MERS CoV: Epidemiology, the Disease, Transmissibility and Pandemic Potential

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Overview

MERS CoV
- History
- Microbiology
- Epidemiology
- Transmissibility
- Spatial distribution
- Case Fatality
Mers CoV

- A 60-year-old Saudi man was admitted on June 13, 2012
- 7-day history of fever, productive cough, and shortness of breath.
- He had no history of cardiopulmonary or renal disease, no long-term medications, non-smoker
- PE: BP=140/80 mm Hg, pulse = 117 beats/minute, temperature =38.3°C, and RR=20 breaths/minute.
- Treatment was started with oseltamivir, levofloxacin, piperacillin–tazobactam, and micafungin

Computed Tomography

Meanwhile... From an Admission Sputum

LLC-MK2

LLC-MK2HCoV-EMC

Vero

VeroHCoV-EMC

Sequencing

- Originally named HCoV-EMC (for Erasmus Medical Center)
- Belongs to lineage C of the genus β-coronavirus (with bat coronaviruses HKU4 and HKU5)
- SARS-CoV is lineage B
- 5 other human coronaviruses indicated in red

*1960s  
** post-SARS
Testing with a pancoronavirus RT-PCR yielded a band at a molecular weight appropriate for a coronavirus. The virus RNA was tested also in Dr. Ron Fouchier's laboratory in the Netherlands and was confirmed to be a new member of the beta group of coronaviruses, closely related to bat coronaviruses.
A new human coronavirus was isolated from ... sputum of a male patient aged 60 years old presenting with pneumonia associated with acute renal failure.
The Next SARS?

- Tests for specific and well-known coronaviruses were negative but general test for coronavirus family positive.
- Sequence showed genus β-coronavirus, with closest relationships to bat coronaviruses HKU4 and HKU5.
- Sequenced and compared to results from Fouchier: 99.5% identity with one nucleotide mismatch over regions (replicase) compared.
- 13 close contacts with mild self-limiting respiratory illnesses (all HCWs).
  - 10 had nose and throat swabs tested by pan-coronavirus assay and were negative.

WHO Global Alert:
September 23, 2012

Global Alert and Response (GAR)

Novel coronavirus infection in the United Kingdom

23 SEPTEMBER 2012 - On 22 September 2012, the United Kingdom (UK) informed WHO of a case of acute respiratory syndrome with renal failure with travel history to Saudi Arabia and Qatar.

The case is a previously healthy, 49 year-old male Qatari national that presented with symptoms on 3 September 2012 with travel history to Saudi Arabia prior to onset of illness. On 7 September he was admitted to an intensive care unit (ICU) in Doha, Qatar. On 11 September, he was transferred to the UK by air ambulance from Qatar. The Health Protection Agency of the UK (HPA) conducted laboratory testing and has confirmed the presence of a novel coronavirus.
The Jordan Cluster: Earliest Cases

• In April 2012, the MOH in Jordan reported an outbreak of acute respiratory illness largely affecting healthcare workers (HCWs) who worked in an ICU of a Zarqa hospital.

• The 2 deceased patient specimens were available tested positive for MERS CoV.

• Retrospective case-finding for the 6 week period encompassing the confirmed cases identified 11 additional probable cases, 9 of whom were HCWs.
Timeline of 13 Cases of MERS, Jordan
March to May 2012

Case 13  mother of case 2
Case 12  Nurse
Case 11  Internist
Case 10  Nurse Emergency Ward
Case 9  CCU Nurse
Case 8  brother of case 3
Case 7  Nurse Emergency Ward
Case 6  Nurse CCU
Case 5  Nurse Internal ward
Case 4  Internist
Case 3  Nurse ICU
Case 2  staff CCU
Case 1  student

Date of Onset of Symptoms

Mildly ill (home sick)  Admission to ward  Zarqa Hospital CCU  Hamza Hospital CCU  Islamic Hospital CCU  Possible contact period  Death  HOV  Health Care worker
Evolution of the Epidemiology

Spatial distribution of MERS CoV cases
Al Hasa Intra-Hospital Outbreak

Outbreak based in multiple hospitals in Al Hasa serving a governate of 1.1 million of rural and urban dwellers

Initial focus was in two dialysis units and several ICUs

Team performed chart review, survey collection to investigate hospital based outbreak

Assiri et al, NEJM, 2013
Al Hasa Epidemic Curve

Assiri et al, NEJM, 2013
Cases

- 21/23 (+2 probable cases) acquired by person-to-person transmission in HD units, ICUs, or in-patient units in 3 facilities
- Among 217 household contacts and > 200 HCW contacts, MERS-CoV infection developed in
  - 5 family members (3 laboratory-confirmed)
  - 2 HCW (both laboratory-confirmed)

Assiri et al, NEJM, 2013
### Identifying Timing of Symptom Onset and Spatial Location

**Assiri et al., NEJM, 2013**

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#### Table: Health Care Facility of Transmission

<table>
<thead>
<tr>
<th>Patient acquiring infection</th>
<th>Health care facility of transmission, if healthcare acquired</th>
<th>Most likely exposure in healthcare</th>
<th>Day(s) of illness in source patient</th>
<th>Other potential healthcare exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Hospital A, ward 1</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
</tr>
<tr>
<td>D</td>
<td>Hospital A, dialysis unit</td>
<td>Adjacent bed, dialysis session patient C for 3.3 hours</td>
<td>First</td>
<td>None identified</td>
</tr>
<tr>
<td>E</td>
<td>Hospital A, dialysis unit</td>
<td>Adjacent bed, dialysis session patient C for 1.0 hour</td>
<td>Third</td>
<td>Same dialysis session, patient D, 2 beds apart for 1.25 hours</td>
</tr>
<tr>
<td>F</td>
<td>Hospital A, dialysis unit</td>
<td>Adjacent bed, dialysis session patient C for 1.3 hours</td>
<td>Third</td>
<td>None identified</td>
</tr>
<tr>
<td>G</td>
<td>Hospital A, dialysis unit</td>
<td>Same dialysis session as patient C, 3 beds apart for 3.5 hours</td>
<td>First</td>
<td>Same dialysis session, patient D, 2 beds apart for 0.75 hours</td>
</tr>
</tbody>
</table>
Figure 2. Transmission Map of Outbreak of MERS-CoV Infection.

