

Global Reverberations Coronavirus-19

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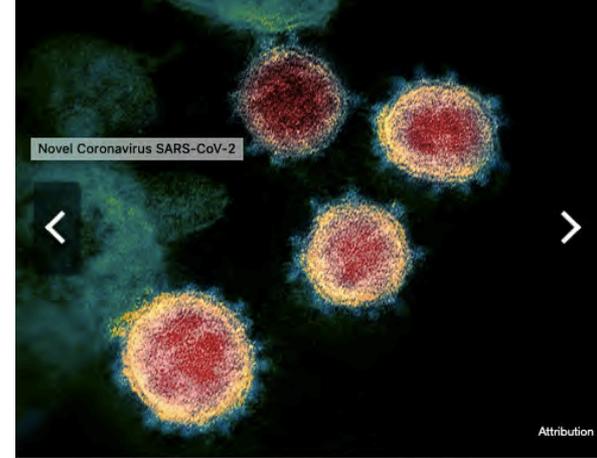
April 15, 2020

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)



Novel Coronavirus SARS-CoV-2

This transmission electron microscope image shows SARS-CoV-2—also known as 2019-...

Coronavirus Epidemics/Pandemic

Outbreaks of coronavirus-related diseases

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

Outbreak	Virus type	Deaths
2003 severe acute respiratory syndrome outbreak	SARS-CoV	774 ^[42]
2012 Middle East respiratory syndrome coronavirus outbreak	MERS-CoV	Over 400 ^[43]
2015 Middle East respiratory syndrome outbreak in South Korea	MERS-CoV	36 ^[44]
2018 Middle East respiratory syndrome outbreak	MERS-CoV	41 ^[45]
2019–2020 coronavirus pandemic	SARS-CoV-2	At least 15,328 ^[46]

Deadly Viruses and Epidemics

Viruses

- SARS-CoV-2
- Ebola
- Hanta
- Lassa
- Rabies
- Small Pox
- Dengue
- Influenza

Epidemics

- | | | |
|---|---------|-----------|
| • HIV | 36M | 2005-2012 |
| • Flu (Hong Kong) | 1M | 1968 |
| • Flu (Asian) | 2M | 1956-58 |
| • Flu (Spanish) | 20-50M | 1918-20 |
| • Cholera (6 th)
1910-11 | 800K | |
| • Flu (Russian) | 1M | 1889-90 |
| • Cholera (3 rd)
1860 | 1M | 1852- |
| • Plague (Black Death) | 75-200M | 1346-53 |
| • Justinian (Bubonic) | 25M | 541-42 |
| • Antonine (Galen) | 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)



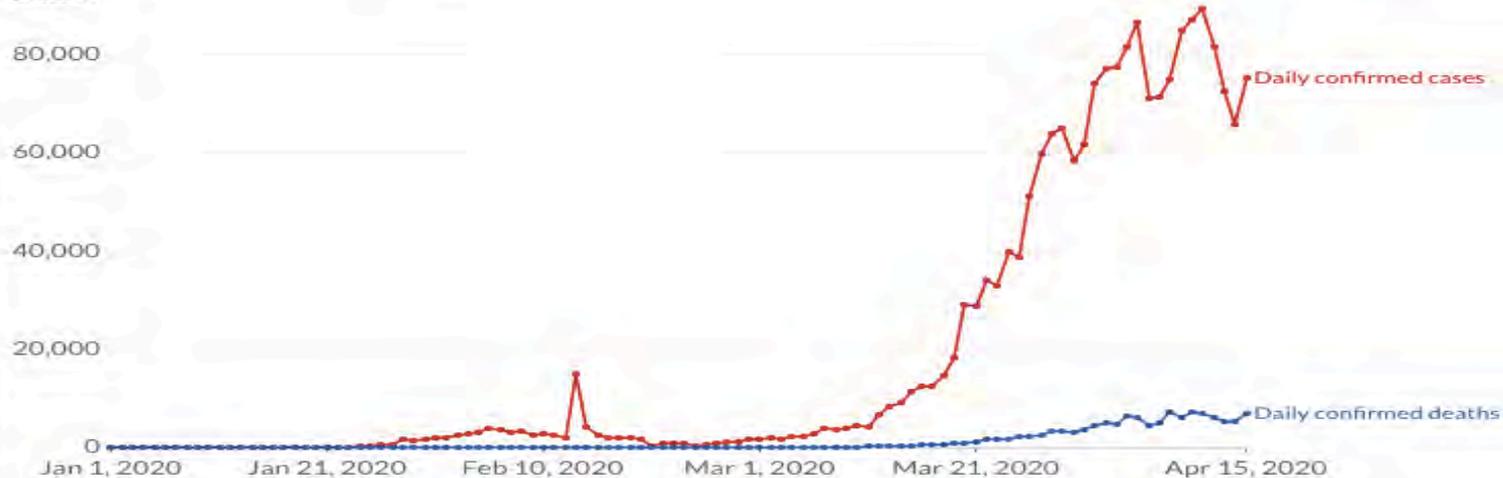
Daily COVID-19 Cases and Deaths Worldwide

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)

