Of Camels, Bats and Coronaviruses: the (beginning of the) story of MERS-CoV

Allison McGeer, MSc, MD, FRCPC
Mount Sinai Hospital
University of Toronto
Objectives

• Discuss the epidemiology, clinical presentation, diagnosis, and management of MERS
• Review hospital outbreaks of MERS
Coronaviruses

- Group: IV (+)ssRNA
- Order: Nidovirales
- Family: Coronaviridae
- Sub-family: Coronavirinae
Phylogenetic relationships among members of the subfamily Coronavirinae and taxonomic position of MERS-CoV.

**Virus**

- Miniopterus bat coronavirus 1A AFCD62
- Miniopterus bat coronavirus HKU8 AFCD77
- Porcine epidemic diarrhea virus CV777
- Scotophilus bat coronavirus 512/2005
- Human coronavirus 229E
- Human coronavirus NL63 Amsterdam 1
- Rhinolophus bat coronavirus HKU2-GD/430/2006
- Transmissible gastroenteritis virus PUR46-MAD

**Species**

- Miniopterus bat coronavirus 1
- Miniopterus bat coronavirus HKU8
- Porcine epidemic diarrhea virus
- Scotophilus bat coronavirus 512
- Human coronavirus 229E
- Human coronavirus NL63
- Rhinolophus bat coronavirus HKU2

**Genus**

- **Alphacoronavirus**
  - Betacoronavirus 1
  - Murine coronavirus
  - Human coronavirus HKU1
- **Betacoronavirus**
  - SARS-related coronavirus
  - Rousettus bat coronavirus HKU9-1 BF-0051
- **Gammat coronavirus**
  - Tylochistis bat coronavirus HKU4-1 B04f
  - Pipistrellus bat coronavirus HKU5 LMH03f
  - MERS coronavirus Hu/Jordan-N3/2012
- **Deltacoronavirus**
  - Infectious bronchitis virus Beaudette
  - Beluga whale coronavirus SW1
  - Munia coronavirus HKU13-3514
  - Bulbul coronavirus HKU11-934
  - Thrush coronavirus HKU12-600
  - Avian coronavirus
  - Beluga whale coronavirus SW1
  - Munia coronavirus
  - Bulbul coronavirus
  - Thrush coronavirus

---

**PIG VIRUS ON THE WING**

Porcine epidemic diarrhoea virus, a type of coronavirus that can kill piglets, has been detected in 14 US states.

Date of first detection
- April 2013
- May 2013
- June 2013
HCoVs: 229E, OC-43, NL-63, HKU1

- Worldwide distribution
- Most often URIs in children
  - LRIs/more severe disease in elderly, immunocompromised
  - Mixed infections; exacerbations chronic illness
- Seasonal in temperate climates
- Transmission likely droplet/contact
- Incubation period ~2 days (1.5-5)
- Viral loads highest early in illness
SARS-CoV

- Clinical illness: non-specific fever and cough, followed by progressive pneumonia
  - CRF 3-20% overall, 50-60% in older adults and hospitalized patients
- Incubation period: 5 days (2-12 days)
- Viral load low early in illness – peaks at day 7-9
  - Much less infectious early in illness
Dr. Ali Zaki
Dr. Solomon Fakeeh Hospital
Jeddah, Saudi Arabia
The First Report

- A 60-year-old Saudi man was admitted to Dr. Solomon Fakeeh Hospital in Jeddah on June 13, 2012
- 7-day history of fever, productive cough, and shortness of breath.
- Admitted with progressive, multifocal pneumonia
  - BAL grew *S. aureus* and *K. pneumoniae*
  - Renal failure developed on day 3
  - Died on day 11 of respiratory and renal failure

Chest Radiography

Admission

HD#2

Computed Tomography

From an Admission Sputum

- Familywide PCR assays for coronaviruses yielded fragments of expected sizes
- Strong positive IF for IgG antibodies with patient serum at 1:20 (HD #10)
  - 2400 control samples from 2010-2012 were negative
A new human coronavirus was isolated from a patient with pneumonia by Dr. Ali Mohamed Zaki. The virus was isolated from sputum of a male patient aged 60 years old presenting with a form of rounding and synacta formation.

