



Summer of our discontent: COVID-19 Still Rages

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SOME HISTORY OF PLAGUES



Plagues have been recorded over at least 5 millennia



Mass grave: China, 3000 BC

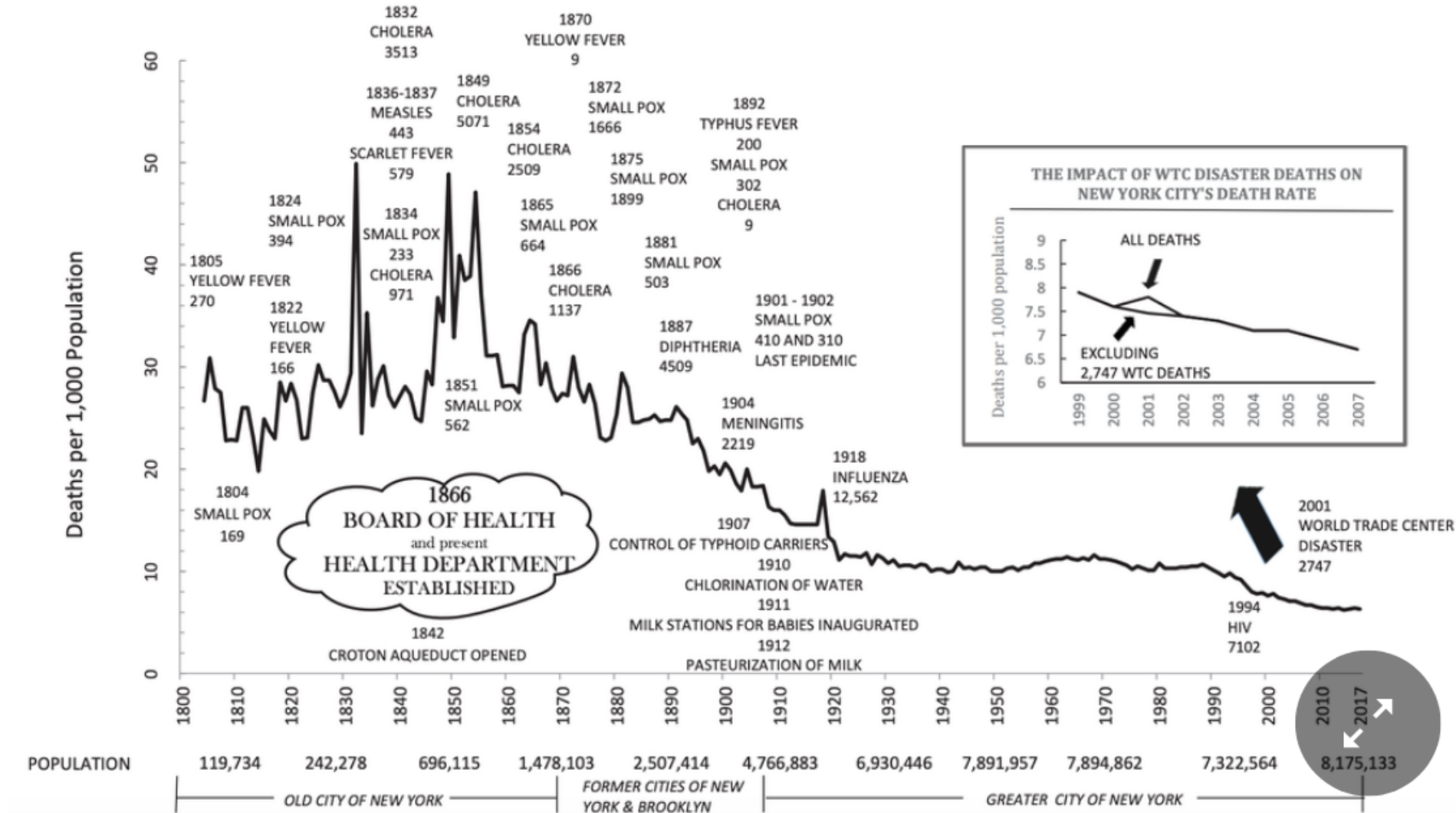
Just in case you thought COVID was somethings new.....

Common underlying features are crowding and increased transport

	Dates	Deaths	Cause
Prehistoric epidemics	c3000 BC	?	?
Plague of Athens	430 BC	100,000	?
Antonine Plague	165-180	>5 million	?smallpox
Plague of Cyprian	250-271	?	?
Plague of Justinian	541-542	10% of global population	Bubonic plague
The Black Death	1346-1353	Half of Europe's population	Pneumonic plague
Cocoliztli epidemic	1545-1548	15 million	Salmonella paratyphi C
American plagues	16 th century	Decimated Inca and Aztecs	Several including smallpox
Great Plague of London	1665-1666	>100,000	Pneumonic plague
Great Plague of Marseille	1720-1723	30% of population	Plague
Russian Plague	1770-1772	>100,000	Plague
Philadelphia Yellow Fever	1793	>5,000	Yellow fever
Flu Pandemic	1889-1890	> 1 million	Influenza
American Polio Epidemic	1916	6000	Polio
Spanish Flu	1918-1920	500 million	Influenza
AIDS		35 million	HIV
COVID-19	2019-??	?690,0000 & counting	Coronavirus

The Conquest of Pestilence in New York City

...As Shown by the Death Rate as Recorded in the Official Records of the Department of Health and Mental Hygiene.



1918



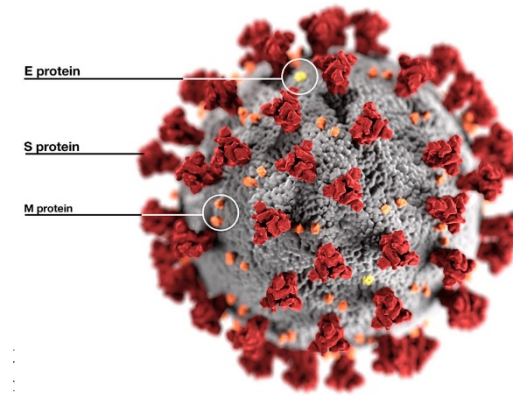
2020



THE CORONAVIRUSES

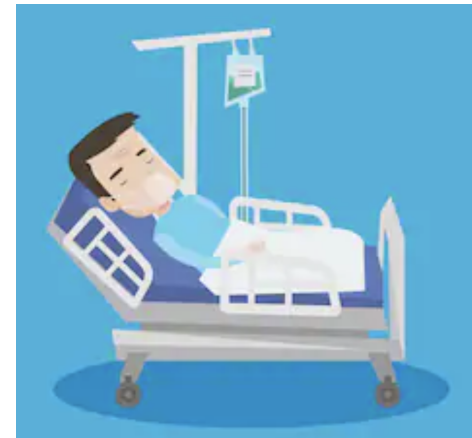
WHAT IS A CORONAVIRUS?

**The virus is
named
SARS-CoV-2**



**Virus made of
Proteins and RNA**

**The disease is
named
COVID-19**



There are millions, billions or more likely trillions of viruses everywhere in nature including many unknown coronaviruses:

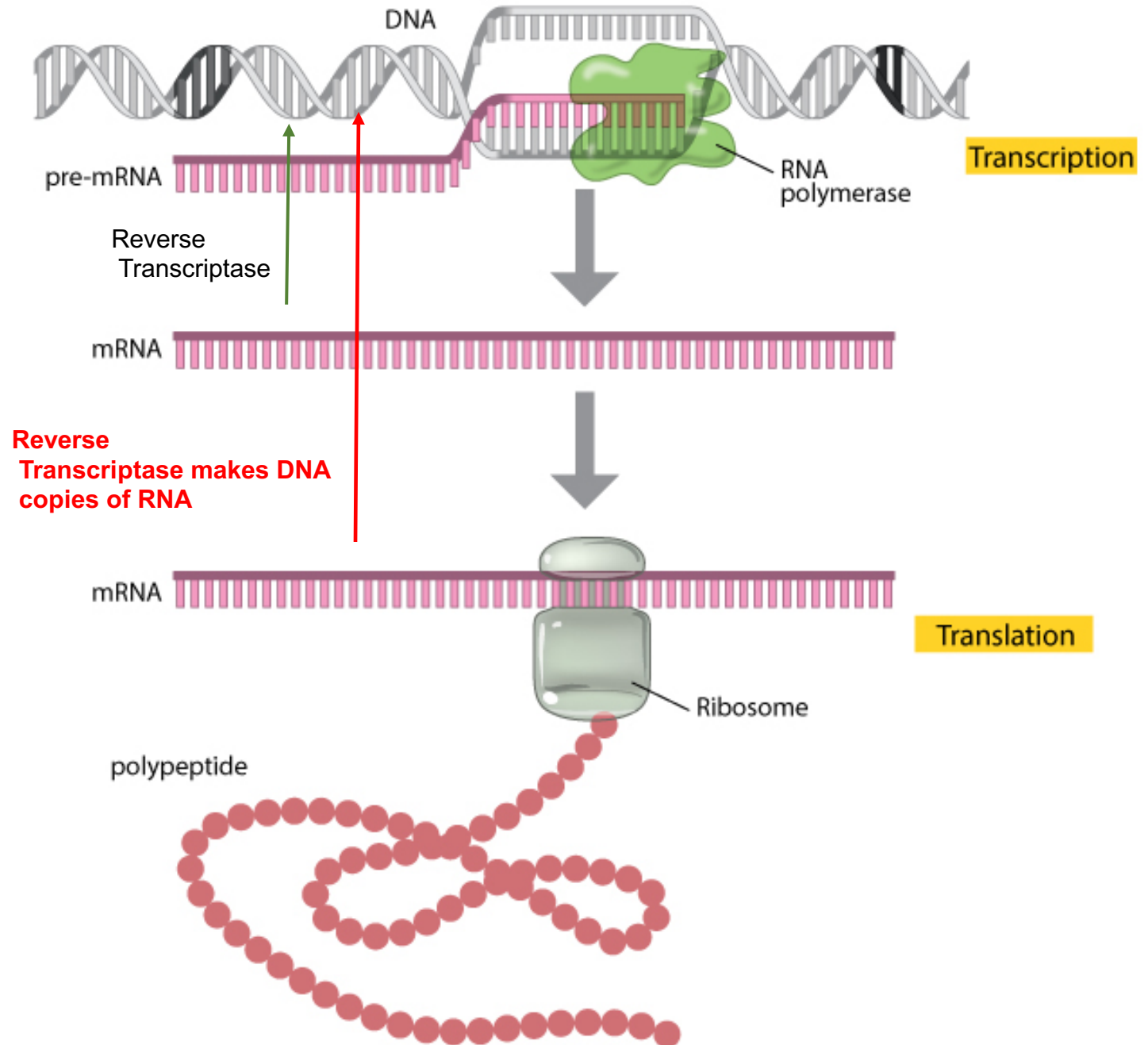
KNOWN CORONAVIRUS FACTS

- **There are at least 36 known animal coronaviruses**
- **There are four human coronaviruses**
 - **They cause 1/3 of all common colds**
 - **They are winter viruses**
 - **Immunity lasts less than a year**
- **SARS-CoV-2 infects both upper and lower airways.**
- **Its spikes attach to the ACE-2 receptor, common receptors found throughout the body and in the lung**
- **The spike is then cleaved by furin which allows it so enter the cell. Furin is ubiquitous in cells.**

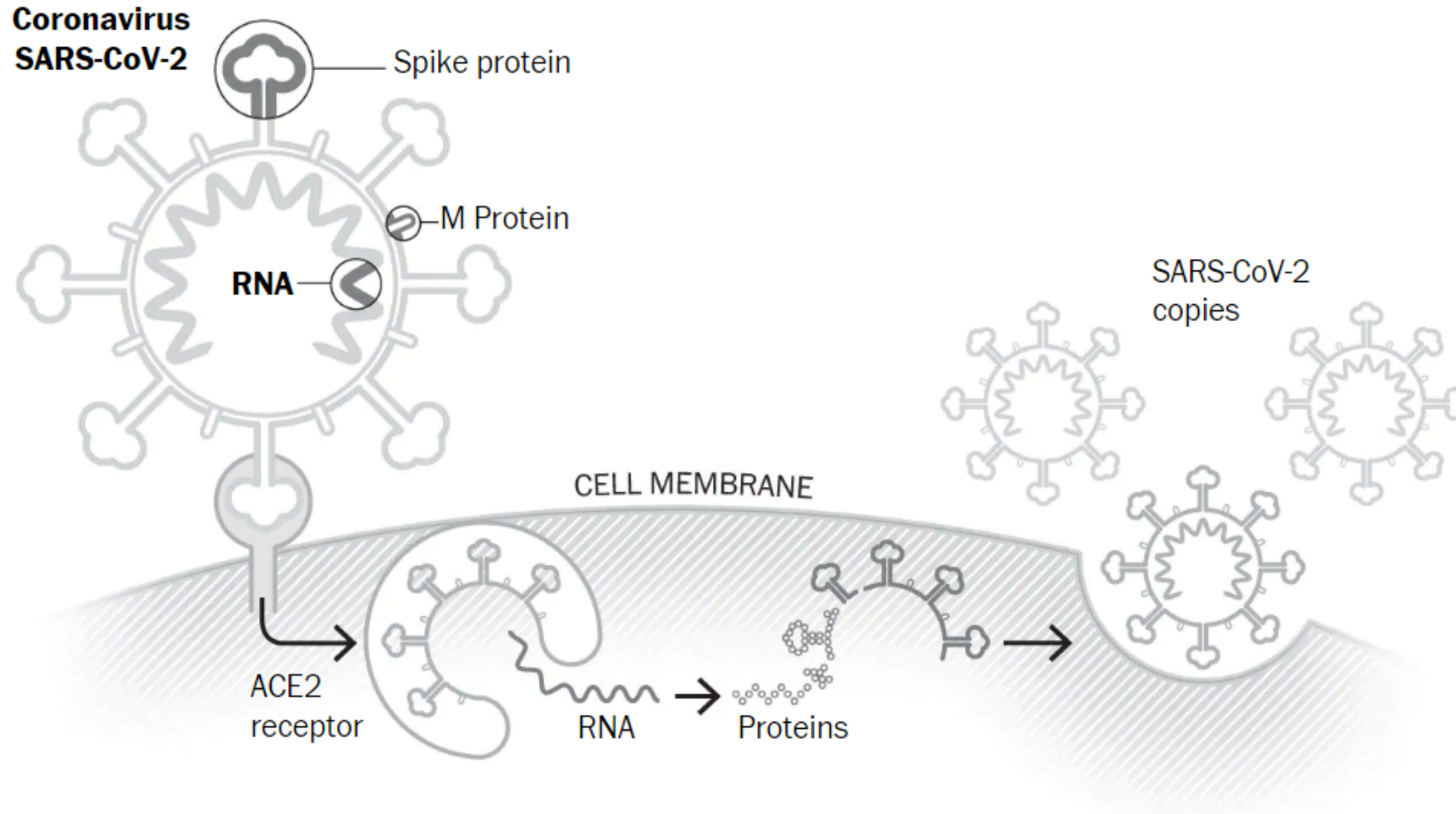
DNA viruses: Herpes, CMV, smallpox, adenoviruses, chickenpox

Negative Strand RNA viruses: HIV, Polio, Influenza, Ebola, measles, mumps,

Positive Strand RNA viruses: **SARS-CoV-2, Dengue, west Nile, Zika, rhinoviruses, rubella**