CC BY

▶ Dec 31, 2019 Apr 15, 2020

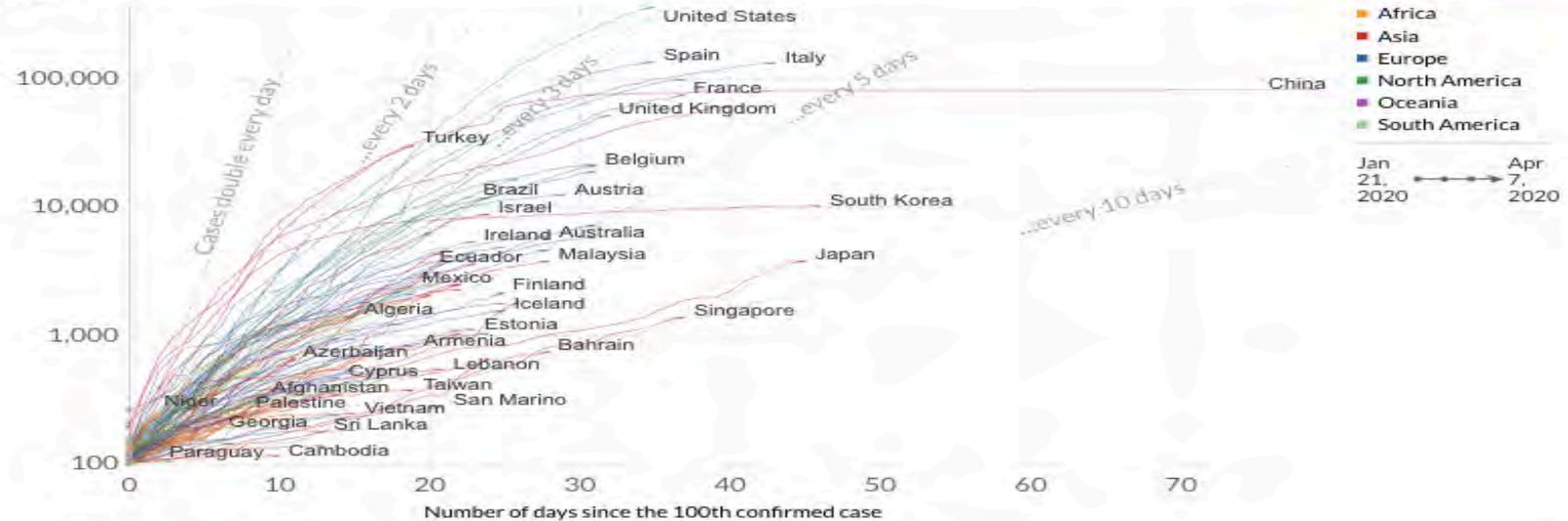
Total Confirmed COVID-19

Starting after first 100 cases

Total confirmed cases of COVID-19

The number of confirmed cases is lower than the number of total cases. The main reason for this is limited testing.

LOG



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

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Jan 21, 2020

Apr 7, 2020

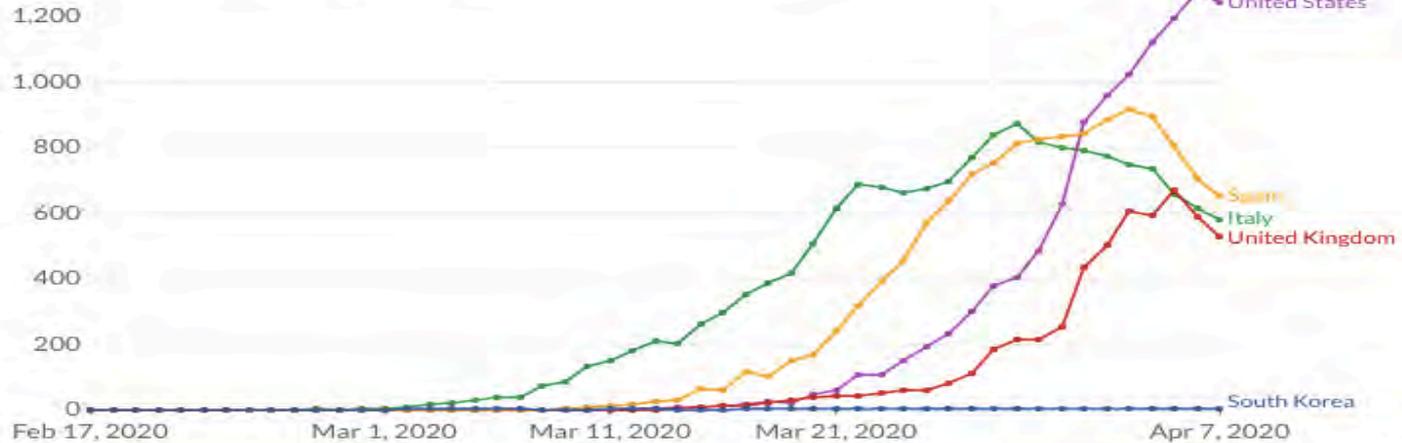
COVID-19 Deaths per Country

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.

Our World in Data

LINEAR



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.

CC BY

▶ Dec 31, 2019

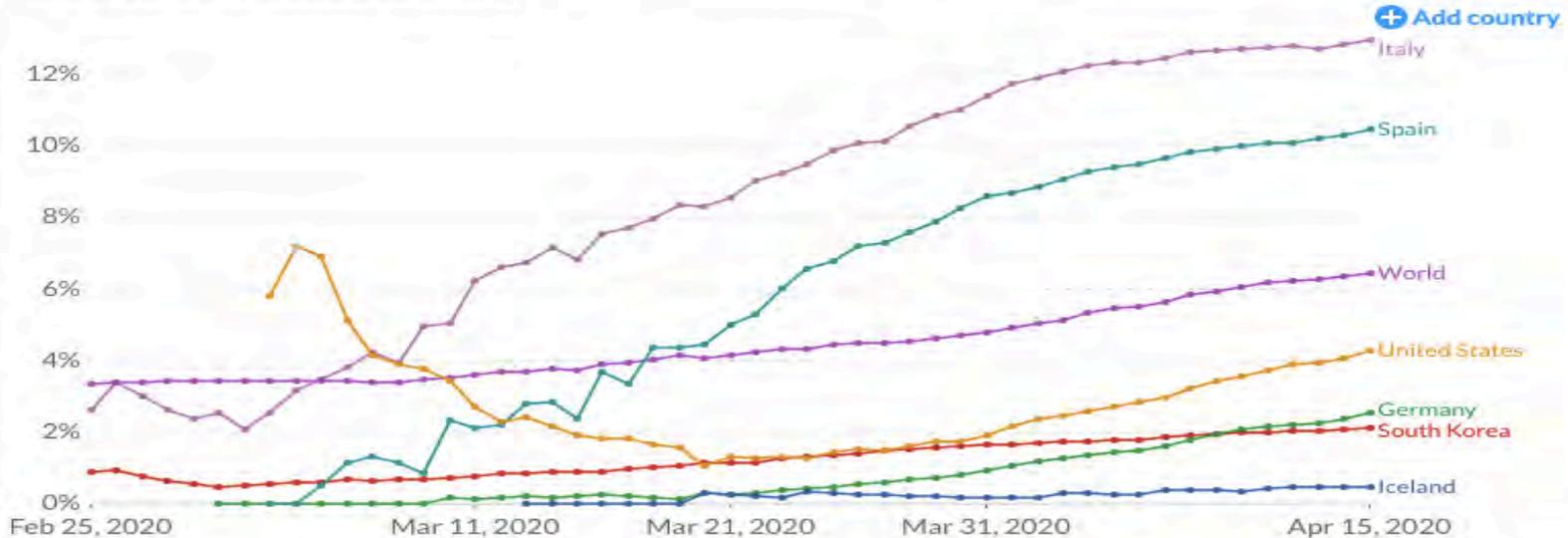
▶ Apr 7, 2020

Case Fatality by Country

Our World in Data

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.

