COVID-19: the science of how we got here and where we are headed

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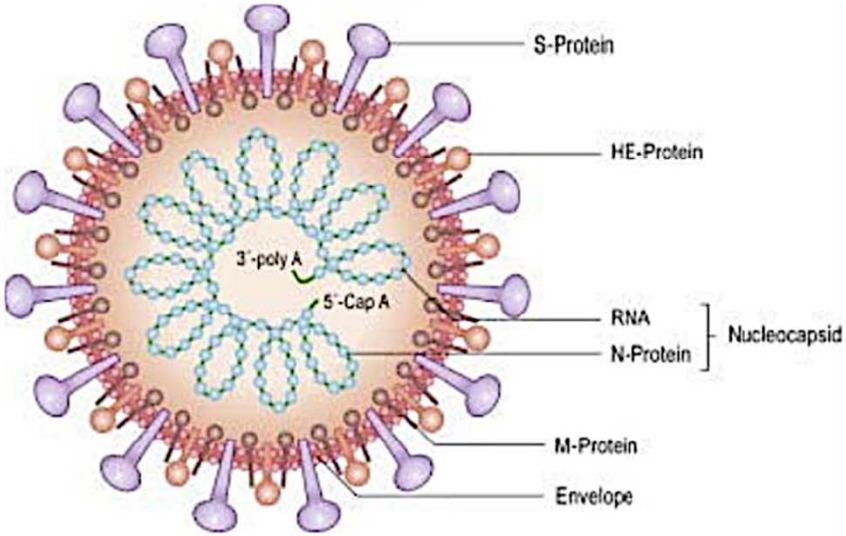
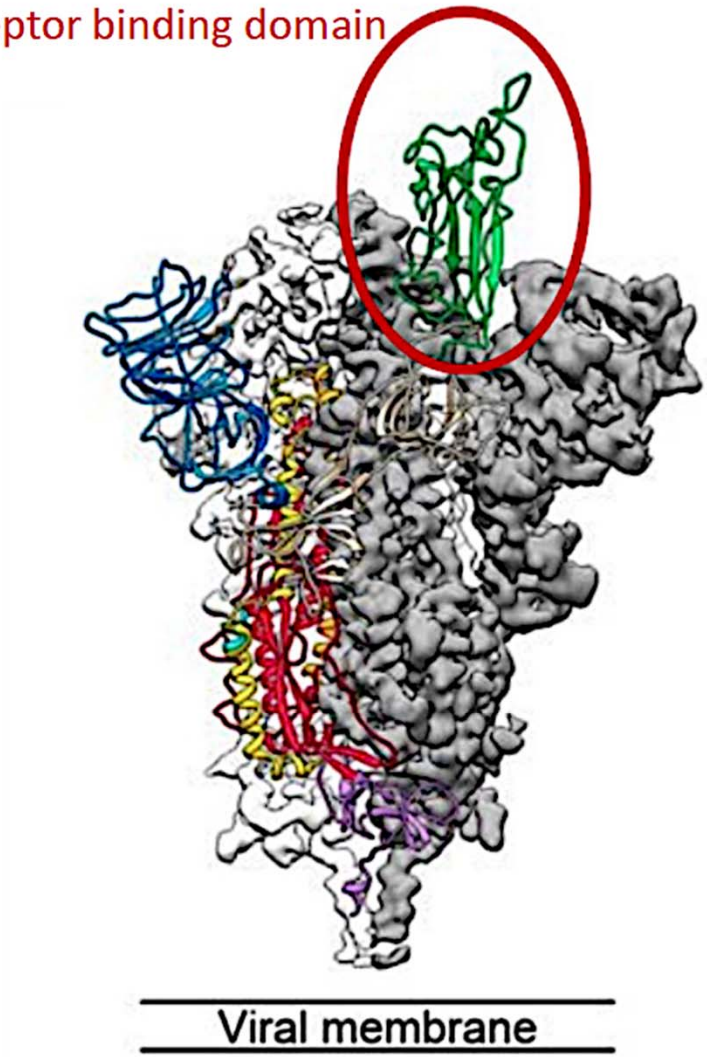
11 November 2020

SARS-CoV-2

- Spike (S) protein binds to angiotensin-converting enzyme 2 (ACE2) on the membranes of lung alveolar cells, upper airway epithelial cells and glandular cells of the GI tract



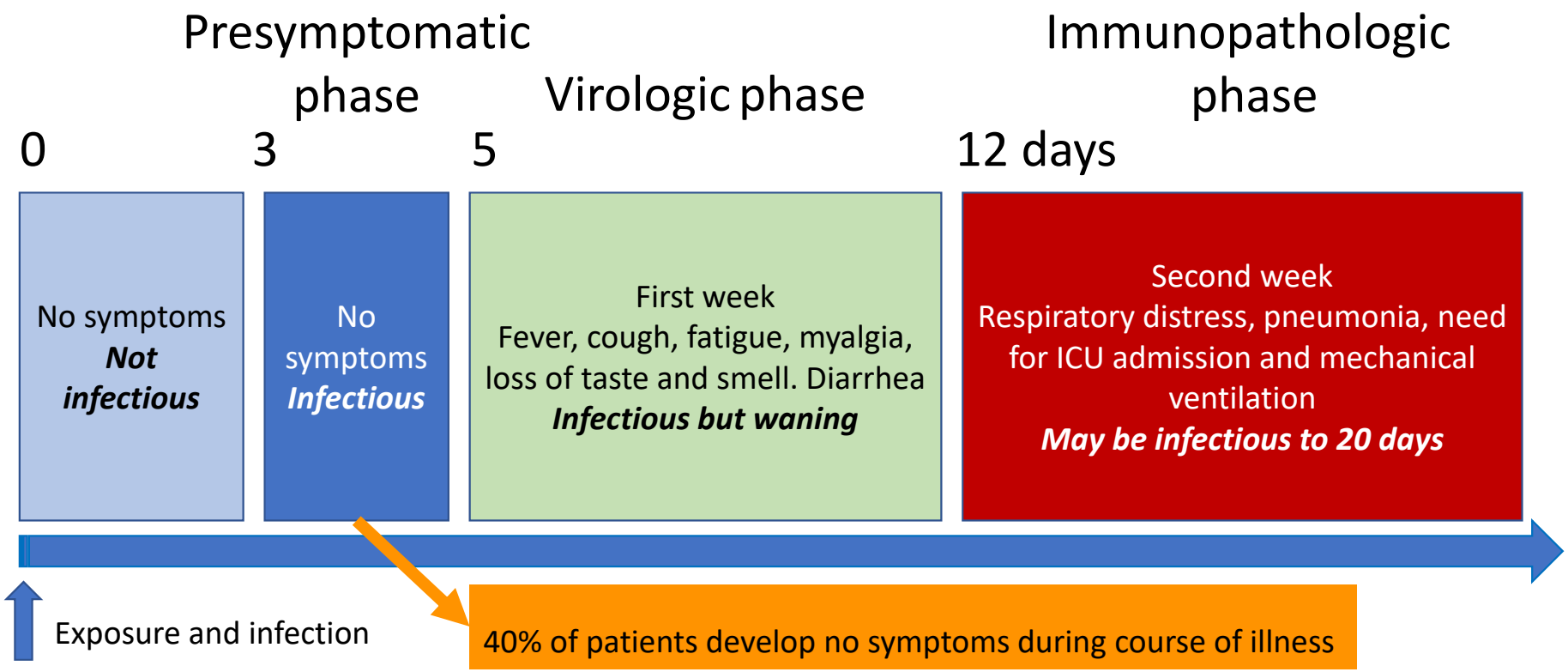


Routes of transmission

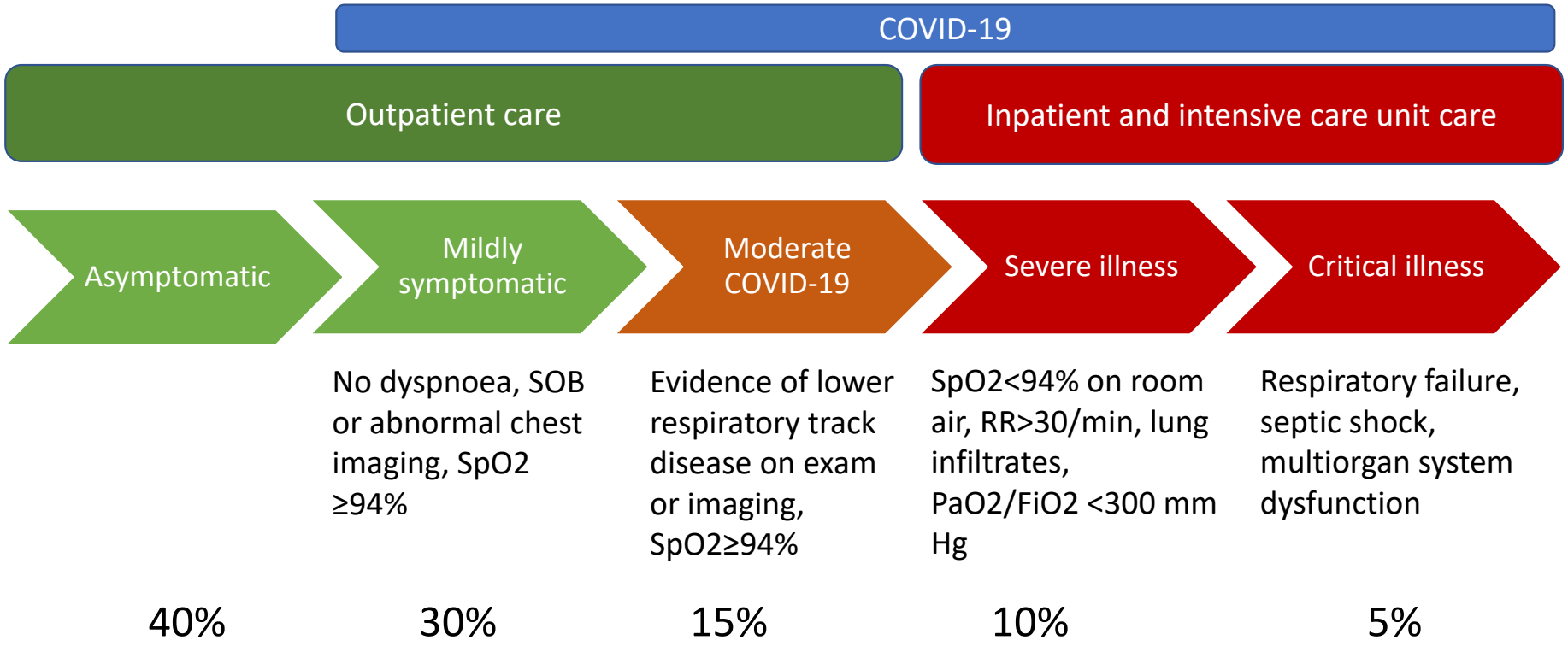
- SARS-CoV-2 spread by three routes:
  - Respiratory droplets spread (≥5μ)
  - Aerosol (airborne) spread (<5μ)
  - Fomite (surface) transmission
- Droplet spread is far and away the most common
- Target = respiratory epithelial cells with ACE2 receptor (including conjunctivae)

- Number of droplets exhaled depends on force of exhalation
  - Breathing 50-5,000 droplets (=200-1000 viral particles/min for influenza)
  - 10x increase when speaking
  - 30,000 droplets when sneezing (=2M viral particles)

Natural history of SARS-CoV-2 infection

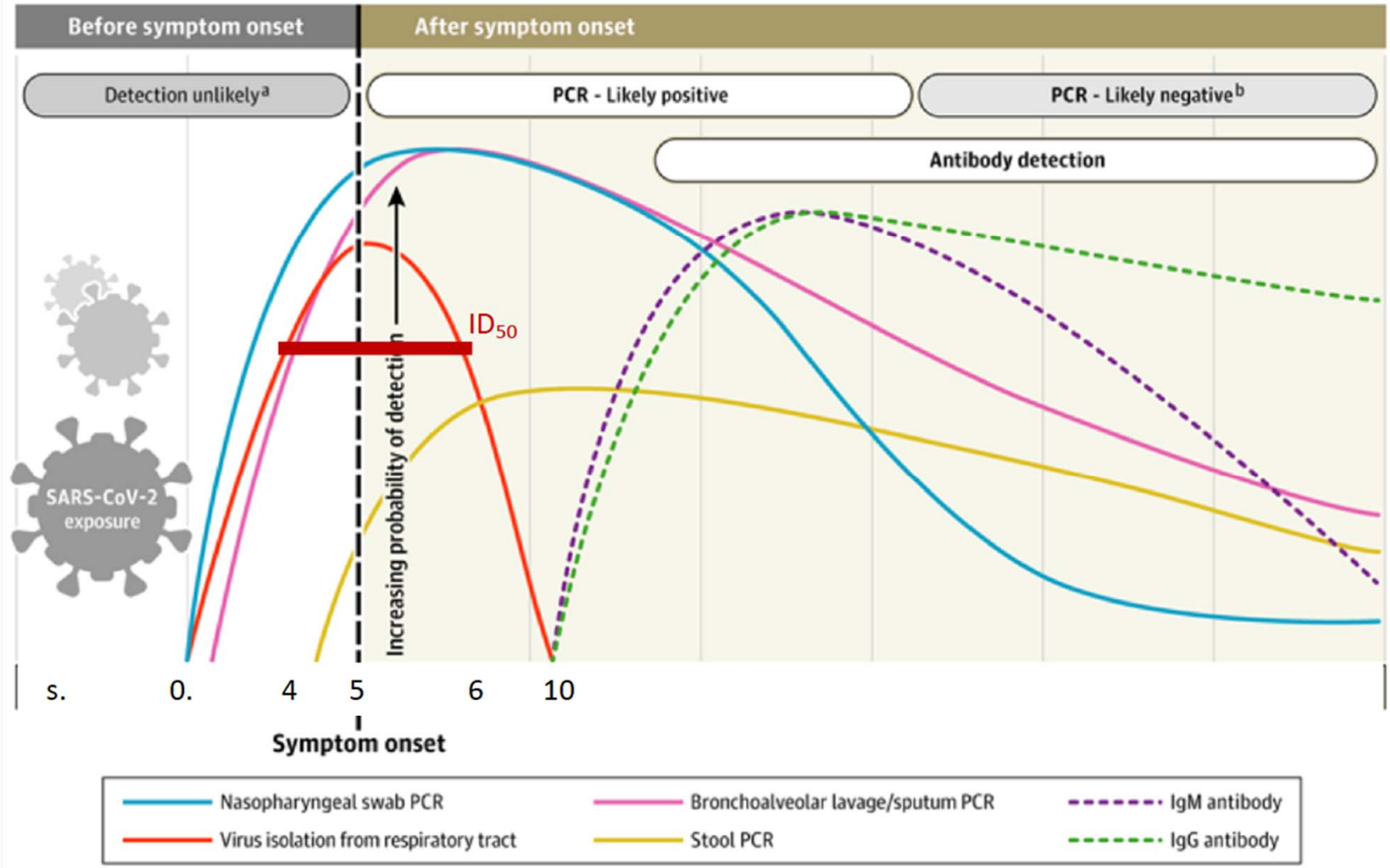


Spectrum of severity of illness from SARS-CoV-2 infection



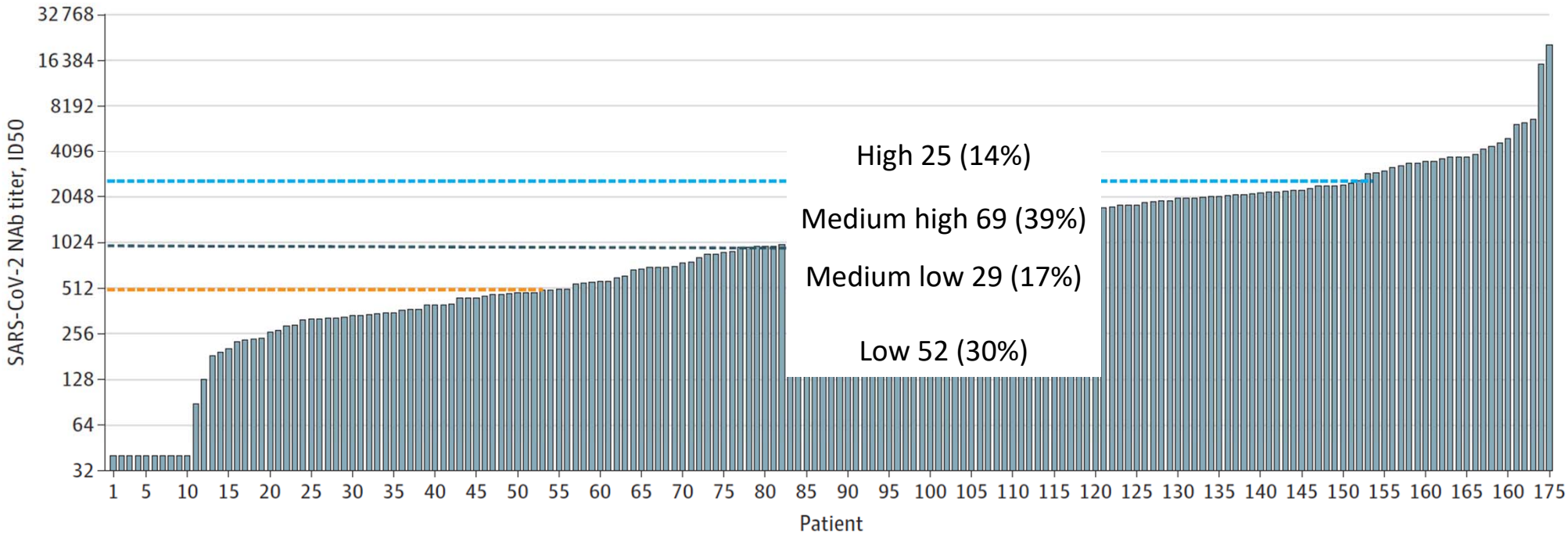
Predictors of COVID-19 progression

Strongest predictors	Mixed evidence	More data needed
Age	Asthma	Liver disease
Active malignancy	Cerebrovascular disease	Neurologic conditions
Chronic kidney disease	Hypertension	HIV
COPD	Pregnancy	Bone marrow transplant
Cardiovascular disease (CAD, CHR)	Immunosuppressive medications	Other immune deficiencies
Diabetes mellitus, type 2		Inherited metabolic disorders
Obesity (BMI >30)		Diabetes mellitus, type 1
Smoking		Thalassemia
Sickle cell disease		Overweight (BMI 25-29)
Solid organ transplant		Other chronic lung conditions



From Sethuraman N, Jermiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA 2020; 323:2249-51.