The clinical isolate was initially tested for influenza virus A, influenza virus B, paramyxovirus, and molecular weight appropriate for a coronavirus. The virus RNA was tested also in Dr. Zaki's laboratory for human and related to bat coronaviruses. Further analysis is being carried out in the Netherlands.

The Virology Laboratory at Dr. Fakieh Hospital will be happy to collaborate with other laboratories.

---

Ali Mohamed Zaki
Professor of Microbiology
Dr. Fakieh Hospital, Jeddah, Saudi Arabia
azaki53@hotmail.com

[ProMED-mail welcomes the opportunity to communicate Dr. Ali Mohamed Zaki's invitation to collaborate.]
WHO reports to March 27, 2014

Laboratory-confirmed cases of MERS-CoV by month (n=206)

- Number of cases
- Deaths
- Cases

Data valid 26.03.2014
What do we know about MERS clinical infection?

• Median incubation period 5 days (95% by 12 days)
• Causes severe, multifocal pneumonia
### Symptoms at Presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>46 (98%)</td>
</tr>
<tr>
<td>Fever with chills or rigors</td>
<td>41 (87%)</td>
</tr>
<tr>
<td>Cough</td>
<td>39 (83%)</td>
</tr>
<tr>
<td>Dry</td>
<td>22 (47%)</td>
</tr>
<tr>
<td>Productive (sputum)</td>
<td>17 (36%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>34 (72%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (26%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (13%)</td>
</tr>
</tbody>
</table>

# Progression of pulmonary disease

<table>
<thead>
<tr>
<th>Time from onset of symptoms to:</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>4 days</td>
<td>0-16 days</td>
</tr>
<tr>
<td>ICU admission</td>
<td>5 days</td>
<td>1-15 days</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>7 days</td>
<td>3-11 days</td>
</tr>
<tr>
<td>Death</td>
<td>11.5 days</td>
<td>4-298 days</td>
</tr>
</tbody>
</table>

Assiri et al. NEJM 2013;369:407
WHO MERS-CoV Research group PLOS Currents Outbreaks. 2013 Nov 12.
What do we know about MERS clinical infection?

- Median incubation period 5 days (95% by 12 days)
- Causes severe, multifocal pneumonia
  - Case fatality rate ~40%
  - ?may be some component of renal disease
- Some mild/asymptomatic cases in younger healthy adults and children
- Very few infections in children
  - most in hospitalized children with severe underlying conditions
Comparison of case fatality rates

- Influenza (hospitalized)
- Invasive pneumococcal disease
- SARS
- MERS

Percent fatal

- <18 years
- 18-64 years, healthy
- >=65 years, ill
- Nosocomial
What do we know about MERS pathogenesis/treatment?

• Presumptive binding domains/proteins identified (lower respiratory tract)
• 3 animal models: mice, rhesus macaques, marmosets
  - In rhesus macaques, ribavirin + interferon seems to have some effect

• Lesson learned:
  - Developing treatments for new infections takes time
  - Convalescent serum may be the most effective initial option
Convalescent plasma therapy
1918 H1N1 pandemic

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Mortality Rate, n/n (%)</th>
<th>Risk Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>Stoll (17)</td>
<td>25/56 (45)</td>
<td>201/379 (53)</td>
</tr>
<tr>
<td>O’Malley and Hartman (18)*</td>
<td>3/46 (7)</td>
<td>28/111 (25)</td>
</tr>
<tr>
<td>Ross and Hund (19, 20)</td>
<td>6/28 (21)</td>
<td>9/21 (43)</td>
</tr>
<tr>
<td>Kahn (21)</td>
<td>12/25 (48)</td>
<td>12/18 (67)</td>
</tr>
<tr>
<td>Gould (22)</td>
<td>2/30 (7)</td>
<td>82/290 (28)</td>
</tr>
<tr>
<td>McGuire and Redden (23, 24)*</td>
<td>6/151 (4)</td>
<td>120/400 (30)</td>
</tr>
<tr>
<td>Overall</td>
<td>54/336 (16)</td>
<td>452/1219 (37)</td>
</tr>
</tbody>
</table>