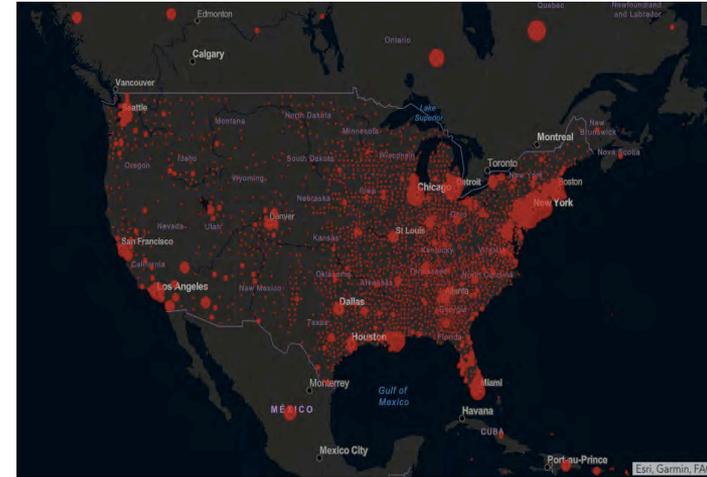
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▶ Jan 19, 2020

Apr 15, 2020

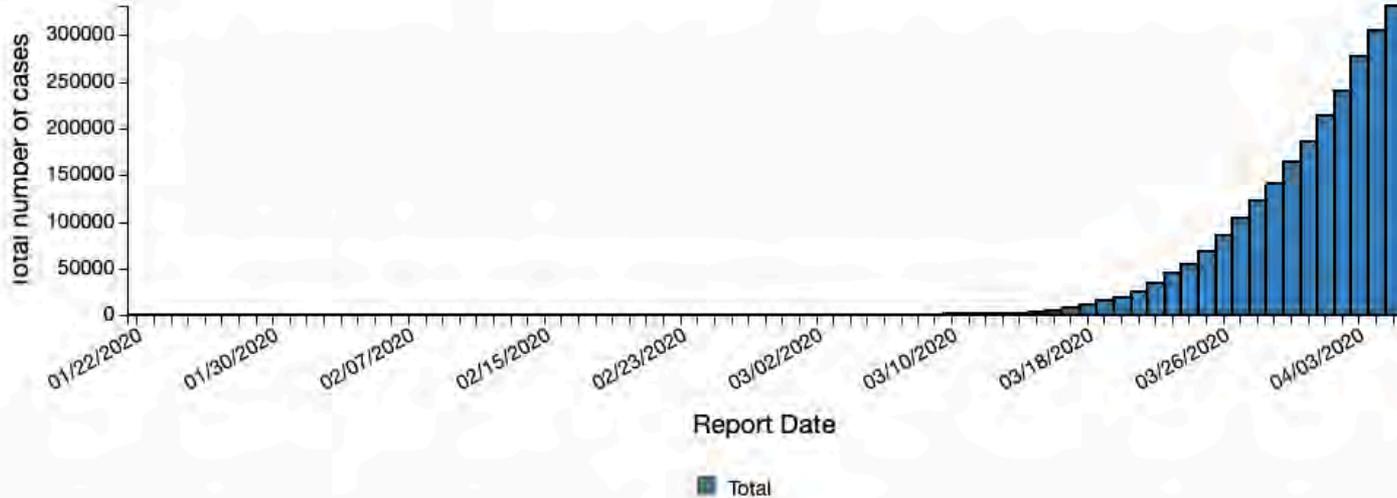
National Statistics as of April 15, 2020

• 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)



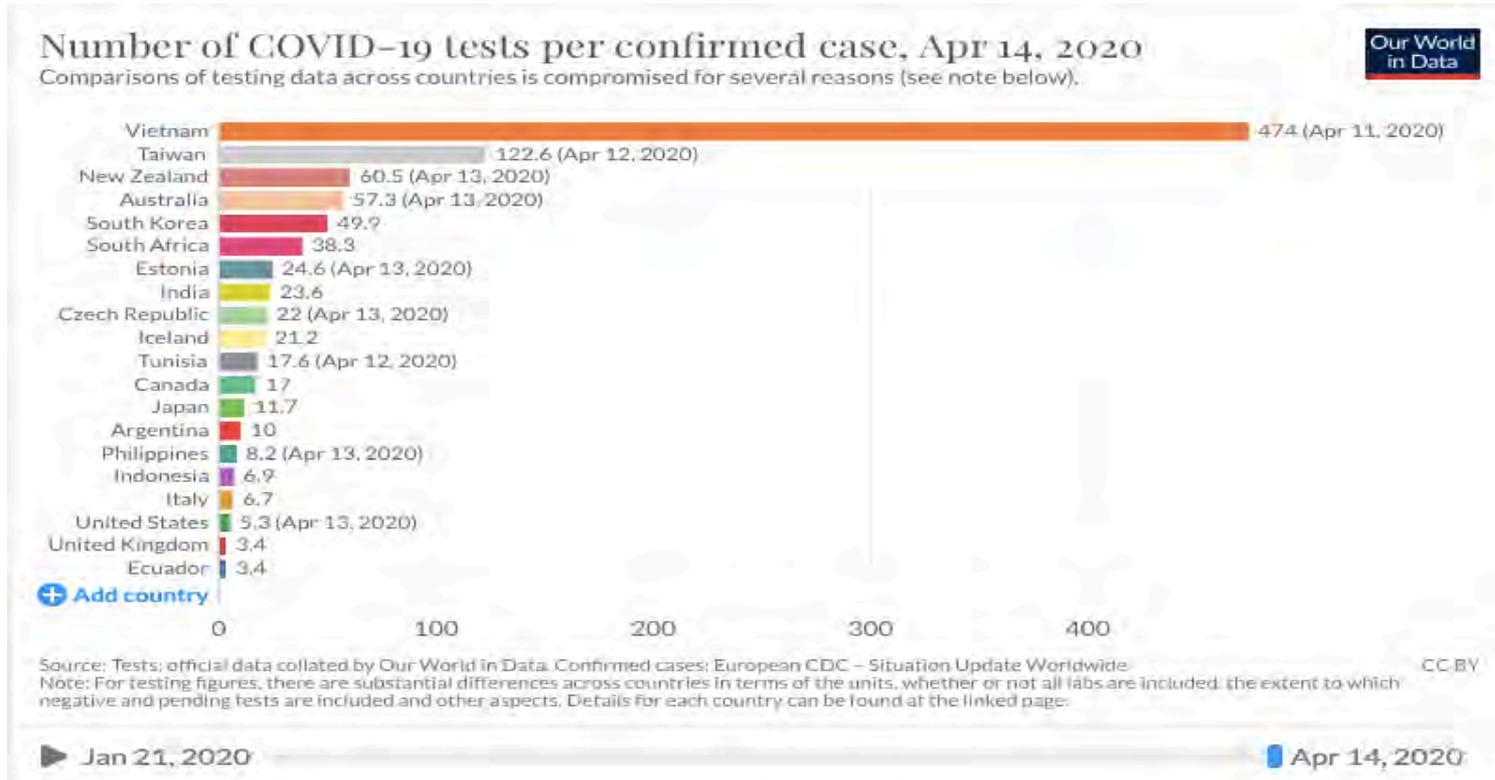
US COVID-19 through April 2020

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



US Outcomes up to March 16, 2020. (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

