

# Middle East respiratory syndrome coronavirus (MERS-CoV) infections in two returning travellers in the Netherlands, May 2014

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**Two patients, returning to the Netherlands from pilgrimage in Medina and Mecca, Kingdom of Saudi Arabia, were diagnosed with Middle East respiratory syndrome coronavirus (MERS-CoV) infection in May 2014. The source and mode of transmission have not yet been determined. Hospital-acquired infection and community-acquired infection are both possible.**

On 13 May 2014, a Dutch patient, returning to the Netherlands from pilgrimage in Medina and Mecca, Kingdom of Saudi Arabia, was diagnosed with Middle East respiratory syndrome coronavirus (MERS-CoV) infection, followed by diagnosis of a second patient, belonging to the same tour group, the day after. Here we describe the two cases and the public health response. The case definition that is used in the Netherlands is outlined in the Box.

## Case 1

A 70 year-old male patient with cardiovascular comorbidities and diabetes mellitus was diagnosed with MERS-CoV infection on 13 May. He had been in Medina since 26 April, together with a group of 30 other travellers. During the whole journey, he shared the hotel rooms with his adult son and another family member (see below). On 29 April, while still in good health, he accompanied his son to two hospitals (Hospitals 1 and 2), both in Medina, as the son had a minor health problem unrelated to MERS CoV. He spent 45 minutes in the waiting room, reportedly among many coughing people in Hospital 1. On 1 May, he experienced diarrhoea,

nausea and anorexia and felt feverish, but had no respiratory complaints. The diarrhoea remitted after loperamide treatment. On 4 May, the group of travellers, including the patient, continued to Mecca. On 5 May, he was seen at Hospital 3 for malaise, again diarrhoea, anorexia. On 7 May, he was physically examined at Hospital 4 and dismissed after three hours of observation and intravenous cefuroxime. During the flight home to the Netherlands, on 10 May, the patient's condition deteriorated: on arrival, he visited a Dutch hospital, presenting with cough and dyspnoea. Apart from a temperature of 38.2 °C (after paracetamol 37.3 °C, both measured in the ear), the physical examination was normal. Laboratory results showed a mild leuco- and lymphopenia, a C-reactive protein level of 72 mg/L (norm: 0–8 mg/L) and slightly elevated levels of troponin T (0.034 µg/L; norm: <0.014 µg/L) and creatinine (123 µmol/L; norm: 65–115 µmol/L). In 2012, the patient had had a troponin T level of 0.010, with a stable and mild pre-existing chronic kidney disease with a creatinine level of 113–136 µmol/L. He was admitted to the cardiology ward with possible cardiovascular disease and isolation precautions were taken because of an unspecified infection. Reassessment of his chest X-ray the next day revealed an infiltrate. On 13 May, MERS-CoV infection was confirmed. Lung examination then revealed extensive crepitations and a chest-X-ray showed bilateral infiltrates. Myocarditis was ruled out by magnetic resonance imaging of the heart. He is currently recovering.

## Box

### Middle East respiratory syndrome coronavirus (MERS-CoV) case definition and definition of contacts used in the Netherlands

