Global Reverberations
Coronavirus-19

Rob Murphy, M.D.
John P. Phair Professor of Infectious Diseases
Executive Director, Institute for Global Health
Feinberg School of Medicine
Northwestern University
Chicago

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Outline of Discussion

• Coronavirus-19 virology
• Epidemiology
• Interventions
• Impact on healthcare systems and clinical research
• Designing the optimal global health response
Human Coronavirus (HCoV): Virology and Human Pathology

• HCoV-OC43
• HCoV-HKU1
• HCoV-NL63
• HCoV-229E
• Severe acute respiratory syndrome (SARS-CoV)
• Middle East respiratory syndrome (MERS-CoV)
• SARS-CoV-2 (coronavirus 19; covid 19)
## Coronavirus Epidemics/Pandemic

### Outbreaks of coronavirus-related diseases

Outbreaks of coronavirus types of relatively high mortality are as follows:

<table>
<thead>
<tr>
<th>Outbreak</th>
<th>Virus type</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003 severe acute respiratory syndrome outbreak</td>
<td>SARS-CoV</td>
<td>774[42]</td>
</tr>
<tr>
<td>2012 Middle East respiratory syndrome coronavirus outbreak</td>
<td>MERS-CoV</td>
<td>Over 400[43]</td>
</tr>
<tr>
<td>2015 Middle East respiratory syndrome outbreak in South Korea</td>
<td>MERS-CoV</td>
<td>36[44]</td>
</tr>
<tr>
<td>2018 Middle East respiratory syndrome outbreak</td>
<td>MERS-CoV</td>
<td>41[45]</td>
</tr>
<tr>
<td>2019–2020 coronavirus pandemic</td>
<td>SARS-CoV-2</td>
<td>At least 15,328[46]</td>
</tr>
</tbody>
</table>
# Deadly Viruses and Epidemics

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Epidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2</td>
<td>HIV</td>
</tr>
<tr>
<td>Ebola</td>
<td>Flu (Hong Kong)</td>
</tr>
<tr>
<td>Hanta</td>
<td>Flu (Asian)</td>
</tr>
<tr>
<td>Lassa</td>
<td>Flu (Spanish)</td>
</tr>
<tr>
<td>Rabies</td>
<td>Cholera (6th)</td>
</tr>
<tr>
<td>Small Pox</td>
<td>Flu (Russian)</td>
</tr>
<tr>
<td>Dengue</td>
<td>Cholera (3rd)</td>
</tr>
<tr>
<td>Influenza</td>
<td>Plague (Black Death)</td>
</tr>
</tbody>
</table>

|                       | 36M  | 2005-2012 |
|                       | 1M   | 1968      |
|                       | 2M   | 1956-58   |
|                       | 20-50M | 1918-20  |
|                       | 800K |           |
|                       | 1M   | 1889-90   |
|                       | 1M   | 1852-1860 |
|                       | 75-200M | 1346-53   |
|                       | 25M  | 541-42    |
|                       | 5M   | 165 AD    |
Clinical Features: Covid-19

- Fever - 99%
- Fatigue - 70%
- Dry cough - 59%
- Anorexia - 40%
- Myalgias - 35%
- Dyspnea - 31%
- Sputum production - 27%
- Loss of smell
Global Statistics as of April 15, 2020

• Global case load - 1,999,628 (deaths, 128,011)
  - USA - 609,685 (26,059)
  - Spain - 177,633 (18,579)
  - Italy - 162,488 (21,067)
  - Germany - 132,210 (3,489)
  - France - 131,362 (15,750)
  - China - 83,355 (3,346)
  - Iran - 76,389 (4,777)
  - United Kingdom - 94,847 (12,131)
  - South Korea - 10,423 (225)
Daily COVID-19 Cases and Deaths Worldwide

Cases vs. deaths: we show the correlation between confirmed cases and deaths here.

Daily new confirmed COVID-19 cases and deaths, World, Jan 1, 2020 to Apr 15, 2020
The confirmed counts shown here are lower than the total counts. The main reason for this is limited testing and challenges in the attribution of the cause of death.