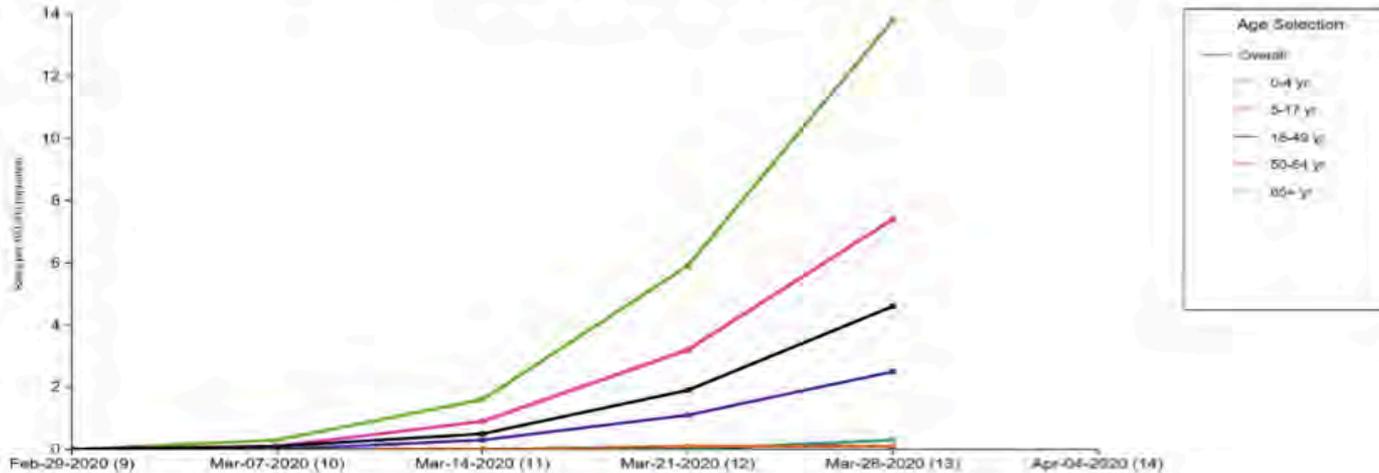
- ≥ 85	9%	7%
- 65-84	26%	46%
- 55-64	17%	36%
- 45-54	18%	36%* (included in 55-64s)
- 20-44	20%	12%
- < 20	$< 1\%$	0%

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).

Laboratory-Confirmed COVID-19-Associated Hospitalizations

Preliminary cumulative rates as of Mar 28, 2020



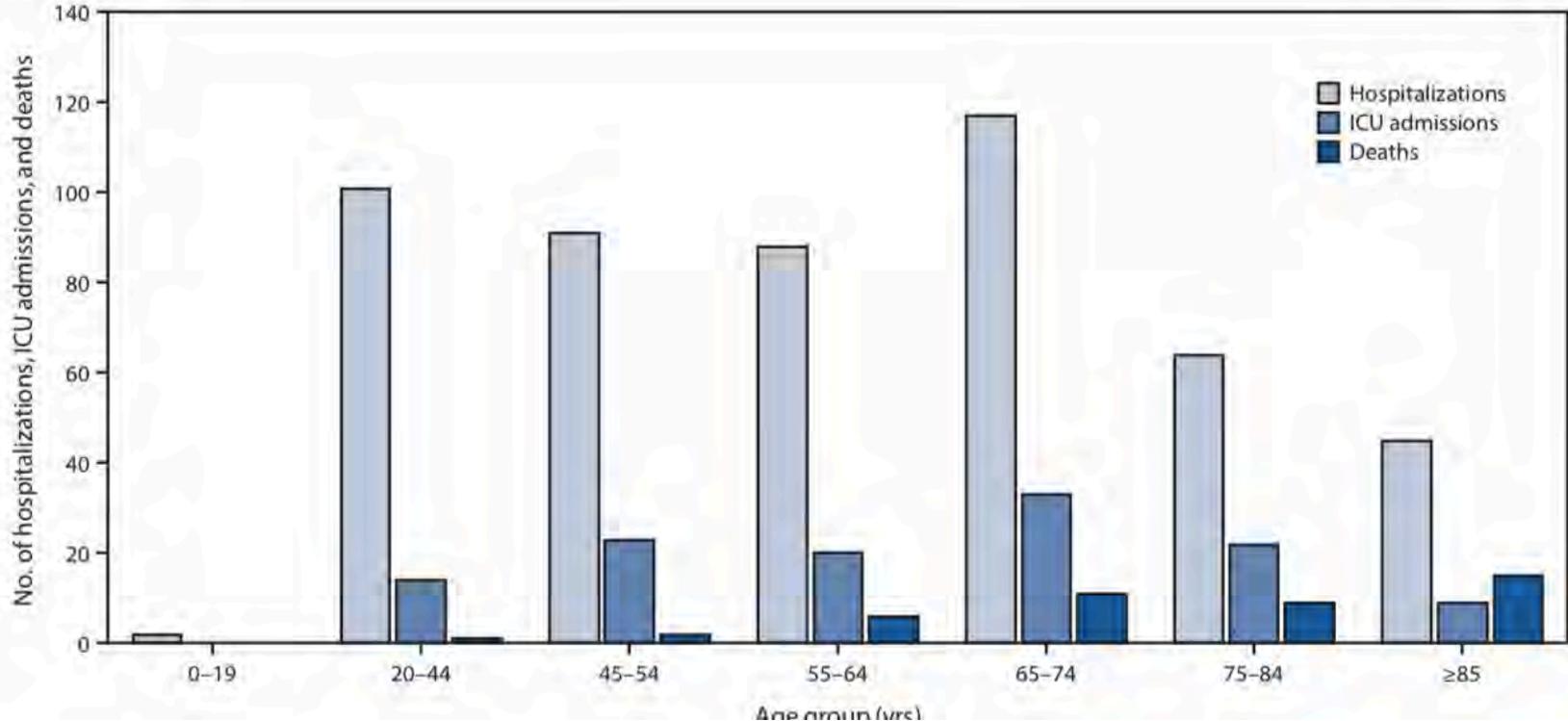
US Outcomes up to March 16, 2020. (N=4,226)

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



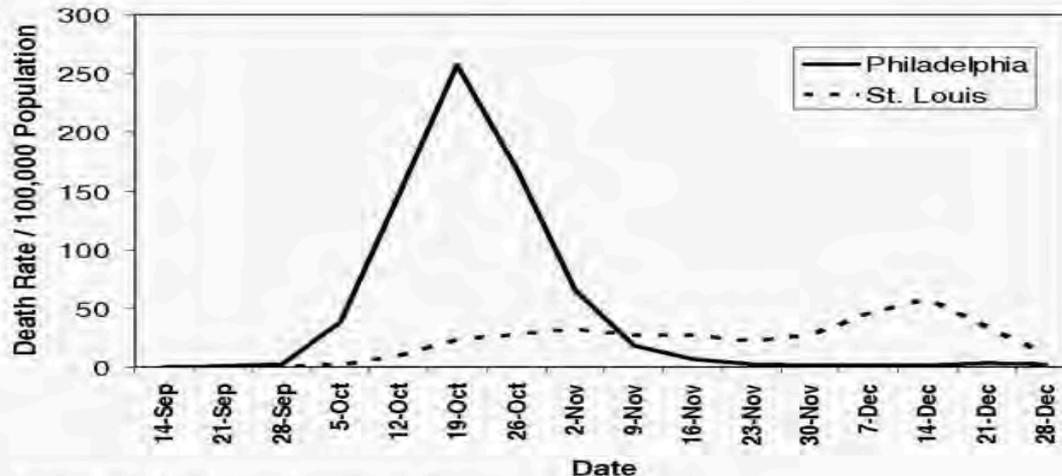
Interventions

- 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

Social Distancing: Nothing New

Influenza Epidemic 1918 (aka Spanish Flu)

