected contacts were younger (median of 31 vs. 48 years) and had a higher education (88% vs. 31%) than unprotected contacts. The mean IES-R score of all contacts was 7.9 (95% CI 5.5–10.3); the score was  $\geq 20$  for 16 (22%) contacts. Unprotected contacts had a significantly higher mean IES-R score (10.4 95% CI 7.2–13.6 versus 2.9, 95% CI 0.6–5.3); this result was also seen on the different subscale domains (Table 2).

## Conclusions

We monitored 131 contacts of 2 case-patients with imported MERS-CoV infections in the Netherlands. Laboratory testing did not indicate transmission of the virus, including among contacts with high-risk exposures or those who developed respiratory symptoms. We also found no infections among travelers from the same group. Our findings agree with reports from Greece and Italy, in which no and limited secondary transmission, respectively, was found among close contacts of MERS-CoV patients (12,13).

Survey results show a substantial psychological effect of monitoring on contacts, especially unprotected contacts. As with other emerging infections, such as Marburg hemorrhagic fever and severe acute respiratory syndrome, quarantine or monitoring of contacts leads to psychological

**Table 2.** Results of survey assessing psychological effects of monitoring among 72 contacts of 2 patients with imported MERS-CoV infections, stratified by unprotected versus protected contacts, the Netherlands, 2014\*

Category	Mean IES-R score (95% CI)		
	All contacts	Unprotected contacts	Protected contacts
Total IES-R score	7.9 (5.5–10.3)	10.4 (7.2–13.6)	2.9 (0.6–5.3)
Avoidance	2.2 (1.3–3.1)	3.1 (1.8–4.3)	0.5 (–0.04–1.1)
Intrusion	3.4 (2.5–4.4)	4.3 (3.1–5.5)	1.8 (0.5–3.0)
Hyperarousal	2.0 (1.3–2.7)	2.7 (1.7–3.6)	0.6 (–0.04–1.3)

\*IES-R, Revised Impact of Event Scale.

distress, measured by high IES-R scores (10,11,14). When stratifying by type of contact, the total mean IES-R score and the subscale scores were highest for unprotected contacts—those with the highest risk for exposure. We found increased symptoms of posttraumatic stress disorder in a considerable number of contacts, similar to findings by Hawryluck et al. (11) and Reynolds et al. (10).

The survey response rate of 55% limits interpretation of results; motives for noncompliance remain unknown. Also, recall bias might influence recollection of experiences. Besides exposure, monitoring has contributed to the psychological effect. Whether the number of questions induced stress is not known, but participants did not mention this as a concern.

Our findings illustrate the feasibility of comprehensive follow-up of contacts of MERS-CoV patients and clarify the risk for asymptomatic secondary transmission. The psychological effect of contact monitoring and the observed low rates of MERS-CoV transmission in several studies, including this investigation, indicate that thoughtful but limited assessment of close contacts is prudent. Identification of close contacts of those who are infected should be carefully considered, and decisions about monitoring and testing of contacts should be made primarily on the basis of clinical and epidemiologic risk factors.

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## Technical Appendix

### **Part 1: Laboratory methods for PCR detection of MERS-CoV and antibody detection**

Total RNA was extracted from 200  $\mu$ L Universal Transport medium (COPAN) by using the High Pure RNA isolation kit (Roche, Mannheim, Germany) and tested for MERS-CoV RNA by internally controlled real-time reverse transcription PCR targeting Orf1A, nucleocapsid, and UpE with the TaqMan Fast Virus 1-Step Master Mix (Applied Biosystems, Bleiswijk, the Netherlands) as described (1–3). The results were independently confirmed in 2 laboratories (RIVM and Erasmus MC) and samples were considered MERS-CoV positive when at least 2 different MERS-CoV specific targets were reactive (4).

Serum samples were tested in at a 1:20 dilution for IgG reactive with MERS-CoV (residues 1–747), severe acute respiratory syndrome–CoV (residues 1–676) and human coronavirus OC43 (residues 1–760) spike domain S1 antigens by using extensively validated protein-microarray technology, as described (3,5). Confirmation was performed by using a neutralization assay (4).

### **Part 2: Questionnaire to assess knowledge, quality of information, perceptions of severity and vulnerability and interference of measures with daily life**

All contacts received an invitation by post including a link and a unique code to access an online questionnaire (Formdesk, Innovero Software Solutions B.V., The Hague, The Netherlands). The questionnaire contained precoded questions on demographics, type of contact, quality of information received, perceived severity and vulnerability, feelings of anxiety, perceived interference with daily life, and knowledge (including questions regarding travel advice for the travel group). The questionnaire was based on questionnaires used in

similar studies on severe acute respiratory syndrome, infection with avian influenza, infection with influenza A (H1N1) virus, and Marburg hemorrhagic fever (6–10), with some alterations.

Questions on perceived severity and vulnerability, feelings of anxiety, and perceived interference with daily life (e.g., restrictions on social life and fear of becoming infected) were based on an integrated model designed to explain health behavior (11,12). Knowledge of MERS-CoV was examined with 7 true/false/don't know statements. The members of the travel group (n = 29) were also asked to answer questions regarding the travel advice they had received before their trip to Saudi Arabia. The presence of concurrent conditions and use of medicines were not part of this questionnaire, but were addressed in another study and published elsewhere (13). The questionnaire took ≈15 min to fill out and the information was processed anonymously.

## **Data Analysis**

Differences in knowledge, impact of monitoring measures, quality of information, and perception between unprotected and protected contacts were compared in contingency tables by using the  $\chi^2$  test. For assessing knowledge, a summary score was created on the basis of the number of correct answers (range 0–7). Significance was determined at the 5% level ( $p \leq 0.05$ ). Data analysis was performed with SAS 9.3 (SAS Institute, Cary, NC, USA).

