Case Study 1: MERS-CoV

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Learning Objectives

- Upon completion, participants should be able to:
  - Recognize when to be concerned about potential emerging infections
  - Understand universal actions that can and should be taken to care for patients, staff, and public
Outline

- Part I: Background on emerging respiratory infections
- Part II: Case study: MERS-CoV
- Part III: Reflections and recommendations

Part I: Background on Emerging Respiratory Infections
When Should You Be Concerned About an Emerging Infection?

- An unusual case or cluster of cases
- A previously undetected or unknown infectious agent
- A known agent that has:
  - Spread to new geographic locations or new populations
  - Re-emerged following a declining incidence of disease
  - A genetic adaptation changing illness severity
- Examples: SARS, MERS-CoV, measles, Zika, human adenovirus 14p1, influenza (variants H3N2, H7N9)

Geographic Distribution of Recent Outbreaks*

Transmission of Respiratory Viruses

- Remains a source of controversy
- Observational studies in healthcare settings indicate that contact (direct and indirect) and droplet transmission are the primary means of spread
- Relative contributions of each type of transmission is unknown
- Anecdotal experience with airborne transmission can be helpful in understanding the factors that contribute to transmission


Which Interventions Are Best at Preventing Respiratory Infections?

Comparison 1. Case Control Studies

<table>
<thead>
<tr>
<th>Outcome or Subgroup Title</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Statistical Method</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorough disinfection of living quarters</td>
<td>1</td>
<td>990</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.30 [0.23, 0.39]</td>
</tr>
<tr>
<td>Frequent handwashing</td>
<td>6</td>
<td>2,077</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.45 [0.36, 0.57]</td>
</tr>
<tr>
<td>Wearing mask</td>
<td>5</td>
<td>1,991</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.32 [0.25, 0.40]</td>
</tr>
<tr>
<td>Wearing N95 mask</td>
<td>2</td>
<td>340</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.09 [0.03, 0.30]</td>
</tr>
<tr>
<td>Wearing gloves</td>
<td>4</td>
<td>712</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.43 [0.29, 0.65]</td>
</tr>
<tr>
<td>Wearing gowns</td>
<td>4</td>
<td>712</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.23 [0.14, 0.37]</td>
</tr>
<tr>
<td>All interventions</td>
<td>2</td>
<td>369</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.09 [0.02, 0.35]</td>
</tr>
</tbody>
</table>

Effectiveness of Precautions: Lessons From SARS

- Case-control study in 5 Hong Kong hospitals with 241 noninfected and 13 infected staff
- Retrospective cohort study in 2 Toronto critical care units with 35 noninfected and 8 infected nurses

<table>
<thead>
<tr>
<th>Precaution</th>
<th>Hong Kong</th>
<th>Toronto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handwashing</td>
<td>0.2 (0.07-1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gloves</td>
<td>0.5 (0.14-1.6)</td>
<td>0.45 (0.14-1.46)</td>
</tr>
<tr>
<td>Gown</td>
<td>Undef ($P=0.066$)</td>
<td>0.36 (0.10-1.24)</td>
</tr>
<tr>
<td>Mask</td>
<td>0.08 (0.02-0.33)</td>
<td>0.23 (0.07-0.78)</td>
</tr>
</tbody>
</table>

Source Control: Efficacy of Surgical and N95 Masks to Filter Influenza in Positive Patients

<table>
<thead>
<tr>
<th>Patient or Variable</th>
<th>Influenza Type</th>
<th>Nasal Swab</th>
<th>No Mask, Before Control (Step 1)</th>
<th>N95 Mask (Step 2)</th>
<th>Surgical Mask (Step 3)</th>
<th>No Mask, After Control (Step 4)</th>
<th>Duration of Illness, Days Per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 A</td>
<td>31</td>
<td>38</td>
<td>Negative</td>
<td>Negative</td>
<td>39</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Patient 2 A</td>
<td>26</td>
<td>40</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 3 A</td>
<td>22</td>
<td>34</td>
<td>Negative</td>
<td>Negative</td>
<td>40</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Patient 4 A</td>
<td>26</td>
<td>34</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 5 A</td>
<td>23</td>
<td>32</td>
<td>Negative</td>
<td>Negative</td>
<td>33</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Patient 6 A</td>
<td>25</td>
<td>27</td>
<td>Negative</td>
<td>Negative</td>
<td>25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 7 B</td>
<td>22</td>
<td>38</td>
<td>Negative</td>
<td>Negative</td>
<td>27</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Patient 8 A</td>
<td>29</td>
<td>34</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Patient 9 B</td>
<td>27</td>
<td>30</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>39</td>
<td>3</td>
</tr>
</tbody>
</table>