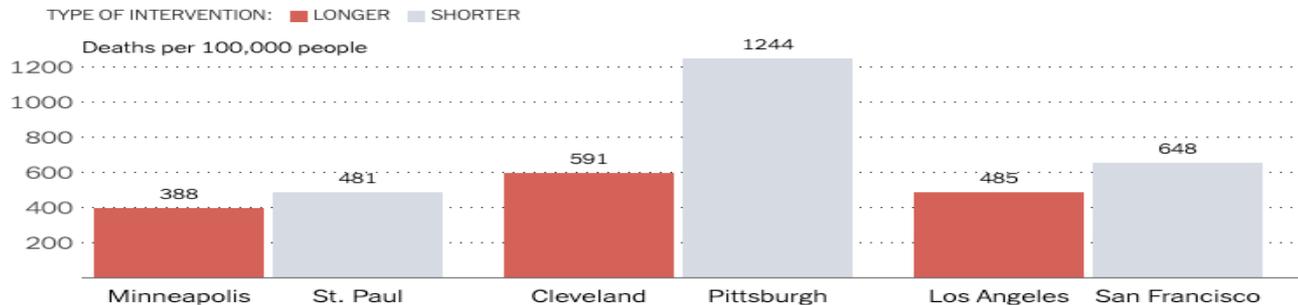
By the end of the week, more than 4,500 were dead in an outbreak that would claim as many as 100 million people worldwide. By the time Philadelphia's politicians closed down the city, it was too late.



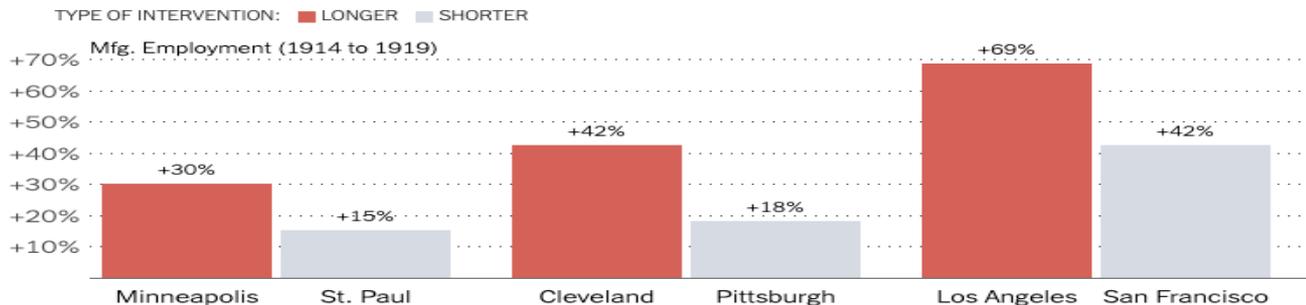
Proceedings of the National Academy of Sciences

Intervention Length, Mortality and Employment

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



Those same cities also had higher employment gains

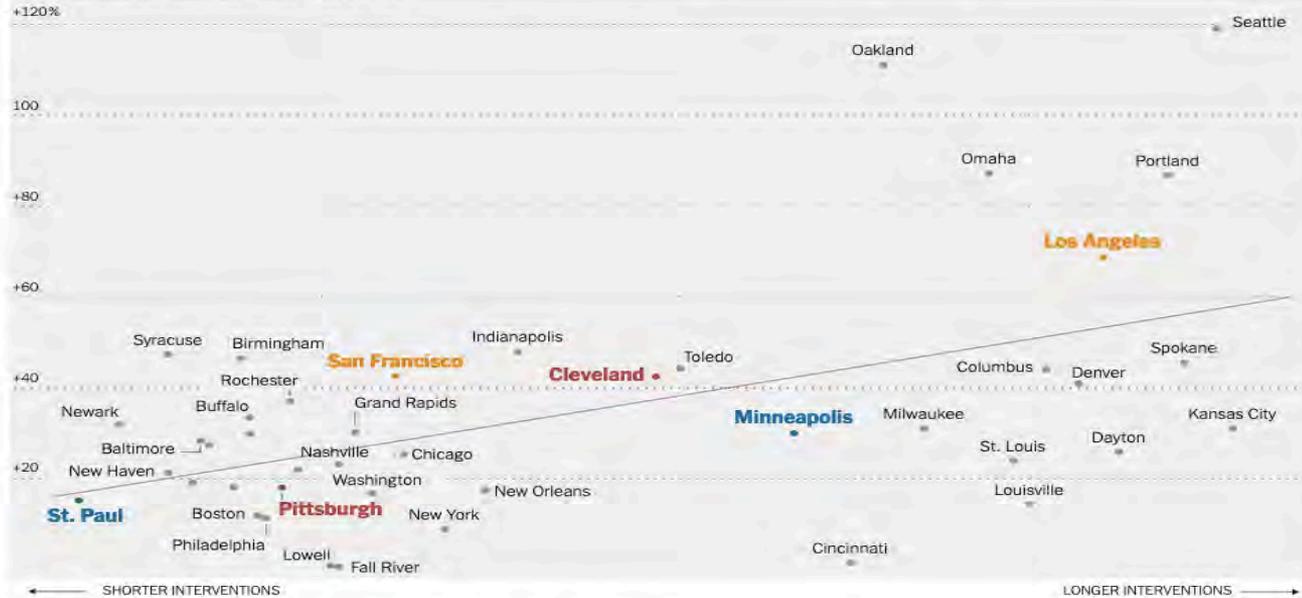


Cities, Intervention and Employment

Flu of 1918

Cities That Had More Aggressive Interventions Tended to Have Higher Employment Growth

