

COVID-19 Perspectives: A Work in Progress

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Yale '56 Reunion
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Powerpoint Slides will be available
Recording to be available**

Outline of Topics

- Recent pandemics
- Why was this such a “successful” pathogen?
- The virus (SARS-CoV-2) and the disease (COVID-19)
- **High transmissibility**
- Epidemiology, **Prevention** and Treatment
- Emerging **Variants**
- **Vaccines**
- What went wrong and **What are we learning?**
- Questions and comments

Zoonoses

Diseases that come to humans from the
(rest of the) animal world

- HIV: Chimpanzees
- Ebola: Fruit bats
- SARS 1: Bats > Civet cats
- Middle East Respiratory Syndrome (MERS): Camels
- **Avian Influenza (Bird Flu): Birds** (1918 and out there again)
 - **thus far unable to spread from human to human**
- COVID-19: Bats. (? laboratory research and escape)

Bats harbor a large number of genetically different coronaviruses.

? Role of laboratory experiments and laboratory accidents

What makes for a successful pathogen?

1. Capacity for **human-to-human** transmission
2. High proportion of infected persons who **aren't too sick**
Asymptomatic and mildly ill individuals who are virus transmitters
3. Novelty: No immunity in the population. World population wide open for the novel coronavirus

*The USPHS has traditionally protected us by going abroad and protecting our ports of entry.
(e.g. Ebola, Cholera.....).*

SARS-CoV-2 Checks all the boxes.

Smallpox kills or immunizes all of its victims. No animal reservoir. Finally eradicated in 1979 in Somalia (CDC, WHO).

Not a successful pathogen.

How do viruses differ from bacteria? What is their place in the living world?

