COVID-19 (SARS Co-V-2)

David Jay Weber, M.D., M.P.H., FSHEA, FIDSA, FRSM (London)
Professor of Medicine, Pediatrics, Epidemiology
Associate Chief Medical Officer, UNC Hospitals
Medical Director, Hospital Epidemiology
University of North Carolina at Chapel Hill

Disclosures: Consultant to PDI, Germitec, Lumagenics, Pfizer; Past Consultant, Merck

"emerging," "re-emerging," or "endemic"

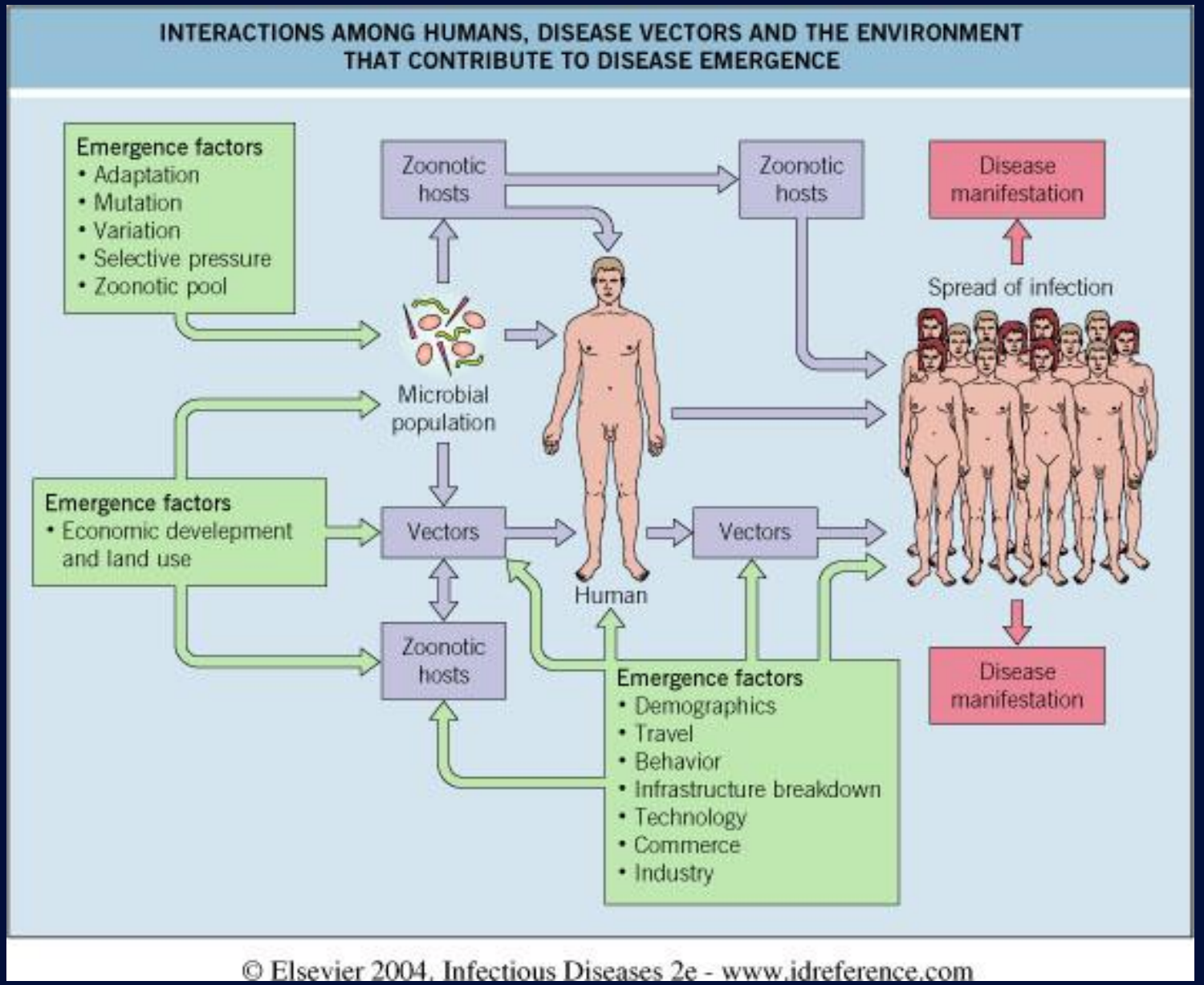
Emerging = diseases that have not occurred in humans before or that occurred only in small numbers in isolated places.

"endemic"
a long term problem.
Never significantly declining
Eg. pneumonia

Re-emerging

= diseases that once were major health problems globally or in a particular country, and then declined dramatically, but are again becoming health problems for a significant proportion of the population.

- Diseases thought to be adequately controlled making a “comeback” are “re-emerging”


INTERACTIONS AMONG HUMANS, DISEASE VECTORS AND THE ENVIRONMENT THAT CONTRIBUTE TO DISEASE EMERGENCE
Emergence factors
• Adaptation
• Mutation
• Variation
• Selective pressure
• Zoonotic pool
Zoonotic hosts
Zoonotic hosts
Disease manifestation
Spread of infection
Microbial population
Human
Emergence factors
• Economic development and land use
Vectors
Vectors
Zoonotic hosts
Emergence factors
• Demographics
• Travel
• Behavior
• Infrastructure breakdown
• Technology
• Commerce
• Industry
Disease manifestation
© Elsevier 2004. Infectious Diseases 2e - www.idreference.com

BASIC CONCEPTS IN DISEASE EMERGENCE

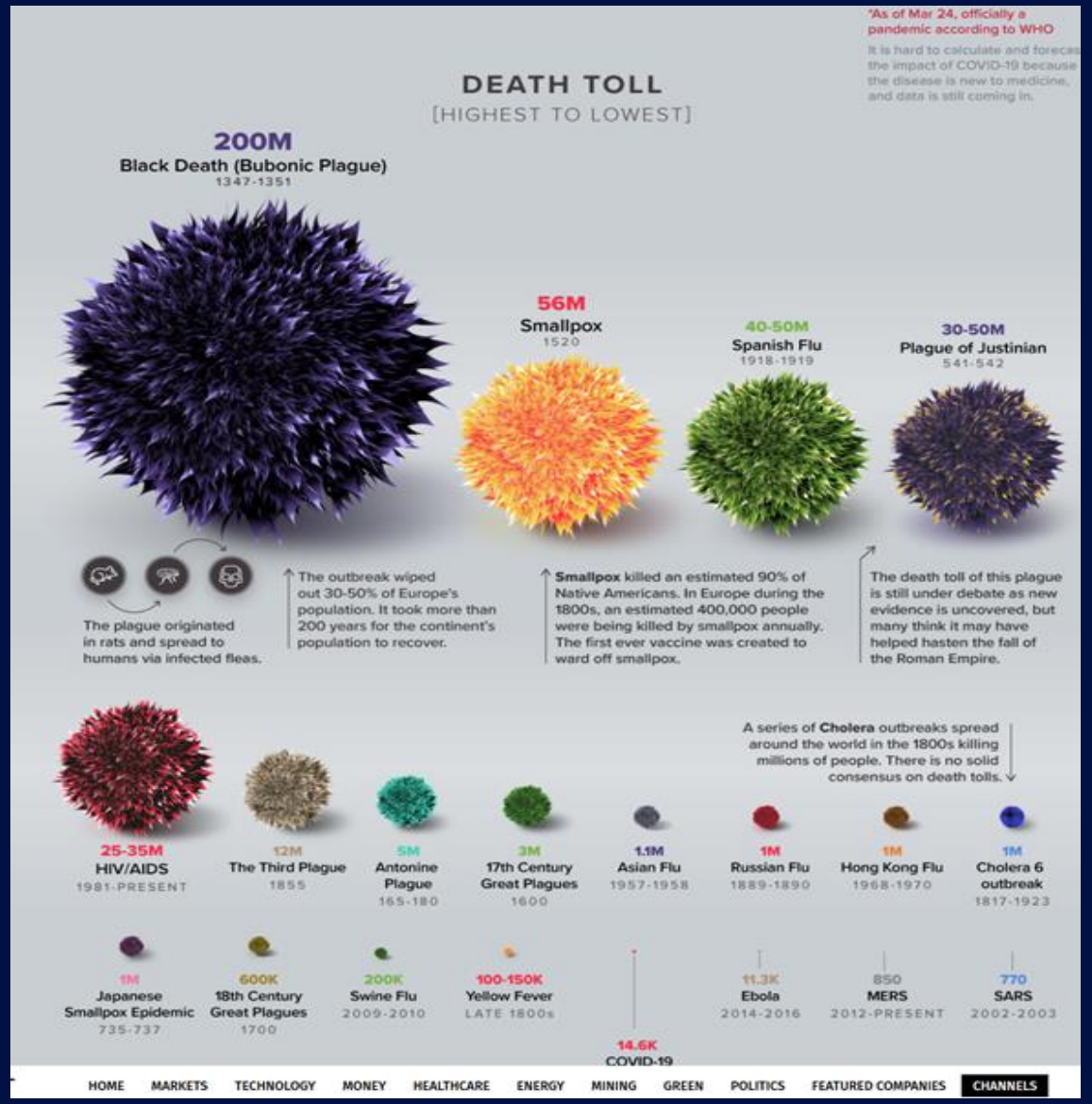
- Emergence of infectious diseases is complex
- Infectious diseases are dynamic
- Most new infections are not caused by genuinely new pathogens
- Agents involved in new and reemergent infections cross taxonomic lines
- The concept of the microbe as *the* cause of disease is inadequate and incomplete
- Human activities are the most potent factors driving disease emergence
- Social, economic, political, climatic, technologic, and environmental factors shape disease patterns and influence emergence
- Understanding and responding to disease emergence require a global prospective, conceptually and geographically
- The current global situation favors disease emergence

