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Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus

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ABSTRACT

BACKGROUND

In September 2012, the World Health Organization reported the first cases of pneumonia caused by the novel Middle East respiratory syndrome coronavirus (MERS-CoV). We describe a cluster of health care–acquired MERS-CoV infections.

METHODS

Medical records were reviewed for clinical and demographic information and determination of potential contacts and exposures. Case patients and contacts were interviewed. The incubation period and serial interval (the time between the successive onset of symptoms in a chain of transmission) were estimated. Viral RNA was sequenced.

RESULTS

Between April 1 and May 23, 2013, a total of 23 cases of MERS-CoV infection were reported in the eastern province of Saudi Arabia. Symptoms included fever in 20 patients (87%), cough in 20 (87%), shortness of breath in 11 (48%), and gastrointestinal symptoms in 8 (35%); 20 patients (87%) presented with abnormal chest radiographs. As of June 12, a total of 15 patients (65%) had died, 6 (26%) had recovered, and 2 (9%) remained hospitalized. The median incubation period was 5.2 days (95% confidence interval [CI], 1.9 to 14.7), and the serial interval was 7.6 days (95% CI, 2.5 to 23.1). A total of 21 of the 23 cases were acquired by person-to-person transmission in hemodialysis units, intensive care units, or in-patient units in three different health care facilities. Sequencing data from four isolates revealed a single monophyletic clade. Among 217 household contacts and more than 200 health care worker contacts whom we identified, MERS-CoV infection developed in 5 family members (3 with laboratory-confirmed cases) and in 2 health care workers (both with laboratory-confirmed cases).

CONCLUSIONS

Person-to-person transmission of MERS-CoV can occur in health care settings and may be associated with considerable morbidity. Surveillance and infection-control measures are critical to a global public health response.

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RESPIRATORY VIRUSES ARE AN EMERGING threat to global health security and have led to worldwide epidemics with substantial morbidity, mortality, and economic consequences. Since the severe acute respiratory syndrome (SARS) pandemic in 2003–2004,^{1,3} two additional human coronaviruses — HKU-1 and NL-63 — have been identified, both of which cause mild respiratory infection and are distributed worldwide.^{4,5} In September 2012, the World Health Organization (WHO) reported two cases of severe community-acquired pneumonia caused by a novel human β -coronavirus, subsequently named the Middle East respiratory syndrome coronavirus (MERS-CoV).^{6–8} Since then, MERS-CoV has been identified as the cause of pneumonia in patients in Saudi Arabia,^{7,9} Qatar,^{7,10} Jordan,^{11,12} the United Kingdom,^{13,14} Germany,¹⁵ France,¹⁶ Tunisia,¹⁷ and Italy.¹⁷ Phylogenetic analysis shows that the MERS-CoV defines a novel lineage C, making this coronavirus a lineage C β -coronavirus known to infect humans.^{18,19}

The natural host and reservoir of MERS-CoV remain unknown. We describe human-to-human transmission of MERS-CoV in a health care setting, estimate the incubation period and serial interval (the time between the successive onset of symptoms in a chain of transmission), and describe the clinical features of the disease.

METHODS

SETTING

The governorate of Al-Hasa, in eastern Saudi Arabia, serves a mixed urban and rural population of 1.1 million persons. Hospital A is a 150-bed general hospital in the largest urban area (Al-Hufuf). The dialysis unit, which cares for 43 patients in two shifts per day, is an open unit with 16 beds spaced 1.3 to 1.5 m apart. The intensive care unit (ICU) contains two open 6-bed bays. Hospitals B and C are also general hospitals in Al-Hufuf. Hospital D is a regional referral hospital located 160 km from Al-Hufuf.

DEFINITIONS

A person was considered to have a confirmed case of MERS-CoV infection if there was laboratory evidence of MERS-CoV and the person had either fever and at least one respiratory symptom or two respiratory symptoms without another identifiable cause. A person was considered to

have a probable case of MERS-CoV infection if he or she was a household, family, or health care contact of a person with a confirmed case and if pneumonia developed without another confirmed cause and either laboratory testing for MERS-CoV was not performed or a single test was negative and no other specimens were available for testing. The date of onset was defined among febrile patients as the first day of fever that persisted for more than 48 hours and among afebrile patients as the first day of new cough or shortness of breath. A person was considered to have been exposed if he or she had had any face-to-face contact with a symptomatic patient who had a confirmed or probable case, was in the same hospital room or ward as a symptomatic case patient for more than 1 hour, moved into a bed vacated by a symptomatic case patient, was being cared for by a health care worker who was also caring for a symptomatic case patient, or was sharing hospital equipment with a symptomatic case patient.