LINEAR

Source: European CDC – Situation Update Worldwide – Last updated 15th April, 11:15 (London time)

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Total Confirmed COVID-19
Starting after first 100 cases
COVID-19 – Daily new confirmed deaths – rolling 3-day average

Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.

Source: European CDC – Situation Update Worldwide – Last updated 7th April, 12:15 (London time)

Note: The rolling average is the average across three days – the confirmed deaths on the particular date, and those on the previous and the following day. For example, the value for 26th March is the average over the 25th, 26th and 27th March. The latest value is calculated as the average of confirmed deaths on the particular date and the previous day.

Our World in Data
Case Fatality by Country

Case fatality rate of the ongoing COVID-19 pandemic

The Case Fatality Rate ( CFR ) is the ratio between confirmed deaths and confirmed cases. During an outbreak of a pandemic, the CFR is a poor measure of the mortality risk of the disease. We explain this in detail at OurWorldInData.org/Coronavirus

Source: European CDC – Situation Update Worldwide – Last updated 15th April, 11:15 (London time)
Note: Only countries with more than 100 confirmed cases are included.
National Statistics as of April 15, 2020

- New York - 203,377 (10,842)
- New Jersey - 47,437 (2,805)
- Massachusetts - 28,164 (957)
- Michigan - 27,001 (1768)
- California - 25,779 (790)
- Pennsylvania - 25,551 (702)
- Illinois - 23,248 (869)
- Florida - 21,628 (571)
- Louisiana - 21,518 (1013)
- Texas - 15,343 (362)
US COVID-19 through April 2020

Cumulative total number of COVID-19 cases in the United States by report date, January 12, 2020 to April 5, 2020, at 4pm ET (n=330,891)*†

Total number of COVID-19 cases in the United States by date reported
Number of Tests per Confirmed Case

Number of COVID-19 tests per confirmed case, Apr 14, 2020
Comparisons of testing data across countries is compromised for several reasons (see note below).

- Vietnam: 474 (Apr 11, 2020)
- Taiwan: 60.5 (Apr 13, 2020)
- New Zealand: 49.9 (Apr 13, 2020)
- Australia: 57.3 (Apr 13, 2020)
- South Korea: 38.3
- South Africa: 24.6 (Apr 13, 2020)
- India: 23.6
- Czech Republic: 22 (Apr 13, 2020)
- Iceland: 21.2
- Tunisia: 17.6 (Apr 12, 2020)
- Canada: 17
- Japan: 11.7
- Argentina: 10
- Philippines: 8.2 (Apr 13, 2020)
- Indonesia: 6.9
- Italy: 6.7
- United States: 5.3 (Apr 13, 2020)
- United Kingdom: 3.4
- Ecuador: 3.4

Note: For testing figures, there are substantial differences across countries in terms of the units, whether or not all labs are included, the extent to which negative and pending tests are included, and other aspects. Details for each country can be found at the linked page.
(N=4,226)
MMWR, March 18, 2020

- **Fatality**
  - >85  10% - 27%
  - 65-84  3% - 11%
  - 55-64  1% - 3%
  - 20 -54  <1%
  - <20  0
### Hospitalizations (N=508)

- **Number of hospitalization by age and ICU Admission**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hospitalization</th>
<th>ICU Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;85</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>65-84</td>
<td>26%</td>
<td>46%</td>
</tr>
<tr>
<td>55-64</td>
<td>17%</td>
<td>36%</td>
</tr>
<tr>
<td>45-54</td>
<td>18%</td>
<td>36%* (included in 55-64s)</td>
</tr>
<tr>
<td>20-44</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>&lt;20</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
</tbody>
</table>
COVID-19 Hospitalizations by Age

A total of 1,482 laboratory-confirmed COVID-19-associated hospitalizations were reported by COVID-NET sites between March 1, 2020 and March 28, 2020. The overall cumulative hospitalization rate was 4.6 per 100,000 population with the highest rates in those aged 65 years and older (13.8 per 100,000) followed by adults aged 50-64 years (7.4 per 100,000).
US Outcomes up to March 16, 2020. (N=4,226)