Wilson ME. Emerging Infectious Diseases 1995;1:39.

HISTORY OF PANDEMICS

Name	Time period	Type / Pre-human host	Death toll
Antonine Plague	165-180	Believed to be either smallpox or measles	5M
Japanese smallpox epidemic	735-737	Variola major virus	1M
Plague of Justinian	541-542	Yersinia pestis bacteria / Rats, fleas	30-50M
Black Death	1347-1351	Yersinia pestis bacteria / Rats, fleas	200M
New World Smallpox Outbreak	1520 – onwards	Variola major virus	56M
Great Plague of London	1665	Yersinia pestis bacteria / Rats, fleas	100,000
Italian plague	1629-1631	Yersinia pestis bacteria / Rats, fleas	1M
Cholera Pandemics 1-6	1817-1923	V. cholerae bacteria	1M+
Third Plague	1885	Yersinia pestis bacteria / Rats, fleas	12M (China and In
Yellow Fever	Late 1800s	Virus / Mosquitoes	100,000-150,000 (U
Russian Flu	1889-1890	Believed to be H2N2 (avian origin)	1M
Spanish Flu	1918-1919	H1N1 virus / Pigs	40-50M
Asian Flu	1957-1958	H2N2 virus	1.1M
Hong Kong Flu	1968-1970	H3N2 virus	1M
HIV/AIDS	1981-present	Virus / Chimpanzees	25-35M
Swine Flu	2009-2010	H1N1 virus / Pigs	200,000
SARS	2002-2003	Coronavirus / Bats, Civets	770
Ebola	2014-2016	Ebolavirus / Wild animals	11,000
MERS	2015-Present	Coronavirus / Bats, camels	850
COVID-19	2019-Present	Coronavirus – Unknown (possibly pangolins)	14,500 (as of Mar 2 2020)

Note: Many of the death toll numbers listed above are best estimates based on available research. Some, such as the i of Justinian, are subject to debate based on new evidence.



www.visualcapitalist.com/history-of-pandemics-deadliest

KEY CONSIDERATIONS IN ASSESSING AND MANAGING THE THREAT OF AN EMERGING INFECTIOUS DISEASE

- Pathogen
  - Taxonomy (provides clues regarding transmission routes, environmental stability, germicide susceptibility)
  - Hosts
- Epidemiology
  - Locations of endemicity (i.e., locations in the world where sources or reservoirs reside)
  - Incubation period
  - Transmission routes
  - Infectivity (i.e., communicability)
  - Duration of infectivity

Weber DJ, et al. Am J Infect Control 2016;44:e91-100

- Clinical
  - Symptoms
  - Signs
  - Risk factors for acquisition of infection
  - Morbidity
  - Mortality
  - Risk factors for morbidity and mortality
  - Diagnostic methods (sensitivity, specificity, biosafety)
  - Therapy (availability, efficacy, safety)
- Managing a pandemic
  - Sensitive and specific (ideally rapid) diagnostic test
  - Early identification of patients
  - Protecting our healthcare personnel (PPE, donning, doffing)
  - Sufficient staff, inpatient/ICU beds, ventilators
  - Managing shortages

CORONAVIRUSES LIKELY TO CONTINUE TO MOVE FROM BATS TO HUMANS

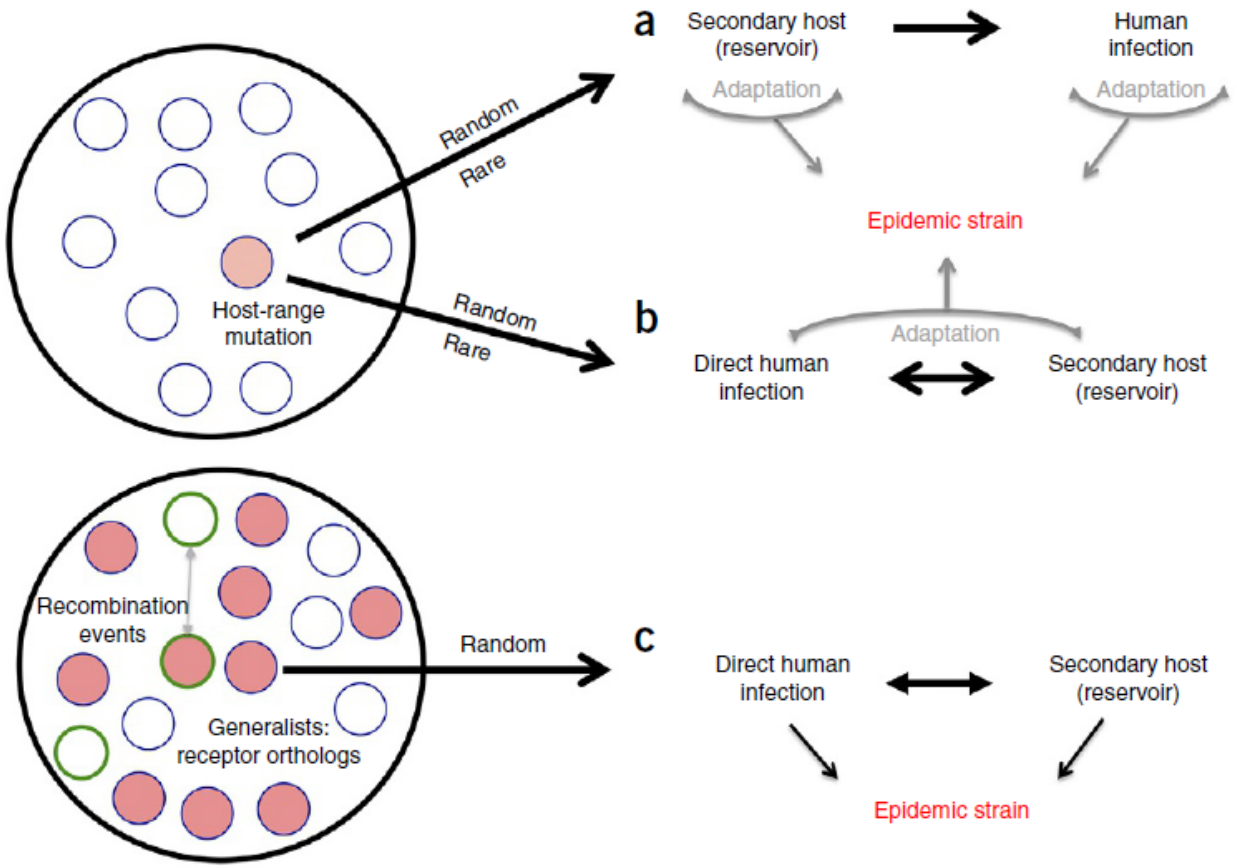


Figure 4 Emergence paradigms for coronaviruses. Coronavirus strains are maintained in quasi-species pools circulating in bat populations. (**a**,**b**) Traditional SARS-CoV emergence theories posit that host-range mutants (red circle) represent random and rare occurrences that permit infection of alternative hosts. The secondary-host paradigm (**a**) argues that a nonhuman host is infected by a bat progenitor virus and, through adaptation, facilitates transmission to humans; subsequent replication in humans leads to the epidemic viral strain. The direct paradigm (**b**) suggests that transmission occurs between bats and humans without the requirement of an intermediate host; selection then occurs in the human population with closely related viruses replicating in a secondary host, permitting continued viral persistence and adaptation in both. (**c**) The data from chimeric SARS-like viruses argue that the quasi-species pools maintain multiple viruses capable of infecting human cells without the need for mutations (red circles). Although adaptations in secondary or human hosts may be required for epidemic emergence, if SHC014 spike–containing viruses recombined with virulent CoV backbones (circles with green outlines), then epidemic disease may be the result in humans. Existing data support elements of all three paradigms.