LABORATORY SURVEILLANCE

Beginning in September 2012, the Saudi Arabian Ministry of Health requested that all patients with pneumonia requiring admission to the ICU be tested for MERS-CoV. Throat-swab (Eurotubo, Deltalab), sputum, tracheal-aspirate, or bronchoalveolar-lavage specimens were obtained and were placed in viral transport medium (Vircell), stored at 28°C, and transported within 72 hours to the Ministry of Health regional reference laboratory in Jeddah, Saudi Arabia, where they were subjected to real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays to test for MERS-CoV.²⁰ For all patients, the results of RT-PCR tests were confirmed by measuring cycle-threshold values for viral load.

IDENTIFICATION OF CLUSTERS, COLLECTION OF CASE DATA, AND ASSESSMENT OF EXPOSURE

In response to an increase in the incidence of pneumonia among patients undergoing hemodialysis, Hospital A initiated active surveillance for pneumonia on April 20, 2013, and conducted a retrospective review of in-hospital deaths and cases of pneumonia from March 1 through April 19. We also reviewed the medical charts of patients with confirmed MERS-CoV infection to identify symptoms, laboratory findings, and clinical course. The Ministry of Health interviewed

household contacts of patients with confirmed MERS-CoV infection and followed them for 14 days after exposure.

We mapped confirmed and probable MERS-CoV cases in time and in space within health care facilities. For each case, we identified potential exposures, with the assumption that face-to-face contact or time spent in the same area conferred a greater risk than shared caregivers, which in turn conferred a greater risk than shared equipment. No assumptions were made about incubation periods. Three of the authors reviewed potential exposures independently; when more than one potential exposure was possible, the most likely source of exposure was identified by consensus among those authors and an additional author. The corresponding author vouches for the accuracy and completeness of the data.

SEQUENCING AND PHYLOGENETIC ANALYSIS

Full-genome sequences were obtained from specimens from four patients (Patients I, J, K, and V) (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Amplicon products were sequenced with the use of the Illumina MiSeq sequencer and assembled into full genomes by means of assembly with the SPAdes 2 genome assembler, version 2.4.0. Assemblies were validated with the use of reference-based assembly (SMALT, version 0.7.4). The open reading frames of the novel genomes and a comparison of nucleotide changes relative to the closest existing MERS genome (England2_HPA) were analyzed with the use of Python scripts.

Full-length genomes were combined with five previously identified MERS-CoV genomes (KC776174, JX869059, KC667074, EMC/Munich/AbuDhabi/2013, and England2) and aligned with the use of Molecular Evolution Genetics Analysis, version 5 (MEGA5), software. A second alignment was created to include only coding regions (ORF1ab, S, ORF3, ORF4a, ORF4b, ORF5, E, M, N). Maximum-likelihood phylogenies were inferred with the use of Phylogenetic Estimation Using Maximum Likelihood (PhyML), version 3.0, software and bootstrapped 1000 times to assess confidence. Further time-resolved phylogenetic trees were obtained from concatenated coding alignment with the use of Bayesian evolutionary analysis by sampling trees (BEAST), version 1.7.5, software. The likelihoods of runs under different models were compared, and a maximum clade

credibility tree was used to summarize the most likely model.

STATISTICAL ANALYSIS

We calculated empirical cumulative density functions of the incubation period and serial intervals by computing the cumulative fraction of all observations that fell below each observed value in the respective data sets. We estimated the incubation period by identifying the earliest and latest time of possible exposure and the time of symptom onset for each case. Treating these times as interval-censored estimates of the incubation period for each person, we fit a log-normal distribution to these data using maximum-likelihood techniques. We then examined the robustness of our estimates with multiple definitions of onset and with the exclusion of particular cases.

We estimated the serial interval by identifying the times of symptom onset in the patient and in the person who transmitted the infection (infected–infector pairs) and then fitting a log-normal distribution to these interval-censored data.²¹ We estimated the medians and 5th and 95th percentiles of the incubation period and the serial interval using the quantiles of the log-normal distribution fit to each data set (R statistical package, version 2.15.1, and coarseDataTools library).²¹

RESULTS

DESCRIPTION OF THE OUTBREAK

Between April 1 and May 23, 2013, a total of 23 confirmed cases of human infection with MERS-CoV were identified in the eastern province of Saudi Arabia (Fig. S1 in the Supplementary Appendix). All confirmed cases and 11 probable cases were part of a single outbreak involving four health care facilities (Fig. 1).

ILLNESS IN PATIENTS AT HOSPITAL A

Community Introductions

On April 5, 2013, Patient A was admitted to the medical ward with dizziness and diaphoresis. On hospital day 4, fever and progressive pulmonary infiltrates developed. The patient was not tested for MERS-CoV, but his son (Patient O) subsequently had a confirmed case of MERS-CoV infection (Fig. S2 and Table S1 in the Supplementary Appendix).