Figure 3. Variable Levels of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-Specific Neutralizing Antibodies (NAbs) in Patients Who Recovered From Coronavirus Disease 2019



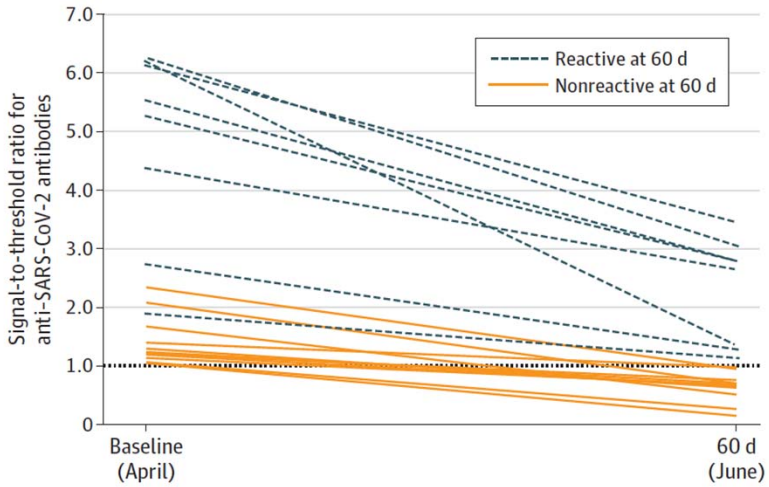
The SARS-CoV-2–specific NAb titer (50% inhibitory dose [ID50]) for each patient at the time of discharge is shown as an individual histogram. The dashed lines show the cutoff values of different NAb levels: low (ID50, <500), medium-low (ID50, 500-999), medium-high (ID50, 1000-2500), and high (ID50, >2500). Fifty-two patients (30%) had low levels (orange dashed line); 29 patients (17%) had medium-low levels, 69 patients (39%) had medium-high levels (dark blue dashed line), and 25 patients (14%) had high levels (bright blue dashed line).

Wu F, Liu M, Wang A, et al. Evaluating the association of clinical characteristics with neutralizing antibody levels in patients who have recovered from mild COVID-19 in Shanghai, China. JAMA Intern Med 2020 Aug 18 [Epub ahead of print].

Persistence of neutralizing antibodies

- 18 HCWs neutralizing antibody seropositive at baseline
- 8 (42%) had persistent antibody 2 months later
  - 6 (75%) of 8 symptomatic HCWs persistently seropositive
  - 2 (25%) of 8 asymptomatic HCWs persistently seropositive
  - P=0.35 by Fisher's exact test
- Take home message, 58% of seropositive HCWs "lost" neutralizing antibody within two months

Figure. Anti–SARS-CoV-2 Signal-to-Threshold Ratios at Baseline and 60 Days in Health Care Personnel Seropositive at Baseline

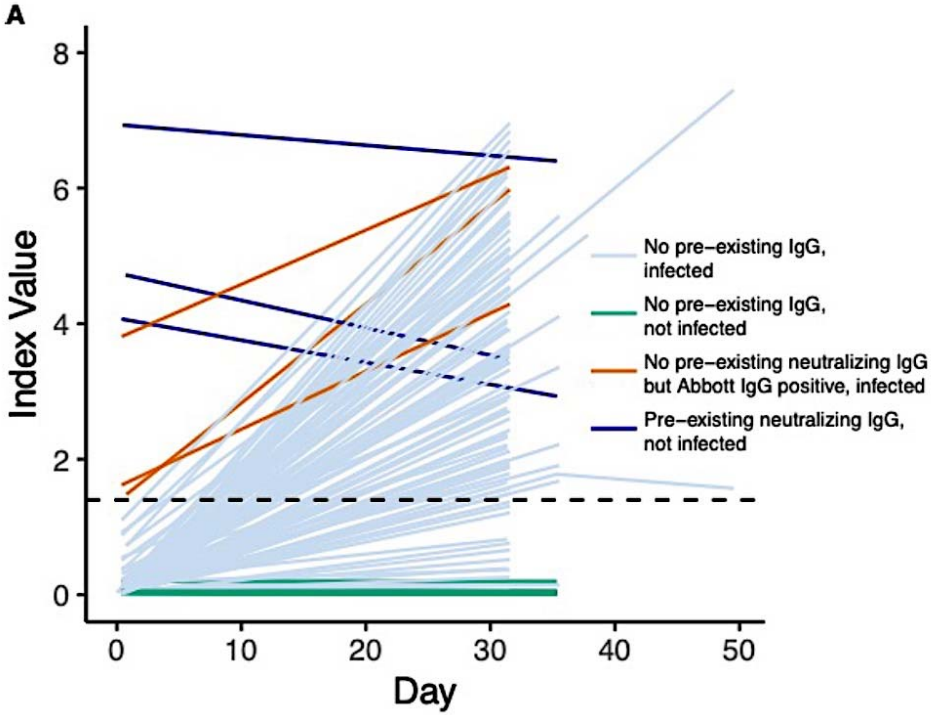


SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2. The dotted line at y = 1.0 indicates the threshold for seropositivity.

Patel MM, Thornburg NJ, Stubblefield WB, et al. Change in antibodies to SARS-CoV-2 over 60 days among health care personnel in Nashville, Tennessee. JAMA 2020 Sep 17 [Epub ahead of print].

Pre-existing neutralizing antibody associated protection in outbreak on a U.S. fishing vessel

- 120 of 122 crew members consented to testing pre-voyage
- 103 (86%) attack rate
- 3 of 3 crew members with pre-existing neutralizing antibody to RDC did not become infected



		Pre-departure	
		Neutralizing Ab (+)	Neutralizing Ab (-)
On boat	Infected	0	103
	Not infected	3	14

p=0.0024

Addetia A, Crawford KHD, Dingens A, et al. Neutralizing antibodies correlate with protection from SARS-C-V-2 in humans during a fishery vessel outbreak with high attack rate. medRxiv 2020 Aug 14 [Preprint].

Is reinfection possible?

- 33-year-old man in Hong Kong
  - Two diagnoses of SARS-CoV-2 infection 4.5 months apart (first mild, second asymptomatic)
  - Second infection was acquired in Europe
  - On genetic analysis, the strains from the first and second infection do not match – indicates new infection rather than prolonged viral shedding
- Two additional cases from Europe reported on August 25
  - One older patient from the Netherlands with a weakened immune system, the other a Belgian woman who was infected with mild symptoms in March and again in June
- One additional case from Nevada on August 28
  - 25-year-old man reinfected 62 days later, more symptomatic the second time
- Implications
  - Immunity wanes after 4 months?

To JJ-W, Hung I F-N, Ip JD, et al. COVID-19 re-infection by a phylogentically distinct SARS-conronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis 2020 Aug 24 [Epub ahead of print].
Tillett R, Sevinsky JR, Hartley PD, et al. Genomic evidence for a case of reinfection with SARS-CoV-2. medRxiv 2020 Aug 28 [Preprint]

Super spreading events – point source exposures

	Date of exposure	Setting	Number at gathering (excluding primary case)	Subsequently infected
Harbin, Heilongjiang, China	Jan 24, 2020	Meal (home)	8	8
Shuangyashan, Heilongjiang, China	Jan 24, 2020	Meal (home)	13	4
Hangzhou, Zhejiang, China	Jan 17, 2020	Meal (unknown location)	1	1
Nanjing, Jiangsu, China	Jan 23, 2020	Meal (unknown location)	8	7
Nanjing, Jiangsu, China	Jan 24, 2020	Meal (restaurant)	14	3
Enshi, Hubei, China	Unknown	Meal (unknown location)	17	2
Enshi, Hubei, China	Unknown	Meal (unknown location)	47	10
Haute-Savoie, France	Jan 24–28, 2020	Chalet	11	5
Hong Kong	Unknown	Meal (home)	18	8

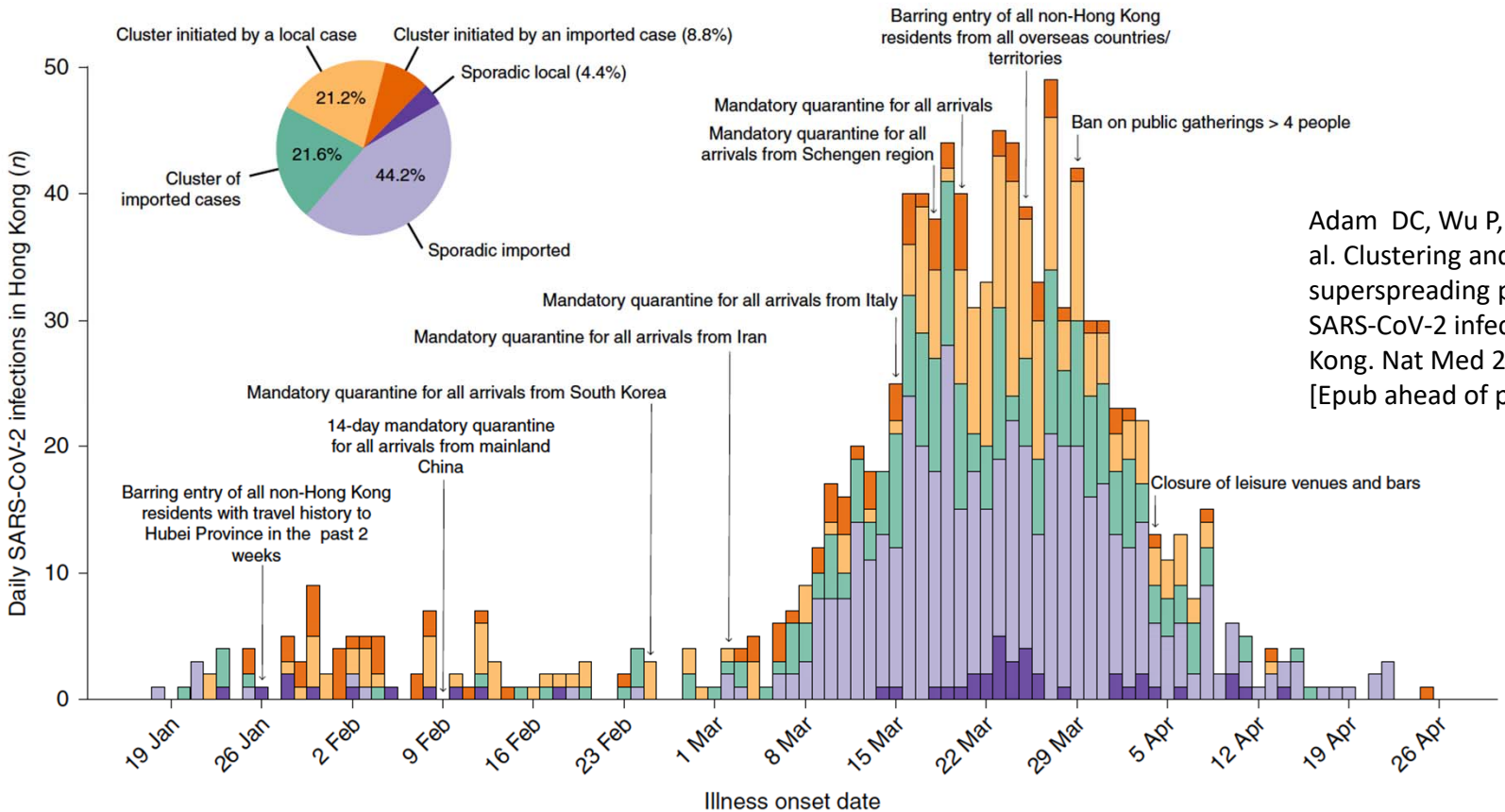
Full details are provided in the appendix.

Table: **Summary of severe acute respiratory syndrome coronavirus 2 transmission events where the numbers of people exposed and subsequently infected were known, assuming a single primary case, by location**

- Review of nine point-source SARS-CoV-2 exposures
- Overall secondary attack rate 35% (95% confidence interval, 27-44%) (varied from 21%-100%)
- Suggests transmission is driven by relatively small number of high-risk, close contacts

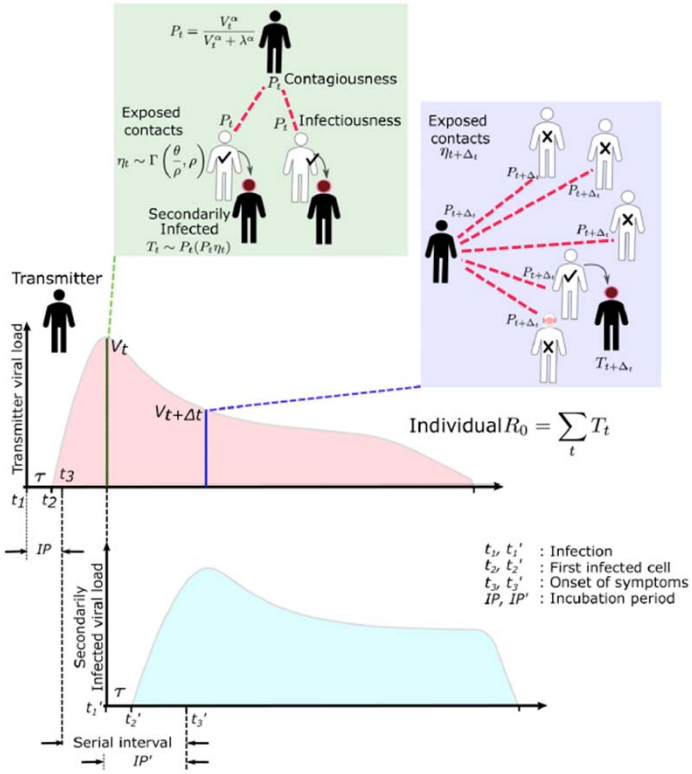
Liu Y, Eggo RM, Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2 [Letter]. Lancet 2020; 395:e47.

Source of SARS-CoV-2 infection by time, Hong Kong



Adam DC, Wu P, Wong JY, et al. Clustering and superspreading potential of SARS-CoV-2 infection in Hong Kong. Nat Med 2020 Sep 17 [Epub ahead of print].

