No financial disclosures
Overview

- Virology
- Epidemiology
- Clinical features
- Diagnostic testing
- Public health measures
- Treatment trials
- PEP and vaccines
- Q&A
What is the novel coronavirus?

Coronaviruses are large, enveloped, positive-strand RNA viruses
- ~ 50 known strains, mostly birds and mammals
- Seven strains can infect humans
  - Four account for 10% -30% of all common colds
  - Three strains known to cause epidemics
    - Zoonotic: ‘jump’ from animal reservoir (bats) to humans
    - Intermediary hosts, e.g., civet cats, camels

Name of virus ≠ name of disease

Structure: outer fringe, or “corona” (crown in Spanish) of embedded proteins, including the spike “S” protein, in lipid envelope

<table>
<thead>
<tr>
<th>Name of Virus</th>
<th>Name of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)</td>
<td>Severe Acute Respiratory Syndrome (SARS)</td>
</tr>
<tr>
<td>Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV)</td>
<td>Middle Eastern Respiratory Syndrome (MERS)</td>
</tr>
<tr>
<td>Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or 2019-nCoV)</td>
<td>Coronavirus Disease 2019 (COVID-19)</td>
</tr>
</tbody>
</table>

J.S.M. Peiris, *Medical Microbiology*, 2012
How Does SARS-CoV-2 Bind to Cells?

**Binding**: Viral envelope spike ("S") protein binds to angiotensin-converting enzyme 2 (ACE2) receptor

(Y Wan et al., J Virol 2020)

**Receptor distribution** (Hamming et al., 2004):
- ACE2 on surface of lung alveolar epithelial cells
- ACE2 on surface of enterocytes of the small intestine

**Affinity**: SARS-CoV-2 S protein binds ACE2 with higher affinity than SARS-CoV S (Wrapp 2020)

Structure of 2019-nCoV "S" protein, prefusion conformation
Wrapp et al., Science 2020
As of March 29th
- 685,623 confirmed cases globally
- 32,137 reported deaths*
- 145,706 reported recoveries

By Region
- 12% of global cases in China
- 48% of global cases in Europe
- 18% of global cases in the US
  - NYC has 26% of US cases
- ~0.6% of global cases in Africa*

Top five: US, Italy, China, Spain, Germany
How does COVID-19 Spread?

**CDC Guidance**
- Person-to-person spread through:
  - **Respiratory droplets**
    - produced during coughing or sneezing
  - Close contact with an infected person (within ~2 meters) for >10 min
  - Likely main way of transmission
- Contact
  - Direct or indirect
  - Touching a surface or object that has virus on it and then touching one’s mouth, nose, or possibly eyes
  - This is **not thought to be the** main way the virus spreads

**WHO Guidance**
- Respiratory droplets and contact
  - produced during coughing or sneezing

Airborne spread is not believed to be a major driver of transmission
How big are respiratory droplets?

Respiratory droplets: > 5 microns

Aerosol droplets: 1-5 microns

Red blood cell: 7 microns

Droplets are larger than the particles (e.g., evaporated droplets) involved with airborne transmission

Source: https://www.youtube.com/watch?v=wnofrAtfMzE
Viable SARS-CoV-2 could be detected in:
- aerosols (< 5 microns) for up to 3 h (experiment lasted for 3 h, titers decreased each h)
- up to 4 hours on copper
- up to 24 hours on cardboard (but dropped by 1 log at 8 hours)
- up to 2-3 days on plastic and stainless steel (declined to 0.02% of initial concentration)

Data support respiratory droplet (aerosol) and contact transmission of SARS-CoV-2 is plausible, as the virus can remain viable in aerosols for multiple hours and on surfaces for up to days

Artificial laboratory model
Transmission not assessed
Aerosol ≠ airborne
COVID-19 Preventive Measures: Personal protective equipment (PPE) and handwashing

WHO: use a mask if you are coughing or sneezing, have other mild coronavirus-like symptoms or are caring for someone suspected of having a coronavirus infection.

WHO: wearing an N95 mask can help to limit the spread of some respiratory diseases, it is not enough to stop all infections.

The best precautions are simple: wash your hands frequently, try not to touch your face, avoid crowded places and try to stay a meter from other people.
Household contacts and those travelling with a case were 6 to 7 times more likely to develop infection than other close contacts.

Household secondary attack rate was 15%.

Children were as likely to be infected as adults.
What is the basic reproductive number?

$R_0 = b \times c \times d$

- $R_0$: average number of infections produced by 1 infected person
- **Estimate for COVID-19 is 1.5-4**
- Varies by location
- Driven by 3 things, 2 of which we have some control over now:
  - $b$: per-contact transmission probability (handwashing)
  - $c$: average number of susceptible-infectious contacts (social distancing)
  - $d$: average duration of infectiousness

Adapted slide from Matthew Lamb, ICAP at Columbia University
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Prognosis by Clinical Initial Presentation
44,672 confirmed COVID-19 cases, Mainland China as of Feb 11, 2020

- **Mild-moderate disease:** 81%
- **Severe disease:** 14%
- **Critical illness:** 5%

**Incubation**
- Average: 5 days (2-14)

**Recovery time:** 5-32 days after symptom onset
Clinical features among an “average adult” first confirmed COVID-19 case in the US

Holshue ML, et al. NEJM Feb 4, 2020
What about COVID-19 and Pregnant Women, Children, and PLWH?

