Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Information and Guidance for Clinicians

Clinician Outreach and Communication Activity (COCA) Conference Call
June 13, 2013
Objectives

At the conclusion of this session, the participant will be able to accomplish the following:

- Describe the key components in the surveillance case definition for a patient under investigation for MERS-CoV infection
- Identify specimens to be obtained and the appropriate laboratory test to diagnose a patient with MERS-CoV infection
- List infection control measures appropriate for control of MERS-CoV
TODAY’S PRESENTER

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Emergence of a Novel Coronavirus in the Arabian Peninsula, Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

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Objectives

• Describe the clinical spectrum of disease caused by MERS-CoV
• Identify the key components in the surveillance case definition for a patient under investigation for MERS-CoV
• Identify specimens to be obtained and the appropriate laboratory test to diagnose a patient with MERS-CoV
• List infection control measures appropriate for control of MERS-CoV
Coronaviruses (CoVs)

- Enveloped positive strand RNA virus
- Human CoVs isolated in the 1960s
- Six human CoVs (HCoVs) have been identified to date:
  - HCoV-229E
  - HCoV-OC43
  - HCoV-NL63
  - HCoV-HKU1
  - SARS-CoV
  - Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
Coronavirus Classification

• Alpha
  – Human examples: HCoV-229E, HCoV-NL63
  – Pig, dog, and cat CoVs
• Beta
  – HCoV-OC43, HCoV-HKU1, HCoV-SARS
  – MHV, rat, pig and cow CoVs
  – **MERS-CoV**
• Gamma
  – Chicken and turkey CoVs
• Delta
  – Bird CoVs
Clinical Spectrum of Illness: HCoVs: 229E, NL-63, OC-43, HKU1

- Most often associated with upper respiratory tract infections in children
- Pneumonia and lower tract infections in immunocompromised individuals and the elderly
- May play a role in exacerbations of underlying respiratory diseases
Epidemiology: HCoVs: 229E, NL-63, OC-43, HKU1

- Worldwide
- Seasonality: Winter and spring in temperate climates
- Exposure common in early childhood
- Transmission likely to be droplet, contact, and indirect contact
- Symptoms and viral loads high first few days of illness
- Incubation period 2-5 days
Clinical Spectrum of Illness: SARS

- Fever, myalgia, headache, chills 1-2d, followed by a nonproductive cough and shortness of breath 5-7d after onset
- Most identified illnesses recognized in adults
- ~25% diarrhea
- 20-30% management in ICUs
  - ARDS, mechanical ventilation
- ~10-15% mortality rate, higher in adults >60y
Epidemiology: SARS

• First recognized Nov., 2002 as sporadic cases in Guandong province, China
• Outbreak period 2002-2003
• Hong Kong hotel contributed to spread of virus to several countries
• 8,098 probable SARS cases
  – 774 deaths
Epidemiology: SARS

• Incubation period is 2-10d* (median 4d)
• Transmission through droplets
  – Aerosol spread?
  – Fomites?
  – Fecal-respiratory transmission at an apartment complex in Hong Kong
• Transmission most likely during 2\textsuperscript{nd} week of illness
• Super spreading events
First Reported MERS-CoV Case

- 60 year old Saudi man
- Presented on June 13\textsuperscript{th} with 7d h/o fever and cough; recent shortness of breath
- Increasing blood urea nitrogen (BUN) and creatinine, starting day 3 of admission
- White cell count normal on admission (but 92.5\% neutrophils) and increased to a peak of 23,800 cells per cubic millimeter on day 10 with neutrophilia, lymphopenia, and progressive thrombocytopenia

First Case: Chest Radiographs

A: On admission
B: 2 days later

Bilateral enhanced pulmonary hilar vascular shadows (more prominent on the left) and accentuated bronchovascular lung markings. Multiple patchy opacities in middle and lower lung fields.

Opacities more confluent and dense.