Mean cycle time for patients with detected influenza A: $26^a$, $34.17^a$, $0$, $0$, $34.4^a$, $2^b$

Estimated viral load for detected influenza A, copies/mL: $5$ million$^a$, $50,000^a$, $0$, $0$, $50,000^a$, $\ldots$

Note: Cycle number indicates real-time RT-PCR cycle number. The cycle number value is inversely proportional to the titer of virus present.

$a$Mean value calculated from patients with detectable influenza A.

$b$Mean duration.

Nosocomial ARI Outbreaks

- Nosocomial outbreaks documented in a variety of healthcare settings, including general medical wards, LTCFs, and pediatrics and oncology units
- In 2009, among 1,520 hospitalized patients with pH1N1, 30 acquired influenza nosocomially
  - 57% received antivirals, 53% received escalated care, and 27% died
- Nosocomial outbreaks can also result in up to 50% attack rates in staff, staff furloughs, and increased costs for the institution


<table>
<thead>
<tr>
<th>Species</th>
<th>Total No. Outbreaks</th>
<th>Outbreaks Including Some Kind of Closure</th>
<th>Closure Rate</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>223</td>
<td>23</td>
<td>10.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatitis virus</td>
<td>150</td>
<td>6</td>
<td>4.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>130</td>
<td>10</td>
<td>7.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>115</td>
<td>10</td>
<td>8.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Acinetobacter spp</td>
<td>105</td>
<td>24</td>
<td>22.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Serratia spp</td>
<td>94</td>
<td>14</td>
<td>14.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Enterococci</td>
<td>67</td>
<td>8</td>
<td>11.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>66</td>
<td>10</td>
<td>15.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Streptococci</td>
<td>63</td>
<td>18</td>
<td>28.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>56</td>
<td>4</td>
<td>7.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Legionella spp</td>
<td>48</td>
<td>2</td>
<td>4.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Norovirus</td>
<td>34</td>
<td>15</td>
<td>44.1%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Clostridium spp</td>
<td>14</td>
<td>4</td>
<td>11.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>11</td>
<td>3</td>
<td>27.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Shigella spp</td>
<td>11</td>
<td>4</td>
<td>36.4%</td>
<td>0.04</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>27</td>
<td>7</td>
<td>25.9%</td>
<td>0.05</td>
</tr>
<tr>
<td>SARS coronavirus</td>
<td>12</td>
<td>4</td>
<td>33.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>1,561</td>
<td>194</td>
<td>12.4%</td>
<td>—</td>
</tr>
</tbody>
</table>

*Only pathogens that had been reported in at least 10 outbreaks are included.
*Multiple answers possible.

Part II: MERS-CoV Outbreaks

MERS-CoV: Saudi Arabia, 2012

- 60-year-old Saudi man admitted to hospital on June 13, 2012
  - 7-day history of fever, productive cough, and shortness of breath
  - No history of cardiopulmonary or renal disease, no long-term medications, nonsmoker

**Treatment**

- Oseltamivir, levofloxacin, piperacillin-tazobactam, and micafungin

**Physical Examination Findings**

<table>
<thead>
<tr>
<th>Physical Findings</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>140/80 mm Hg</td>
</tr>
<tr>
<td>HR</td>
<td>117 beats/min</td>
</tr>
<tr>
<td>Temp</td>
<td>38.3° C</td>
</tr>
<tr>
<td>RR</td>
<td>20 breaths/min</td>
</tr>
</tbody>
</table>

Immediate Steps

- Data to collect and/or consider
  - Exposures
    - Other ill persons
    - Animals
  - Season
  - Travel
- How do I protect HCP, visitors, and other patients?
  - Isolation/cohorting
  - PPE
  - Source control

Re-Evaluate

- Data to collect and/or consider
  - Exposures
    - Other ill persons
    - Animals
  - Season
  - Travel
- Do I need additional measures in place to protect HCP, visitors, and other patients?
  - Isolation/cohorting
  - PPE
  - Source control
What Now?