<b>Suspected case</b> Patient with a severe acute respiratory tract infection with: – fever ( $\geq 38$ °C) <sup>a,b</sup> and respiratory symptoms AND – an infiltrate on an X-ray of the lungs, or acute respiratory distress syndrome AND – travel history to an area <sup>c</sup> with notified MERS-CoV ( $< 14$ days before the onset of symptoms) OR a patient who has been in contact with a confirmed symptomatic MERS-CoV case ( $< 14$ days before onset of symptoms) OR a patient who is part of a cluster of two or more epidemiologically linked cases with an unknown causal agent for whom admission to an intensive-care unit is necessary, within a period of 14 days, irrespective of travel history.
<b>Confirmed case</b> A person with laboratory-confirmation of MERS-CoV infection (positive PCR, with or without confirmation by sequencing).
<b>Close contact</b> – face-to-face contact ( $> 15$ minutes) within a household or other closed setting OR – a healthcare worker, providing clinical or personal care to a confirmed, symptomatic case or who was in the same room as a patient during an aerosol-generating procedure and who did not wear adequate personal protection – flight contact (seated in the same row or three rows in front of/behind a confirmed case).
<b>Protected hospital contact</b> A healthcare worker, providing clinical or personal care to a confirmed, symptomatic case or who was in the same room as a patient during an aerosol-generating procedure and who did wear adequate personal protection.
Contacts were requested to measure their temperature twice daily and report any episode of fever, cough, dyspnoea or diarrhoea for a period of 14 days post exposure. Close contacts were approached on a daily basis by the regional public health service. Protected hospital contacts were expected to report health complaints without having daily follow-up. Throat and serum samples of all contacts were examined on days 7 and 14 (molecular testing) and 7 and 21 (serology) post exposure.

<sup>a</sup> Or a feverish feeling in elderly people, as they do not always develop fever.

<sup>b</sup> An immunocompromised patient with a severe infection of any origin, who meets the epidemiological criteria, i.e. contact with a MERS-CoV confirmed case or stay in area with MERS-CoV notified cases, both  $< 14$  days before onset of symptoms.

<sup>c</sup> Since 1 April 2013, the Middle East, especially Jordan, Saudi Arabia, Qatar and the United Arab Emirates.

## Case 2

During contact investigations, the 73 year-old sister of the patient (with cardiovascular co-morbidities, chronic kidney disease and diabetes mellitus) was found to be symptomatic and was diagnosed with MERS-CoV infection late in the night of 14 May. She had shared the hotel rooms during the entire trip with Case 1 and his adult son and developed symptoms on 5 May, having diarrhoea, feeling feverish (not measured, slight cough and slight dyspnoea). She had not sought medical care in Saudi Arabia. During a routine check-up by a general practitioner in the Netherlands on 12 May, she did not have a fever, but a slight cough and extensive crepitations of both lungs. The general practitioner considered MERS-CoV infection, because of the recent travel history, but did not arrange for diagnostic tests to be carried out as the patient did not meet the definition of a suspected case (no fever, no acute respiratory distress syndrome). Following contact tracing for Case 1, samples were taken from her and she was diagnosed with MERS-CoV infection. Following the diagnosis, she was admitted to hospital on 15 May where a chest X-ray showed bilateral infiltrates. She is currently recovering.

The travel route and a timeline of events for the two cases are shown (Figures 1 and 2).