First Case Outcome

- Patient developed acute respiratory distress syndrome (ARDS) and multiorgan dysfunction syndrome
- Died June 24th
- No close contacts with severe illnesses reported

Second Case

• 49 year old Qatari national
• Onset of illness September 3rd with mild respiratory symptoms
• September 9th- admission to Qatar hospital with bilateral pneumonia- subsequent intubation
• September 12th admitted to London ICU with respiratory failure and renal failure
• Fully dependent on ECMO
• History of travel to Saudi Arabia July 31- Aug. 18, where noted to have URI symptoms (and traveling companions)
• History of farm (camels and sheep) exposure, but no history of direct contact with these animals

Second Case: Management

- Airborne precautions
- Close contacts monitored for at least 10d
- 64 contacts identified among healthcare personnel (HCP), family, and friends
  - No severe acute respiratory illnesses identified
  - 13 HCP with mild respiratory symptoms
  - 10 HCP negative for MERS-CoV

MERS-CoV: Link

- Virus from second case compared to virus isolated from lung tissue of first case
- 99.5% identity: One nucleotide mismatch over regions (replicase) compared
- Genome sequence: JX869059.1
Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Emergence of a Novel Virus

Recognition of a novel coronavirus, Saudi Arabia and Qatar

April, 2012

Jordan cluster

Sept., 2012

1st family cluster, Saudi Arabia

Nov., 2012

UK family cluster

Feb., 2013

Imported UAE case into Germany

March, 2013

Healthcare facility cluster, Saudi Arabia

April, 2013

Healthcare facility cluster, France

May, 2013
Saudi Arabia Household Cluster

- A cluster of 4 respiratory illnesses in a family who lived in an apartment
  - All males; ages 16-70y
- All hospitalized
- 3 of 4 confirmed with MERS-CoV
- 3 of 4 patients with gastrointestinal symptoms: diarrhea, abdominal pain, anorexia)
- 2 deaths

Memish ZA et al. NEJM epub May 29, 2013
Saudi Arabia Household Cluster: Virus Detection

- Patient 1: Positive bronchial lavage specimen
- Patients 2 and 4: Sputum positive
- Patient 3’s illness milder and no lower respiratory tract specimens available; upper respiratory tract swabs negative

Memish ZA et al. NEJM epub May 29, 2013
124 healthcare workers remained healthy as of Jan., 2013
Jordan Cluster, April, 2012

- 2 confirmed cases reported retrospectively
- Both cases fatal
- Occurred at the same time as a cluster of severe respiratory illness among healthcare workers, N=13

Hijawi et al. EMHJ 2013; 19: Suppl 1: S12-S18
UK Cluster

Index case - traveled from SA and Pakistan; onset 1-24-13 Severe illness

2nd patient - onset 2-6-13 died

3rd patient - onset 2-5-13 Mild illness, recovered

HPA UK Novel Coronavirus Investigation Team; Eurosurv 2013; 18(11)
Timeline of UK Cluster

**Figure 1**
Timeline of three novel coronavirus cases, United Kingdom, December 2012 to February 2013

HPA UK Novel Coronavirus Investigation Team; Eurosurv 2013; 18(11)
UK Cluster: Public Health Implications

- Evidence of person-to-person transmission
- Coinfection with influenza (index case) and parainfluenza type 2 (both secondary cases)
- No sustained chains of transmission
- Incubation period may be 1-9 days

HPA UK Novel Coronavirus Investigation Team; Eurosurv 2013; 18(11)
Nosocomial Transmission in France, Index Patient

- 64 year old man, returned from travel to Dubai 5 days earlier
- History of renal transplantation
- Onset of symptoms: Diarrhea, fever, chills
- Abdominal CT showed pulmonary infiltrates 2d after onset
- Developed cough and dyspnea 4d after onset; initial NP swab deemed negative, but bronchoalveolar lavage specimen positive
- Respiratory failure, renal failure- death, 36 days after onset of illness

Guery et al. Lancet 2013; epub May 30
Nosocomial Transmission in France, Patient 2

- 51 year old man with history of myocardial infarction, arterial hypertension, and steroid therapy for histamine-induced angioedema. Also had history of several episodes of deep venous thrombosis
- Shared a hospital room with index patient during day 4-day 7 of index patient’s illness (index patient mostly confined to bed, while Patient 2 moved around)
- Shared bathroom
- NP swabs inconclusive; induced sputum positive for MERS-CoV
- No aerosolizing procedures performed for index patient
- No suspicion of MERS-CoV