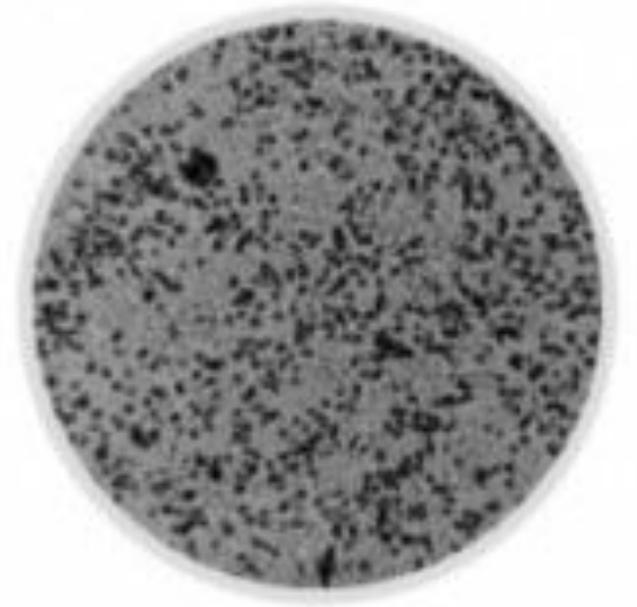
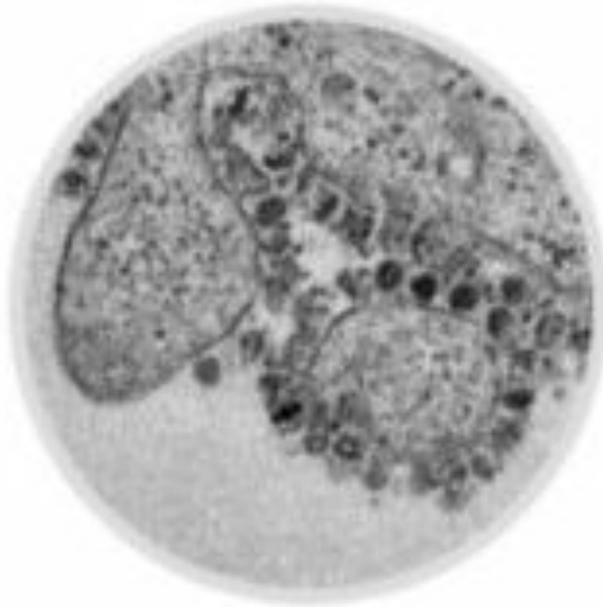
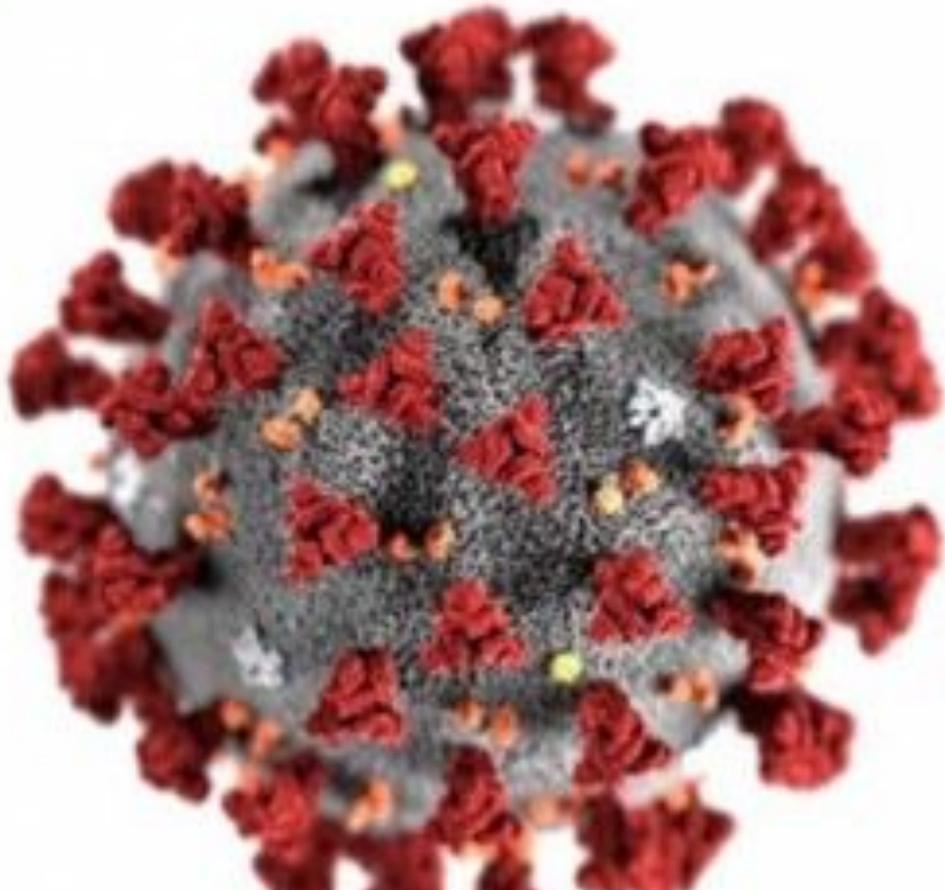
- Viruses are too small to be visible by light microscopes
 - RBC's ~ 7 microns. Bacteria 0.4 microns to 1 micron
micron= millionth of meter
 - Viruses, SARS-CoV-2 ~ 60-140 nanometers
nm=billionth of a meter

Can replicate only in living cells (obligate intracellular parasites).

- **Can put viral DNA or RNA away as crystals on a shelf (TMV)**
- Pure biologic information (DNA or RNA) wrapped in tiny capsule