MMWR, March 18, 2020

• Adults ≥65 years
  - 31% of all cases
  - 53% of ICU admissions
  - 80% of deaths
    • 15 (34%) ≥85 years
    • 20 (46%) 65-84 years
    • 9 (20%) 20-64 years
    • 0 (0%) <20 years
Hospitalization, ICU Admits, Deaths

March 16, 2020

No. of hospitalizations, ICU admissions, and deaths

Age group (yrs)

0–19 20–44 45–54 55–64 65–74 75–84 ≥85

Hospitalizations
ICU admissions
Deaths
Interventions

• Do nothing
  - Wait for a vaccine
  - Wait for a new treatment
• Case isolation
• Case isolation and household quarantine
• Closing schools and universities
• Case isolation, home quarantine, social distancing
• Mandatory quarantine, government takeover, martial law

Interventions based on Science and Leadership
Social Distancing: Nothing New

Influenza Epidemic 1918 (aka Spanish Flu)

By the end of the week, more than 4,500 were dead in an outbreak that would claim as many as 100 million people worldwide. By the time Philadelphia’s politicians closed down the city, it was too late.
Intervention Length, Mortality and Employment

Between similar cities, places with longer-running interventions had lower mortality

<table>
<thead>
<tr>
<th>City</th>
<th>Long</th>
<th>Short</th>
<th>Deaths per 100,000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minneapolis</td>
<td>388</td>
<td>485</td>
<td>1244</td>
</tr>
<tr>
<td>St. Paul</td>
<td>591</td>
<td>485</td>
<td></td>
</tr>
<tr>
<td>Cleveland</td>
<td>591</td>
<td>485</td>
<td></td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>1244</td>
<td>485</td>
<td></td>
</tr>
<tr>
<td>Los Angeles</td>
<td>485</td>
<td>643</td>
<td></td>
</tr>
<tr>
<td>San Francisco</td>
<td>485</td>
<td>643</td>
<td></td>
</tr>
</tbody>
</table>

Those same cities also had higher employment gains

<table>
<thead>
<tr>
<th>City</th>
<th>Long</th>
<th>Short</th>
<th>Employment Gain (1914 to 1919)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minneapolis</td>
<td>+30%</td>
<td>+15%</td>
<td>+70%</td>
</tr>
<tr>
<td>St. Paul</td>
<td>+42%</td>
<td>+18%</td>
<td>+60%</td>
</tr>
<tr>
<td>Cleveland</td>
<td>+42%</td>
<td>+18%</td>
<td>+50%</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>+69%</td>
<td>+42%</td>
<td>+40%</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>+69%</td>
<td>+42%</td>
<td>+30%</td>
</tr>
<tr>
<td>San Francisco</td>
<td>+69%</td>
<td>+42%</td>
<td>+20%</td>
</tr>
</tbody>
</table>
Cities, Intervention and Employment

Flu of 1918

Source: Sergio Correia, Stephan Luck, and Emil Vosner
New York City and Social Distancing 2020

Times Square in New York yesterday. Mark Lennihan/Associated Press

What social distancing looks like
Transmission and Clinical Dynamics

**Transmission Dynamics**
- **Population Inputs**
  - Size of population: 300,000
  - Number of initial infections: 2,000

**Basic Reproduction Number** $R_0$:
- Measure of contagiousness; the number of secondary infections each infected individual produces.

