COVID-19 Pathogenesis

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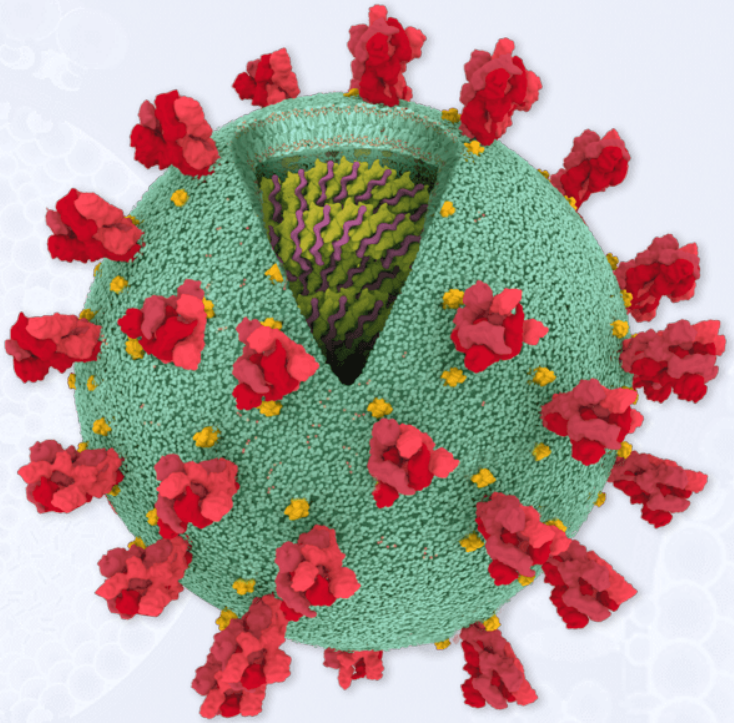


Jonathan Corum & Carl Zimmer
The New York Times, April 3rd 2020

Speaker Disclosure

Speakers are required to disclose any commercial relationships before today's presentation.

Contents

- Basics of COVID-19 disease
- Appearance and spread
- Current status of the pandemic
  - Recent developments in testing, vaccines, and treatment
- Emergence from an animal reservoir
  - Likelihood of other coronavirus emergence

Kevin Olival, EcoHealth Alliance

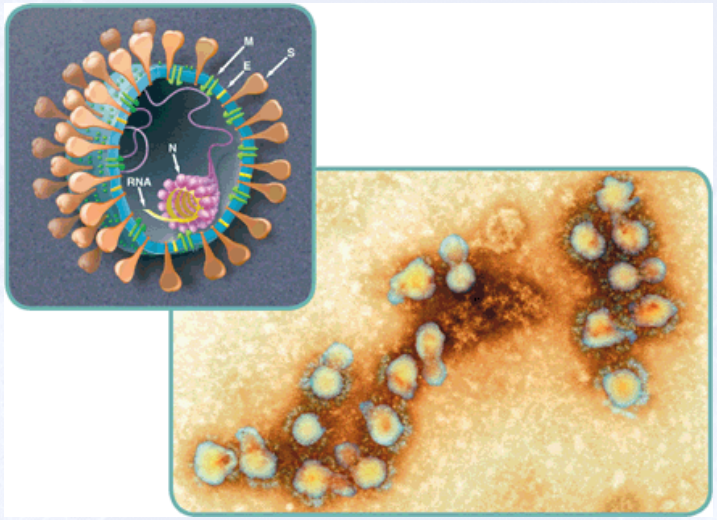
Basics of COVID-19 disease

COVID-19 and SARS-CoV-2

- Coronavirus Disease 2019 (COVID-19) is the disease
- SARS-Coronavirus type 2 (SARS-CoV-2) is the virus that causes COVID-19
- SARS-CoV-2 is closely related to SARS-CoV, the virus that caused Severe Acute Respiratory Syndrome (SARS) in 2002
- SARS-CoV and SARS-CoV-2 are also related to MERS-CoV, the virus that causes Middle Eastern Respiratory Syndrome (MERS) in 2012/2013
- All are a type of virus called *Coronaviruses*

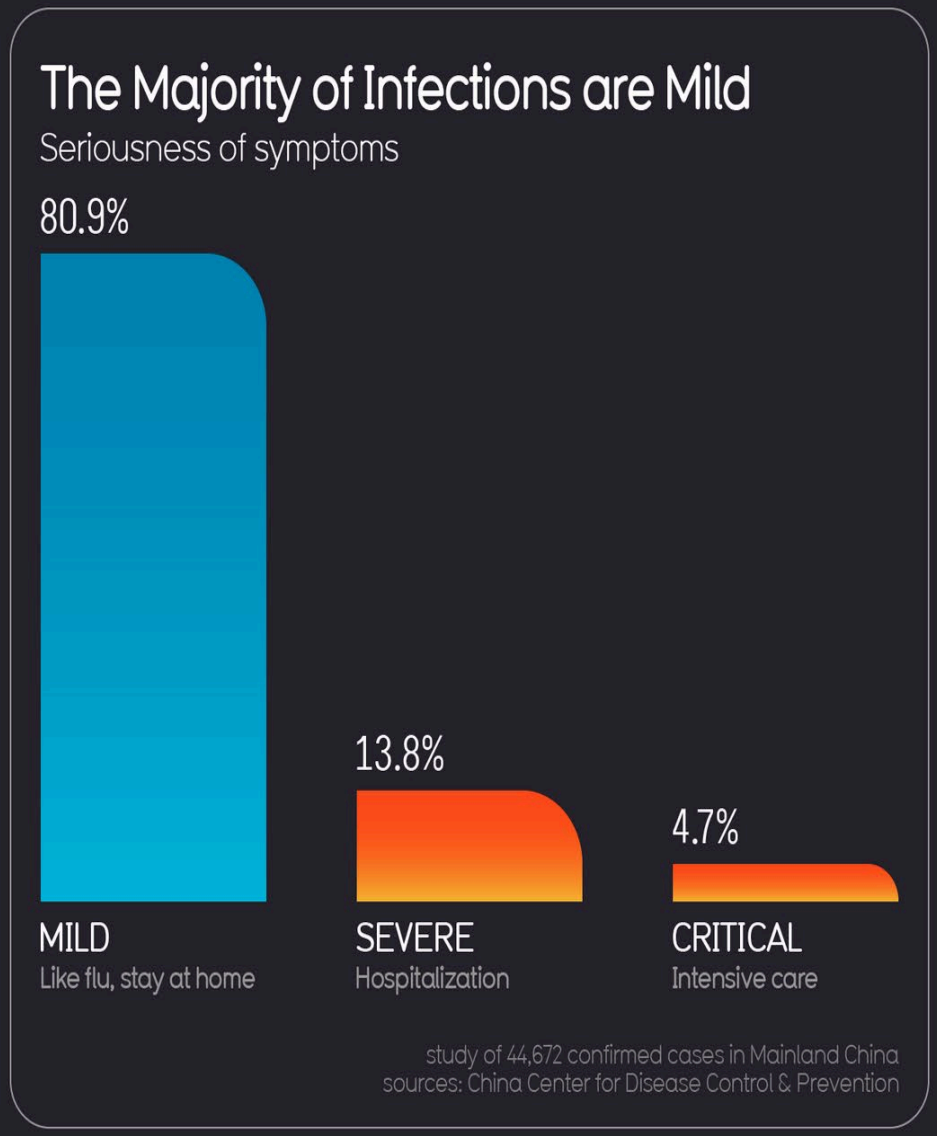
Coronaviruses

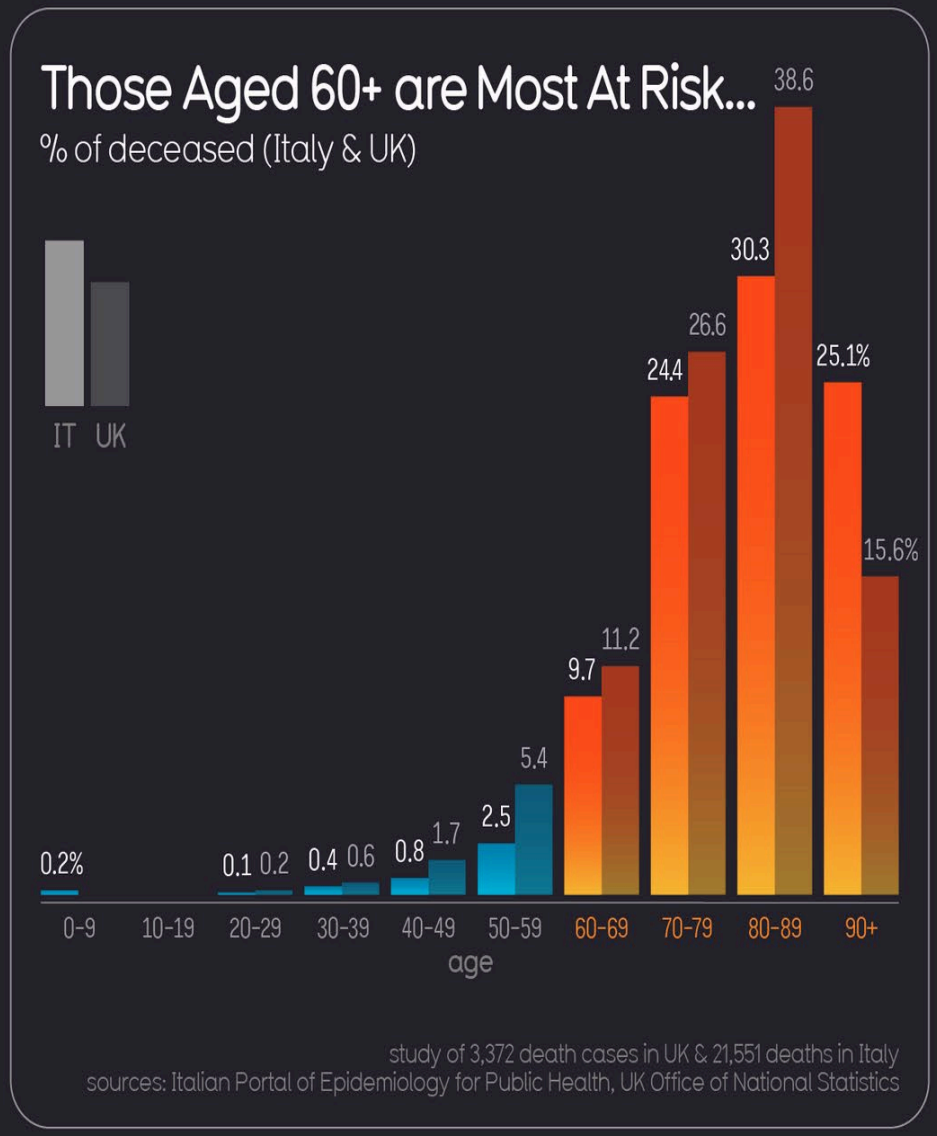
- Spike proteins form a crown shape (or corona) on virus surface
- Prior to SARS outbreak in 2002, coronaviruses were thought to be harmless in humans
- One of the causes of the common cold (15%)
- 3 human outbreaks
  - SARS (2002) – 8,098 cases, 774 deaths (10% CFR)
  - MERS (2013) – 2,519 cases, 866 deaths (34% CFR)
  - COVID-19 (2020) – 16.5 million cases, 650,000 deaths* (4% CFR, likely an overestimate as we do not have reliable case counts)



Science vol **339** pp1269-1273 (2013)

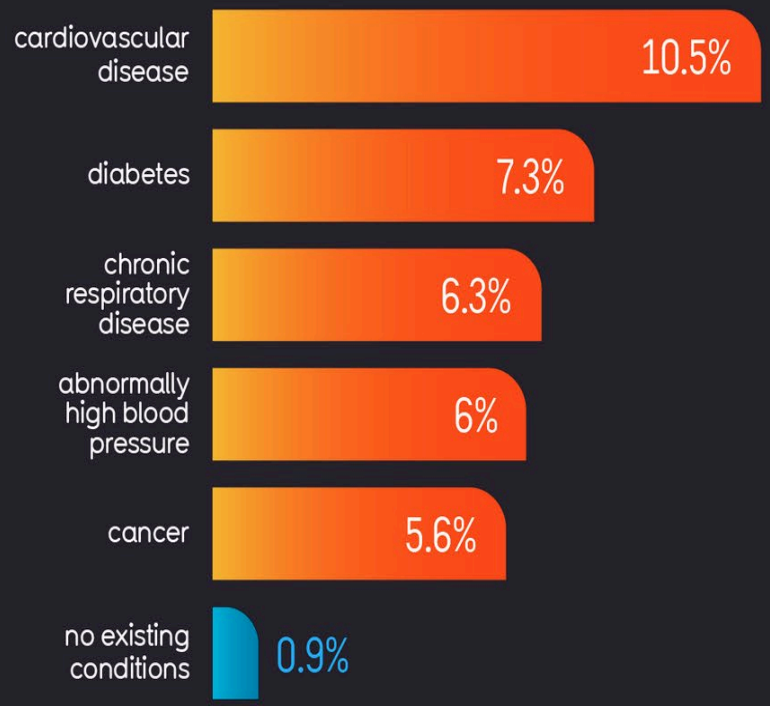
*as of 07/28/2020, data from Johns Hopkins University COVID-19 dashboard


The Majority of Infections are Mild
Seriousness of symptoms
80.9%
13.8%
4.7%
MILD
Like flu, stay at home
SEVERE
Hospitalization
CRITICAL
Intensive care
study of 44,672 confirmed cases in Mainland China
sources: China Center for Disease Control & Prevention


Those Aged 60+ are Most At Risk...
% of deceased (Italy & UK)
IT UK
0.2%
0.1 0.2
0.4 0.6
0.8 1.7
2.5 5.4
9.7 11.2
24.4 26.6
30.3 38.6
25.1%
15.6%
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
90+
age
study of 3,372 death cases in UK & 21,551 deaths in Italy
sources: Italian Portal of Epidemiology for Public Health, UK Office of National Statistics

Especially Those with Existing Conditions

% of deceased with serious ailments

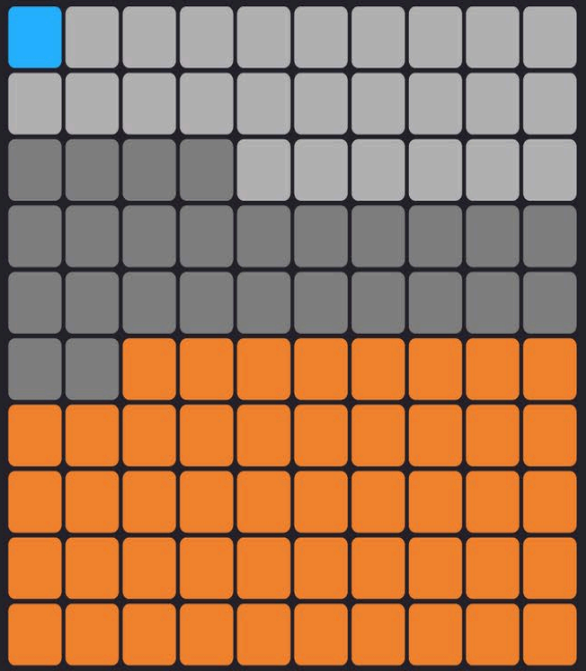


study of 44,672 confirmed cases in Mainland China
sources: China Center for Disease Control & Prevention, Statista