Models of super spreading



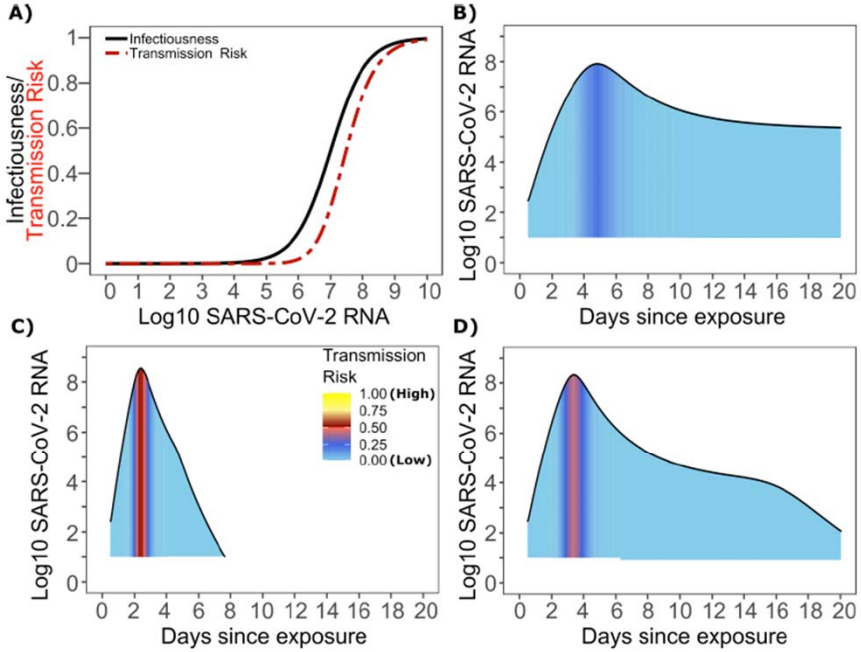
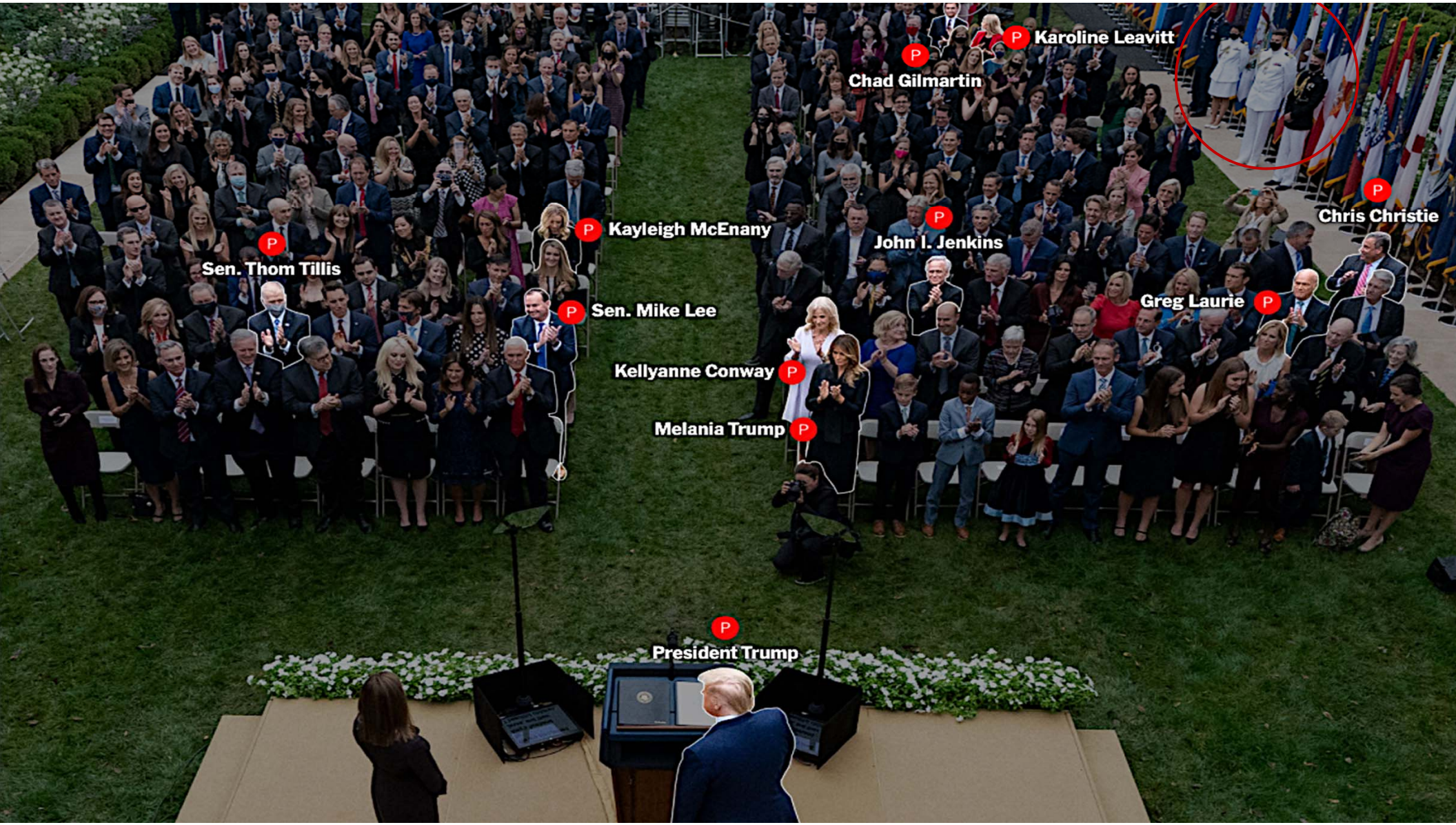


Fig 3. SARS-CoV-2 transmission probability as a function of shedding. A. Optimal infectious dose (ID) response curve (infection risk = P_t) and transmission dose (TD) response curve (transmission risk = $P_t * P_t$) curves for SARS-CoV-2. Transmission probability is a product of two probabilities, contagiousness and infectiousness. **B-D.** Three simulated viral shedding curves. Heat maps represent risk of transmission at each shedding timepoint given an exposed contact with an uninfected person at that time.

Goyal A, Reeves DB, Cardozo-Ojeda EF, Schiffer JT, Mayer BT. Wrong person, place, and time: viral load and contact network structure predict SARS-CoV-s transmission and super-spreading events. medRxiv 2020 Aug 7 [Preprint].


Karoline Leavitt
Chad Gilmartin
Chris Christie
Kayleigh McEnany
John I. Jenkins
Sen. Thom Tillis
Sen. Mike Lee
Greg Laurie
Kellyanne Conway
Melania Trump
President Trump

COVID cases by country and WHO region, worldwide, 2020

- 50,913,451 cases
- 1,242,263 deaths
- 35,323,467 recovered
- Leading countries
  - United States 10.11M
  - India 8.59M
  - Brazil 5.68M
  - France 1.86M
  - Russia 1.78M
  - Spain 1.38M
  - Argentina 1.25M
  - United Kingdom 1.22M
  - Colombia 1.15M
  - Italy 1.00M

Figure 1: Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 1 November 2020**

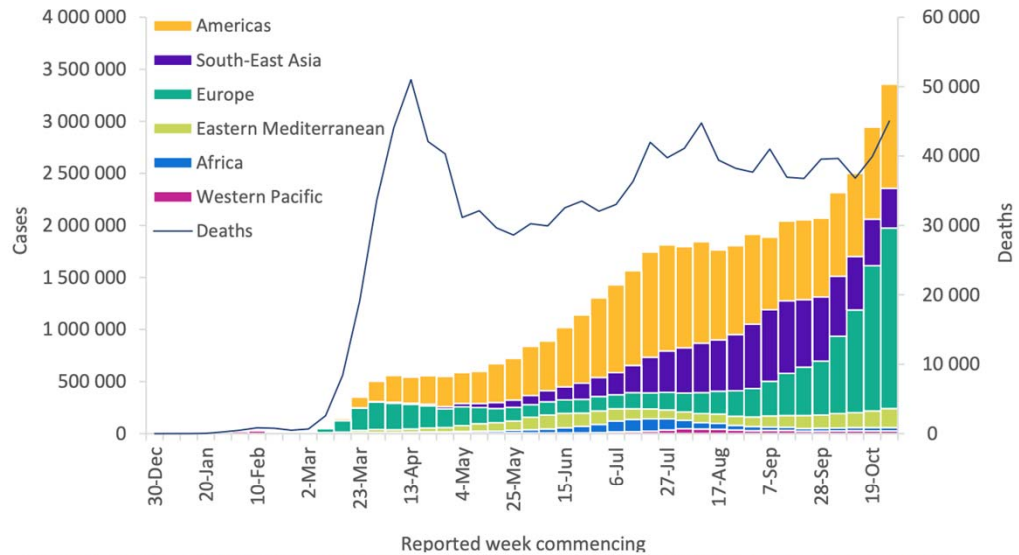


Figure 8: Number of COVID-19 cases and deaths reported weekly by the WHO European Region, as of 1 November 2020**

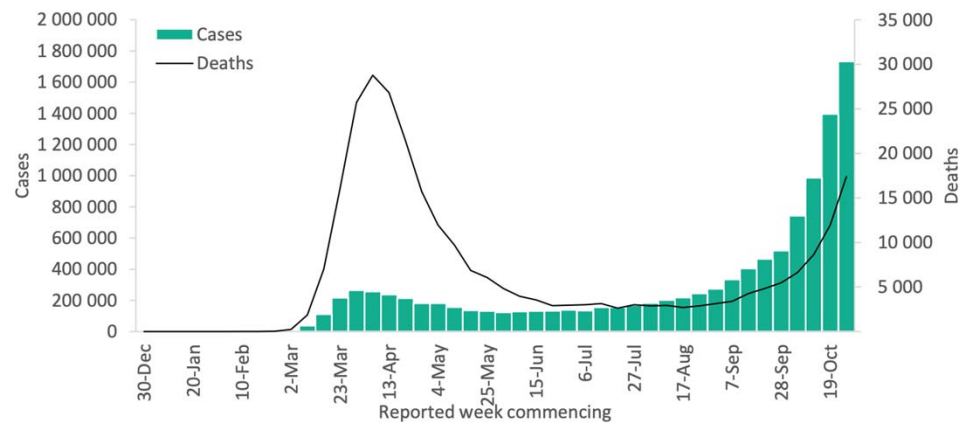
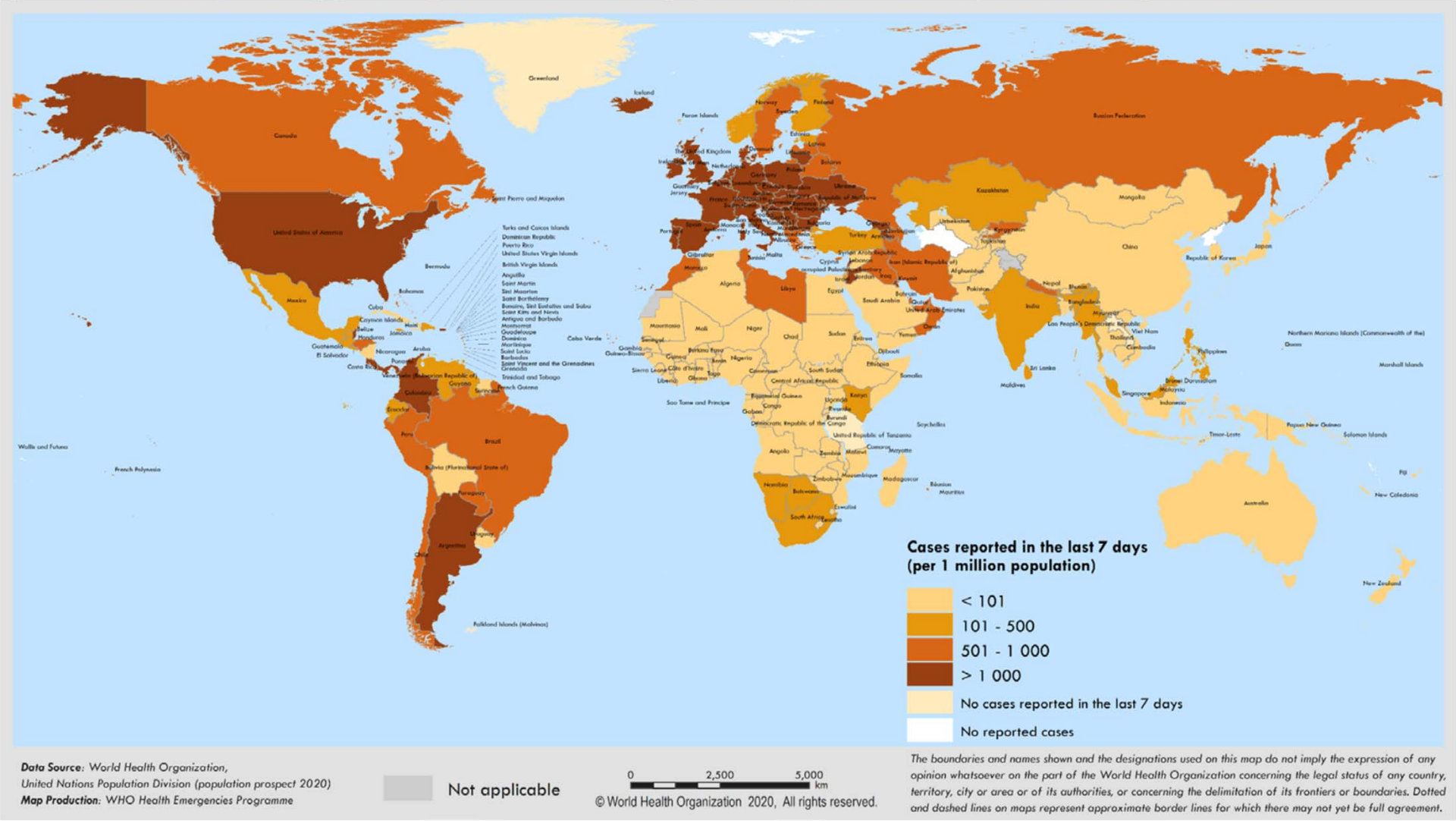


Figure 2. COVID-19 cases per million population reported in the last seven days by countries, territories and areas, 26 October through 1 November 2020**



***Data Source**: World Health Organization,*
United Nations Population Division (population prospect 2020)
***Map Production**: WHO Health Emergencies Programme*

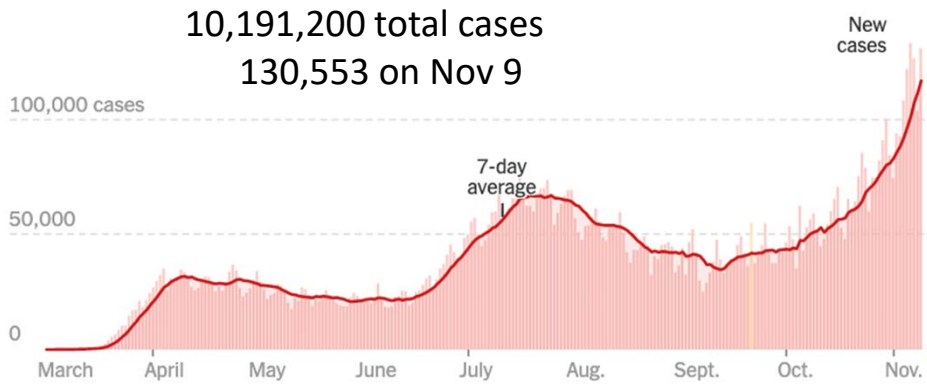
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

**See *data, table and figure notes*

COVID-19 cases and deaths, United States, 2020

- Cases continue to rise explosively across much of the country, and rise will likely accelerate as people move indoors for winter
- Rapidly increasing everywhere but the CA, HI, NH, ME, VT
- Largest number of cases in past 7 days
  - ND, SD, IA, WI, NE, WY, MN, MT, IL, UT per capita
  - IL, TX, WI, CA, FL, MI, OH, MN, IN, IA absolute cases
  - With surge, TX has passed CA as having the most cases since beginning of the pandemic

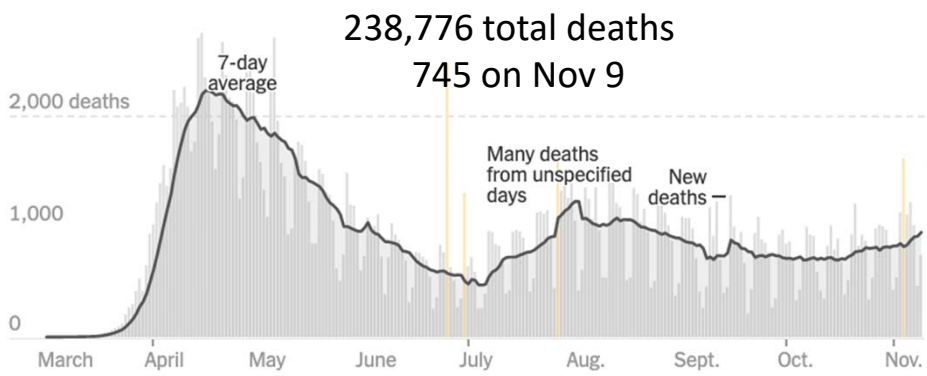
New reported cases by day in the United States



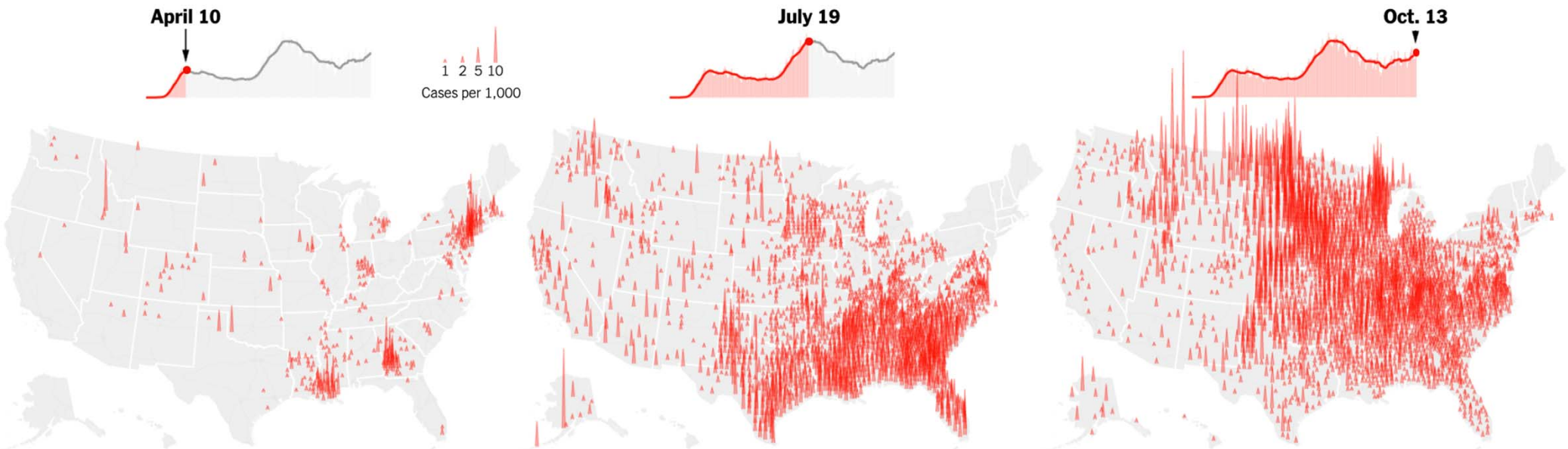
These are days with a data reporting anomaly. Read more here.