GROWTH IN MANUFACTURING EMPLOYMENT 1914 TO 1919



Source: Sergio Correia, Stephan Luck, and Emil Verner

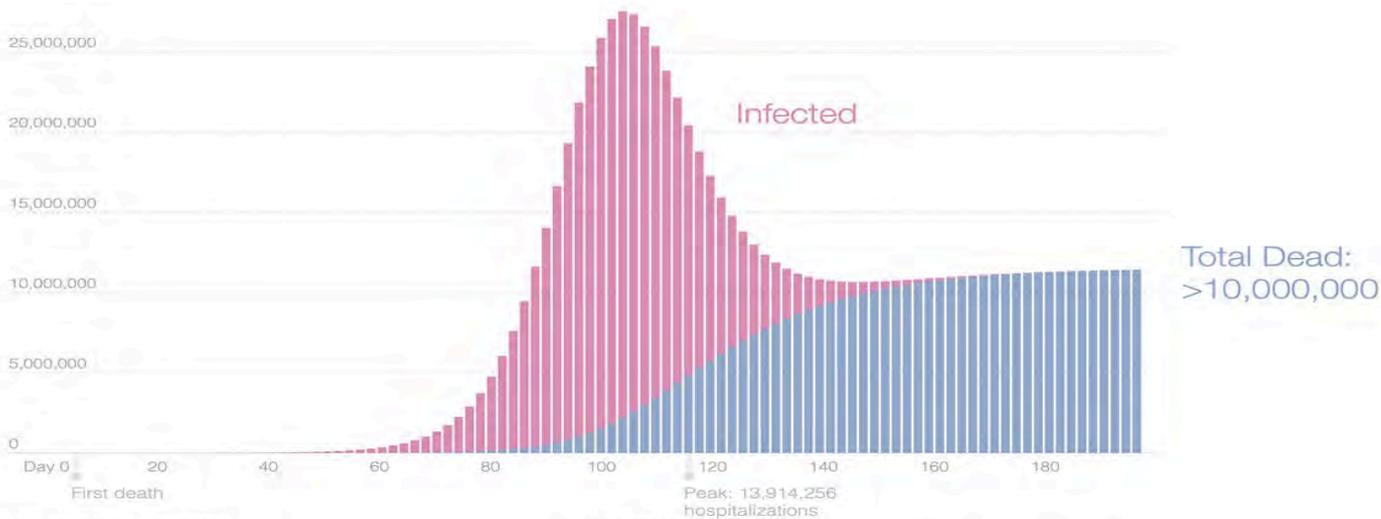
New York City and Social Distancing 2020



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.

328,484,431

Number of initial infections.

246

Basic Reproduction Number \mathcal{R}_0

Measure of contagiousness: the number of secondary infections each infected individual produces.

2.4

Transmission Times

Length of incubation period, T_{inc} .

5.29 days

Duration patient is infectious, T_{inf} .

2.9 Days

Clinical Dynamics

Morbidity Statistics

Case fatality rate.

4.08 %

Time from end of incubation to death.

21.3 Days

Recovery Times

Length of hospital stay

10 Days

Recovery time for mild cases

11.1 Days

Care statistics

Hospitalization rate.

14.08 %

Time to hospitalization.

5 Days

Source: Epidemic Calculator, Gabriel Goh, <http://gabgoh.github.io/COVID/index.html>.



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

CAUSE OF DEATH	U.S. DEATHS
Heart disease	655,381
Cancer	599,274
Alzheimer's, dementia and brain degeneration	267,311
4 Coronavirus (estimate)	165,000
Emphysema and COPD	154,603
Stroke	147,810
Diabetes	84,946
Drug overdoses	67,367
Pneumonia/flu	59,690
Liver disease and cirrhosis	55,918
Renal failure	50,404
Car crashes	42,114
Septicemia	40,718
Guns	39,201



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:

How Coronavirus Deaths Could Compare With Other Major Killers

CAUSE OF DEATH	U.S. DEATHS
Heart disease	655,381
2 Coronavirus (estimate)	633,000
Cancer	599,274
Alzheimer's, dementia and brain degeneration	267,311
Emphysema and COPD	154,603
Stroke	147,810
Diabetes	84,946
Drug overdoses	67,367
Pneumonia/flu	59,690
Liver disease and cirrhosis	55,918
Renal failure	50,404
Car crashes	42,114
Septicemia	40,718
Guns	39,201



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:

How Coronavirus Deaths Could Compare With Other Major Killers

CAUSE OF DEATH	U.S. DEATHS
Heart disease	655,381
Cancer	599,274
3 Coronavirus (estimate)	313,000
Alzheimer's, dementia and brain degeneration	267,311
Emphysema and COPD	154,603
Stroke	147,810
Diabetes	84,946
Drug overdoses	67,367
Pneumonia/flu	59,690
Liver disease and cirrhosis	55,918
Renal failure	50,404
Car crashes	42,114
Septicemia	40,718
Guns	39,201



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:

How Coronavirus Deaths Could Compare With Other Major Killers

CAUSE OF DEATH	U.S. DEATHS
1 Coronavirus (estimate)	809,000
Heart disease	655,381
Cancer	599,274
Alzheimer's, dementia and brain degeneration	267,311
Emphysema and COPD	154,603
Stroke	147,810
Diabetes	84,946
Drug overdoses	67,367
Pneumonia/flu	59,690
Liver disease and cirrhosis	55,918
Renal failure	50,404
Car crashes	42,114
Septicemia	40,718
Guns	39,201



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:

How Coronavirus Deaths Could Compare With Other Major Killers

CAUSE OF DEATH	U.S. DEATHS
Heart disease	655,381
Cancer	599,274
3 Coronavirus (estimate)	473,000
Alzheimer's, dementia and brain degeneration	267,311
Emphysema and COPD	154,603
Stroke	147,810
Diabetes	84,946
Drug overdoses	67,367
Pneumonia/flu	59,690
Liver disease and cirrhosis	55,918
Renal failure	50,404
Car crashes	42,114
Septicemia	40,718
Guns	39,201