## Laboratory findings

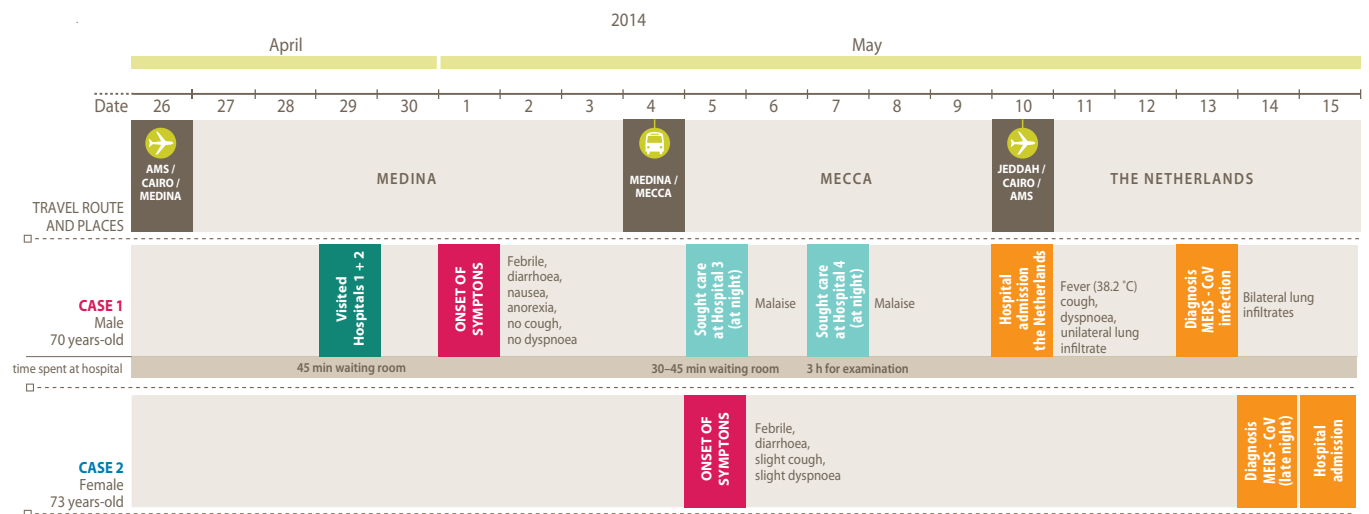
Diagnosis of MERS-CoV infection was done using an internally controlled real-time reverse transcription (RT)-PCR using nucleic acid extracts from throat swabs and published upE, N-gene and ORF1A primers [1,2] according to International Organization for Standardization (ISO) guidelines (ISO 15189:2003) [3]. The results were independently confirmed in two laboratories, Erasmus MC in Rotterdam and the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Netherlands [4]. During extensive follow-up sampling, MERS-CoV RNA was detected in throat swabs, serum and stools from both cases (Table). Case 2 had detectable MERS-CoV RNA in a throat swab, but not in a nose swab (data not shown), both collected on day 0 (date of diagnosis). Follow-up of the patients is still ongoing.

Throat swabs of both cases tested on day 0 (the day MERS-CoV was diagnosed) were negative by real-time RT-PCR for 15 other respiratory viruses (influenza A and B virus, respiratory syncytial virus types A and B, human metapneumovirus, HCoV-OC43, -229E, -NL63, rhinovirus, parainfluenza type 1, 2, 3, 4, adenovirus and bocavirus) as described elsewhere [5].

To characterise the virus strain, partial genome sequencing was done as described by Haagmans et al. [2]. Sequence analysis was carried out directly from clinical specimens (respiratory samples) of both cases, yielding in total 4 kb of genome sequence for Case 1 and 2.4 kb for Case 2 (GenBank accession numbers KJ858495-KJ858500). The sequences were nearly identical (one nucleotide difference) and were distinct from

**FIGURE 1**

Timeline of events for two MERS-CoV patients returning to the Netherlands from Saudi Arabia, May 2014



MERS-CoV: Middle East respiratory syndrome coronavirus.

recently published sequences from a hospital cluster in Jeddah, Saudi Arabia] [6]. However, the sequences clustered with that from a recently diagnosed traveller returning to the United States (US) from Saudi Arabia [7] (Figure 2).

### Visits while in Saudi Arabia

The group of 31 people travelled together in Saudi Arabia, used private transport, went on a joint trip to several mosques around Medina and spent the other days individually performing religious rituals in different mosques, visiting local markets and eating in different establishments. On 3 May, 12 members of the group (not including the two cases) visited Wadi-e-Jinn near Medina and came across a dromedary camel herd with a few farmers who created a temporary shelter. All 12 drank raw dromedary milk, offered to them by the farmer. The group did not take any animal products back for Cases 1 and 2.

### Contact investigations

A total of 78 close contacts were identified (among which were the travel group, relatives and flight contacts) and monitored as described in the Box. All healthcare workers were well protected. The number of flight contacts was limited (n=18) due to the fact that both cases were seated together on the last row in the plane. All flight contacts were Dutch residents. The monitoring period has come to an end for 70 close contacts and will be finalised by 29 May for the last group (n=8). No additional cases of MERS-CoV infection have been found during this period. All molecular (throat swabs) and serological samples taken from the contacts have been negative for MERS-CoV so far. The testing will be completed by mid-June.