On April 4, Patient B was admitted to the ICU

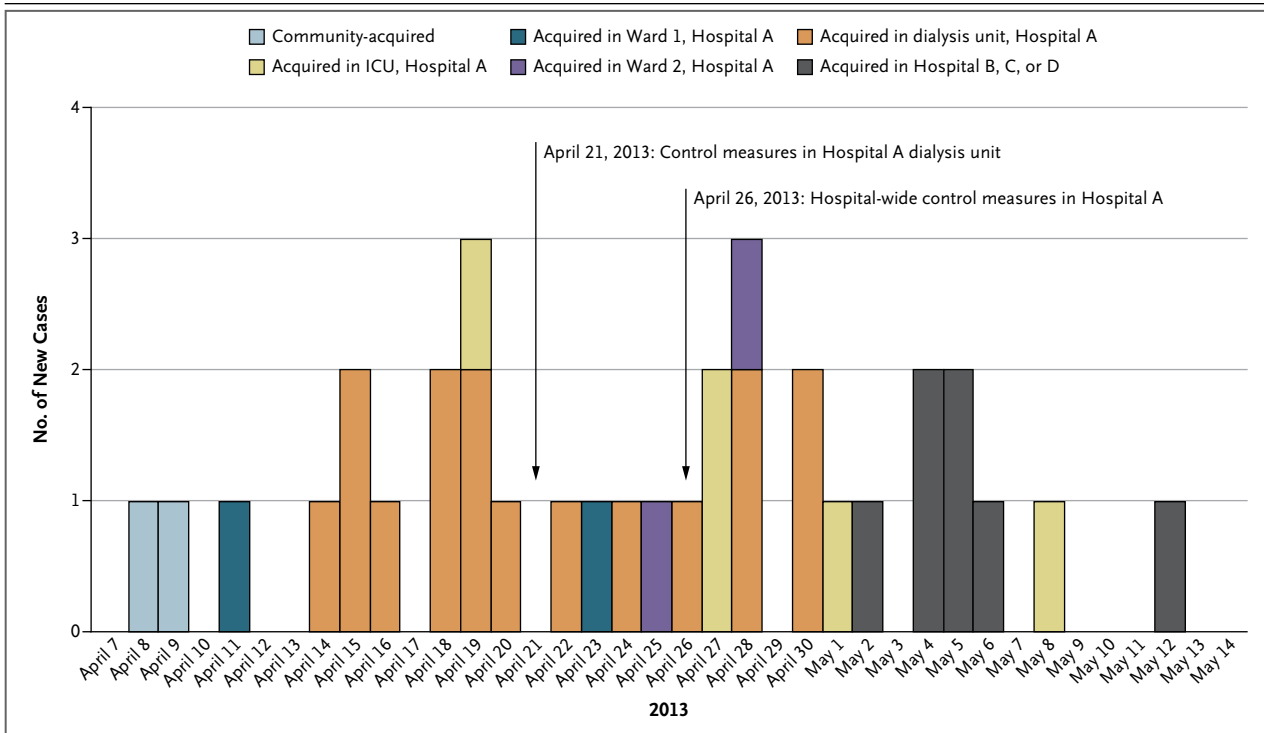


Figure 1. Epidemiologic Plot of Confirmed and Probable Cases of MERS-CoV Infection in Saudi Arabia, April 1–May 23, 2013.

All confirmed and probable cases are shown, according to the location of the most probable transmission. One of the five family contacts (Patient M) who is included as having been exposed in Hospital A was also exposed through caring for the patient at home and may have acquired the infection either in the hospital or in the community.

with a diagnosis of stroke. On hospital day 6, fever developed, and a throat-swab specimen was obtained, which was negative for MERS-CoV. When pneumonia developed in the patient, MERS-CoV was identified on repeat testing. No epidemiologic link between Patients A and B could be established.