**Pregnant Women**

Mixed data suggest **minimal evidence of vertical transmission** based on three small clinical series and **one case study of possible vertical transmission**

However, reports of neonates acquiring COVID-19 from secondary transmission have occurred

*Fauvre et al., The Lancet; Zhu et al., Translational Pediatrics; Yu et al., The Lancet Infectious Diseases; Dong et al., JAMA*
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**Children**

Hospitalized children (n = 74)

- Predominant symptoms
  - Cough (32%) and fever (27%)
- Presentation
  - 27% asymptomatic
  - 32% acute URTI
  - 39% mild pneumonia
- Median hospitalization duration of 11 days

*Wu Sr. et al., MedRxiv Pre-Print*
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#### People Living with HIV
Limited information regarding COVID-19 infection or outcomes. However, overall data indicate higher death rate for older persons and those with comorbidities or immunocompromise.

**CDC’s specific COVID-19 recommendations for PLHIV:**
- Always ensure ample medication supply (30 days)
- Keep vaccinations up to date
- Establish plan for clinical care if isolated/quarantined
- Maintain a social network but remotely

*Huang et al., The Lancet*
What is the risk of re-infection?

Limited data but re-infection appears unlikely

• Rhesus macaque model: no potential for SARS-CoV-2 re-infection in 2 macaques (Bao et al. (BioRxiv pre-print paper))

• 5-10% of recovered patients in Wuhan with repeated nasopharyngeal sampling had positive samples after several negative samples. Unclear whether this might reflect sampling or true persistence or reinfection
How do Coronavirus tests work?

All laboratory diagnostic tests currently rely on molecular testing (RT-PCR) performed at commercial, state or city laboratories.

Specimens used for testing include:

- **Mainly nasopharyngeal swabs**
- bronchoalveolar lavage, tracheal aspirates, and sputum

**CDC Test:** 6-8 hours to complete (from sample extraction to RT-PCR testing), ~50-100 tests/day

**Roche Cobas:** 3-4 hours to complete, 1440 or 4128 samples per day depending on platform

**Thermo Fisher:** 4 hours to complete, 600 or 6000 samples per day depending on platform

Rapid Point-of-Care Testing

Relies on molecular testing to detect active infection

Currently 2 have been approved by FDA under EUA:

• Cepheid Xpert® Xpress SARS-CoV-2 using the GeneXpert platform
  • 45 mins to complete
  • Can run 1, 2, 4, 16 or 1300 simultaneously depending on system used
  • 23,000 instruments worldwide
  • Cost per cartridge?

• Abbott ID NOW COVID-19
  • 5-15 mins to complete
  • Can only run 1 sample at a time
  • 18,000 instruments through the US
  • Cost per test?

Both these instruments are used routinely in the US for Influenza A and B, Strep and RSV already
Testing to Date in the US, March 2020

From covidtracking.com; as of 3/28/20 4pm
Is Home Testing the New Frontier?

- Number of test kits available online
- Relies on self-swabbing and sending sample for analysis
- Turn-around time varies
- NONE are FDA approved currently and FDA has warned against their use until approved
- Test performance has not been validated
Are there antibody tests being developed?

Serological assays to measure presence or absence of antibodies to the virus in people’s blood being developed, (e.g., F. Amanat et al. 2020), including POC rapid tests for detection of both IgG and IgM

Evidence that immune system has encountered virus and generated antibodies in response

No data on whether development of antibodies is associated with protection

Advantages

• Accurate picture of how many people have been infected, i.e., seroprevalence studies
• Potential to identify people with antibodies to SARS-CoV-2
  • if proven to be protective, could identify who can care for COVID-19 patients at no or low risk
• Identify people without immunity who would benefit from a future vaccine
• Identify newly recovered patients with high antibody levels
  • who can donate their antibody-rich blood, known as convalescent plasma, to potentially save other patients with severe COVID-19
Public Health Measures for Control of All Epidemics

- **Surveillance systems**
  - To track number of tests performed, and test results by demographic and geographic features

- **Containment: slow the spread**
  - Contact investigation, quarantine

- **Mitigation: reduce severity of epidemic**
  - Reduce incidence, morbidity and mortality and disruptions to economic, political and social systems
  - Social distancing (e.g., school closure)

- **Communication**

- **Protecting health workforce**

https://www.who.int/emergencies/diseases/managing-epidemics-interactive.pdf
What Does Flattening the Curve Mean?

Number of cases exceeds healthcare system capacity
Flattening the Curve

Containment and mitigation measures
How are people being treated for COVID-19?

There is **no specific antiviral treatment recommended for COVID-19**. People with COVID-19 should receive supportive care to help relieve symptoms. For severe cases, treatment should include care to support vital organ functions.

