The World of Coronaviruses: SARS, MERS, and COVID-19

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18-Mar-2020
Respiratory Viruses

- Influenza
- Parainfluenza
- RSV
- Rhinovirus
- Adenovirus
- **Human Coronavirus**

- Enteroviruses (Coxsackie, Echo)
- Human Parechovirus (1999)
- Human Metapneumovirus (2001)
- Bocavirus (2005)

Responsible for 15-40% of all common cold-like infections
Coronaviruses

- Single-stranded positive-sense RNA viruses
- 4 seasonal human coronaviruses (HCoV): 229E, NL63, OC43, HKU1
- Endemic in bats – risk of zoonotic infection to humans
3 Novel Coronaviruses emerged in the last 18 years

**SARS-CoV (2002)**
Severe Acute Respiratory Syndrome-associated coronavirus
- 8098 cases w/774 deaths, ~10% CFR
- 30 countries affected
- Economic loss ~$80-100 billion

**MERS-CoV (2012)**
Middle East Respiratory Syndrome-associated coronavirus
- 2499 cases w/861 deaths, ~35% CFR
- 27 countries affected
- Economic loss?
- April 2012 – present

**COVID-19**
SARS-CoV-2
- 60,363 cases w/1,370 deaths, ~1-2% CFR
- 28 countries affected
- Economic loss?
- Dec 2019 – present
Recent History of Other Zoonotic Infections
(Emerging & Re-emerging Diseases)

- Hendra 1994
- H5N1 1997
- Nipah 1998
- West Nile (Americas) 1999
- SARS 2003
- H1N1pdm 2009
- H3N2v 2011
- MERS-CoV 2012
- H7N9 2013
- Chikungunya 2013
- Ebola 2014
- Zika (Americas) 2015
- Dengue (Americas) 2016
- Ebola (Central Africa) 2018
- nCoV 2019
Predicting Zoonotic Threats
(lessons from Pandemic Influenza)

Flyways of migratory birds

WHO Surveillance of circulating influenza viruses

Nat Rev Micro 2014; 12:822-31
U.N. Food and Agriculture Organization
Science 2008; 320: 340-6

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What’s in a name?

Coronavirus or COVID-19 or SARS-CoV-2 or Wuhan or novel coronavirus or...

The disease: 
**CoronaVirus Infectious Disease 2019 (COVID-19)**
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The virus:
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
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The disease: **CoronaVirus Infectious Disease 2019 (COVID-19)**

The virus: **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)**

80% sequence identity to SARS-CoV

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Emergent Coronaviruses

Coronavirus have emergence potential

Coronavirus infect many different mammals and birds
All human coronavirus are believed to have emerged as zoonoses

CoV outbreaks: Severe Acute Respiratory Syndrome

2002, China: ~8437 infected worldwide, 774 deaths. (10% CFR)

- Severe atypical pneumonia

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- Single spillover - controlled by public health measure alone
- Progressive age-dependent mortality

<table>
<thead>
<tr>
<th>Age</th>
<th>Mortality³</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>0%</td>
</tr>
<tr>
<td>25-44</td>
<td>6%</td>
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<tr>
<td>45-65</td>
<td>15%</td>
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<tr>
<td>65+</td>
<td>52%</td>
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</tbody>
</table>

CoV outbreaks: Middle East Respiratory Syndrome Syndrome

2012, Saudi Arabia: 2494 cases (lab-confirmed), 858 deaths. (35% CFR)

• Severe atypical pneumonia
• Progressive age-dependent mortality
• Ongoing primary infections (camels)

CoronaVirus Infectious Disease 2019 (COVID-19)

12/31/2019 atypical pneumonia identified in Wuhan, China
1/13/2020 Case in Thailand
1/20/2020 1st Case in Washington State, US
1/30/2020 WHO declared Public Health Emergency of International Concern
2/27/2020 updated global risk to High Risk
2/29/2020 1st US death

CoronaVirus Infectious Disease 2019 (COVID-19)

100,330 infections; 3408 deaths (crude CFR 3.4%)

- Severe atypical pneumonia
CoronaVirus Infectious Disease 2019 (COVID-19)

200K infections; 8008 deaths (crude CFR 4%)

- Severe atypical pneumonia

https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
CoronaVirus Infectious Disease 2019 (COVID-19)

200K infections; 8008 deaths (crude CFR 4%)

- Severe atypical pneumonia
COVID-19 diagnosis

• 90% of patients with COVID-19 are febrile *at some point* during hospitalization, but only 44% were febrile on admission

• 80-100% of hospitalized patients with imaging abnormalities
  • Usually bilateral, ground glass progressing to consolidation, peripheral and posterior


COVID-19 diagnosis

Nonspecific CT findings:
- GGO
- Consolidations
- Crazy paving
- Rarely nodular
- Occasional pleural effusions

Admission

Day +3

COVID-19 diagnosis

• 90% of patients with COVID-19 are febrile at some point during hospitalization, but only 44% were febrile on admission

• 80-100% of hospitalized patients with imaging abnormalities
  • Usually bilateral, GGO progressing to consolidation, peripheral and posterior
  • Sensitivity 97%, Specificity 25% (in a time of pandemic)

Table 2: The performance of chest CT for COVID-19 infection with RT-PCR result as reference.