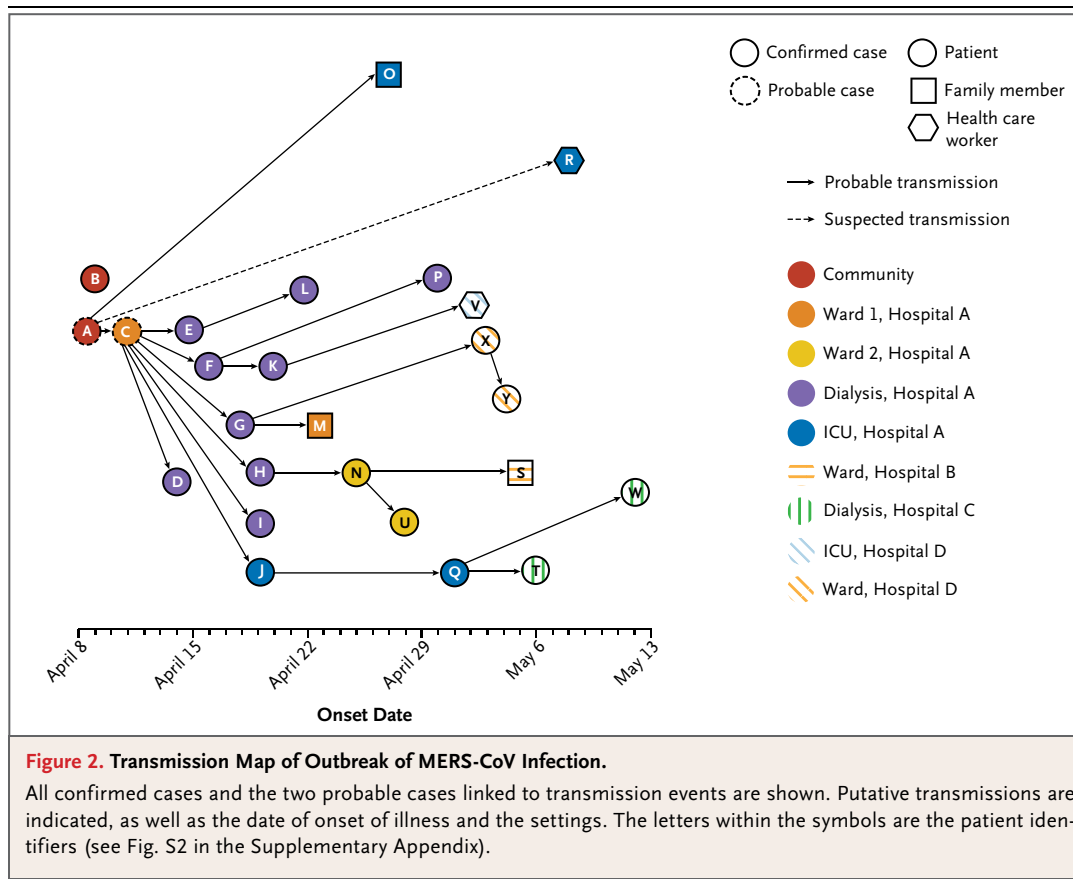
Patient C, who had been undergoing long-term hemodialysis, was admitted to Hospital A on April 6 to the room adjacent to Patient A. He was still in that room on April 8, which was the day on which fever developed in Patient A. Fever developed in Patient C 3 days later. He underwent dialysis in the hospital's outpatient hemodialysis unit twice after the onset of symptoms — on April 11 and April 13.

Hemodialysis Unit

Between April 14 and April 30, MERS-CoV infection was confirmed in nine additional patients, who were undergoing hemodialysis in Hospital A (Fig. S2 in the Supplementary Appendix). Six of these patients (Patients D, E, F, G, H, and I) un-

derwent hemodialysis at times that overlapped with the times Patient C was undergoing hemodialysis on either April 11 or April 13; three of them underwent the procedure in beds adjacent to Patient C's bed. Two patients (Patients K and P) underwent hemodialysis at times that overlapped with the times Patient F was undergoing hemodialysis after the onset of his symptoms, and one patient (Patient L) underwent hemodialysis in a bed adjacent to symptomatic Patient E. Eight additional probable cases occurred among patients undergoing hemodialysis between April 15 and April 30. There were no links between individual dialysis nurses or machines and case patients.

Among the nine patients undergoing hemodialysis at Hospital A who had confirmed MERS-CoV infection, eight had an onset of disease before or within 24 hours after infection-control interventions were implemented on April 21. These interventions included monitoring hand hygiene, implementing droplet and contact precautions for febrile patients, testing patients with fever for MERS-CoV, putting masks on all pa-



patients undergoing hemodialysis, not allowing patients with suspected MERS-CoV infection into the dialysis unit, enhancing environmental cleaning, and excluding visitors and nonessential staff. In the 8 days after implementation of precautions, illness developed in six patients: MERS-CoV infection was confirmed in one patient (Patient P) and was classified as probable in five patients; no additional confirmed cases occurred from May 1 to May 23.

ICU

Between April 9 and April 26, Patients A, C, D, and E were treated with continuous positive airway pressure and received nebulized medications; six cardiac arrests occurred among these four patients. MERS-CoV infection developed in two additional patients (Patients J and Q, both with confirmed cases) who were present in the same ICU during this time. Infection-control measures similar to those in the hemodialysis unit were implemented throughout the hospital on April 26. No further confirmed cases occurred in the ICU.