**Transmission Times**
- Length of incubation period, $T_{inc}$: 5.26 days
- Duration patient is infectious, $T_{inf}$: 2.4 days

**Clinical Dynamics**
- **Morbidity Statistics**
  - Case fatality rate: 4.00%
  - Time from onset of illness to death: 11.9 days
- **Recovery Times**
  - Length of hospital stay: 10 days
  - Recovery time for mild cases: 11.1 days
- **Care statistics**
  - Hospitalization rate: 44.00%
  - Time to hospitalization: 9 days


**Infected**

Total Dead: >10,000,000
### Infection rate | Fatality rate | Percentage
---|---|---
10% | 0.5% | 0.5%
19% | 0.5% | 0.5%
29% | 0.5% | 0.5%
39% | 0.5% | 0.5%
50% | 0.5% | 0.5%
60% | 0.5% | 0.5%

Here is where coronavirus deaths would rank in the U.S., assuming an overall infection rate of **10%** and fatality rate of **0.5%** over the next year:

#### How Coronavirus Deaths Could Compare With Other Major Killers

<table>
<thead>
<tr>
<th>Cause of Death</th>
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<tbody>
<tr>
<td>Heart disease</td>
<td>655,393</td>
</tr>
<tr>
<td>Cancer</td>
<td>599,274</td>
</tr>
<tr>
<td>Alzheimer's, dementia and brain degeneration</td>
<td>267,311</td>
</tr>
<tr>
<td>Coronavirus (estimate)</td>
<td>165,000</td>
</tr>
<tr>
<td>Emphysema and COPD</td>
<td>164,603</td>
</tr>
<tr>
<td>Stroke</td>
<td>147,651</td>
</tr>
<tr>
<td>Diabetes</td>
<td>84,948</td>
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<td>Drug overdoses</td>
<td>67,367</td>
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<td>Pneumonia/flu</td>
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<tr>
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<td>40,718</td>
</tr>
<tr>
<td>Guns</td>
<td>39,201</td>
</tr>
</tbody>
</table>

Here is where coronavirus deaths would rank in the U.S., assuming an overall infection rate of **19%** and fatality rate of **0.5%** over the next year:

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Here is where coronavirus deaths would rank in the U.S., assuming an overall infection rate of **29%** and fatality rate of **0.5%** over the next year:

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Here is where coronavirus deaths would rank in the U.S., assuming an overall infection rate of **39%** and fatality rate of **0.5%** over the next year:

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Here is where coronavirus deaths would rank in the U.S., assuming an overall infection rate of **50%** and fatality rate of **0.5%** over the next year:

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Here is where coronavirus deaths would rank in the U.S., assuming an overall infection rate of **60%** and fatality rate of **0.5%** over the next year:

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Hospital System Capacity: possibility of implosion

Chart 4: Hospitalized Coronavirus Patients vs. System Capacity

Source: Tomas Pueyo analysis
ICU patients using ~25% of hospitalizations that require ICU support, from China CDC
Number of current + repurposed ICU beds = ~100,000 (Johns Hopkins, http://www.centerforhealthsecurity.org/cbn/2020/cbnreport-02272020.html)
Impact of Social Distancing

Social distancing for **14 days**

128 million total infections

Social distancing for **2 months**

14 million total infections

Note: “Social distancing” also includes a reduction in large gatherings; some school closures and working from home; and efforts to support hospitals and diagnostic testing. Based on a simulation between January and late October using an epidemic model. See full methodology for details.
### US Capacity Statistics: AHA Statistics 2020

**Stats**
- # hospitals: 6146
- # hospital beds: 924,107
- # hospital admits: 36,353,946
- # ICU beds
  - Med/Surg: 46,825
  - Cardiac: 14,439
  - Community: 7,323
- # ventilators: 160,000
  - Nat’l SS: 12,700
  - Made in US: ~50%
  - Cost: $25,000+
- #Deaths 2017: 2,813,503

**Unmet needs**
- Beds
- Hospitals
- ICU beds
- Ventilators
- PPE
- Swabs
- Test kits
- Surge personnel
ICU Bed Needs and Social Distancing

Chart 5: Peaks in Need for ICU Beds in the UK for Different Social Distancing Measures

- Surge critical care bed capacity
- Do nothing
- Case isolation
- Case isolation and household quarantine
- Closing schools and universities
- Case isolation, home quarantine, social distancing of >70s

Sources: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Neil Ferguson et al., Imperial College
ICU Capacity is Deficient

Government intervention has been done many times, during war periods.

