GASTROENTEROLOGY/HEPATOLOGY | GENERAL INTERNAL MEDICINE | INFECTIOUS DISEASES | HOSPITAL MEDICINE | NEUROLOGY | PSYCHOLOGY

2020 Learning Together in the 21st Century

PROGRESS

Educating health care providers together to improve interprofessional patient care.

COVID-19 Update

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Director, Division of Infectious Diseases

Disclosure

- Daniel J. Diekema reports:
  - Grant/research support from bioMerieux, Inc
  - Is a consultant for JMI Laboratories
  - Is a consultant for OpGen, Inc.
  - Is a consultant for Inflammatix

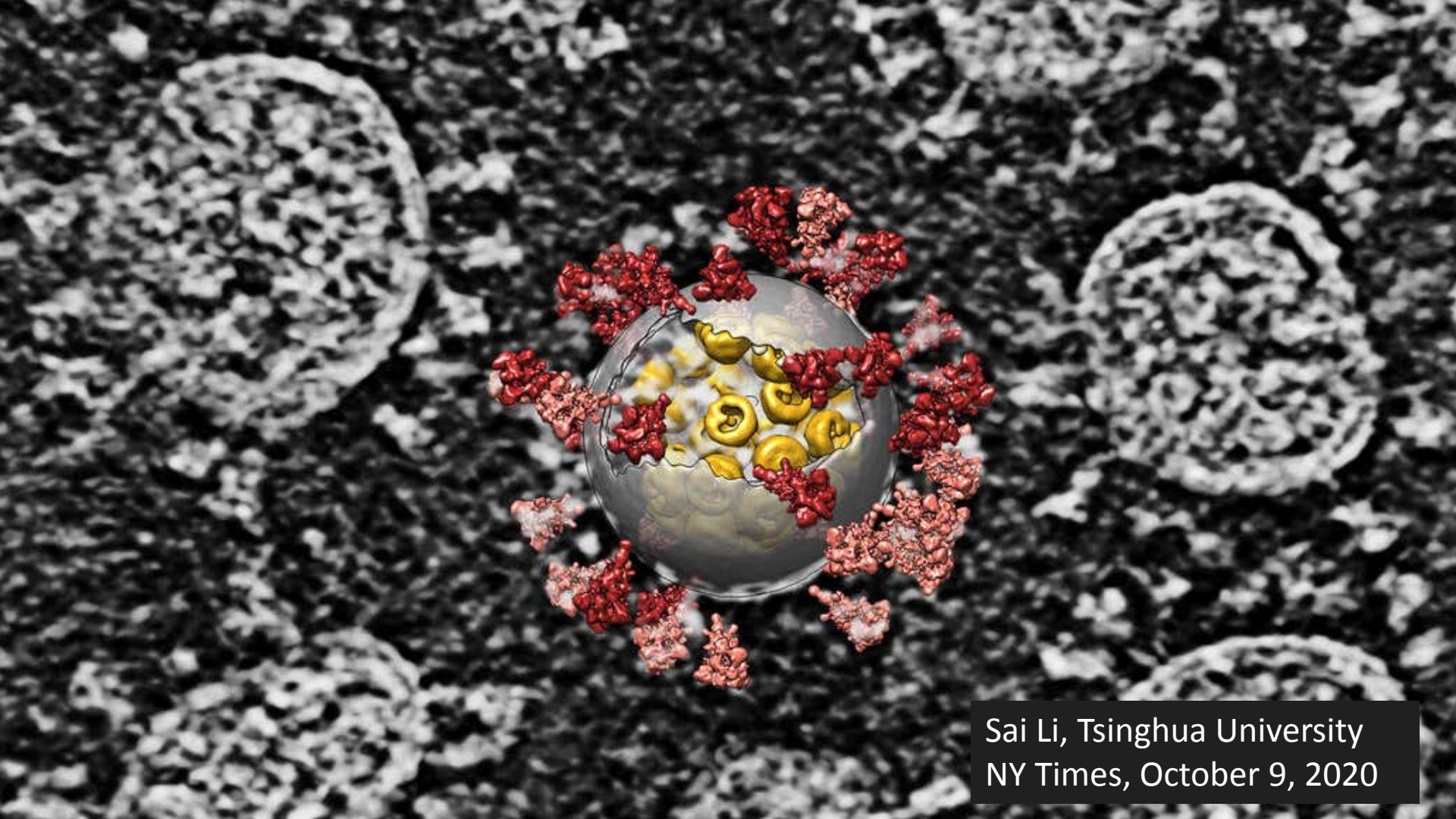
Learning Objectives

Upon successful completion of this activity, participants should be able to:

1. Apply the best test(s) to diagnose acute vs prior COVID-19 infection, and for screening populations for COVID-19
2. Select COVID-19 treatments that have demonstrated benefit in randomized controlled trials.
3. Recommend strategies to prevent SARS-CoV-2 transmission

COVID-19 Update

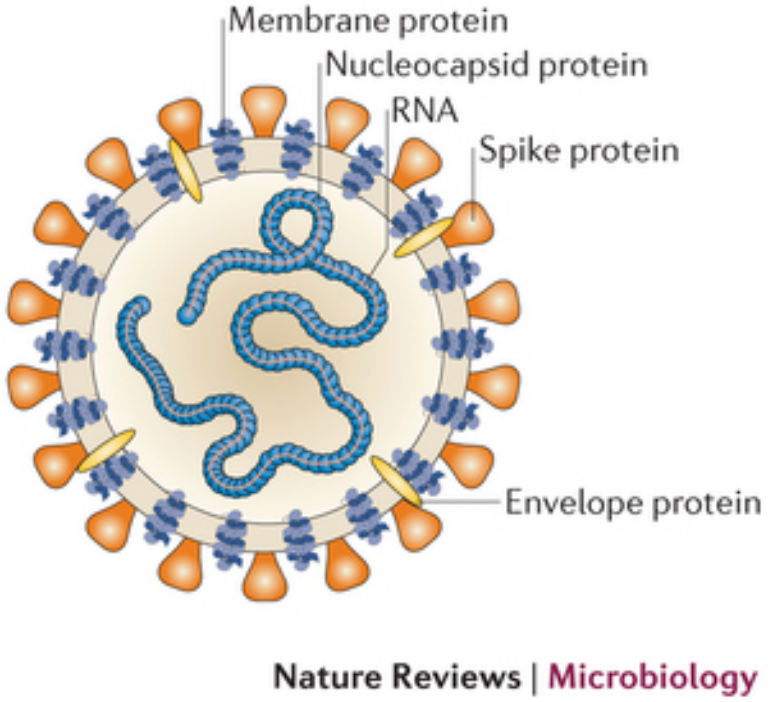
- What is it? *Cause, clinical manifestations*
- How is it spread? *Current state of the pandemic*
- How is it diagnosed? *What tests and when*
- How is it treated? *Summary of current approach*
- How can we prevent it? *Ending the pandemic*



Sai Li, Tsinghua University
NY Times, October 9, 2020

Coronaviruses

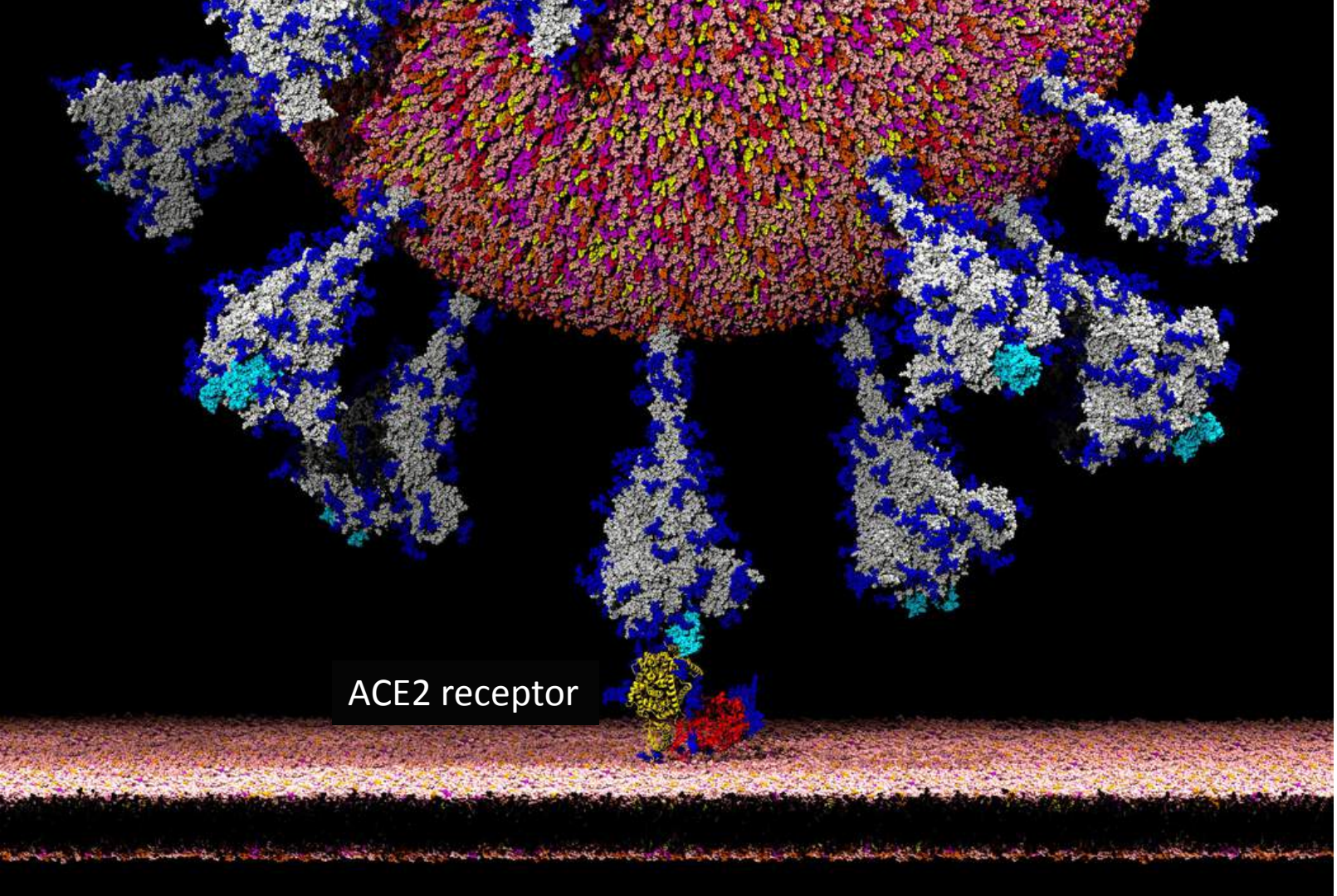
- Large, enveloped, ss + sense RNA viruses, family *Coronaviridae*
- First isolated from humans in 1965
- 4 are endemic in humans, cause URI
  - 229E, OC43, NL63, and HKU1
- 2 recently from zoonotic reservoirs
  - SARS CoV (civet-bat), MERS CoV (camel)
- Outer surface projections (corona)



Comparing the coronaviruses

	SARS-CoV-2	MERS-CoV	SARS-CoV-1	Other human Coronaviruses
First reports	Wuhan, China 2019	Saudi Arabia 2012	Southern China 2002	4 strains cause ~15-30% of URIs
Source and Transmission	Bats R0 ~2-5	Camels R0 ~0-4*	Civets via bats R0 ~2-4*	Homo sapiens R0 ~1-2
Cases Mortality	40 million 2.5% (>1 million)	2,499 confirmed 34% (n=861)	8,096 confirmed 10% (n=774)	Millions yearly Very low
Current status	Global spread continues	All cases linked to Gulf states. Declining #'s	No new cases since 2004. 87% in China/HK	Year-round transmission

*in context of hospital outbreaks (e.g. MERS-CoV R0 <1, no sustained H2H)



L. Casalino
Amaro Lab
UCSD
NYT 10/9/20

SARS-CoV-2 Infection

Viral entry →

TMPRSS2 (serine protease):

- Activates viral S protein
- Cleaves ACE2 receptor

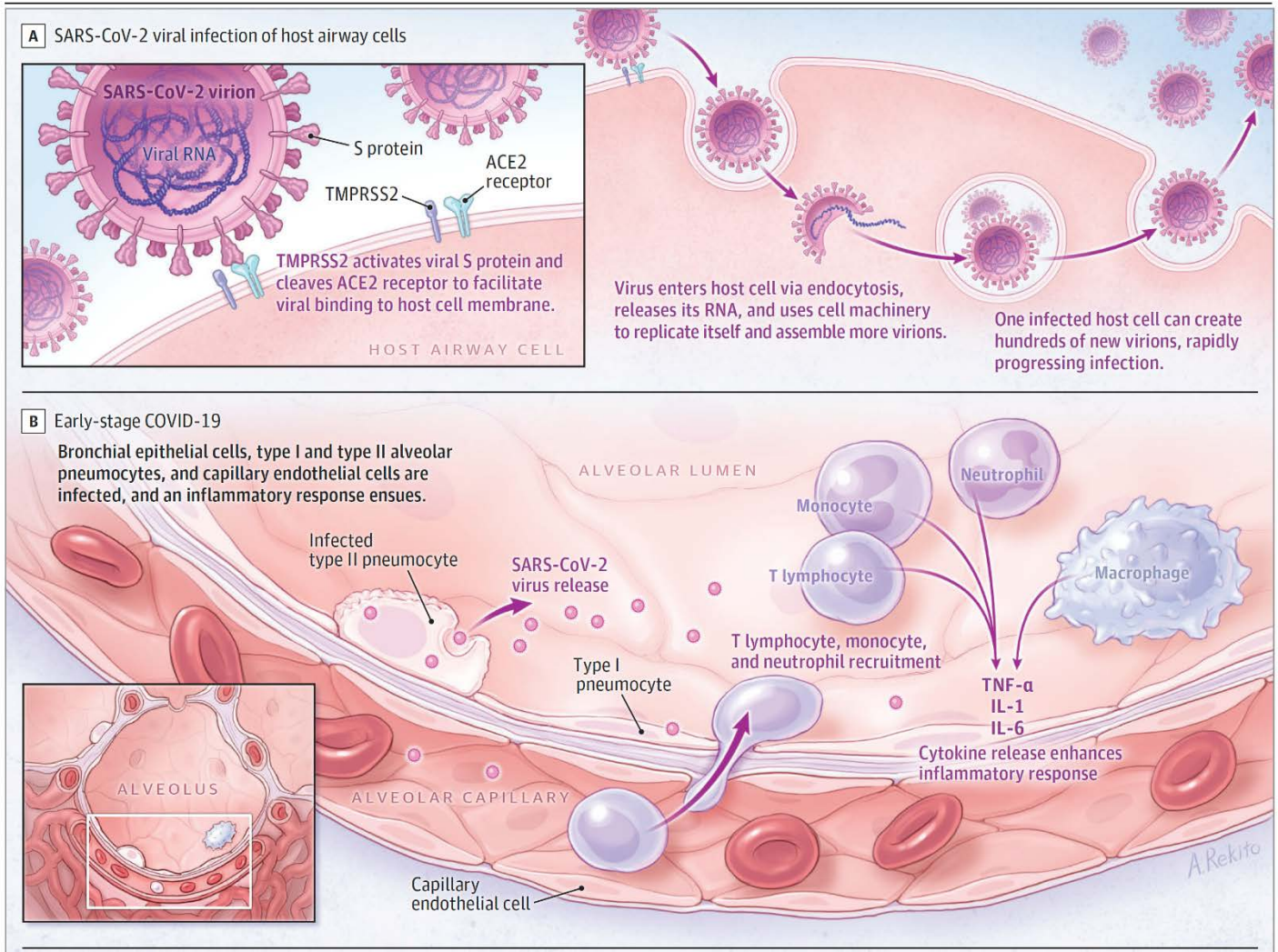
Can also infect capillary endothelial cells

