Middle East Respiratory Syndrome coronavirus (MERS-CoV)

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• Twelve years after the outbreak of Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) 2002-2003

   Another threat to global public health.

• In September 2012, the virus discovered in Saudi Arabia, causes infections with a clinical manifestation similar to SARS-CoV.

   This virus was identified as a novel human coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) or EMC/2012 (HCoV-EMC/2012), is novel species of the genus Betacoronavirus.
Although certain aspects related to this novel virus have already been unraveled

But still knowledge of its source, pathogenesis and ways of transmission remains limited.
What are Corona viruses?
Coronaviruses are large enveloped virions 80 to 160 nm,

- Helical nucleocapsids.
- ssRNA Virus
- 2 serogroups: OC43 and 229E
- Severe Acute Respiratory Syndrome (SARS)
- Middle East Respiratory syndrome MERS-CoV
Properties of cornaviruses

- Morphology: “Crown-like” appearance under EM
- Genome: 80~160nm, ssRNA (+), 27-31 kb (longest RNA)
- Sensitive to acid, ether, chloroform, lipid solvents, drying, heating to 56°C/15-20 minutes, but some can through GIT (optimum temperature for virus: 33~35°C).
- Inactivation within few minutes at room temperature in 1% formalin, 1% cresol and 70% alcohol

They are difficult to isolate in cell culture so rarely diagnosed in clinical practice
The gene order for the proteins encoded by all coronaviruses is Pol-S-E-M-N-3'. Several open reading frames encoding nonstructural proteins and the HE protein differ in number and gene order among coronaviruses. The SARS virus contains a comparatively large number of interspersed genes for nonstructural proteins at the 3' end of the genome.
Genetic variation & evolution of new strains

a high frequency of:

• deletion mutations

• high frequency of recombination during replication which is unusual for an RNA virus with unsegmented genome
The International Committee on Taxonomy of Viruses (ICTV) has divided the family Coronaviruses based on genome sequence analysis, into four genera Alpha-, Beta-, Gamma- and Delta coronavirusidae.

- Sixth different currently known strains of Coronavirus infect humans.
- SARS–Co V represents a new fourth antigenic group intermediate between groups I & III
- A sixth was discovered at 2012, known as Novel Coronavirus or MERS-CoV.
## Host Ranges and Disease of Cornviruses

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th>Virus</th>
<th>Host</th>
<th>Respiratory</th>
<th>Enteric</th>
<th>Other Site</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCoV-229E</td>
<td>human</td>
<td>X</td>
<td></td>
<td></td>
<td>* APN CD 13</td>
</tr>
<tr>
<td></td>
<td>TGEV</td>
<td>pig</td>
<td>(X)</td>
<td>X</td>
<td></td>
<td>CEACAM1 CD66a</td>
</tr>
<tr>
<td></td>
<td>PRCoV</td>
<td>pig</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>PEDV</td>
<td>pig</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FIPV</td>
<td>cat</td>
<td>X</td>
<td>X</td>
<td>Systemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FCoV</td>
<td>cat</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CCoV</td>
<td>dog</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>HCoV-OC43</td>
<td>human</td>
<td>X</td>
<td>??</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HE)</td>
<td>MHV</td>
<td>mouse</td>
<td>X</td>
<td>X</td>
<td>CNS, systemic +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCoV</td>
<td>rat</td>
<td>X</td>
<td></td>
<td>Eye, GU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HEV</td>
<td>pig</td>
<td>X</td>
<td></td>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BCoV**</td>
<td>cattle</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>IBV</td>
<td>chicken</td>
<td>X</td>
<td>X</td>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TCoV</td>
<td>turkey</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SARS-CoV</td>
<td>human</td>
<td>X</td>
<td>(X)</td>
<td>(Kidney)</td>
<td>??</td>
</tr>
</tbody>
</table>

* APN (Aminopeptidase N; CD13): Antigen processing & presentation
The three major antigenic groups of CoV