Guery et al. Lancet 2013; epub May 30
Radiographs of Patient 2

A. Consolidation of right upper lobe, 1 day after onset of illness

B. 4 days after onset of illness, Ground glass opacity and consolidation of left lower lobe

C and D. Bilateral ground-glass opacities and consolidation, 7 days and 9 days after onset of illness, respectively

Guery et al. Lancet 2013; epub May 30
Timeline of French Cluster

Figure 3: Timeline of pertinent exposure, dates of illness, and virological findings in patients 1 and 2. Exposure (bold red line) shows the period during which the two patients shared the same room. BAL = bronchoalveolar lavage. NP = nasopharyngeal swab. SP = sputum. Inc = inconclusive. ECMO = extracorporeal membrane oxygenation. ICU = intensive care unit.

Guery et al. Lancet 2013; epub May 30
French Cluster: Public Health Implications

• Nosocomial transmission
• Initial presentation without respiratory symptoms
• Incubation period up to 9-12 days
• Lower respiratory tract specimens may be preferred samples for detection of MERS-CoV

Guery et al. Lancet 2013; epub May 30
MERS-CoV Outbreak in Saudi Arabia
April – May 2013

- Al-Ahsa governorate in eastern region
- Cluster currently being investigated
- 25 confirmed cases, 14 confirmed deaths
- 18 males, 7 females; Ages 14 - 94 years, median age: 58
- Initial cases associated with one hospital but now also:
  - Family contacts
  - Healthcare workers
  - Cases with no link to hospital
- Most cases with comorbidities
MERS-CoV- Overall Epidemiology

- Approximately 50% mortality rate
- Onsets between April 2012 and May 29, 2013
- Median age ~ 56 y
  - 2 pediatric cases reported
- Male predominance
- Most cases reported with comorbidities
- Cases by country of residence:
  - Saudi Arabia 40, UK 3, Jordan 2, Qatar 2, UAE 1, France 2, Tunisia 2, Italy 3
  - Three were returning travelers, 3 medical transfers
Confirmed cases of MERS-CoV \((n=55)\) and history of travel from the Arabian Peninsula
A Patient Under Investigation (PUI) is a person with:

- an acute respiratory infection, which may include fever (≥ 38°C, 100.4°F) and cough; AND
- suspicion of pulmonary parenchymal disease (e.g., pneumonia or acute respiratory distress syndrome based on clinical or radiological evidence of consolidation); AND
- history of travel from the Arabian Peninsula or neighboring countries within 14 days; AND
- not already explained by any other infection or etiology, including all clinically indicated tests for community-acquired pneumonia according to local management guidelines.
CDC Case Definition: Surveillance

- Persons who develop severe acute lower respiratory illness of known etiology within 14 days after travel from the Arabian Peninsula or neighboring countries but do not respond to appropriate therapy; OR

- Persons who develop severe acute lower respiratory illness who are close contacts of a symptomatic traveler who developed fever and acute respiratory illness within 14 days after travel from the Arabian Peninsula or neighboring countries. Close contact is defined as providing care for the ill traveler (e.g., a healthcare worker or family member), or having similar close physical contact; or stayed at the same place (e.g. lived with, visited) as the traveler while the traveler was ill.
Close contact is defined as:

- Any person who provided care for the patient, including a healthcare worker or family member, or had similarly close physical contact.
- Any person who stayed at the same place (e.g. lived with, visited) as the patient while the patient was ill.
CDC Case Definitions:

Probable Case

• Any person who-
  – meets the criteria above for “Patient Under Investigation” and has clinical, radiological, or histopathological evidence of pulmonary parenchyma disease (e.g. pneumonia or ARDS), but no possibility of laboratory confirmation exists, either because the patient or samples are not available or there is no testing available for other respiratory infections, AND
  – is a close contact with a laboratory-confirmed case, AND
  – has illness not already explained by any other infection or etiology, including all clinically indicated tests for community-acquired pneumonia according to local management guidelines.