Host response →

- Inflammatory signaling
- Macrophage, neutrophil, lymphocyte recruitment
- Cytokine release

Wiersinga, et al. JAMA 2020

Figure 2. Immunopathogenesis of Coronavirus Disease 2019 (COVID-19)



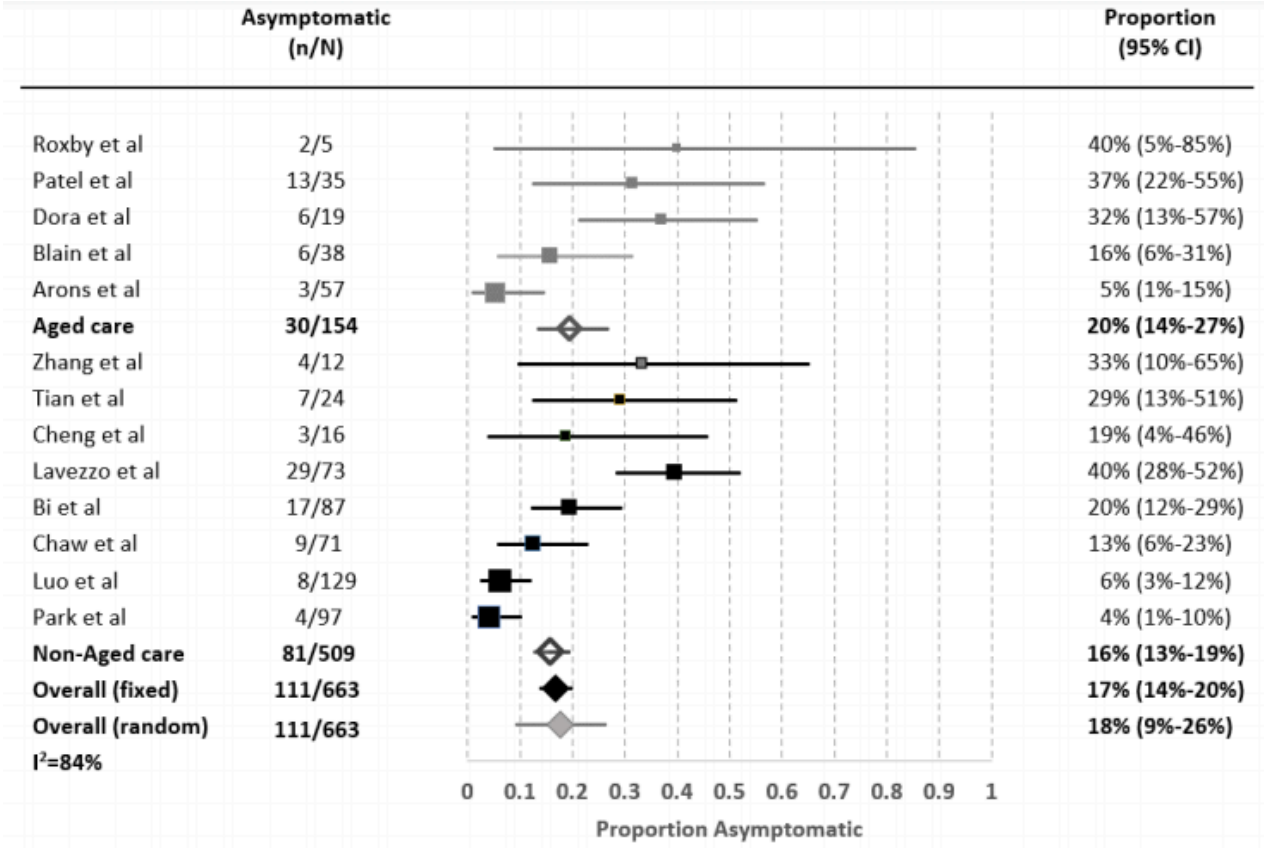
COVID-19 Clinical Presentation

- Mean incubation period 5 days
  - 2-14 days (almost all within 11 d)
- Severity depends upon age distribution and comorbidities
  - 80% mild
  - 15% severe
  - 5% critical
- For hospitalized, median of 7 days from symptom onset to admission

Wiersinga, et al. JAMA 2020:July 10 (online).

- Most common symptoms:
  - Fever 80-90%
  - Cough (dry) 60-86%
  - Shortness of breath 53-80%
  - Change in smell/taste 64-80%
  - Fatigue 38-70%
  - N/V or diarrhea 15-39%
  - Myalgias 15-44%
- Complications are protean
  - All major organ systems
  - Thromboembolic events 31-59%

How many COVID-19 cases are **asymptomatic**: A meta-analysis



~18%

Byambasuren, et al. JAMMI 2020;online 10/9/20.

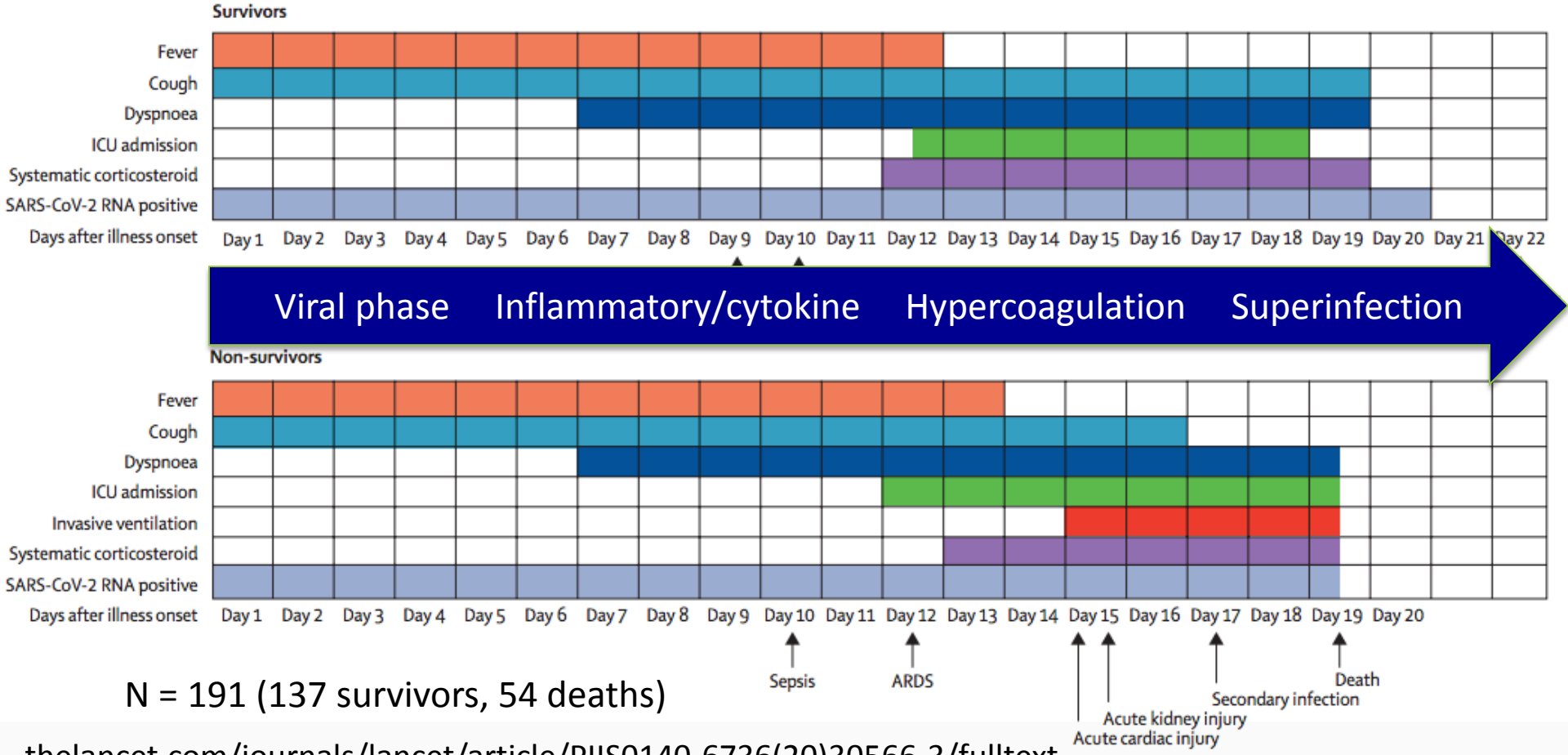
COVID-19: Lab and radiology

- COVID-19 PCR, Ag, serology
  - Consider site, duration of sx
- Lymphopenia most common
  - >80% of hospitalized patients
- Elevated CRP & PCT
- ↑ PT, ↓ platelets, ↑ D-dimer
  - Lymphopenia and D-dimer may have prognostic value as well

Scattered ground glass opacities, nonspecific. Normal in ~15% early in illness.

Wu et al. JAMA Intern Med 2020;March 13.

Time course for the 15-20% with COVID-19 requiring hospitalization



N = 191 (137 survivors, 54 deaths)

thelancet.com/journals/lancet/article/PIIS0140-6736(20)30566-3/fulltext

COVID-19: Long term illness

- Extreme fatigue
- Muscle weakness
- Low grade fever
- Shortness of breath
- Inability to concentrate
- Memory lapses
- Mood changes
- Sleep difficulties
- Headaches
- Diarrhea and/or vomiting
- Skin rashes
- Chest pains and palpitations

ACCEPTED MANUSCRIPT

Post-Acute COVID-19: An Overview and Approach to Classification

Eva M Amenta, MD, Amy Spallone, MD, Maria C Rodriguez-Barradas, MD, Hana M El Sahly, MD, Robert L Atmar, MD, Prathit A Kulkarni, MD

Open Forum Infectious Diseases, ofaa509,
https://doi.org/10.1093/ofid/ofaa509
Published: 21 October 2020 **Article history**

Univ. Iowa Health Care clinic to study long term issues caused by COVID-19

Amenta, et al. Open Forum Infectious Diseases 2020; October 21.

COVID-19 Infection Fatality Rate (%) vs accident deaths, by age

Age Group	COVID-19 IFR	Auto deaths	Other accident deaths
0 to 34	0.004	0.015	0.032
35 to 44	0.07	0.012	0.043
45 to 54	0.23	0.013	0.043
55 to 64	0.75	0.013	0.043
65 to 74	2.5	0.013	0.040
75 to 84	8.5	0.017	0.094
85 +	28.3	0.019	0.349

Levin, et al. https://www.medrxiv.org/content/10.1101/2020.07.23.20160895v6

Underlying medical conditions among those who di -19

Most common is cardiovascular (~60%)

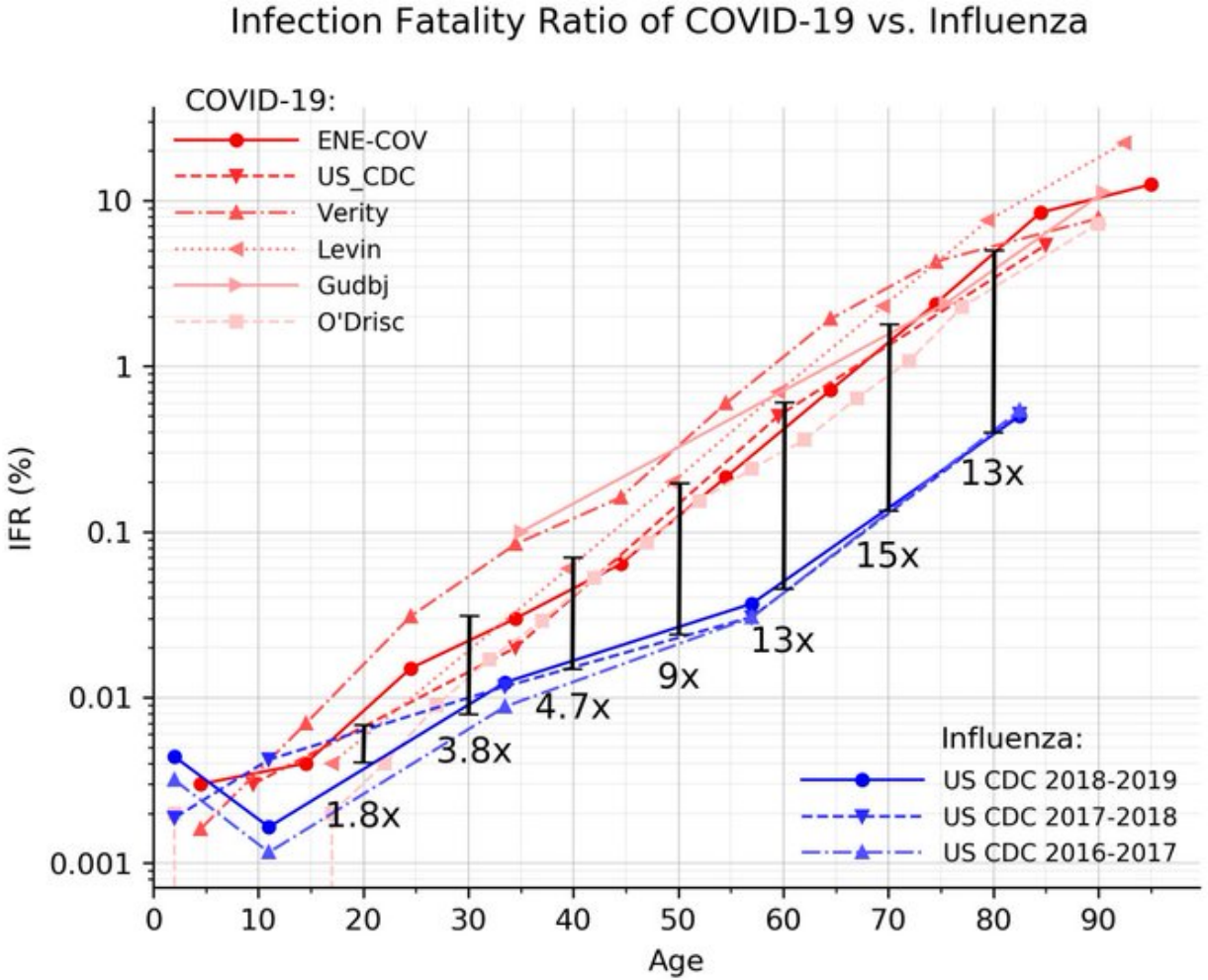
Over 75% of those who die from COVID-19 have >=1 underlying medical condition

Black, LatinX, Native Americans are vastly over-represented among COVID-19 deaths

TABLE 2. Clinical features of decedents collected t United States, February 12–April 24, 2020