<table>
<thead>
<tr>
<th>Results (n)</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
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<tr>
<td>Specificity</td>
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<td>PPV</td>
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<td>NPV</td>
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<tr>
<td>Accuracy</td>
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<tr>
<td>[95% CI]</td>
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<td>[95% CI]</td>
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</tbody>
</table>

Overall

580 105 308 21

97 (580/601) 25 (105/413) 65 (580/888) 83 (105/126) 68 (685/1014)

[95-98] [22-30] [62-68] [76-89] [65-70]


Spectrum of Illness

- ~80% mild-moderate
- 13.8% severe
  - dyspnea, RR ≥30/minute, O2 sat ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours
- 6.1% are critical
  - respiratory failure, septic shock, and/or multiple organ dysfunction/failure
- Crude CFR 1.4-4%

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Mortality by age


MERS mortality by age courtesy of Vineet Menachery (personal communication)
Clinical Course

191 patients in 2 hospitals in Wuhan, China
- 137 discharged, 54 died (28%)

Clinical Course

- 191 patients in 2 hospitals in Wuhan, China
  - 137 discharged, 54 died (28%)
  - 48% had comorbidity:
    - 58 (30%) hypertension, 36 (19%) diabetes, 15 (8%) coronary artery disease


In Children?

Retrospective study of 366 children with respiratory infections admitted to hospitals in Wuhan

- 23 (6.3%) Influenza A
- 20 (5.5%) Influenza B
- 6 (1.6%) SARS-CoV-2
- No deaths

All hospitalized infants (28d to 1 year) diagnosed with COVID-19 Dec through Feb 6 in China:

→ 9 infants (7 female)

- All presumed from a family member
- 4 with fever, 2 mild URI, 1 asymptomatic, 2 unknown

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>CT findings</td>
<td>Patchy ground-glass opacities in both lungs</td>
<td>NA</td>
<td>Patchy shadows in both lungs</td>
<td>Patchy shadows in both lungs</td>
<td>Patchy shadows in both lungs</td>
<td>Normal</td>
</tr>
</tbody>
</table>

In pregnancy?

19 women in published or pre-published studies, delivering 20 babies

- All 3rd trimester
- 1 ICU admission (5%)
- 8 (42%) pre-term deliveries
  - none spontaneous
- 1 neonatal death

<table>
<thead>
<tr>
<th>Stage of pregnancy</th>
<th>COVID-19</th>
<th>SARS</th>
<th>MERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3rd Trimester</td>
<td>1st trimester</td>
<td>2nd Trimester</td>
</tr>
<tr>
<td>N</td>
<td>19 (20 infants)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Women with co-morbidities</td>
<td>4 (21%)</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Admitted asymptomatic</td>
<td>3 (16%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ICU admission %</td>
<td>1 (5%)</td>
<td>1 (14%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Maternal mortality %</td>
<td>0*</td>
<td>1 (14%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Miscarriage or intra-uterine death</td>
<td>0</td>
<td>4 (58%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Any pre-term delivery</td>
<td>8/19 (42%)*</td>
<td>not reported</td>
<td>2 (40%)</td>
</tr>
</tbody>
</table>

COVID-19 treatment options?

SARS convalescent sera associated with reduction in mortality:
- Absolute reduction ranged from 7% (95% CI, −2.39 to 18.68) to 23% (95% CI, 5.59–42.02) (2 studies, +risk of bias)
- 4 noncomparative studies – CFR 0 to 12%

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COVID-19 treatment options?

Lopinavir  Chloroquine  Convalescent sera  Remdesivir  Steroids

Harmless  Harmful*

*not to scale  **educated guesswork

Suspected efficacy?**

Robustly inhibits SARS-CoV-2 in cell culture

COVID-19 treatment options?

Chloroquine:
- Robustly inhibits SARS-CoV-2 in cell culture
- Ongoing study(ies) – may improve clinical outcomes
- Available, known safety and dosing profile

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COVID-19 treatment options?

- Remdesivir
- Convalescent sera
- Lopinavir
- Chloroquine
- Steroids

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Remdesivir

Harmful*

- Steroids

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**educated guesswork

Suspected efficacy?**

![Graphs showing percent starting weight over days post infection for different treatments.

1. Graph a: Percent starting weight over days post infection for Vehicle and Remdesivir treatments.
2. Graph b: Percent starting weight over days post infection for Vehicle, LPV/RTV-IFN low, and LPV/RTV-IFN high treatments.](image-url)
COVID-19 treatment options?