The Washington Post, August 13



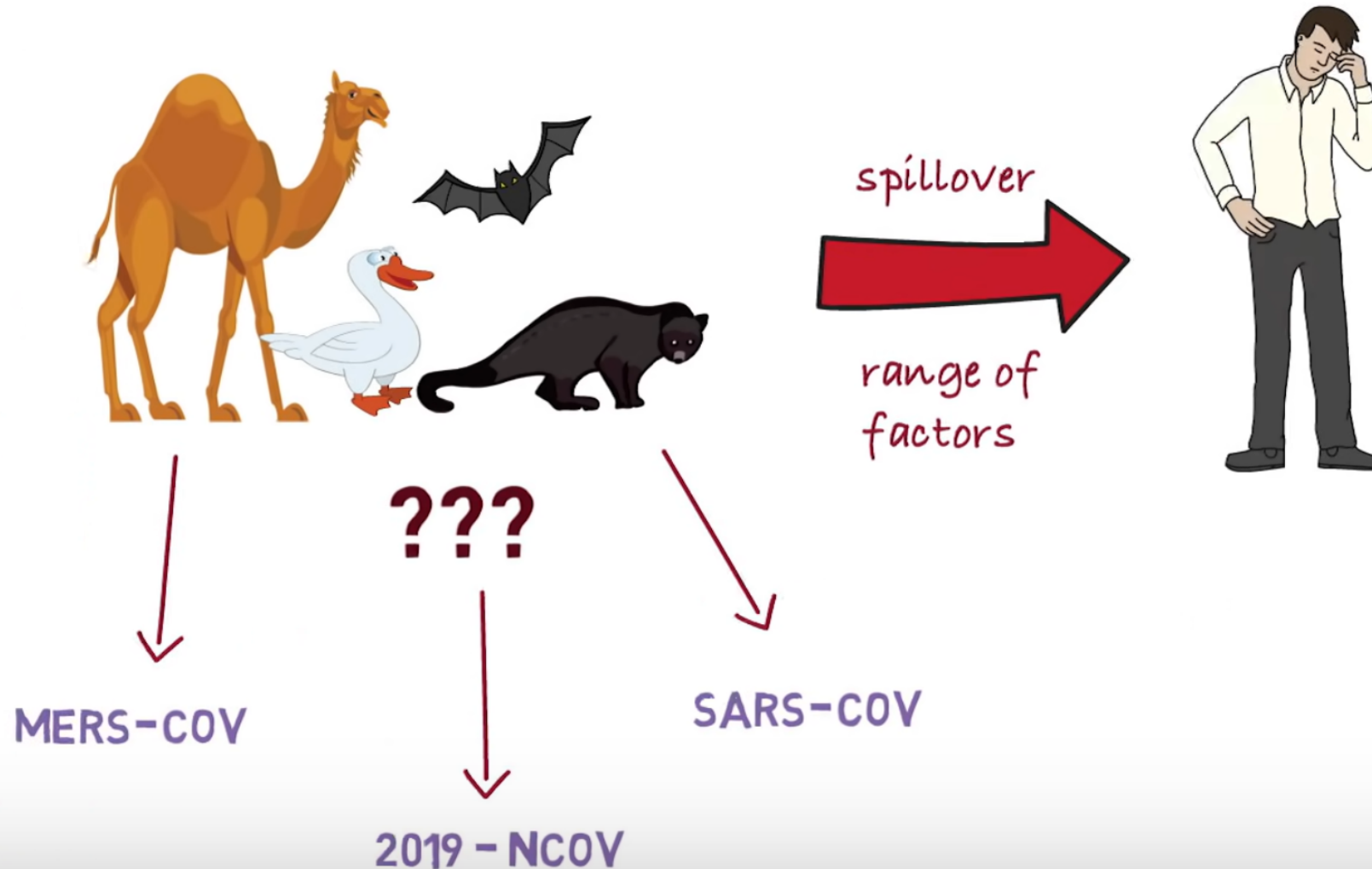
SARS-CoV-2 uses its spike to bind to the ACE2 receptor, allowing access into the cell.

The virus's RNA is released into the cell. The cell reads the RNA and makes proteins.

The viral proteins are then assembled into new copies of the virus.

The copies are released and go on to infect more cells.

Coronaviruses can 'species jump'
When they do the results can be unexpected
The original host may have no disease, the new host very sick.



THE DISEASE

Clinical signs

Laboratory Diagnosis

CLINICAL SIGNS AND SYMPTOMS

MILD DISEASE

- **Asymptomatic (50-80%)**
- **Body aches, headache**
- **Tightness of chest**
- **Dry cough**
- **Short of breath**
- **Los of taste and smell**
- **Fatigue**

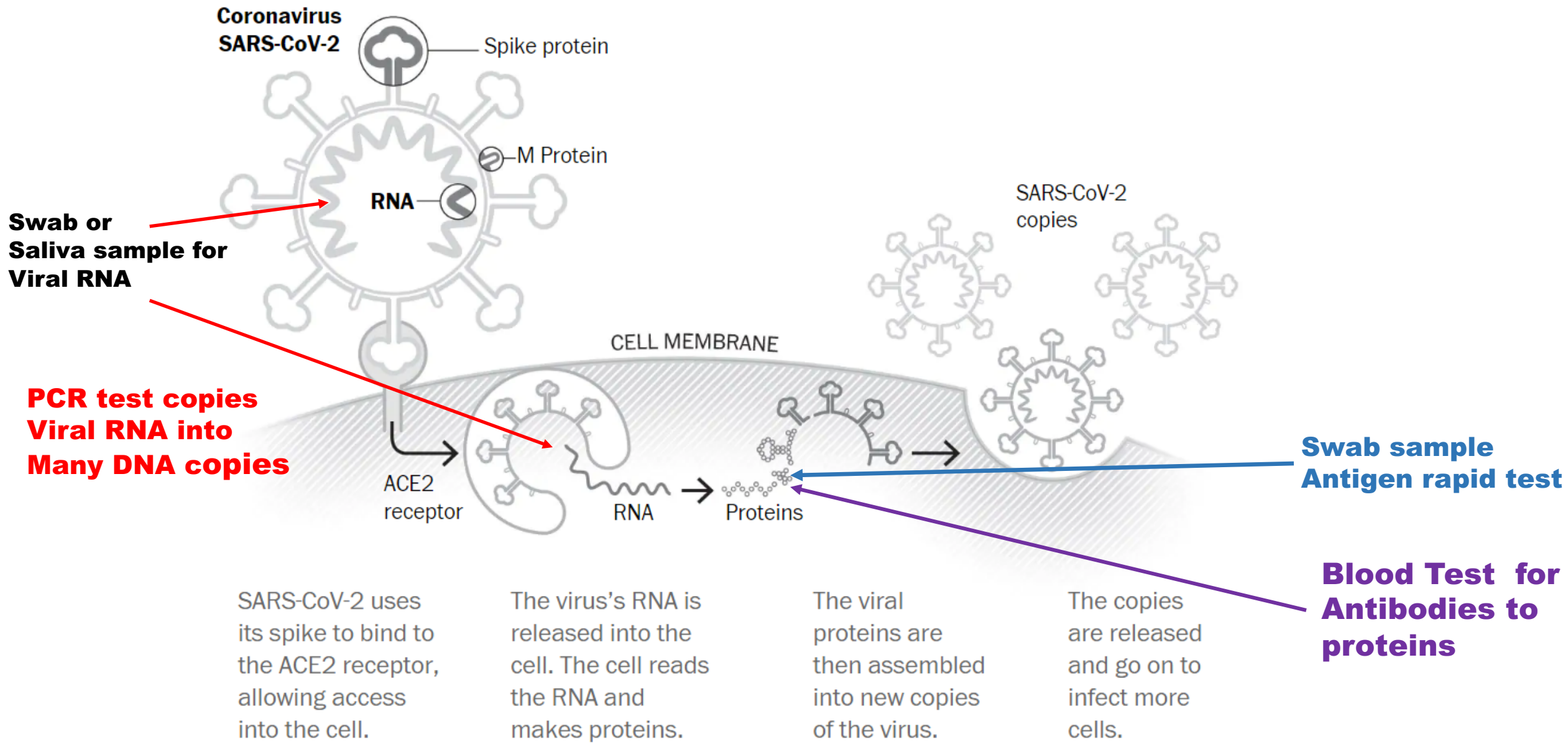
‘LONG’ COVID DISEASE

- **Younger patients**
- **Intermittent fevers**
- **Body aches**
- **Extreme fatigue**
- **Persists for months**

SEVERE DISEASE

- **Can be biphasic (sick, better, sicker)**
- **Widespread viral pneumonitis**
- **Acute Respiratory Distress Syndrome**
- **Cytokine storm**
- **Cardiac injury; heart failure**
- **Kidney failure**
- **Multi system failure**
- **Abnormal bleeding/clotting**
- **Mortality 5-16% (Hospitalized)**

Viral targets for detection in the laboratory



DIAGNOSIS: ACUTE PHASE

- **Polymerase Chain Reaction (PCR): detects and makes many copies viral RNA to DNA specific for SARS-CoV-2.**
 - **Specimen is swab from nose or pharynx or saliva**
 - **Only valid the day it is taken**
 - **Result may be false negative**
-
- **Antigen tests: detects viral protein**
 - **Specimen is swab from nose or pharynx**
 - **Only valid the day it is taken**
 - **Result may be false positive or negative**
 - **Less sensitive than PCR because cannot be copied**

DIAGNOSIS: CONVALESCENT PHASE

- **Antibody tests for IgG proliferating**
- **Specimen is peripheral blood**
- **Persistence of antibody unknown, but may be short (only a year or two) based on known coronaviruses causing common cold**
- **Result can be false positive or negative**
- **DOES NOT DIAGNOSE ACUTE DISEASE**
- **ONLY INDICATES PAST INFECTION**

Multiple reasons for false-negative PCR or Antigen test

- **Patient may be in the early stage with a low viral load**
- **Patient may have no major respiratory symptoms.**
- **Problem with sample collection, so very little sample to test.**
- **Poor handling and shipping of samples and test materials.**
- **There may have been technical issues inherent in the test.**
- **The antigen test is less sensitive so more false negatives**

The WHO suggests that these issues should be taken into account and that for some people, tests should be carried out several times

Transmission

Yes, the Coronavirus Is in the Air

Transmission through aerosols matters — and probably a lot more than we've been able to prove yet.

- **Experts have been saying the SARS-CoV-2 virus can be spread by aerosol. WHO finally agreed.**
- **Aerosols are very small particles that float in the air for several meters and hang around for hours in closed spaces.**
- **The consensus is that large (droplet) and small (aerosol) particles contain the virus**
- **These particles come from deep in the lungs of infected people.**
- **The risk is greater the closer to the patient. This is rather like passing a person smoking.**
- **Droplets from someone talking, coughing, laughing, or singing, and sneezing travel even further.**

OPINION | Yes, the Coronavirus Is in the Air



SOME AEROSOL DATA

L.C.Marr, NYT, July 30th, professor of civil and environmental engineering

- **Aerosols collected in hospital rooms of COVID-19 patients contained detectable coronavirus. *Nature July 29, University of Florida***
- **WHO defines aerosols as 5 microns or less, these are tiny specks of liquid over a wide spectrum of sizes containing virus from the lungs**
- **These tiny droplets fly through the air like miniature cannonballs travelling many meters**
- **It takes about half an hour for them to drop**
- **The smaller the droplet the more important short range is**
- **Whether the virus can move through air vents in aerosols is not proven.**

Potential air duct spread

- **Diamond Princess cruise ship off Japan. 712/3711 infected**
- **Choir rehearsal in March, 51/60 infected from just one person.**

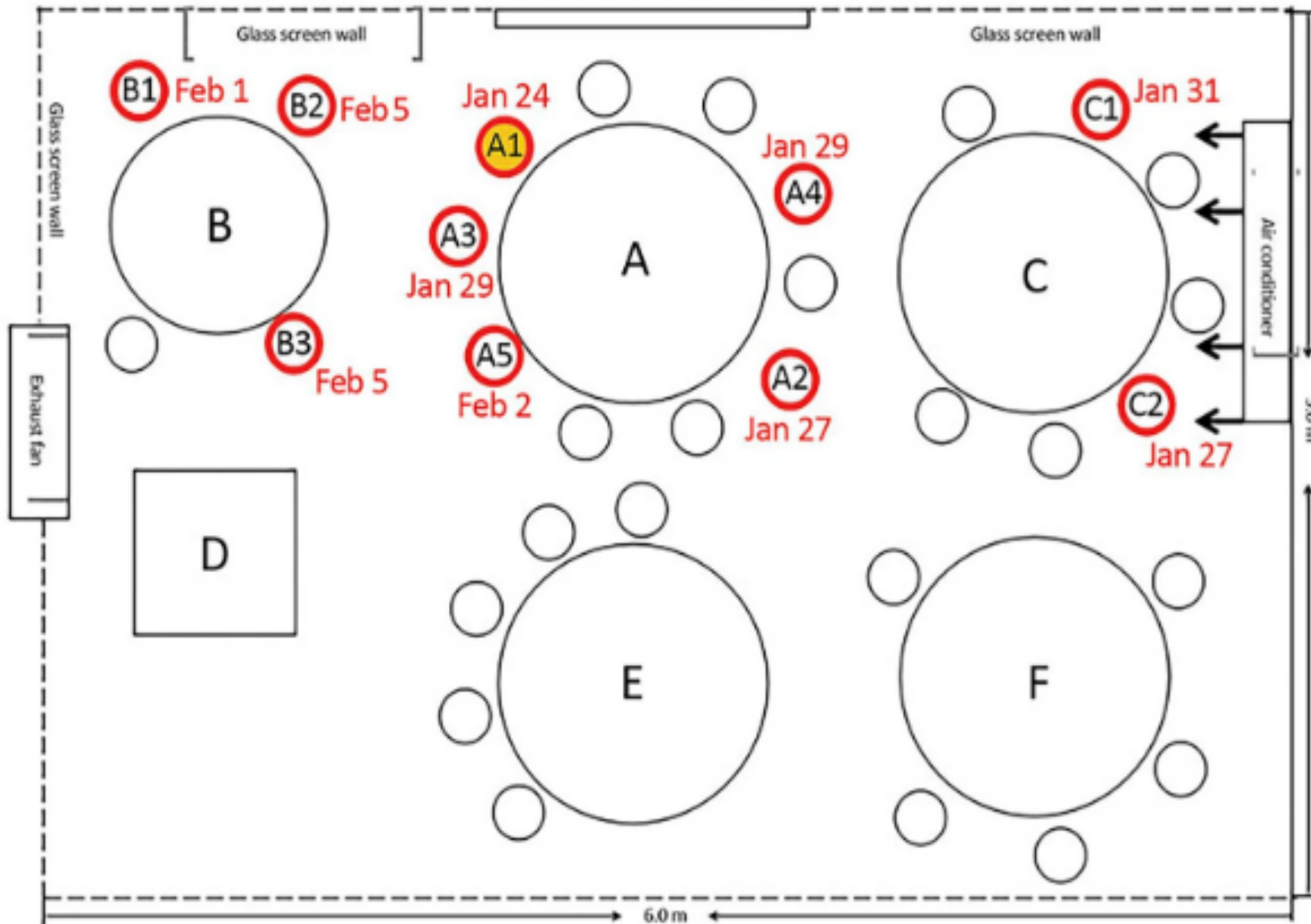
Super spreading event: March

- **About 50 people gathered for a birthday party in the upscale suburb of Westport, CT then scattered across the region and the world, taking the coronavirus with them.**
- **Westport, a town of 28,000 on the Long Island Sound, did not have a single known case of the coronavirus on the day of the party. It had 85 ten days later, up more than 40-fold in 11 days.**
- **The partygoers — more than half of whom became infected — left that evening for Johannesburg, New York City and other parts of Connecticut and the United States, seeding infections on the way.**