Montgomery Wards didn't want to cooperate.

Sewell Avery removed from his office.

Government Options

- USG takes over critical hospital supply industries, "Defense Production Act 1950"
- More PPE
- More ventilators
- More reagents
- More testing facilities
- More quarantine facilities (hotels; arenas, sports facilities)
- Pre-agreed upon national and international emergency plans for equipment, personnel, diagnostic, and treatment.
Clinical Research and COVID-19

- >84 vaccine trials planned or underway worldwide
- >100 drug candidates

- Hydroxychloroquine/Chloroquine +/- azithromycin
- Lopinavir/ritonavir and other HIV antivirals
- Corticosteroids
- Tocilizumab
- Convalescent plasma
- Ribavirin
- Oseltamivir
- IVIG
- MTase inhibitors
Methodology for Evaluation of COVID-19 Therapy
IDSA, April 11, 2020

GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)

1. **Establish initial level of confidence**
   - **Study design**
     - Randomized trials
     - Observational studies
   - **Initial confidence**
     - High confidence
     - Low confidence

2. **Consider lowering or raising level of confidence**
   - **Reasons for considering lowering or raising confidence**
     - Lower if
       - Risk of bias
       - Inconsistency
       - Indirectness
       - Imprecision
       - Publication bias
     - Higher if
       - Large effect
       - Dose response
      - All plausible confounding & bias
        - would reduce any observed effect
        - would suggest or prove no effect if no effect was observed

3. **Final level of confidence rating**
   - **Confidence in an estimate of effect across those considerations**
     - High
     - Moderate
     - Low
     - Very low

2. **Determinants of the strength of recommendation**
   - **Balance between benefits, harms & burdens**
   - **Quality (certainty) of evidence**
   - **Patients’ values & preferences**
   - **Resources and cost**

3. **Implication of the strength of recommendation**
   - **Strong**
     - Population: Most people in this situation would want the recommended course of action and only a small proportion would not
     - Health care workers: Most people should receive the recommended course of action
     - Policy makers: The recommendation can be adapted as a policy in most situations
   - **Weak**
     - Population: The majority of people in this situation would want the recommended course of action, but many would not
     - Health care workers: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making
     - Policy makers: There is a need for substantial debate and involvement of stakeholders
COVID-19 Therapies

• **Hydroxychloroquine/Chloroquine**
  - Formerly used for malaria and immunosuppressive therapy
  - 2 RCTs: failed show effect on clinical progression, viral clearance; possibly some clinical improvement; no data on mortality, ICU admission, ventilation.
  - Adding azithromycin may have less viral failure (Selection bias?); no change in mortality or ICU admissions; increases QT intervals
  - Risks: QT prolongation (>500 ms), GI toxicities (7%), death, affected by renal clearance, in a randomized study in Brazil one treatment arm stopped due to toxicity

• **Lopinavir/ritonavir and other HIV therapies**
  - 1 RCT and 2 cases studies
  - No benefit on mortality or clinical progression
  - 14% discontinued due to AEs
COVID-19 Therapies

• Corticosteroids
  - No RCT, 4 retrospective analyses
  - No clear benefit observed
  - May increase viral replication especially early in the infection course

• Tocilizumab
  - 1 uncontrolled study, N=21
  - Assuming mortality of 60% in critically ill/11% in severely ill, less mortality than expected (9.5% vs 20%)
  - IL6 upregulation may impact P450 system
COVID-19 Therapies

• Convalescent Plasma
  - 2 case series, N=15; no controls, most patients very ill
  - No deaths (30% expected)

• Ribavirin
  - Antiviral drug; many toxicities, has Black Box warning
  - 26 studies, most inconclusive, 4 showed harm

• Osetamivir
  - Influenza drug, no evidence yet; studied in combination with other drugs, ongoing.