Medical Ward

One patient undergoing hemodialysis (Patient H) who had confirmed infection was admitted to a medical ward (Fig. 2) on April 21. Patient N, who was separated from Patient H by two rooms, became ill on April 25, and Patient U, who was separated from Patient H by three rooms, became ill on April 28.

ILLNESS IN STAFF MEMBERS AT HOSPITAL A

One of the 124 health care worker contacts of patients with confirmed MERS-CoV infection reported a 48-hour history of febrile illness without respiratory symptoms beginning on May 5; testing for MERS-CoV was not performed. On May 8, MERS-CoV infection developed in a nurse administrator (Patient R), who was not known to have been exposed to any patients identified as having MERS-CoV infection. She was in the ICU during two simultaneous cardiac resuscitations on April 15 and had face-to-face contact on May 5 with the febrile health care worker described above. No other potential exposures were identified.

ILLNESS IN FAMILY MEMBERS

A total of 217 household contacts of patients with confirmed cases were followed up, including 120 adults (median age, 26 years; range, 18 to 100) and 97 children. MERS-CoV infection developed in 5 adult family members who were hospital visitors of Patients A, G, and N; 3 were confirmed cases (in patients M, O, and S) and 2 were probable (Fig. 2, and Fig. S2 and Table S1 in the Supplementary Appendix).

ILLNESS WITH ONSET IN OTHER HEALTH CARE FACILITIES

Patient Q, who became infected with MERS-CoV in the ICU of Hospital A, had been undergoing long-term hemodialysis at an outpatient clinic in Hospital C and underwent hemodialysis in that unit while he was symptomatic. MERS-CoV infection developed in two additional patients (Patients T and W) at Hospital C. Patient T regularly traveled from home to the dialysis unit with Patient Q. Patient W underwent hemodialysis in the same 13-bed room and during the same shift as Patient Q.

Eight patients (Patients B, E, F, G, H, I, K, and L) with confirmed MERS-CoV infection were transferred to Hospital D between April 18 and April 27. MERS-CoV infection developed in two patients (Patients X and Y) who were hospitalized on the same ward as Patient G and in a physician (Patient V) who cared for Patient K. Overall, two laboratory-confirmed cases occurred among more than 200 health care worker contacts who were followed after exposure.

DEMOGRAPHIC AND CLINICAL FEATURES

Most of the case patients were men, and the median age was 56 years (Table 1). The most common signs and symptoms were fever (in 87% of the patients) and cough (in 89%), and 35% presented with vomiting or diarrhea. Among patients in whom the illness progressed, the median time from the onset of symptoms to ICU admission was 5 days (range, 1 to 10), the median time to the need for mechanical ventilation was 7 days (range, 3 to 11), and the median time to death was 11 days (range, 5 to 27). Three of four patients (75%) whose cases were detected by active surveillance during the outbreak, as compared with 3 of 19 (16%) whose cases were identified clinically, have recovered ($P=0.04$).

TRANSMISSION, INCUBATION PERIOD, AND SERIAL INTERVAL

One patient transmitted the infection to seven persons, one patient transmitted the infection to three persons, and four patients transmitted the infection to two persons each. The incubation period of confirmed cases was 5.2 days (95% confidence interval [CI], 1.9 to 14.7) (Fig. 3); distributions that were fit to our observed data indicated that 95% of infected patients would have an onset of symptoms by day 12.4 (95% CI of 95th percentile, 7.3 to 17.5), whereas 5% would have an onset of symptoms by day 2.2 (95% CI of 5th percentile, 1.2 to 3.1).

We estimated that the serial interval was 7.6 days (95% CI, 2.5 to 23.1) (Fig. 3). The distributions that were fit to our observed data indicate that the serial interval was less than 19.4 days in 95% of cases (95% CI of 95th percentile, 11.7 to 27.0) and less than 3.0 days in 5% of cases (95% CI of 5th percentile, 1.8 to 4.2).

SEQUENCING AND PHYLOGENETIC ANALYSIS

Among the four MERS-CoV isolates, Al-Hasa_1_2013 (GenBank accession number, KF186567) from Patient V and Al-Hasa_4_2013 (KF186564) from Patient K have identical genomes, whereas Al-Hasa_2_2013 (KF186566) from Patient J and Al-Hasa_3_2013 (KF186565) from Patient I have two or three nucleotide differences from Al-Hasa_1_2013 (Fig. 4A).