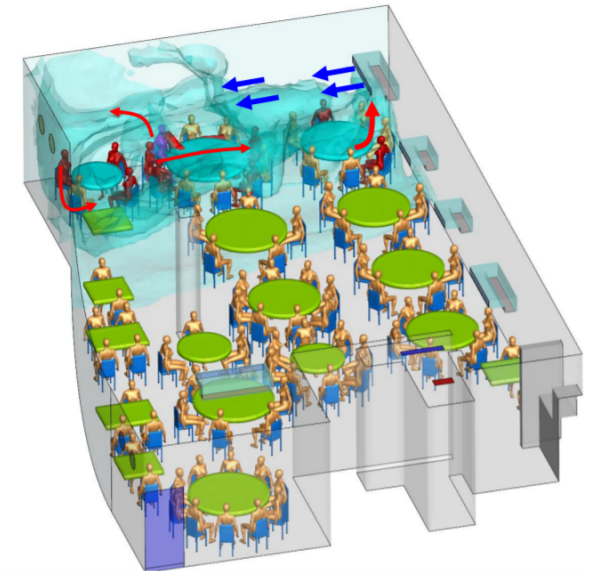


Aerosol transmission in a restaurant in Guangzhou

Li et al preprint

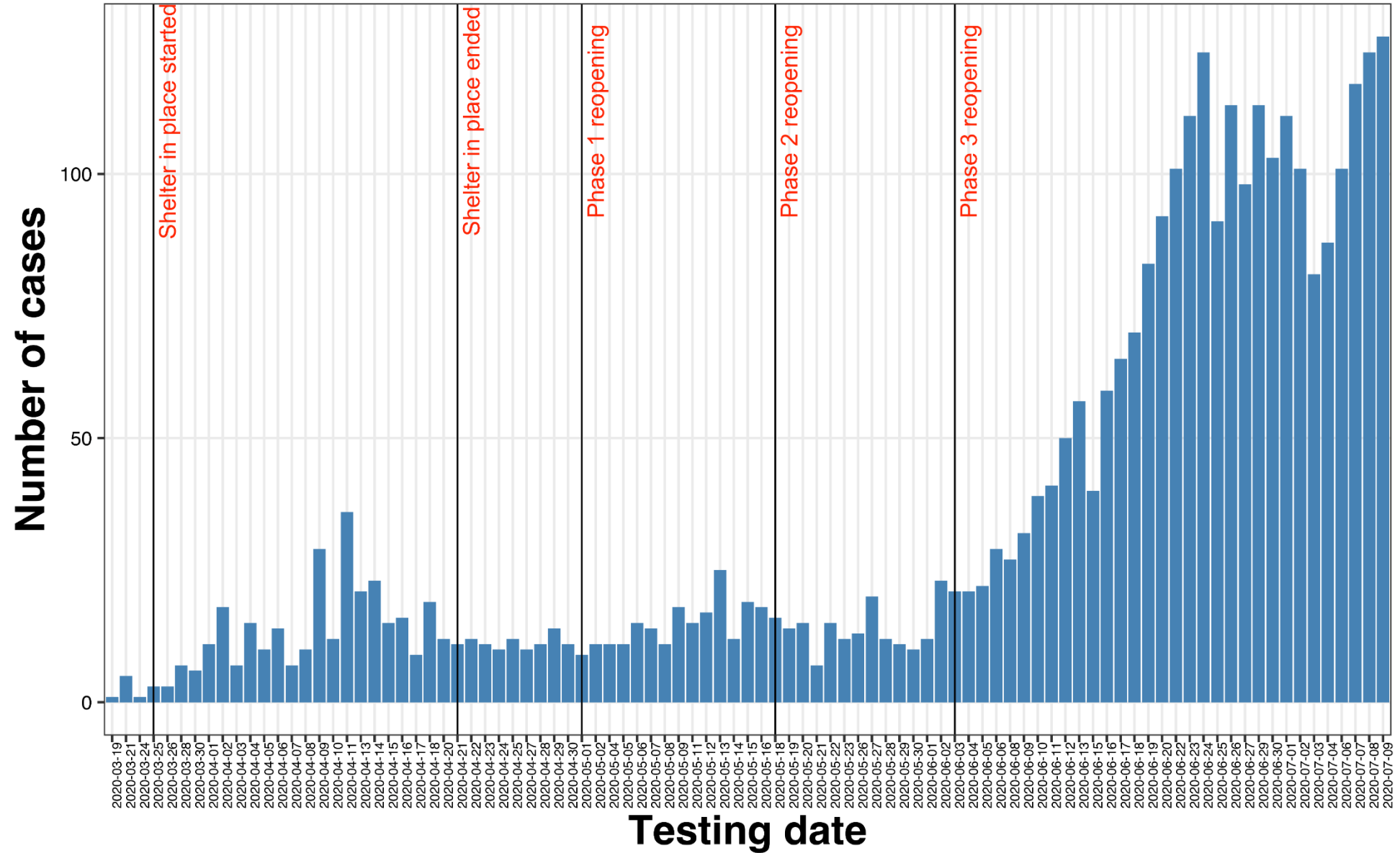


3 families, A B and C, ate lunch at this restaurant on the eve of the Chinese New Year. Individual A1 was already infected. 10 were later found to have SARS-CoV2. This part of the restaurant was poorly ventilated. No one in the rest of the restaurant became infected

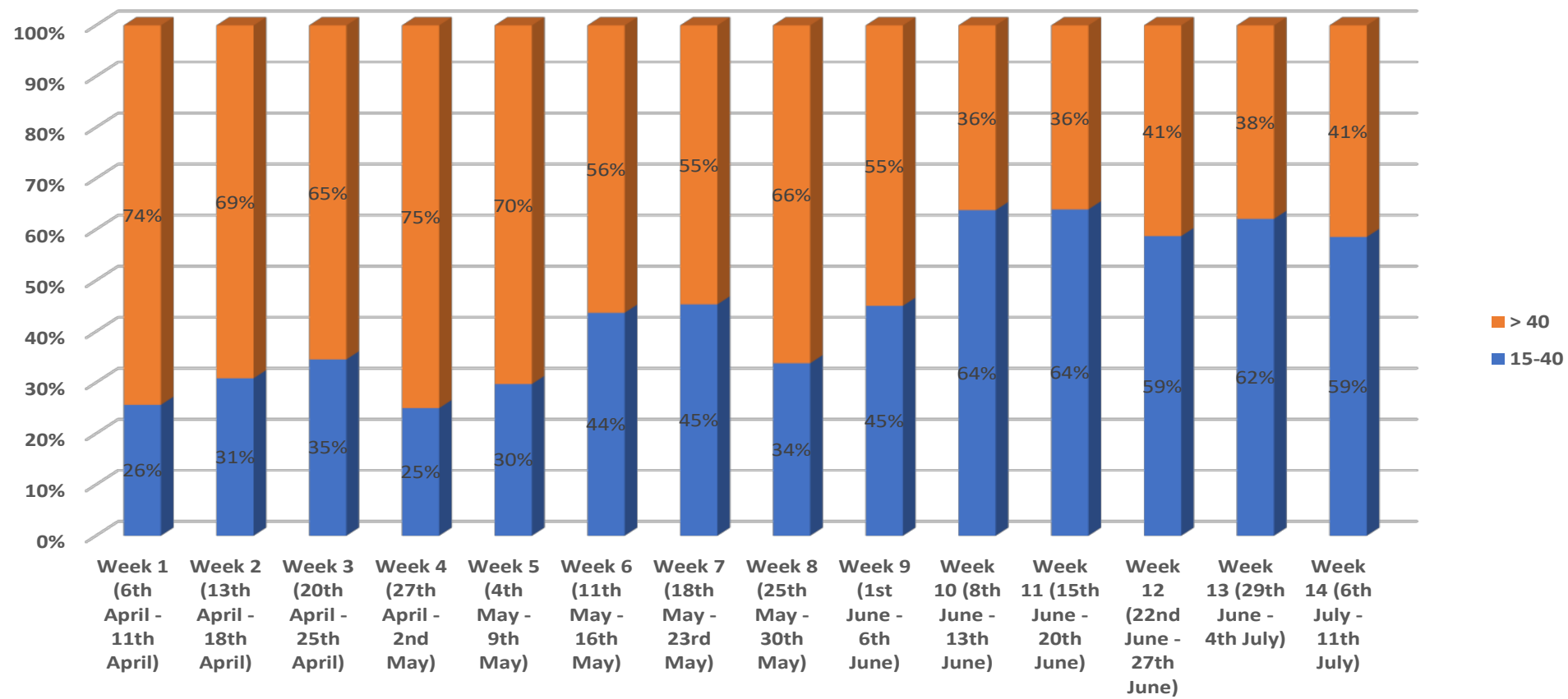


Cameron County Daily Cases of COVID19

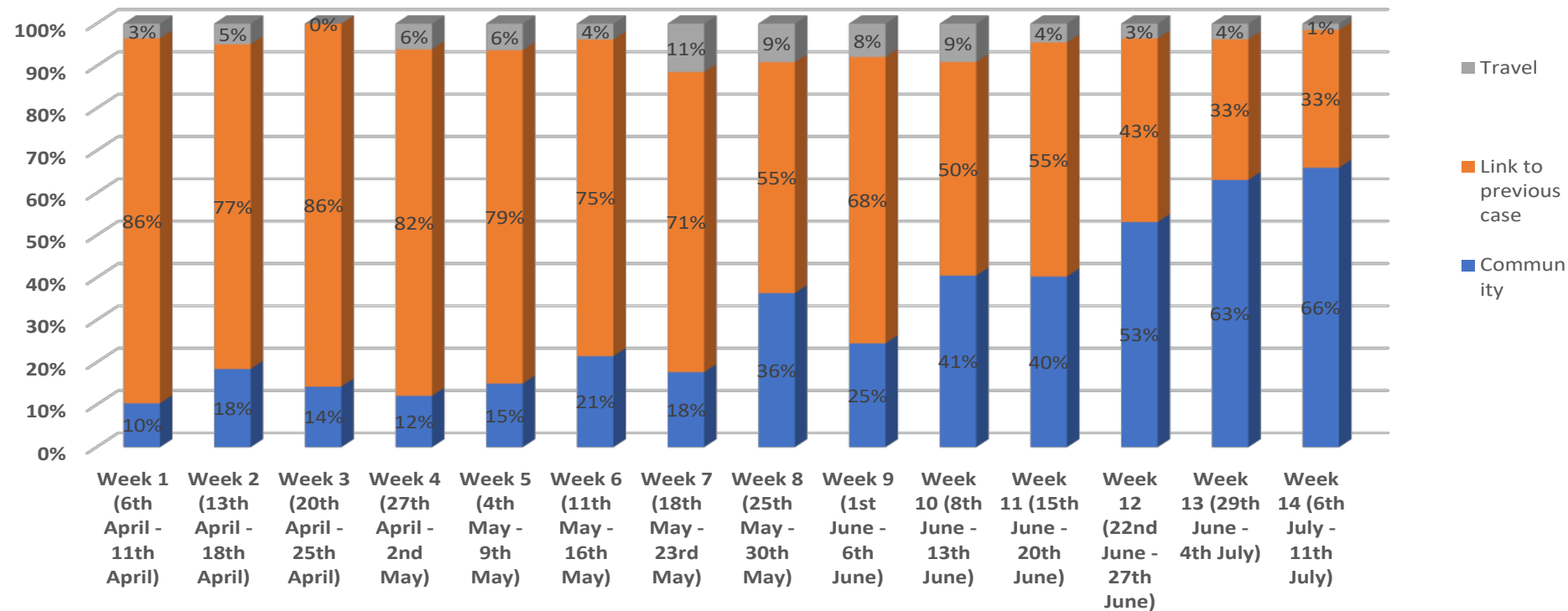
Daily new cases



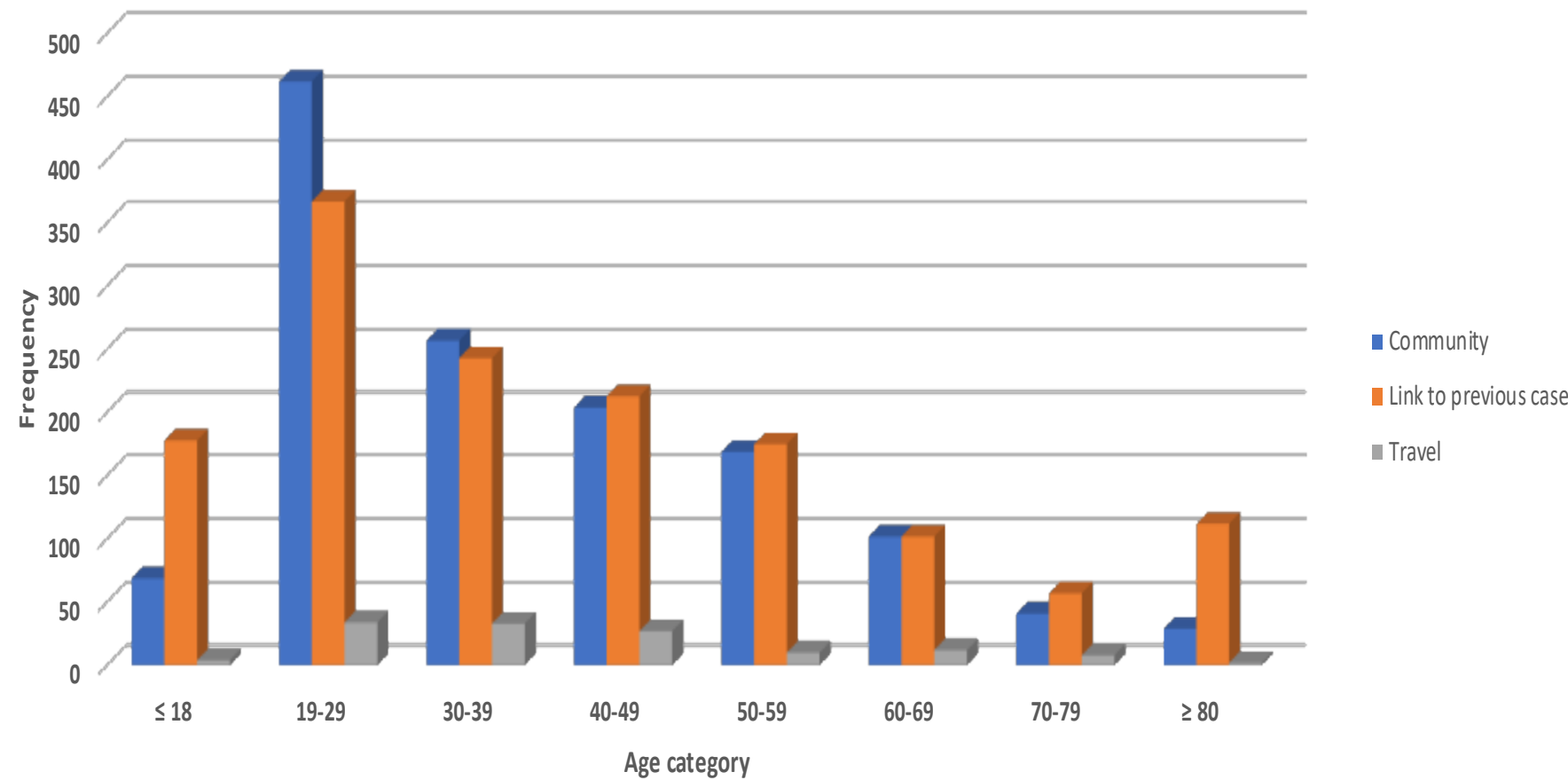
Cameron County COVID-19 Case Report: Percentage of Cases by Age Group per Week



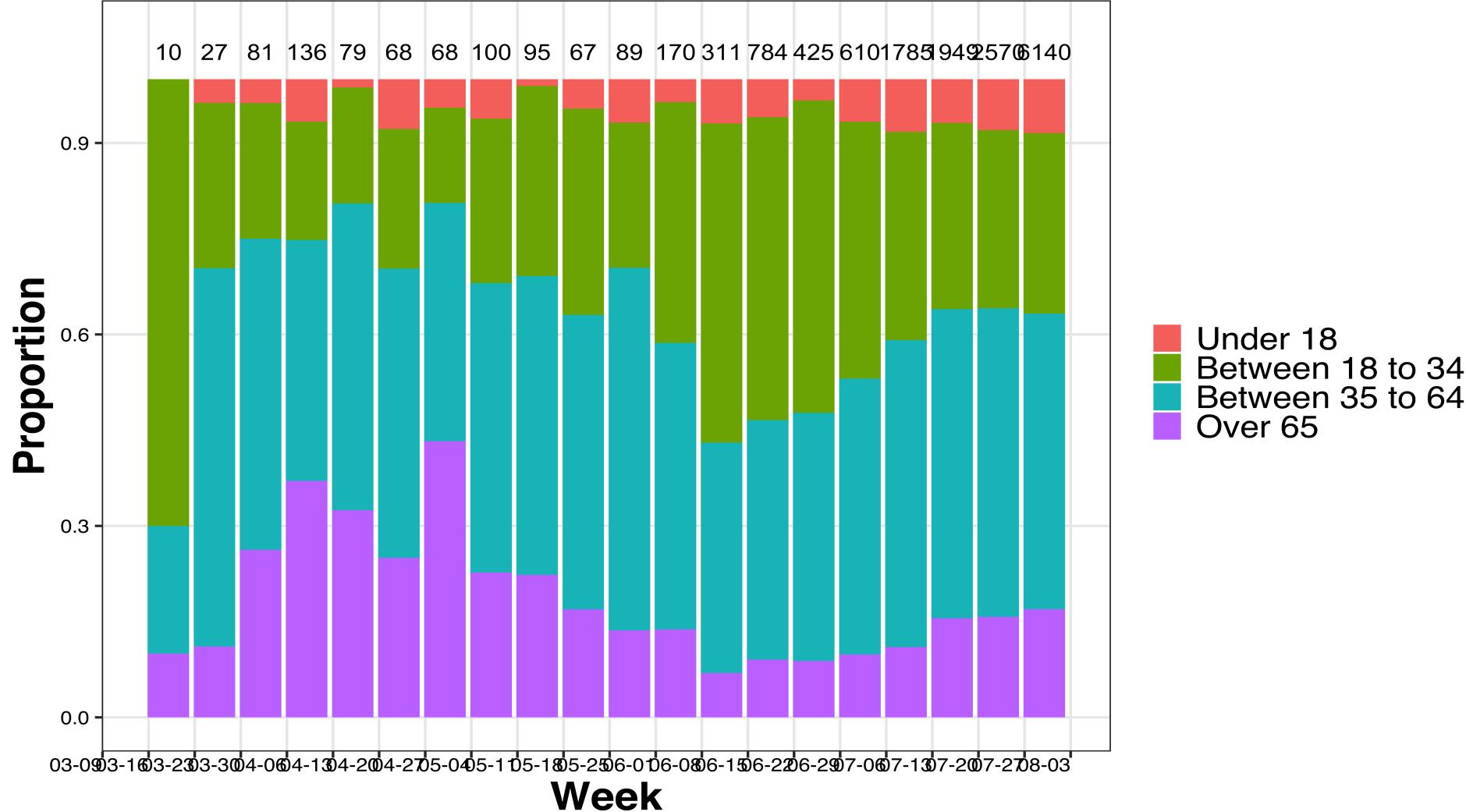
Cameron County COVID-19 Daily Case Reporting: Mode of Disease Spread per Week