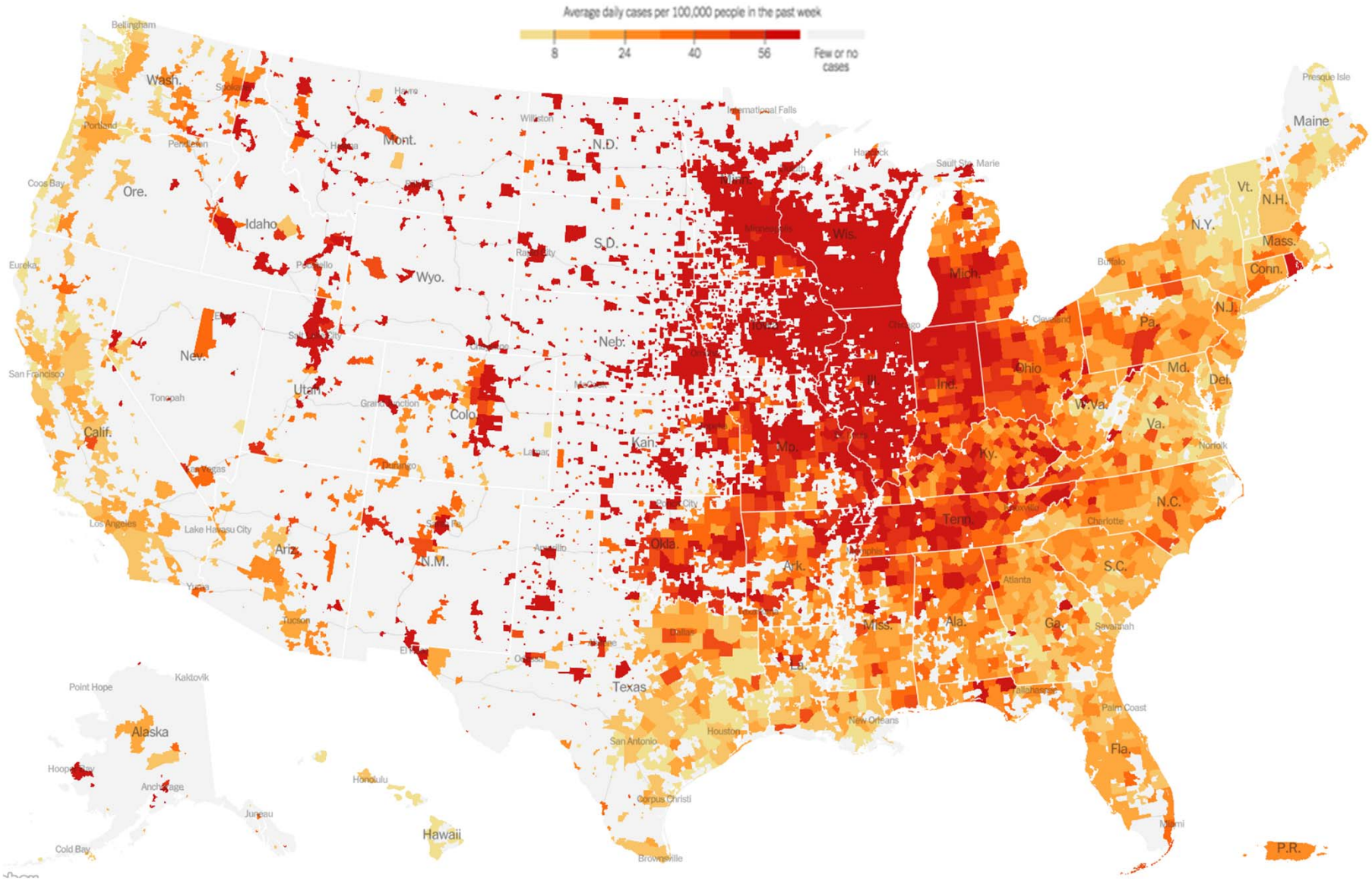
Note: The seven-day average is the average of a day and the previous six days of data.

New reported deaths by day in the United States

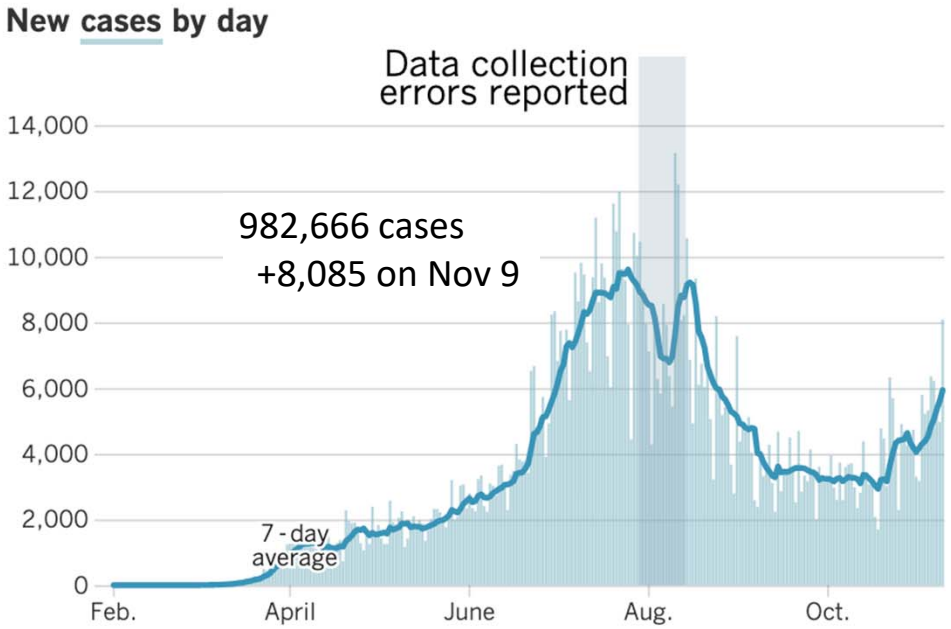


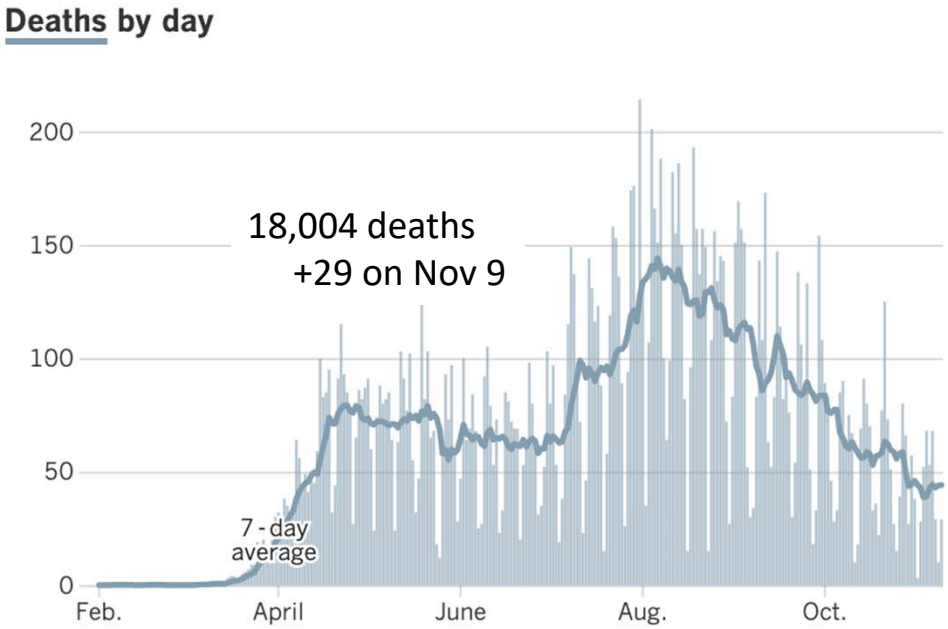
COVID-19 cases by day at three peaks, United States, 2020




Average daily cases per 100,000 people in the past week
8
24
40
56
Few or no cases
Wash.
Ore.
Calif.
Idaho
Nev.
Mont.
Wyo.
Utah
Colo.
Ariz.
N.M.
N.D.
S.D.
Neb.
Kan.
Okla.
Texas
Minn.
Iowa
Mo.
Ark.
La.
Wis.
Ill.
Mich.
Ind.
Ohio
Ky.
Tenn.
Miss.
Ala.
Ga.
Fla.
S.C.
N.C.
Va.
W.Va.
Md.
Del.
Pa.
N.J.
N.Y.
Vt.
N.H.
Maine
Mass.
Conn.
R.I.
P.R.
Alaska
Hawaii
Bellingham
Portland
Pendleton
Coos Bay
Eureka
San Francisco
Tonopah
Las Vegas
Los Angeles
Lake Havasu City
Yuma
Tucson
Kaktovik
Point Hope
Anchorage
Juneau
Cold Bay
Honolulu
Spokane
Helena
Havre
Williston
International Falls
Minneapolis
Duluth
Hancock
Sault Ste. Marie
Presque Isle
Buffalo
Cleveland
Chicago
Detroit
Rapid City
Pueblo
Denver
Grand Junction
Durango
Lubbock
Amarillo
Dallas
Houston
San Antonio
Corpus Christi
Brownsville
New Orleans
Memphis
Atlanta
Charlotte
Savannah
Palm Coast
Miami
Norfolk

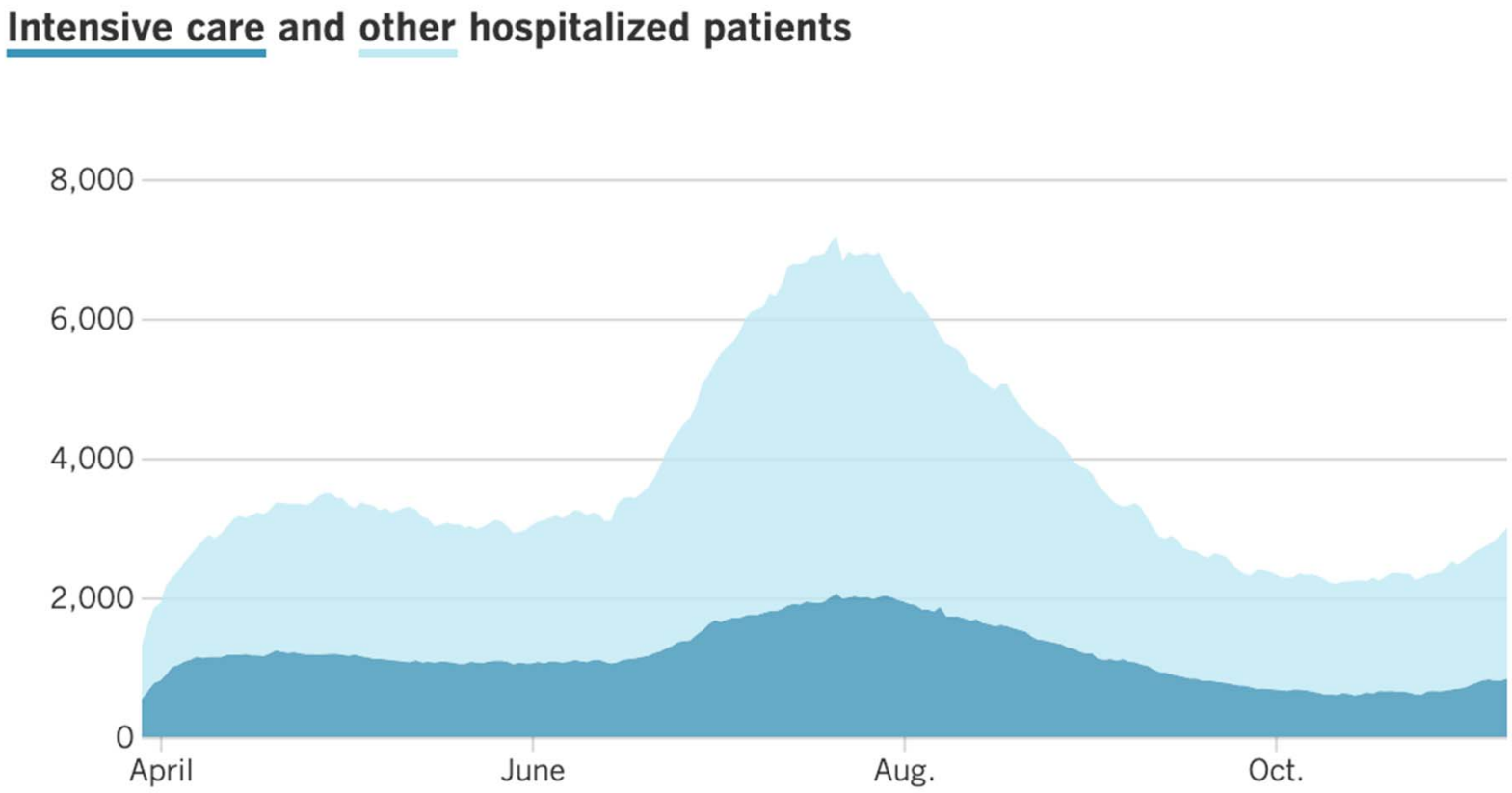
COVID-19 cases and deaths by day, California, 2020



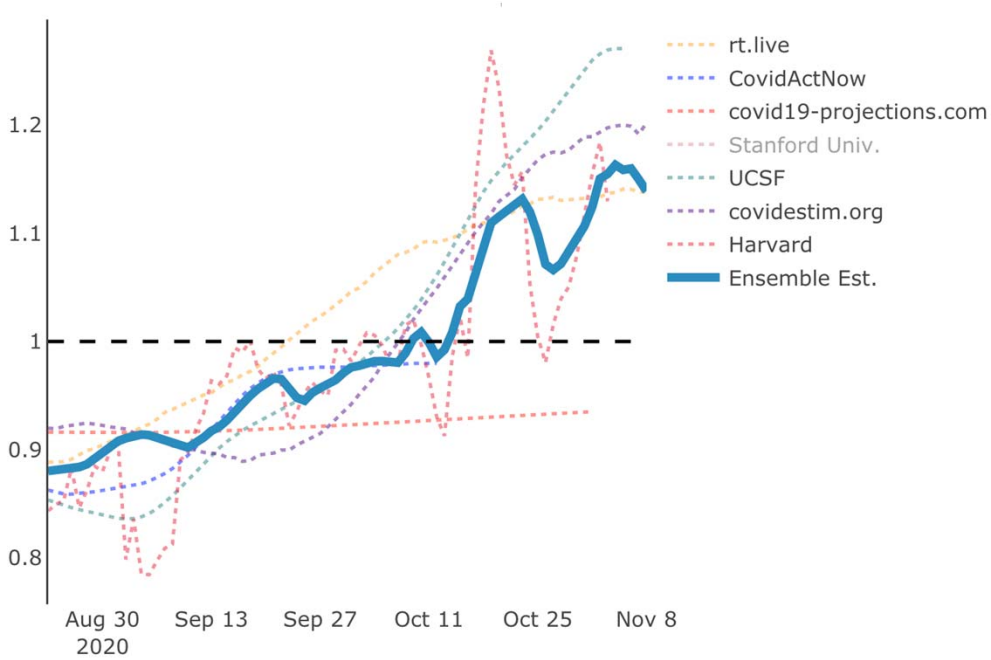


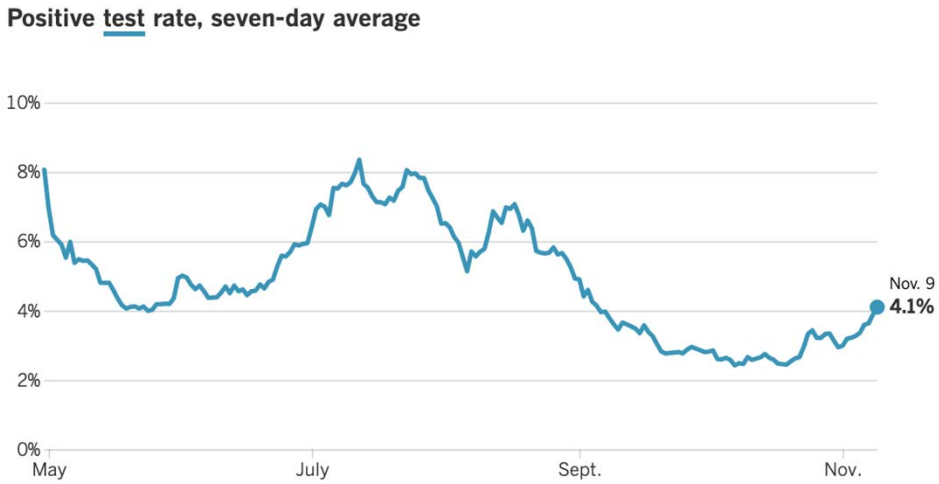
Most new cases in past 7 days: Los Angeles, San Bernardino, San Diego, Riverside, Orange, Sacramento, Santa Clara, Fresno, Alameda, Kern
Most new cases per capita: Alpine, Mono, Kings, Shasta, Modoc, Trinity, San Bernardino, Imperial, San Luis Obispo, Napa