Phylogenetic analysis of the four MERS-CoV genomes showed that the viruses form a monophyletic clade with a bootstrap support of 100% (Fig. 4B). The most closely related sequence to this clade is England2, with a genetic distance of 0.0008 substitutions per site. The Al-Hasa lineage has 15 defining mutations (4 nonsynonymous: A1643S and V2550I in ORF1ab, Q1208H in S protein, and F58S in ORF3).

We estimated that the date of the most recent common ancestor of MERS-CoV was August 18, 2011 (95% highest posterior density [HPD, intervals for nucleotide sequences], November 1, 2009, to April 14, 2012). The date of the divergence of the Al-Hasa lineage was December 6, 2012 (95% HPD, July 18, 2012, to February 3, 2013), and the date of the most recent common ancestor of the Al-Hasa lineage was April 2, 2013 (95% HPD, February 7, 2013, to April 21, 2013) (Fig. 4C).

DISCUSSION

Acute viral respiratory tract infections cause considerable morbidity and mortality and pose a risk of outbreaks in health care settings.²⁵⁻²⁷ We describe a cluster of MERS-CoV infections and report health care-associated human-to-human transmission of MERS-CoV. The 65% case fatality rate in this outbreak is of concern.

We and others have found that the severity of illness associated with MERS-CoV infection ranges from mild to fulminant.^{7,9-17} The clinical syndrome is similar to SARS, with an initial phase of nonspecific fever and mild, nonproductive cough, which may last for several days before progressing to pneumonia.²⁸ Some patients with MERS-CoV infection also had gastrointestinal symptoms, a finding similar to that with SARS.²⁹ MERS-CoV is known to infect cell lines of the intestinal tract,³⁰ but it is not yet known what proportion of ill patients shed virus in their stool. In the majority of patients in this cluster, fever was high and persistent, but the pattern of pulmonary involvement on chest radiography was variable. It is noteworthy that the survival rate was higher among patients whose cases were identified by means of active surveillance during the outbreak than among those whose cases were identified clinically. Although a possible explanation is that the patients whose cases were identified by means of active surveillance were younger and healthier than the patients with primary cases, it is more likely that enhanced surveillance was more effective at detecting less severe disease than was identification of clinical features.

Our estimates of the distribution of the incubation period are similar to those for SARS-CoV infection, which was estimated to have a median incubation period of 4.0 days, with 5% of cases developing within 1.8 days and 95% within 10.6 days.³¹ Our estimates of the serial interval of MERS-CoV infection are somewhat shorter than those for SARS-CoV (median, 7.6 days vs. 8.4 days), perhaps because transmission of MERS-CoV infection appears to occur earlier in the course of the illness.³² Our small sample led to wide confidence intervals; however, bootstrapped sampling of our data showed the robustness of our estimates with the inclusion and exclusion of particular cases.

The rapid transmission and high attack rate in the dialysis unit raises substantial concerns

Table 1. Characteristics and Symptoms of Patients with Laboratory-Confirmed Middle East Respiratory Syndrome Coronavirus Infection, April–May 2013.