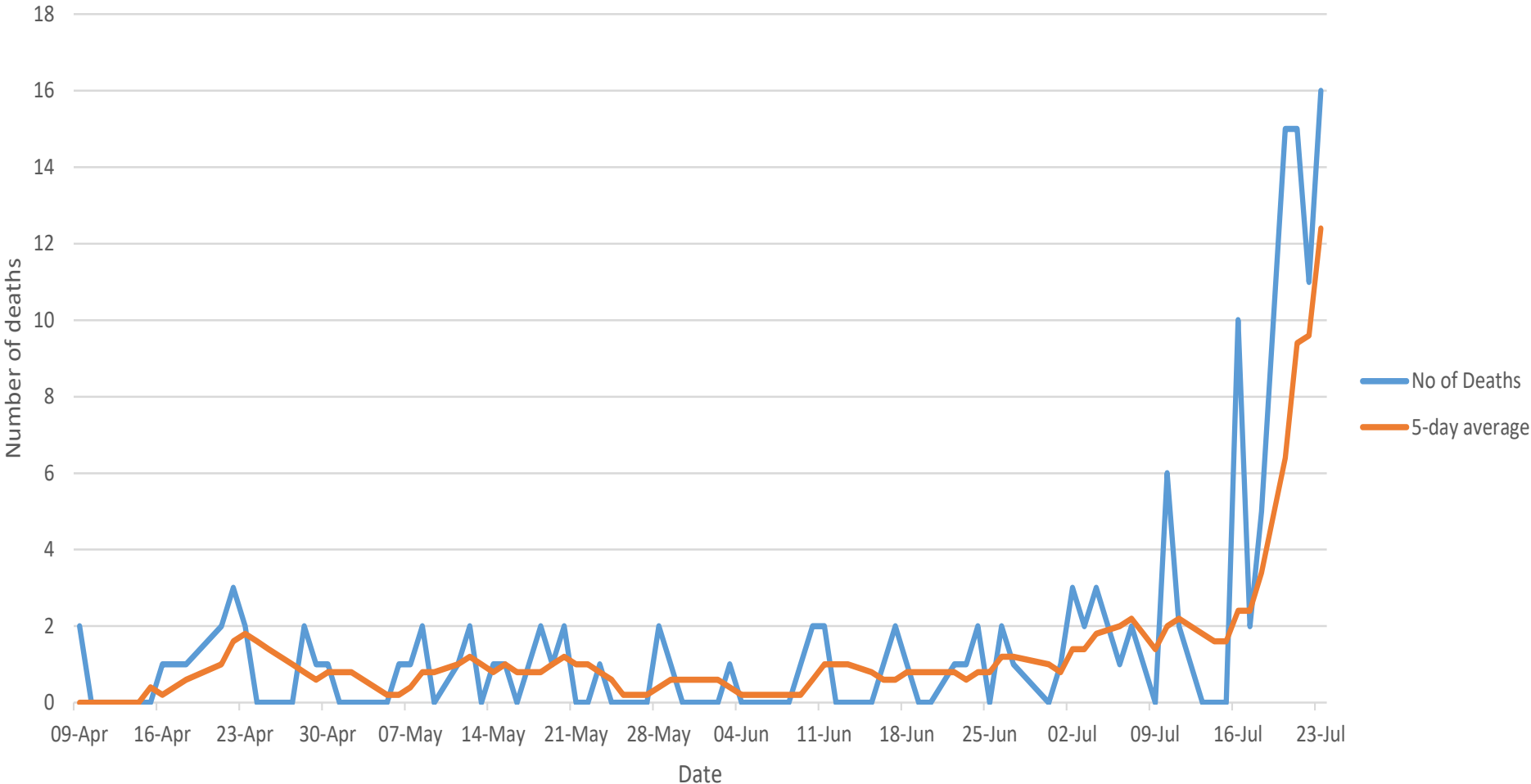
Cameron County COVID-19 Daily Case Report: Age Distribution by Type of Transmission



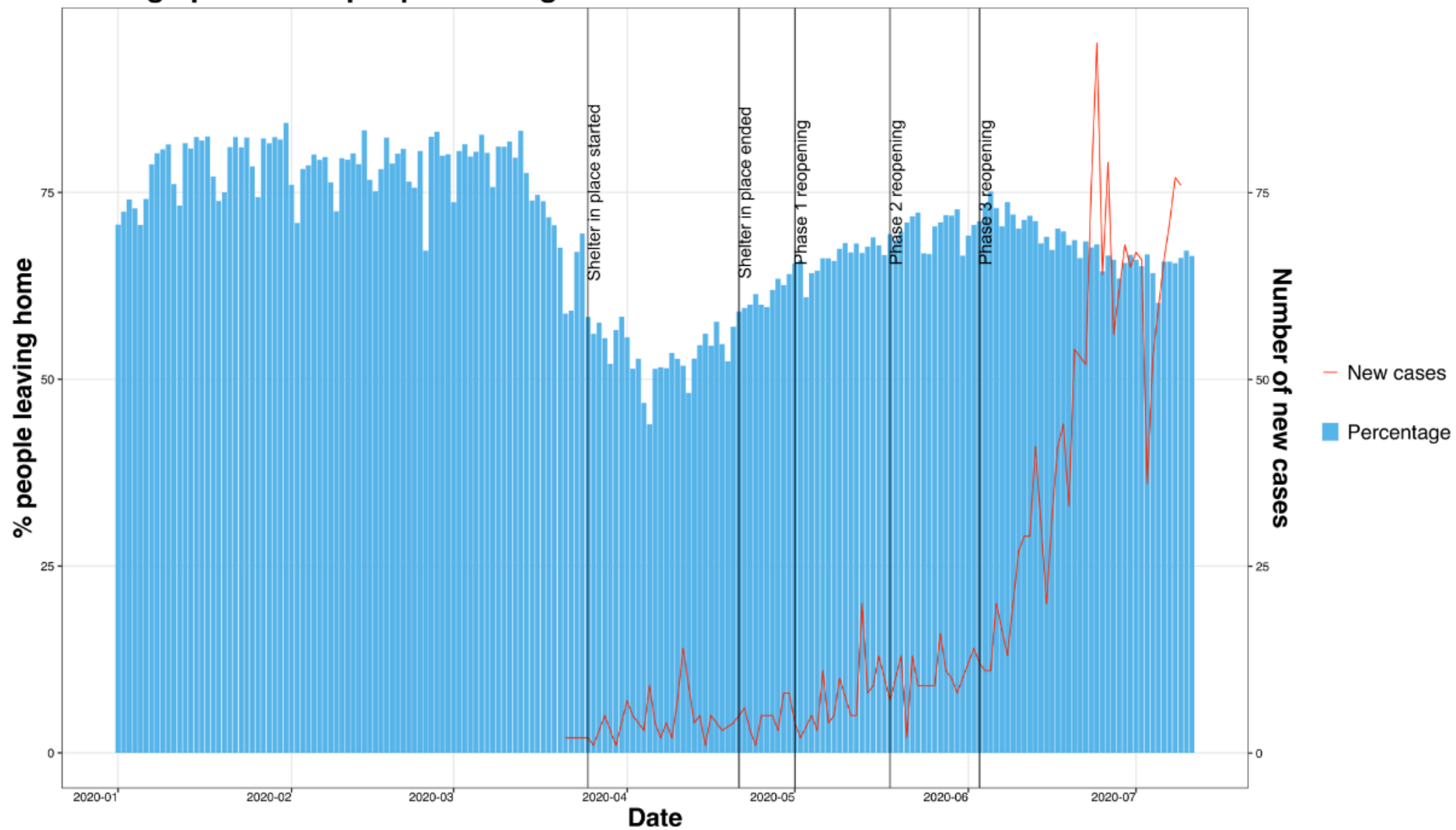
Weekly new cases by age group



Cameron County Covid-19 Related Deaths (9th April - 23rd July)

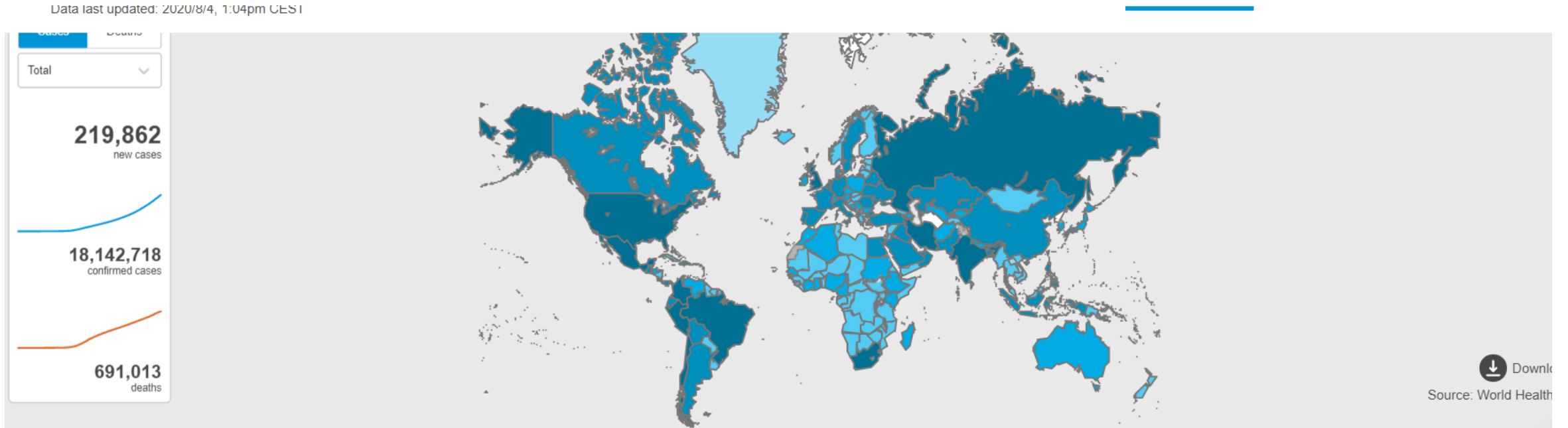


Average percent of people leaving home over time in 2020



EPIDEMIOLOGY

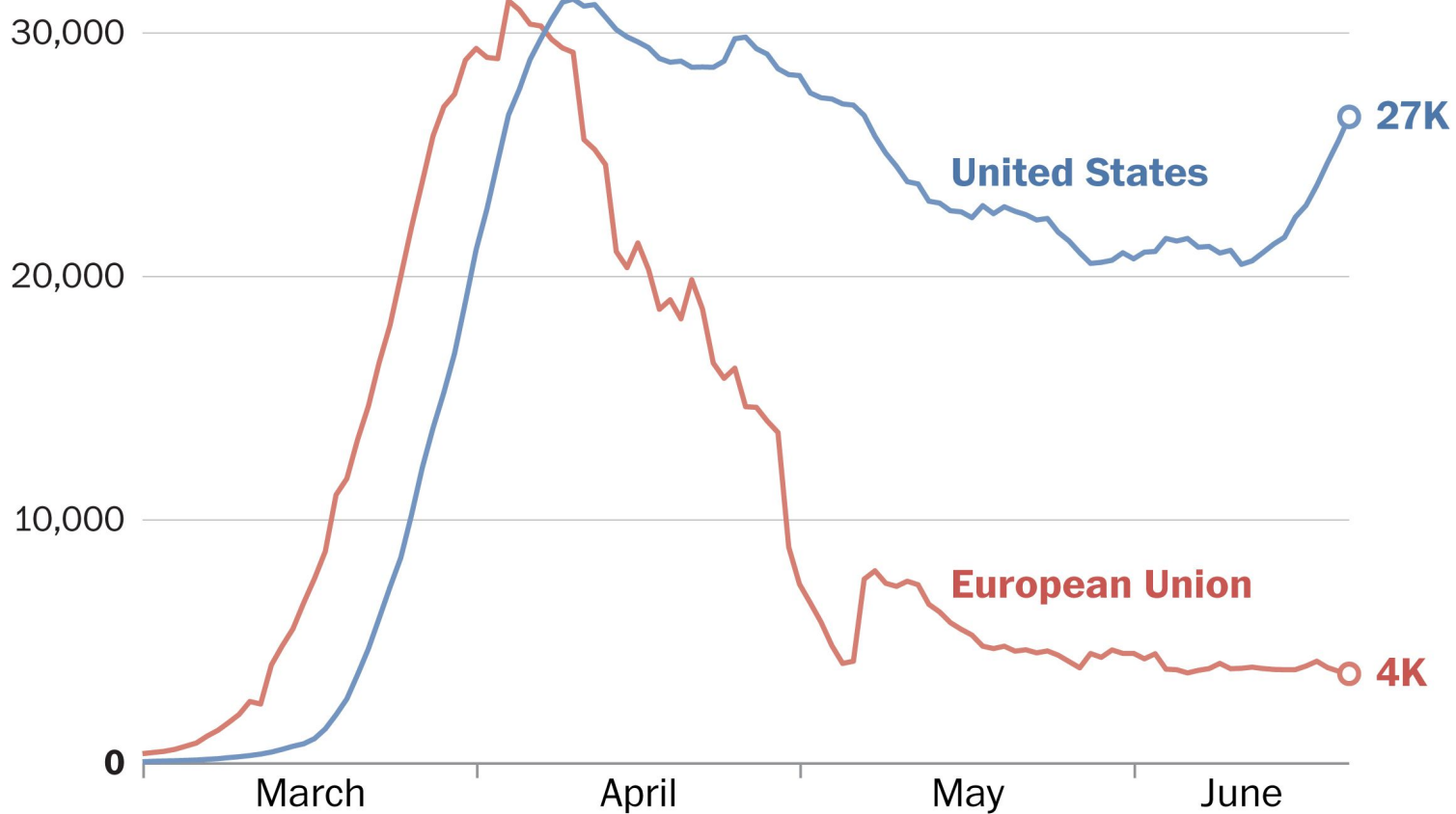
GLOBAL OVERVIEW: WHO updated August 4



Globally, as of **1:04pm CEST, 4 August 2020**, there have been **18,142,718 confirmed cases** of COVID-19, including **691,013 deaths**, reported to WHO.