- **Group I** contains canine, feline, swine coronaviruses and a human corona virus **HCoV 229E** the prototype of the group

- **Group II** contains bovine, swine, rat and mouse CoV and the other human strain which is **OC43**

- **Group III** no human strains only Turkey and Avian CoV
Evolution of SARS 2002

• A novel human corona virus named SARS associated corona virus represents a new fourth antigenic group intermediate between groups I & III
A NOVEL FOURTH ANTIGENIC GROUP

SARS

Evolution of SARS

gp I (229E)

gp II (OC43)

gp III

SARS CoV

NO HUMAN strains
Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Novel coronavirus that emerged in 2012, Causes severe acute respiratory illness
Coronaviruses Replication

Attachment and entry

Spike protein

Uncoating

CEACAM-1

Genomic RNA (positive)

5'

Translation of ORF1a and ORF1b

RNA-dependent RNA polymerase

Transcription Replication

Exocytosis

Vesicle

Golgi

Rough ER

Virial release

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Nature Reviews | Microbiology
Due to the clinical similarity between MERS-CoV and SARS-CoV. Exopeptidase, Angiotensin converting enzyme 2 (ACE2) Neutralization of ACE2 by recombinant antibodies does not prevent MERS-CoV infection. Dipeptidyl peptidase 4 (DPP4; also known as CD26) as a functional cellular receptor for MERS-CoV.
## Coronavirus Infections in Humans

### Pathogenesis

- Limited knowledge
- Highly *species-specific*
- Typically *mild upper respiratory infections* ("colds") that remain localized
  - Exception: SARS
- Immunity is *not durable*
  - Many people become resusceptible after a few years
Susceptibility studies testing the ability of MERS-CoV to infect cell lines derived from different organs provided indications about the tissue tropism of the virus. MERS-CoV was found to infect cells of the human respiratory tract, kidney, intestine and liver.

Tropism of MERS-CoV for cells of the respiratory tract, kidney and intestine is correlated with the detection of the virus in respiratory swabs, tracheal aspirates, sputum, urine and stool of MERS.
How are Novel Coronavirus transmitted?
How are Novel Coronaviruses transmitted?

Airborne
Incubation period is 10-14 days

- Transmitted between family members or in a health care setting, the WHO said in an update.

- Human-to-human transmission, the exact mode of transmission is unknown.
• Transmission between close contacts
Different between SARS-CoV and MERS-CoV
How a zoonotic MERS-CoV infection may be indirectly acquired from a primary or secondary animal host.

- **Insects**: Attract bats
- **Bats**
  - Excreta
  - Saliva
  - Parturition
- **Dust/dirt**: Contaminated
- **Palms**
  - Dates
  - Sap/Drinks
  - Shade
  - Contact (climbing)
- **Wind**
  - Stirs up dust
- **Baboons**
  - Fresh excreta
- **Cats**
  - Fresh excreta
  - Pets
  - Close contact
- **Structures/Caves**
  - Bat roosts
  - Baboon/cat contact
- **Humans**
  - Aerosol
  - Inhalation
  - Ingestion?

Additional notes:
- Fresh excreta can attract bats and contaminate dust/dirt.
- Palms can provide shade and shelter, promoting contact with bats.
- Wind can stir up dust, potentially spreading contaminated particles.
- Baboons and cats may have contact with contaminated excreta.
- Humans can be exposed to aerosols or ingested contaminated substances.
Clinical picture & epidemiology

• Upper respiratory infections, similar to “colds” caused by rhinoviruses, but with a longer incubation period (average three days).

  – 15-30% of respiratory illness in adults during winter months but lower respiratory infections were rare.

  – Antibodies appear early in childhood and are found in 90% in adults
SARS Corona Virus

This has a unique pathogenesis because it causes both upper and lower respiratory tract infections and can also cause Gastroenteritis.

Recent History

- In 2003 The SARS epidemic resulted in over 8,000 infections, about 10% of which resulted in death.
MERS- CoV Symptoms

• A person will show the symptoms after a week

• Flu-like symptoms, a heavy cough.