Multiple Conditions Increase Risk

Serious conditions present in those who have died

1% no conditions



average age of victim in this analysis was 79

25% 1 condition

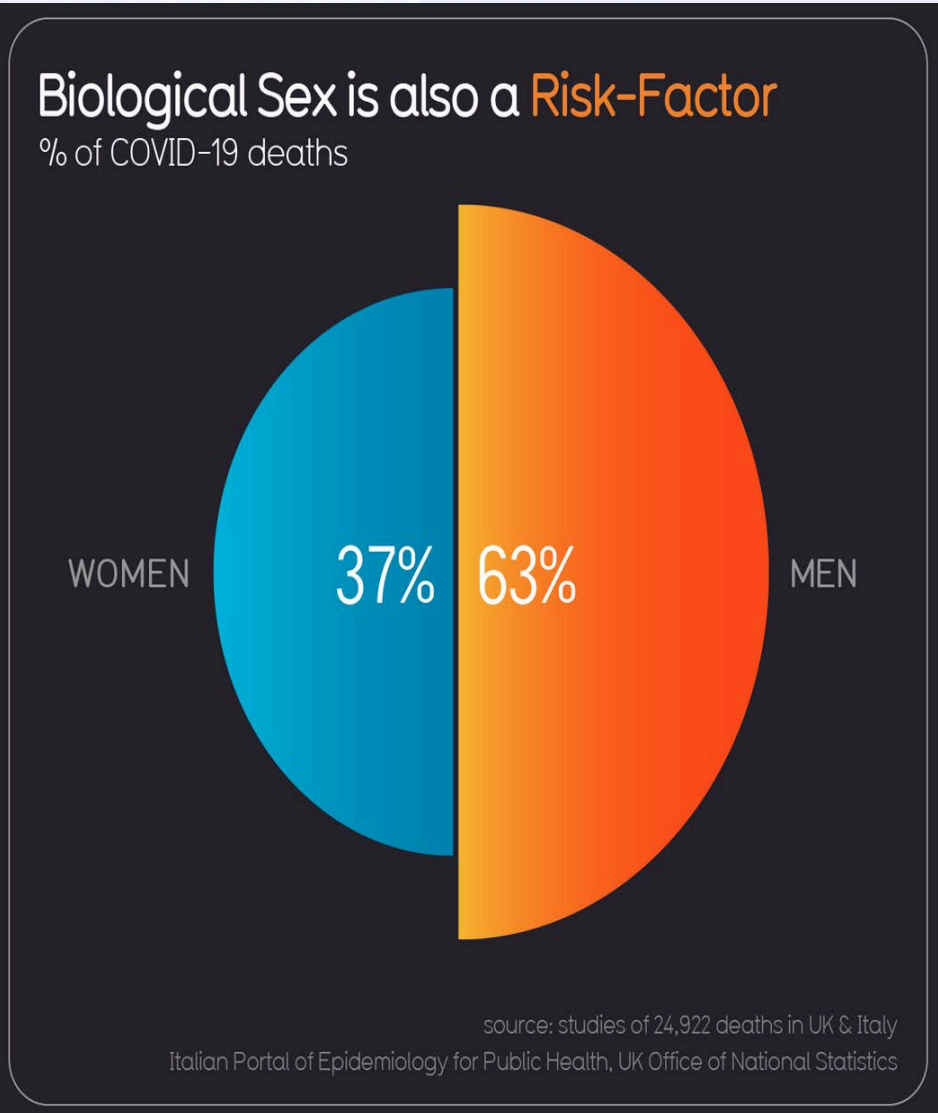
26% 2 conditions

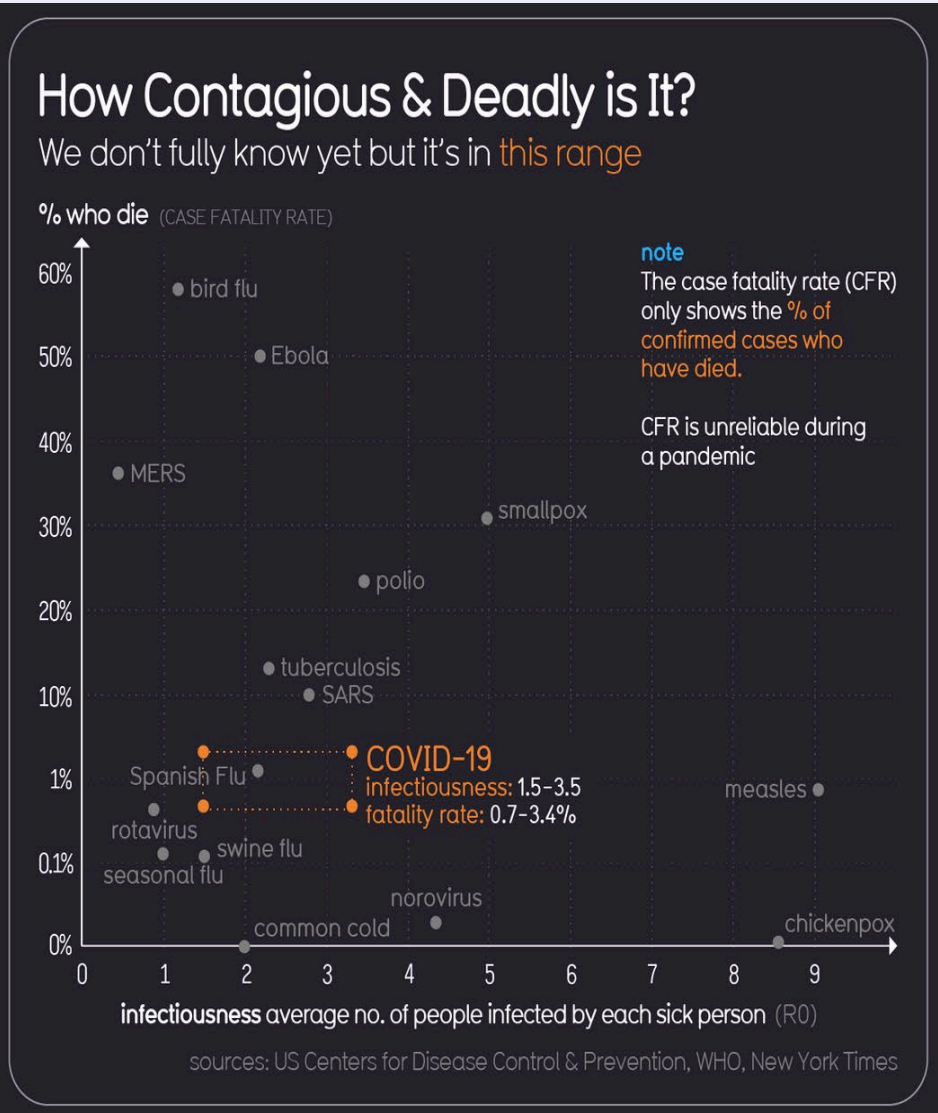
having these conditions does not mean you will die of the disease - they are just risk factors

48% 3+ conditions

Active cancer, Atrial fibrillation, Chronic Obstructive Pulmonary Disease (COPD) Dementia, Diabetes, Heart disease, Hypertension, Liver disease (chronic), Renal failure (chronic), Stroke

study of 355 deaths from 16,925 confirmed cases in Italy
source: Italian Portal of Epidemiology for Public Health


Biological Sex is also a Risk-Factor
% of COVID-19 deaths
WOMEN
37%
63%
MEN
source: studies of 24,922 deaths in UK & Italy
Italian Portal of Epidemiology for Public Health, UK Office of National Statistics

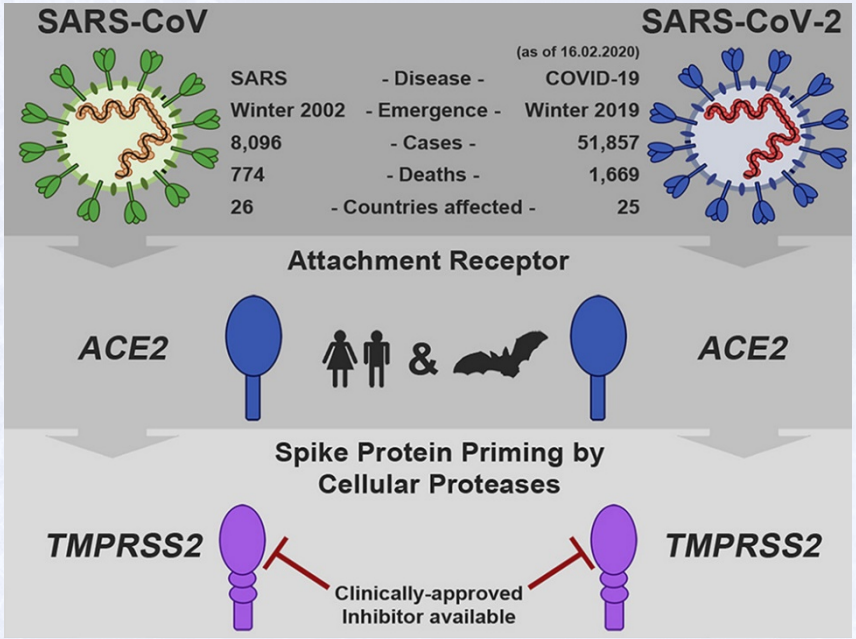

How Contagious & Deadly is It?
We don't fully know yet but it's in this range
% who die (CASE FATALITY RATE)
60%
50%
40%
30%
20%
10%
1%
0.1%
0%
bird flu
Ebola
MERS
smallpox
polio
tuberculosis
SARS
COVID-19
infectiousness: 1.5-3.5
fatality rate: 0.7-3.4%
Spanish Flu
measles
rotavirus
swine flu
seasonal flu
norovirus
common cold
chickenpox
0
1
2
3
4
5
6
7
8
9
infectiousness average no. of people infected by each sick person (R0)
note
The case fatality rate (CFR) only shows the % of confirmed cases who have died.
CFR is unreliable during a pandemic
sources: US Centers for Disease Control & Prevention, WHO, New York Times

Infection with a virus

- In the first step of infection, any virus has to recognize and interact with a specific receptor protein on the target cell's surface
- Each type of virus recognizes a different receptor
- Different cells have different proteins on their cell surface
- So, each virus can infect a specific set of cells, and not others
- SARS-CoV and SARS-CoV-2 both use the same receptor: ACE2

Infectious mechanism used by SARS-CoV-2

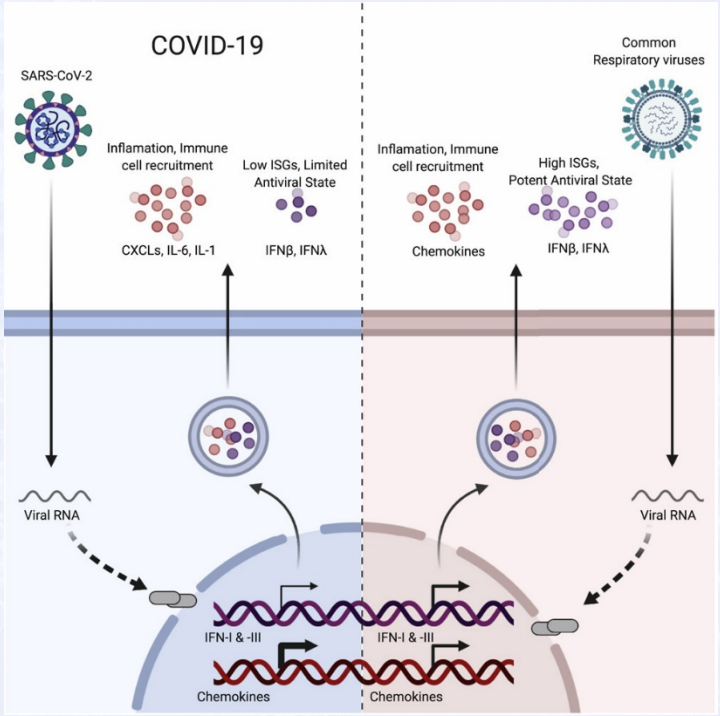
- ACE2 is found of pneumocytes in the lung; also enterocytes in the gut
- The spike protein of SARS-CoV and SARS-CoV-2 is cleaved by the human enzyme TMPRSS2
  - the drug camostat mesylate inhibits this
- This drug is already licensed in Europe & Japan (as a treatment for pancreatitis), and is now in a clinical trial for COVID-19



Cell vol **181** 271-280.e8 (2020)

COVID-19 subversion of the immune response

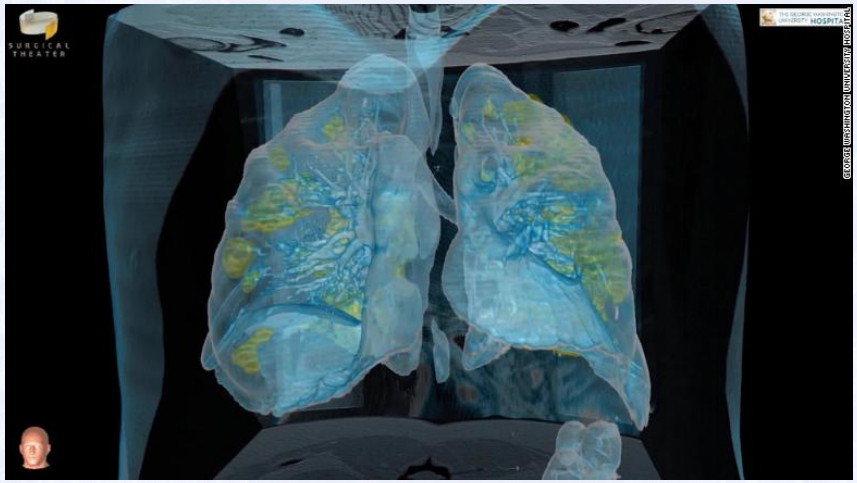
- Viral infection normally induces type I interferon response in immune cells
- COVID-19 proteins block interferon α/β expression and signaling
- Viral clearance is delayed; robust B cell, T cell and cytokine response develops
- “Cytokine storm” results in lung tissue damage



Cell vol **181** pp1046-1045e9 (2020)

Infection and disease in COVID-19

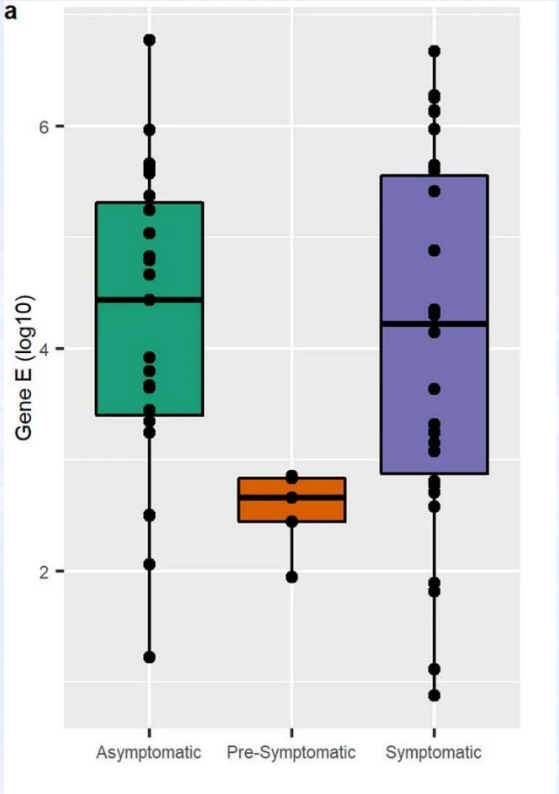
- Respiratory infection, primarily through droplets and contact with contaminated surfaces
- The extent of aerosol infection is not clear
- Many infections are mild or asymptomatic, so it is hard to determine the true case count
- Severe acute respiratory distress syndrome (ARDS) and extensive lung damage



Dr. Keith Mortman,
George Washington University

COVID-19 distinguishing features

- Spread by droplet infection (like SARS, MERS, and also influenza), **BUT**
- COVID-19 patients produce infectious virus well before they feel ill (if they feel ill at all)
  - Spreads in the general population
  - Many asymptomatic (but infectious) infections
- SARS and MERS patients only shed virus after the onset of symptoms
  - Secondary infections were most common in family members and healthcare workers