Menachery VD, et al
Nature Medicine;
2015;21:1507

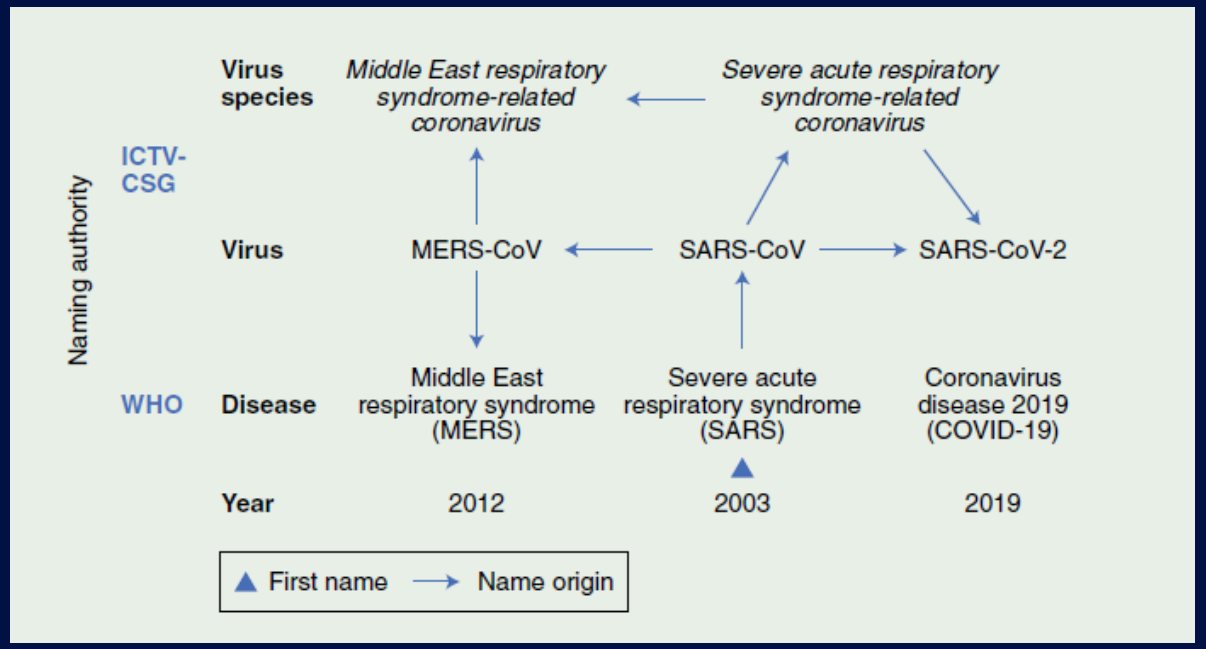
TIMELINE: EMERGING NIDOVIRUSES

Virus	Species	Emergence
HCoV-NL63	**Human**	500-800 years
HCoV-229E	**Human**	200-300 years
HCoV-OC43	**Human**	~120 years
PEDV	Porcine	~25 years
PRRSV	Porcine	~25 years
BCoV	Bovine	~20 years
SARS-CoV*	**Human**	~16 years
MERS-CoV*	**Human**	~7 years
SADS-CoV (HKU2)	Porcine	~2 years
SARS-CoV-2*	**Human**	~4 months

Accelerating transmission from bats to humans

Source: Ralph Baric

DEVELOPMENT OF NOVEL CORANAVIRUSES



Category	Coronaviruses	Humans	Divergence
Realm	*Riboviria*		
Order	*Nidovirales*	Primates	
Suborder	*Cornidovirineae*		
Family	*Coronaviridae*	Hominidae	
Subfamily	*Orthocoronavirinae*	Homininae	
Genus	*Betacoronavirus*	*Homo*	
Subgenus	*Sarbecovirus*		
Species	*Severe acute respiratory syndrome-related coronavirus*	*Homo sapiens*	
Individuum	SARS-CoVUrbani, SARS-CoVGZ-02, Bat SARS CoVRf1/2004, Civet SARS CoVSZ3/2003, SARS-CoVPC4-227, SARSr-CoVBtKY72, SARS-CoV-2 Wuhan-Hu-1, SARSr-CoVRatG13, and so on.	Dmitri Ivanovsky, Martinus Beijerinck, Friedrich Loeffler, Barbara McClintock, Marie Curie, Albert Einstein, Rosalind Franklin, Hideki Yukawa, and so on.	

COVID-19: EPIDEMIOLOGY, COMMENTS

- Cases: Global: >1,800,000 (>113,000 deaths), ~175 countries with cases
  - China: ~81,500 (~3,300 deaths); cases and deaths stable
  - US cases (deaths): >580,000 (>23,000): All 50 states have cases; community acquisition in multiple states; outbreaks in nursing homes across the US: NY >195,000 (>10,000); NJ >64,000 (>2,400); MA >26,000 (>800); MI >25,000 (>1,600); CA >24,000 (>700); PA >24,000 (>500); IL >22,000 (>800); LA >21,000 (>900); FL >21,000 (>500); TX >13,000 (>400)
  - Outside China: Continuing increasing prevalence in Europe
  - NC, >5,000 cases (313 deaths); hospitalized, 313
- Comments
  - Main inflection point = community acquisition without a contact to a known case (esp., sustained transmission)
  - Role of super-spreaders important (likely cause of outbreak at Biogen meeting in Boston)
  - Frequency of asymptomatic infection unknown and possibility of transmission undefined
  - Risk of dying highly dependent on age
  - Major limitations on our COVID-19 response: Limited ability to test patients (rapid tests), lack of PPE/critical supplies, inpatient floor and ICU beds, ventilators


SOLD OUT!
NEWS
COVID-19 LEADS TO SHORTAGES
PSST!
MASKS, SANITIZERS AND TOILET PAPER !!
©DAVEGRANLUND.COM

Table 4 Main epidemiological indicators of COVID-19 research articles in January 2020

Indicators	Description
Age of patients	• Cases range between 25 and 89 years, with most patients aged between 35 and 55 years and fewer cases among children and infants [14]
	• Median age of patients is 59 years, ranging from 51 to 89 [2]
	• Average age of patients was 55.5 years; age distribution: ≤ 39: 10%; 40–49: 22%, 50–59: 30%; 60–69: 22%, ≥ 70: 15% [19]
	• Cases range from 2 to 72 years [20]
Sex of patients	• More cases were males [20]
	• 59% males [2]
	• 68% males [19]
Age of the deaths	• Median age of death was 75 (with a range between 48 and 89 years) [21]
Exposure history	• Huanan Seafood Market in Wuhan [19, 22]
	• Wuhan residents or people who visited Wuhan [20]
Incubation time	• 4.8 ± 2.6 days (2–11 days) [15]
	• 5.2 days (4.1–7 days) [2]
	• Average of 7 days (2–14 days) [23]
	• Average of 10 days [22]
	• 5–6 days [24]
	• Average of 6.4 days (5.6–7.7 days) [20]
Basic Reproduction (R_0)	• 2.6 (uncertainty range: 1.5–3.5) [25]
	• 3.8 (95% *CI*: 3.6–4.0) [26]
	• 2.2 (1.4–3.8) [27]
	• 4.71 (4.50–4.92) [24]
	• 2.68 (95% *CI*: 2.47–2.86) [28]
Susceptible populations	• Elderly people [21]
	• People with poor immune function [2]
	• People with chronic co-morbidities [2, 15, 19, 21]
	• People with long-term use of immunosuppressive agents [19]
	• Surgery history before admission [21]
Mortality rate	• 3% (between 29 December 2019 to 23 January, 2020) [15]
	• 2.3% (as of 28 January 2020) [29]
	• 2.8% (as of 25 January, 2020) [21]
	• 2.9% (as of 25 January, 2020) [30]
	• 11% (as of 25 January, 2020) [19]
	• 3.1% (as of 24 January 2020) [31]