• OR any person with-
  – severe acute respiratory illness with no known etiology, AND
  – an epidemiologic link to a confirmed MERS case.

Confirmed Case

• A person with laboratory confirmation of infection with MERS-CoV.
Interim Infection Prevention and Control Recommendations for Hospitalized Patients

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Interim Infection Prevention and Control Recommendations for Hospitalized Patients

- Standard, contact, and airborne precautions are recommended for management of hospitalized patients with known or suspected MERS-CoV infection
- These recommendations are consistent with those recommended for the coronavirus that caused severe acute respiratory syndrome (SARS)
- As information becomes available, these recommendations will be re-evaluated and updated as needed
Infection Control Recommendations for Hospitalized Patients

- These recommendations are for hospitalized patients who meet the case definition and are based on the following issues:
  - Poorly characterized clinical signs and symptoms, and a suspected high rate of morbidity and mortality among infected patients
  - Unknown modes of transmission of MERS-CoV
  - Lack of a vaccine and chemoprophylaxis
  - Evidence of limited, not sustained, human-to-human transmission
  - Absence of confirmed or probable MERS-CoV cases in the United States
Patient Placement

• Airborne Infection Isolation Room (AIIR)
  – If an AIIR is not available, the patient should be transferred as soon as is feasible to a facility where an AIIR is available.
  – Pending transfer, place a facemask on the patient and isolate him/her in a single-patient room with the door closed.
  – The patient should not be placed in any room where room exhaust is recirculated without high-efficiency particulate air (HEPA) filtration.
• Once in an AIIR, the patient’s facemask may be removed.
• When outside of the AIIR, patients should wear a facemask to contain secretions.
Patient Placement

• Limit transport and movement of the patient outside of the AIIR to medically-essential purposes.
• Implement staffing policies to minimize the number of personnel who must enter the room.
Personal Protective Equipment (PPE) for Healthcare Personnel (HCP)

- Gloves
- Gowns
- Eye protection (goggles or face shield)
- Respiratory protection that is at least as protective as a fit-tested NIOSH-certified disposable N95 filtering facepiece respirator
Personal Protective Equipment (PPE) for Healthcare personnel (HCP)

• Recommended PPE should be worn by HCP upon entry into patient rooms or care areas.
• Upon exit from the patient room or care area, PPE should be removed and either:
  – Discarded, or
  – For re-useable PPE, cleaned and disinfected according to the manufacturer’s reprocessing instructions.
Environmental Infection Control

• Follow **standard procedures**, per hospital policy and manufacturers’ instructions, for cleaning and/or disinfection of:
  – Environmental surfaces and equipment
  – Textiles and laundry
  – Food utensils and dishware
Laboratory Testing

• Lower respiratory specimens (sputum, bronchoalveolar lavage, endotracheal) are a priority respiratory specimen for real time reverse transcription polymerase chain reaction (RT-PCR) testing

• Respiratory (lower and upper tracts), stool, and serum specimens

• Specimen collection at different times
Emergency Use Authorization

• FDA issued an EUA on June 5, 2013, to authorize use of CDC's “Novel coronavirus 2012 real-time reverse transcription–PCR assay” to test for MERS-CoV in clinical respiratory, blood, and stool specimens.

• Assay will be deployed to Laboratory Response Network (LRN) laboratories in all 50 states over the coming weeks.
**Alphacoronavirus: TGEV**

- Leader
- ORF1a
- ORF1b
- S
- E
- M
- N
- 7
- Poly(A)

**Betacoronavirus: SARS-CoV**

- Leader
- ORF1a
- ORF1b
- S
- 3a
- E
- M
- N
- 8a
- 7a
- 7b
- 8b
- 9b
- Poly(A)

**Gammacoronavirus: IBV**

- Leader
- ORF1a
- ORF1b
- S
- 3a/b
- E
- M
- N
- Poly(A)

Figure 2 | **Structure of coronavirus genome and virion.**

- **a** | Schematic diagram of representative genomes from each of the coronavirus groups. Approximately the first two-thirds of the 26–32 Kbp, positive-sense RNA genome encodes a large polyprotein (ORF1a/b; green) that is proteolytically cleaved to generate 15 or 16 non-structural proteins (nsps; nsps for Severe acute respiratory syndrome coronavirus (SARS-CoV) are illustrated). The 3'-end third of the genome encodes four structural proteins — spike (S), membrane (M), envelope (E) and nucleocapsid (N) (all shown in blue) — along with a set of accessory proteins that are unique to each virus species (shown in red). Some group 2 coronaviruses express an additional structural protein, haemagglutinin-esterase (not shown).