Some cases have had atypical presentations: Initially presented with abdominal pain and diarrhea and later developed respiratory complications.
Signs and symptoms of MERS coronavirus infection:

- Coughing
- Fever
- Vomiting
- Diarrhea
- Shortness of breath
- Pneumonia
- Severe pneumonia
- Renal (kidney) failure

In some cases:
- In advanced cases, the patient can have very serious complications, which can lead to death, such as:
As of 16 April 2014, MERS-CoV cases have been reported in several countries, including Saudi Arabia, Malaysia, Jordan, Qatar, the United Arab Emirates, France, Germany, Italy, UK, USA, Tunisia, Philippines.

- The official WHO MERS count
- In 6 May 2014 there are 339 confirmed cases in Saudi Arabia, with 115 deaths.
MERS cases and deaths
Cases of Middle East respiratory syndrome coronavirus (MERS) worldwide as of today.

MERS world totals
Infections: 55
Deaths: 31
Mortality: Around 60 percent of those infected die

Sources: CDC, World Health Organization, MCT
Confirmed cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (N = 55) reported as of June 7, 2013, to the World Health Organization, and history of travel from the Arabian Peninsula or neighboring countries within 14 days of illness onset—worldwide, 2012–2013.

MERS-CoV cases by reporting country as of 19 July 2013

- Type: imported (blue), local (red)
- Number of cases: United Arab Emirates 68, Saudi Arabia 56, United Kingdom 4, Germany 2, France 2, Italy 3, Tunisia 2, Jordan 2, United Arab Emirates 5.
As with other respiratory viruses, immunity develops but is not absolute.

Immunity against the surface projection antigen is probably most important for protection.

Resistance to reinfection may last several years, but reinfections with similar strains are common.

Most patients (>95%) with SARS developed an antibody response to viral antigens detectable by a fluorescent antibody test or ELISA.

It was important that the convalescent serum be collected more than 28 days after symptom onset.
Figure 5. Schematic representation of key responses to MERS-CoV related to outcome.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0088716
DIRECT DETECTION:

• **Antigen detection** in cells of respiratory secretions by IF or ELISA

• **NA detection** in respiratory secretions by RT-PCR
  The detection of MERS-CoV in the first reported case was performed by a pan-coronavirus RT-PCR assay. This assay targets the gene of the RNA-dependent RNA polymerase

ISOLATION:

• **CoV are difficult to grow in CC.**

• Reliable isolation of the virus is accomplished using **human embryonic tracheal organ cultures.**

• These methods are not routinely available.
Serology:

• Serologic tests are not routinely available. An alternative diagnostic approach is the detection of an antibody response against MERS-CoV, by immunofluorescence microscopy.

Practical means to confirm coronavirus infection using paired sera to detect rising or stationary high antibody level by:

- PASSIVE HAEMAGGLUTINATION TEST
- ELISA
TREATMENT

• TREATMENT TRAILS

• TRAILS FOR PRODUCTION OF MERS-COV VACCINE

VACCINE STUDIES IN MICE.
## Compounds that have been suggested as possible drug candidates against MERS-CoV infections