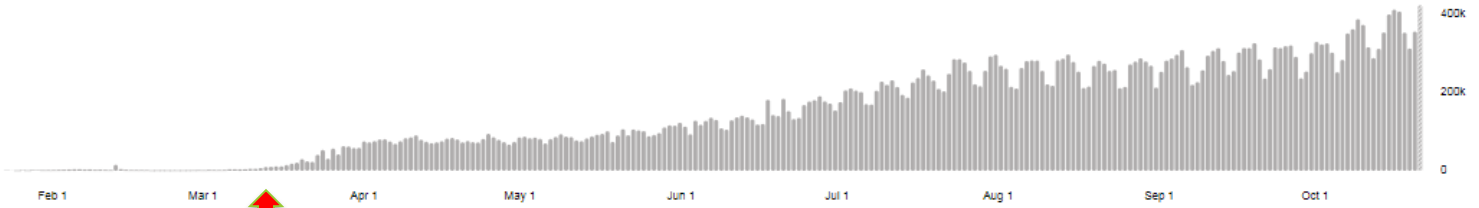
Characteristic					≥85
					2,603
Race/Ethnicity					
Hispanic/Latino			(22.5)		431 (16.6)
White, NH				1,082 (37.3)	1,421 (54.6)
Nonwhite, NH			(39.1)	1,007 (34.7)	607 (23.3)
Black, NH			715 (29.0)	731 (25.2)	406 (15.6)
Asian, NH		(6.3)	157 (6.4)	189 (6.5)	156 (6.0)
Multiracial/Other ra		222 (2.8)	90 (3.7)	87 (3.0)	45 (1.7)
Unknown		(7.6)	461 (5.8)	158 (6.4)	159 (5.5)	144 (5.5)
≥1 underlying medic		2,228 (83.1)	5,906 (74.1)	1,922 (78.0)	2,175 (75.0)	1,809 (69.5)
≥2 underlying medica	(54.2)	1,647(61.4)	4,125 (51.8)	1,403 (57.0)	1,549 (53.4)	1,173 (45.1)
≥3 underlying medical	3,269 (30.7)	1,012 (37.8)	2,257 (28.3)	803 (32.6)	844 (29.1)	610 (23.4)

https://www.cdc.gov/mmwr/volumes/69/wr/mm6928e1.htm

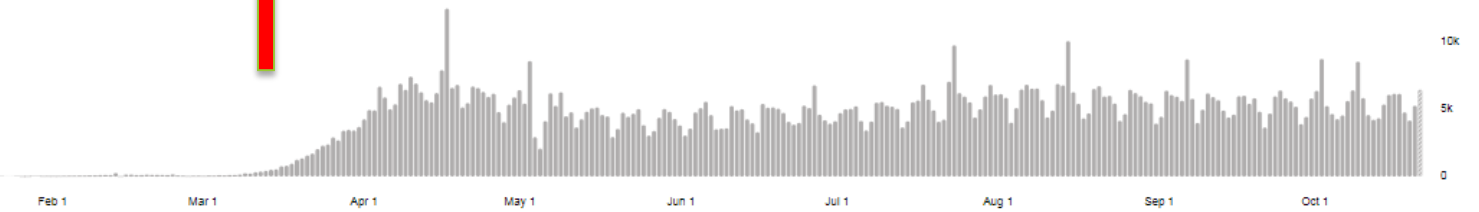


https://www.medrxiv.org/content/10.1101/2020.07.23.20160895v6

41,104,946
confirmed cases



1,128,325
deaths

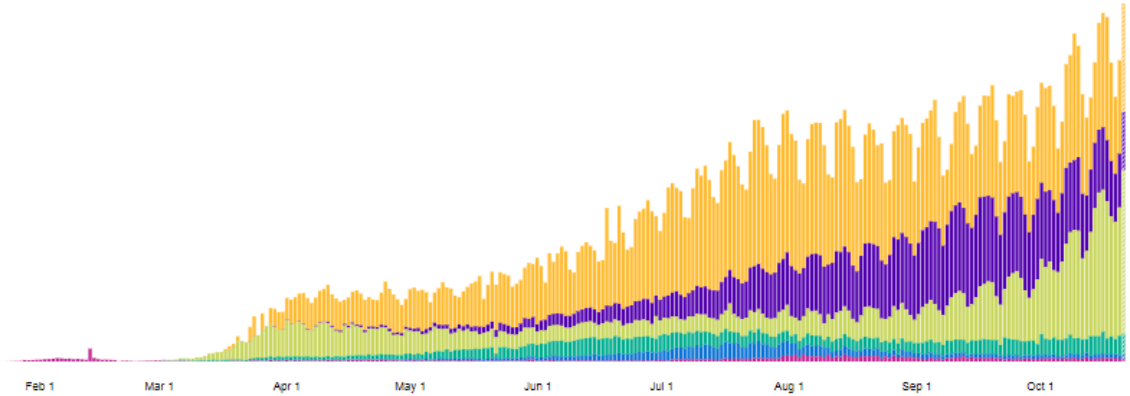


Source: World Health Organization
Data may be incomplete for the current day or week.

Situation by WHO Region

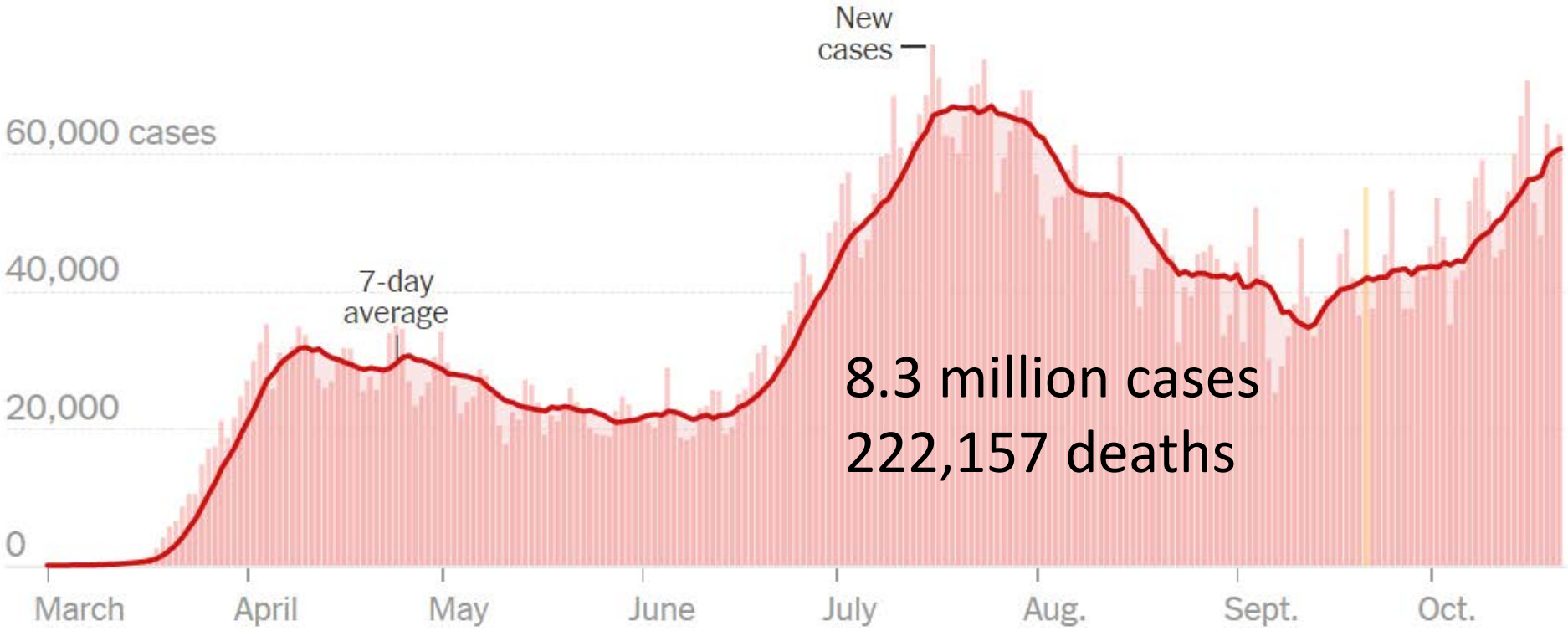
Daily | Weekly | Cases | Deaths | Count

Americas	19,040,071 confirmed
South-East Asia	8,679,128 confirmed
Europe	8,576,945 confirmed
Eastern Mediterranean	2,836,187 confirmed
Africa	1,276,311 confirmed
Western Pacific	695,563 confirmed



covid19.who.int 10/22/20

New reported cases by day in the United States



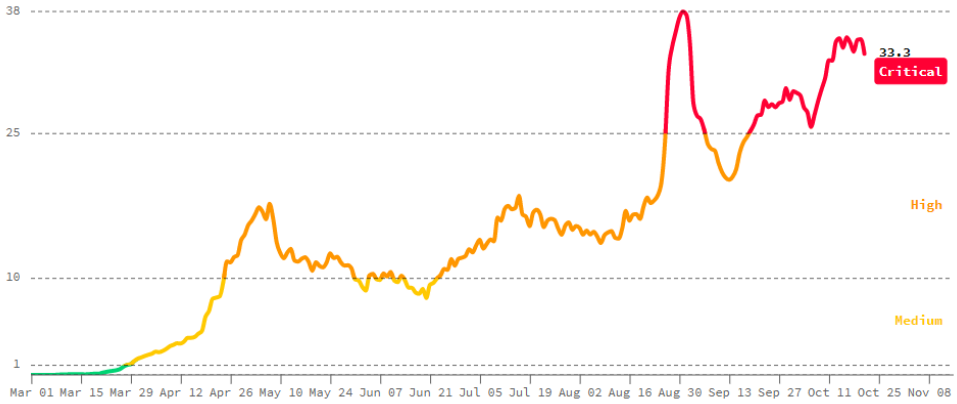
8.3 million cases
222,157 deaths

www.nytimes.com 10/22/20

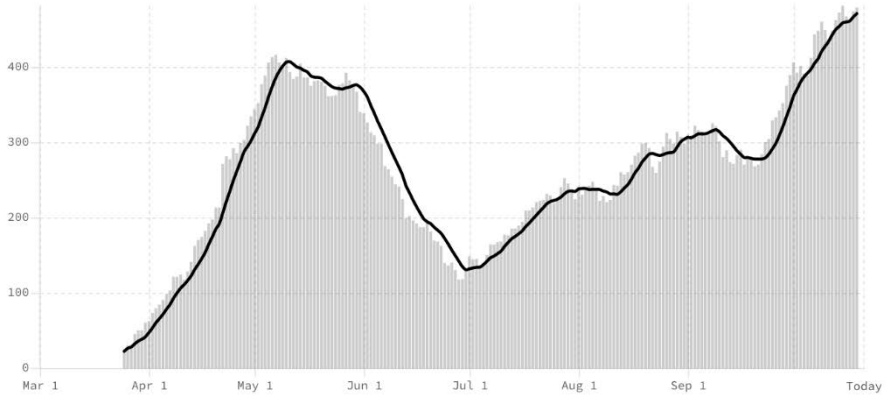
COVID-19 in Iowa

- **111,166** total cases reported
- **1599** total deaths reported
- **70** LTCF outbreaks detected
- **794** deaths in LTCF reported

New cases per 100K population



Current hospitalizations



New COVID-19 deaths per day

10/22/20, via covidactnow.org and Iowa Department of Public Health

University of Iowa Health Care situation

Thursday, Oct. 22, 2020, update

Note: The numbers reflect only patients seen within UI Health Care, which includes patients from all counties seen here in Iowa City. They will not match the totals reported by the Iowa Department of Public Health for several reasons, including different testing time intervals and geographic scope. Also, numbers are reported only Monday through Friday and might not reconcile from one day to the next.

	Yesterday	Calendar year-to-date
Current COVID-19 adult inpatients	26	626
Current COVID-19 pediatric inpatients (age <18 years old)	1	33
% Positive symptomatic COVID-19 test results*	16%	18%
Number of UI Health Care employees who have tested positive for COVID-19**	2	639
Telehealth Influenza-Like-Illness (ILI) screening (telephone & video appointments)***	302	53,158
ILI clinic visits***	595	65,354

http://medcom.uiowa.edu/theloop/covid-19-by-the-numbers

How is SARS-CoV-2 Transmitted?

Summary of COVID-19 contact investigations

Country	COVID + index cases	Contacts (total/HCW)	Attack rate overall	Attack rate household	Attack rate HCW
U.S.	10	445/100	0.45%	10.5%	0%
China*	347	4950/679	2.6%*	10.2%	1.0%
Korea	30	2370/233	0.55%	7.6%	0%
Taiwan**	100	2716/698	0.8%	4.6%	0.9%

*included repeated PCR on all contacts

**Face-to-face without PPE for >15 minutes

Burke, et al. MMWR 2020;69:245-246.
https://www.medrxiv.org/content/10.1101/2020.03.24.20042606v1
Ostong Public Health Res Perspect 2020;11:81-84.
Cheng et al. JAMA Intern Med 2020;May 1, 2020.

JAMA Internal Medicine | Original Investigation

Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset

Hao-Yuan Cheng, MD, MSc; Shu-Wan Jian, DVM, MPH; Ding-Ping Liu, PhD; Ta-Chou Ng, BSc; Wan-Ting Huang, MD; Hsien-Ho Lin, MD, ScD; for the Taiwan COVID-19 Outbreak Investigation Team

- 100 confirmed cases of COVID-19 in Taiwan
- Careful contact tracing of 2716 close contacts
- All contacts quarantined for 14 days from last contact
- Any symptoms triggered COVID-19 PCR testing
- Close household and healthcare contacts all tested

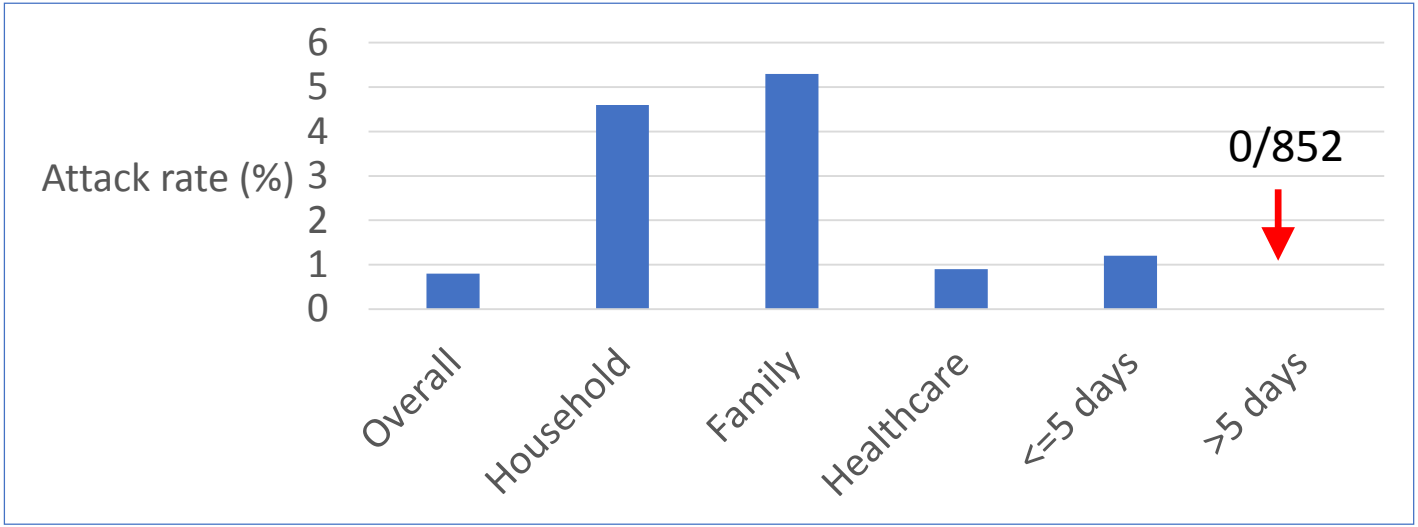
Definition of close contacts

- Outside healthcare settings: Did not wear appropriate PPE during face-to-face contact with a confirmed case for > 15 min
  - *Household contacts*: same household with the index case
  - *Family contacts*: family members not in same household