• IVIG
  - Has been used in many other infections; no data here
COVID-19 Therapies

• Remdesivir
  - Broad spectrum antiviral active against many RNA viruses including SARS, MERS, Ebola, RSV, Nipah, Marburg, Hendra
  - Lowers viral load of SARS-CoV in mice
  - 53 patients treated compassionately has generally positive outcomes, no controls
  - RCT underway, including NU/NMH, sample size >700

• MTase Inhibitors
  - Developed under a research program here at NU (Karla Satchell, PI).
  - Inhibits and identified target. In development.

• Summary
  - No antiviral treatment recommended outside of a clinical trial
Science and Leadership

Science
• NIH, NSF, CDC, DoD now focusing on COVID-19
• Vaccine development vigorous: 84 trials in planning or development
• Therapeutics: >100
  - Refocusing old drugs
    • Hydroxychloroquine/Chloroquine
    • Lopinavir/ritonavir
    • Azithromycin
    • HIV, HCV, other antivirals
  - Developing new drugs
    • MTase inhibitors

Leadership
• Coronavirus Task Force
  - VP Pence, chair
  - J Adams, Surgeon General
  - A Fauci, director NIAID
  - D Birx, response coordinator
  - R Redfield, director CDC
  - S Hahn, director, FDA
  - Alex Azar, secretary DHHS
  - L Kudlow, director National Econ Council
  - S Mnuchin, secretary of Treasury
  - B Carson, secretary of Housing
Leadership Quotes

• 01/22  We have it totally under control (CNBC)
• 02/10  Looks like by April, you know, in theory, when it gets a little warmer, it miraculously disappears. (NH rally)
• 02/24  The coronavirus is very much under control in the USA...stock market starting to look very good to me
Leadership Quotes

• 02/28  It’s going to disappear, one day, it’s like a miracle, it will disappear (News Conference)
• 03/07  Anyone who wants a test can have one (NY Times);  the FDA regulations have not hindered or been a roadblock to the rollout of tests during this pandemic (Reuters)
• 03/09  I don’t need to have the numbers double because of one ship that wasn’t our fault (Diamond Princess passengers) (The Guardian)
• 03/10  We’re prepared, and we’re doing a great job with it.  And it will go away.  Just stay calm, it will go away.  (Meeting with Republican Senators)
• 03/17  I felt it was a pandemic long before it was called a pandemic (News Conference)
  - 03/11/20  WHO declares coronavirus-19 a pandemic
• 03/24  I’d love the country to open up and just be raring to go by Easter (Fox News)
US Impact to Date...Science good but...  Ed Yong, The Atlantic

3/25/20

• **Rudderless**
  - The President, the Vice President, Head of the CDC, Head of NIAID Dr Fauci, Dr Birx, Jared Kushner, Peter Navarro, Andrew Cuomo, Larry Kudlow, Fox News

• **Blindsighted**
  - December 31, 2019: WHO informed about mysterious pneumonia in 41 people from Wuhan, ultimately called “nCoV”
  - January 20, first US case in man from Washington State
  - January 30, WHO declares global public health emergency
  - January 31, The President bans travelers from China
  - February 11, COVID-19 becomes the new name
  - March 8, Italy declares lockdown in northern part of country
  - March 11, WHO declares full pandemic
  - March 13, US declares national emergency
  - March 26, COVID-19 in US highest in world
  - April 9, 95% of US under some form of lockdown

• **Lethargic**
  - 60 day lag in recognizing the pandemic

• **Uncoordinated**
  - The Feds, the states, neighboring countries, lack of equipment/supplies, national plan, leadership
Best Way Forward: *It is all doable!*

- Social Distancing as much as possible for as long as necessary
- Keep schools and universities closed
- Support the mass of unemployed with funds and health insurance (ACA)
- Ramp up testing
  - South Koreans test 15,000 people/day at 43 drive through facilities
  - That translates to 4000+ people/day for Illinois; 100,000+ people/day for US
- Ramp up diagnostics/supplies and hospital capacity. (DPA if necessary)
- Enforce public health policy vigilantly
- Massive vaccine development initiatives
- Massive antiviral drug development programs
- Restore the Pandemic Response Team and internationalize it

*The more forcefully we act now, the shorter the problem*
Thank you
Questions?