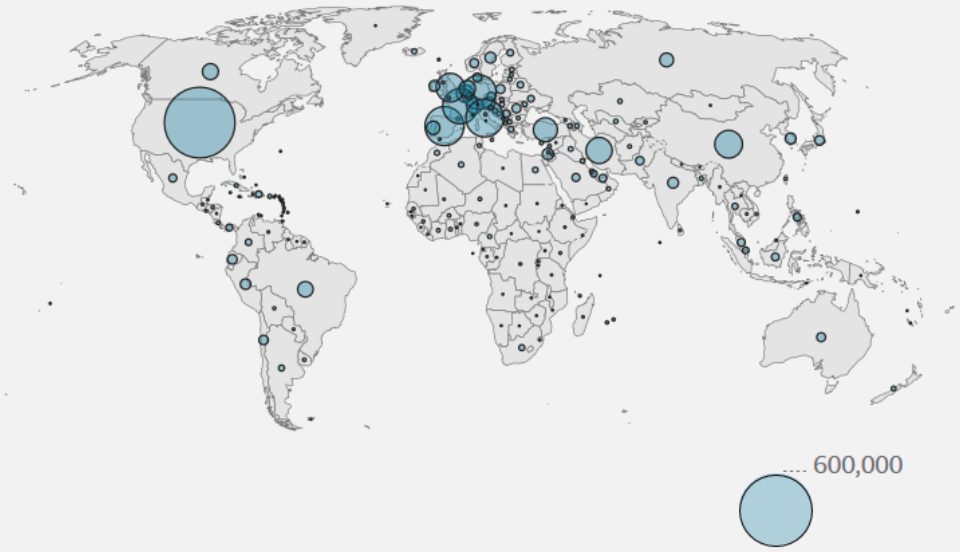
Poudel S, et al.
Infect Dis Poverty 2020;9:29

CORONAVIRUS mapped

Click to show confirmed cases in

The world

1,920,648	119,716	456,910
cases	deaths	recoveries

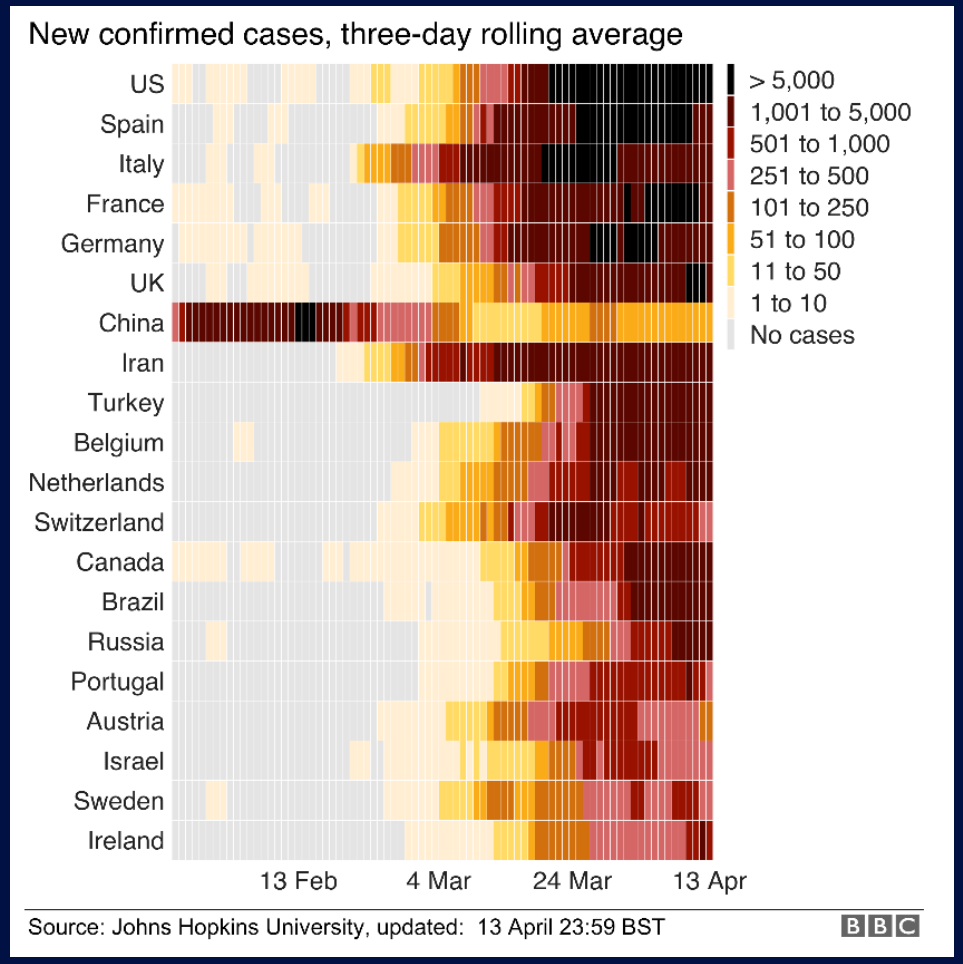


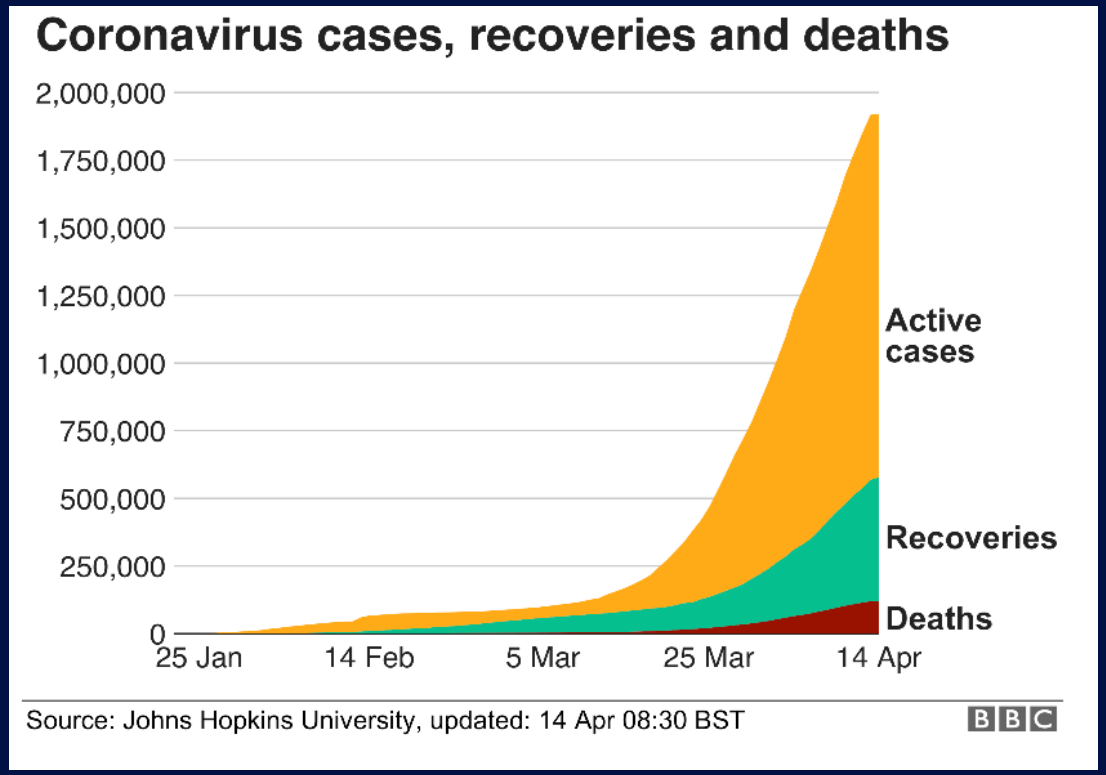
Circles show number of confirmed coronavirus cases per country.