Coronavirus cases in the United States have not fallen as much as in the European Union

Seven-day rolling average of new coronavirus cases, March 1 to June 21



Pop 330 million

Pop 446 million

Source: Johns Hopkins University

HARRY STEVENS/THE WASHINGTON POST

Infections by Country

(million)

2.0

US has 4% of world population
But 25% of cases and 22.4% of deaths

United States

1.5

1.0

0.5

0

3/7 3/14 3/21 3/28 4/4 4/11 4/18 4/25 5/2 5/9 5/16 5/23 5/30 6/6

Populations

China	1.4 billion
US	330 million
Brazil	210 million
Russia	145 million
Japan	127 million
Italy	60 million

Brazil

Russia

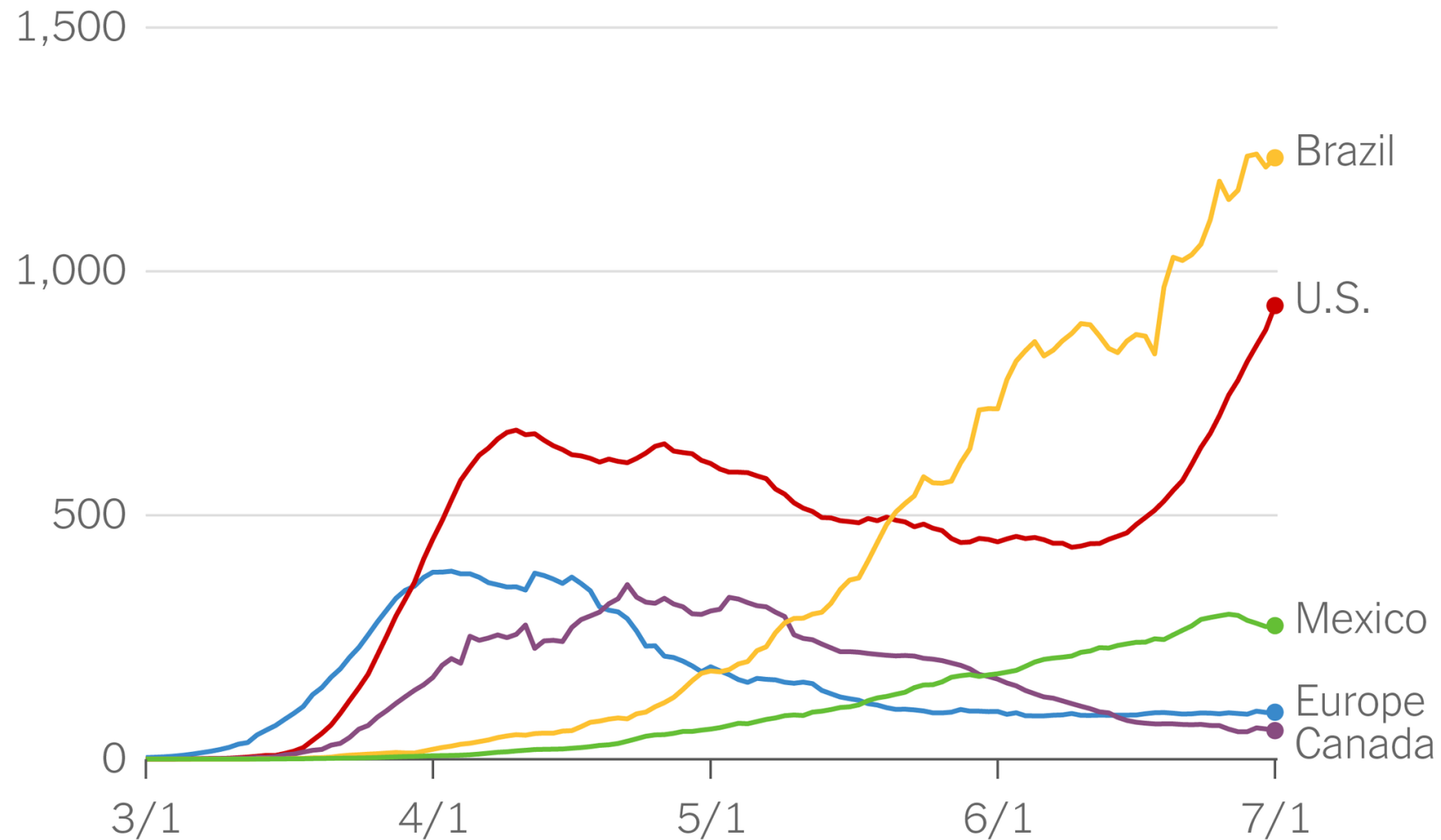
Italy

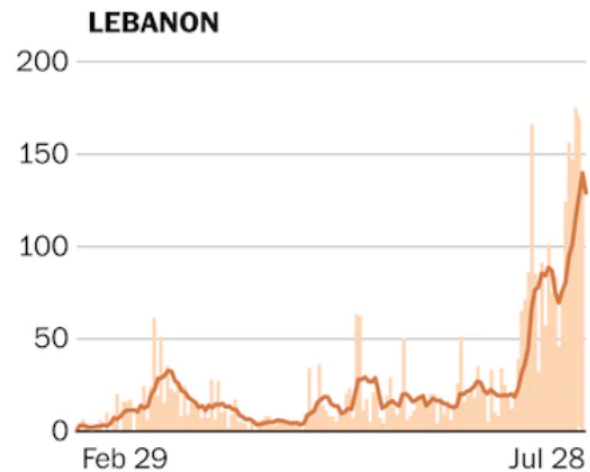
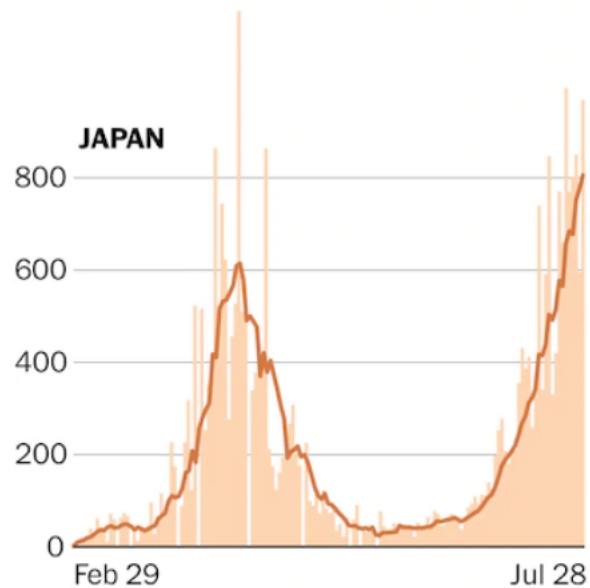
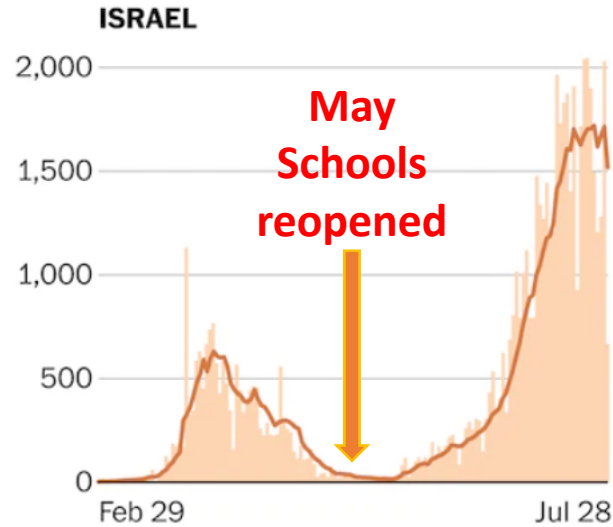
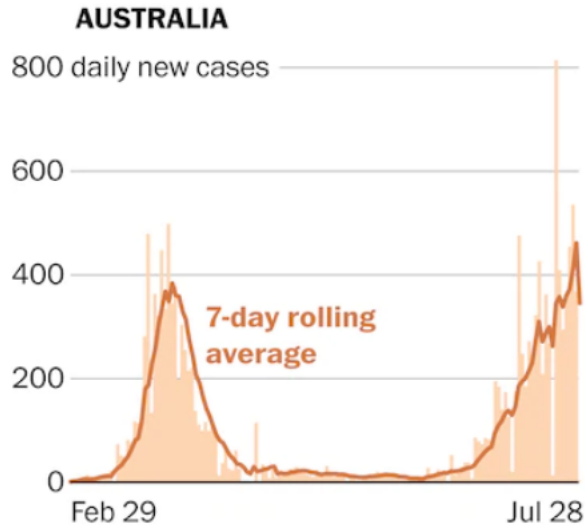
China

Japan

Created by *Nippon.com* based on data from the Ministry of Health,
Labor, and Welfare. Dates are for MHLW announcements.

New coronavirus cases each week, per one million residents





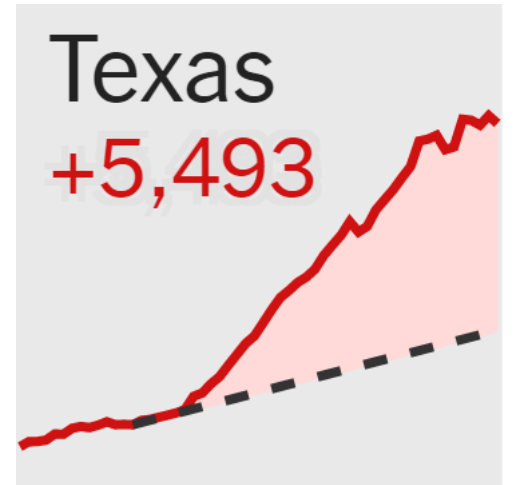
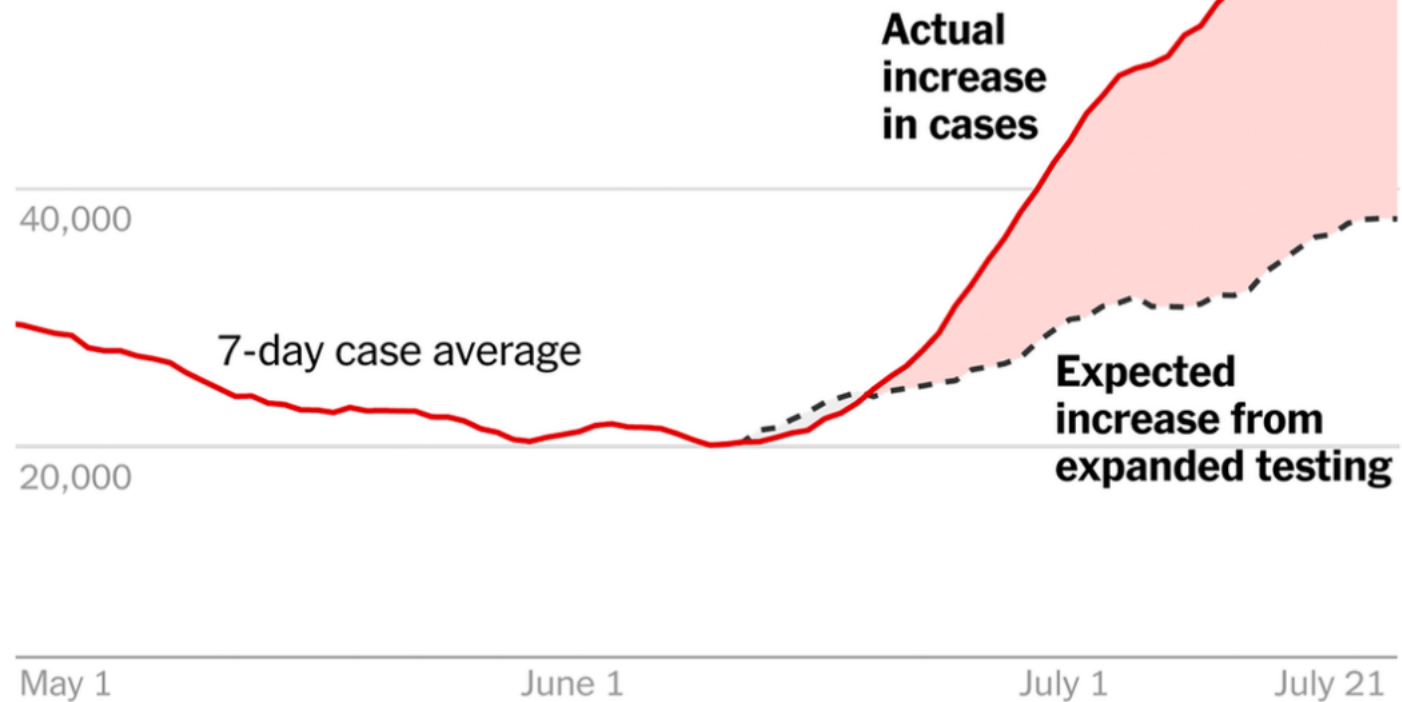
In countries that had the virus under 'control' it is making a comeback

Predictions for the fall when influenza joins the fray are not good.

New York Times July 22, 2020

How Virus Cases Compare With Expectations

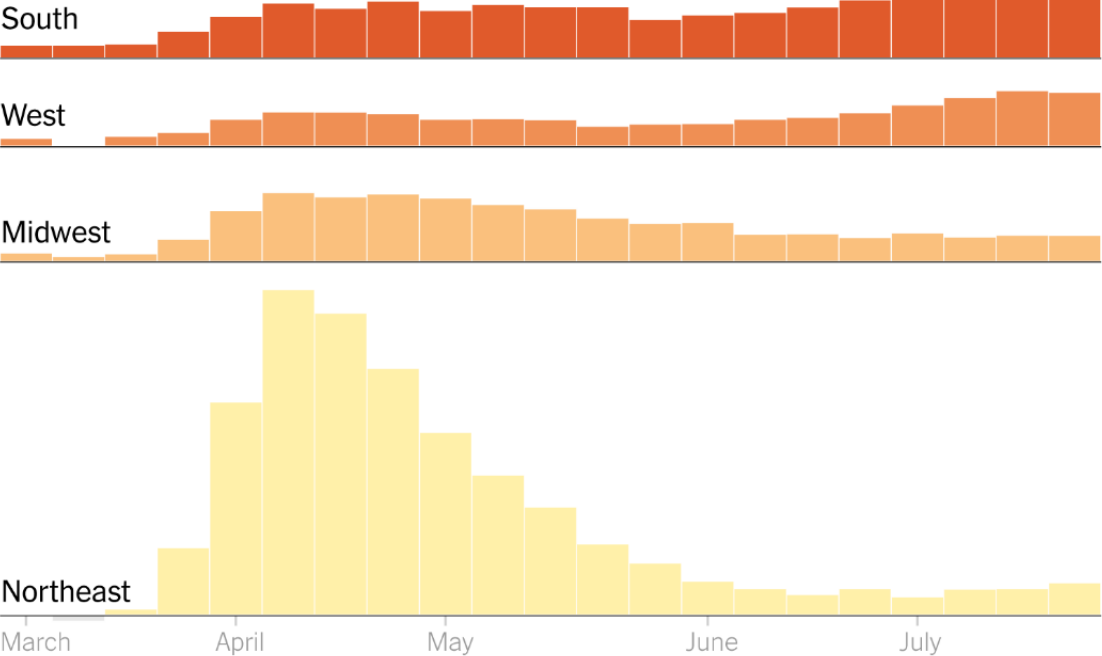
60,000 cases per day



**If Texas were a country
It would have the 6th
Highest Cases
in the world**

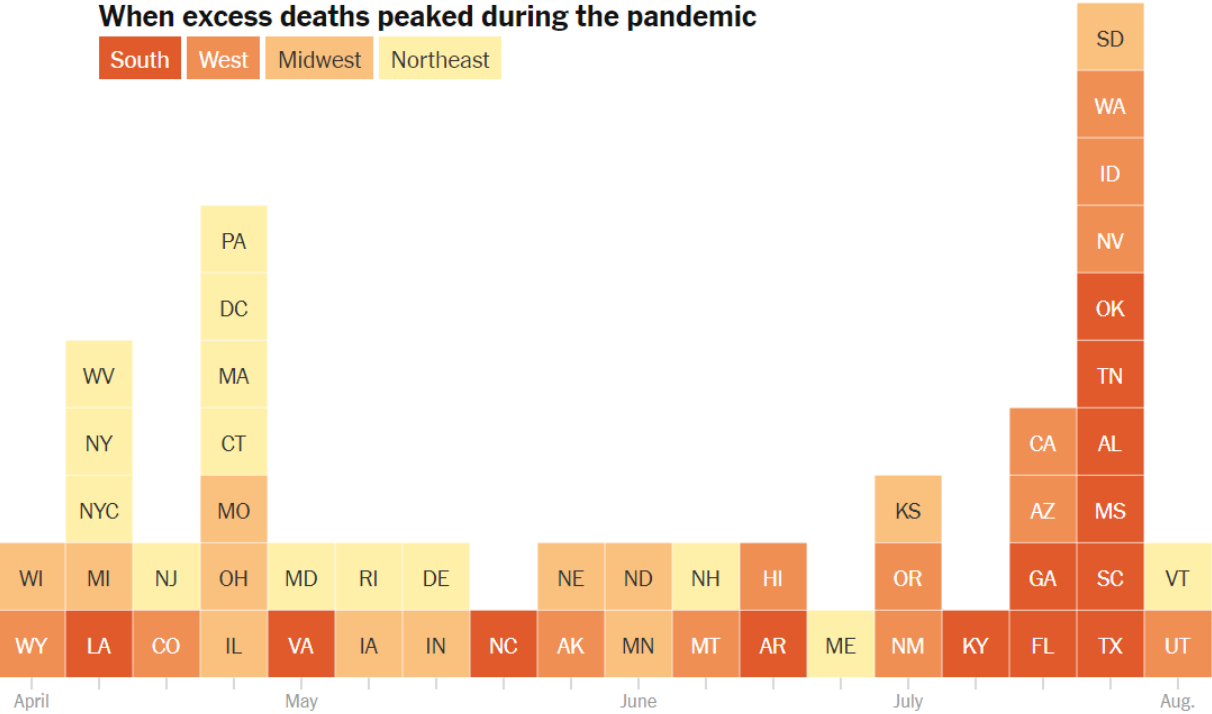
However, excess deaths suggest that the real numbers may already be over
200,000 nationally
NYT August 13