We have:
- Atypical and severe respiratory illness with routine diagnostic testing not revealing expected pathogens
- Unusual finding on viral cultures
- No expected “exposures”

We should:
- Send specimen for additional testing
- Ensure appropriate isolation and PPE
- Conduct a literature search
- Call public health authorities regarding other potential cases
- Call colleagues regarding other potential cases

ProMED-mail:
Saturday, September 15, 2012

A new human coronavirus was isolated from sputum of a male patient aged 60 years old presenting with pneumonia associated with acute renal failure.

Testing with a pancoronavirus RT-PCR yielded a band at a molecular weight appropriate for a coronavirus. The virus RNA was also tested 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.
What Do We Know About Coronavirus?

- Single-stranded RNA
- Common cause of respiratory virus infections
  - Mild infections: alpha 229E and NL63, beta OC43
  - Severe infections: SARS-CoV, MERS-CoV
- Natural hosts include bats, civet cats, dogs, and rodents

Sequencing MERS-CoV

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

- On September 14, 2012, a patient with unexplained severe respiratory illness was transferred to intensive care in London after traveling from Qatar
  - Negative for specific and well-known coronaviruses
  - Positive for general coronavirus family
  - Sequence showed genus β-coronavirus with closest relationships to bat coronaviruses HKU4 and HKU5
    - 99.5% sequence similarity to novel human coronavirus recovered from a Saudi Arabian man who died in June 2012
  - 13 close contacts (all HCWs) with mild self-limiting respiratory illnesses


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.
Evaluating the Situation Further

- What key facts do you need to determine?
  - Who?
  - What?
  - Where?
  - When?

- What is the likely transmission? Or source?
  - What is the incubation period? Serial interval?

- What is a case?

- Important epidemiologic findings from the Al-Hasa outbreak
  - Interhospital transmission
  - Transmission in ICU and crowded settings
  - Key individuals who spread to many other individuals

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 settings.

Transmission Dynamics

- Incubation period
  - The time from exposure to developing symptoms

- Serial interval
  - The time between successive cases
    - Ex: the time between when the first case develops symptoms and the onset in a secondary case
Estimated incubation period: \textbf{5.2 days} (95\% CI, 2.2-12.4) (SARS 4.0 days [95\% CI, 1.8-10.6])
Estimated serial interval: \textbf{7.6 days} (95\% CI, 3.0-19.4) (SARS median 8.4 days)

MERS-CoV: South Korea, 2015

- A 68-year-old South Korean man developed fever and myalgia on May 11, 2015, after returning from a business trip to the Middle East
- He was diagnosed with MERS-CoV on May 20, 2015, after contacting approximately 600 people during his visits to health centers
- 26 cases were confirmed from these initial contacts; transmission via nosocomial infection followed after that
MERS-CoV: South Korea, 2015

- Approximately one-half of the MERS-CoV cases (92/186) in South Korea were associated with a 1,950-bed, tertiary care university hospital
- 82 cases originated from one unprotected exposure
  - Crowded emergency department
- Experimental evidence later supported the possible contribution of MERS-CoV contamination of air and surrounding materials in the outbreak

Environmental Contamination: South Korea, 2015

- Rooms of 4 patients in 2 hospitals examined for environmental contamination of MERS-CoV
- Gathered air samples and swabbed high-touch and ventilation surfaces for viral culture and PCR
- 4/7 air samples tested positive
- 15/68 surfaces contaminated with MERS-CoV live virus
  - Room, anteroom, medical equipment (bed sheets and rails, IV fluid hangers, tables, outlets)
- Many surfaces PCR-positive up to 27 days after symptom onset

### Comparison of Case and Environment: South Korea, 2015

**Patient Case Status and Environmental Test Results in 2 MERS-Designated Hospitals, Republic of Korea**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>No.</th>
<th>Case Status</th>
<th>Time of Sampling for PCR (Days After Symptom Onset)</th>
<th>MERS-CoV PCR Results</th>
<th>Environmental Sampling</th>
<th>RT-PCR From Samples</th>
<th>RT-PCR From Viral Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>Pneumonia on mechanical ventilation and ECMO</td>
<td>22</td>
<td>(+) at the time of sampling</td>
<td>Air sampling</td>
<td>2/2</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fomites swab</td>
<td>4/6</td>
<td>2/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fixed-structure swab</td>
<td>7/13</td>
<td>2/13</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Pneumonia on mechanical ventilation</td>
<td>16</td>
<td>(+) at the time of sampling</td>
<td>Air sampling</td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fomites swab</td>
<td>4/4</td>
<td>3/4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fixed-structure swab</td>
<td>12/12</td>
<td>5/12</td>
</tr>
<tr>
<td>Elevator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fixed-structure swab</td>
<td>1/5</td>
<td>0/5</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>Pneumonia and bedridden</td>
<td>19</td>
<td>(-) at the time of sampling</td>
<td>Air sampling</td>
<td>3/3</td>
<td>1/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fomites swab</td>
<td>5/6</td>
<td>2/6</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fixed-structure swab</td>
<td>8/17</td>
<td>0/17</td>
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<tr>
<td>Elevator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fixed-structure swab</td>
<td>1/5</td>
<td>1/5</td>
</tr>
</tbody>
</table>