Coronavirus and infection of cells

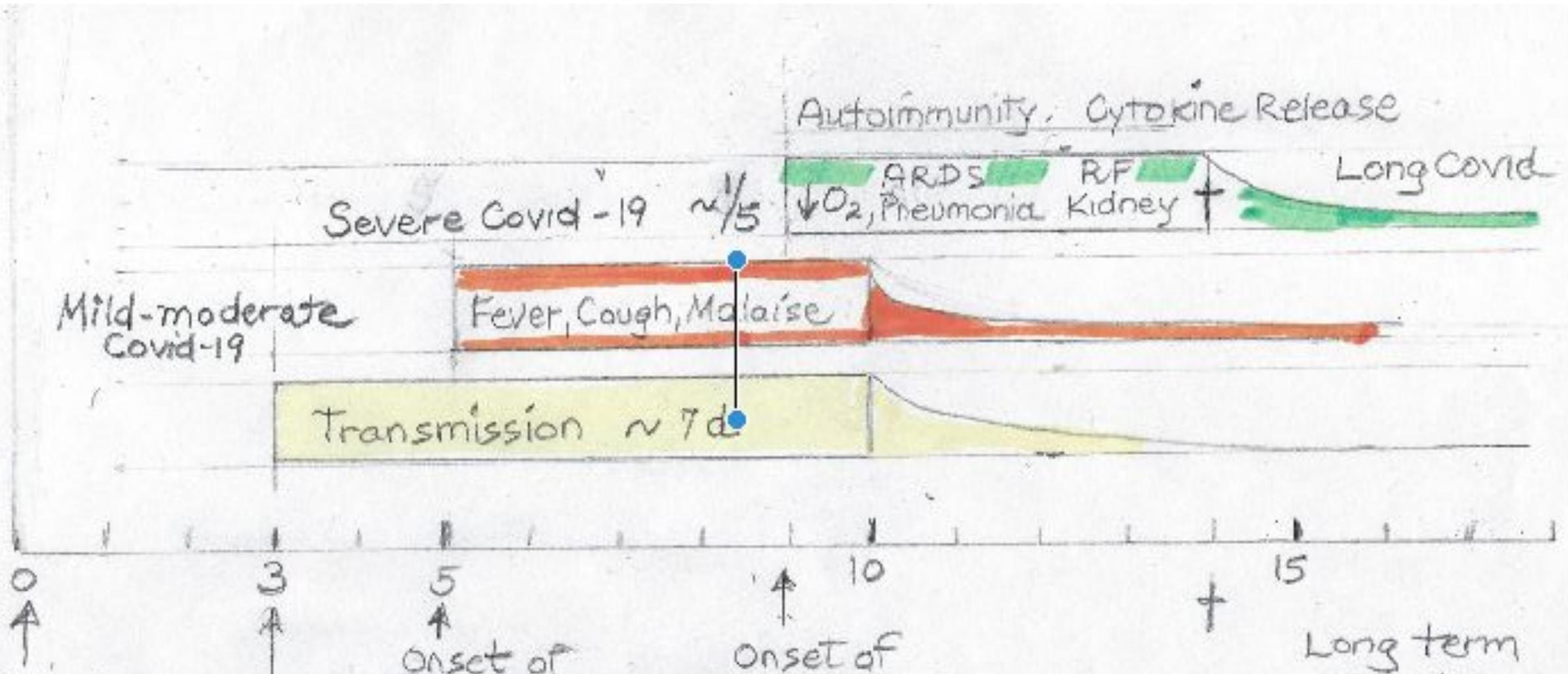
ZOOM_{IN} **CORONAVIRUS**



Course of COVID-19 Illness

Composite Clinical Timeline

Clinical Characteristics , 104 Patients with COVID-19 on the Cruise Ship Diamond Princess, (Lancet Infectious Disease, June 12, 2020) and Wikipedia