## **Results**

### **Demographics**

Of the 131 contacts, 72 (55%) filled out the questionnaire. Among the unprotected contacts, the response rate was highest for the travel group (22 [76%] of 29), compared with 19 (59%) of 32 for the other unprotected contacts and 7 (41%) of 17 for the aircraft contacts. Among the protected contacts the response rate was 24 (45%) of 53. The median age of respondents was 39 years (range 9–77 years), 53% were female, and 51% had at least a college education. Protected contacts were younger (median of 31 years vs. 48 years) and had more education (88% vs. 31%) than unprotected contacts.

### **Knowledge of MERS-CoV**

Most (83%) contacts were aware of the symptoms related to MERS-CoV infection and knew that MERS-CoV is not common in the Netherlands (83%) (Table 1). In total, 76% of

the contacts knew that MERS-CoV could spread by having contact with a camel. Half of the contacts knew MERS-CoV can be transmitted from person to person. Half of the respondents knew that there is no specific treatment for MERS-CoV; one-third (36%) thought a vaccine was available. On the knowledge sum score, protected contacts (5.1, 95% CI 4.5–5.6) scored significantly higher than unprotected contacts (3.8, 95% CI 3.3–4.3).

### **Perception of MERS-CoV and Interference of the Measures with Daily Life**

#### Perception

Most contacts (n = 54; 75%) perceived MERS-CoV as being (very) serious (Table 2). In addition, 69% of contacts (n = 50) thought MERS-CoV would have a (very) negative impact on their health. However, only 49% (n = 35) of the persons thought about MERS-CoV (very) often in the last month. Unprotected contacts thought significantly more often about MERS-CoV than did protected contacts (p = 0.02).

#### Interference of the Measures with Daily Life

Only 4% (n = 3) of contacts regularly perceived measuring or reporting their temperature as a burden. Most contacts (90%, n = 65) were not planning to leave the Netherlands and 93% experienced no problems with this measure. Extra costs were involved for 21 (29%) of the contacts. Being identified as a contact caused anxiety in respondents, and 38 (53%) of them were afraid of contracting MERS-CoV or infecting their families (53%, n = 38). These numbers were higher for unprotected than protected contacts (69%, [n = 33] vs. 21%, [n = 5] and 65%, [n = 31] vs. 29%, [n = 7]) respectively. Furthermore, approximately one-third of the contacts reported that their family members expressed anxiety about becoming infected (35%, n = 25). There were no protected contacts who felt seriously limited in their social contacts because of the measurements they had to take, compared with 16 unprotected contacts (22%) who did feel limited.

#### Information on MERS-CoV

Written instructions with detailed information on the monitoring measures and their rationale were received by 53 (74%) of 72 respondents. Of these 53 respondents, 41 (77%) found the information to be clear, 33 (73%) complete, 30 (56%) unequivocal. Only 4 (8%) thought the information was confusing, and 2 (4%) thought it was redundant. In total, 25 (47%) thought the information was clear, complete, and unequivocal.



## Travel Advice

Twenty-three of the 29 participants to the pilgrimage trip to Saudi Arabia filled out this part of the questionnaire; 21 (91%) received travel advice or vaccinations before the trip (the other 2 were already vaccinated, for example against meningococcal disease and DTP, because of previous traveling). During the pretravel consultation, only 1 person received information on the possible transmission of MERS-CoV in the Middle East (avoid contact with animals, avoid drinking unpasteurized milk, and when having symptoms contact a doctor when returning to the Netherlands). However, although most did not receive any advice, 8 persons watched their health more carefully (35%), 9 reported that they were more compliant with personal hygiene measures during the trip (39%), 3 avoided contact with animals (13%), and 3 avoided contact with animals' waste (13%). Twelve did not change their behavior after receiving travel advice (52%).

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**Table 1.** Middle East respiratory syndrome coronavirus general knowledge among contacts (n = 72) stratified by protected vs. unprotected contacts, the Netherlands 2014

Statement (correct answer)	All contacts (n = 72)		Unprotected contacts (n = 46)		Protected contacts (n = 26)		p value
	No. correct	% Correct	No. correct	% Correct	No. correct	% Correct	
Patients with MERS have a fever, are coughing, are short of breath, have difficulties breathing and have diarrhea (true)	60	83	37	77	23	96	0.04
MERS is prevalent in the Netherlands (false)	60	83	38	79	22	92	0.20
MERS is a bacterium causing severe lung disease (false)	13	18	6	13	7	31	0.08
In the Middle East MERS can be contracted through contact with camels or their products such as meat, milk, urine or feces (true)	55	76	34	71	21	88	0.11
MERS can be spread from person to person (true)	36	50	20	42	16	69	0.05
There is no specific treatment once you contract MERS (true)	36	50	24	50	12	50	1.00
There is a vaccine available for MERS (false)	46	64	48	56	19	81	0.06
Average number of correct answers (95% CI)	4.3 (3.8–4.7)		3.8 (3.3–4.3)		5.1 (4.5–5.6)		0.01

**Table 2.** MERS-CoV general perception among all contacts (n = 72) and stratified by unprotected- vs. protected contacts, the Netherlands 2014

Perception	Total (n = 72)		Unprotected contacts (n = 46)		Protected contacts (n = 26)		p value
	No.	%	No.	%	No.	%	
MERS is (very) serious to contract	54	75	34	71	20	83	0.3
MERS is (very) bad for my health	50	69	32	67	18	75	0.5
I have thought about MERS (very) often in the last month	35	49	28	60	7	29	0.02