- In healthcare settings: Did not wear appropriate PPE when within 2 meters of a confirmed case (HCW or other patient)
  - Appropriateness of PPE dependent upon setting/procedures
    - e.g. aerosol-generating without N95 = close contact

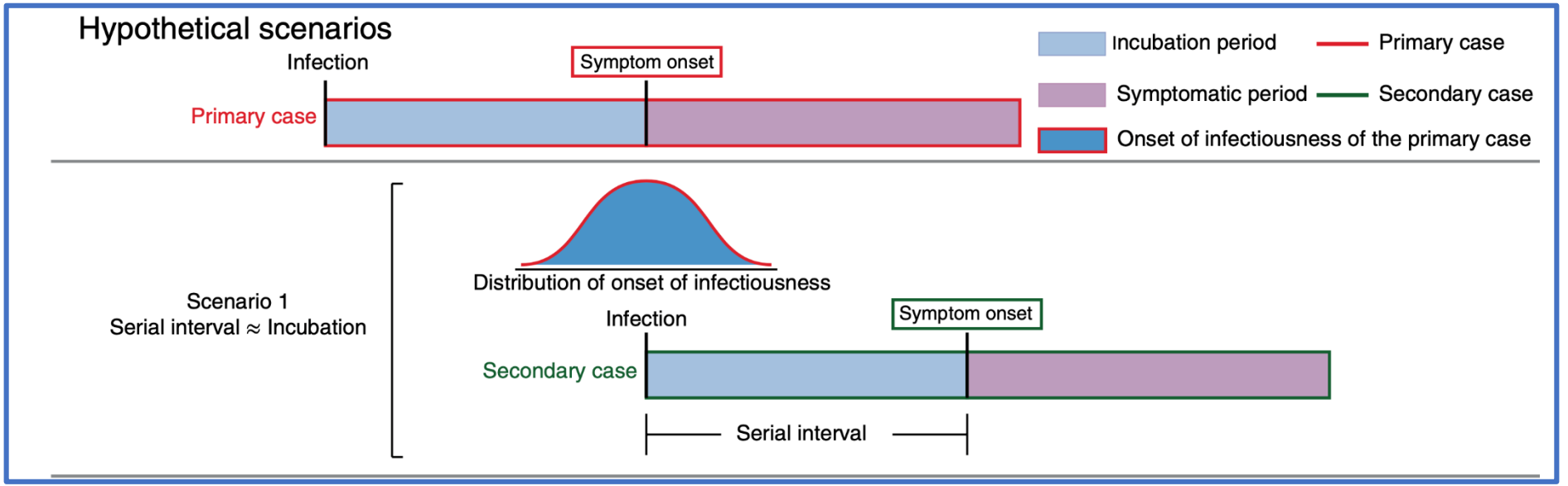
Results

- 22 secondary cases among 2716 close contacts (0.8% [0.5-1.2])
- Median incubation period = 4.1 days
- Median serial interval = 4.1 days
  - *Time from onset of index case symptoms to onset of secondary case*



Viral shedding dynamics and transmissibility

- Transmission pairs (n = 77) separately analyzed
  - Mean serial interval = 5.8 days
  - Mean incubation period = 5.2 days



He, et al. Nature Medicine 2020 https://doi.org/10.1038/s41591-020-0869-5

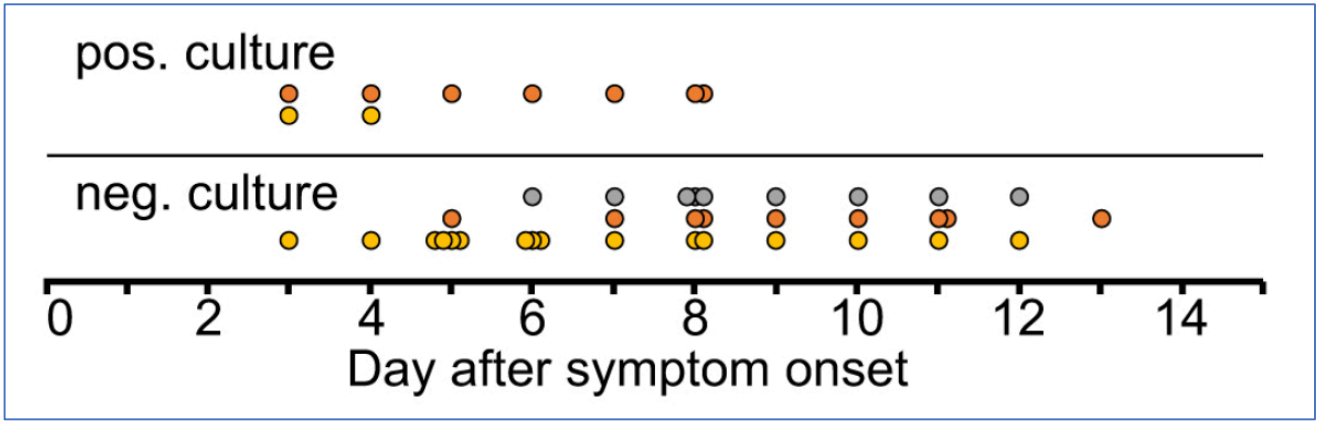
Secondary transmission rate from asymptomatic vs symptomatic

Study	Asymptomatic transmission rate	Symptomatic transmission rate	Pooled Relative Risk
Zhang, et al	1/119 (0.8)	11/250 (4.4)	
Cheng, et al	0/91 (0)	22/2644 (0.8)	0.58
Chaw, et al	15/691 (2.2)	28/1010 (2.8)	
Luo, et al	1/305 (0.3)	117/2305 (5.1)	
Park, et al	0/4 (0)	34/221 (15.4)	

Byambasuren, et al. JAMMI 2020;online 10/9/20.

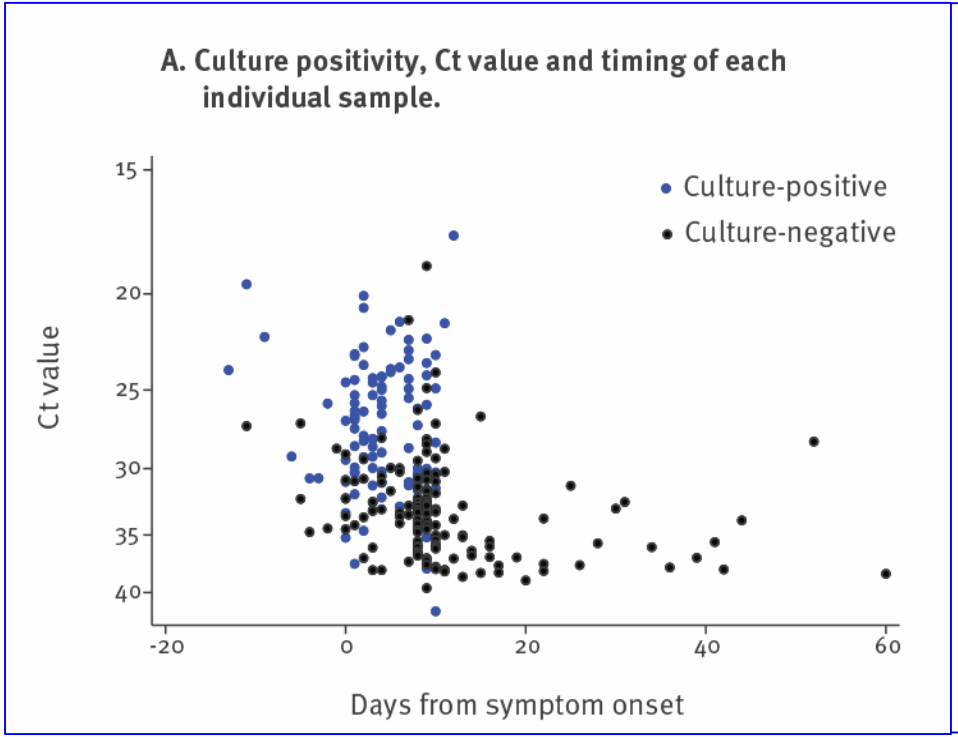
Viral shedding in pts hospitalized with COVID-19

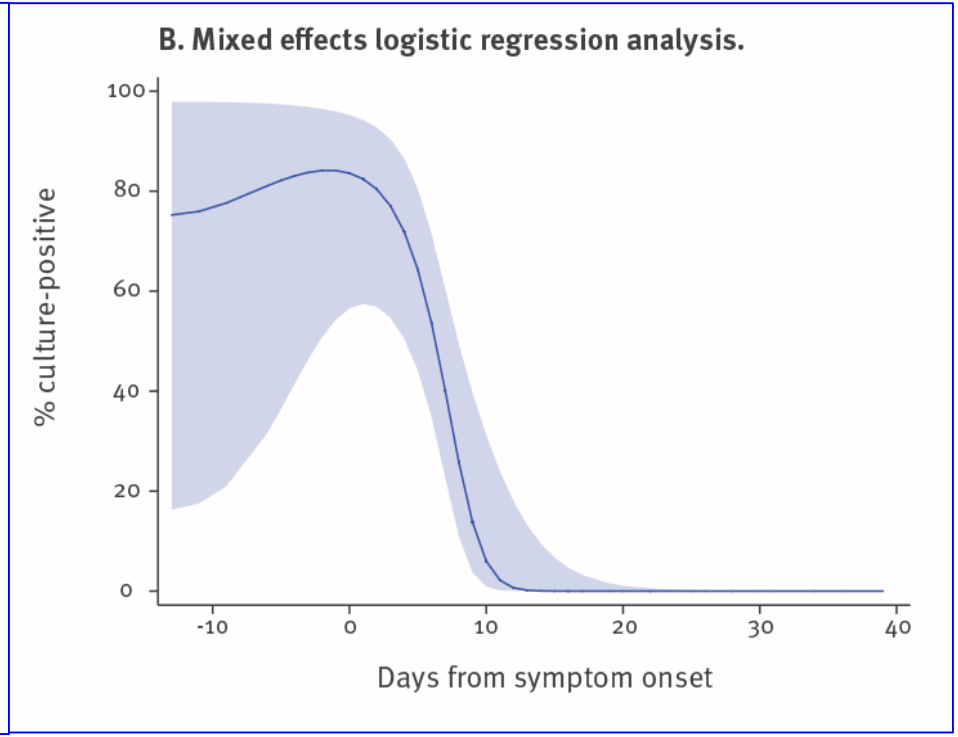
- Careful virologic assessment of 9 pts in Germany
- Very high levels of virus from URT in early infection
- Rapid reduction by day 7 after symptom onset
- Shift to lower respiratory tract shedding
- Cultures + from resp tract, not stool, urine or blood



Wolfel R, et al. Nature 2020;581:465-69.

Culture positivity over time among 246 mild-to-moderate COVID-19 cases in UK





Singanayagam, et al. Eurosurveillance 2020;25:pii=2001483

Summary of contact investigations and viral shedding studies:

- Infectivity highest day -2 to day 5, then drops quickly
- Short casual contacts are very low risk
- “Meaningful” contacts required (close & prolonged)
  - Translated into “6 feet and 15 minutes”
- Suggests droplets or “short-range aerosols” involved
- Fomite (contact) transmission also possible
- What about “airborne”?

https://www.cdc.gov/coronavirus/

Comparing SARS-CoV-2 to airborne pathogens

Pathogen	R_0	Household attack rate
SARS-CoV-2	2-4	10-30%
Measles	12-18	>90%
Varicella Zoster	10	85%
TB (cavitary, +)	~10/year	>50%

https://haicontroversies.blogspot.com/2020/04/airborne-vs-droplet-turbulent-gas.html

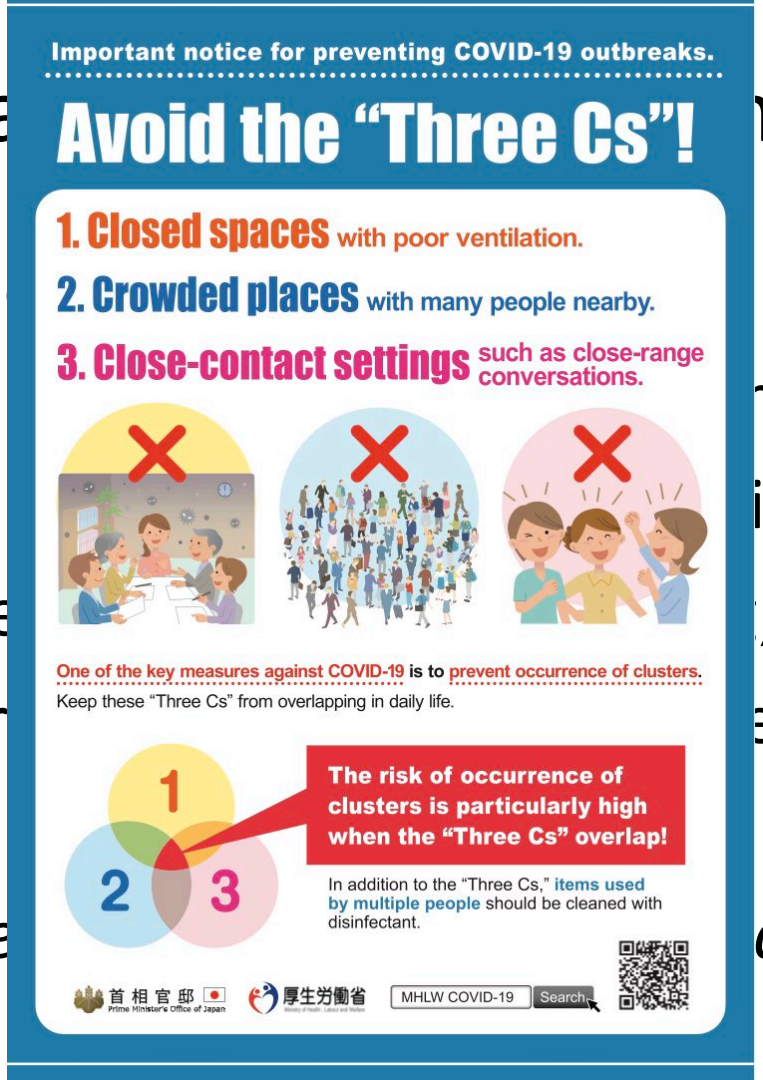
“Superspread” events: Early examples

Location	Setting	Activities	Attack rate	Deaths	References
Washington	Choir Practice	Singing	53/61 (87%)	2	MMWR 5/12/20
Arkansas	Church events Multiple days	Singing Close contact	35/92 (38%)	3	MMWR 5/19/20
Illinois	Funeral Birthday party	Close contact Singing	Unknown 7/9 (78%)	3	MMWR 5/19/20
South Korea	Fitness classes	Aerobics	8/27 (30%) 54/217 (26%)	0	Emerging ID August 2020