### Background

MERS-CoV was first recognised in 2012, when it caused severe pneumonia in a patient from Saudi Arabia [8]. Since then, cases have been notified from several countries in the Arabian peninsula, with occasional exportation through infected travellers [9]. The exact epidemiology of the infection remains to be determined, but contact with animals, particularly dromedary camels, as well as contact with patients with MERS-CoV infection are risk exposures [10,11]. A recent upsurge in the number of primary cases in the community in the Kingdom of Saudi Arabia, possibly associated with the weaning season in dromedary cases, has been amplified by person-to-person transmission due to poor hospital hygiene measures in some hospitals in the Kingdom of Saudi Arabia [10,11].

### Discussion

There are several options for the possible source of the infection of the two Dutch cases: Case 1 could have been infected during the hospital visit of his child on 29 April, after which he infected Case 2. Alternatively, both could have been exposed to a common, as yet unknown, source in Medina. Thirdly, each case could have been infected through different sources (hospital/community), though this seems unlikely, as the (partial) virus sequence of both cases was nearly identical. The resemblance in strain sequence between the Dutch cases and the case from the US is remarkable as the cases did not visit the same places in the Kingdom of Saudi Arabia. Exchange of information between the US Centers for Disease Control and Prevention and Dutch experts did not reveal any clues about mutual exposure of the Dutch and US cases. The current, limited scientific information does not support any conclusion on

the meaning of this genetic resemblance, knowing that multiple lineages of the virus can be found in camels and people [2,12]. Continued vigilance in evaluation of contacts of imported cases, including molecular testing and serology, will hopefully lead to better insights.

The public health response to these two imported cases was in line with the procedures put in place in the Netherlands [4,13]. Healthcare professionals in the Netherlands have been made aware of MERS-CoV since its emergence in 2012. MERS-CoV laboratory testing protocols have been implemented, including 24-hour availability of parallel testing in two separate laboratories if suspected cases are identified. These preparations facilitated the rapid follow-up and diagnosis of Case 2.

A national outbreak investigation team was formed of clinicians, medical virologists, public health specialists, epidemiologists, staff members from the national response unit and a press officer. This team convened in a nearly daily teleconference to (i) share new developments regarding the cases, their laboratory follow-up and case histories; (ii) to perform a structured assessment of the public health risks for the contacts; (iii) perform risk classification of contacts; (iv) issue guidelines for follow-up; (v) provide information to professionals and the media; and (vi) monitor progression of the response [13].

Immediately after the diagnosis was confirmed in Case 1, on 14 May, a press release was issued, followed by regular updates to emphasise the control measures designed to prevent secondary transmission. The World Health Organization was notified according to the International Health Regulations (IHR) by the National Focal Point, and international warnings were issued through the European Union Early Warning and Response System. The IHR Focal Point of the Kingdom of Saudi Arabia was notified as well.

Finally, updated guidelines for case finding, laboratory diagnosis, contact investigation and monitoring and infection control were revised and disseminated to the health professionals in the Netherlands using an electronic alerting system.

#### MERS-CoV outbreak investigation team of the Netherlands (in alphabetical order)

Christel Bank (Medical Centre Haaglanden); Kees Dirksen (Public Health Service The Hague); Willem Geerlings (Medical Centre Haaglanden); Luc Gelinck (Medical Centre Haaglanden); Paul Groeneveld (Isala Klinieken); Bart Haagmans (Erasmus MC); Casper Jansen (Medical Centre Haaglanden); Marcel Jonges (RIVM Centre for Infectious Disease Research, Diagnostics and Screening); Michiel Knaven (Medical Centre Haaglanden); Marion Koopmans (Erasmus MC and RIVM Centre for Infectious Disease Research, Diagnostics and Screening); Marleen Kraaij – Dirkzwager (RIVM National Coordination Centre for Communicable Disease Control); Eliane Leyten (Medical Centre Haaglanden); Johan Mutsaers (Medical Centre Haaglanden); Suzan Pas (Erasmus MC);