Luke AIM 2006
Hung et al.
RCT IVIG v. H-IVIG
Chest 2013;144:464

Table 3—Multivariate Analysis of Clinical Factors Independently Associated With Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-IVIG treatment within 5 d of symptom onset</td>
<td>0.14</td>
<td>0.02-0.92</td>
<td>.04</td>
</tr>
</tbody>
</table>
# SARS vs. MERS

## Incubation period
- **SARS-CoV**: 4.6 days (95% with onset by 12.9 days)
- **MERS-CoV**: 5.2 days (12.4 days)

## Serial interval
- **SARS-CoV**: 8.4 days
- **MERS-CoV**: 7.6 days

## Household attack rate
- **Toronto**: 10.2% (95% CI 6.7-23.5%)
- **Vietnam**: 4.2% (95% CI 1.5-7%)
- **Singapore**: 6.2% (95% CI 3.9-8.5%)
- **Hong Kong**: 8% (12% early - 6% late)
- **Beijing**: 4.6%
- **KSA**: 11% (4/36)
- **Elsewhere**: 5% (1/20)
First 179 cases MERS-CoV primary and secondary cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary (N=74)</th>
<th>Secondary (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>58 years</td>
<td>48 years</td>
</tr>
<tr>
<td>Gender</td>
<td>80% male</td>
<td>58% male</td>
</tr>
<tr>
<td>Healthcare worker</td>
<td>3%</td>
<td>35% (80% female)</td>
</tr>
<tr>
<td>Hospitalized patient</td>
<td>-</td>
<td>~35%</td>
</tr>
</tbody>
</table>

WHO MERS CoV Update 27 March 2014
Dialysis patient
Hospitalized for CHF
Infected on Ward A
(April 5-8)

6 dialysis patients infected
April 11-13 (shared shifts)

3 other dialysis patients and one
Family member infected secondarily

Dialysis unit ICU

Dialysis patient from *different*
unit hospitalized for pulmonary
edema; infected in ICU (April 20-22)

Hospital 2: 18 infections
(one MD died)

Dialysis unit 2: 2 patients infected
(adjacent chair, and shared transport)

Ward B – 2 patients and 1 visitor infected
What is important about hospitals?

1. On-going clusters
   • Due to difficulty in recognizing and diagnosing disease

2. Proportion of cases in hospital clusters
   • 60 /146 (41%) initial cases attributed to transmission in healthcare settings
   • 30 healthcare workers; 19 patients; 6 visitors

3. Case fatality rate
   • Among patients with hospital-acquired disease: >70%
   • Among HCWs: 4/32 (12.5%)

WHO MERS-CoV Research group PLOS Currents Outbreaks. 2013 Nov 12.
## SARS versus MERS

<table>
<thead>
<tr>
<th>Percent of healthcare-acquired cases:</th>
<th>Hong Kong</th>
<th>Toronto</th>
<th>Beijing</th>
<th>Taiwan</th>
<th>MERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare workers</td>
<td>23%</td>
<td>39%</td>
<td>16%</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Hospital patients</td>
<td>-</td>
<td>22%</td>
<td>6%</td>
<td>-</td>
<td>13%</td>
</tr>
<tr>
<td>Visitors</td>
<td>-</td>
<td>16%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patients and visitors</td>
<td>53%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4%</td>
</tr>
</tbody>
</table>
Disease distribution in healthcare workers

- Al-Musa outbreak
  - 100 exposed HCWs, including 18 full-time staff of dialysis unit – 1 case; one ARI (untested)

- Reported from KSA
  - 12 HCWs; 3 asymptomatic, 4 ILI, 3 severe disease, 2 deaths

- WHO update Jan 2014
  - 32 HCWs: 7 severe disease, 4 died

Taphozous perforatus

Memish et al. EID Nov 2013
*Neoromicia* cf. *zuluensis*

![Image of bat and map of Africa with highlighted areas in yellow, labeled HKU4/HKU5-related MERS-CoV Clade 2c.]