COVID-19 in a Restaurant

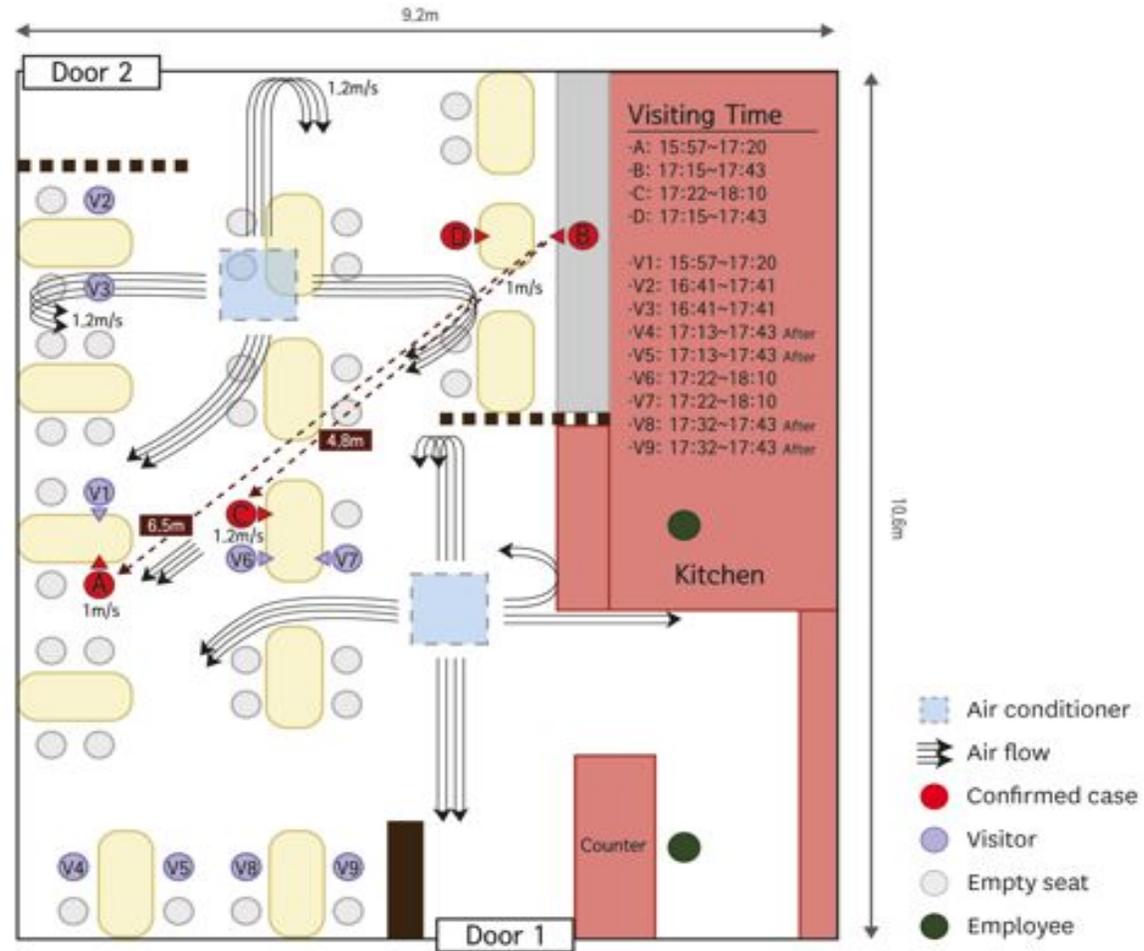


Fig. 3. Schematic diagram of the outbreak restaurant equipped with ceiling-type air conditioners. The arrowed solid streamlines represent the air flow directions in the restaurant. Curved air streamlines represent that air streams from the ceiling air

Prevention via Public Health

- (Medieval) Strategy of Isolation - Newton moved to Woolsthorpe Manor (1665-1667) after first death in Cambridge
- Initial control of the pandemic in Taiwan, New Zealand, Singapore, Vietnam, Wuhan

Before vaccines become available:

Public health strategy works

Strict social distancing (self-quarantine of the healthy) -home

Sequestration of the ill - - hotel and health care facility

Contact tracing of infected persons

Treatment of COVID-19

- Safety & Efficacy Established by Clinical Trials in COVID-19
 - Remdesivir (Gilead). Antiviral, “small molecule” drug. Given IV.
 - Dexamethasone (generic) Corticosteroid, anti-inflammatory.
 - Monoclonal antibodies (Regeneron, Lilly)
 - Tocilizumab (Genentech) IL-6 Inhibitor (sarilumab, siltuximab)
 - (anticoagulants, O2, mechanical ventilation, ECMO, etc....)
- > 200 Ongoing Clinical Trials (Phases 1, 2 and 3)
 - Antiviral drugs
 - Pooled plasma and monoclonal antibodies (designer antibodies)
 - Drugs directed at autoimmunity (repurposed oncology, RA, Psoriasis, etc..)

reference. Mcintosh K., UpToDate Management of Hospitalized Adults with COVID-19, May 28, 2021