- **b** | Schematic diagram of the coronavirus virion. 2′OMT, ribose-2′-O-methyltransferase; ExoN, 3′→5′ exonuclease; Hel, helicase; IBV, infection bronchitis virus; NendoU, uridylate-specific endoribonuclease; RDRP, RNA-dependent RNA polymerase; ssRBP, single-stranded RNA binding protein; ssRNA, single-stranded RNA; TGEV, transmissible gastroenteritis virus.
Perform NCV.E, NCV.N2 and RNP Assays

NCV Assay Pos Control Negative
- Repeat NCV Assay(s)

NCV Assay Pos Control Positive
- NCV Assay Neg Control Positive
  - Decontaminate Laboratory
  - Repeat NCV Assay(s)
- NCV Assay Neg Control Positive
  - RNP Assay Control Negative
    - Repeat NCV & RNP Assays from Same Extract or Re-extracted Sample
    - Repeat NCV Assay(s) if Unsure About Curve
- NCV Assay Neg Control Negative
  - RNP Assay Control Positive
    - Evaluate NCV.E & NCV.N2 Assay Results
    - NCV.E and/or NCV.N2 Assay Positive
      - Confirm with NCV.N3 Assay
        - NCV.N3 Assay Positive
          - Send Sample to Reference Laboratory
        - NCV.N3 Assay Negative
          - Report Negative
      - NCV.E and NCV.N2 Assay Negative
        - Report Negative
  - RNP Assay Control Negative

Courtesy of Dean Erdman
Approach to Serology

• Identify and generate candidate CoV antigens
  – Using proteins from similar bat viruses
• Develop ELISA-based assay
• Evaluate assay with an extensive panel of negative (specificity) and positive sera (sensitivity)
Location of Bat Sampling Sites

A - Ghana
B - Europe

Therapeutics

• No vaccines developed as of yet
• No antivirals identified as of yet
• Treatment is supportive
MERS-CoV Snapshot: June, 2013

- May cause mild to severe illness
- Evidence of person-to-person transmission
- Nosocomial spread with healthcare personnel transmission
- Focus in the Arabian Peninsula
- ~ 50% mortality rate
- No cases identified in the U.S.
Conclusions:

- MERS-CoV is a different virus than SARS-CoV, but also virulent
- More reported cases in past 2 months
- Persons with underlying health conditions at increased risk of severe disease
  - And transmission?
MERS Coronavirus Issues

• Human surveillance for additional cases
  – Laboratory diagnostics
  – Surveillance for severe acute respiratory infections
• Need for more investigations to understand human-to-human routes of exposure
• Animal surveillance
• Geography
• Management of patients under investigation
  – Rule out other etiologies
  – Infection control
  – Therapeutics
Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
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Thank you for joining!
Please email us questions at coca@cdc.gov

Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Information and Guidance for Clinicians

Date: Thursday, June 13, 2013
Time: 2:00 - 3:00 pm (Eastern Time)
Join by Phone:
Dial: 888-469-1678
Passcode: 3109821
Join by Webinar: https://www.mymetings.com/vc/join.php?v=PW1088072&amp;u=3109821&amp;t=c

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Overview:
Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a newly identified virus that can cause severe acute respiratory illness and death. MERS cases have been linked to the Middle East, and there is documented spread of the virus internationally. So far, no cases of MERS have been reported in the United States. However, clinicians need to remain vigilant. Epidemiologic investigations have demonstrated that this unique virus spreads from person to person during close contact, such as within families and healthcare facilities. Clinicians have a critical role in recognizing and managing suspect cases of MERS. During this COCA call, a CDC subject matter expert will discuss the clinical signs, epidemiology and infection control recommendations for MERS-CoV.
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