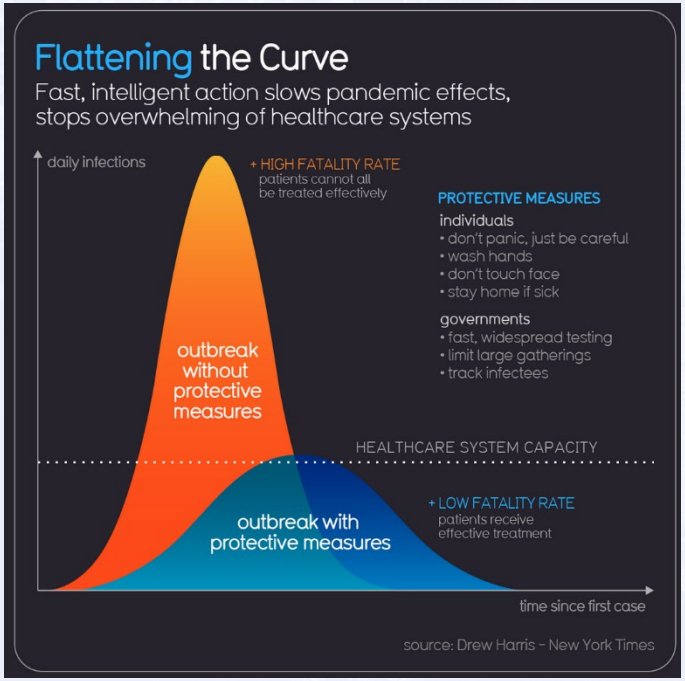


Nature (2020)
https://doi.org/10.1038/s41586-020-2488-1

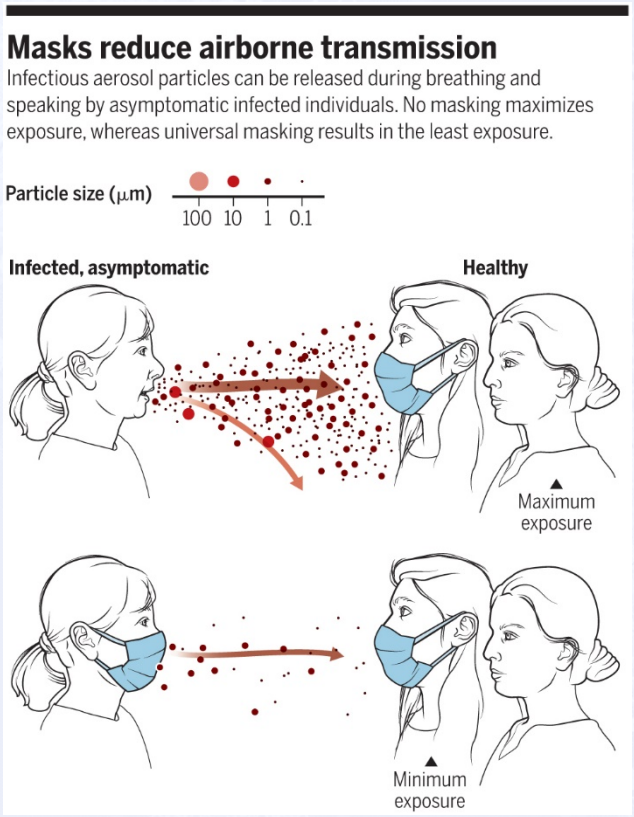
Superspreaders in COVID-19

- Individual person who infects a large number of others
- Daegu, South Korea, Feb 2020; 70 cases linked to “patient 31” at the Shinceonji Church of Jesus
- New Rochelle NY, USA, March 2020; one person spread the virus to at least 20 individuals, creating a cluster of infections that ultimately exceeded 100
- Rheda-Wiedenbrück, Germany, March-April 2020; one asymptomatic worker at a meat packing plant infected 60% of other workers within a 25-foot radius

Prevention is better than cure

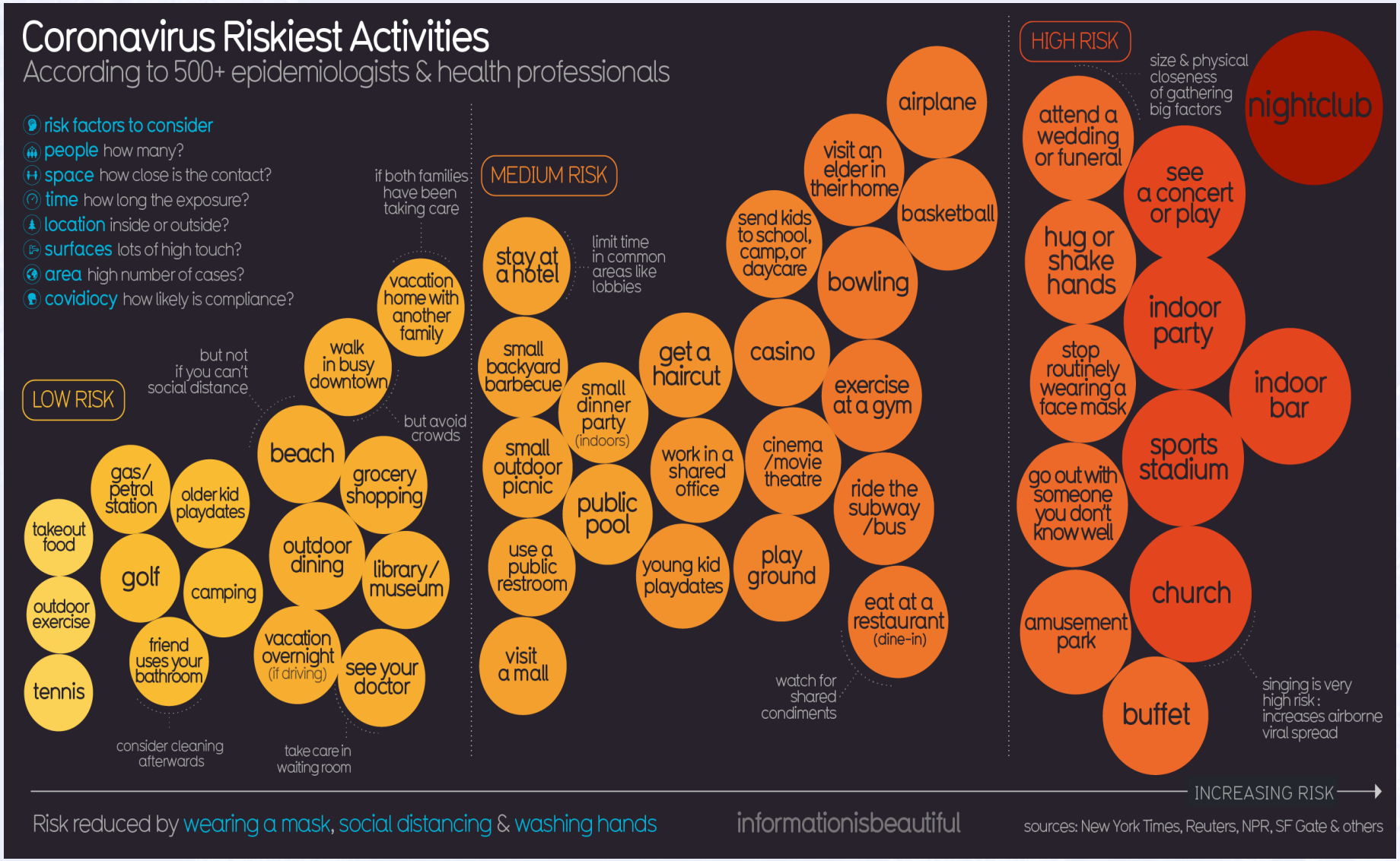


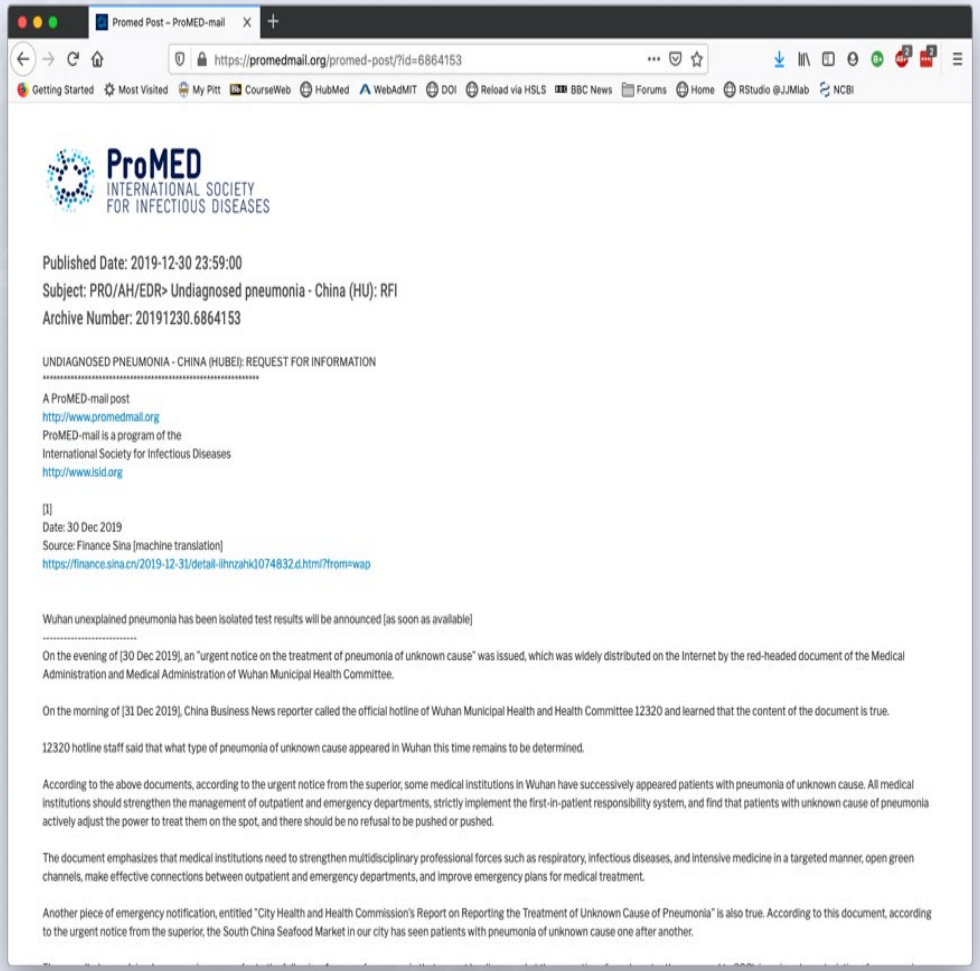
Masks work



Science vol **368** pp1422-1424 (2020)

- SARS-CoV-2 replicates three times faster than other coronaviruses
- Can spread rapidly to the pharynx and be exhaled before the innate immune response becomes activated and the infected person shows symptoms


Coronavirus Riskiest Activities
According to 500+ epidemiologists & health professionals
risk factors to consider
people how many?
space how close is the contact?
time how long the exposure?
location inside or outside?
surfaces lots of high touch?
area high number of cases?
covidiocy how likely is compliance?
LOW RISK
but not if you can't social distance
if both families have been taking care
but avoid crowds
takeout food
outdoor exercise
tennis
gas/ petrol station
golf
friend uses your bathroom
older kid playdates
camping
consider cleaning afterwards
beach
walk in busy downtown
vacation home with another family
outdoor dining
vacation overnight (if driving)
grocery shopping
library/ museum
see your doctor
take care in waiting room
MEDIUM RISK
limit time in common areas like lobbies
stay at a hotel
small backyard barbecue
small outdoor picnic
use a public restroom
visit a mall
small dinner party (indoors)
public pool
get a haircut
work in a shared office
young kid playdates
casino
cinema /movie theatre
play ground
send kids to school, camp, or daycare
exercise at a gym
ride the subway /bus
eat at a restaurant (dine-in)
watch for shared condiments
visit an elder in their home
bowling
airplane
basketball
HIGH RISK
size & physical closeness of gathering big factors
attend a wedding or funeral
hug or shake hands
stop routinely wearing a face mask
go out with someone you don't know well
amusement park
buffet
nightclub
see a concert or play
indoor party
indoor bar
sports stadium
church
singing is very high risk: increases airborne viral spread
INCREASING RISK
Risk reduced by wearing a mask, social distancing & washing hands
informationisbeautiful
sources: New York Times, Reuters, NPR, SF Gate & others



Promed Post – ProMED-mail

https://promedmail.org/promed-post/?id=6864153

Getting Started · Most Visited · My Pitt · CourseWeb · HubMed · WebAdMIT · DOI · Reload via HSLS · BBC News · Forums · Home · RStudio @JJMlab · NCBI

ProMED
INTERNATIONAL SOCIETY
FOR INFECTIOUS DISEASES

Published Date: 2019-12-30 23:59:00
Subject: PRO/AH/EDR> Undiagnosed pneumonia - China (HU): RFI
Archive Number: 20191230.6864153

UNDIAGNOSED PNEUMONIA - CHINA (HUBEI): REQUEST FOR INFORMATION

A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

[1]
Date: 30 Dec 2019
Source: Finance Sina [machine translation]
https://finance.sina.cn/2019-12-31/detail-ihnzahk1074832.d.html?from=wap

Wuhan unexplained pneumonia has been isolated test results will be announced [as soon as available]

On the evening of [30 Dec 2019], an "urgent notice on the treatment of pneumonia of unknown cause" was issued, which was widely distributed on the Internet by the red-headed document of the Medical Administration and Medical Administration of Wuhan Municipal Health Committee.

On the morning of [31 Dec 2019], China Business News reporter called the official hotline of Wuhan Municipal Health and Health Committee 12320 and learned that the content of the document is true.

12320 hotline staff said that what type of pneumonia of unknown cause appeared in Wuhan this time remains to be determined.

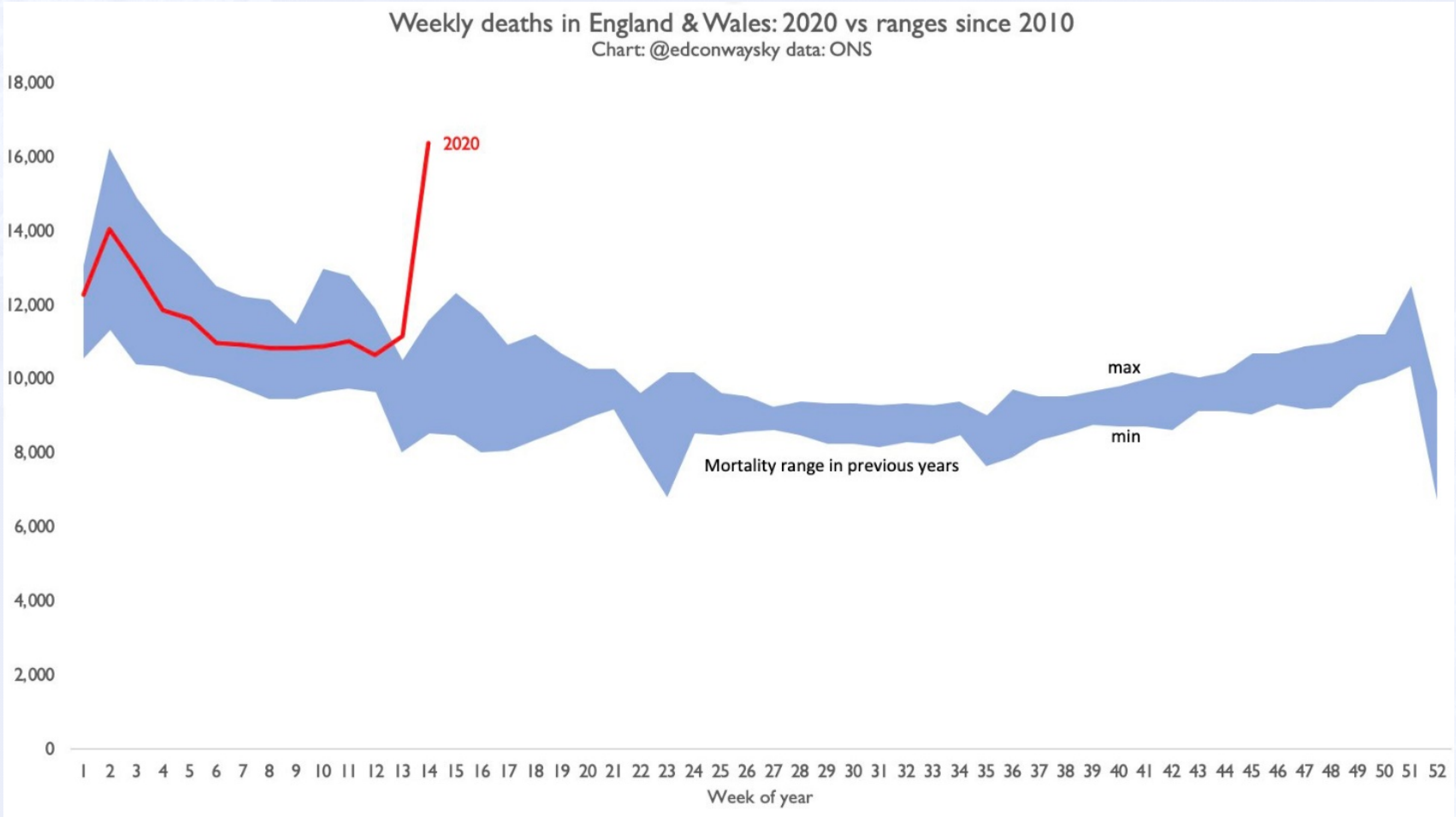
According to the above documents, according to the urgent notice from the superior, some medical institutions in Wuhan have successively appeared patients with pneumonia of unknown cause. All medical institutions should strengthen the management of outpatient and emergency departments, strictly implement the first-in-patient responsibility system, and find that patients with unknown cause of pneumonia actively adjust the power to treat them on the spot, and there should be no refusal to be pushed or pushed.