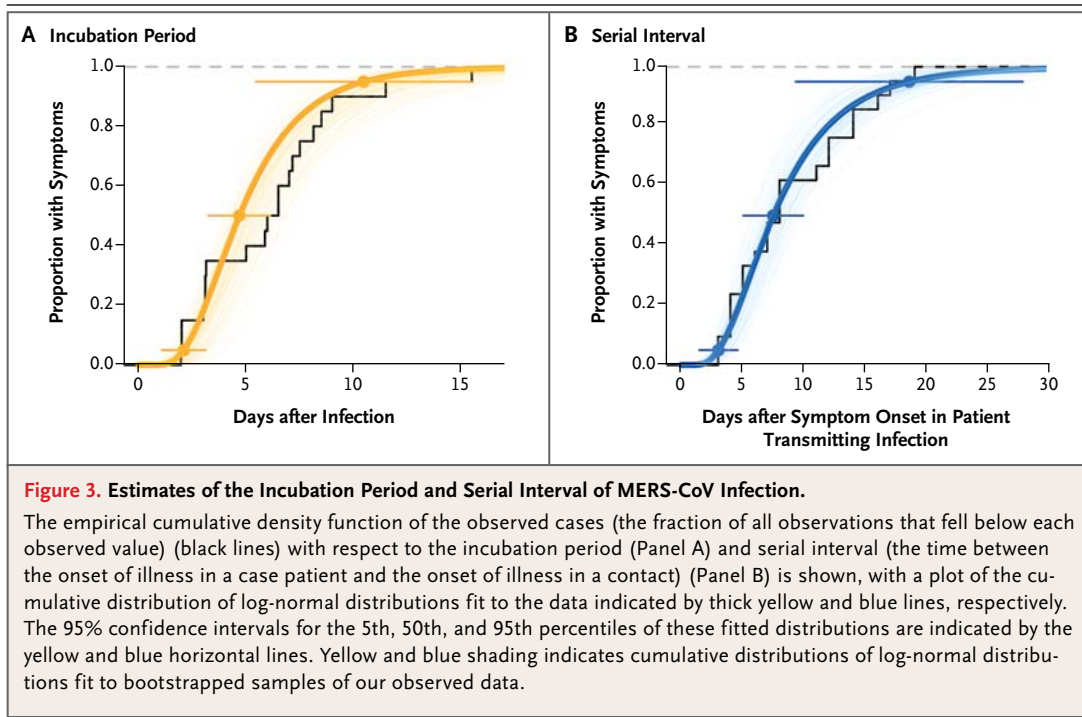
Characteristic	Patients with Confirmed Cases (N=23)
Male sex — no. (%)	17 (74)
Age — yr	
Median	56
Range	24–94
Age ≥50 yr — no. (%)	17 (74)
Age ≥65 yr — no. (%)	6 (26)
Obesity — no./total no. (%) [*]	5/21 (24)
Underlying illness — no. (%)	
End-stage renal disease	12 (52)
Diabetes mellitus	17 (74)
Cardiac disease	9 (39)
Lung disease, including asthma	10 (43)
Immunosuppressive condition other than renal disease	0
Symptoms before presentation — no. (%)	
Fever	20 (87)
Cough	20 (87)
Shortness of breath	11 (48)
Gastrointestinal symptoms	
Any	8 (35)
Vomiting	4 (17)
Diarrhea	5 (22)
Laboratory testing at presentation — no./total no. (%)	
Abnormal white-cell count [†]	5/23 (22)
Abnormal platelet count [‡]	5/23 (22)
Elevated aspartate aminotransferase	3/13 (23)
Oxygen saturation <95% while breathing ambient air	7/23 (30)
Chest radiographic findings at presentation — no. (%)	
Normal	3 (13)
Increased bronchovascular markings	4 (17)
Unilateral infiltrate	10 (43)
Bilateral infiltrates	5 (22)
Diffuse reticulonodular pattern	1 (4)
Clinical course — no. (%)	
Admitted to hospital	22 (96)
Admitted to intensive care unit	18 (78)
Received mechanical ventilation	18 (78)
Outcome as of June 12, 2013 — no. (%)	
Recovered	6 (26)
Remained in hospital [§]	2 (9)
Died	15 (65)

^{*} Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more.

[†] Two patients had an abnormally low white-cell count (2.2×10^9 per liter and 3.1×10^9 per liter), and three had abnormally high counts (12.1×10^9 , 17.9×10^9 , and 22×10^9 per liter).

[‡] Four patients had abnormally low platelet counts (ranging from 110×10^9 to 122×10^9 per liter) and one had an abnormally high count (468×10^9 per liter)

[§] Both of these patients remain in the intensive care unit and continue to receive mechanical ventilation.