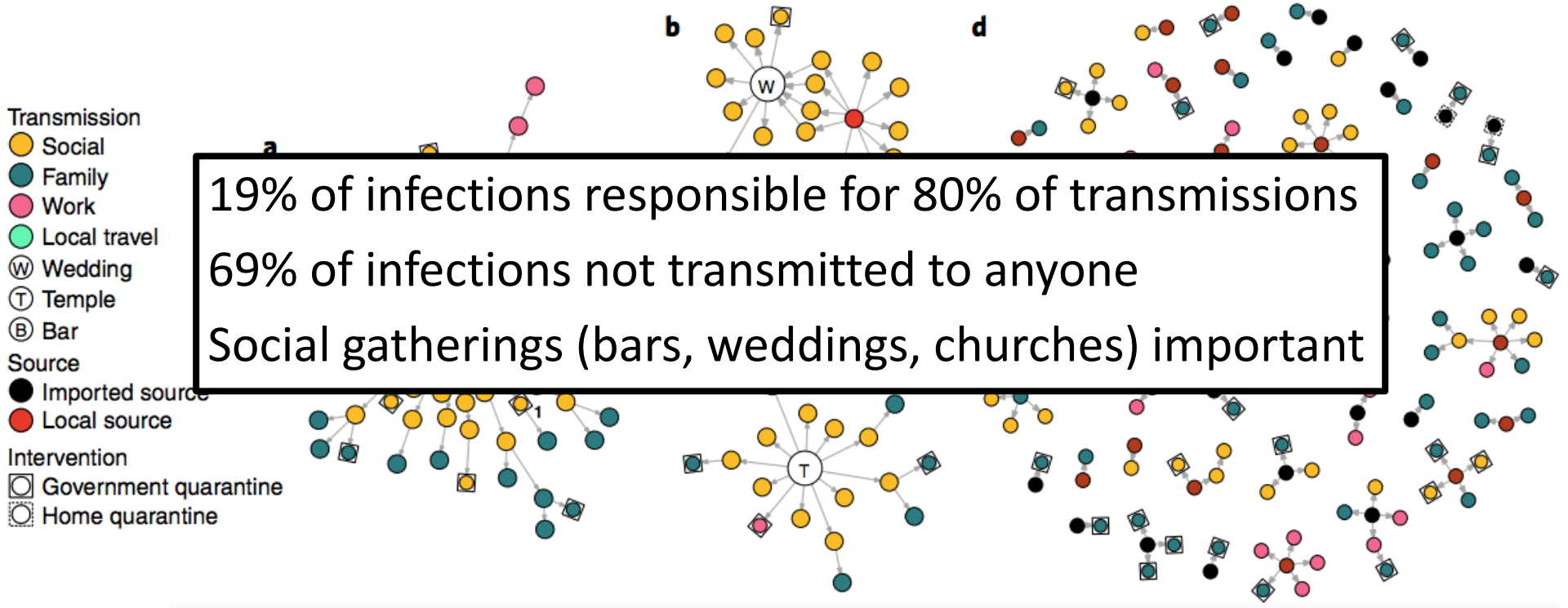
Superspread… …non features

- Prolonged …
- Crowded a… …ndoor spaces
- Inability to … …ing
- Vigorous re… …, exercise)
- Lack of per… …ent

Apply the… …approaches



Heterogeneity in COVID-19 transmission



19% of infections responsible for 80% of transmissions

69% of infections not transmitted to anyone

Social gatherings (bars, weddings, churches) important

Adam, et al. Nature Medicine 2020; September 17

SARS-CoV-2 diagnostic testing

- **PCR/NAAT: Detects viral nucleic acid sequences**
  - Highest analytic sensitivity
  - Can remain positive long after acute infection
- **Antigen testing: Detects viral proteins**
  - Lower analytic sensitivity
  - Positive test: intact/viable virus more likely present
- **Serology: Detects antibody response to the virus**
  - Negative during early viral phase of illness
  - Antibody response detectable 1-3 weeks into illness

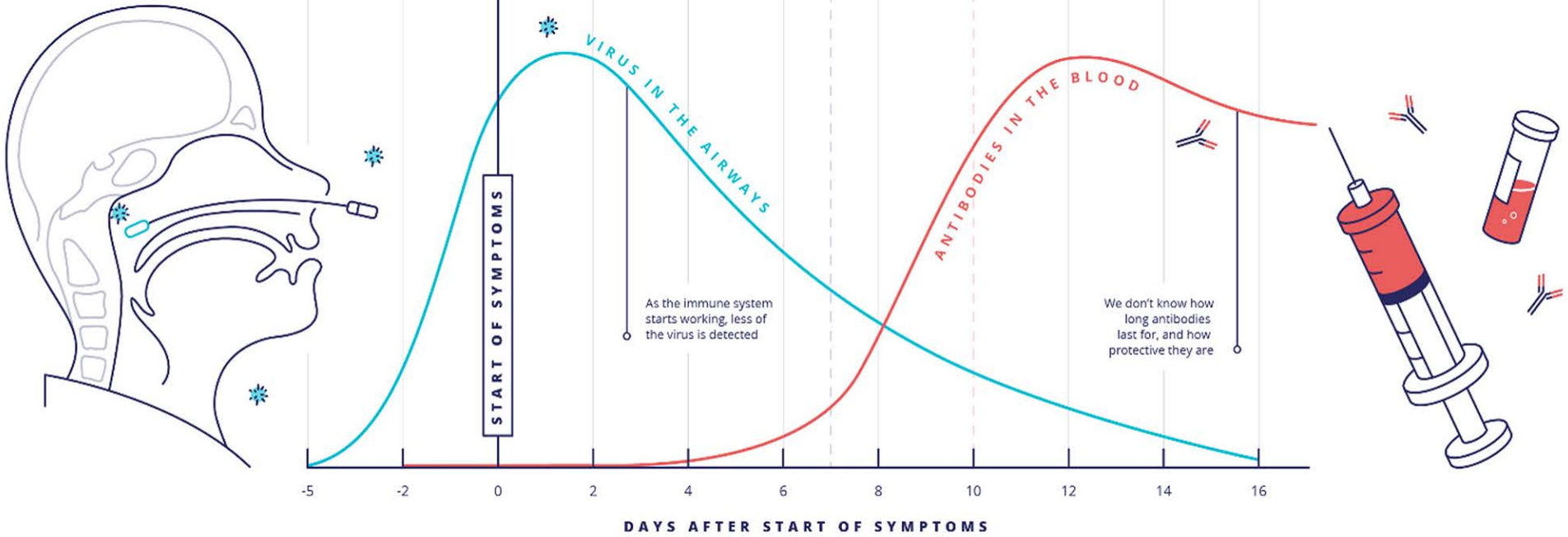
Sensitivity: Analytic vs. Clinical

- Analytic: How much viral nucleic acid or antigen must be present in a sample for test to be positive?
  - Independent of clinical situation
  - Can also be expressed as ‘limit of detection’ (LOD)
- Clinical: How likely is the test to be positive if my patient’s symptoms are due to COVID-19?
  - Varies by test type, sampling site, symptom duration

PCR +

Antigen +

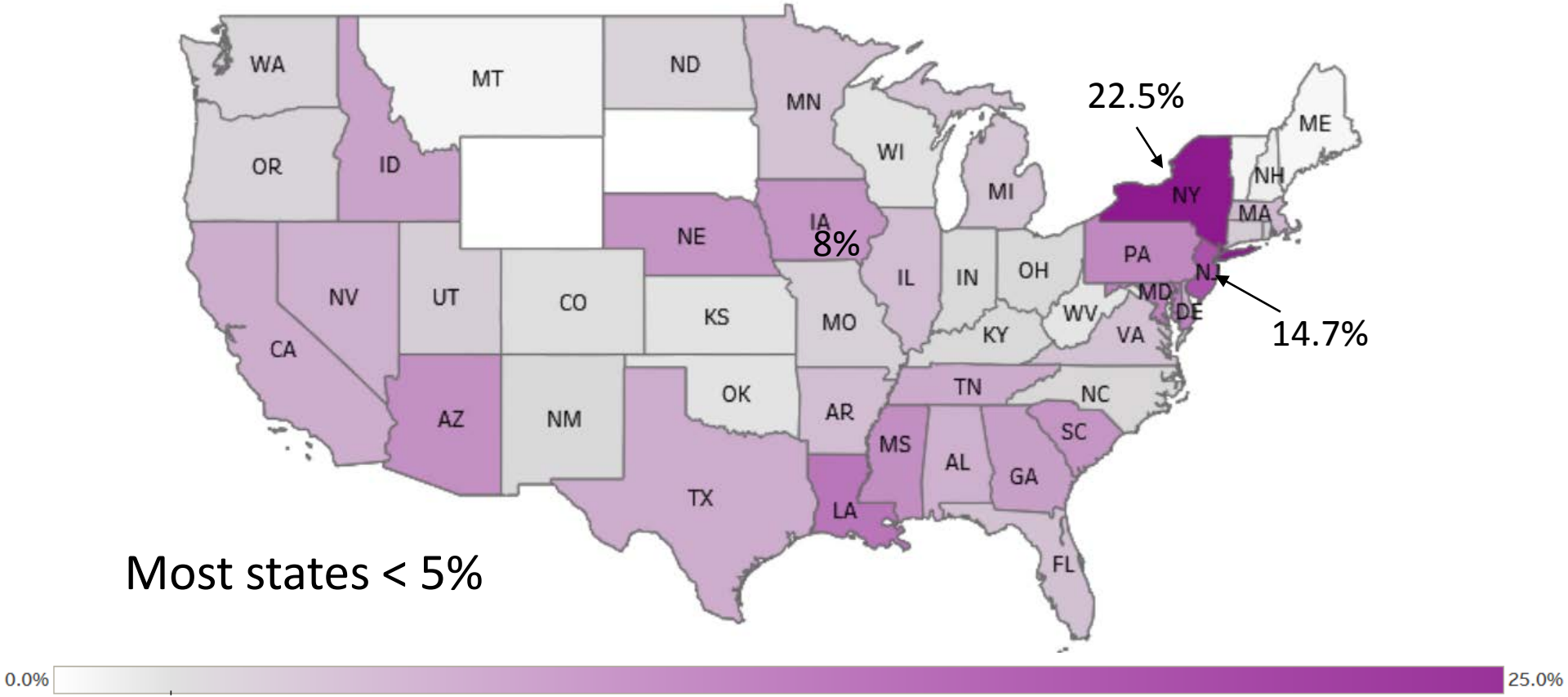
Serology +



How will serology be helpful?

- Two major areas of value:
  - Diagnostic test when high pretest-likelihood but more than a week from sx onset & negative PCR
  - Seroprevalence surveys to define epidemiology
    - Can adjust for test performance

CDC seroprevalence estimates by state



Most states < 5%

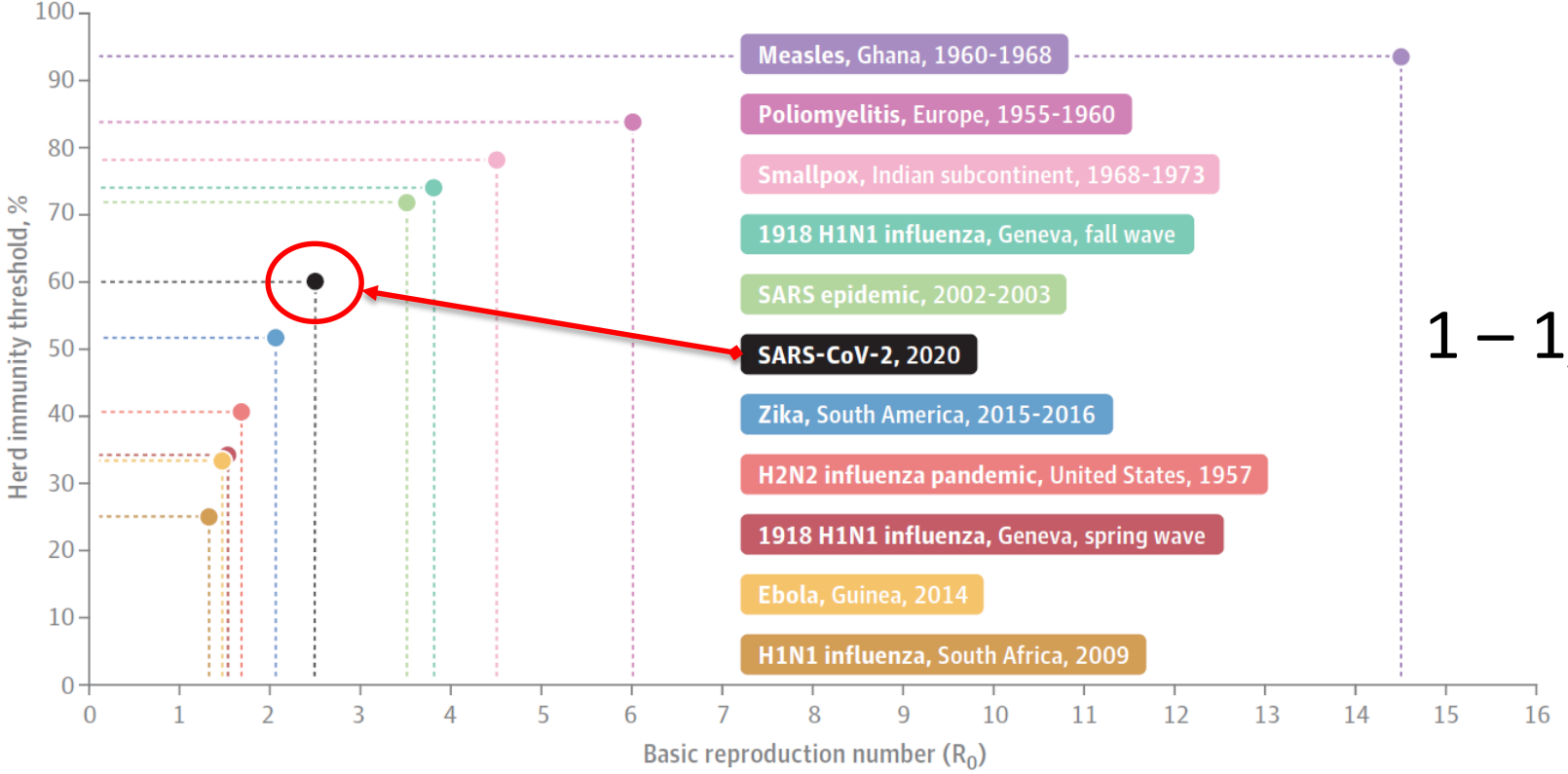
www.covid.cdc.gov/covid-data-tracker

Serology surveys: Takeaway points

- 1-5% seroprevalence in most areas
- 10-25% in hardest hit locations
- Two conclusions, seemingly at odds:
  - MASSIVE UNDERCOUNTING OF CASES
  - HUGE PROPORTION OF POPULATION UNINFECTED
    - (We are a long way from “herd immunity”)

COVID-19 will be with us for the long haul.

Figure. Herd Immunity Thresholds by Disease



$1 - 1/R_0$

The locations included are the locations in which the threshold was measured.