**Approximately 54 clinical treatment trials** in progress

- Antiviral trials (Phase 3 or 4) specifically remdesivir, lopinavir and ritonavir, and oseltamivir and arbidol
- Hydroxychloroquine for Treatment of Pneumonia Caused by SARS-CoV-2 (Phase 3)
- Pirfenidone (anti-inflammatory) (Phase 3), Bevacizumab (anti-VEGF) (Phase 3), Fingolimod (immunomodulating) (Phase 2), Carrimycin (Phase 4)
- Mesenchymal stem cell trials (Phase 1 & 2)
- Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2)
- Other trials (e.g., Vit C, traditional meds, natural killer cells)

**Approximately 40 trials** covering new diagnostics, clinical presentations, and prevention in progress
WHO’s SOLIDARITY Trial

Remdesivir
- Nucleotide analog antiviral with existing safety data from 500 patients with Ebola
- Used for two early cases in the United States, both improved and recovered from COVID-19

Chloroquine and hydroxychloroquine
- Medication used for the prevention and treatment of certain types of malaria, as well as other conditions
- French study: 20 COVID-19 patients treated with hydroxychloroquine had lower viral load in nasal swabs
- Poor study design (no randomization) and clinical outcomes not yet reported

Outcomes:
- Date of discharge, date of death, duration of the hospital stay, and need for oxygen or ventilation

Ritonavir/lopinavir
- HIV combination anti-viral drug
- Recent study in critically ill did not show clinical benefit compared to standard care
- May show benefit if used differently

Ritonavir/lopinavir and interferon-beta
- Two antivirals with interferon-beta, a molecule involved in regulating inflammation in the body that has also shown an effect in marmosets infected with MERS

INSERM adding on trial named Discovery: same drugs as SOLIDARITY, with the exception of chloroquine, for 3200 patients from Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand
What about ibuprofen?

There are some suggestions from the global community that ibuprofen makes COVID-19 illness worse. However:

• No clear evidence has been presented on ibuprofen, NSAIDs, and COVID-19
• The hypothesis that ACE2 can be increased by ibuprofen and facilitate infection with COVID-19 has not been proved
  • There is currently no scientific evidence that having increased ACE2 expression means you're more susceptible to infection.
• As of March 19th, the World Health Organization does not recommend against the use of NSAIDs during COVID-19 infection
Convalescent Plasma as Post-Exposure Prophylaxis

• Passive antibody therapy for prevention or treatment of an infectious disease
• Mechanism: viral neutralization, possibly antibody-dependent cellular cytotoxicity &/or phagocytosis
• History of use from 1890s, pre antibiotic era
  • Treatment: Ebola, pneumococcal pneumonia, SARS, MERS and COVID-19  No large RCTs
  • Prevention: HBV, rabies, botulism, RSV  Widespread use
• Dose must have sufficiently high antibody titer, duration of action is weeks to months and most effective when given early in course of illness
• Good safety profile from treatment trials but ~ anecdotal
• Risks:
  • antibody dependent enhancement of infection
  • attenuation of immune response to infection: then need vaccine later
  • Adverse events most common flushing, fever
• Clinical trial planning is underway
What about vaccines for COVID-19?

There are currently 5 ongoing vaccine trials according to Clinicaltrials.gov, these include:

1. Safety and Immunogenicity Study of 2019-nCov Vaccine (mRNA-1273) : STARTED MARCH 16th

2. Immunity and Safety of Covid-19 Synthetic Minigene Vaccine

3. INO 4800

4. Phase I Clinical Trial in Healthy Adult (PICTHA)

5. Safety and Immunity of Covid-19 aAPC Vaccine
COVID-19 and Africa

Current Snapshot:
• >4100 confirmed cases (0.6% of global cases)
• 31 deaths (0.1% of global deaths)
• 41 countries/territories effected

Response:
• Diagnostic capacity established in most countries
• Surveillance systems in progress
• Social distancing/lockdowns in place in ~12 countries

Challenges:
• Health system infrastructure fragile and ill-prepared
• Social distancing and frequent hand washing often not feasible
• Limited PPEs
• Limited intensive care beds and ventilators
Summary and Conclusions

Epidemiological Takeaways

- Expect change: rapidly shifts in diagnostic capacity and guidance from departments of health
- Mortality: estimates in early stages of outbreak should be interpreted with caution
- Respiratory droplets via close contact as main way virus spreads
- Social distancing as major public health intervention

Clinical Takeaways

- Flu-like illness for most
- 2 weeks to recover from milder illness, longer if more severe
- Re-infection after initial infection unlikely

Treatment and Prevention Takeaways

- Several treatment trials in progress
- Clinical vaccine trials have begun
- Convalescent plasma trial preparation underway
COVID-19 Resources

Additional Helpful Resources

- Lancet, NEJM, Nature, and JAMA publications
- Preprint platforms: MedRxiv, BioRxiv
- [https://covidtracking.com/data/](https://covidtracking.com/data/)
Thank you!