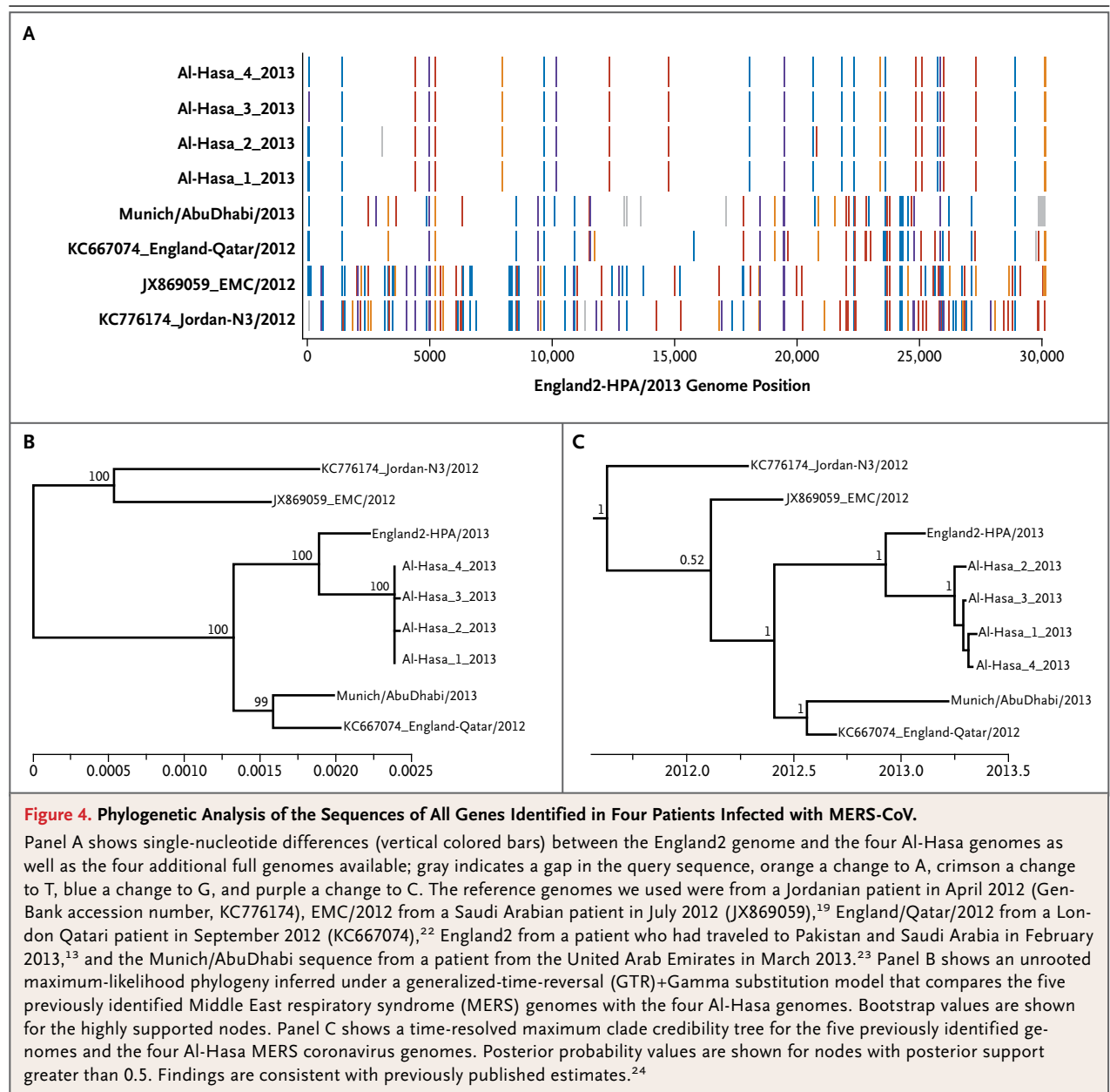
about the risk of health care–associated transmission of this virus. The apparent heterogeneity in transmission, with many infected patients not transmitting disease at all and one patient transmitting disease to seven others, is reminiscent of SARS.^{33,34}

Epidemiologic and phylogenetic analyses support person-to-person transmission; however, it is not possible to be certain about whether there were single or multiple introductions from the community. Similarly, we are unable to determine whether person-to-person transmission occurred through respiratory droplets or through direct or indirect contact and whether the virus was transmitted when the contact was more than 1 m away from the case patient. Because some patients presented with gastrointestinal symptoms, and transmission appeared to occur between rooms on the ward, the current WHO recommendations for surveillance and control should be regarded as the minimum standards³⁵; hospitals should use contact and droplet precautions and should consider the follow-up of persons who were in the same ward as a patient with MERS-CoV infection.

It is possible to explain all the episodes of transmission in this outbreak by assuming that patients were infectious only when they were

symptomatic; however, this does not rule out transmission during the incubation phase or during asymptomatic infection. Because this was a retrospective investigation, we may have missed exposures that were not documented or that were forgotten; we may also have misclassified community-acquired cases as health care–associated cases. Our choice of the most likely exposure to link patients may have been incorrect. Despite these limitations, multiple iterations of transmission mapping resulted in maps with similar overall results.

Laboratory testing for MERS-CoV remains a challenge. Validated serologic assays are not yet available, and this may have limited the identification of cases. In this cluster, results of throat swabs were occasionally negative and repeat testing for MERS-CoV was required. It is not clear whether sputum or nasopharyngeal samples might be superior to throat samples or whether virus is shed more abundantly later in the course of the illness or in more severe illness, as it is in SARS.³⁶ It seems prudent to conclude that one cannot reliably rule out MERS-CoV disease on the basis of a single negative test when a patient presents with the appropriate clinical syndrome and epidemiologic exposure. There is evidence that repeat testing and tests on sputum or



bronchoalveolar-lavage fluid are of value in improving diagnostic accuracy.

The repeated introduction of the infection into the community, the ongoing detection of new illness, and the substantial impact of hospital transmission in this outbreak underscore the importance of investigations into the community source of MERS-CoV. Without the ability to prevent community infection, prevention of health care transmission will remain a challenge. Outbreak-control measures included precautions for

patients until 24 hours after symptoms resolved. To date, the Ministry of Health has found no evidence of transmission from patients in whom precautions have been discontinued. Further investigations to identify the duration of viral shedding as well as the complete spectrum of disease are needed to refine public health recommendations.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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