The document emphasizes that medical institutions need to strengthen multidisciplinary professional forces such as respiratory, infectious diseases, and intensive medicine in a targeted manner, open green channels, make effective connections between outpatient and emergency departments, and improve emergency plans for medical treatment.

Another piece of emergency notification, entitled "City Health and Health Commission's Report on Reporting the Treatment of Unknown Cause of Pneumonia" is also true. According to this document, according to the urgent notice from the superior, the South China Seafood Market in our city has seen patients with pneumonia of unknown cause one after another.

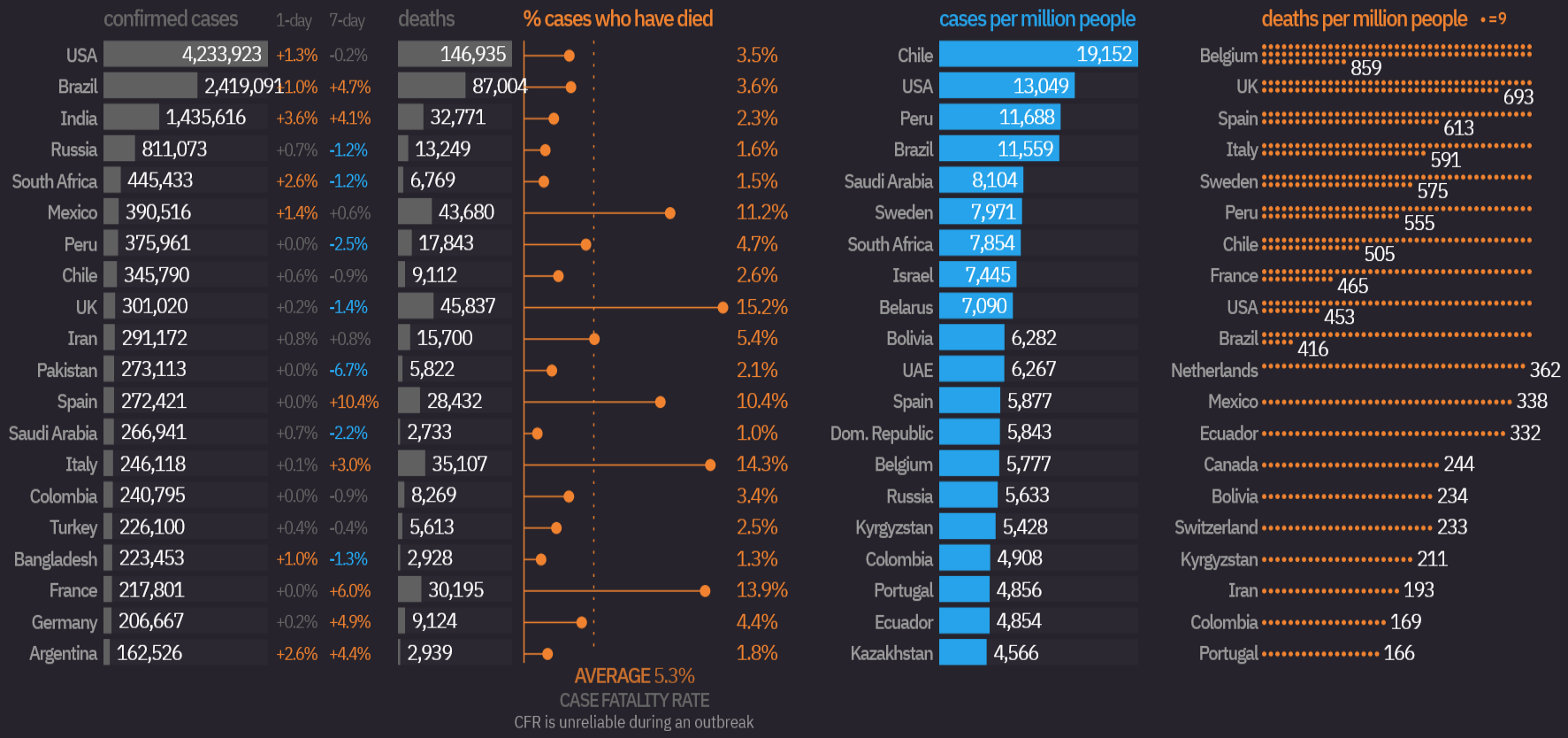
Current status of the pandemic

Impact of COVID-19



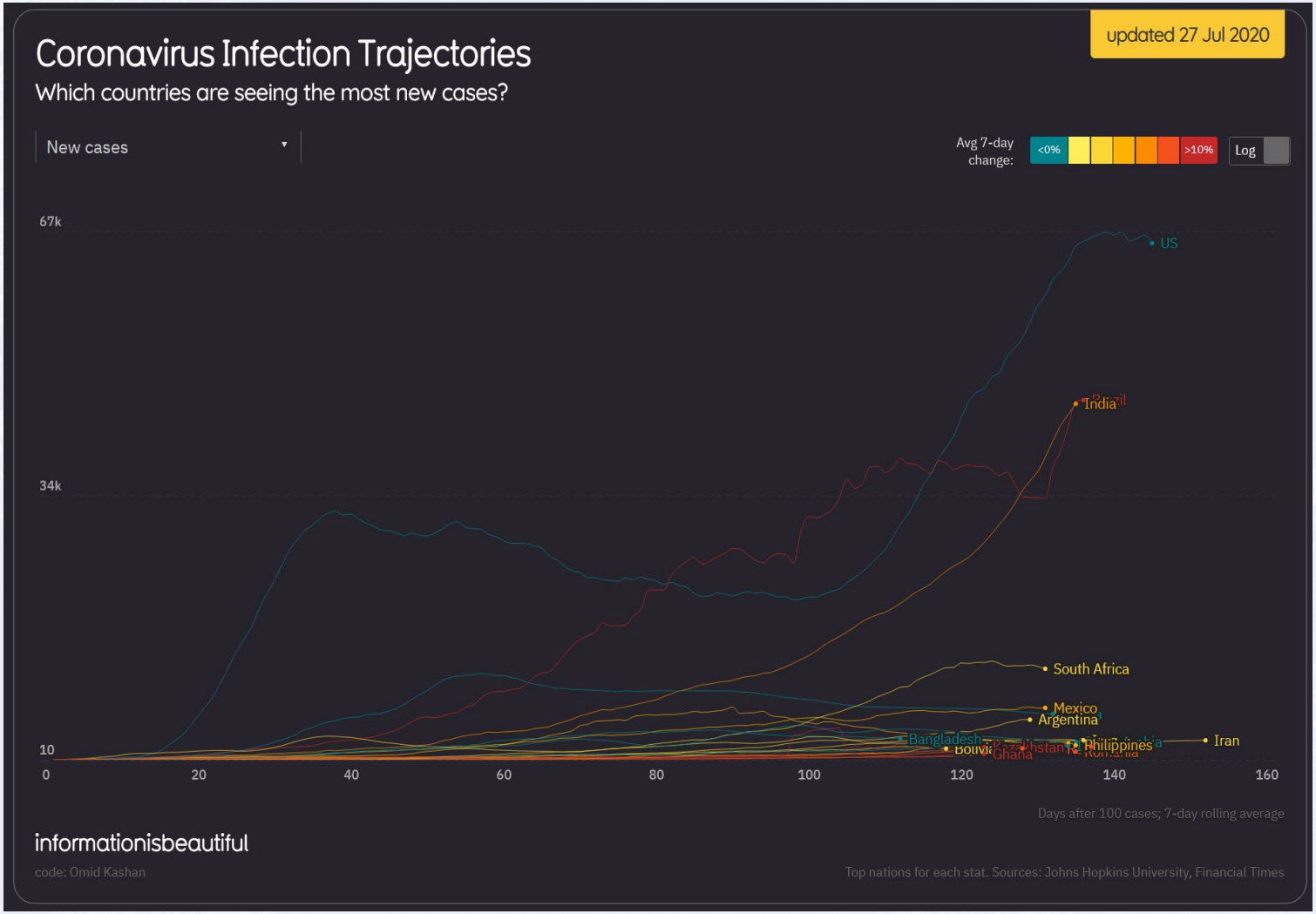
updated 27 July 2020

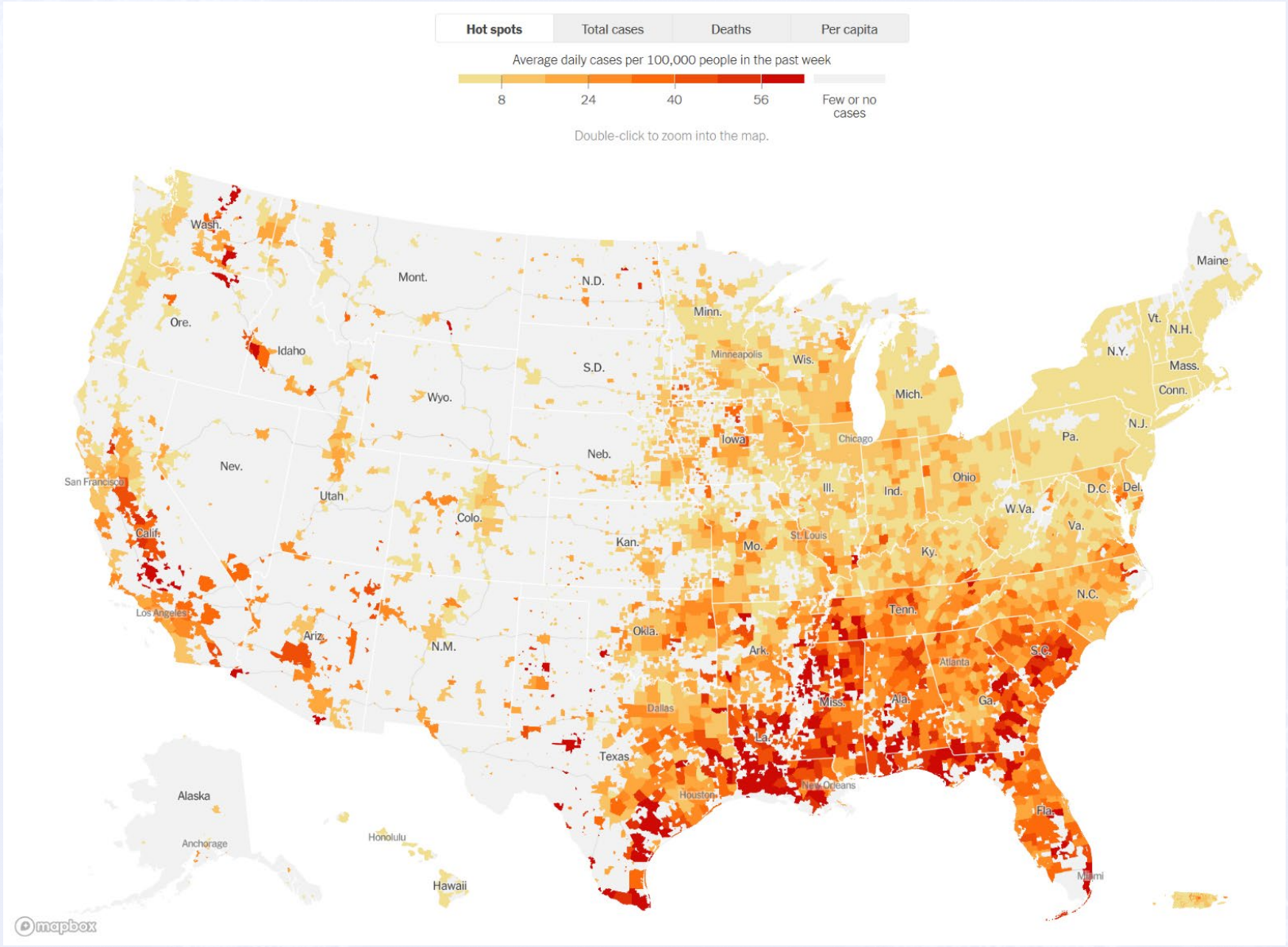
Infection & Fatality Rates Vary by Country