Hospitalized COVID-19 patients by date and level of care, California, 2020



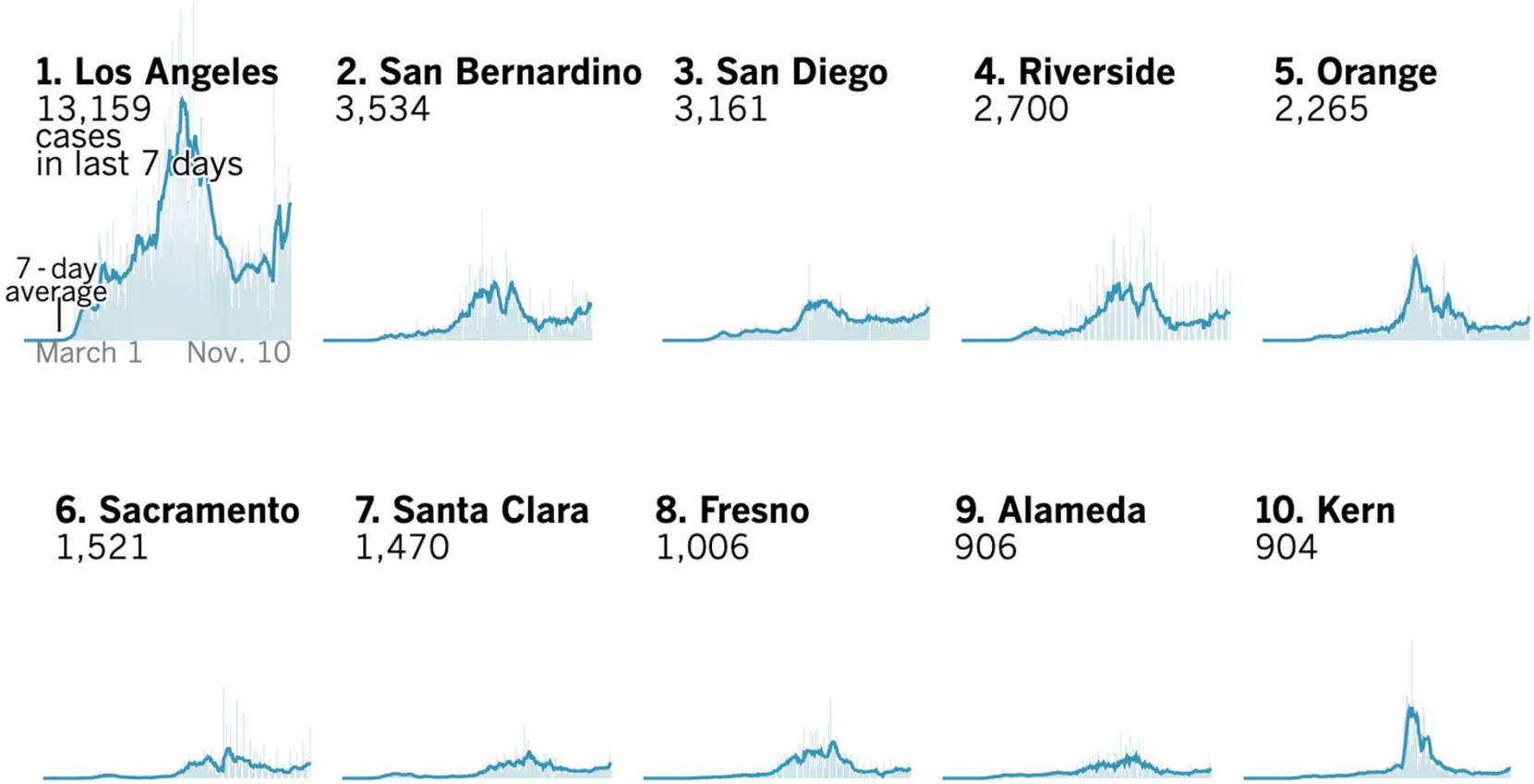
R_e and test positivity for SARS-CoV-2 infection, California, 2020



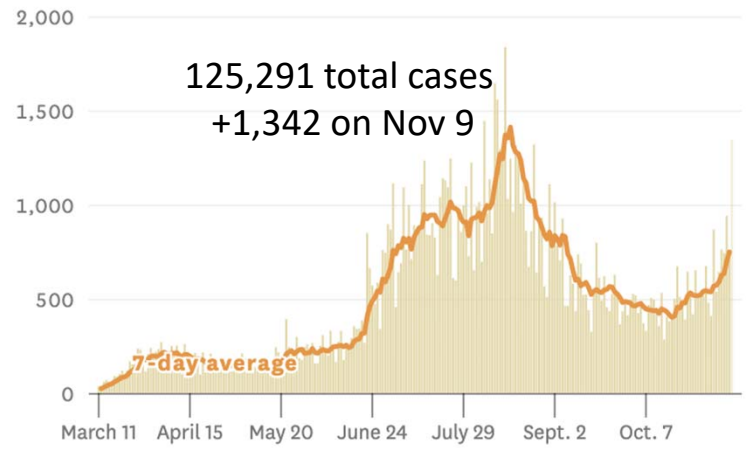


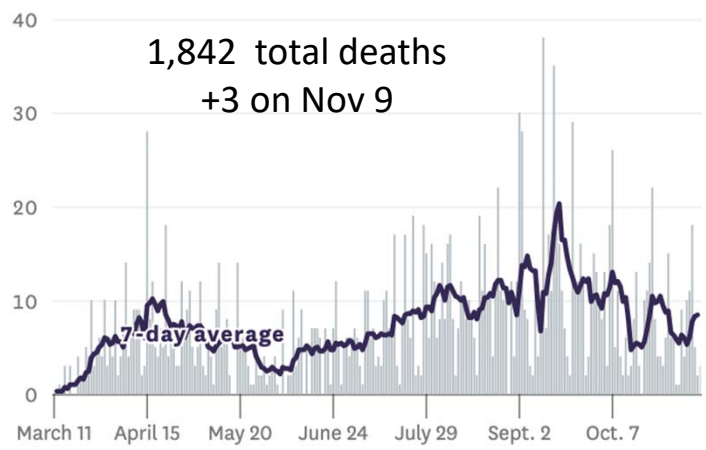
As of November 9, 2020

SARS-CoV-2 infections by county, California, November 10, 2020



County	Total deaths	Total cases	New cases curve	Weekly change in new cases		Cases/ 10^5/ d*	R_e
Santa Clara	433	26,747	193 (March 11 – Nov. 9)	▲ 356	+36%	3.2	1.04
Alameda	475	25,001	122	▲ 175	+26%	3.2	0.99
Contra Costa	253	20,166	109	▲ 202	+36%	4.8	1.07
San Francisco	151	13,081	73	▲ 162	+46%	1.7	0.98
San Mateo	162	11,937	63	▲ 143	+48%	2.9	1.02
Sonoma	146	10,424	80	▲ 188	+50%	11.1	1.01
Solano	79	8,366	71	▲ 150	+43%	6.5	1.03
Marin	128	7,270	14	▲ 29	+43%	2.6	1.03
Napa	15	2,299	23	▲ 76	+90%	3.1	0.96





*Adjusted for testing rate, 7-day lag

Proportion positive range from 0.9% in San Francisco to 5.2% in Sonoma

San Francisco

Latest Estimate of R-effective is:

0.98

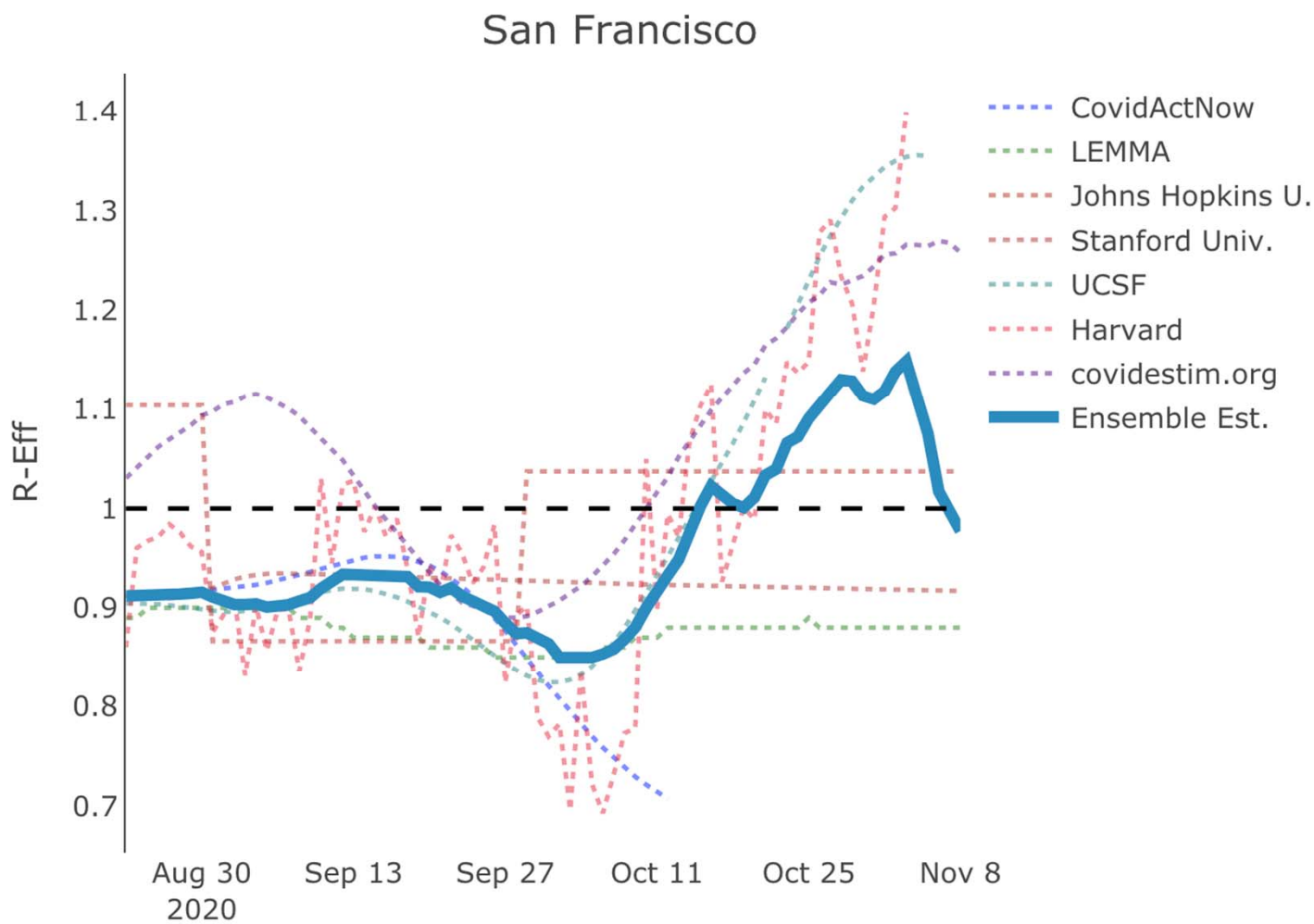
Spread of COVID-19 is likely stable

Download County R-eff Trenc

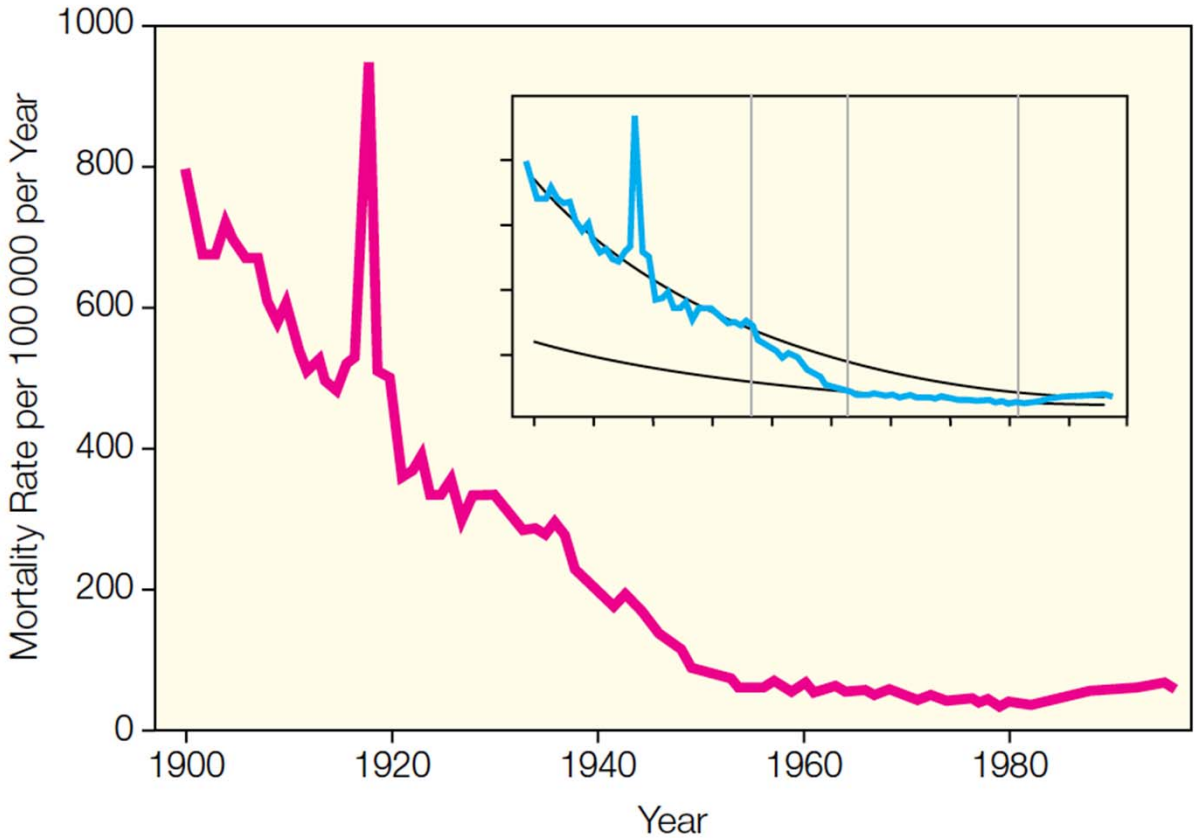
NOTE: Some counties do not have sufficient case numbers in order for modelers to estimate R-effective.

R-effective Trends by County

Select a county to see how R-effective has changed over time



Infectious disease deaths, United States, 1900-1996



Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999; 281:61-66.

Two strategic goals

- Limit new cases by decreasing R_e, the effective reproductive number
- Flatten and prolong the outbreak to (1) assure adequacy of health care resources and (2) buy time for antivirals and eventually vaccine

What interventions do we have available?