<https://www.uptodate.com/contents/covid-19-clinical-features>

Highly Transmissible Variants of SARS-CoV-2

- **Vietnam** Mix of U.K and Indian variants.
 - Highly transmissible. “New variant is very dangerous” Vietnam Health Minister N.T. Long ((NYT. Ang. May 29, 2021)
 - Outbreak at Apple manufacturing facilities
- **Indian Strain B.1.617.2 (Delta)**
 - “Far more transmissible” than U.K variant B.1.1.7.
 - “Could be catastrophic”, “Terrible outbreaks in Indian and Nepal” (Z. Tufekci, NYT May 28, 2021)
- South African Strain B. 1. 351 U.K. Strain B.1.1.7 (Beta)
 - 30—70% more transmissible, ? more virulent
- Brazil Strain P.1. (Gamma)
 - Severe outbreak in Manaus following ~75% herd immunity
 - Some confirmed second infections
 - U.S. case first detected in Minnesota
- U.K. Strain B.1.1.7 30—70% more transmissible, ? more virulent. (Alpha)
 - Widely distributed in U.S., most prevalent strain in U.S
 - Higher concentrations in nose, more adherent to ACE2 receptor
 - Neutralizable by convalescent sera from prevalent COVID-19 patients
- Mutations: **minor changes of the region of the spike protein** that binds to the ACE2 receptor of human cells. Ergo: tweak to mRNA vaccine. Already testing vaccine for SA variant.

The Road to the Vaccines

- Vaccines for coronaviruses SARS-CoV-1 and MERS \geq 2004
- SARS-2 genome sequenced in China & published online 12/31/19
- Spike protein mRNA (wrapped in lipids as nanoparticle)
 - mRNA tells our cells how to make the spike protein.
 - Spike protein goes into our bloodstream.
 - Our immune system recognizes the spike protein as foreign.

Two types of immune protection

- B-cells: make antibody vs. spike proteins
- T-cells: cellular immunity “ “

Pfizer/BioNTech and Moderna mRNA Vaccines

- mRNA sequence designed in as briefly as one day

What's behind "design-in-a-day" – a Revolution in Biology and Biotechnology

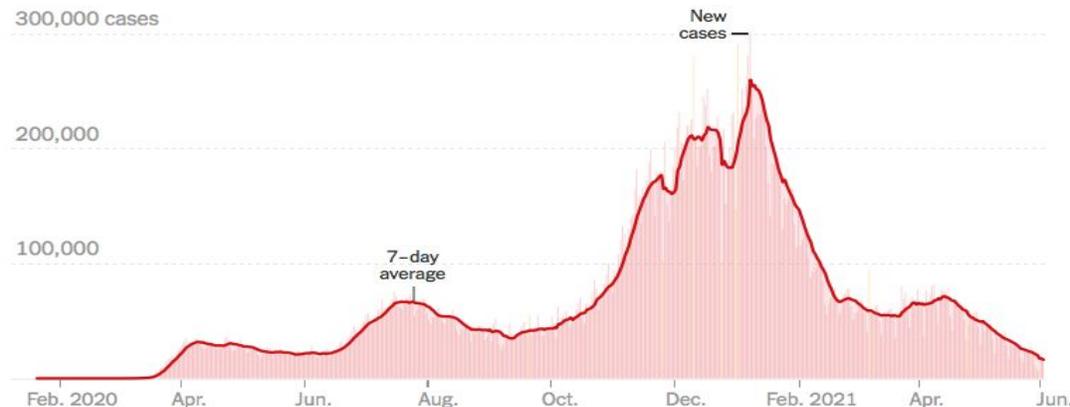
- Mendel ~rediscovered in 1900 , T.H.Morgan (1910's), Oswald Avery (1930s)
- the Double Helix of DNA (1953) – Watson, Crick and Rosalind Franklin (Nobel)
- Breaking the Genetic Code- Marshall Nirenberg (Nobel 1968)
- Transcription/translation of DNA to mRNA to protein – Roger Kornberg (1980s)
- DNA sequencing (1977)- Frederick Sanger- U.Cambridge (two Nobels)
- High-throughput sequencing (1990s)
- **Synthetic mRNA-Kati Kariko, 1980s Hungarian immigrant in the scientific wilderness (adopted by Moderna and BioNTech ~2020) ~ 40 years of work***
- Vaccine work on SARS, MERS (spike proteins) since ~2004
- **Nanotechnology and lipid nanoparticles (LNPs) 25 years of work-Cullis/UBC**