Omer SB, et al. JAMA 2020;October 19, 2020

COVID-19 treatment

- Evidence accumulates daily, difficult to keep up!
- Treatment based upon severity of COVID-19 infection:
  - Asymptomatic or pre-symptomatic
  - Mild: no dyspnea, normal imaging
  - Moderate: evidence of LRT disease, O2 sat >=94%
  - Severe: O2 sat <94%, RR>30, infiltrates > 50%
  - Critical: Respiratory failure, septic shock, MODF
- Published guideline links below (NIH, IDSA, UIHC):

https://www.covid19treatmentguidelines.nih.gov/

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

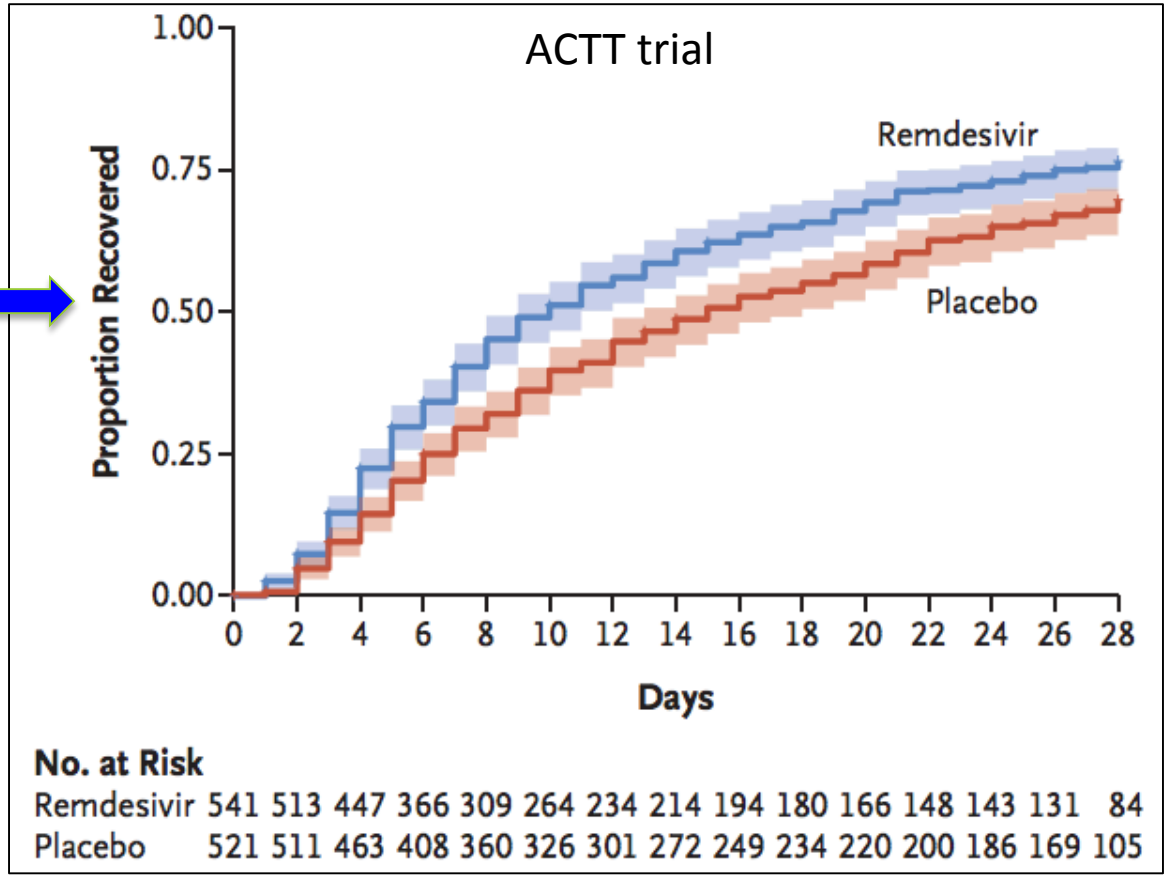
https://medcom.uiowa.edu/theloop/covid-19-clinical-information#covid-19-treatment-guide

COVID-19: Treatment update (summary)

- Supportive care and respiratory support
  - Early detection, home monitoring and treatment, early admission
  - Supplemental 02, prone positioning, noninvasive ventilation
- Antiviral therapy
  - **Remdesivir (shorter time to recovery—10 vs 15 days)**
  - Convalescent plasma, monoclonal antibodies targeting SARS-CoV-2
- Anti-inflammatory and immunomodulatory agents
  - **Dexamethasone (improved survival if sx >7 days or mech vent)**
  - Toculizumab, sarilumab, anakinra
- Thromboembolic prophylaxis, ? anticoagulation
- Assessment for bacterial or fungal superinfection

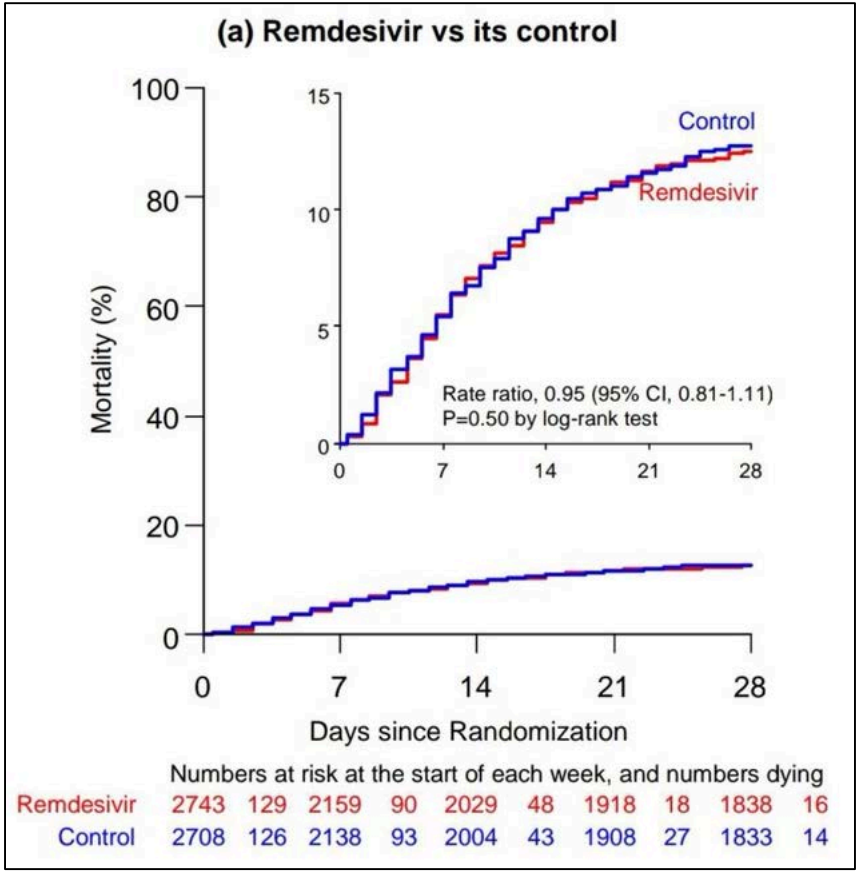
Remdesivir vs placebo in hospitalized COVID pts

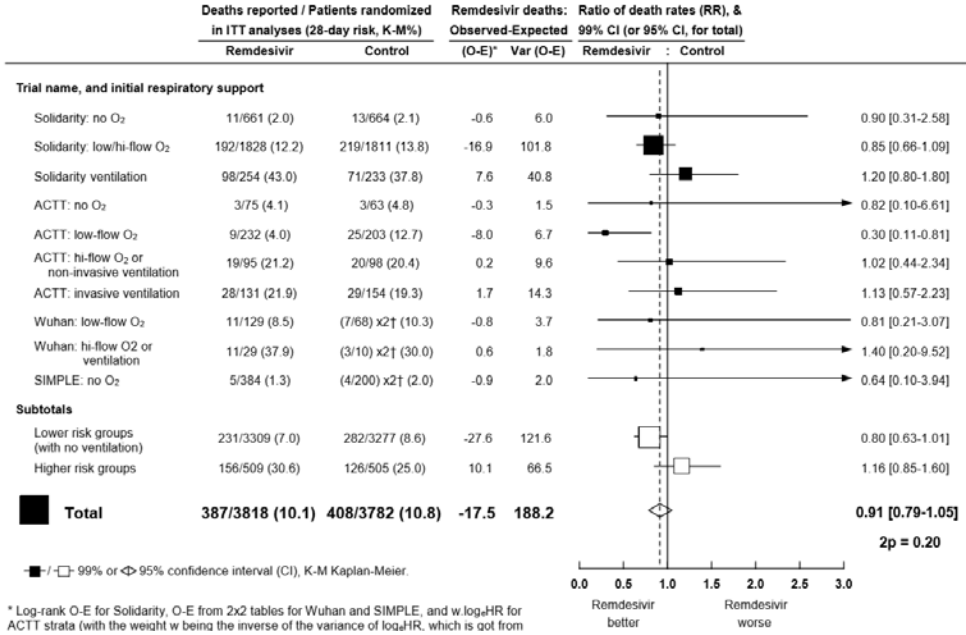
Discharged or ready for d/c



Beigel, et al. N Engl J Med 2020;October 9

Remdesivir vs placebo in SOLIDARITY trial





- Jury is still out on remdesivir
- Benefit may be confined to lower risk gps
  - **Earlier** in course (viral phase)

https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1

Dexamethaxone vs placebo in hospitalized COVID pts

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

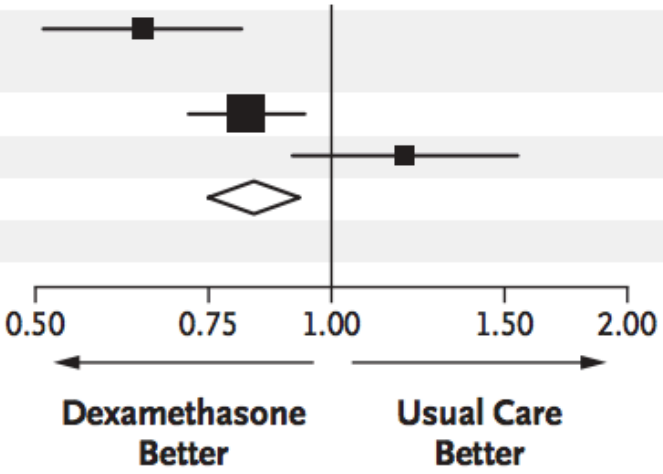


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Horby et al [RECOVERY investigators]. N Engl J Med 2020; July 17.

Treatment: Many questions remain!

- Effectiveness of passive immunotherapy
  - Convalescent plasma, antibody combinations
- Role for non-steroid immunomodulatory agents
- Impact of combining existing therapies
- Indication(s) for anticoagulation
- Timing of each treatment according to disease stage
  - Early outpatient treatments?

Prevention measures

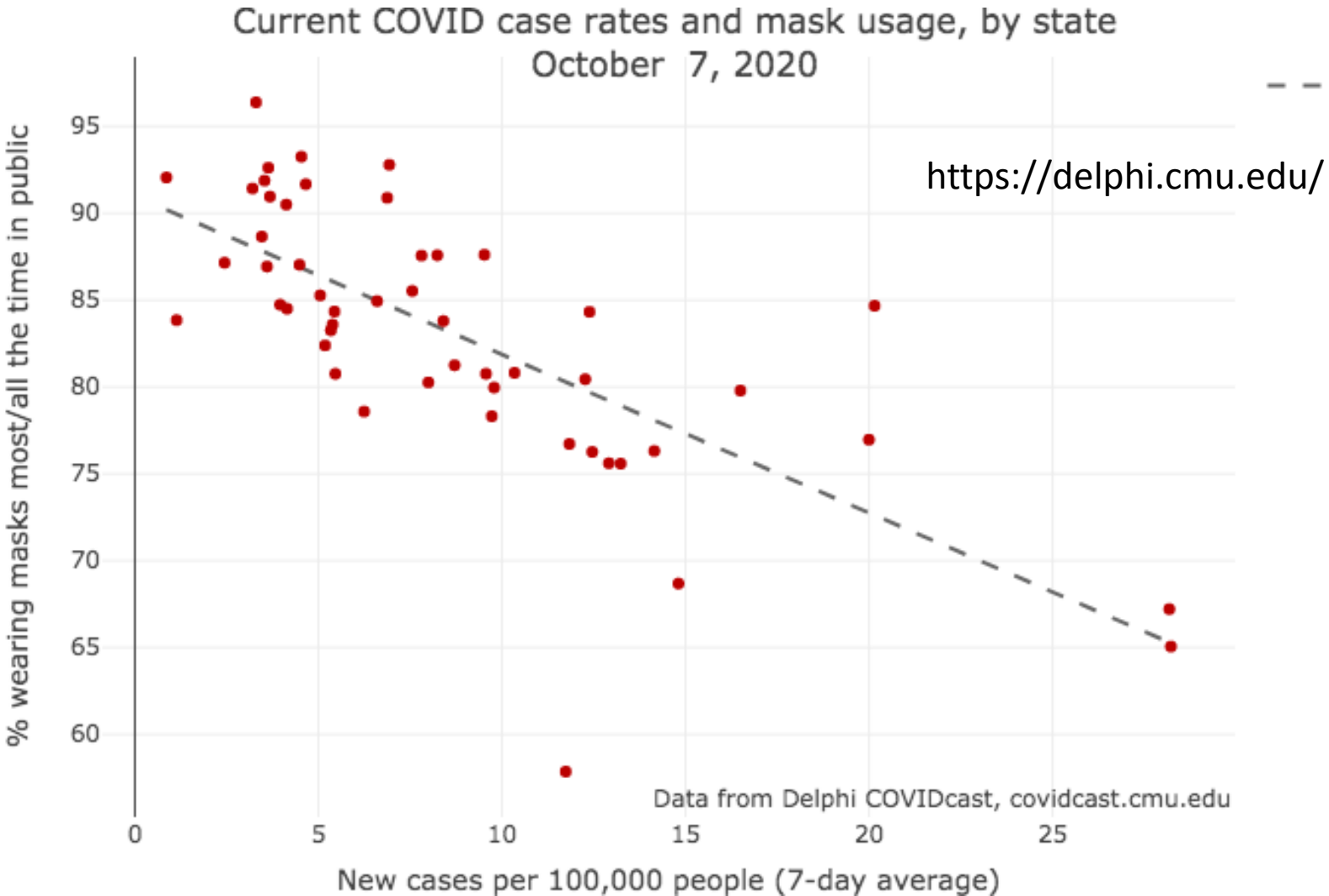
- Early detection and contact tracing
- Isolation (infected), 10 days from sx onset + improved
- Quarantine (exposed), 14 days from last contact
- Physical distancing
- Mask use, eye protection in selected settings
- Social mitigation (limit gatherings, restrict travel)
- Future: Immunization