informationisbeautiful **Univers Labs**

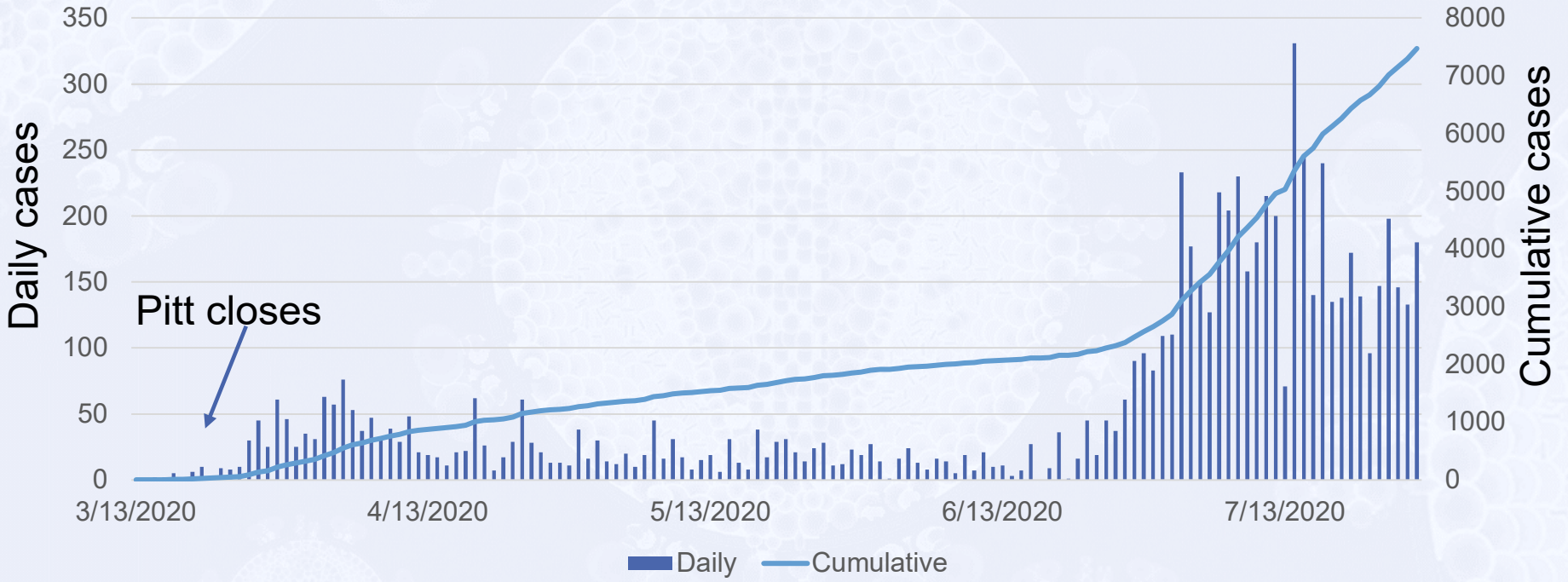
sources: Johns Hopkins University

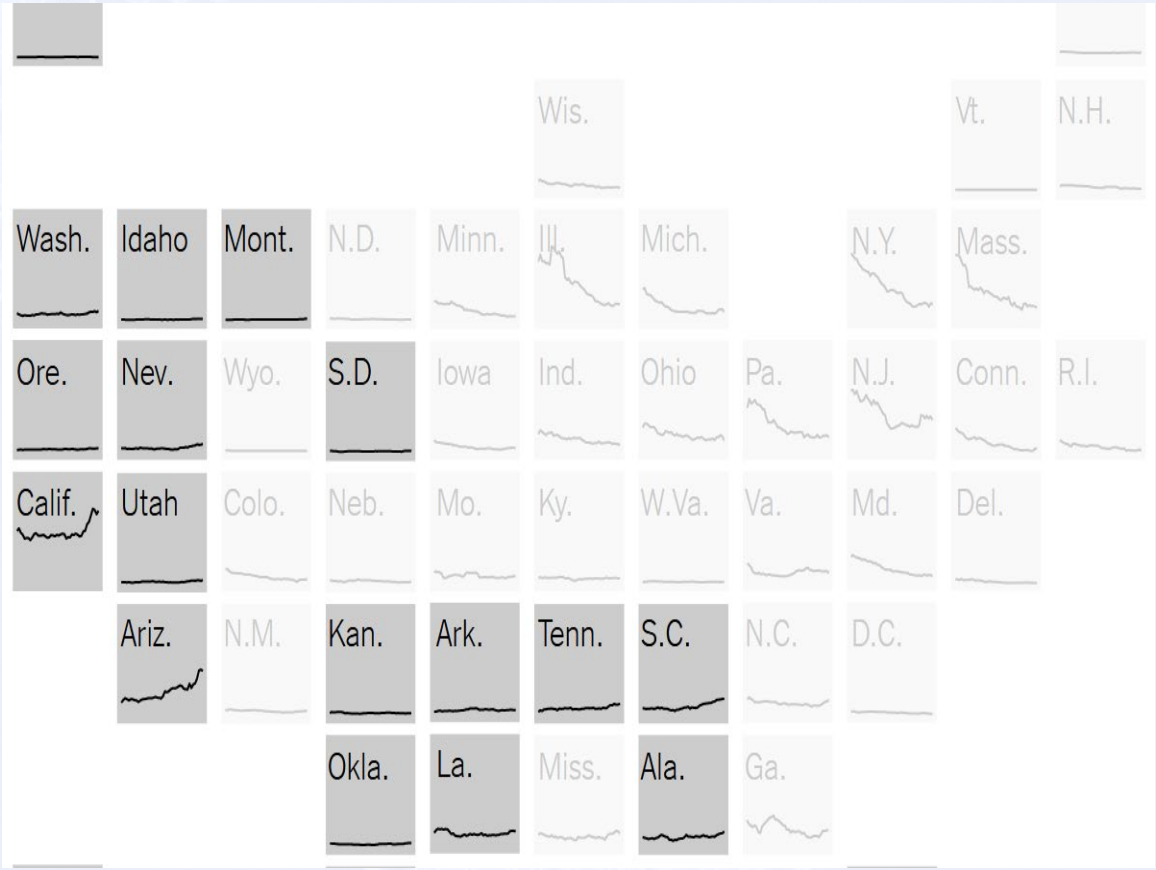

Coronavirus Infection Trajectories
Which countries are seeing the most new cases?
updated 27 Jul 2020
New cases
Avg 7-day change:
<0%
>10%
Log
67k
34k
10
US
India
South Africa
Mexico
Argentina
Bangladesh
Bolivia
Ghana
Philippines
Iran
0
20
40
60
80
100
120
140
160
Days after 100 cases; 7-day rolling average
informationisbeautiful
code: Omid Kashan
Top nations for each stat. Sources: Johns Hopkins University, Financial Times



The New York Times, July 27th 2020

COVID-19 in Allegheny County

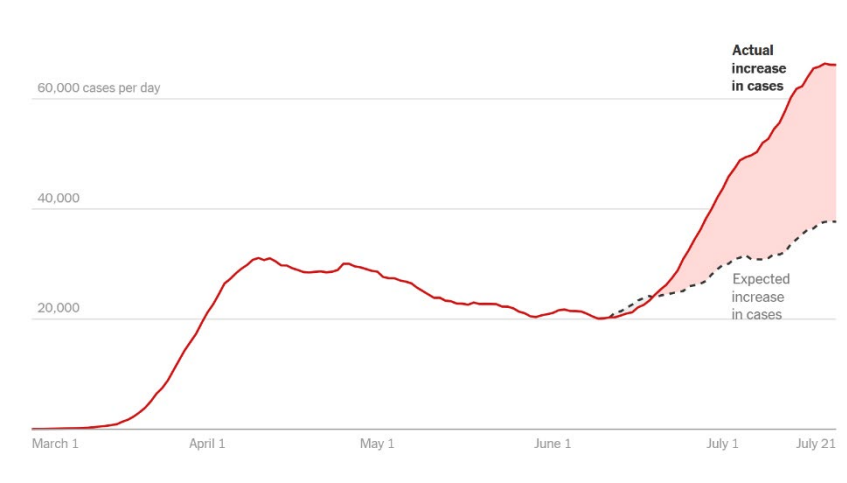


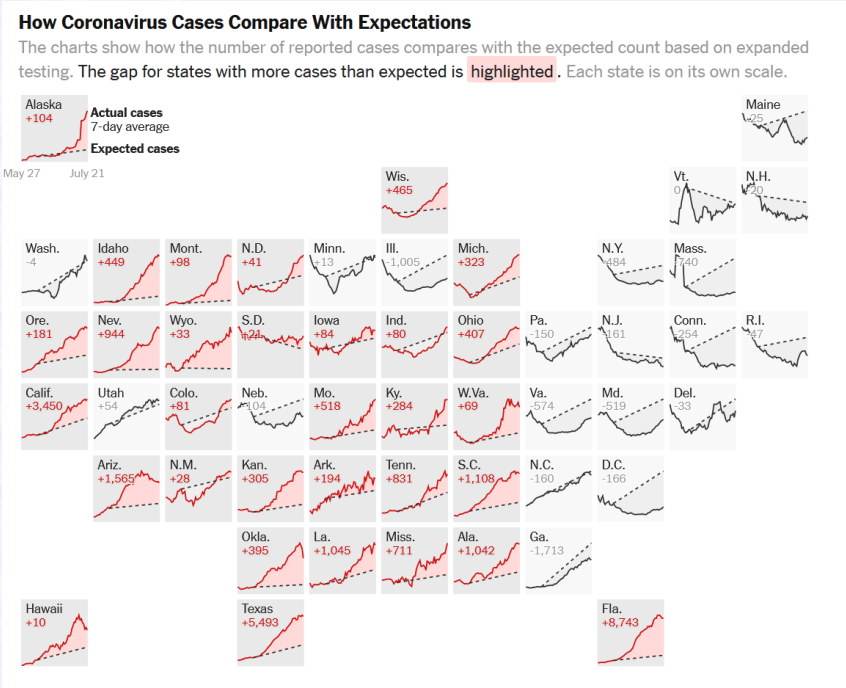


Recent updates in cases, treatment, and vaccines

Figure from *The New York Times*, July 20th 2020

COVID-19 detections are rising. It's not due to increased testing.

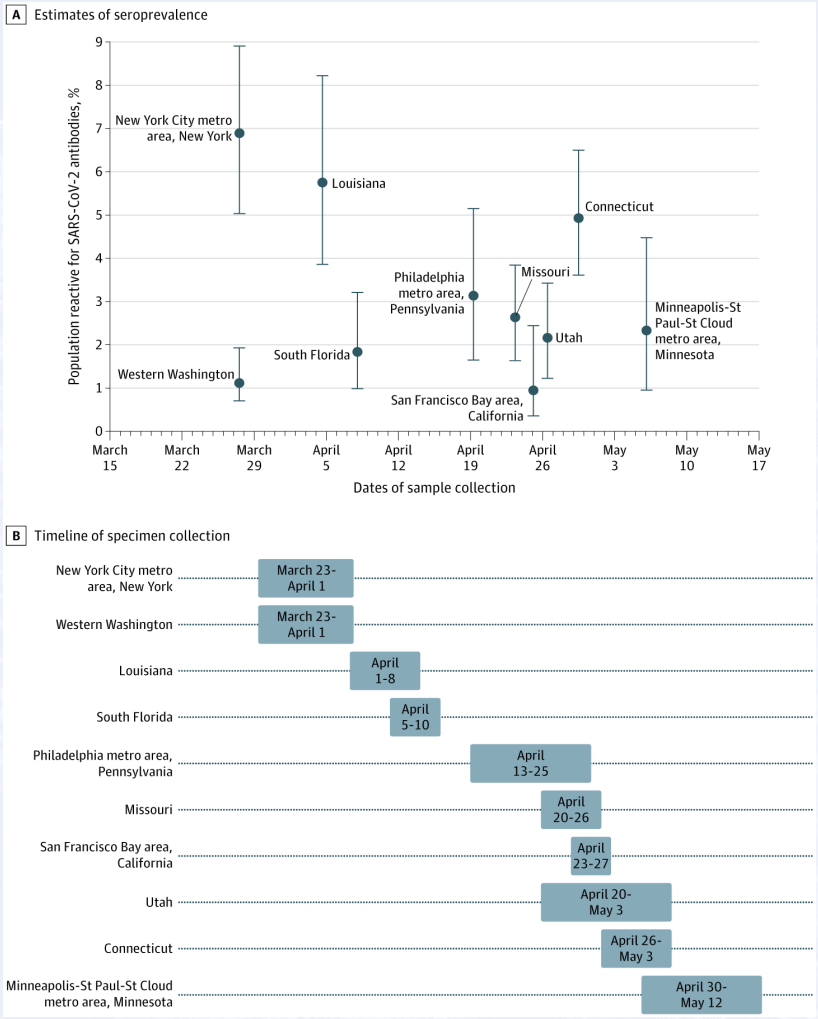




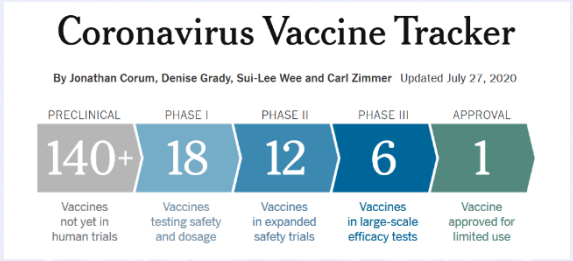
The New York Times, July 24th 2020

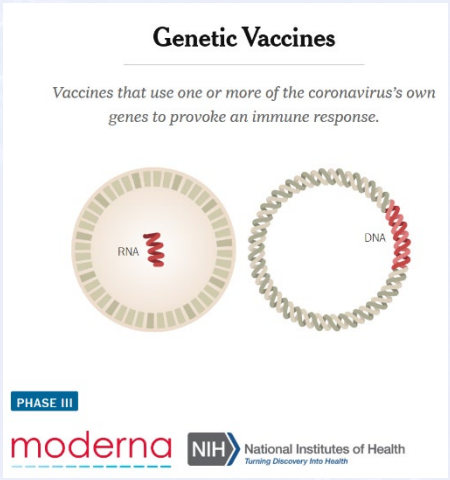
Seroprevalence of antibodies to SARS-CoV-2 in the USA

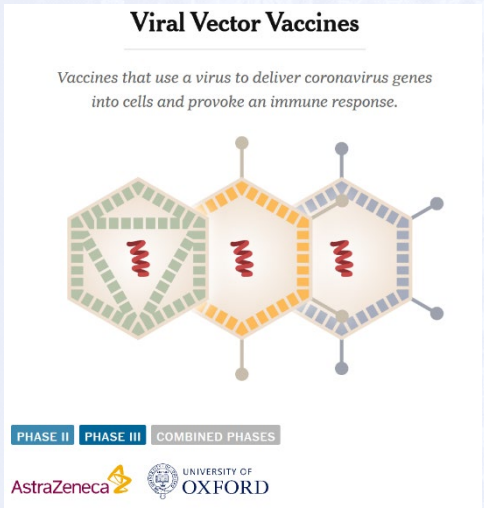
- Convenience sample of sera collected for routine clinical testing, March – May 2020
- 16,025 samples tested
- Most had no evidence of SARS-CoV-2 antibodies
  - Proportion of reactive sera ranged from 1-7%
- But the proportion of reactive sera was much greater than the number of reported cases in each area
  - Between 6 and 24 times greater

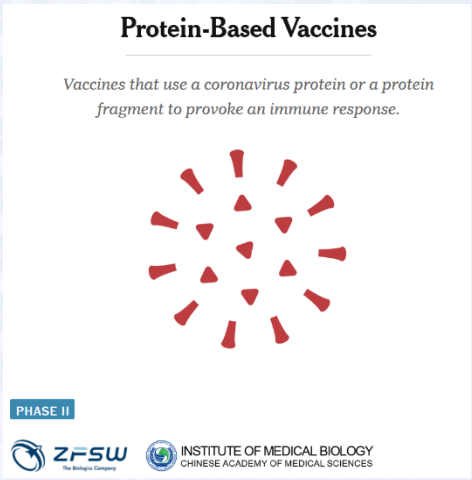


JAMA Internal Medicine (2020)
doi:10.1001/jamainternmed.2020.4130







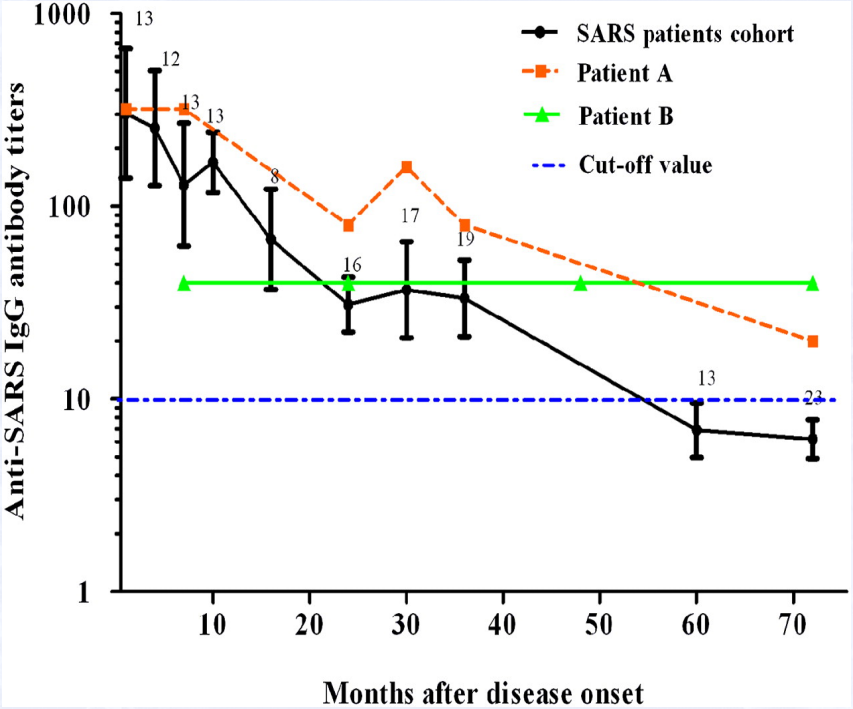


The New York Times, July 27th 2020

Immunity to coronaviruses after vaccination or infection

- There is no COVID-19 vaccine yet, although many are now beginning to undergo clinical trials, and COVID-19 survivors have only been infected a few months ago at most
- In the case of SARS, many infected-recovered people showed waning immunity a few years afterwards
- Responses to experimental coronavirus vaccines also decline after one year

- Will we have lifelong immunity to COVID-19?