* Kati Kariko helped shield the world from the coronavirus. G. Kolata, NYT, April 8, 2021.
<https://www.nytimes.com/2021/04/08/health/coronavirus-mrna-kariko.html>

Latest Map and Case Count

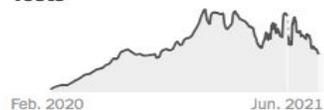
Updated June 3, 2021

New reported cases



These are days with a reporting anomaly. Read more [here](#).

Tests



Hospitalized



Deaths



	AVG. ON JUN. 2	14-DAY CHANGE	TOTAL REPORTED
Cases	16,270	-46%	33,320,771
Tests	660,757	—	—
Hospitalized	24,661	-22%	—
Deaths	397	-35%	595,321

► About this data

Vaccinations

Fully vaccinated

41%

At least one dose

51%

[See more details >](#)

► About this data

State of the virus

Update for May 28

- Case numbers in the United States continue to plummet. About 23,000 new infections are being identified each day, the fewest in nearly a year.
- Several states in the Midwest and Northeast have seen reports of new cases decline by more than 50 percent over the last two weeks. No state is seeing a major increase in cases.
- Half of all people in the United States have started the [vaccination](#) process, and 40 percent are fully vaccinated. But the number of doses administered each day has fallen by about half from its April peak.

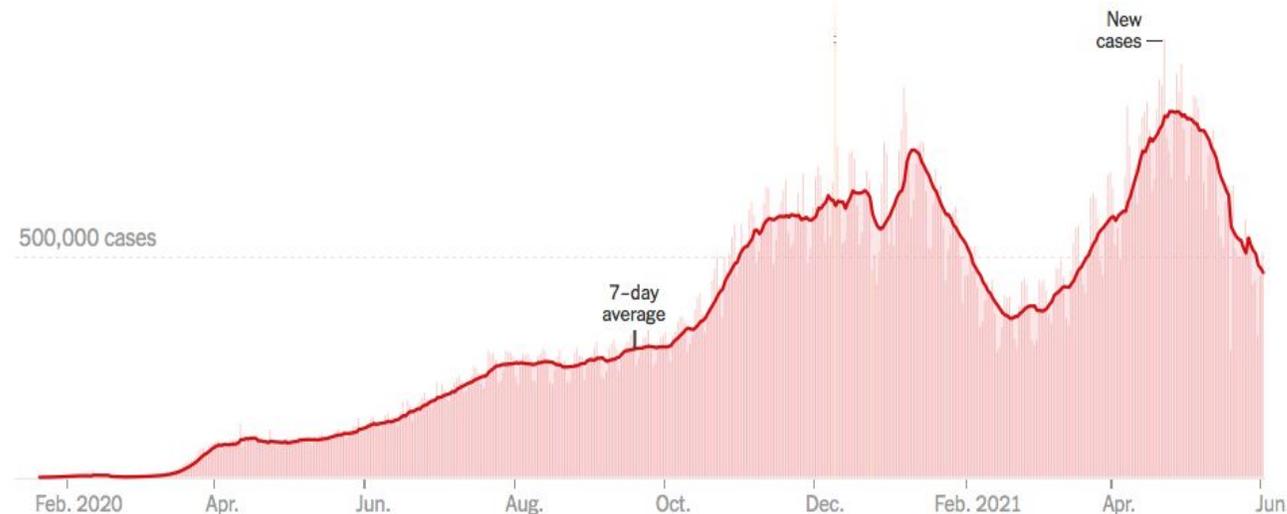
[Read more](#)

Coronavirus World Map: Tracking the Global Outbreak

Updated June 3, 2021

NEW: We are rolling out changes to our virus tracking pages. [Read more here.](#)

New reported cases



These are days with a reporting anomaly. [Read more here.](#)