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

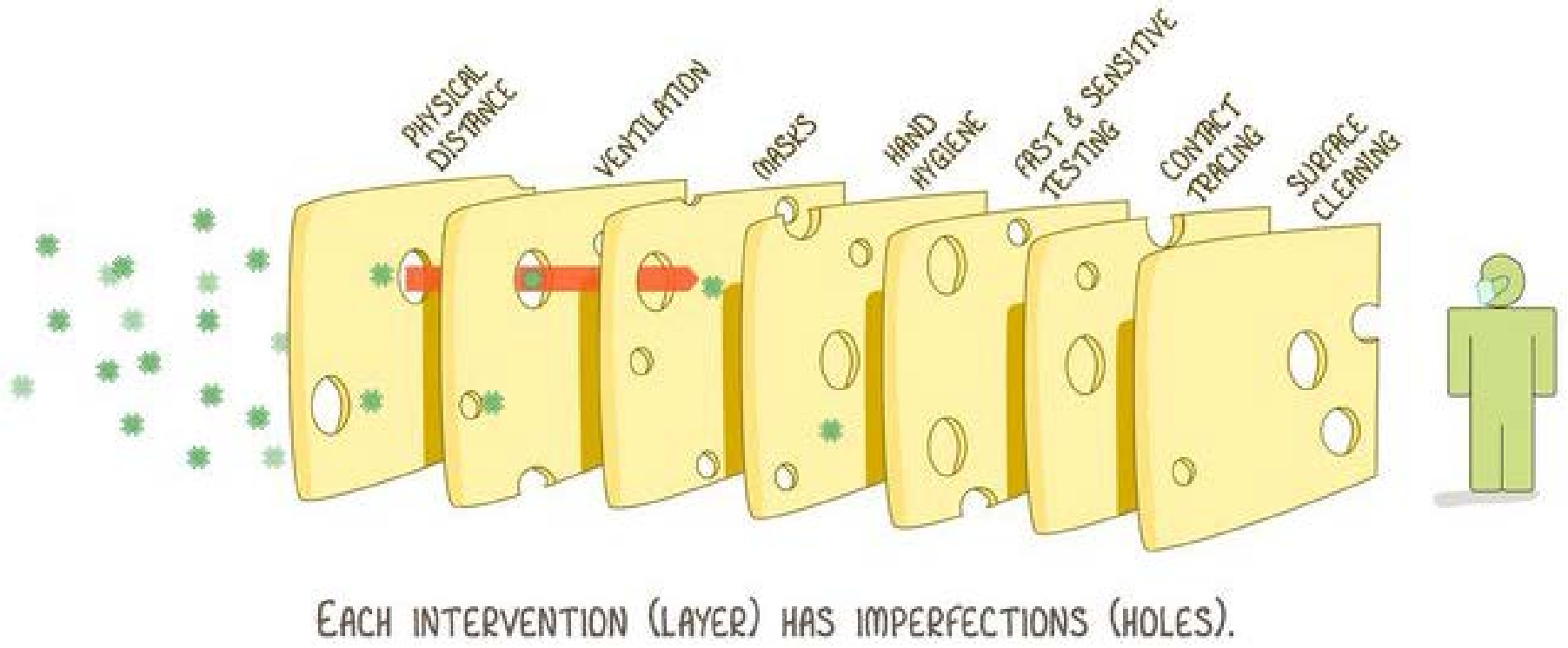
*Derek K Chu, Elie A Akl, Stephanie Duda, Karla Solo, Sally Yaacoub, Holger J Schünemann, on behalf of the COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors**

Intervention	Number studies	Adjusted OR	Absolute effect
Distance (> 1 m)	38	0.18 [0.09-0.38]	12.8% vs. 2.6%
Face mask	39	0.15 [0.07-0.34]	17.4% vs. 3.1%
Eye protection	13	0.34 [0.22-0.52]	16.0% vs. 5.5%

Lancet 2020;395:1973


Current COVID case rates and mask usage, by state
October 7, 2020
https://delphi.cmu.edu/
% wearing masks most/all the time in public
95
90
85
80
75
70
65
60
0
5
10
15
20
25
New cases per 100,000 people (7-day average)
Data from Delphi COVIDcast, covidcast.cmu.edu

The Swiss Cheese of Prevention Approaches



Source: Ian M. Mackay, PhD (@MackayIM)

Preventing COVID-19 transmission on rounds

- Keep 6 feet of space between yourself and others
- Personal protective equipment (masks + eye protection)
- Hand hygiene and disinfection of high touch surfaces
- Avoid rounding in groups and congregating in hallways
- Alternatives:
  - Larger spaces
  - Smaller teams
  - Asynchronous rounds

Take Home Points

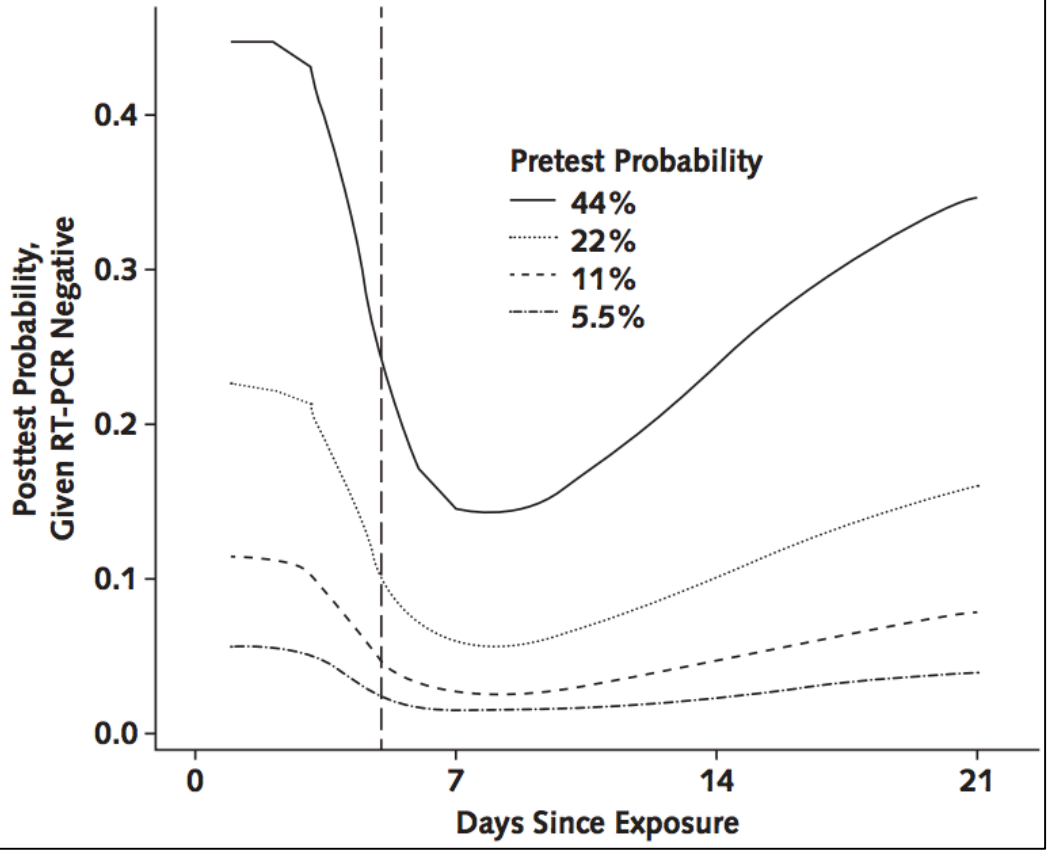
- The COVID-19 situation is worsening overall, and in Iowa
- Adverse outcomes associated with age, comorbidity, disparities
- Phases of illness are important to keep in mind
  - PCR/antigen detect early infection, serology + only after 1-3 weeks
  - Remdesivir may be helpful earlier, in non-ventilated patients
  - Dexamethasone has mortality impact, including in mech vent pts
- Transmission mostly by droplet and close proximity aerosol
  - Longer range aerosol (?) in specific settings (superspread events)
- **Prevention**: test/trace/isolate, distance, mask, eye protection, hand hygiene, disinfection, avoid indoor crowded places

Questions?

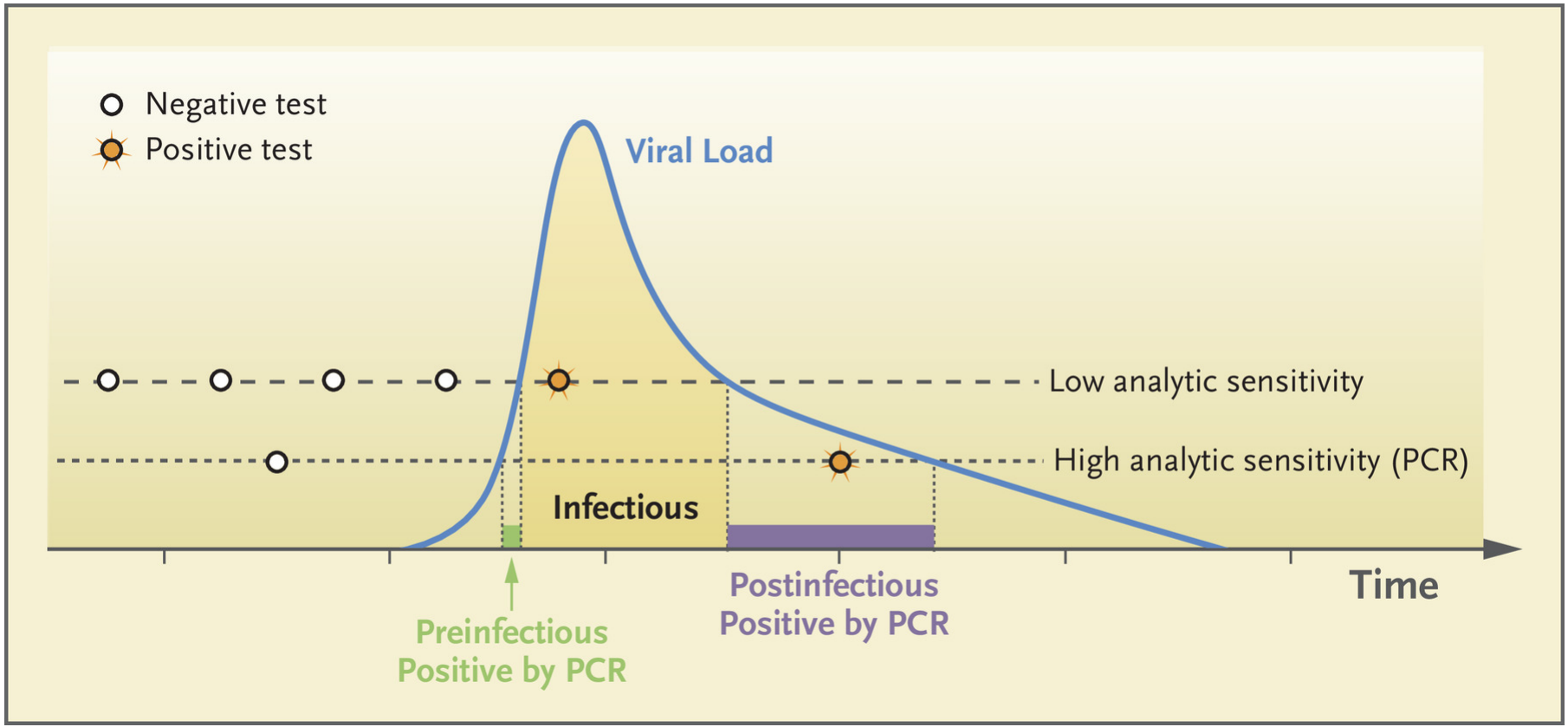
Clinical sensitivity and post-test probability vary by time since viral exposure and symptom onset.

Kucirka, et al. Annals IM 2020;173:262

Figure 3. Posttest probability of SARS-CoV-2 infection after a negative RT-PCR result, by pretest probability of infection.

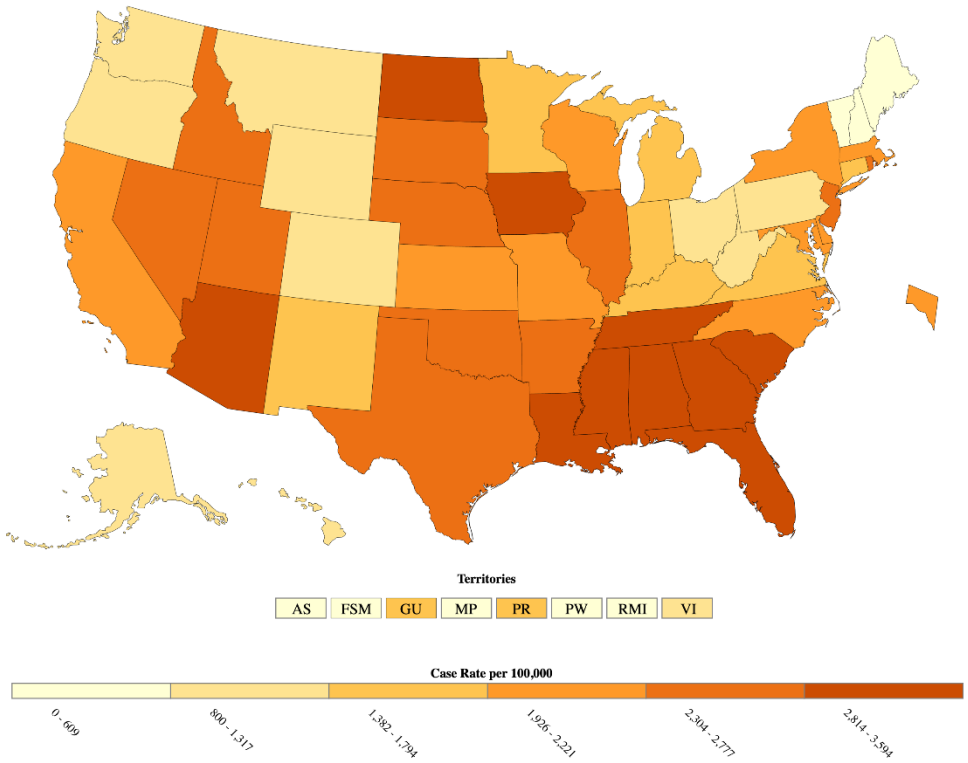


Diagnostic or “infectiousness” test?