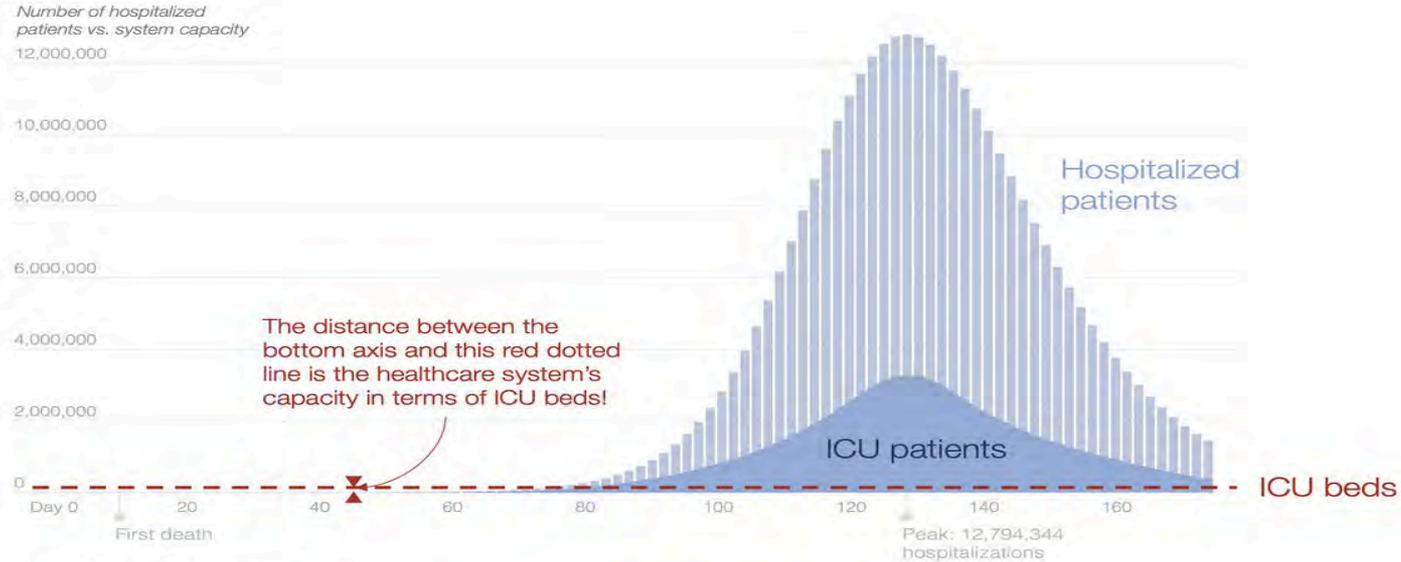
Here is where coronavirus deaths would rank in the U.S., assuming an overall infection rate of **60%** and fatality rate of **0.5%** over the next year:

How Coronavirus Deaths Could Compare With Other Major Killers

CAUSE OF DEATH	U.S. DEATHS
1 Coronavirus (estimate)	961,000
Heart disease	655,381
Cancer	599,274
Alzheimer's, dementia and brain degeneration	267,311
Emphysema and COPD	154,603
Stroke	147,810
Diabetes	84,946
Drug overdoses	67,367
Pneumonia/flu	59,690
Liver disease and cirrhosis	55,918
Renal failure	50,404
Car crashes	42,114
Septicemia	40,718
Guns	39,201

Hospital System Capacity: possibility of implosion

Chart 4: Hospitalized Coronavirus Patients vs. System Capacity



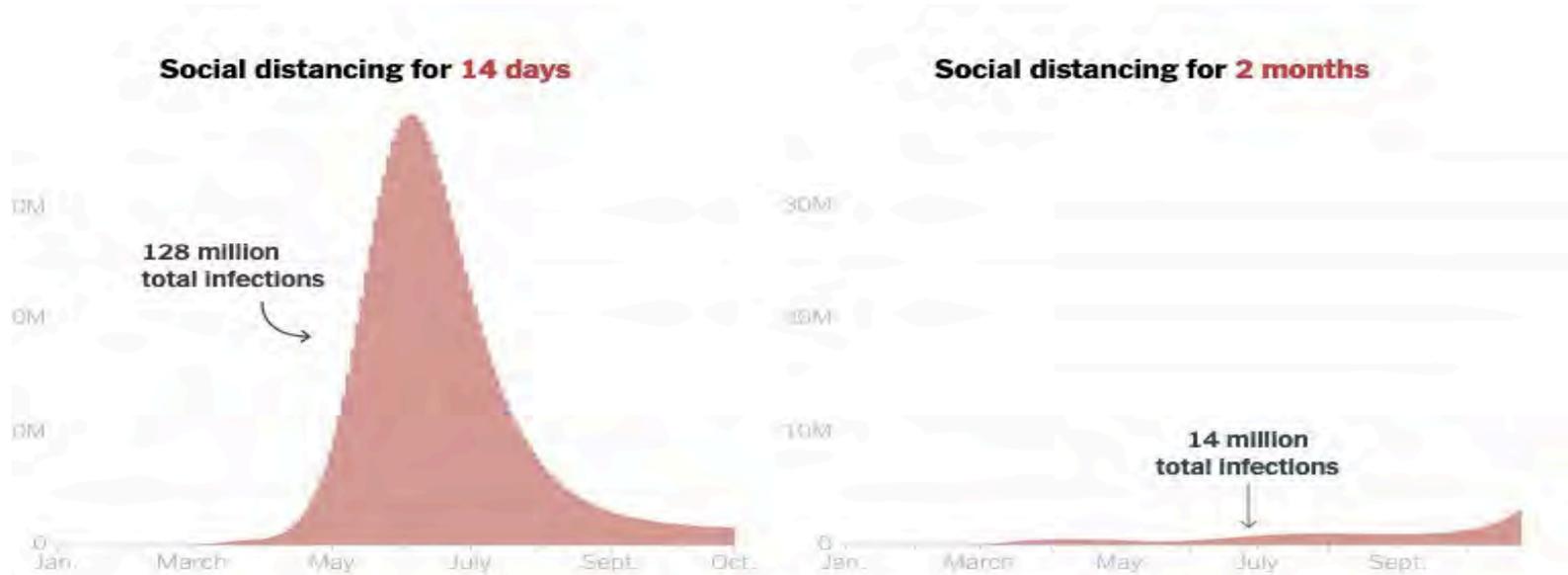
Source: Tomas Pueyo analysis

Epidemic Calculator, Gabriel Goh, <http://gabgoh.github.io/COVID/index.html> for Hospitalized patients

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



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

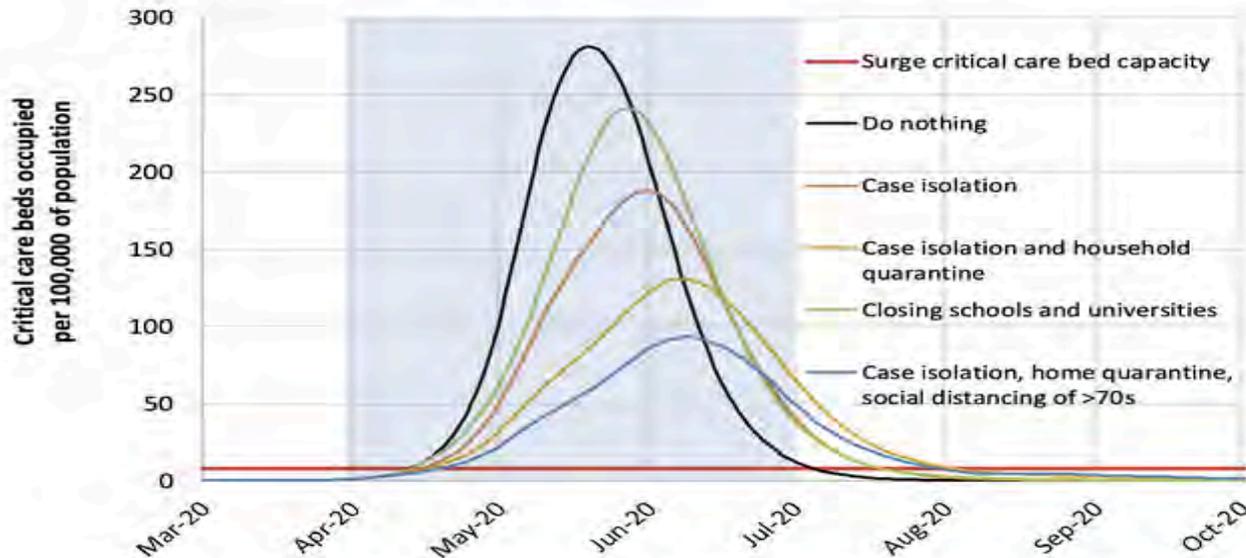
- # hospitals 6146
- # hospital beds 924,107
- # hospital admits 36,353,946
- # ICU beds
 - Med/Surg 46,825
 - Cardiac 14,439
 - Community 7,323
- # ventilators 160,000
 - Nat'l SS 12,700
 - Made in US ~50%
 - Cost \$25,000+
- #Deaths 2017 2,813,503