<table>
<thead>
<tr>
<th>Drug candidate</th>
<th>Observed effect</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-α</td>
<td>Reduction of MERS-CoV replication in pseudo-stratified HAE cultures</td>
<td><em>Kindler et al.</em> (2013)<em>50</em></td>
</tr>
<tr>
<td>pegylated IFN-α</td>
<td>Inhibition of MERS-CoV-induced CPE and reduction of the viral RNA levels in human lung epithelial and monkey kidney cell lines</td>
<td><em>de Wilde et al.</em> (2013)<em>52</em></td>
</tr>
<tr>
<td>INF-β</td>
<td>Reduction of the viral load in MERS-CoV-infected human lung epithelial and monkey kidney cell lines</td>
<td><em>Zielecki et al.</em> (2013)<em>48</em></td>
</tr>
<tr>
<td>INF-λ3</td>
<td>Reduction of MERS-CoV replication in pseudo-stratified HAE cultures</td>
<td><em>Kindler et al.</em> (2013)<em>50</em></td>
</tr>
<tr>
<td>INF-α2b</td>
<td>Reduction of the MERS-CoV-induced CPE and the viral protein levels in monkey kidney cell lines (more efficient when combined with Ribavirin)</td>
<td><em>Falzarano et al.</em> (2013)<em>72</em></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Reduction of the MERS-CoV-induced CPE and the viral protein levels in monkey kidney cell lines (more efficient when combined with INF-α2b)</td>
<td><em>Falzarano et al.</em> (2013)<em>72</em></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Significant improvement of the respiratory condition of a MERS-CoV patient (no direct effect has been proved)</td>
<td><em>Guberina et al.</em> (2013)<em>65</em></td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>Inhibition of the MERS-CoV-induced CPE in monkey kidney and a human liver cell lines</td>
<td><em>de Wilde et al.</em> (2013)<em>52</em></td>
</tr>
<tr>
<td>SB203580</td>
<td>Reduction of the viral load in a human lung epithelial cell line</td>
<td><em>Josset et al.</em> (2013)<em>54</em></td>
</tr>
<tr>
<td>ADS-J1</td>
<td>Inhibition of MERS-CoV pseudo-virus infection in human liver and mink lung cell lines</td>
<td><em>Zhao et al.</em> (2013)<em>29</em></td>
</tr>
<tr>
<td>HP-HAS</td>
<td>Inhibition of MERS-CoV pseudo-virus infection in human liver and mink lung cell lines</td>
<td><em>Zhao et al.</em> (2013)<em>29</em></td>
</tr>
<tr>
<td>MDL28170</td>
<td>Inhibition of MERS-CoV-S-mediated transduction of a human fetal lung fibroblast cell line</td>
<td><em>Gierer et al.</em> (2013)<em>25</em></td>
</tr>
<tr>
<td>NH4Cl</td>
<td>Inhibition of MERS-CoV-S-mediated transduction of a human fetal lung fibroblast cell line</td>
<td></td>
</tr>
<tr>
<td>Camostat</td>
<td>Inhibition of MERS-CoV-S-mediated transduction of a human colon cell line</td>
<td><em>Gierer et al.</em> (2013)<em>25</em></td>
</tr>
<tr>
<td>N3</td>
<td>Inhibition of the proteolytic activity of MERS-CoV 3CLpro</td>
<td><em>Ren et al.</em> (2013)<em>73</em></td>
</tr>
<tr>
<td>CE-10</td>
<td>Inhibition of the proteolytic activity of MERS-CoV 3CLpro</td>
<td><em>Kilianski et al.</em> (2013)<em>74</em></td>
</tr>
<tr>
<td>MERS-CoV RBD</td>
<td>Reduction of the viral load in a MERS-CoV-infected monkey kidney cell line</td>
<td><em>Chen</em></td>
</tr>
</tbody>
</table>
Yet stopping the spread of infection was possible through effective control measures.
Key points in control of any communicable disease

- Early case detection
- Swift isolation
- Thorough control of infection measures
- Vigorous identification and management of close contacts
- Public information for those at risk of infection
- Education of health care professionals
Because there are no treatments and no vaccine,

Keep away from someone with a heavy cough, use a tissue to cover the nose/mouth when coughing

Sneezing, wiping and blowing noses, if a tissue isn’t available, cough or sneeze into the inner elbow rather than the hand

Wash hands with hot water and soap at least six or seven times a day

Disinfect common surfaces as frequently as possible.

Wash hands or use a sanitizer when in contact with common surfaces like door handles.
MERS Resources

• MERS overview: http://www.cdc.gov/coronavirus/mers/index.html

• Case definitions and guidance: http://www.cdc.gov/coronavirus/mers/case-def.html

• Additional MERS resources: http://www.cdc.gov/coronavirus/mers/related-materials.html
MERS-COV RESOURCES