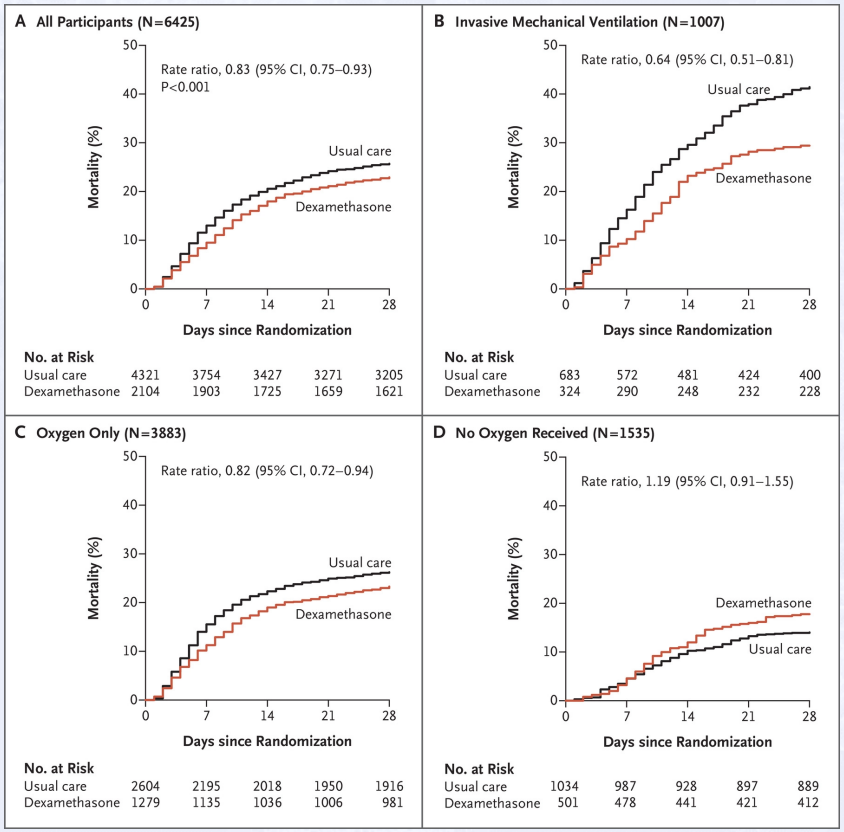
Journal of Immunology vol **186** pp7264-7268 (2011)

Current state of COVID-19 therapies

- The antiviral drug Remdesivir shortens recovery time by 4 days on average but has no impact on mortality, compared to placebo [NEJM 2020; DOI:10.1056/NEJMoa2007764]
- The only drug shown to date to affect mortality is the steroid dexamethasone
  - Effect is greatest for patients needing oxygen, or mechanical ventilation
  - Little to no effect in less severe cases

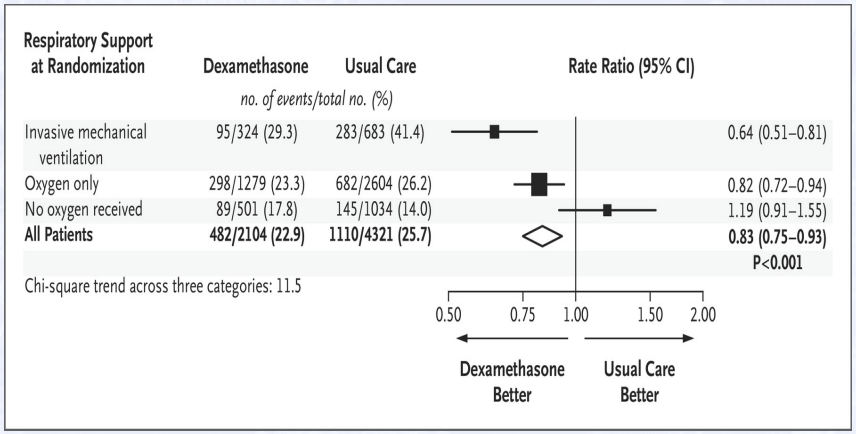
- Other drug discovery pipelines
  - Repurposing of existing drugs [Nature 2020; doi:10.1038/s41586-020-2577-1]
  - Protein-protein interaction screening [Nature 2020; doi:10.1038/s41586-020-2286-9]

The RECOVERY study: impact of dexamethasone on mortality



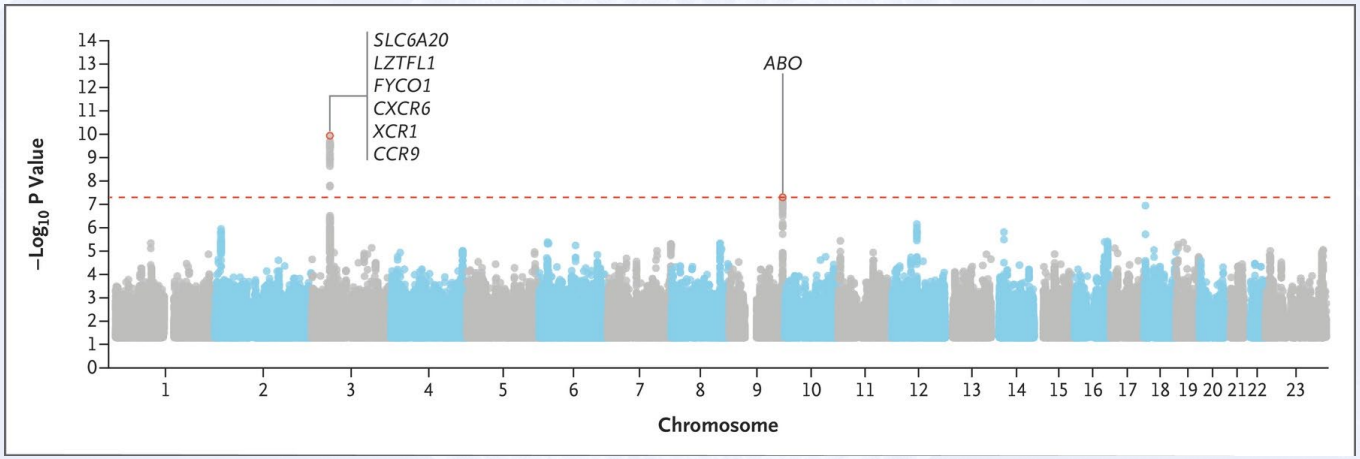
"*Scientifically robust and ethically sound clinical research remains the quickest and most efficient pathway to effective treatment and prevention strategies for patients with Covid-19*"

-accompanying editorial by Lane & Fauci

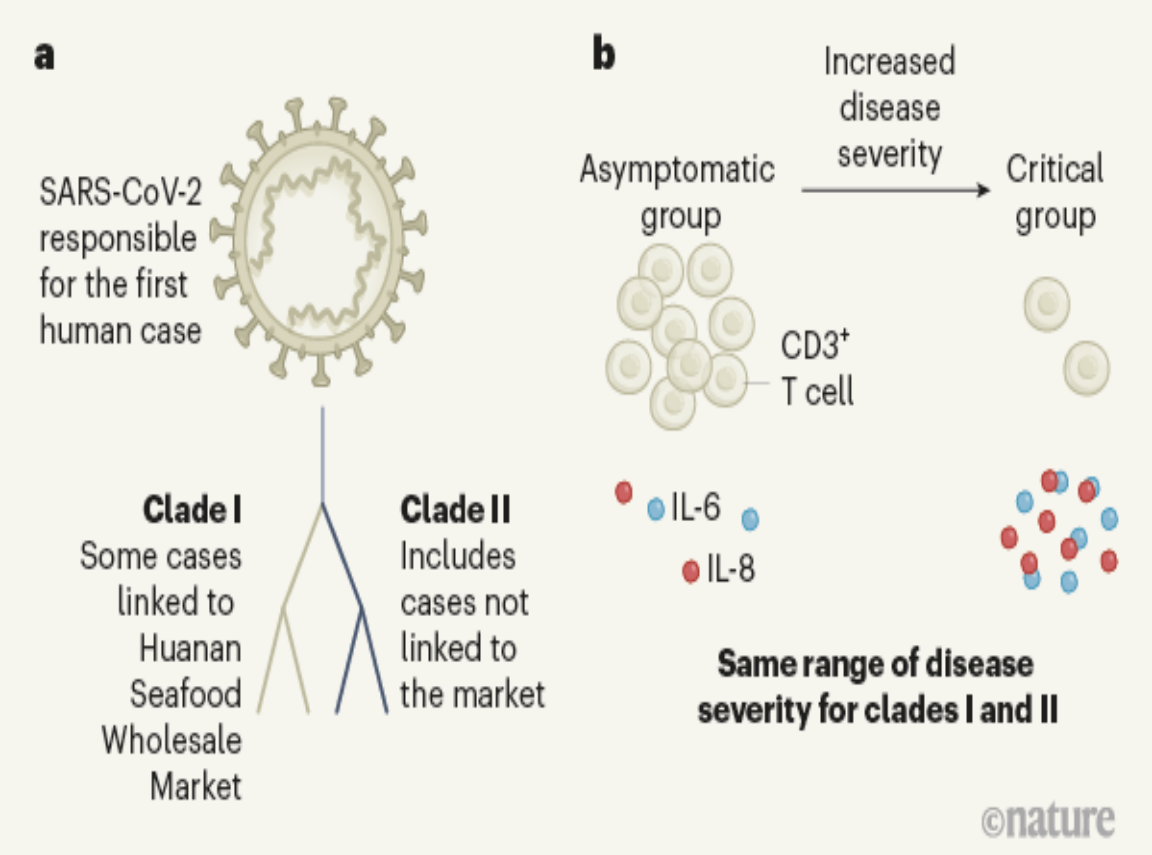


New England Journal of Medicine advance publication
DOI: 10.1056/NEJMoa2021436

Are there any human genes that affect COVID-19 severity?



New England Journal of Medicine, advance publication
DOI: 10.1056/NEJMoa2020283

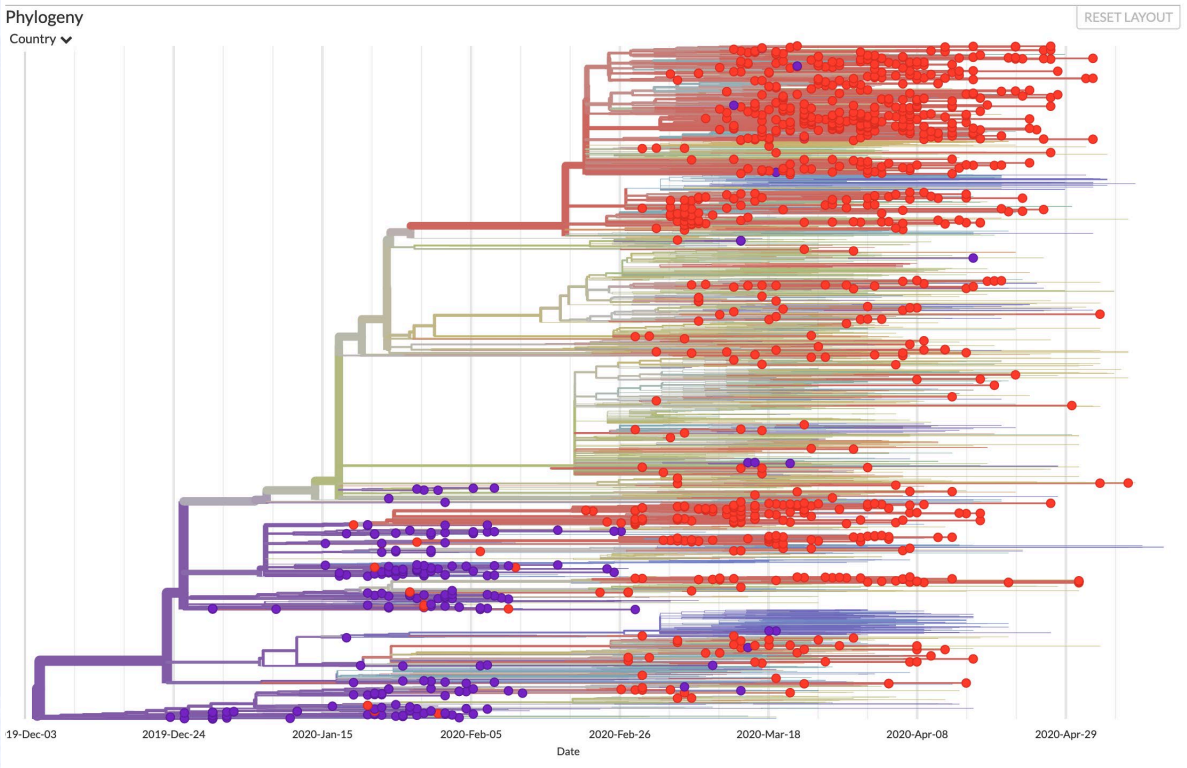


Where did SARS-CoV-2 come from, and are there others?

Nature vol **583** pp366-368 (2020)