Source: Johns Hopkins University
Figures last updated 14 Apr 2020

https://www.bbc.com/news/world-51235105

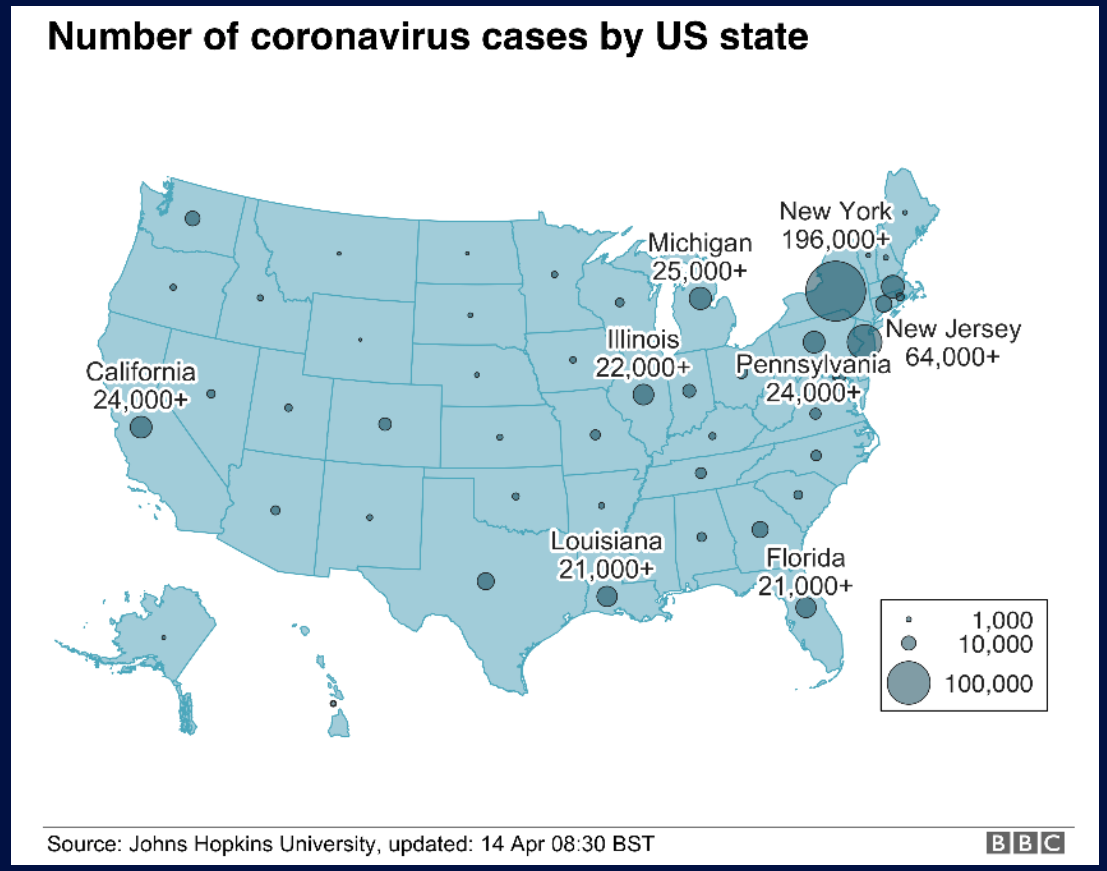
COVID AROUND THE WORLD

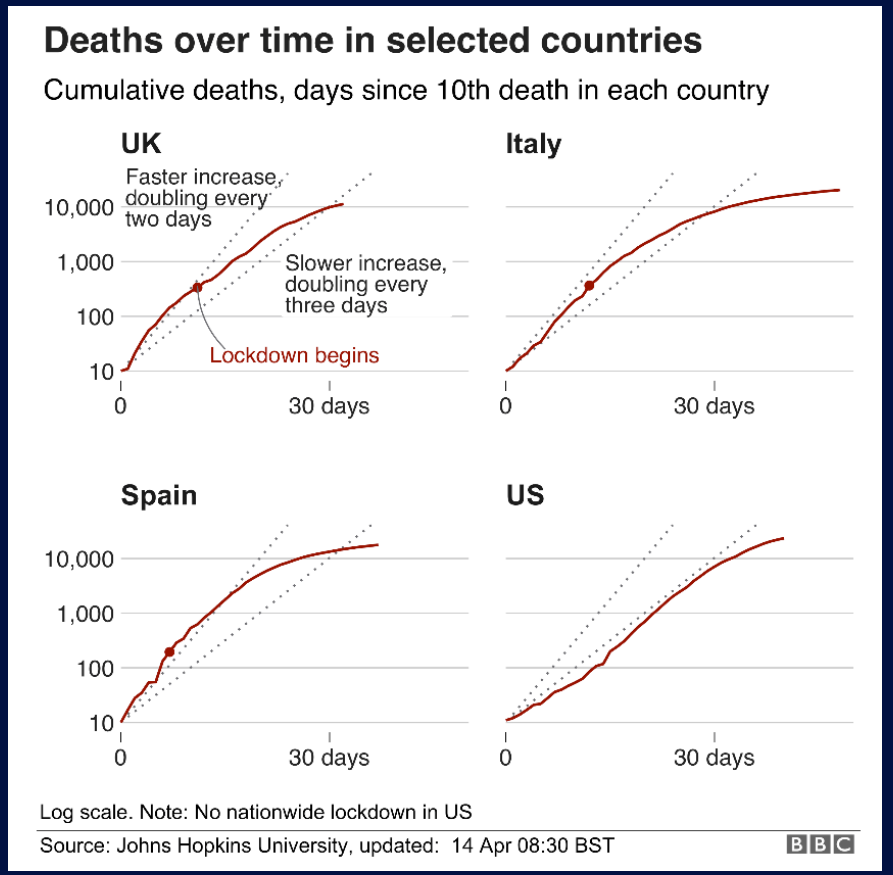




https://www.bbc.com/news/world-51235105

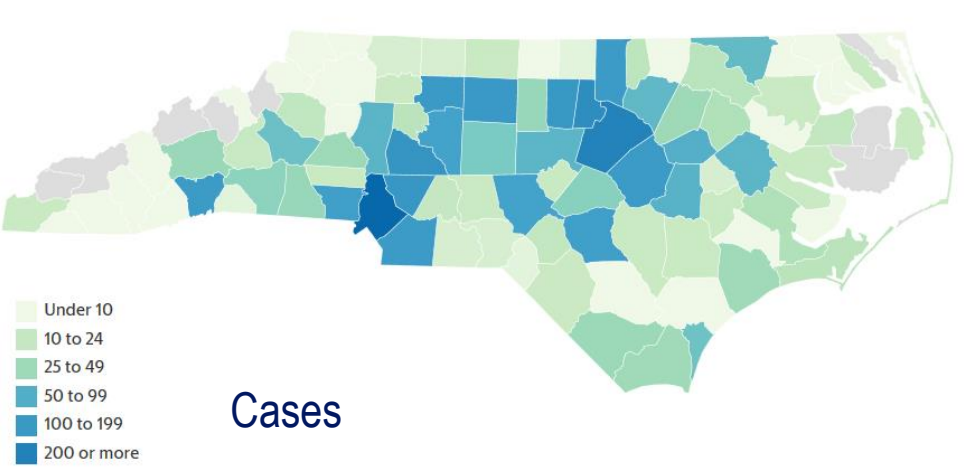
COVID-US



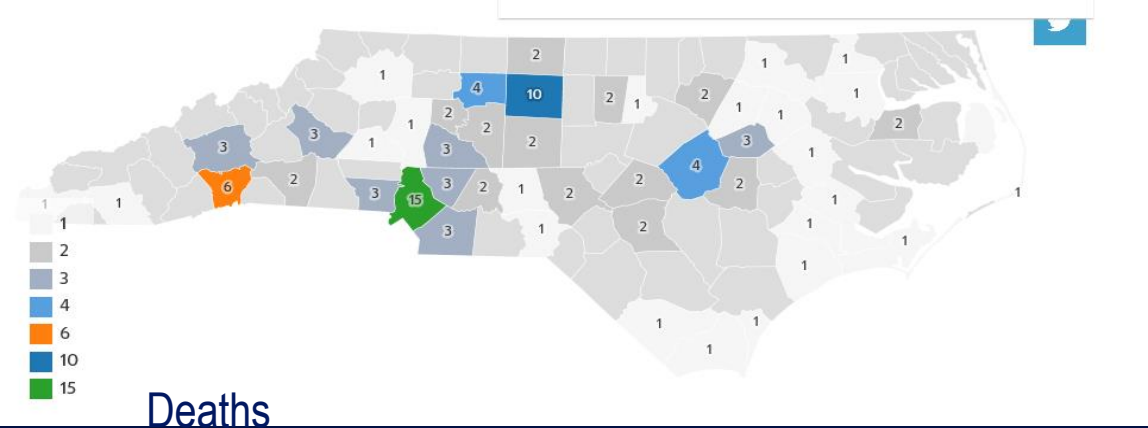


https://www.bbc.com/news/world-51235105

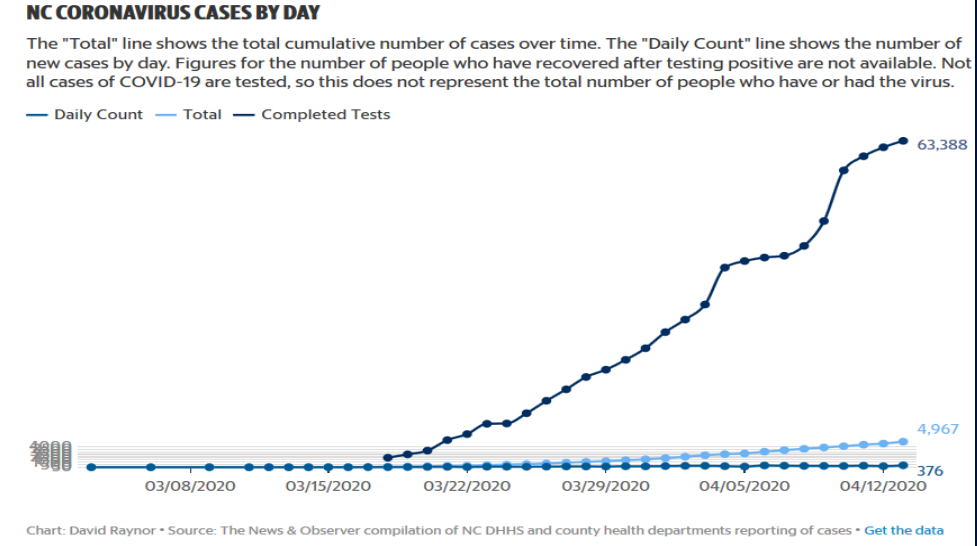
COVID-19, NC AND UNC MEDICAL CENTER



Cases



Deaths

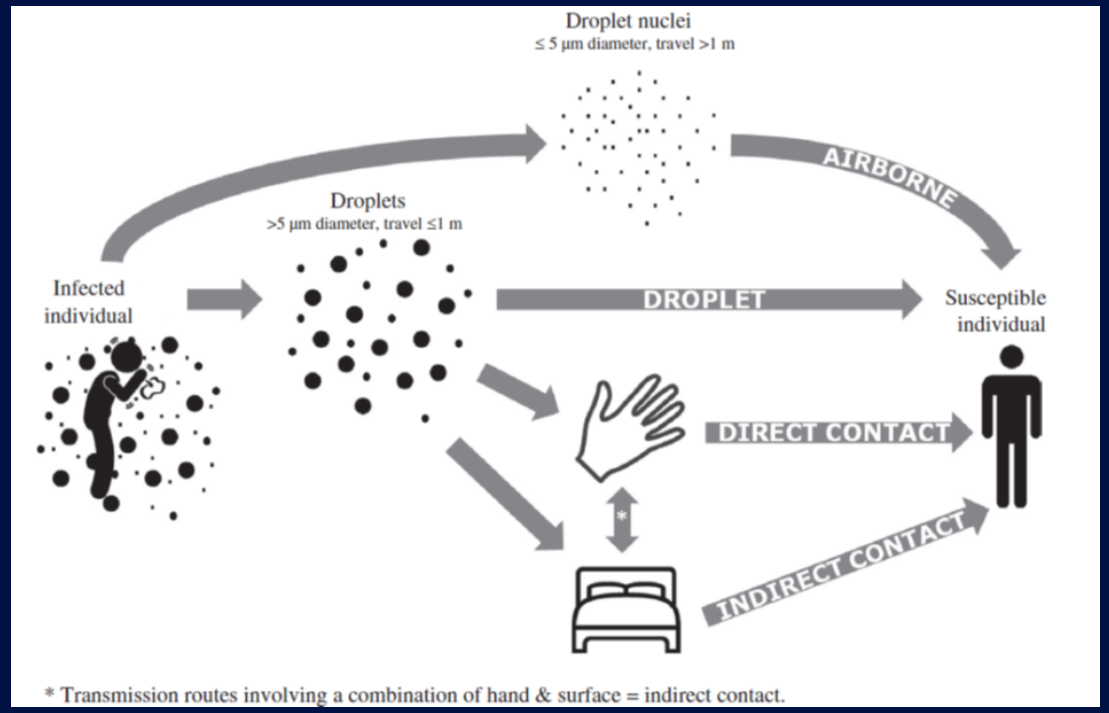


April 15th COVID-19 forecasts – Total Hospital Pt's in Beds *(including ICU)*

			April 2nd Forecasts		April 15th Forecasts			
Hospital	Licensed Beds	Surge Beds	May 1	June 1	May 1	May 15	June 1	June 15
Medical Center	951	1244	190	475	44	91	224	468
Rex	439	768	139	347	32	67	163	342
Chatham	20	46	3	8	1	2	4	8
Rockingham	108	154	11	27	2	5	13	26
Caldwell	110	150	19	47	4	9	22	46
Johnston	199	345	50	126	12	24	60	124
Nash	345	476	57	142	13	27	67	140
Wayne	278	474	51	128	12	25	60	126
Pardee	222	263	37	93	9	18	44	91
Lenoir	261	377	27	67	6	13	31	66
Onslow	160	270	34	84	8	16	39	83
TOTAL	**3093**	**4567**	**618**	**1544**	**143**	**297**	**727**	**1520**