Estimated deaths above normal



When excess deaths peaked during the pandemic

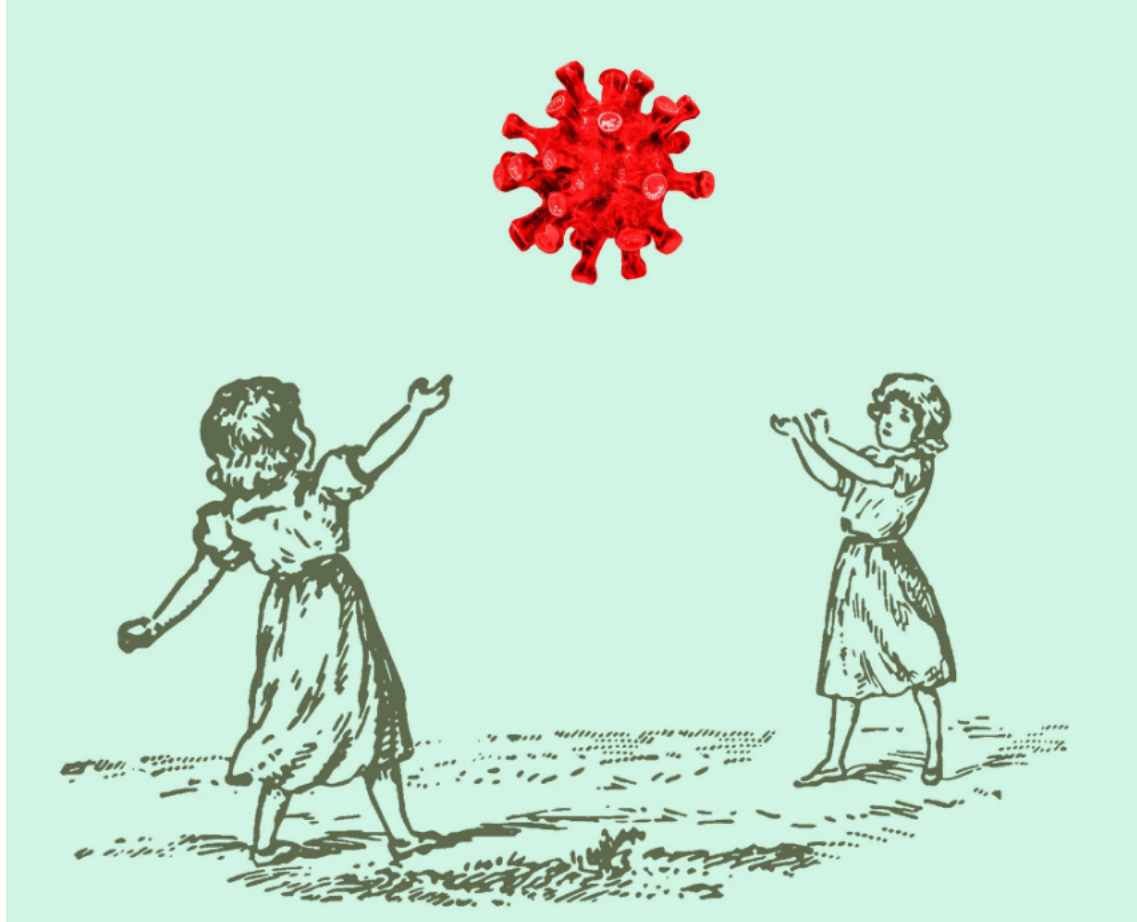
South West Midwest Northeast



Death per 100K population and case fatality in selected countries

COUNTRY	CONFIRMED	DEATHS	CASE-FATALITY	DEATHS/100K POP.
Belgium	70,314	9,850	14.0%	86.24
United Kingdom	307,251	46,295	15.1%	69.63
Spain	297,054	28,472	9.6%	60.94
Italy	248,229	35,166	14.2%	58.19
Sweden	81,012	5,744	7.1%	56.41
US	4,713,540	155,402	3.3%	47.50
Brazil	2,750,318	94,665	3.4%	45.19
France	225,198	30,268	13.4%	45.18
Mexico	443,813	48,012	10.8%	38.05

Should Schools Reopen and When?



SARS-CoV-2 transmission and infections among attendees of an overnight camps: MMWR July 31

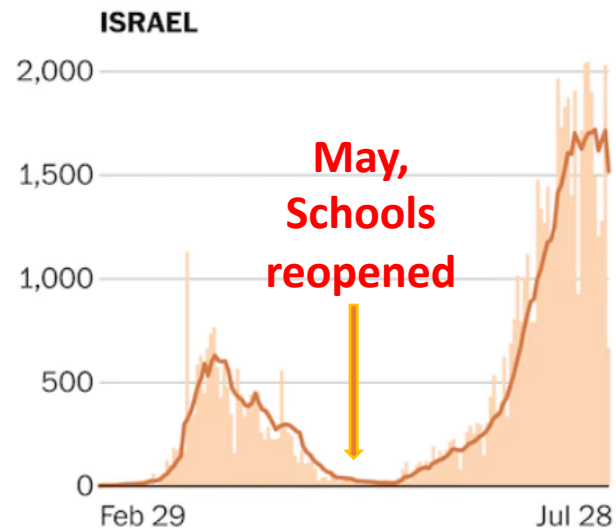
- **During 17 to 20th**
 - **138 trainees and 120 staff members all documented SARS-CoV-2 negative 2 days prior to arrival, media age 17 years**
- **597 Georgia residents attended, median age 12**
 - **Average 15 per cabin**
- **One adolescent became ill and was positive**
- **260/344 available tests were positive**

Age group (yrs.)	No	No positive	Attack rate %
6-10	100	51	51
11-17	409	180	44
18-21	81	27	33
22-59	7	2	29

Auger, K.A. et al, JAMA July 29

In this US population-based time series analysis conducted between March 9, 2020, and May 7, 2020, school closure was associated with a significant decline in both incidence of COVID-19 (adjusted relative change per week, -62%) and mortality (adjusted relative change per week, -58%).

In a model derived from this analysis, it was estimated that closing schools when the cumulative incidence of COVID-19 was in the lowest quartile compared with the highest quartile was associated with 128.7 fewer cases per 100 000 population over 26 days and with 1.5 fewer deaths per 100 000 population over 16 days.



Contact Tracing during Coronavirus Disease Outbreak, South Korea, 2020

- **Detected COVID-19 in 11.8% of household contacts; rates were higher for contacts of children than adults.**
- **The highest COVID-19 rate (18.6%) was for household contacts of school-aged children**
- **The lowest (5.3%) for household contacts of children 0–9 years in mid school closure.**
- **A contact survey in Wuhan and Shanghai, China, showed school closure and social distancing significantly reduced the rate of COVID-19 among contacts of school-aged children.**
- **For seasonal influenza, the highest secondary attack rate occurs among young children.**
- **Children who attend day care or school also are at high risk for transmitting respiratory viruses to household members.**
- **The low detection rate for household contacts of preschool-aged children in South Korea might be attributable to social distancing during these periods.**
- **a recent report from Shenzhen, China, showed that the proportion of infected children increased during the outbreak from 2% to 13%, suggesting the importance of school closure**

Schools should reopen only when the transmission in the community is under reasonable control

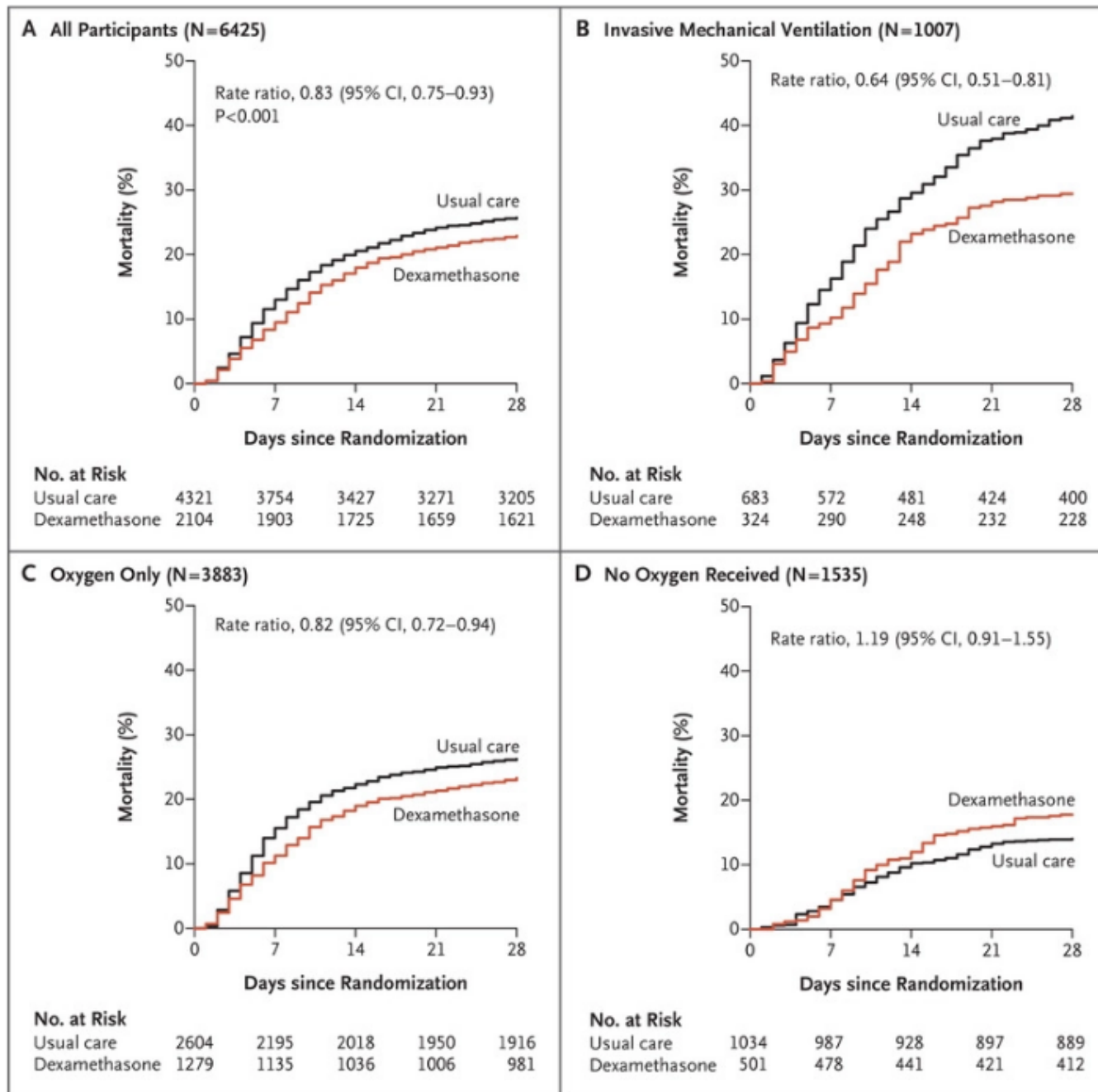
TREATMENT

DEXAMETHASONE

- **Well established drug**
- **Dampens over reactive immune response to the virus**
- **Reduces 28-day mortality**

RECOVERY TRIAL (NEJM July 17 20):

- **Performed in 176 NHS institutions in the UK
by Nuffield Department of Population Health at Oxford University**
- **9355 patients randomized: 2104 dexamethasone, 4321 usual care**
- **Mean age 66.1, 24% diabetes, 27% heart disease, 21% lung disease**
- **Mortality significantly lower on dexamethasone (RR 0.83)**
- **Patients on dexamethasone had shorter duration of hospitalization**
- **Patient on dexamethasone had lower mortality, particularly those ventilated (RR 0.92).**
- **Patients on dexamethasone less likely to need ventilation (RR 0.77)**



Mortality at 28 days according to respiratory support at randomization

- A: All participants**
- B: Invasive mechanical ventilation**
- C: Oxygen only**
- D: No oxygen**

Conclusions:

- **Dexamethasone reduces 28-day mortality in patients on respiratory support**
- **No benefit and possibility of harm in patients not requiring oxygen**
- **Dexamethasone is on WHO list of essential medicines**

REMDESIVIR

- **GS-5734: inhibitor of viral RNA-dependent RNA polymerase**
- **Reduced lung virus levels and lung damage**
- **Antiviral active against SARS-CoV-2**
- **Probably most effective given **early in disease****
- **Adaptive Covid-19 Treatment Trial (ACTT-1)**
- ***Beigel et al. NEJM, May 22. 2020***
 - **1063 patients, randomized: 538 Remdesivir, 521 placebo.**
 - **Multisite international study: 60 trial sites,**
 - **Mean age 59, multiracial, many with pre-existing conditions**
 - **Intravenous delivery**
 - **Time to recovery: 11 days remdesivir, 15 days placebo (RR1.32)**
 - **Mortality by 14 days: 7.1% remdesivir, 11.9% placebo (HR0.70)**
 - **Serious adverse events: 21.1% remdesivir, 27% placebo**
 - **Comment: treatment given late in disease**

estimates of cumulative recoveries with remdesivir treatment

A: Overall

B: Patients not receiving oxygen

C: Patients receiving oxygen

D: Patients receiving high flow oxygen

E: Patients receiving ventilation

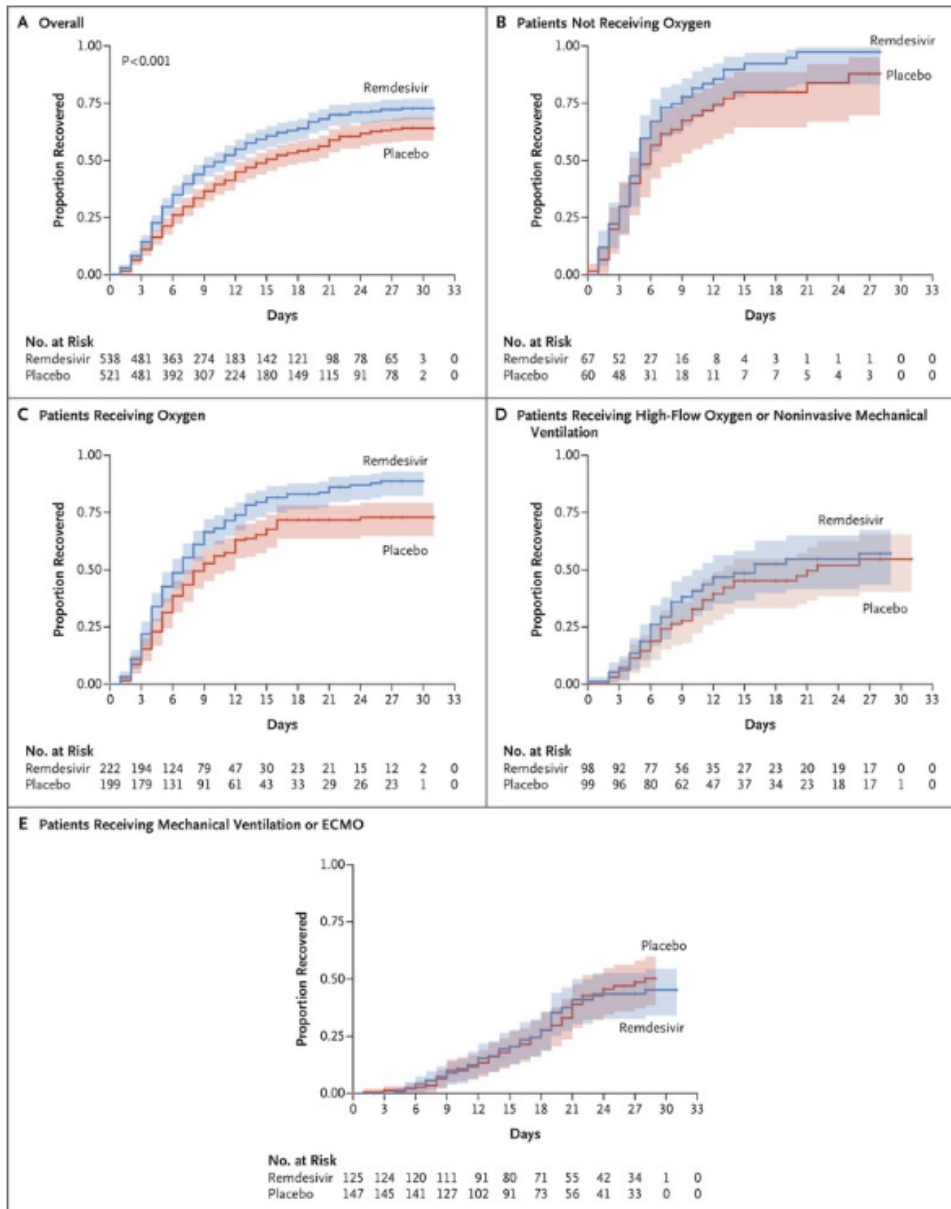
Blue line remdesivir

Red line placebo

Data Safety and Monitoring Board unblinded the study early so that findings could be published