Ithete et al. EID Oct 2013
[http://wwwnc.cdc.gov/eid/article/19/10/13-0946_article.htm](http://wwwnc.cdc.gov/eid/article/19/10/13-0946_article.htm)

Memish et al. EID Nov 2013
Intermediary Host: Camels?
Reactivity of livestock sera with three coronavirus S1 antigens

Chantal B E M Reusken et al, The Lancet 2013
What do we know about MERS-CoV in camels?

- Present (same or highly related virus) since at least 1990s

<table>
<thead>
<tr>
<th>Yr</th>
<th>Location</th>
<th>Age group</th>
<th>No.</th>
<th>% Seropositive (no. positive/total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Riyadh</td>
<td>Adult</td>
<td>1</td>
<td>100 (1/1)</td>
</tr>
<tr>
<td>1993</td>
<td>Riyadh</td>
<td>Adult</td>
<td>2</td>
<td>100 (2/2)</td>
</tr>
<tr>
<td>1994</td>
<td>Empty quarter</td>
<td>Adult</td>
<td>123</td>
<td>93 (114/123)</td>
</tr>
<tr>
<td>1996</td>
<td>Riyadh</td>
<td>Adult</td>
<td>6</td>
<td>100 (6/6)</td>
</tr>
<tr>
<td>2004</td>
<td>Riyadh</td>
<td>Adult</td>
<td>6</td>
<td>100 (6/6)</td>
</tr>
<tr>
<td>2009</td>
<td>Riyadh</td>
<td>Juvenile</td>
<td>56</td>
<td>72 (40/56)</td>
</tr>
<tr>
<td>2009</td>
<td>Rumah</td>
<td>Adult</td>
<td>26</td>
<td>92 (24/26)</td>
</tr>
<tr>
<td>2010</td>
<td>Riyadh</td>
<td>Juvenile</td>
<td>21</td>
<td>76 (16/21)</td>
</tr>
<tr>
<td>2010</td>
<td>Kharj</td>
<td>Adult</td>
<td>23</td>
<td>91 (21/23)</td>
</tr>
</tbody>
</table>
What do we know about MERS-CoV in camels?

• Present (same or highly related virus) since at least 1990s
• Some camels seropositive in all countries tested
• Seropositivity higher in adult (≥2yrs) than juvenile camels (93% vs. 55%)
• Appears to be associated with (mild) respiratory illness in some cases
• Infection rates variable geographically

Chu EID 2014:20 June; Memish EID 2014:20 June; Aligaili mBio 2014:5:2
TABUK
Juveniles (N=24)
63% seropositive
58% PCR pos

HOFUF
Juveniles (N=24)
90% seropositive
0 PCR pos

TAIF
Juveniles (N=24)
41% seropositive
68% PCR pos

UNIZAH
Juveniles (N=18)
83% seropositive
15% PCR pos

GIZAN
Juveniles (N=21)
5% seropositive
0 PCR pos
Phylogeny of camel & human cases
So what is the problem with camels?

• Most cases don’t have direct exposure
Comparison of primary and secondary cases of MERS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary (N=74)</th>
<th>Secondary (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>58 years</td>
<td>48 years</td>
</tr>
<tr>
<td>Gender</td>
<td>80% male</td>
<td>58% male</td>
</tr>
<tr>
<td>Healthcare worker</td>
<td>3%</td>
<td>35% (80% female)</td>
</tr>
<tr>
<td>Hospitalized patient</td>
<td>-</td>
<td>~35%</td>
</tr>
<tr>
<td>Camels Contact</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Any association</td>
<td>55%</td>
<td>4%</td>
</tr>
</tbody>
</table>

WHO MERS CoV Update 27 March 2014
So what is the problem with camels?

• Most cases don’t have direct exposure

• People who DO have direct exposure aren’t getting sick and aren’t seropositive
  – 179 abattoir workers in Egypt

• Disease is limited to the Arabian peninsula and predominantly KSA
  – But only 260,000 of 27,000,000 camels live in KSA
What next?
Next steps

• Identify means of transmission from camels to humans
  – Essential to preventing human infections
• Understand what happened that led to camel-human transmission
• Continue to monitor evolution carefully
• Treatment, vaccines, diagnosis, understanding hospital transmission
Questions?