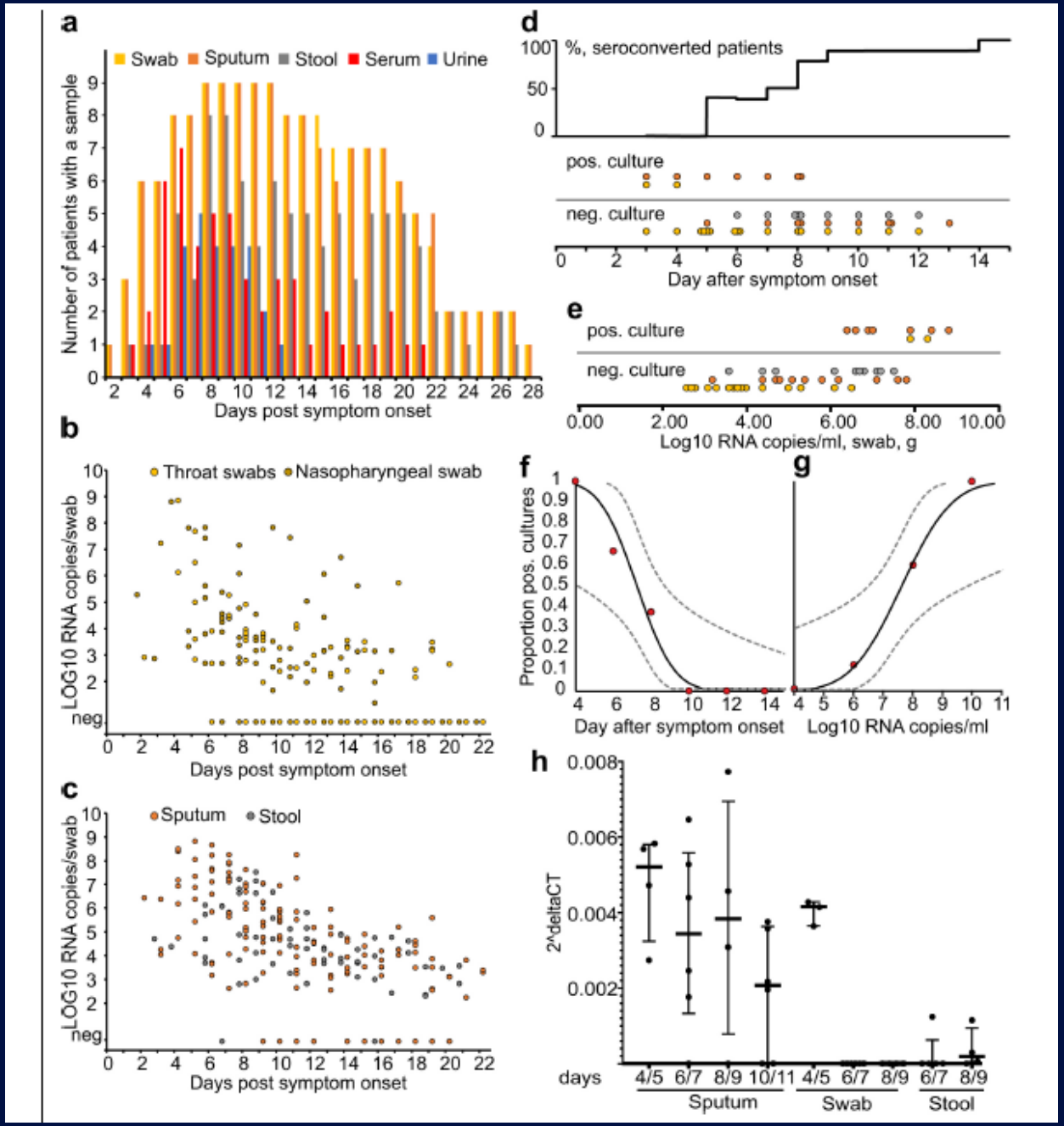
https://www.newsobserver.com/customer-service/investigative-tips/article240855401.html

TRANSMISSION OF SARS CoV-2



- Droplet (<6 feet)
- Direct
- Indirect (via the contaminated environment)
  - SARS CoV-2 inoculated printing and tissue papers = no infectious virus isolated after 3-hour incubation[3]
- Pre-symptomatic – highly likely
- Asymptomatic (infection demonstrated) – infectivity undefined
- Aerosolization of stool (virus demonstrated in stool) – infectivity undefined
- Airborne – no evidence
- Transplacental/vertical – no evidence[1]
- Companion animals[2] – asymptomatic (cats, dogs, tiger)

[1]Proceianoy RS, et al. J Pediatr (Rio J) 2002;11 April; [2] Almendros A, et al. Vet Rec 2020;4; [3]Chin AWH, et al.



Virological Assessment of Hospitalized Patients with COVID-19

- Pharyngeal viral shedding highest in first week of sx
- Infectious virus readily isolated from throat- and lung-derived samples but not from stool samples
- Blood and urine new yielded virus
- Shedding of viral RNA from sputum outlasted end of symptoms
- Seroconversion occurred after 7 days in 50% of patients (14 days in all), but was NOT followed by a rapid decline in viral load
- COVID-19 can present as mild upper respiratory tract disease

Wolfel R, et al. Nature 24 March

ASYMPTOMATIC INFECTION: DETECTION IN A NURSING HOME OUTBREAK

- Outbreak in skilled nursing home
- CDC performed symptom and SARS CoV-2 testing for 76(93%) of 82 residents
- Among 23 (30%) residents with positive test results, 10 (43%) had symptoms on the date of testing, and 13 (57%) were asymptomatic. Seven days after testing, 10 of these 13 previously asymptomatic residents had developed symptoms and were recategorized as presymptomatic at the time of testing.

TABLE 2. Follow-up symptom assessment 1 week after testing for SARS-CoV-2 among 13 residents of a long-term care skilled nursing facility who were asymptomatic on March 13, 2020 (date of testing) and had positive test results — facility A, King County, Washington, March 2020

Symptom status 1 week after testing	No. (%)
Asymptomatic	3 (23.1)
Developed new symptoms	10 (76.7)
Fever	8 (61.5)
Malaise	6 (46.1)
Cough	5 (38.4)
Confusion	4 (30.8)
Rhinorrhea/Congestion	4 (30.8)
Shortness of breath	3 (23.1)
Diarrhea	3 (23.1)
Sore throat	1 (7.7)
Nausea	1 (7.7)
Dizziness	1 (7.7)

CDC. MMWR 2020;69:377-81 (3 April)

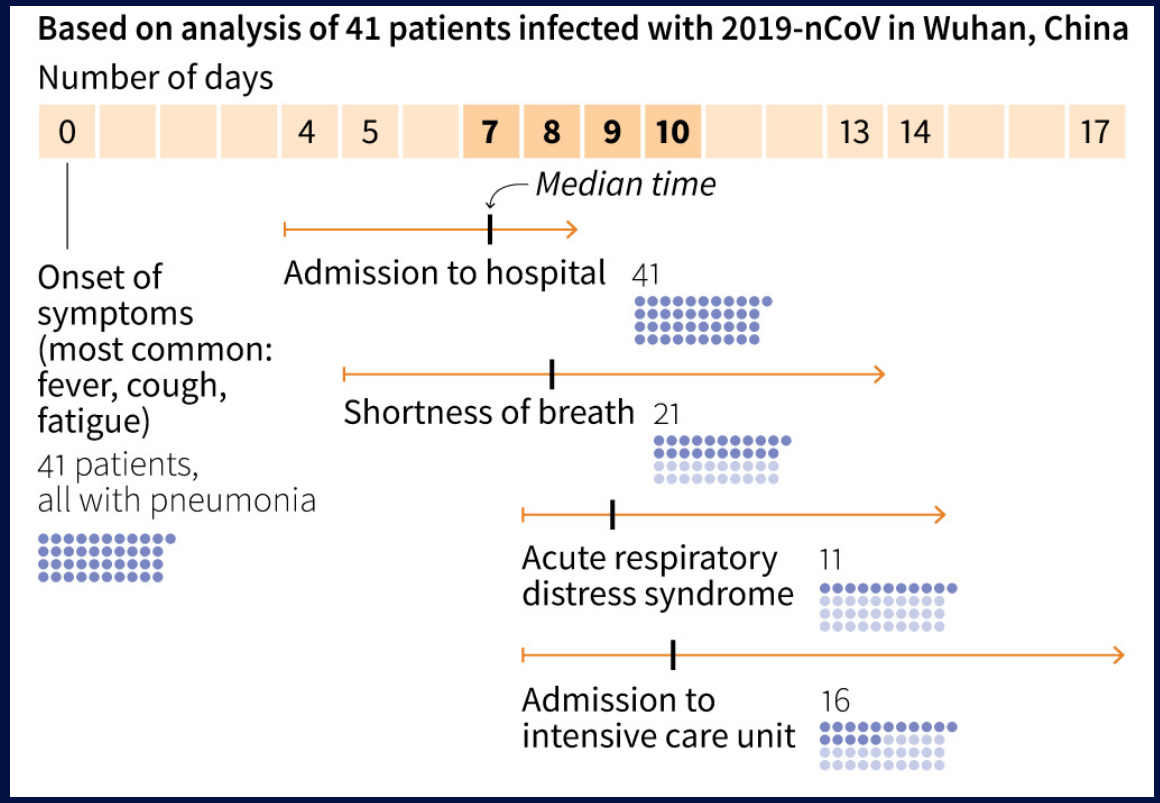
COVID-19, TIME LINE OF INFECTION COURSE

Symptoms begin

4-5 days

after exposure

(range 2-14)