*Harmful*  

*Harmless*

Remdesivir

Convalescent sera

Lopinavir

Chloroquine

Steroids

**not to scale**

**educated guesswork**

Suspected efficacy?**

*Source: Remdesivir*
COVID-19 treatment options?


**Lopinavir/ritonavir:**
Not recommended.
No plausible mechanism and ineffective in animal models.
Targets the HIV protease (aspartyl protease) - quite different from the CoV proteases: PLpro (serine protease) or Mpro (cysteine protease)

**Remdesivir**
Plausible, in vitro activity & animal models.
- Adverse effects in phase 1 clinical trials included: constipation, heartburn, itching, dizziness, loss of appetite, nausea, vomiting
- LFT abnormalities (AST 70s to 290s; ALTs 60s to 250)

Available through compassionate use and (soon) clinical trial.

**Stylistic annotations:**
- Lopinavir
- Chloroquine
- Convalescent sera
- Remdesivir
- Steroids

*not to scale
**educated guesswork

Suspected efficacy???
Corticosteroid use for SARS patients
- Higher plasma RNA levels at weeks 2-3 into illness (likely prolonged viremia)
- Increased 30-day mortality (adjusted OR 26, 95% CI 4.4-154.8).

*Not for treatment. Use may be required for related illness eg. Refractory shock, asthma, COPD, organ transplant.
COVID-19 vaccine?

Mock Vaccine

Killed Vaccine

Vaccine-induced immunopathology after challenge

Unvaccinated

VRP-N vaccinated

Nucleocapsid specific responses (likely cell mediated)

increase immunopathology

What happens next?

- Seasonal coronaviruses?
- Durable immunity?
  - Common coronaviruses (229E) show declining immunity after 1 year

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What happens next?

- Warm weather hypothesis?
  - cold and dry (low absolute humidity) environments facilitate survival of respiratory viral diseases

Circled cities with significant community transmission as of 6-Mar

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Seasonal variations in absolute humidity may be insufficient to prevent widespread transmission

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  • Seasonal variations in absolute humidity may be insufficient to prevent widespread transmission

• Duration of immunity
  • Short term (40 weeks) → annual
  • longer → biennial

Don’t be a “Patient A”

Patient A, stayed at Hotel M:
Feb 15, symptoms began in Guandong, China
Feb 21, traveled to HK to visit family, stayed at Hotel M (9th Floor)
Feb 22, admitted to hospital 2
Feb 23, patient A died

Patient A directly resulted in 12 infections at Hotel M, 4 HCW infections & 2 Family member infections
Indirectly associated with 268 cases
Don’t be a superspreader

Defined as spread to ≥ 8 other patients

**Superspreader**
- Mean age: 56
- 75% mortality
- No. close contacts: 36
- AR close contacts: 43%

**Non-superspreader**
- Mean age: 44
- 16% mortality
- No. close contacts: 0.37
- AR close contact: 18.5%

*Index patient* lead to 4 generations of spread including 76 case-patients

EID 2004
Importance of Non-Pharmaceutical Interventions

NPIs (Community Mitigation):
- Isolation (of known cases)
- Quarantine (potential contacts)
- Social Distancing
  - Closure of schools, businesses
  - Travel restrictions
  - Cancellation of mass gatherings
- Infection Control
Recent Modeling of the Potential Impact of NPIs

Necessary to layer multiple interventions
Potentially Very Protracted Situation
Local Projection, using a model

Assume:
Population of Maryland 6.043M

N=60 current infections
6 days for doubling of infections
5% hospitalization rate
2% ICU rate
1% ventilation rate

Hospital length of stay 10 days
ICU length of stay 7 days
Vent length of 5 days

Penn Medicine, Predictive Healthcare team tool
http://penn-chime.phl.io/
Tips for Staying Safe During COVID-19 (or the next emerging infection)

**Personal Hygiene & Practices**
- Handwashing/Hand sanitizer
- Cough/Sneeze etiquette
- Stay home when sick
- Avoid sick contacts
- Seek medical assistance

**Public Health Authorities**
- Isolation/Quarantine
- Control mass gatherings/travel
- Hospitalize
  - Contact/Droplet Precautions
  - PPE
  - ICU, mech vent support
- Clear & Fast Communication
  - Prevent public panic

**Vaccines**

**Therapeutics**

**Diagnostics**
Thank You

Funding: T32AI007524

Institute of Human Virology & Center for Vaccine Development and Global Health
University of Maryland School of Medicine

mdeming@ihv.umaryland.edu
COVID-19 treatment options?

• Host targeted therapeutics
  • Tocilizumab – calm cytokine storm
  • Tmprss2 – co-receptor SARS-CoV-2 Camostat mesylate
  • ACEi ? Assoc with hypertension?