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



Source: 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 time, during war periods
Montgomery Wards didn't want to cooperate

Government Options

Sewell Avery removed from his office



- 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*

Clinical Research and COVID-19

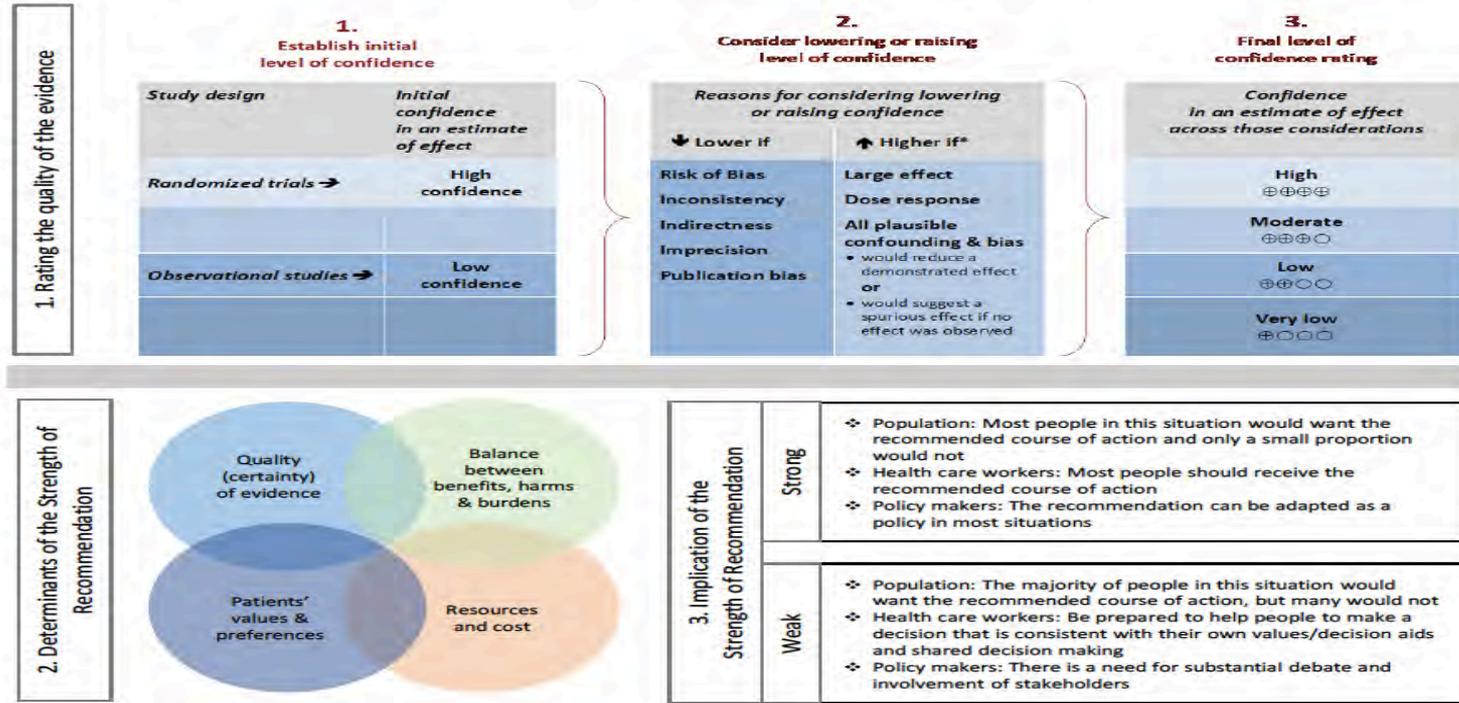
- >84 vaccine trials planned or underway worldwide
- >100 drug candidates

- 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)



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

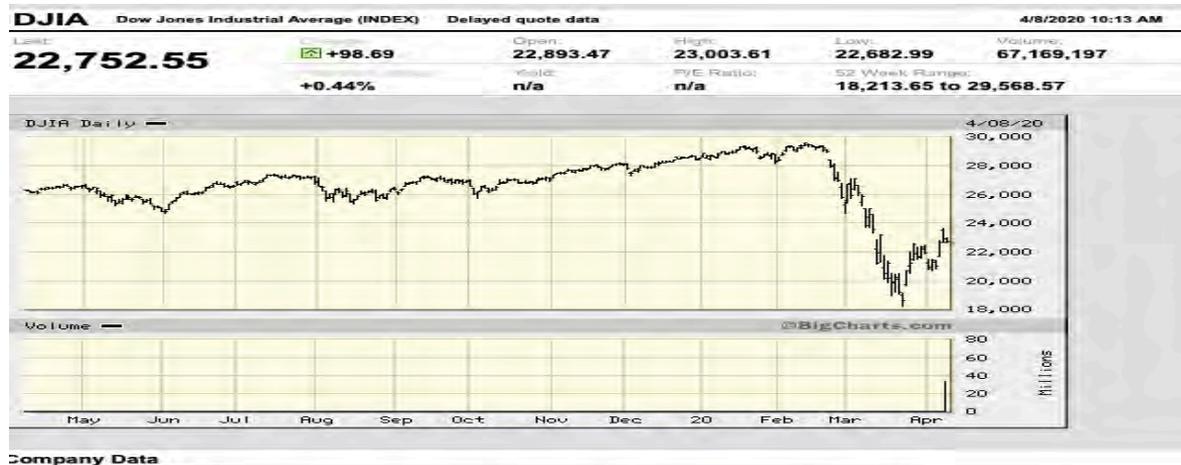
- NIH, NSF, CDC, DoD now focusing on COVID-19
- Vaccine development vigorous: 84 trials in planning or development
- Therapeutics: >100
 - Refocusing old drugs
 - Hydroxychloroquine/Chloroquine
 - Lopinavir/ritonavir
 - Azithromycin
 - HIV, HCV, other antivirals
 - Developing new drugs
 - MTase inhibitors

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

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**

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?