- Individual-level interventions
  - Wearing masks
  - Social distancing
  - Staying home if ill
  - Hand hygiene
- Public health interventions
  - *Cordon sanitaire* and shelter-in-place
  - Case investigation and contact tracing, isolation and quarantine
  - Case finding (focused testing)
  - Increased ventilations (indoor spaces)

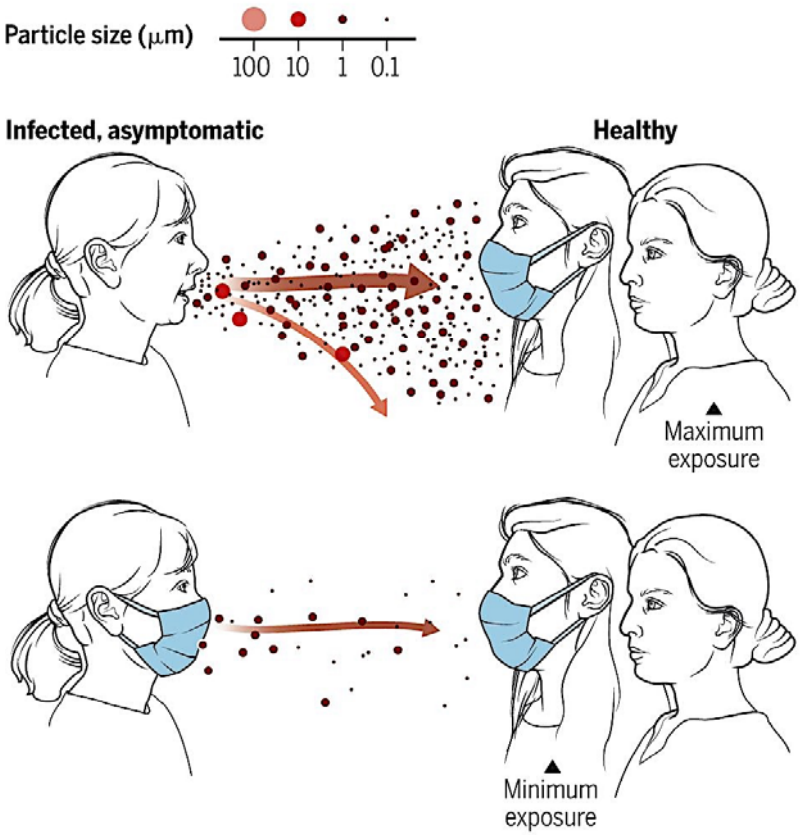
San Francisco and the 1918-19 influenza epidemic

A family wearing masks in San Francisco on November 21, 1918. San Francisco History Center, San Francisco Public Library

A family with their masks off in San Francisco on November 21, 1918. San Francisco History Center, San Francisco Public Library

Masks reduce airborne transmission

Infectious aerosol particles can be released during breathing and speaking by asymptomatic infected individuals. No masking maximizes exposure, whereas universal masking results in the least exposure.

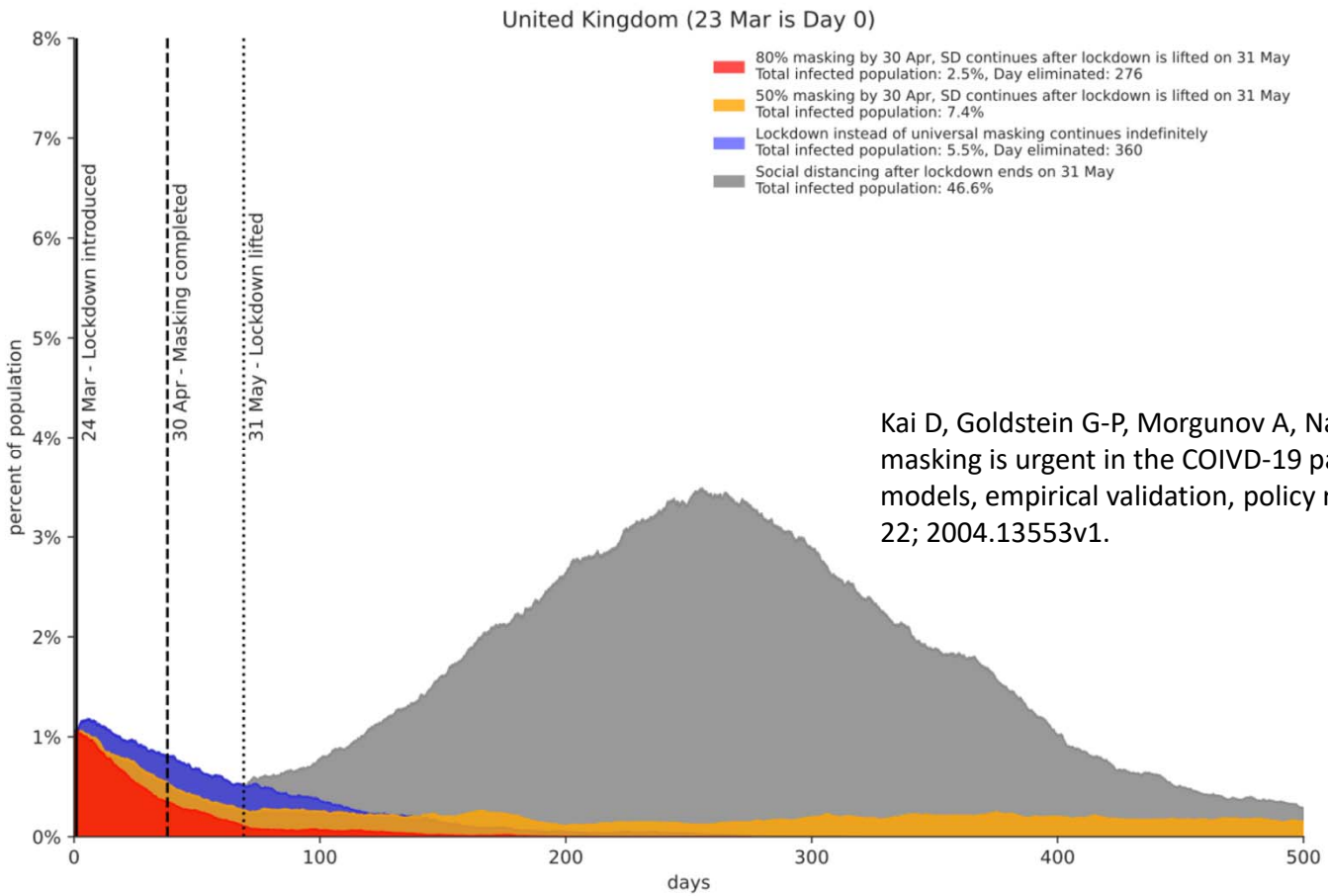


GRAPHIC: V. ALTOUNIAN/*SCIENCE*

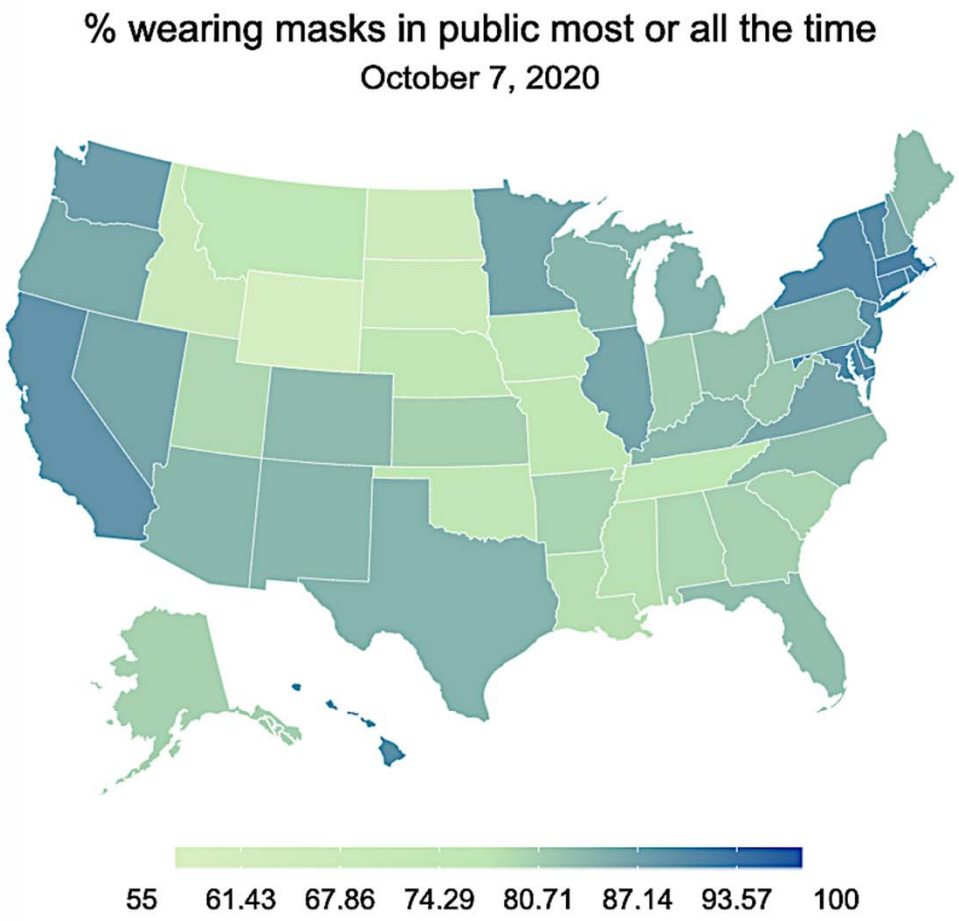
Kimberly A. Prather et al. Science 2020;science.abc6197

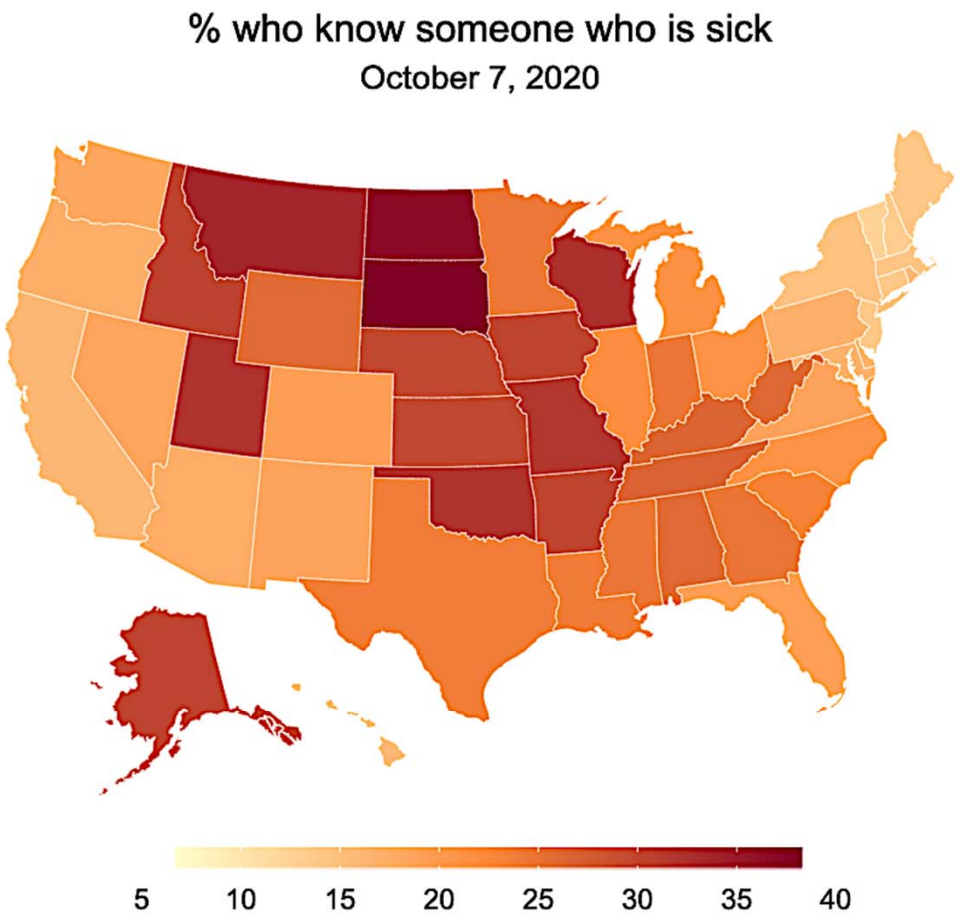
Science AAAS

Modeling benefit of universal masking post-shelter-in-place



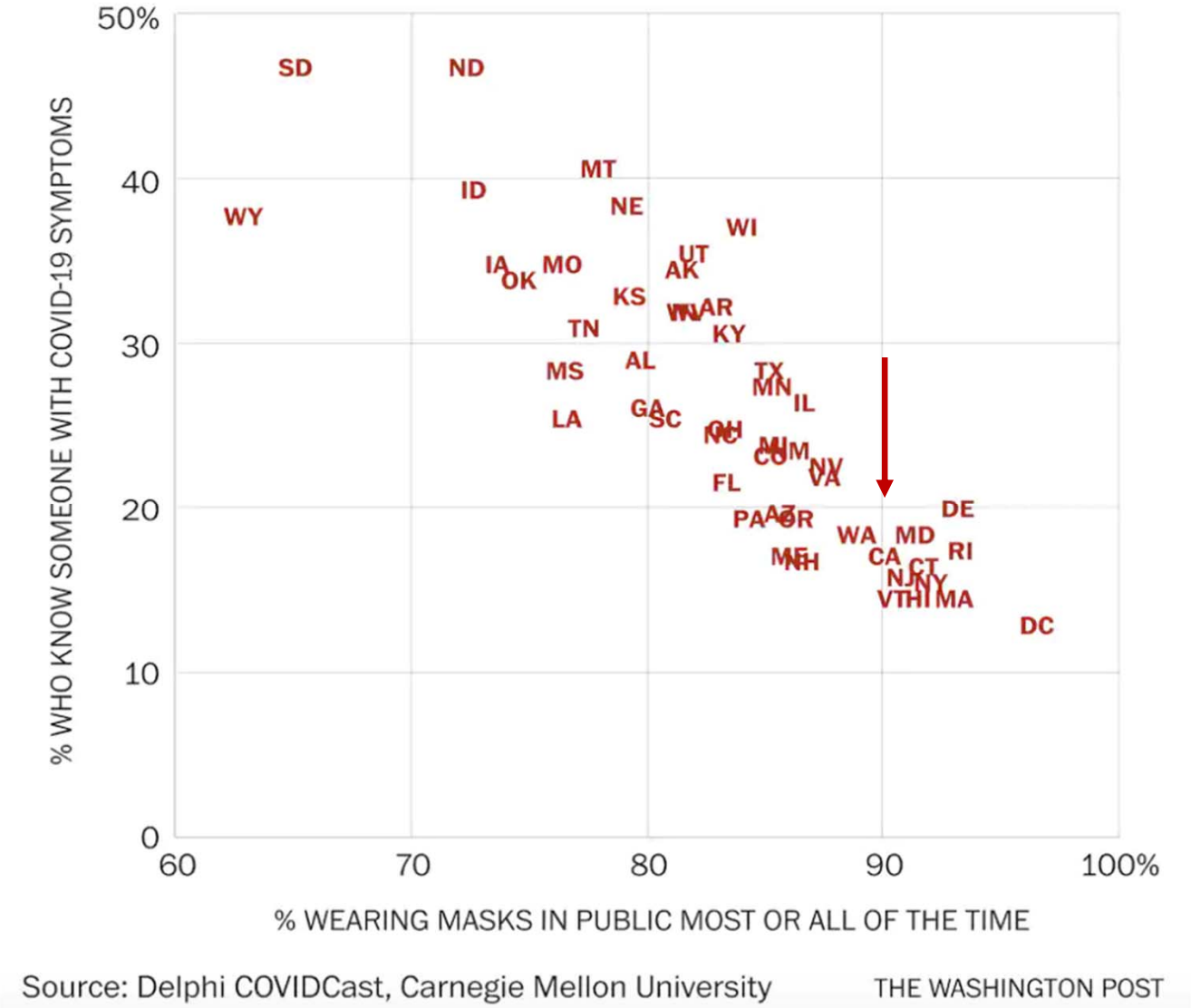
Kai D, Goldstein G-P, Morgunov A, Nangalia V, Rotkirch A. Universal masking is urgent in the COIVD-19 pandemic: SEIR and agent based models, empirical validation, policy recommendations. arXiv 2020 Apr 22; 2004.13553v1.