**TABLE**

Real-time reverse transcription-PCR results from two MERS-CoV patients returning to the Netherlands from Saudi Arabia, May 2014

Day of sampling <sup>a</sup>	Throat swab <sup>b</sup>	Serum <sup>b</sup>	Faeces <sup>b</sup>	Urine <sup>b</sup>
<b>Case 1</b>				
Do	31.3/31.5	–	–	–
D4	29.6/27.2	34.0/30.3	–	ND/ND
D5	34.6/34.2	33.6/31.0	34.6/33.5	–
D6	33.5/31.6	33.7/31.7	–	ND/ND
D7	ND/ND	35.9/33.4	ND/ND	ND/ND
D8	ND/ND	38.3/35.8	ND/ND	ND/ND
D9	37.8/34.9	ND/37.6	–	ND/ND
<b>Case 2</b>				
Do	34.5/32.5	–	ND/ND	–
D1	–	35.5/33.6	38.8/ND	–
D2	–	34.6/36.4	ND/ND	–
D3	–	37.4/38.6	ND/38.4	ND/ND
D4	–	37.8/36.7	38.7/ND	ND/ND
D5	–	36.0/38.3	–	ND/ND

Dashes show where no samples were available.

MERS-CoV: Middle East respiratory syndrome coronavirus; ND: not detected.

<sup>a</sup> Time of sampling starts from the date of diagnosis (Do).

<sup>b</sup> Threshold cycle (Ct) values of MERS-CoV upE PCR/Ct values of N-gene reverse transcription-PCR.