Mina MJ, Parker R, Larremore DB. N Engl J Med 9/30/2020

Rapid daily testing of US population

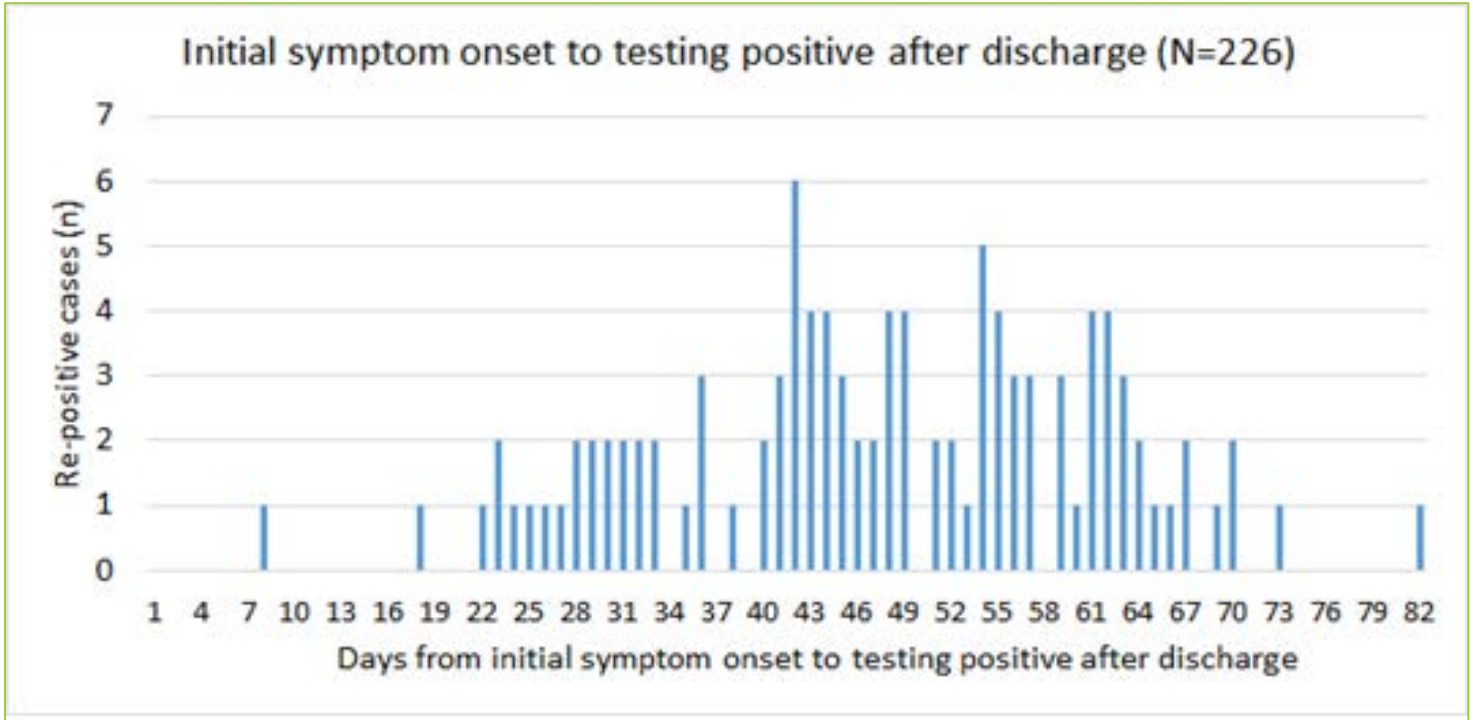


- Population = 325 million
- Assume 98-99% specificity
- 3-6 million false + tests daily
- False > True + in many areas
  - Asymptomatic + rate <1-2%
- NAAT test all positives?
- Repeat antigen testing?
- Isolate and trace all positives?

Pettengill and McAdam. J Clin Microbiol 8/25/20.

Repeated positive SARS-CoV-2 RT-PCR tests: Reinfection or persistent shedding?

- Epidemiological investigation in South Korea
- 285 cases of repeatedly positive cases (mean 45 days from sx onset)

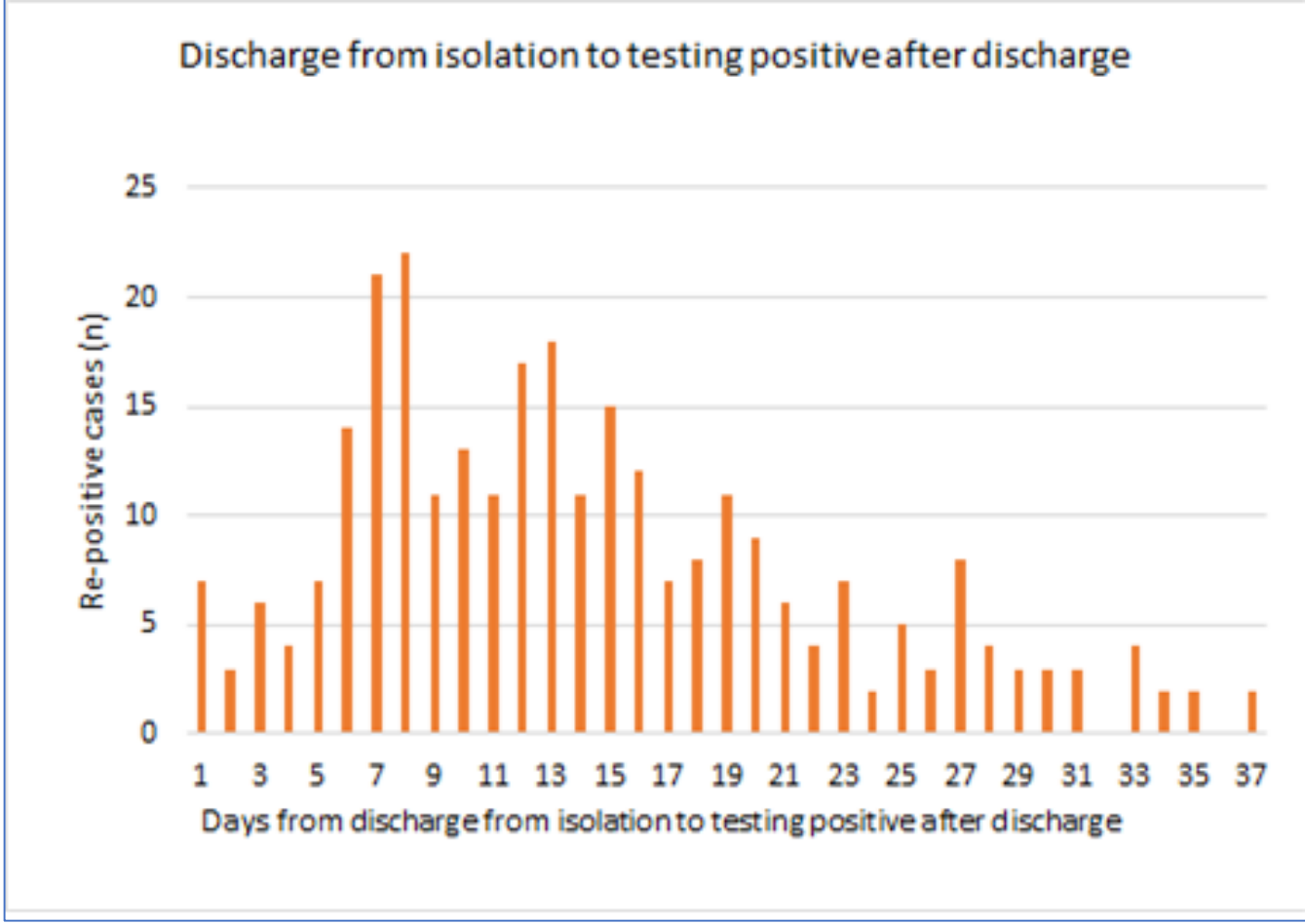


44.7% symptomatic

Mean 14.3 days from discharge to + test

Viral culture attempted for 108 cases
- ALL NEGATIVE
- Ct value > 30 in 90%

23 had serial serology
- 96% neutralizing Ab



790 contacts of re-positive cases traced: No case clearly linked to repeat + case

Summary findings: Repeat + RT-PCR cases

- No evidence that such patients are infectious
  - Inability to culture virus from samples
  - No directly linked cases from contact investigation
  - Almost all already had neutralizing antibodies
- More evidence for low transmission risk if pt is:
  - 10 days from symptom onset, and:
  - 3 days afebrile with symptom resolution

SARS 2003

Estimated incubation period: 4–5 days
Estimated serial interval: 10–11 days

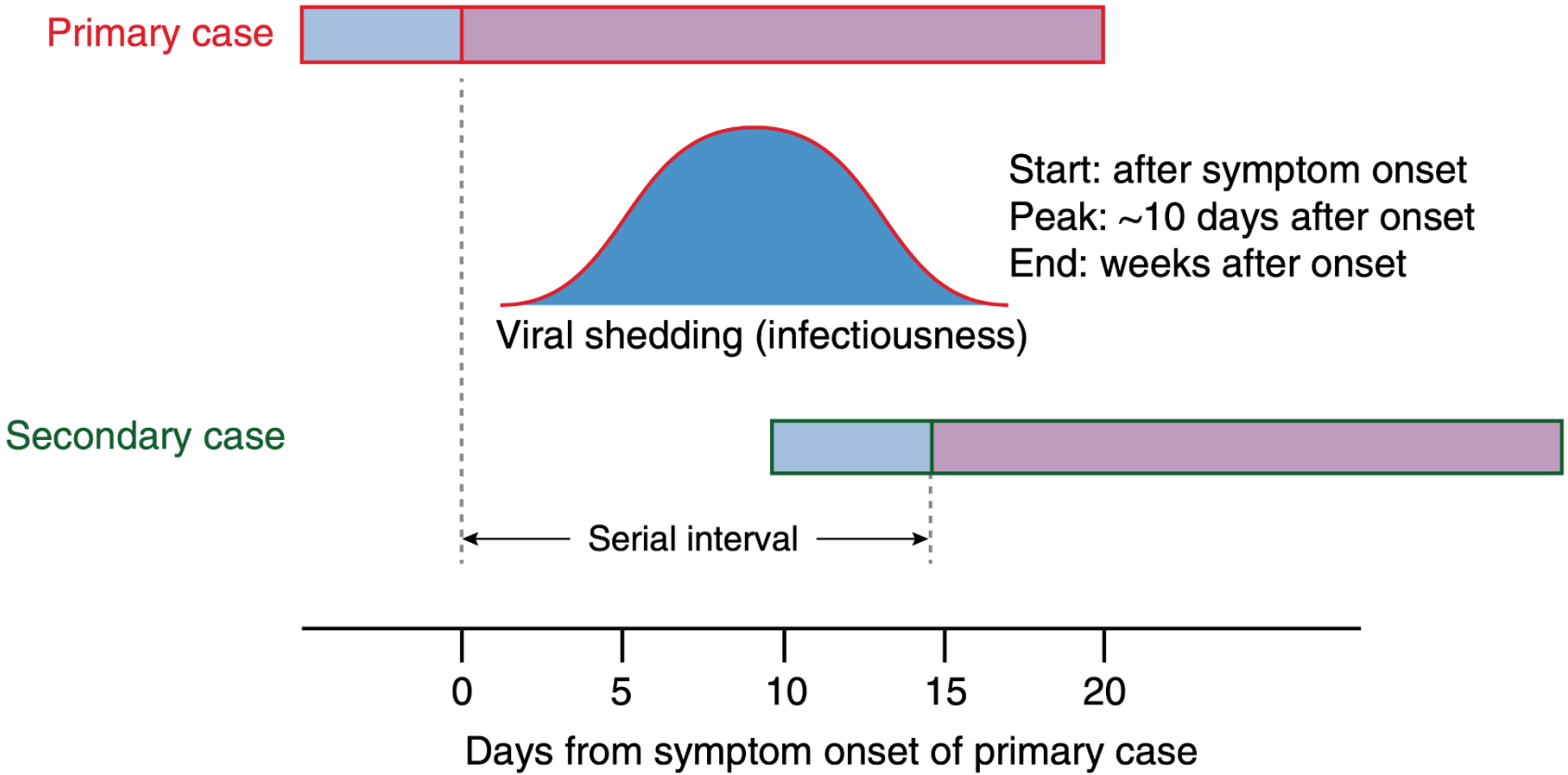
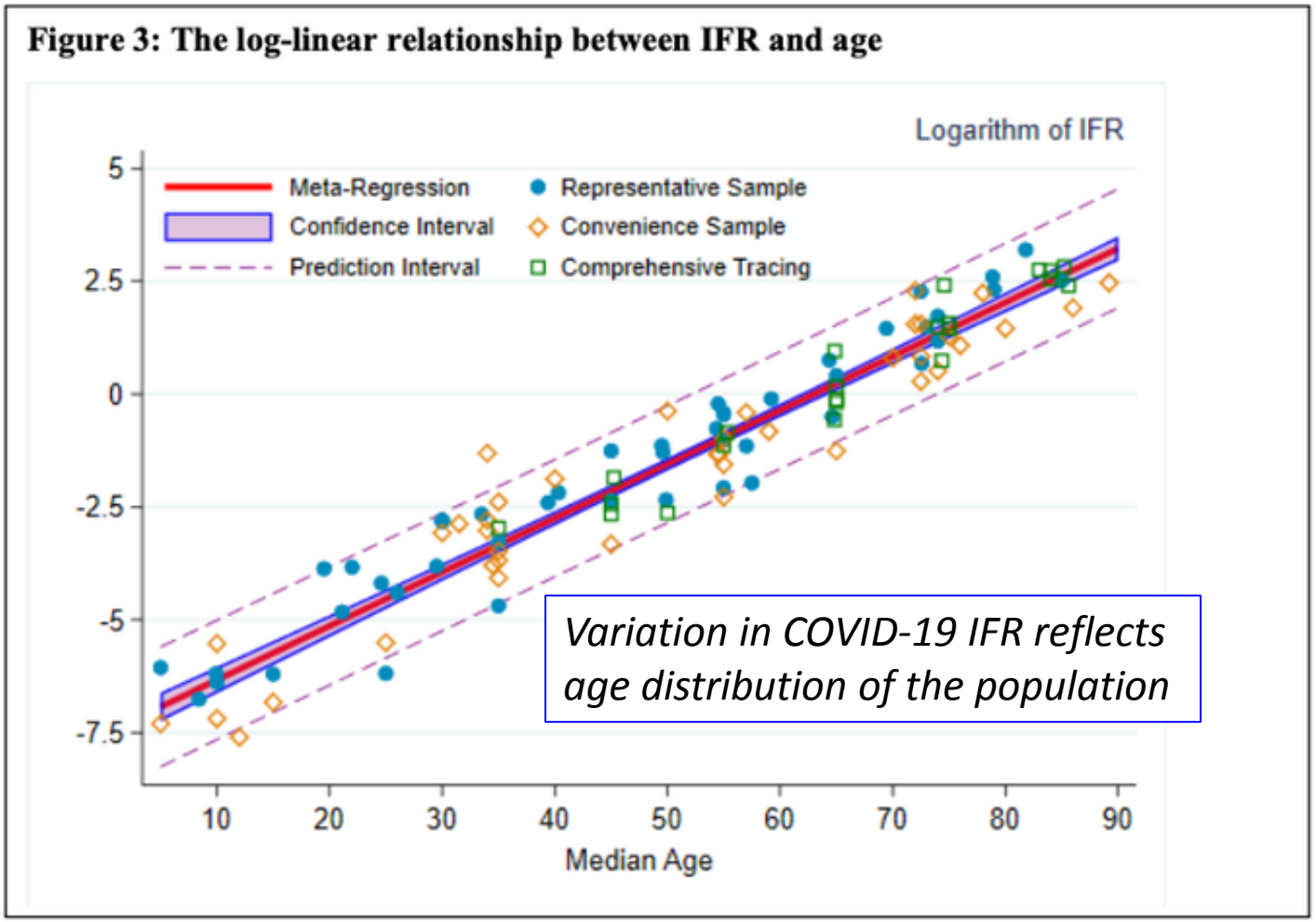


Figure 3: The log-linear relationship between IFR and age



Levin, et al. https://www.medrxiv.org/content/10.1101/2020.07.23.20160895v6

Serology testing for COVID-19: Caveats

- NEGATIVE tests have good NPV (sensitivity 80-90%)
- POSITIVE tests can be difficult to interpret
  - Best FDA-authorized tests have specificity of 96-99%
    - False positives are problem if low prevalence population
  - Seropositive may not equate to “immune”
  - Immunity may not be complete, may not be durable

Individual personnel or public health decisions should NOT be based upon serology results