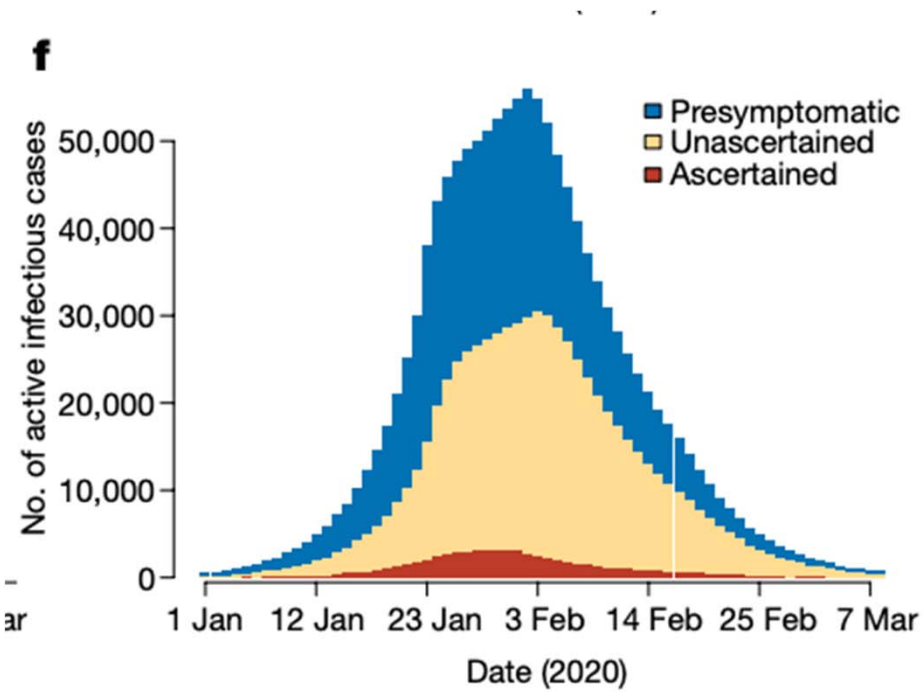
Data from Delphi COVIDcast, covidcast.cmu.edu

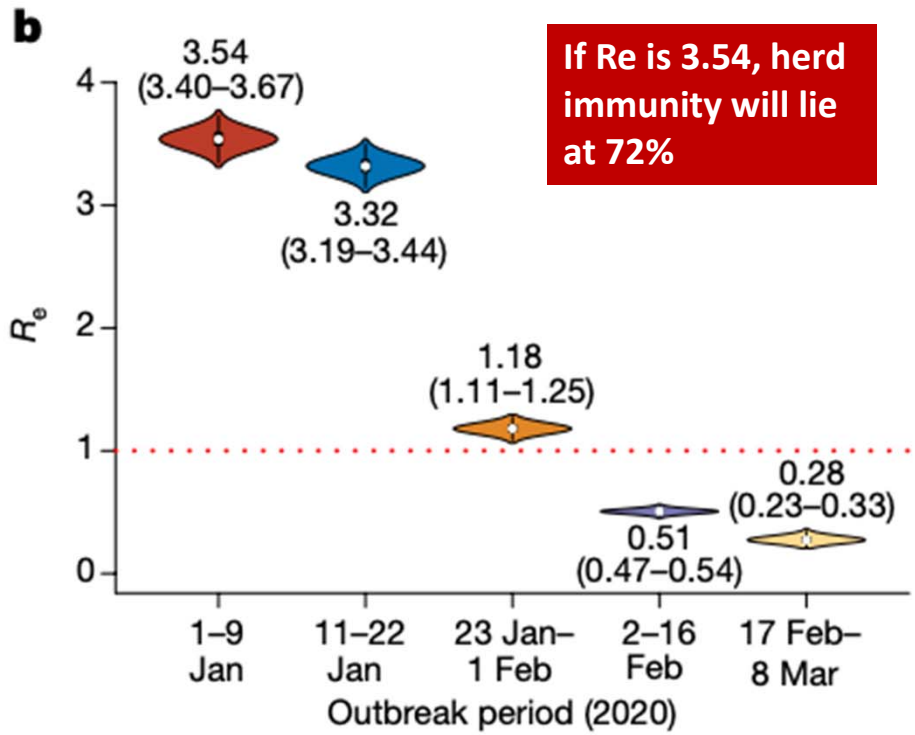
Correlation between mask wearing most or all of the time in public and knowing someone with COVID-19 symptoms




WEAR A MASK
OR GO TO JAIL

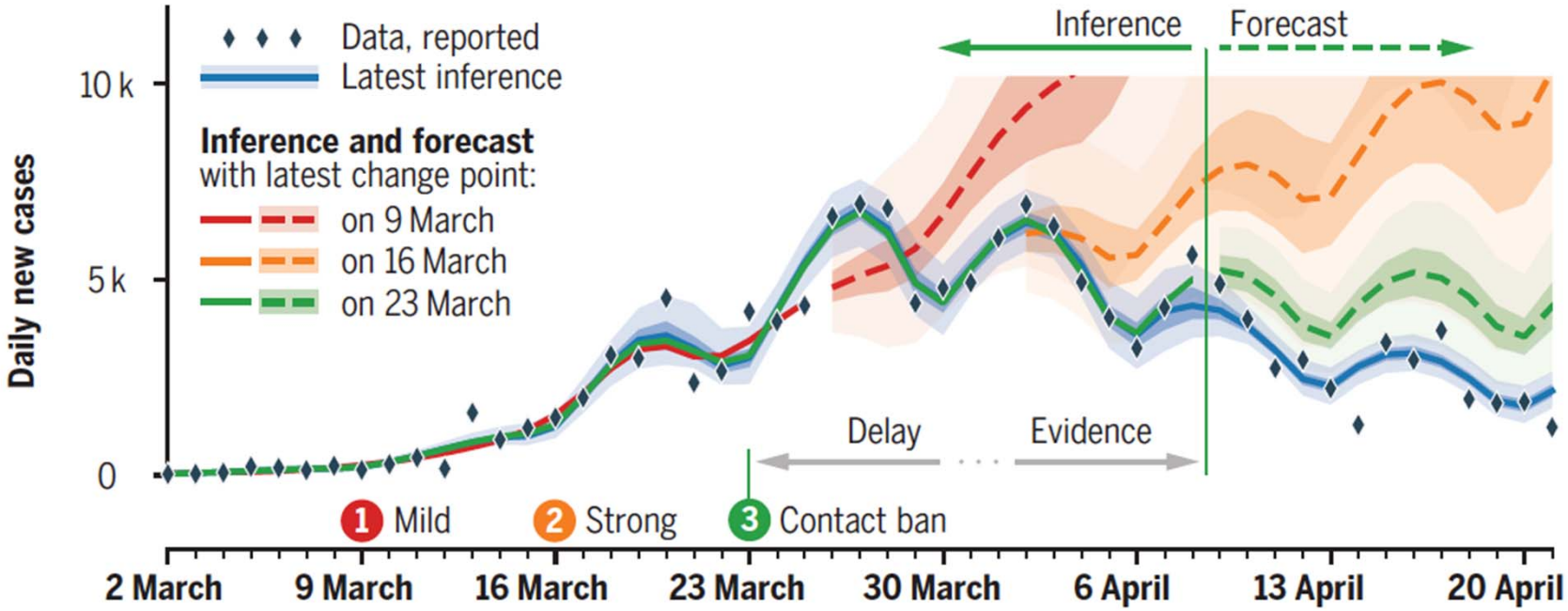
SARS-CoV-2 transmission dynamics, Wuhan, China, 2020





If Re is 3.54, herd immunity will lie at 72%

Hao X, Cheng S, Wu D, Wu T, Lin X, Wang C. Reconstruction of the full transmission dynamics of COVID-19 in Wuhan. Nature 2020 584:420-24.

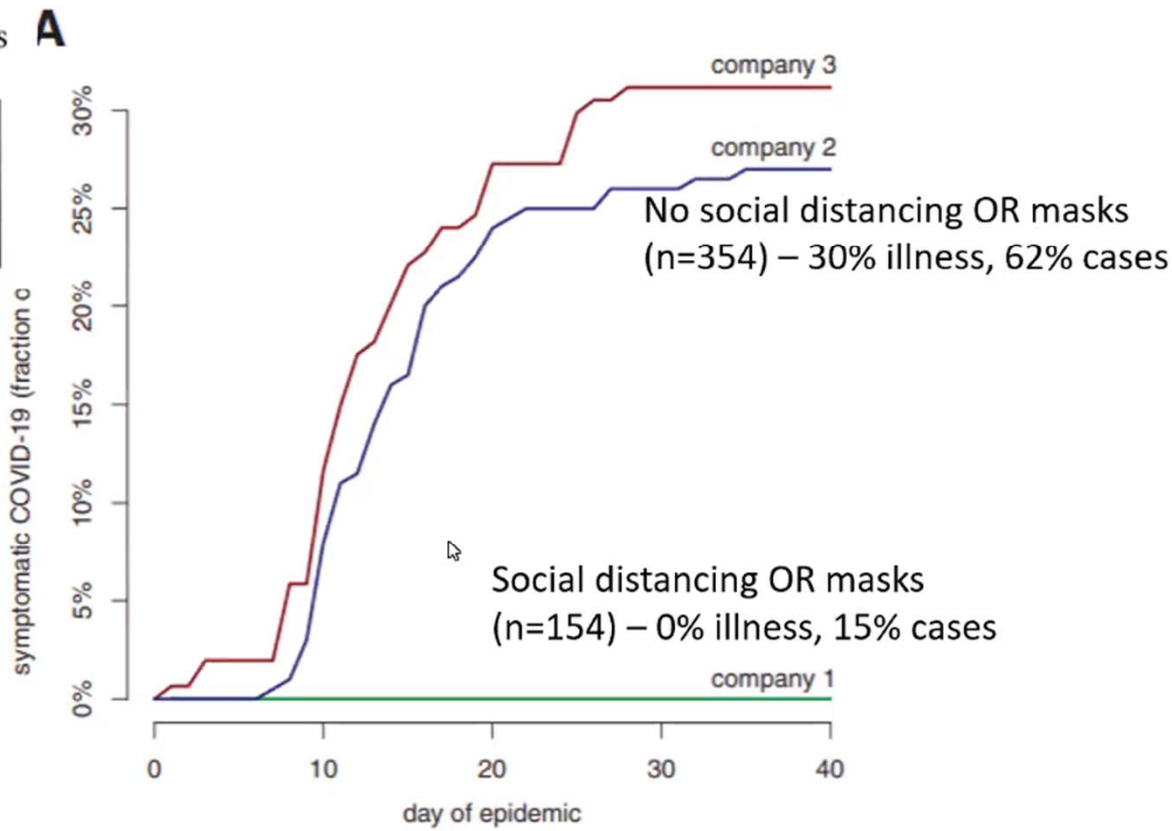


Bayesian inference of SIR model parameters from daily new cases of COVID-19 enables us to assess the impact of interventions. In Germany, three interventions (mild social distancing, strong social distancing, and contact ban) were enacted consecutively (circles). Colored lines depict the inferred models that include the impact of one, two, or three interventions (red, orange, or green, respectively, with individual data cutoff) or all available data until 21 April 2020 (blue). Forecasts (dashed lines) show how case numbers would have developed without the effects of the subsequent change points. Note the delay between intervention and first possible inference of parameters caused by the reporting delay and the necessary accumulation of evidence (gray arrows). Shaded areas indicate 50% and 95% Bayesian credible intervals.

Dehning J. Zierenberg K. Spitzner F, et al. Inferring change points in the spread of COVID-19 reveals the effectiveness of interventions. Science 2-2- Jul 10 [Epub ahead of print].

Social Distancing Alters the Clinical Course of COVID-19 in Young Adults: A Comparative Cohort Study

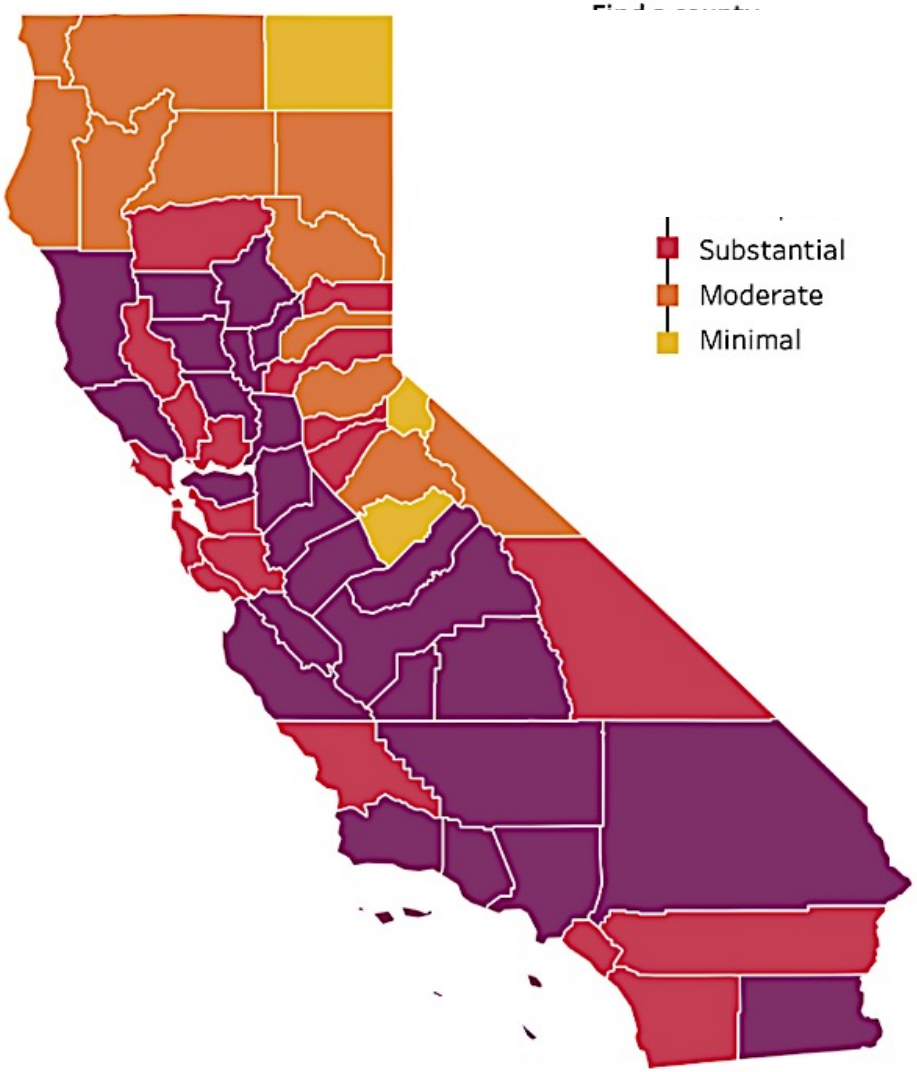
Michel Bielecki,[1,2,3,a] Roland Züst,[4,a] Denise Siegrist,[4] Daniele Meyerhofer,[2] Giovanni Andrea Gerardo Crameri,[1] Zeno Stanga,[1,5] Andreas Stettbacher,[1] Thomas Werner Buehrer,[1] and Jeremy Werner Deuel[1,2,6]



- CID study (June 2020) showed Switzerland soldiers when social distance OR masks established had 0% illness compared to 30% illness without these measures (cases in both)

California's Blueprint for a Safer Economy

County risk level	New cases	positive tests
WIDESPREAD Many non-essential indoor business operations are closed	More than 7 daily new cases (per 100k)	More than 8% positive tests
SUBSTANTIAL Some non-essential indoor business operations are closed	4 - 7 daily new cases (per 100k)	5 - 8% positive tests
MODERATE Some indoor business operations are open with modifications	1 - 3.9 daily new cases (per 100k)	2 - 4.9% positive tests
MINIMAL Most indoor business operations are open with modifications	Less than 1 daily new cases (per 100k)	Less than 2% positive tests



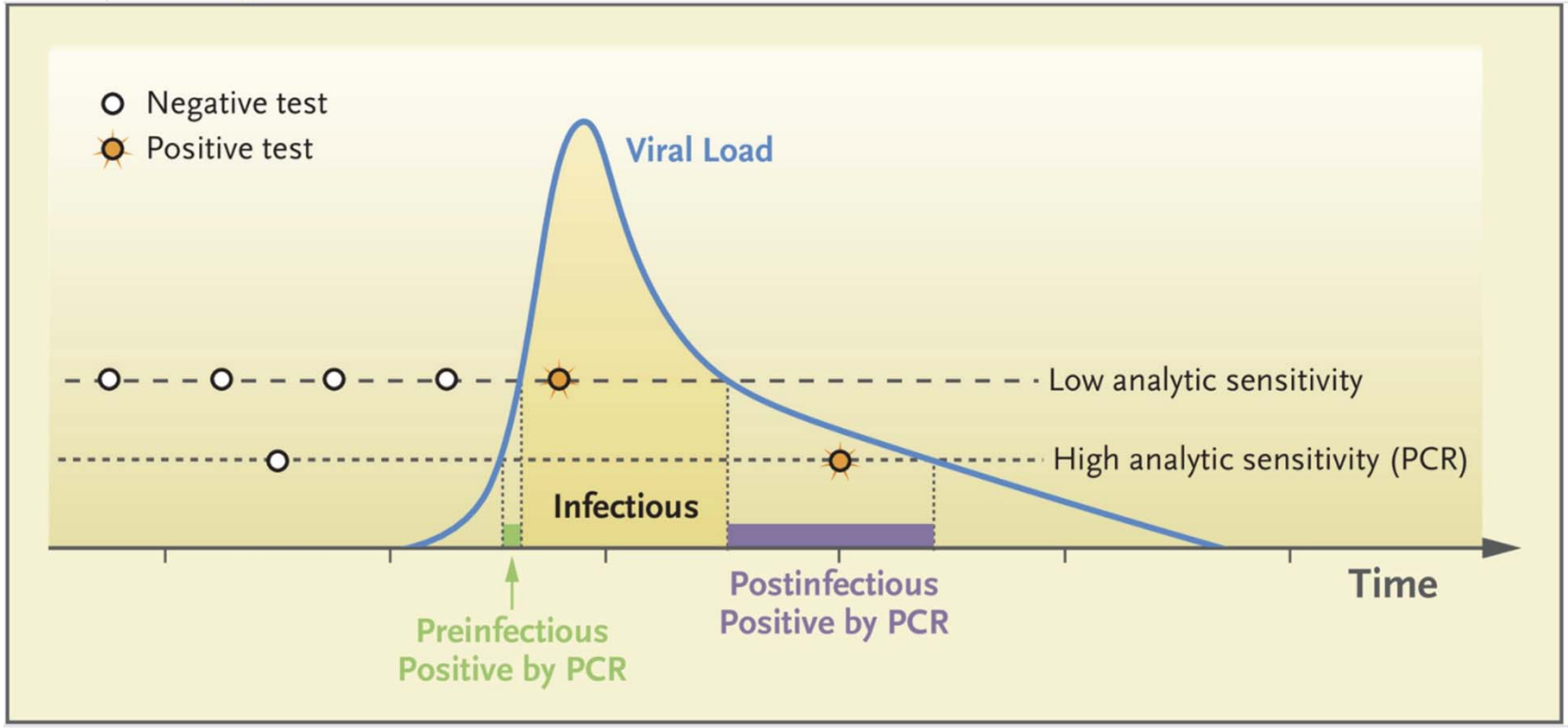
Considerations in testing

- Type of test
  - Sensitivity, specificity
- Frequency of testing
- Turnaround time
  - Point-of-care testing
- Who collects the specimen?
  - Home collection
- Type of biologic fluid tested
  - Nasopharyngeal or oropharyngeal swab
  - Tracheal aspirate
  - Anterior nasal swab
  - Oral sulcus
  - Saliva
- Pooling vs. no pooling

Selected diagnostic tests for SARS-CoV-2

	Molecular tests		Antigen tests	Antibody tests
	Real-time polymerase chain reaction	Loop-mediated isothermal amplification (LAMP)		
What it detects	RNA (quantitative – cycle threshold)	RNA (qualitative)	Viral proteins	IgG, IgM to spike protein or nucleocapsid
When it turns positive	3 days post exposure	3 days post exposure	3 days post exposure	12 days post exposure
Time to result	4-8 hours	<30 minutes	15 minutes	Hours
Sensitivity	High	Lower	Lower	90-100% for IgG

High frequency testing with low analytic sensitivity versus low-frequency testing with high analytic sensitivity



Mina MJ, Parker R, Larrremore DB. Rethinking Covid-19 test sensitivity – a strategy for containment. N Engl J Med 2020 Sep 30 [Epub ahead of print].