	AVG. ON JUN. 2	14-DAY CHANGE	TOTAL REPORTED
Cases	462,330	-27%	171,635,491
Deaths	10,952	-12%	3,689,382

► [About this data](#)

State of the virus

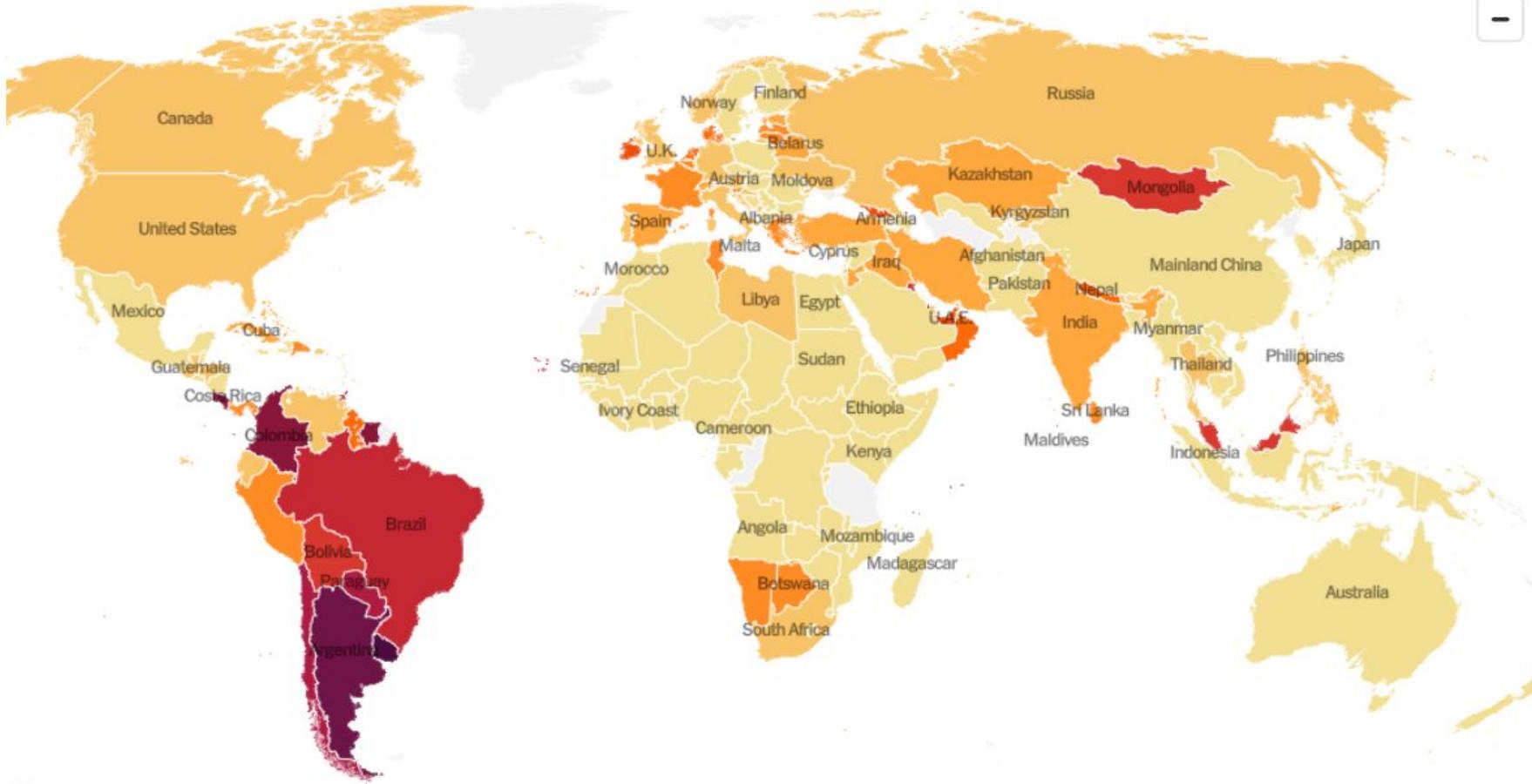
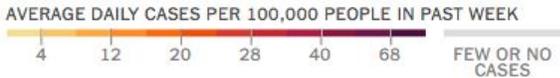
Update for June 1