All confirmed cases and the two probable cases linked to transmission events are shown. Putative transmissions are indicated, as well as the date of onset of illness and the settings. The letters within the symbols are the patient identifiers (see Fig. S2 in the Supplementary Appendix).

Assiri et al, NEJM, 2013
Estimated incubation Period to be 5.2 days (95% CI 2.2 to 12.4 days) (SARS 4.0 (95% CI 1.8, 10.6 days))
Estimated Serial Interval to 7.6 days (95% CI 3.0 to 19.4 days) (SARS Median 8.4 days)

Assiri et al, NEJM, 2013
Genetic Mapping: Al Hasa Outbreak
Genetic Distance of Al-Hasa Isolates from Other MERS CoV Isolates

Cotten et al, Lancet, 2013
Eliminating some transmissions that were inconsistent with genetic evidence has little effect on natural history parameters estimated from Al Hasa outbreak

Estimated incubation period = **5.1 days (95% CI 2.2 to 11.9 days)** (SARS 4.0 (95% CI 1.8, 10.6 days))

Estimated Serial Interval = **7.2 days (95% CI 3.0 to 17.7 days)** (SARS Median 8.4 days)
Age range is 2 - 94 years; median age is 50 years.

Males cases is 62%. In the beginning of the outbreak, the majority of the age groups had more male than female cases.

Comorbidities

- Diabetes: 26%
- Chronic Kidney Disease: 19%
- Chronic Heart Disease: 11%
- Hypertension: 13%
- Chronic Lung Disease: 10%
- Obesity: 7%
- Smoking: 9%
- Malignancy: 1%
- Steroid Use: 2%
- No Comorbidity: 2%

• Bat viruses from Bats in South Africa have been found to be genetically very similar to MERS
• 3.5% of bats in KSA infected with MERS CoV
• 1 bat MERS CoV sequence was identical to a patient MERS CoV sequence
• Serologic evidence of infection in dromedary camels (9 / 11)
• Camels MERS CoV documented in 2/12 animals (99% similar to MERS CoV)
• Clades in camels correlate with those of human clusters
• Testing among sheep, cattle, goats, chickens – No MERS CoV

Mortality

- Over 178 cases reported from primarily 6 countries; 85% from KSA
- Case Fatality Rates by Age
  - >50 77%
  - <50 22%
  - HCW 12.5%
- Cauchemez describe a trend in reducing case fatality rate suggesting a increase in capture of less severe cases
- However, trend isn’t dramatic
- Initial CFR (74% (95% CI 49-91%)-secondary cases (21% 95% CI 7-42%)
- Significant under reporting estimated

Cauchemez et al. Lancet 2014
Basic Reproductive Numbers

- Average number of secondary infections attributable to a single infectious individual in an entirely susceptible population
  - Crude estimate from Al Hasa outbreak of reproductive number 0.6
  - Breban et al, estimated $R_0$ to be 0.69 for MERS
  - SARS during early days was estimated to 0.8
- Lots of uncertainty and as data come out things can change
- Relatively small cluster sizes indicate transmission can be controlled once cluster detected and interventions put in place.
- $R$ of index case of clusters (~ before interventions are in place) in range 0.8-1.3 depending on assumption about generation time.
Reproductive Number

- Analysis of epidemic curve and genetic sequences indicates a slowly growing epidemic either in humans or in an animal reservoir.
- Ranges 0.8-1.3 in the absence of controls
- Chains of transmission not sustained with infection controls measures
Assessing Multiple Transmission Scenarios

Proportion of human cases due to human-to-human transmission in the epidemic - a function of $R_0$, GT-12 days.

Probability that transmission chains will be sustained for a finite period (1 yr) - a function of $R_0$, GT-12 days.

Cauchemez et al. Lancet 2014
Probability of a Self Sustaining Epidemic as a Function of $R_0$ and the Number of Introductions
Genetic Relationship of all Isolates of MERS and Multiple Hypotheses of the Pattern of Introduction
Summary 1

• All cases have been directly or indirectly linked through travel to or residence in Saudi Arabia, Qatar, Jordan, United Arab Emirates, Kuwait and Oman

• Respiratory symptoms almost universal; GI symptoms in ¼; most with comorbidities, age ~50.

• Sequencing data suggests multiple, ongoing community introductions, and human-to-human spread especially in families and healthcare

• Risk factors are not well studied (mostly observational) and case control studies are essential

• Treatment strategies not being systematically evaluated

• Lower respiratory specimens preferred for diagnosis
Summary 2

• Ongoing cases and transmission
  – Transmission not well-defined (person to person; animal to person; what else??) and may be affected by viral evolution
  – Analysis of individual time course of transmissibility may help prioritize intervention
  – Seasonal changes may affect transmission (still don’t know what seasonality is)
  – Amount of asymptomatic transmission poorly characterized
  – Pandemic potential not yet realized

• Synthesis of genetic data and incidence data can yield models to help build case for particular scenarios

• Ongoing sharing of data will facilitate understanding of this virus
Thanks to the team

- All of the infection preventionists in Al Hasa
- Keiji Fukada
- Matt Freiman
- Dan Jernigan and David Sweldlow