Conclusions

- **Supports use of remdesivir in patients requiring oxygen**
- **Treatment with antiviral alone not sufficient**



Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-3 Month Experience

- **Those who received transfusions within three days of diagnosis had a seven-day death rate of 8.7%**
- **Patients who received plasma after four or more days had a mortality rate of 11.9%. The difference met the standard for statistical significance.**
- **35000 patients in a non-randomized trial with no measure of antibody levels**

PREVENTION

?HERD IMMUNITY

- **When people are infected by coronaviruses that cause cold-like symptoms, they are immune for less than a year.**
- **By contrast, those infected by the original more severe SARS virus, stayed immune for much longer.**
- **If SARS-CoV-2 lies somewhere in the middle, people who recover from their encounters might be protected for a couple of years.**
- **We need data to understand when immune citizens can return to work, care for the vulnerable, and anchor the economy during bouts of social distancing.**
- **We need to anticipate new waves of infection, or ongoing smaller epidemics, like the flu, which, like the poor is always with us.**

PREVENTION OF SPREAD

- **Wear a mask in any public or enclosed space or within 6 feet of anyone outside your family**
- **Quilted cloth masks are comfortable and best short of PPE**
- **Consider your mask a fashion statement or a message.**
- **Wash hands frequently, especially when out of home.**
- **Stay 6 feet from anyone outside your family. (10 feet is better)**
- **Avoid entering any enclosed, ill ventilated spaces e.g. bars**
- **Open windows wherever possible**
- **Protect the elderly and anyone with pre-existing conditions (obesity, heart disease, diabetes or immunosuppressed)**

Masks, masks, masks, masks.....

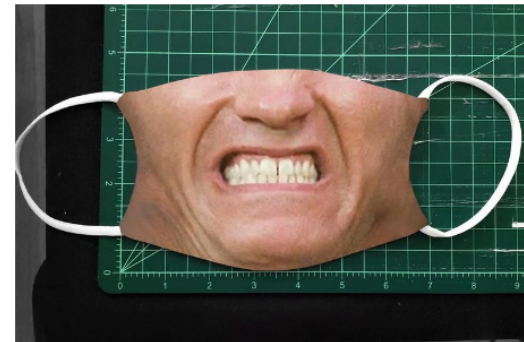


Over 70 Designs
to Choose

- **Masks work!!!!!!**
- **Masks must be worn in crowded and indoor spaces**
- **Not wearing a mask is irresponsible, and disrespectful of others**
- **Masks can be a fashion statement**
- **Balenciaga, Gucci and Yves St Laurent will be making masks. Expensive ones**

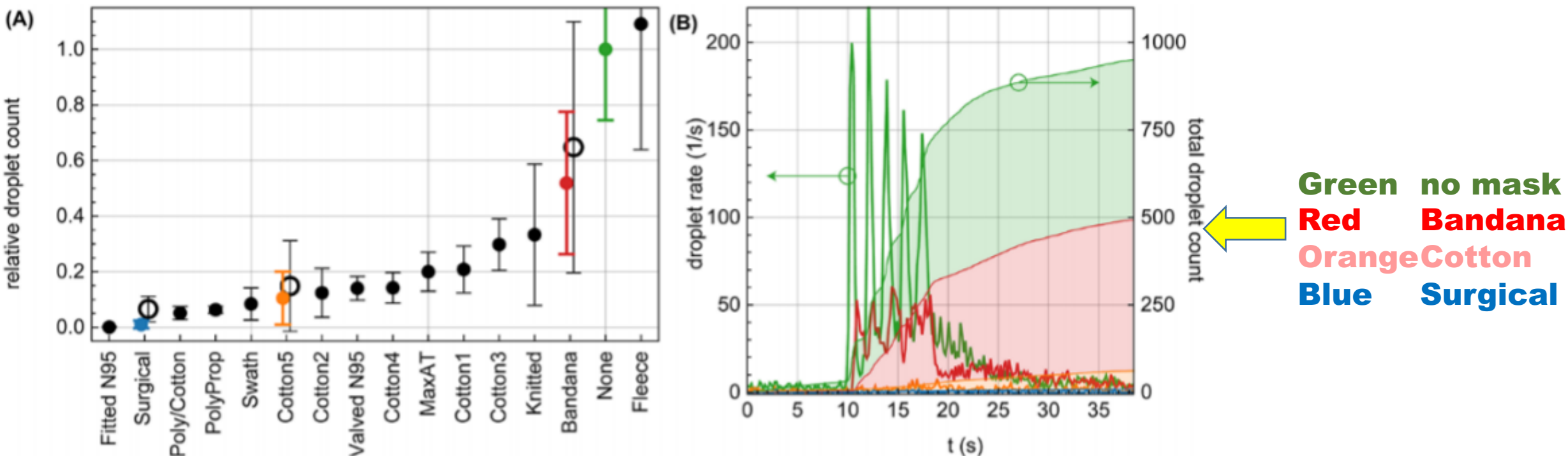


Balenciaga \$\$\$\$



Humor ????



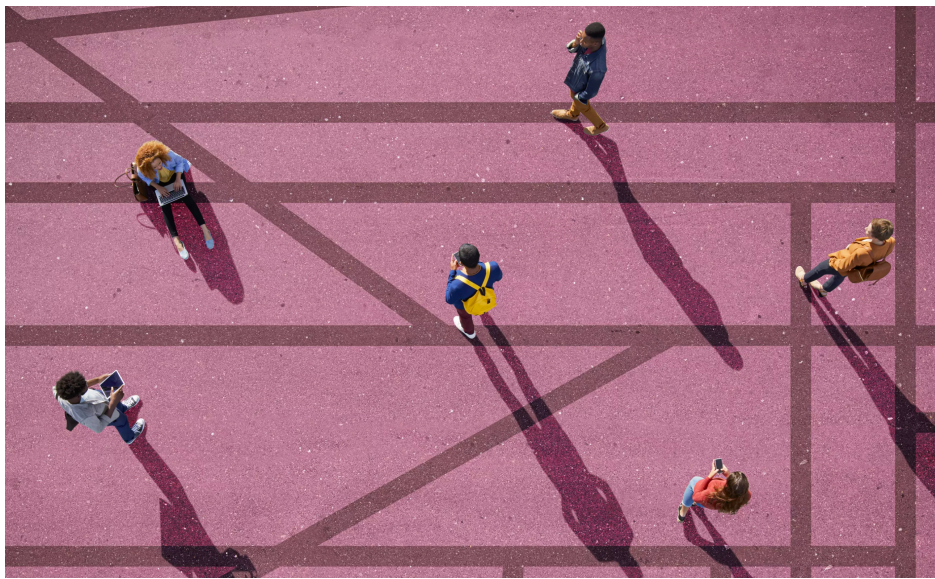


Low-cost measurement of facemask efficacy for filtering expelled droplets during speech

Emma P. Fischer¹, Martin C. Fischer^{2,3,*}, David Grass², Isaac Henrion⁴, Warren S. Warren^{2,3,5,6}, and Eric Vestman⁷

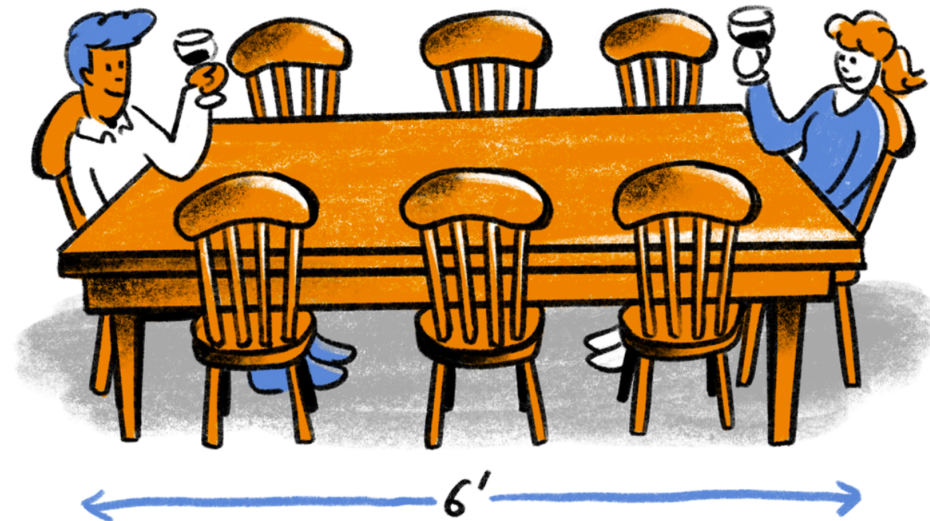
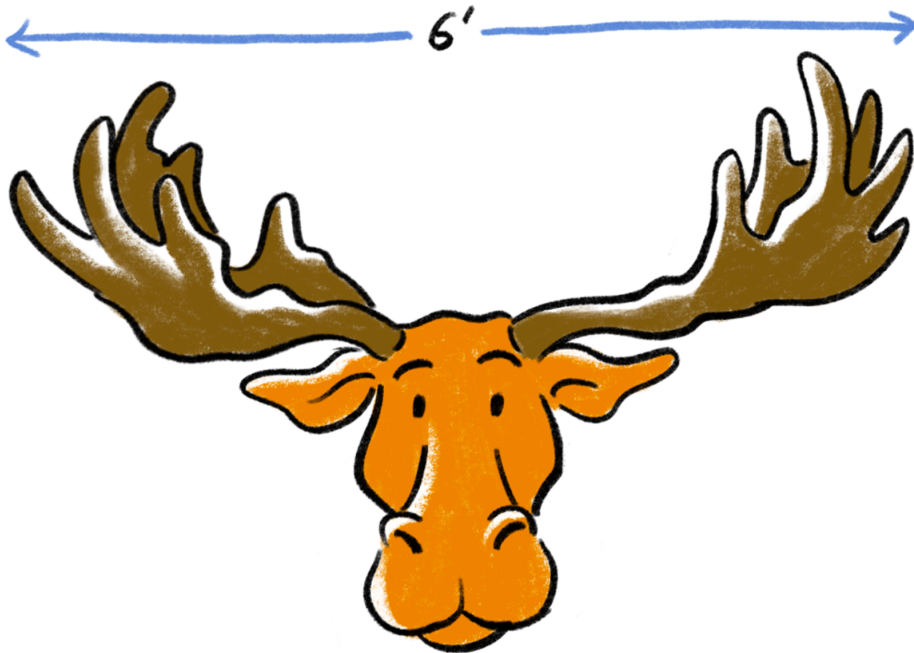
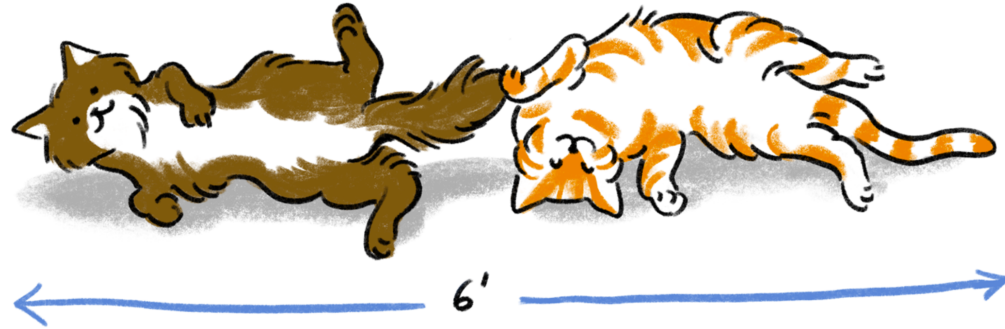
Fig. 3. Droplet transmission through face masks. **(A)** Relative droplet transmission through the corresponding mask. Each solid data point represents the mean and standard deviation over 10 trials for the same mask, normalized to the control trial (no mask), and tested by one speaker. The hollow data points are the mean and standard deviations of the relative counts over four speakers. A plot with a logarithmic scale is shown in Supplementary Fig. S1. **(B)** The time evolution of the droplet count (left axis) is shown for representative examples, marked with the corresponding color in (A): No mask (green), Bandana (red), cotton mask (orange), and surgical (blue – not visible on this scale). The cumulative droplet count for these cases is also shown (right axis).





SOCIAL DISTANCING ALSO WORKS

GUIDE TO SOCIAL DISTANCING



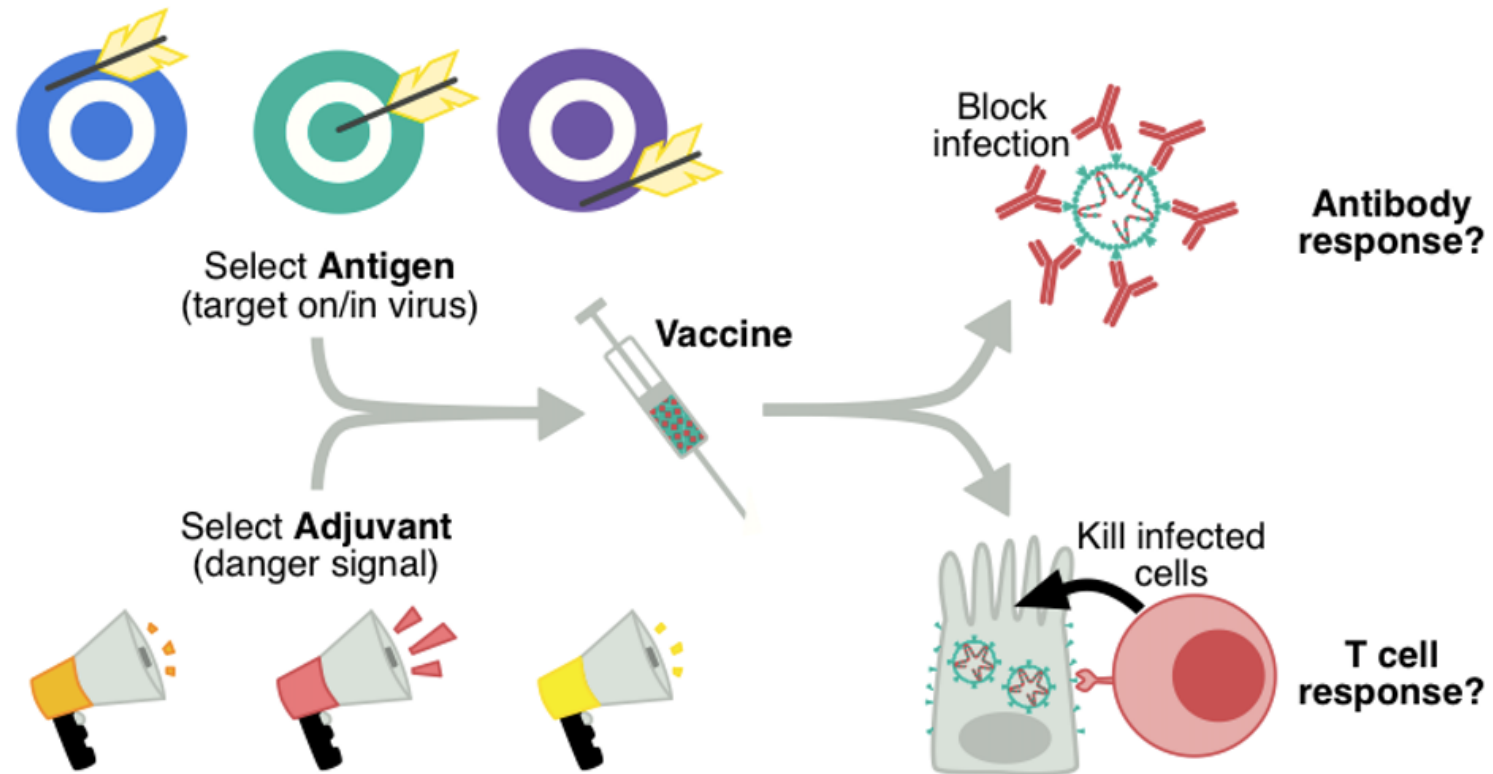
Resistance is not new either: 19th Century York cholera and flu

Libertarians battled almost every step. Some fought sewers and water mains being dug through their properties, arguing that they owned perfectly good wells and cesspools. Some refused smallpox vaccines until the Supreme Court put an end to that in 1905, in [Jacobson v. Massachusetts](#).