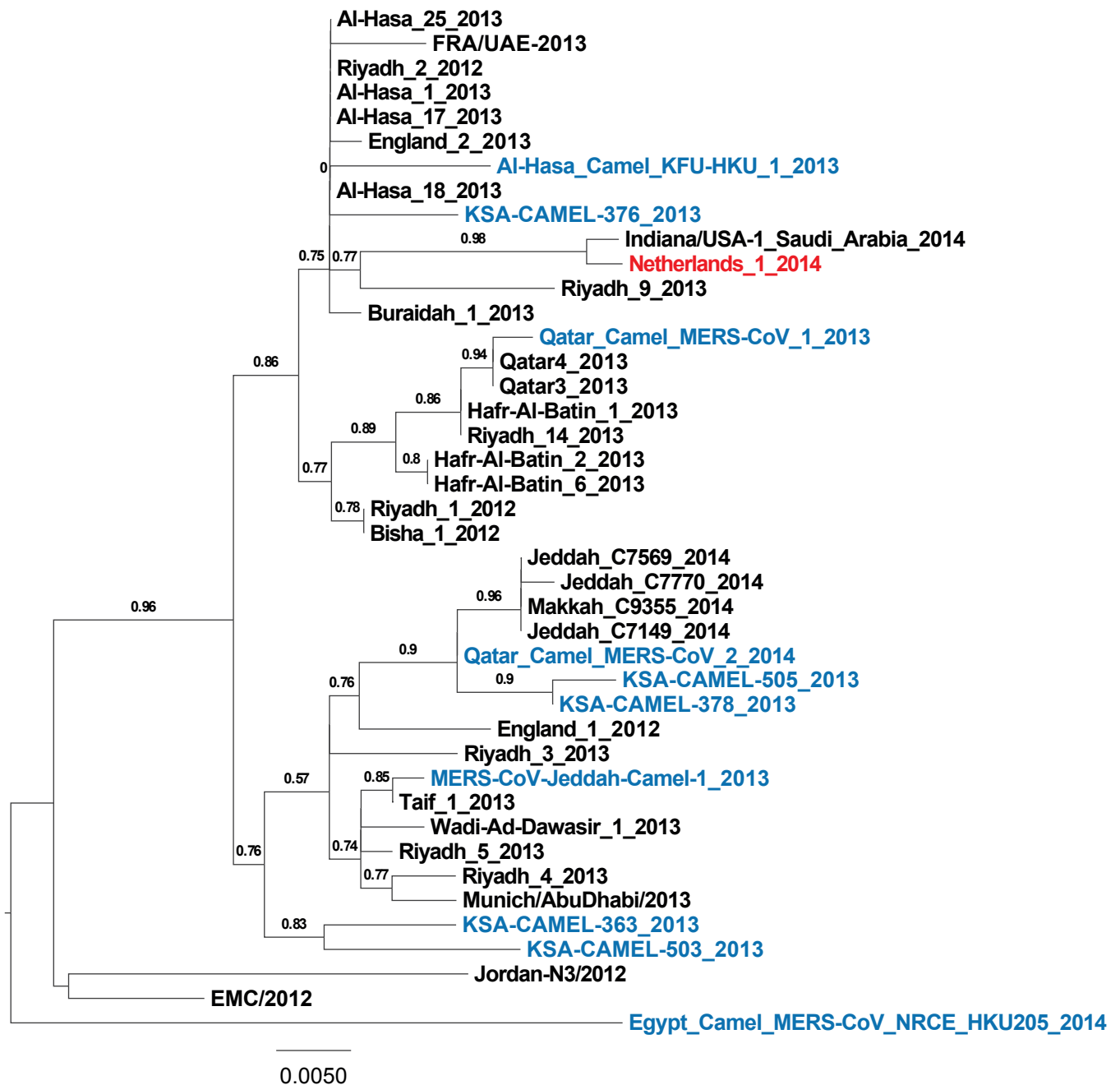
Stalin Raj (Erasmus MC); Chantal Reusken (Erasmus MC); Hella Smit (RIVM Communication); Rita de Sousa (RIVM Centre for Infectious Disease Research, Diagnostics and Screening and The European Programme for Public Health Microbiology Training (EUPHEM), European Centre for Disease Prevention and Control (ECDC)); Corien Swaan (RIVM National Coordination Centre for Communicable Disease Control); Ingeborg Thurkow (Public Health Service IJsselland); Aura Timen (RIVM National Coordination Centre for Communicable Disease Control); Anouk Urbanus (RIVM National Coordination Centre for Communicable Disease Control); Paul van Beek (RIVM National Coordination Centre for Communicable Disease Control); Douwe van de Werf (Public Health Service IJsselland); Annemiek van der Eijk (Erasmus MC); Rianne van Gageldonk-Lafeber (RIVM Centre for Infectious Diseases, Epidemiology and Surveillance); Erik Verschuren (RIVM National Coordination Centre for Communicable Disease Control); Johan Versteegen (Public Health Service The Hague); Caroline Wortman (Medical Centre Haaglanden); Harald Wychgel (RIVM communication).

#### Conflict of interest

None declared.

**FIGURE 2**

Phylogenetic analysis of a MERS-CoV sequence from Case 1 returning to the Netherlands from Saudi Arabia, May 2014



MERS-CoV: Middle East respiratory syndrome coronavirus.

PhyML phylogenetic tree based on 4 kb nucleotide sequence, drawn with Seaview 4 software using the GTR model. Values at branches show the result of the approximate likelihood ratio; values <0.70 are not shown. The scale bar indicates nucleotide substitutions per site.

MERS-CoV isolates from dromedary camels are shown in blue and the human MERS-CoV isolate from the Netherlands is shown in red.

### Authors' contributions

All authors contributed to gathering and analysis of the information. Marleen Kraaij-Dirkzwager, Aura Timen and Marion Koopmans drafted and revised the manuscript based on all authors contributions.

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