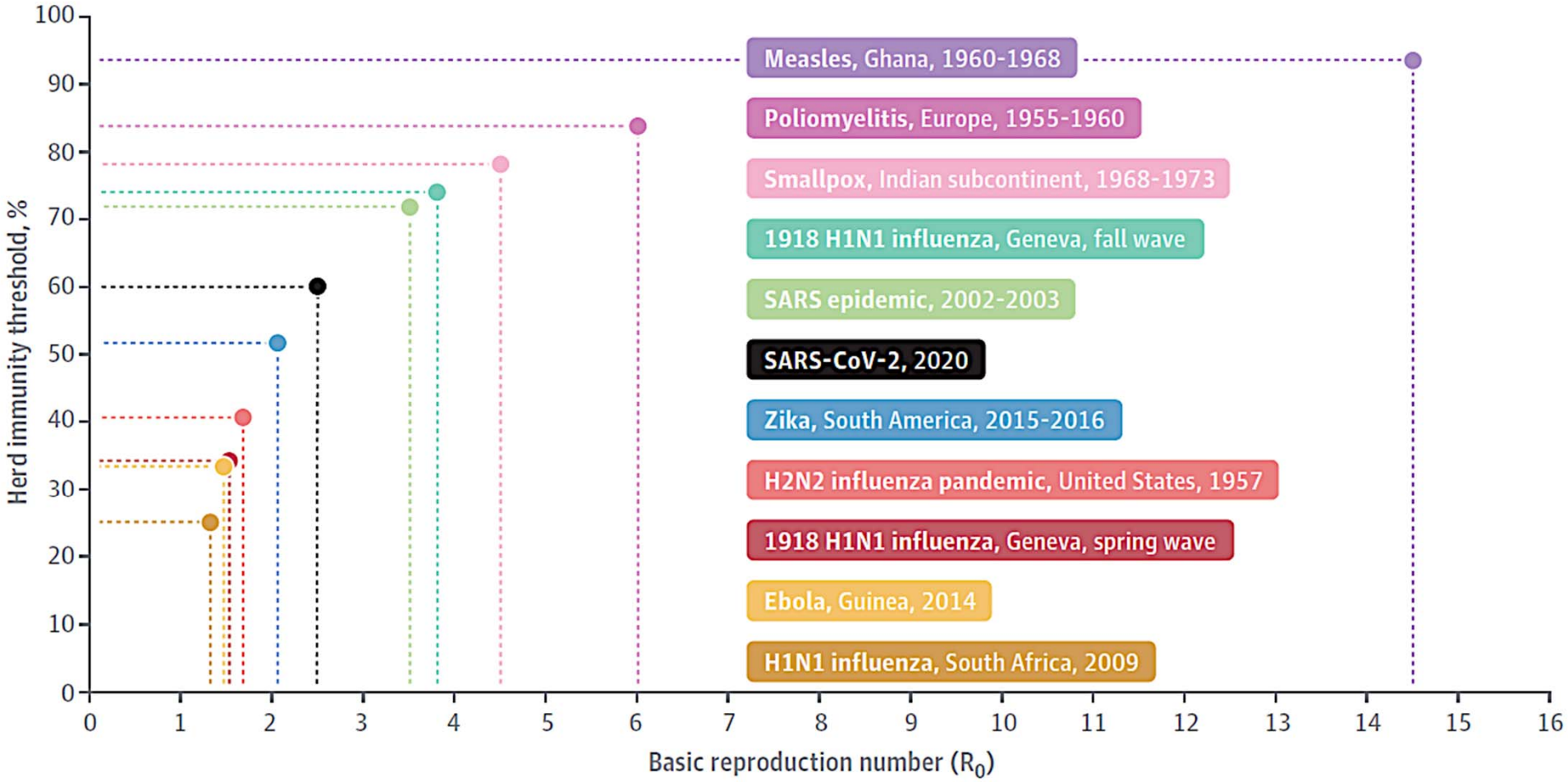
Herd immunity

- Proportion of the population that needs to have durable immunity before viral spread stops

$$\text{Herd immunity (\%)} = (R_e - 1)/R_e$$

- So, if Re = 3, herd immunity = 67%
- From a variety of outbreaks, herd immunity lies probably between 60 and 80%

Figure. Herd Immunity Thresholds by Disease



Omer SB, Yildirim I, Forman HP. Herd immunity and implications for SARS-CoV-2 control. JAMA 2020 Oct 29 [Epub ahead of print].

SARS-CoV-2 phase 3 vaccines in trials

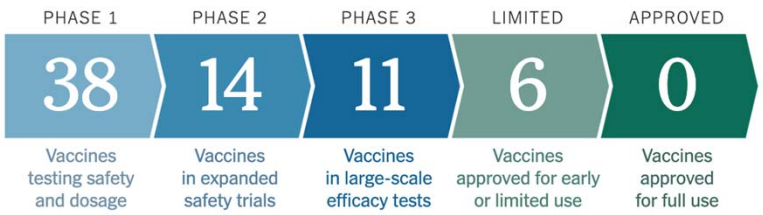
- Nucleic acid vaccines
- Inactivated virus vaccines
- Live attenuated vaccines
- Protein or peptide subunit vaccines
- Viral-vectored vaccines

	Vaccine type	Location	Trial number
(Continued from previous page)			
Phase 3 trials			
AstraZeneca; University of Oxford (30 000 participants)	Chimpanzee adenovirus (ChAdOx1/AXD1222)	UK; India; Brazil, South Africa; USA	NCT04516746
Moderna; National Institutes of Health (30 000 participants)	RNA (mRNA-1273)	USA	NCT04470427
Pfizer; BioNTech (44 000 participants)	RNA (BNT162b1 and BNT162b2)	USA	NCT04368728
The Janssen Pharmaceutical Companies of Johnson & Johnson (60 000 participants)	Adenovirus serotype 26 vector (Ad26.COV2.S)	USA; Argentina; Brazil; Chile; Columbia; Mexico; Peru; Philippines; South Africa; Ukraine	NCT04505722
The Gamaleya National Research Centre for Epidemiology and Microbiology; Academy of Military Medical Sciences (40 000 participants)	Adenovirus serotype 5 vector and adenovirus serotype 26 vector (Sputnik V)	Russia	NCT04530396
CanSino Biologics; Academy of Military Medical Sciences (40 000 participants)	Adenovirus serotype 5 vector (Ad5CoV)	China; Pakistan	NCT04526990
Sinovac Biotech (9000 participants)	Inactivated virus (CoronaVac)	Brazil; Indonesia	..
Sinopharm; Wuhan Institute of Biological Products (21 000 participants)	Inactivated virus	The United Arab Emirates; Bahrain; Peru; Morocco; Argentina; Jordan	..
Sinopharm; Beijing Institute of Biological Products (5000 participants)	Inactivated virus (BBIBP-CorV)	The United Arab Emirates	..

Table: **COVID-19 vaccine clinical trials**

Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. Lancet 2020 Oct 13 [Epub ahead of print].

Progress is vaccines



- Pfizer and BioNTech announced yesterday that interim analysis of their mRNA vaccine BNT162b2 showed 90% efficacy in preventing infection at 7 days after the second dose
- No serious safety concerns
- 43,538 participants, 94 cases to date (need to accumulate 164 for trial to end)
- Likely to be in a position to apply for FDA emergency approval in mid-December
- Issues
  - Vaccine storage and distribution (-70°C)
  - Limited doses available in 2020 – who gets vaccinated first?
  - How well does it work in those most at risk of severe disease?

United States of America

To see results within this country, select a subnational location

Total deaths | Daily deaths | Infections and testing | Hospital resource use | Mask use | Social distancing

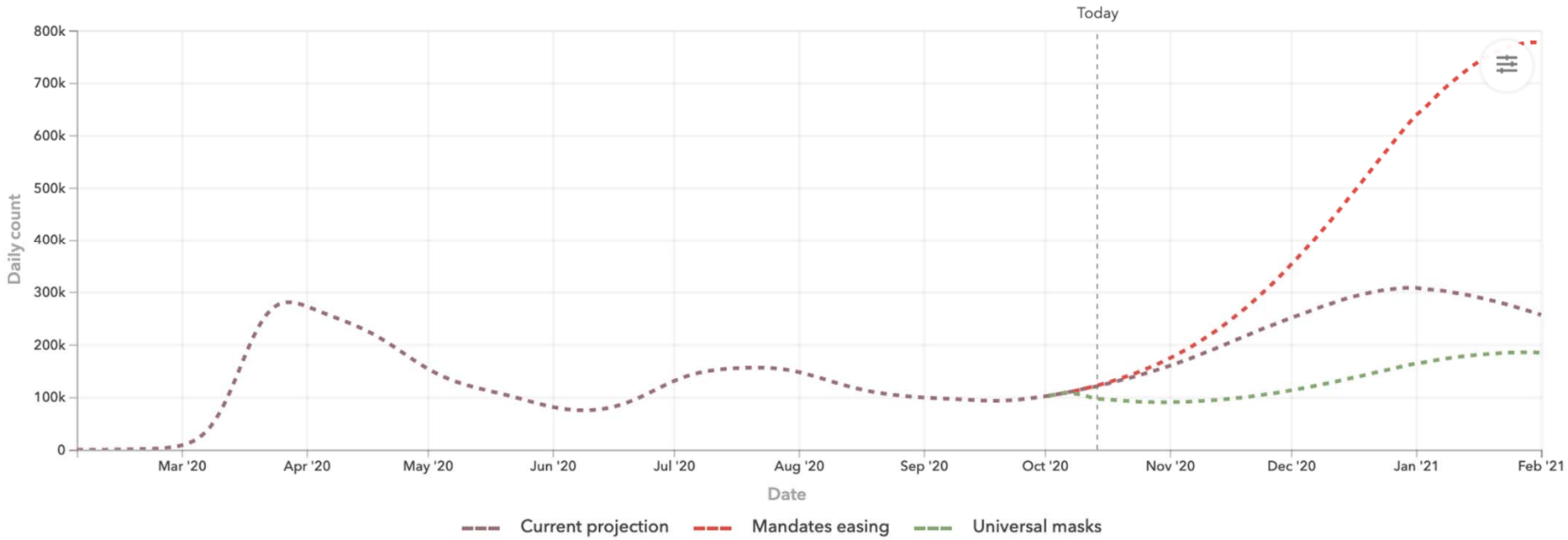
Daily infections and testing

Trend | Compare | Map

Estimated infections are the number of people we estimate are infected with COVID-19 each day, including those not tested.

Estimated infections | Confirmed infections | Tests

Scenario: Projection × Easing × Masks ×



United States of America

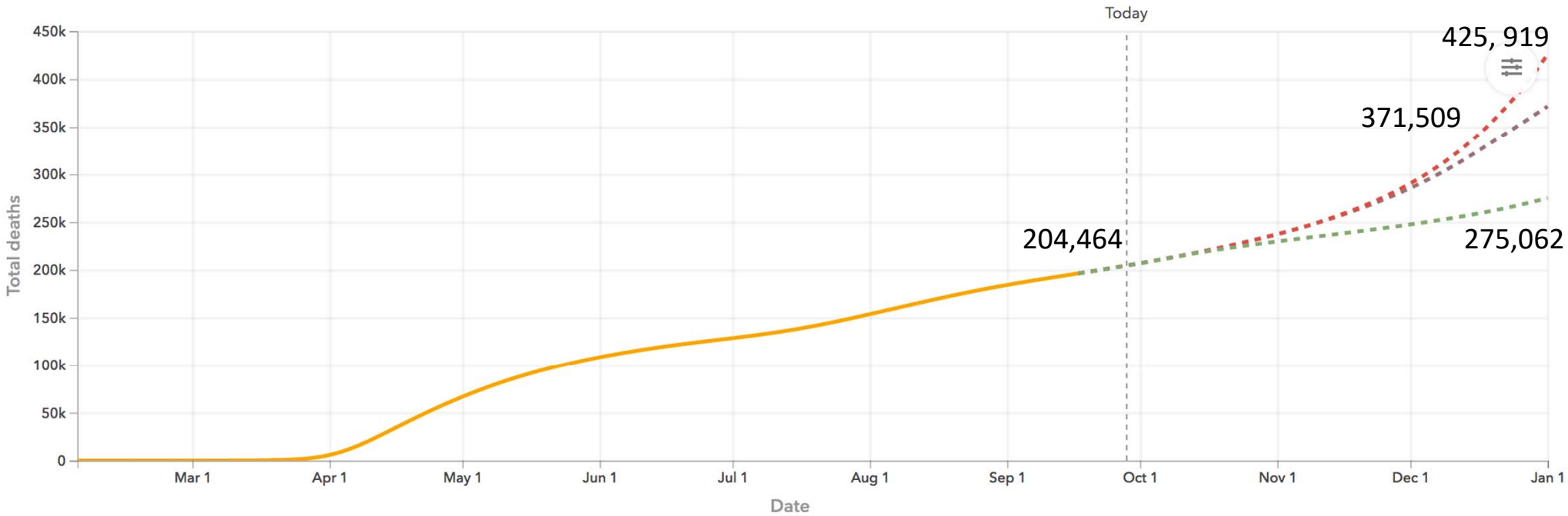
To see results within this country, select a subnational location

Total deaths | Daily deaths | Infections and testing | Hospital resource use | Mask use | Social distancing

371,509 COVID-19 deaths

based on Current projection scenario by January 1, 2021

Scenario: Projection X | Easing X | Masks X



All deaths specific to COVID-19 patients.

What does the future hold?

- Now until the Spring
  - Vaccine(s) not widely available
  - Use only for highest risk populations
  - Well into third wave of infection in the late Fall-Winter
    - Colleges and universities
    - High schools and middle schools
  - Continued need for masks, social distancing, etc.
  - Reopening businesses will depend on local epidemiology and politics
  - Low mortality?
- Spring through late Summer
  - Vaccine(s) go out to general public
  - Variable uptake of vaccine due to vaccine hesitancy, refusal
  - Whether transmission can be sustained depends on vaccine coverage, vaccine efficacy, mass crowd events with super spreading, mask wearing, etc.

What does the future hold

- Likely will need to have vaccination levels in excess of 60-70% to achieve herd immunity
  - Add 10% on top of estimate to account for 90% vaccine efficacy
- If it's <<60%, we may end up with a two-tiered system of people who have been vaccinated or have been recently tested and are uninfected (green) versus those who haven't (red)
- We will likely still need masks and social distancing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Happy (and safe) Thanksgiving

- Risk factors for transmission
  - Community levels of COVID-19
  - Indoors vs. outdoors
  - Duration of the gathering
  - Number of participants
  - Where participants are traveling from
  - Behaviors of attendees prior to gathering
  - Behaviors of attendees during the gathering
- Traveling for the holidays
  - Testing and quarantine
  - https://www.cdc.gov/coronavirus/2019-ncov/travelers/travel-during-covid19.html
- Some additional tips
  - Wear masks and maintain social distance as much as possible
  - Separate tables for separate bubbles
  - Prepare plates in the kitchen rather than passing food or serving it on a buffet
  - Shop online and have food delivered
  - Don’t cook the stuffing inside the turkey!!!
  - Clean cutting boards between poultry and foods that will be eaten raw