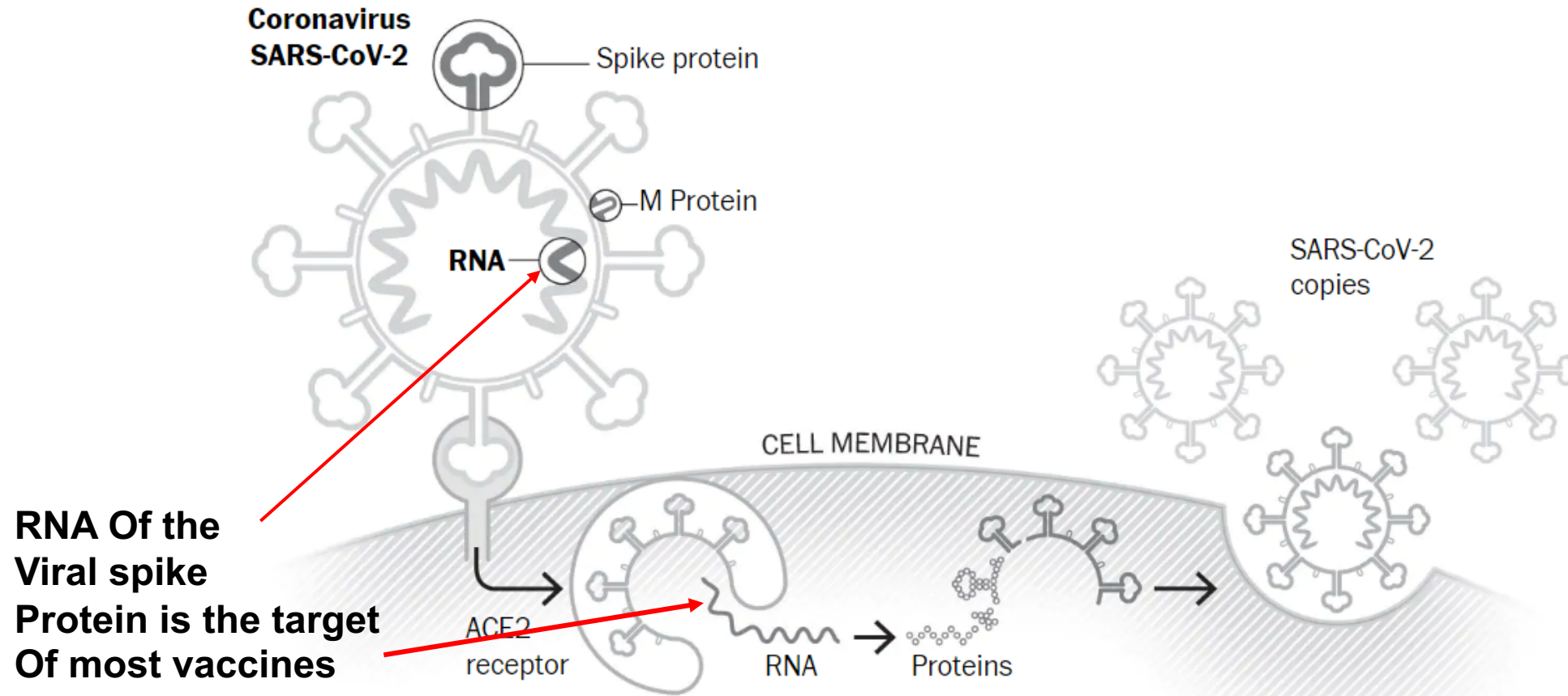
In the Spanish flu epidemic of 1918, many New Yorkers donned masks but 4,000 San Franciscans formed an Anti-Mask League. (The city's mayor, James Rolph, [was fined \\$50](#) for flouting his own health department's mask order.) Slowly, science prevailed, and death rates went down.

Vaccines

Principles of the immune response



Virus Targets for Vaccine development



SARS-CoV-2 uses its spike to bind to the ACE2 receptor, allowing access into the cell.

The virus's RNA is released into the cell. The cell reads the RNA and makes proteins.

The viral proteins are then assembled into new copies of the virus.

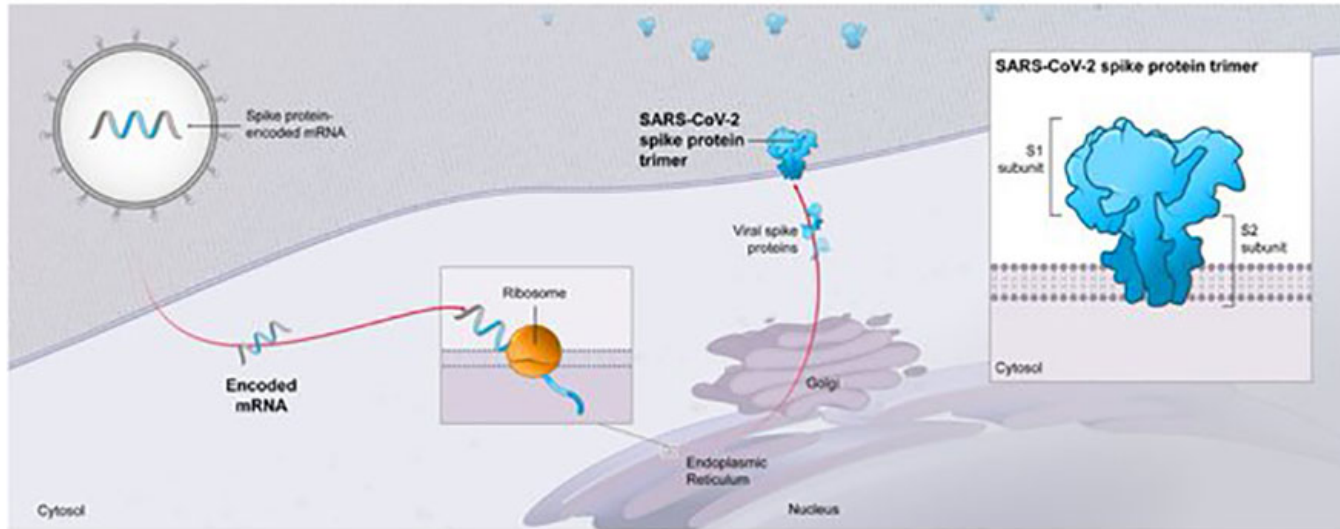
The copies are released and go on to infect more cells.

Washington Post august 13 2020

Moderna vaccine now in Phase Three Trial in US

SARS-CoV-2 vaccine (mRNA-1273)

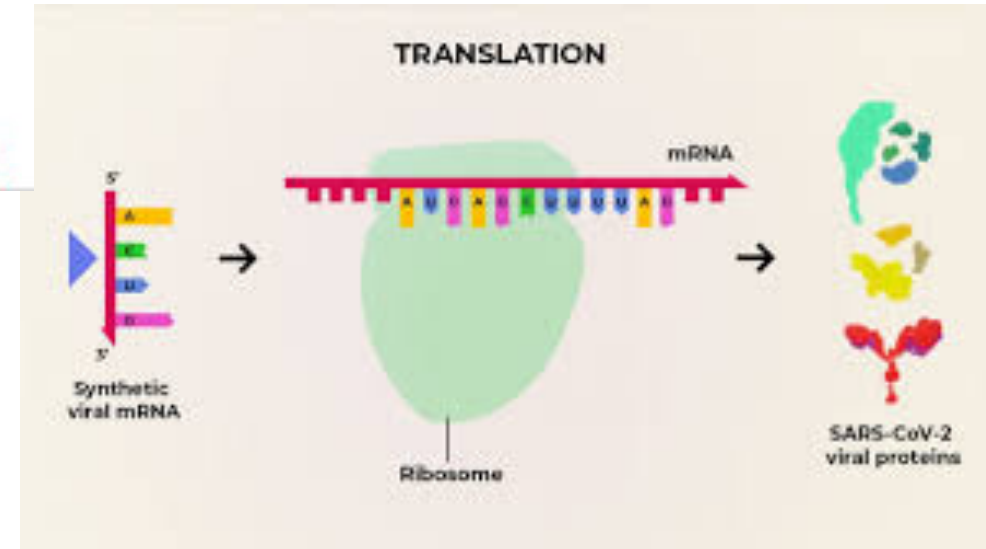
Encodes for the full spike S protein



Slide 171

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moderna



Moderna COVID-19 experimental mRNA vaccine: mRNA-1273

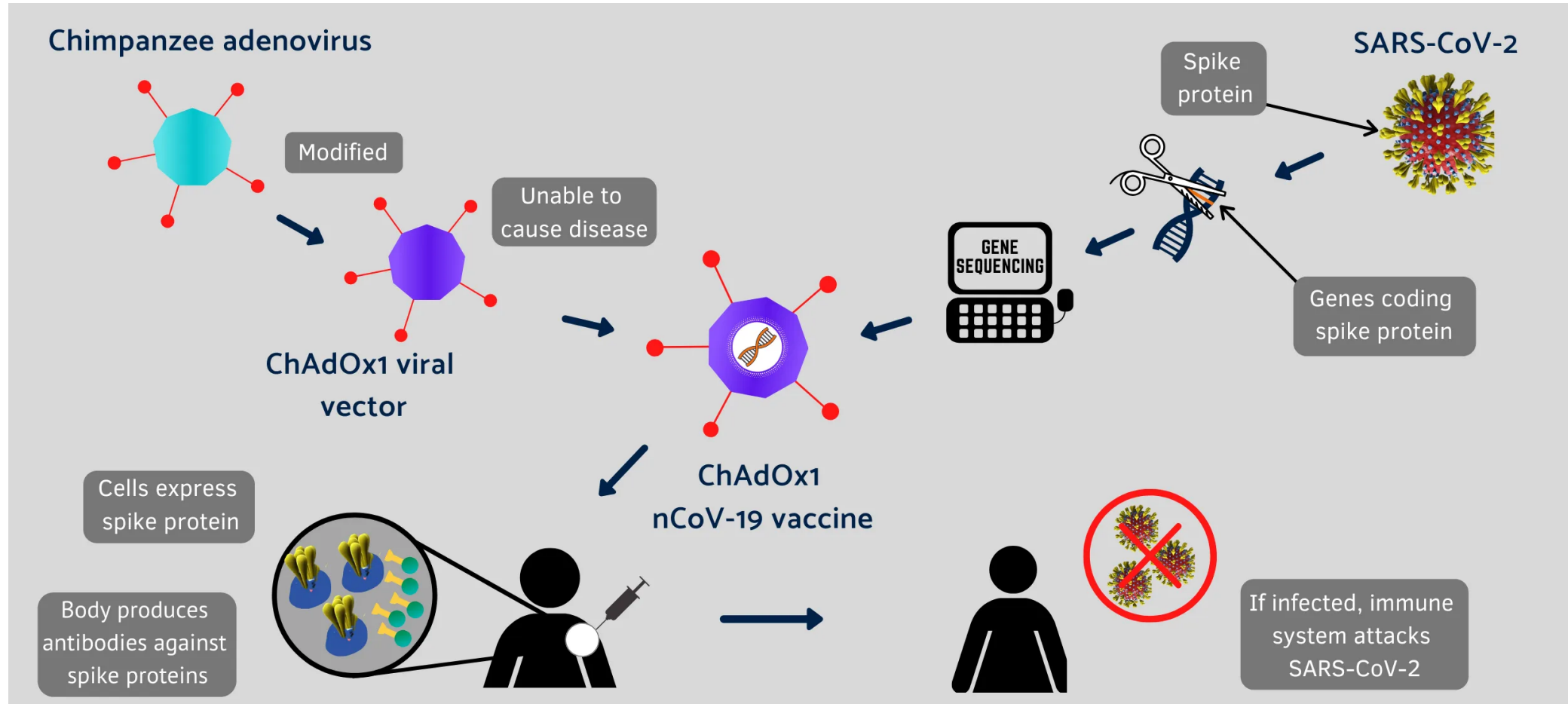
Primate studies:

- **Vaccinated macaques high levels of neutralizing antibodies above natural infection directed at the surface spike protein**
- **Induced cell killing immune response**
- **At challenge none had detectable virus in the nose**

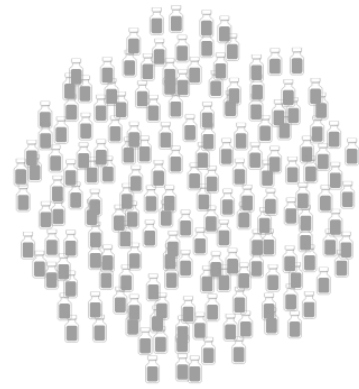
Human studies

- **Phase I and II complete**
 - ❑ **Some pain at injection site**
 - ❑ **Some fever and headache treated with Tylenol**
- **Phase III: initiated July 30th with 30,000 volunteers**

Oxford University Vaccine now in Phase Three Trial in UK



The Washington Post, August 13



Pre-clinical

170+ vaccines

are being tested in
animals and lab
experiments



Phase 1

15 vaccines

are being tested in a
small number of healthy,
young people to assess
safety and correct dose



Phase 2

2 vaccines

are broadened to a larger
group of people, including
people at higher risk of
illness



Phase 3

7 vaccines

are being tested in
thousands of people to
check their effectiveness
and safety

Approved

0 vaccines

have been determined to
provide benefits that
outweigh known and
potential risks

Technology used:



Nucleic acid



Viral-vectored



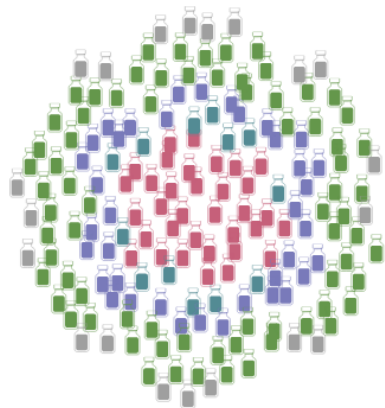
Subunit



Virus



Other



Pre-clinical



Phase 1



Phase 2



Phase 3

Approved

STIGMA AND PERCEPTIONS

Most residents were exercising recommended vigilance, Mr. Haskell said, but one call that stuck out to him was from a woman awaiting test results whose entire family had been exposed to the virus. “She wanted to know whether or not to tell her friends and social network,” he said, because she was worried about “social stigma.”

“I don’t believe I’m the problem anymore,” the South African at the party in Westport told The Sunday Times. “It seems that the real problem is now the people who are too scared to say anything. The problem is the ignorance of the public.”

URGENT

What needs to be done?

- **Wear masks**
- **Stay home, shelter in place, and avoid closed spaces
As much as possible**
- **Social distancing**
- **Dissemination of timely, accurate local information**
- **Widespread random community testing**
- **Prioritize support of hospitals, medical staff, first responders, police etc. for PPE and testing**