### Part III: Reflections and Recommendations
Why Did These Outbreaks Occur?

- Surveillance and case finding are limited
  - Unable to identify cases in a timely fashion (diagnostic and logistics)
    - PCR testing can take 4 or 5 days
    - Serology is unreliable
    - Variable approaches to screening
- Poor recognition of syndromes and risk factors
  - Spectrum of disease not identified early
  - Risk factors for transmission in healthcare not fully understood

Why Did These Outbreaks Occur? (cont.)

- System issues
  - Intrahospital transfers
  - Visitation and family care policies
- Poor internal and external communication
  - Lack of transparency about outbreak facts to public health community
  - Isolation precautions and use of barrier precautions not followed or understood
  - Inadequate quantities of isolation materials
  - Confusion about recommendations for barrier precautions to be used (CDC vs WHO)
Guidelines for MERS-CoV: Before the First Case Preparation

- Surveillance
- Education
- Laboratory readiness
- Communication
- Planning
- Case treatment

Guidelines for MERS-CoV: Management

- Accommodation
- Additional precautions
- Diagnosis
- Communication
- Education/training
- Follow-up for identification of transmission
The Science: SARS vs MERS*

<table>
<thead>
<tr>
<th></th>
<th>SARS</th>
<th>MERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative number of case(s)</td>
<td>8,098</td>
<td>1,905</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>774</td>
<td>677</td>
</tr>
<tr>
<td>Case fatality ratio (%)</td>
<td>9.6%</td>
<td>35%</td>
</tr>
<tr>
<td>Number of countries</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Total publications</td>
<td>2,854</td>
<td>475</td>
</tr>
<tr>
<td>Case reports</td>
<td>135</td>
<td>21</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Comparative studies</td>
<td>145</td>
<td>9</td>
</tr>
<tr>
<td>Evaluation studies</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1</td>
<td>0</td>
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</table>

*As of 2/28/2017.


Summary

- MERS-CoV provides a recent example of an emerging pathogen that was amplified in healthcare where transmission resulted from a failure of recognition, issues with collaboration and communication, and suboptimal laboratory identification
- Risk factors are not well studied (mostly observational), and case-control studies are essential
- Current prevention strategies (including standard recommendations):
  - Early recognition and diagnosis, hand hygiene, isolation, appropriate use of and adherence to PPE, cohorting, reporting, cleaning and disinfection
- Research is essential to answer key questions about transmission and risk factors for transmission
Additional Resources


Case Study 1

ARI = acute respiratory illness
BP = blood pressure
CDC = Centers for Disease Control and Prevention
CI = confidence interval
CoV = coronavirus
DPP4 = dipeptidyl peptidase 4
ECMO = extracorporeal membrane oxygenation
ED = emergency department
FRI = febrile respiratory infection
HCoV-EMC = human coronavirus-Erasmus Medical Center
HCP = healthcare personnel
HCV = hepatitis C virus
HCW = healthcare worker
HIV = human immunodeficiency virus
HR = heart rate
ICU = intensive care unit
IV = intravenous
LTCF = long-term care facility
MERS = Middle East respiratory syndrome
M-H = Mantel-Haenszel
NS = not significant
OR = odds ratio
PCR = polymerase chain reaction
PPE = personal protective equipment
R₀ = basic reproduction number
RR = relative risk
RR = respiratory rate
RSV = respiratory syncytial virus
RT-PCR = reverse transcription-polymerase chain reaction
SARS = severe acute respiratory syndrome
UK = United Kingdom
US = United States
vCJD = variant Creutzfeldt-Jakob disease
WHO = World Health Organization