- South America has the highest rate of new infections in the world: Uruguay, Argentina, Colombia and Paraguay are all in the top 10 in recent cases per 100,000 residents. Even more South American countries are at the top of the recent deaths per capita list.
- Peru said that [its Covid-19 death toll](#) is almost three times as high as it had officially counted until now, making it one of the hardest-hit nations relative to its population.
- [India](#) reported an average of more than 4,000 deaths per day in late May, but reported cases are declining from the peak reached earlier in the month. [Here's what to know about India's coronavirus crisis.](#)

[Read more](#)

Global COVID-19 Hot Spots. June 3, 2021

Hot spots



What are we learning?

- Ongoing **catastrophic event** nationally and globally on par with world wars and economic depressions.
- Pandemic exposed **vast inequality** of risk and resources in the U.S and the world and **multiple shortcomings re health security**.
- Our expensive systems of health care and health insurance are ill-suited to providing health security us, no matter our circumstances. We have **neglected public health**.

What Went Wrong? A Partial List

- **Belated recognition of community spread and exponential growth.** Exponential growth overwhelms isolation/ contact tracing
- **Shortcomings of a medical model** - e.g., Testing only of sick people and requirement for a physician prescription.
- **Acceptance of high toll of illness and fatalities** Objective of policy was “flattening the curve” to prevent hospitals and ICUs going over-capacity vs. objective of stamping out the disease.
- **Inadequacy of testing and test strategies.** Failure to test asymptomatic persons – spreaders and superspreaders –
- **Failures to uphold occupational safety** – e.g. in meat-packing and other work environments.
- **Inconsistent adoption of public health strategies and messaging**– social distancing. use of masks, guidelines re public gatherings
- **Counter-productive behavior at the top** –superspreader events (e.g. Rose Garden and Election Night at W.H.)
- **Neglect and underfunding of public health** resources
- **Nationalism during an international epidemic.** Withdrawal from WHO and other international organizations
- **Absence of national strategy guided by applicable scientific information and policy decisions by medical, scientific and public health professionals and organizations.**
Not just science, but wisdom is needed - the ability to make good decisions under conditions of uncertainty.

Take-aways from 2020

- **Strengthen public health** agencies
- **Restore international** relationships
 - Working relationships with WHO and international, national organizations
 - Infectious disease security at highest level – National Security Council
 - CDC, NIH primary roles in health policy decision-making
- **Cache resources** in place for health emergencies
- **Prioritize early warning of emerging pathogens**, new zoonoses globally
 - Transparent disclosure of new outbreaks
- **Accelerate process of vaccine approval**
- **Research on dangerous pathogens is extremely risky:**
 - Conduct only at BSL4 level of laboratory security, if at all

New Look at the Wuhan Institute of Virology

- Wuhan Institute of Virology (WIV) did **research on bat coronaviruses** for many years
- WIV was funded by EcoHealth Alliance of New York (Dr. Peter Daszak) to grow the bat coronavirus in **human cells and genetically humanized mice**. (“Gain of function” research)
- Work with potentially dangerous pathogen was **not at highest level (BSL4)** of biosecurity or of synthetic gene editing?
- Serious illness of **three WIV workers hospitalized in November of 2019**. Was illness COVID-19? Was this a laboratory accident, viral escape from the lab?
- **? Smoking Gun**. *furin* cleavage site. Is change from bat coronavirus to SARS-CoV-2 the result of mutation/recombination (natural evolution) or of gene editing?

Nicholas Wade, Bulletin of the Atomic Scientists, May 5, 2021

<https://thebulletin.org/2021/05/the-origin-of-covid-did-people-or-nature-open-pandoras-box-at-wuhan/>

Glenn Kessler, Washington Post, May 25, 2021 Less technical than the Bulletin article, with comments on that article by some knowledgeable observers.

<https://www.washingtonpost.com/politics/2021/05/25/timeline-how-wuhan-lab-leak-theory-suddenly-became-credible/>