Multiple early introductions of COVID-19 into the USA from China

- USA
- China

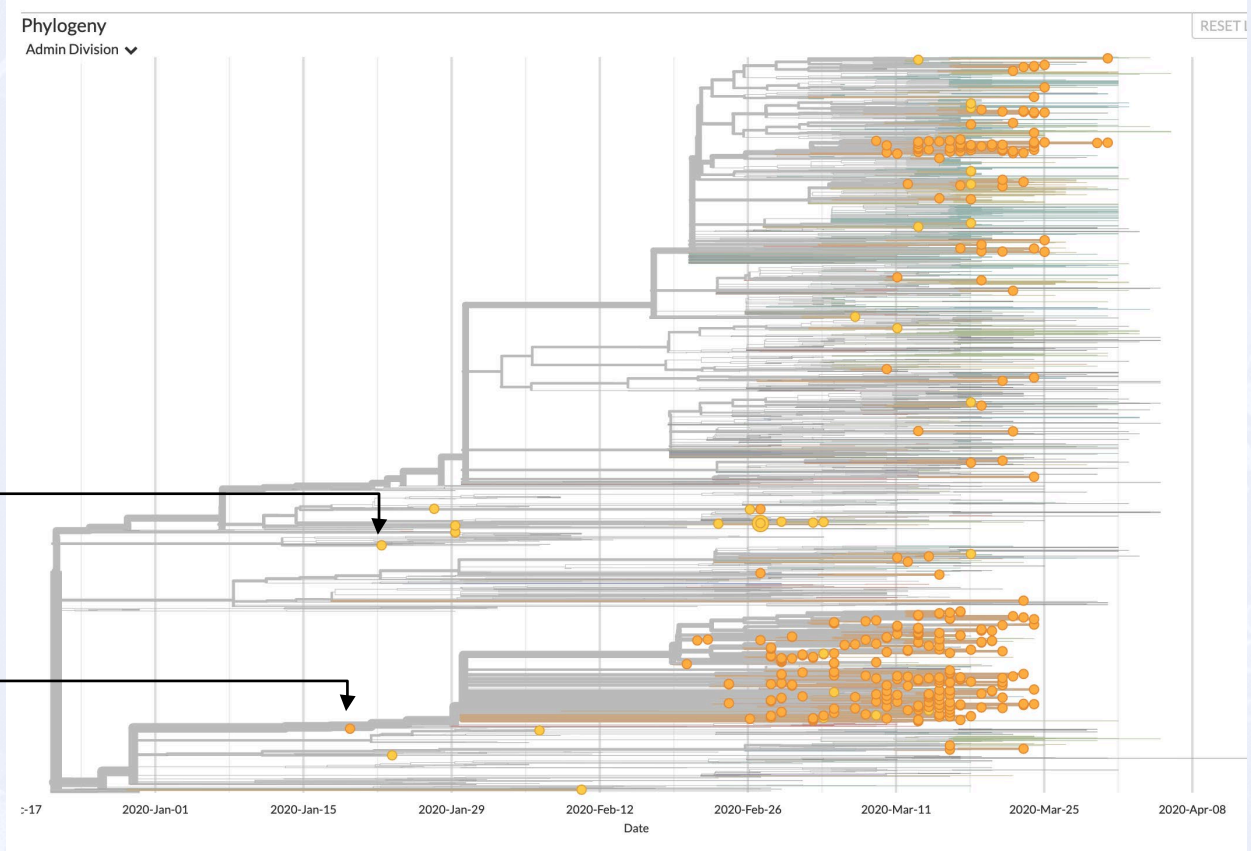


Nextstrain

MAAETC webinar 08-06-2020

Washington state and California cases

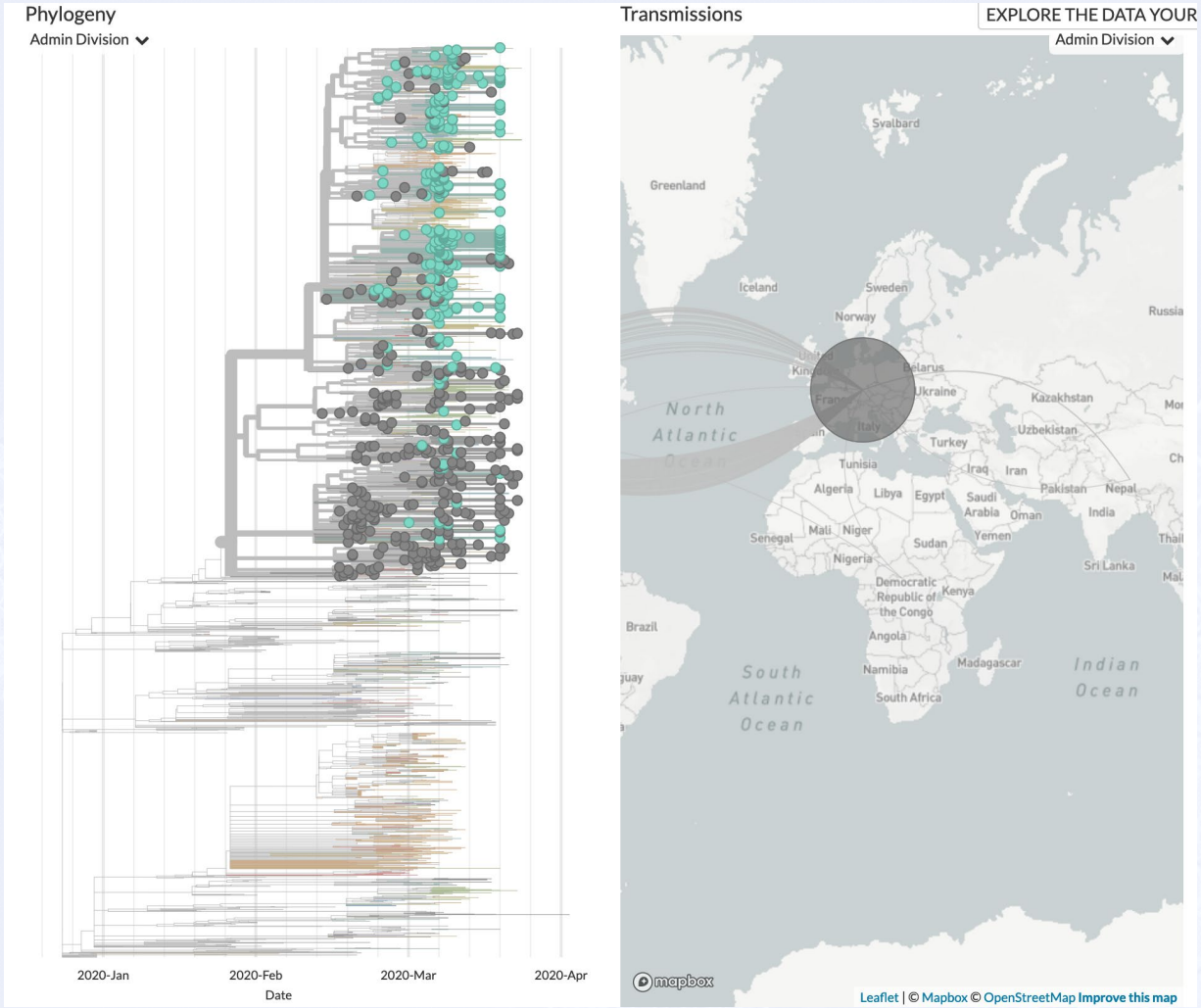
- Washington
- California



Nextstrain

Later introductions from Europe

- New York
- Europe



Nextstrain

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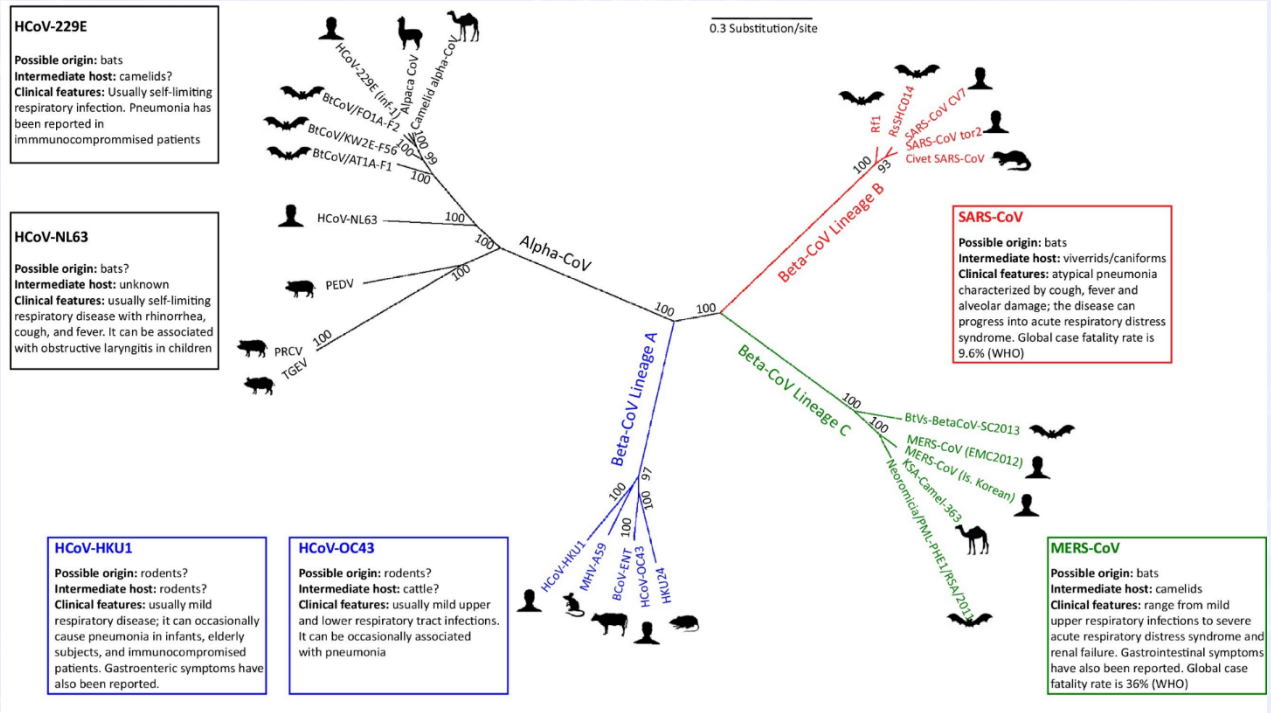
How do coronaviruses infect humans?



Trends in Microbiology vol **25** pp35-48 (2017)

Zoonotic transfer of coronavirus in SARS

Horseshoe bat

Coronavirus 88-92% similarity to human

?

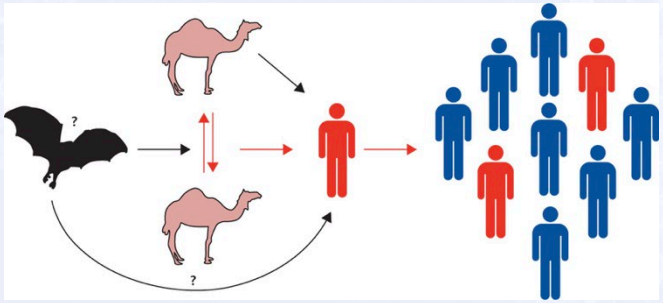
Palm civet

Coronavirus 99.8% similarity to human

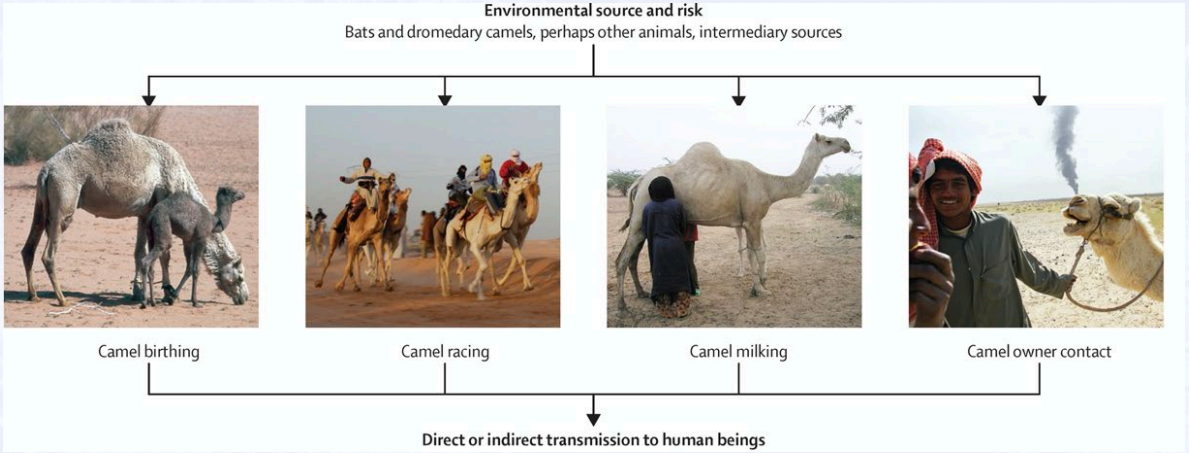
Wet market

After the initial zoonotic transfer to humans, almost all infections were due to human-to-human spread

Zoonotic transfer of coronavirus in MERS

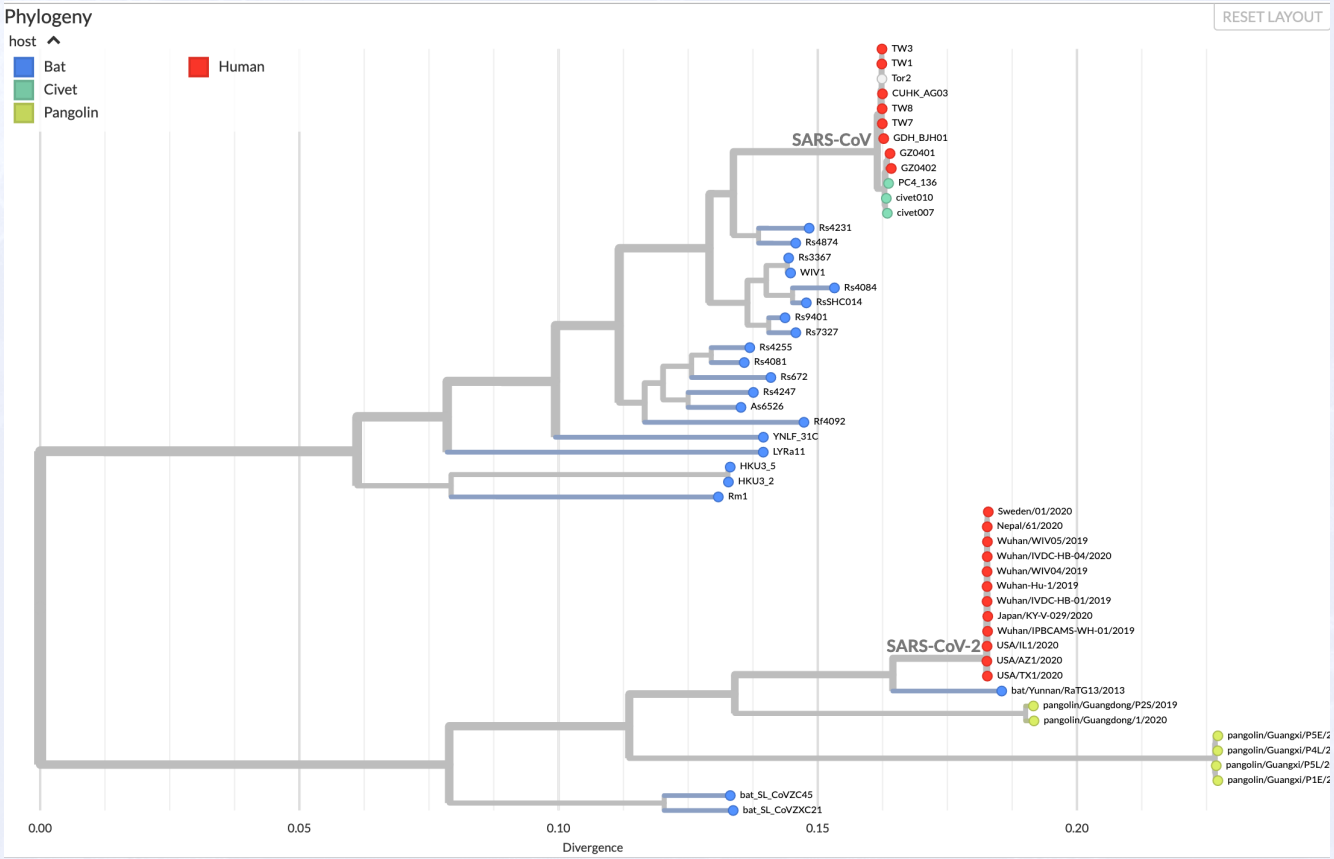


Lancet Infectious Diseases
vol **15** pp495-497 (2015)



Lancet vol **386** pp995-1007 (2015)

Zoonotic transfer of coronavirus in COVID-19?



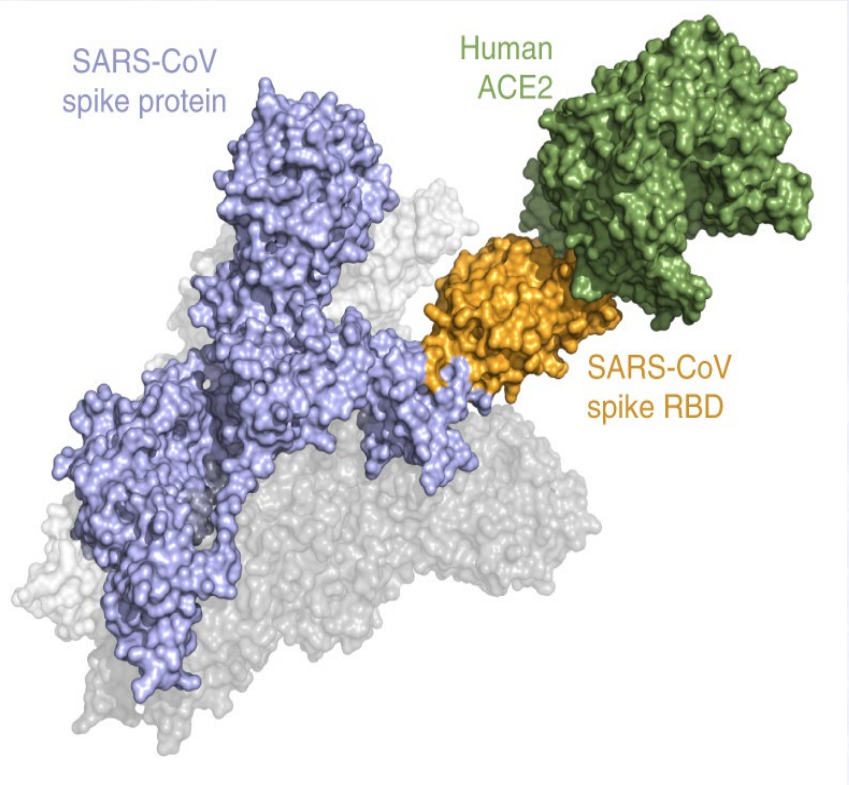
Nextstrain

The Huanan Seafood and Wildlife Market in Wuhan, China

Cell vol **181**, pp223-227 (2020)

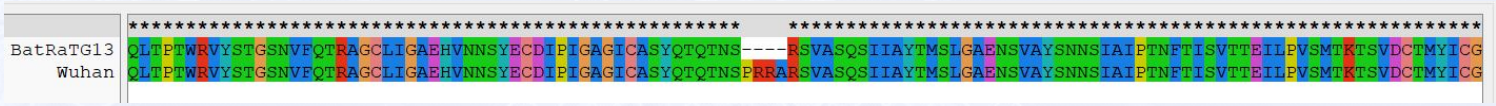
Coronavirus adaptation to humans

- The interaction between the spike protein, especially the receptor-binding domain (RBD) with ACE2, is critical to infection
- Early in the SARS outbreak, the SARS-CoV RBD underwent two small genetic changes that increased its binding affinity for human ACE2 by 1,000 fold
- This allowed for extensive human-to-human transmission after the initial species jump
- Similar small changes seen in MERS



Nature Microbiology vol **5** pp562-569 (2020)

How are SARS-CoV and SARS-CoV-2 different?



- Both use ACE2 as an entry receptor, but the course of disease is very different
- SARS case fatality rate was 10%; COVID-19 is much lower (1-2% current estimate)
- COVID-19 patients have virus in the upper respiratory tract; SARS patients did not
- ACE2 levels are lower on cells of the upper respiratory tract
- SARS-CoV-2 spike protein has an extra region that SARS-CoV does not. This **polybasic furin-type cleavage site** increases fusion activity and may allow the virus to enter cells with lower levels of ACE2

…but it's not an engineered virus (unless they did it really badly)

http://virological.org/t/tackling-rumors-of-a-suspicious-origin-of-ncov2019/

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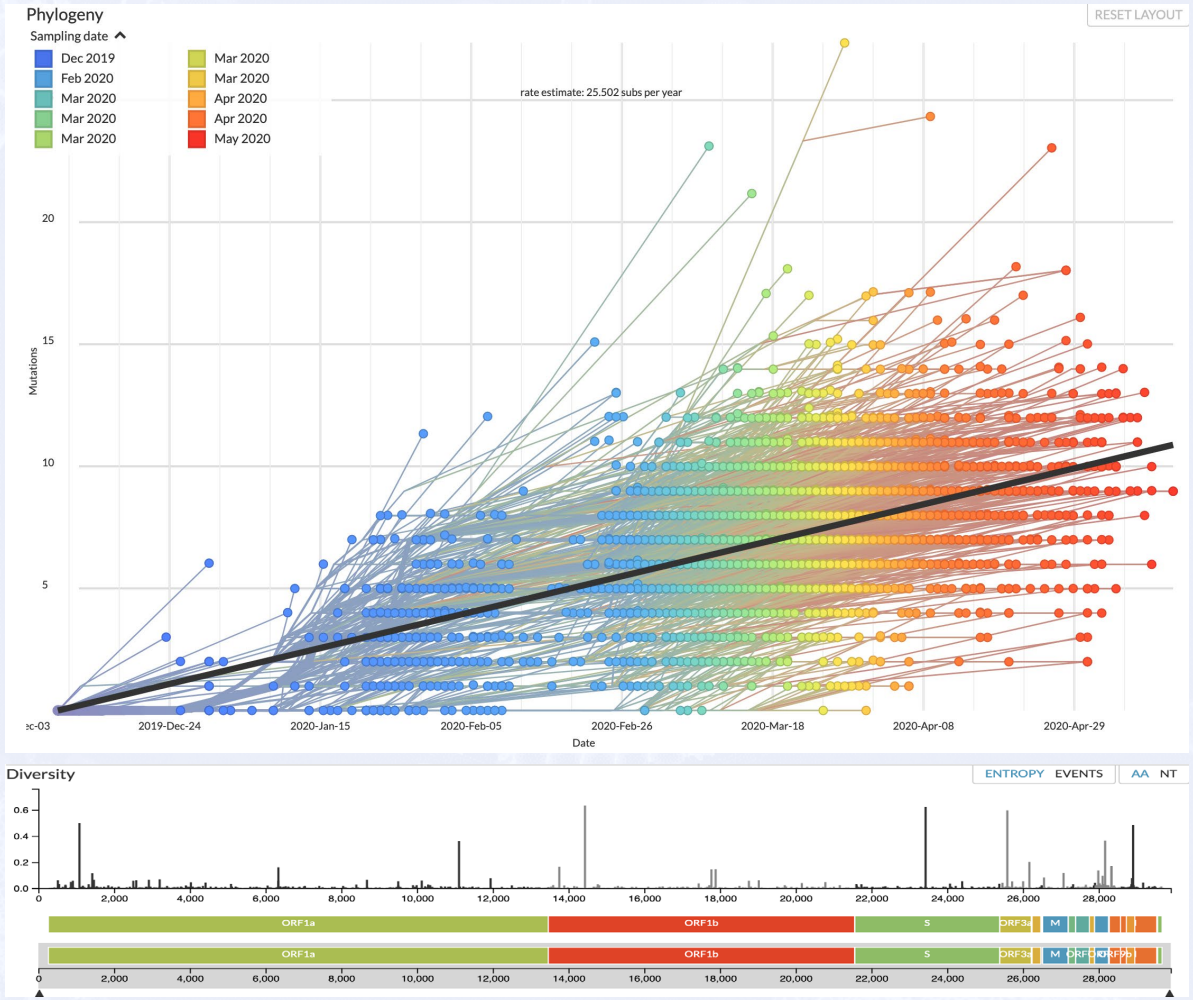
SARS-CoV-2 is mutating like other coronaviruses



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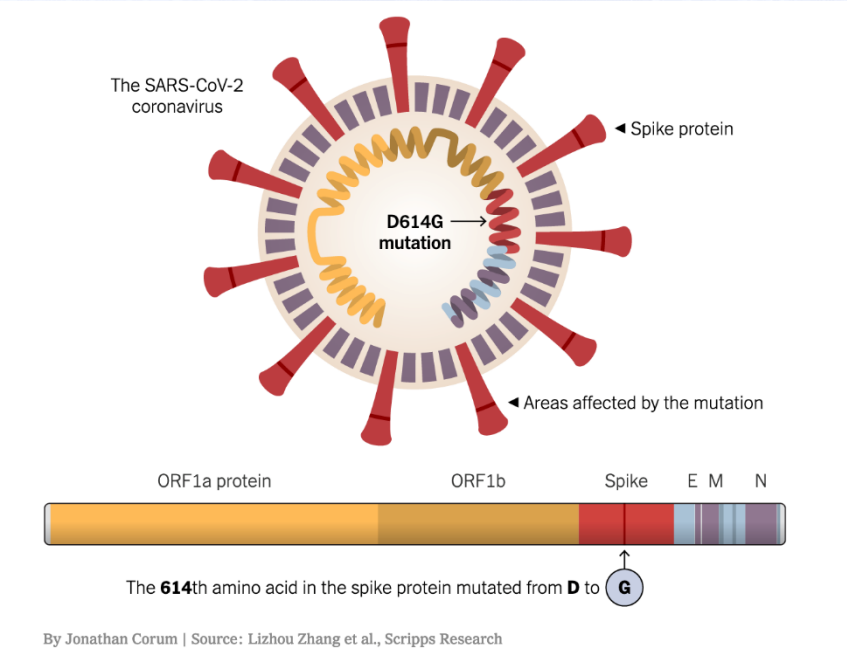
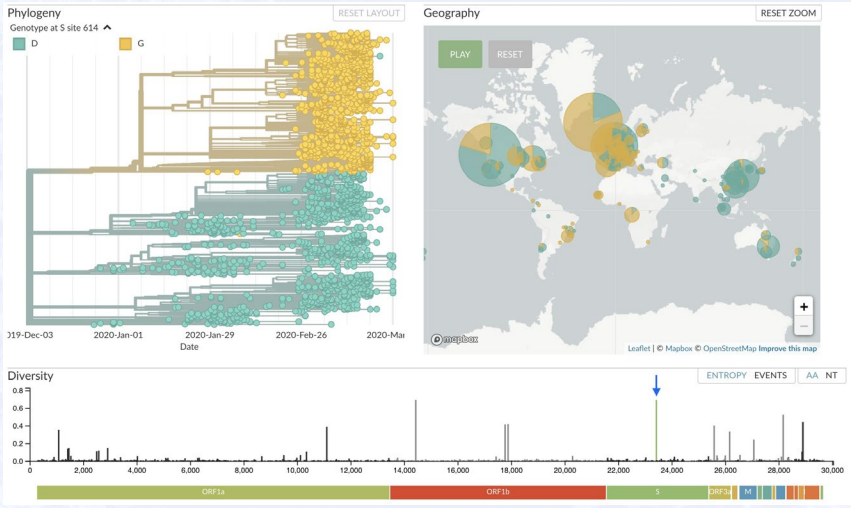
Is COVID-19 evolving to become more deadly?



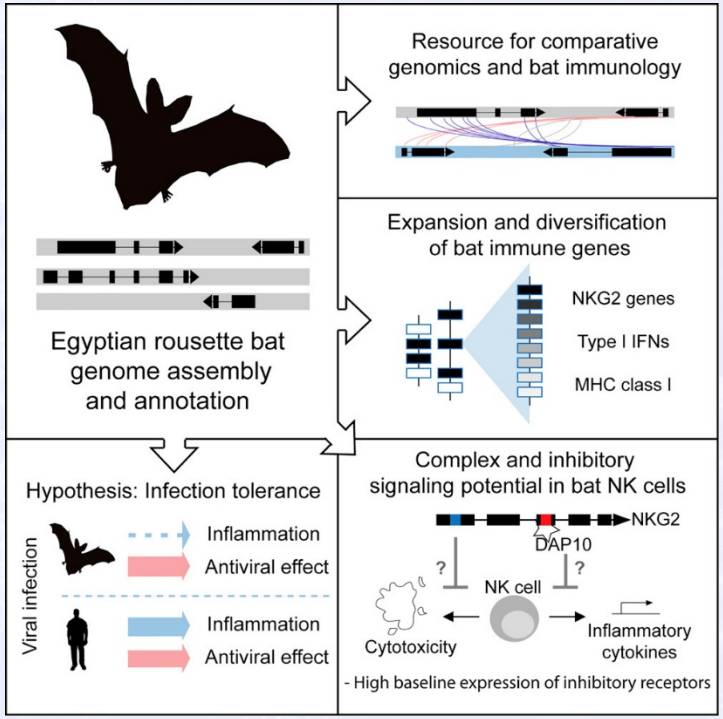


The New York Times, June 12th 2020

Nextstrain

Why do bats carry so many viruses that are fatal to humans?

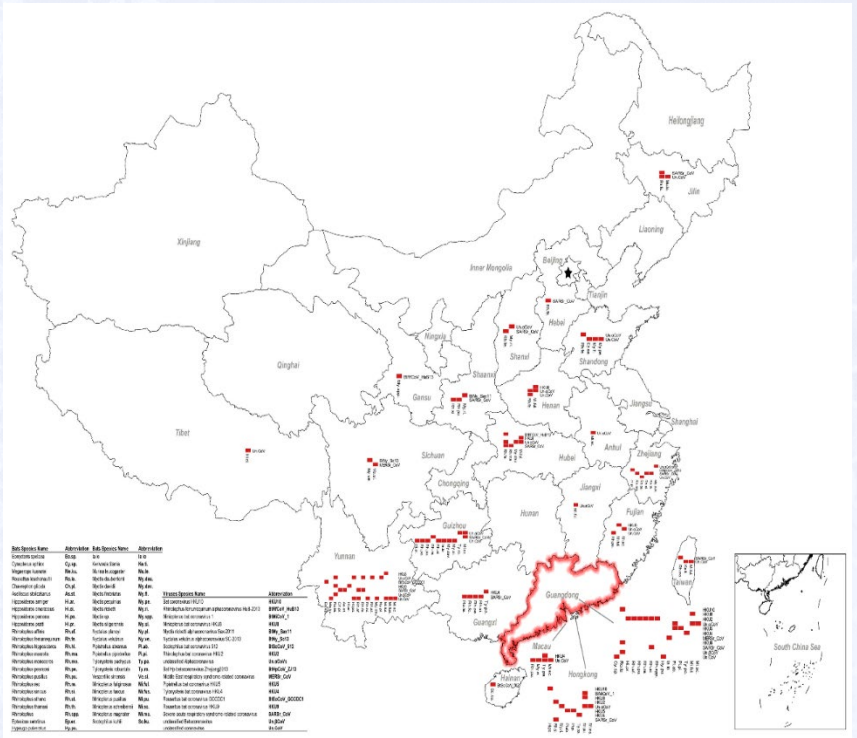
- SARS, MERS, COVID-19, Nipah, Hendra, Ebola, Marburg, *etc*
- Bats roost together in large numbers, often with members of other species
- Bats harbor these viruses but do not get sick and die – how?
  - Bats have evolved a complex series of immune responses that enable them to tolerate the presence of many viruses
- Bats are flying mammals and have a high body temperature
  - viruses that can survive this can survive the high fever in humans that is intended to kill pathogens



Cell vol **173** pp1098-1110 (2018)

Will COVID-19 be the last new coronavirus infection?

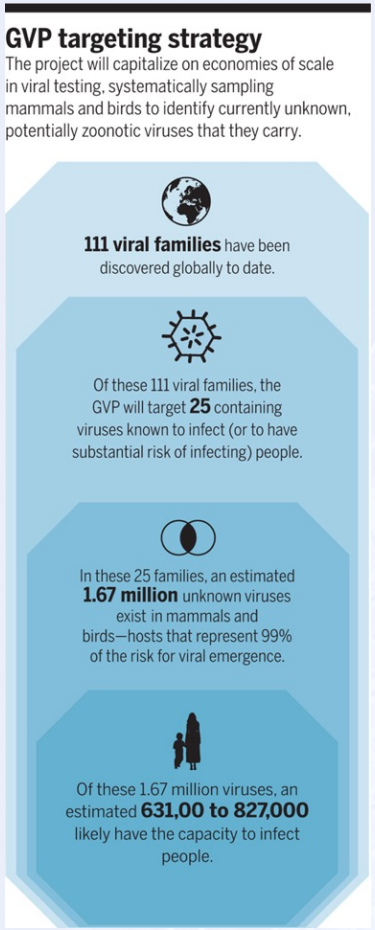
- There are many Coronaviruses circulating in many bat species
- 6.5% of bats surveyed harbor one or more coronaviruses (Tang et al (2006), J. Virol vol **80** pp7481-7490)
- EcoHealth Alliance data: ≈400 novel coronaviruses in bats in China; multiple "spillover" events where these have infected humans, but not spread



Viruses vol **11**, 210 (2019)
Each red block represents one CoV in one bat species

The global virome project

- Around 263 viruses from 25 viral families are currently known to infect humans
- Estimated that ~1.67 million yet-to-be-discovered viral species from key zoonotic viral families exist in mammal and bird hosts
- Reasonable expectation is that between 631,000 and 827,000 of these unknown viruses have zoonotic potential
- GVP launched in 2018, with goal of identifying this viral threat



Science vol **359** pp872-874 (2018)

Summary

- COVID-19 is a severe disease caused by infection with SARS-CoV-2
- Coronaviruses are a widespread family of viruses that typically do not cause severe disease
- SARS-CoV-2 infects cells after its spike protein interacts with ACE2
  - mutations in the spike protein facilitate infection in humans
- The long-term immune response to COVID-19 is unknown
- There are MANY more coronaviruses out there

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