Li Q, et al. N Engl J Med. 2020 Jan 29. doi: 10.1056/NEJMoa2001316 Chan JF, et al. Lancet. 2020 Feb 15;395(10223):514-523
Guan WJ, et al. N Engl J Med. 2020 Feb 28. doi: 10.1056/NEJMoa2002032 **Huang C, et al. Lancet. 2020 Feb 15;395(10223):497-506**

Table 1. Clinical Characteristics of the Study Patients, According to Disease Severity and the Presence or Absence of the Primary Composite End Point.*

Characteristic	All Patients (N=1099)	Disease Severity		Presence of Primary Composite End Point†	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Age					
Median (IQR) — yr	47.0 (35.0–58.0)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	63.0 (53.0–71.0)	46.0 (35.0–57.0)
Distribution — no./total no. (%)					
0–14 yr	9/1011 (0.9)	8/848 (0.9)	1/163 (0.6)	0	9/946 (1.0)
15–49 yr	557/1011 (55.1)	490/848 (57.8)	67/163 (41.1)	12/65 (18.5)	545/946 (57.6)
50–64 yr	292/1011 (28.9)	241/848 (28.4)	51/163 (31.3)	21/65 (32.3)	271/946 (28.6)
≥65 yr	153/1011 (15.1)	109/848 (12.9)	44/163 (27.0)	32/65 (49.2)	121/946 (12.8)
Female sex — no./total no. (%)	459/1096 (41.9)	386/923 (41.8)	73/173 (42.2)	22/67 (32.8)	437/1029 (42.5)
Smoking history — no./total no. (%)					
Never smoked	927/1085 (85.4)	793/913 (86.9)	134/172 (77.9)	44/66 (66.7)	883/1019 (86.7)
Former smoker	21/1085 (1.9)	12/913 (1.3)	9/172 (5.2)	5/66 (7.6)	16/1019 (1.6)
Current smoker	137/1085 (12.6)	108/913 (11.8)	29/172 (16.9)	17/66 (25.8)	120/1019 (11.8)
Exposure to source of transmission within past 14 days — no./total no.					
Living in Wuhan	483/1099 (43.9)	400/926 (43.2)	83/173 (48.0)	39/67 (58.2)	444/1032 (43.0)
Contact with wildlife	13/687 (1.9)	10/559 (1.8)	3/128 (2.3)	1/41 (2.4)	12/646 (1.9)
Recently visited Wuhan‡	193/616 (31.3)	166/526 (31.6)	27/90 (30.0)	10/28 (35.7)	183/588 (31.1)
Had contact with Wuhan residents‡	442/611 (72.3)	376/522 (72.0)	66/89 (74.2)	19/28 (67.9)	423/583 (72.6)
Median incubation period (IQR) — days§	4.0 (2.0–7.0)	4.0 (2.8–7.0)	4.0 (2.0–7.0)	4.0 (1.0–7.5)	4.0 (2.0–7.0)
Fever on admission					
Patients — no./total no. (%)	473/1081 (43.8)	391/910 (43.0)	82/171 (48.0)	24/66 (36.4)	449/1015 (44.2)
Median temperature (IQR) — °C	37.3 (36.7–38.0)	37.3 (36.7–38.0)	37.4 (36.7–38.1)	36.8 (36.3–37.8)	37.3 (36.7–38.0)
Distribution of temperature — no./total no. (%)					
<37.5°C	608/1081 (56.2)	519/910 (57.0)	89/171 (52.0)	42/66 (63.6)	566/1015 (55.8)
37.5–38.0°C	238/1081 (22.0)	201/910 (22.1)	37/171 (21.6)	10/66 (15.2)	228/1015 (22.5)
38.1–39.0°C	197/1081 (18.2)	160/910 (17.6)	37/171 (21.6)	11/66 (16.7)	186/1015 (18.3)
>39.0°C	38/1081 (3.5)	30/910 (3.3)	8/171 (4.7)	3/66 (4.5)	35/1015 (3.4)
Fever during hospitalization					
Patients — no./total no. (%)	975/1099 (88.7)	816/926 (88.1)	159/173 (91.9)	59/67 (88.1)	916/1032 (88.8)
Median highest temperature (IQR) — °C	38.3 (37.8–38.9)	38.3 (37.8–38.9)	38.5 (38.0–39.0)	38.5 (38.0–39.0)	38.3 (37.8–38.9)
<37.5°C	92/926 (9.9)	79/774 (10.2)	13/152 (8.6)	3/54 (5.6)	89/872 (10.2)
37.5–38.0°C	286/926 (30.9)	251/774 (32.4)	35/152 (23.0)	20/54 (37.0)	266/872 (30.5)
38.1–39.0°C	434/926 (46.9)	356/774 (46.0)	78/152 (51.3)	21/54 (38.9)	413/872 (47.4)
>39.0°C	114/926 (12.3)	88/774 (11.4)	26/152 (17.1)	10/54 (18.5)	104/872 (11.9)

Data = 1,099 patients,
552 hospitals, 30 provinces
Through 29 January

Median age = 47

Fever present in only 44% on admission; 89% during Hospitalization
Cough, 68%

Median incubation = 4d

Symptoms — no. (%)					
Conjunctival congestion	9 (0.8)	5 (0.5)	4 (2.3)	0	9 (0.9)
Nasal congestion	53 (4.8)	47 (5.1)	6 (3.5)	2 (3.0)	51 (4.9)
Headache	150 (13.6)	124 (13.4)	26 (15.0)	8 (11.9)	142 (13.8)
Cough	745 (67.8)	623 (67.3)	122 (70.5)	46 (68.7)	699 (67.7)
Sore throat	153 (13.9)	130 (14.0)	23 (13.3)	6 (9.0)	147 (14.2)
Sputum production	370 (33.7)	309 (33.4)	61 (35.3)	20 (29.9)	350 (33.9)
Fatigue	419 (38.1)	350 (37.8)	69 (39.9)	22 (32.8)	397 (38.5)
Hemoptysis	10 (0.9)	6 (0.6)	4 (2.3)	2 (3.0)	8 (0.8)
Shortness of breath	205 (18.7)	140 (15.1)	65 (37.6)	36 (53.7)	169 (16.4)
Nausea or vomiting	55 (5.0)	43 (4.6)	12 (6.9)	3 (4.5)	52 (5.0)
Diarrhea	42 (3.8)	32 (3.5)	10 (5.8)	4 (6.0)	38 (3.7)
Myalgia or arthralgia	164 (14.9)	134 (14.5)	30 (17.3)	6 (9.0)	158 (15.3)
Chills	126 (11.5)	100 (10.8)	26 (15.0)	8 (11.9)	118 (11.4)
Signs of infection — no. (%)					
Throat congestion	19 (1.7)	17 (1.8)	2 (1.2)	0	19 (1.8)
Tonsil swelling	23 (2.1)	17 (1.8)	6 (3.5)	1 (1.5)	22 (2.1)
Enlargement of lymph nodes	2 (0.2)	1 (0.1)	1 (0.6)	1 (1.5)	1 (0.1)
Rash	2 (0.2)	0	2 (1.2)	0	2 (0.2)
Coexisting disorder — no. (%)					
Any	261 (23.7)	194 (21.0)	67 (38.7)	39 (58.2)	222 (21.5)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	6 (3.5)	7 (10.4)	5 (0.5)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Hypertension	165 (15.0)	124 (13.4)	41 (23.7)	24 (35.8)	141 (13.7)
Coronary heart disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (2.3)	4 (6.0)	11 (1.1)
Hepatitis B infection¶	23 (2.1)	22 (2.4)	1 (0.6)	1 (1.5)	22 (2.1)
Cancer‖	10 (0.9)	7 (0.8)	3 (1.7)	1 (1.5)	9 (0.9)
Chronic renal disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)
Immunodeficiency	2 (0.2)	2 (0.2)	0	0	2 (0.2)

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, and IQR interquartile range.
† The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death.
‡ These patients were not residents of Wuhan.
§ Data regarding the incubation period were missing for 808 patients (73.5%).
¶ The presence of hepatitis B infection was defined as a positive result on testing for hepatitis B surface antigen with or without elevated levels of alanine or aspartate aminotransferase.
‖ Included in this category is any type of cancer.

Table 3. Complications, Treatments, and Clinical Outcomes.

Variable	All Patients (N=1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Complications					
Septic shock — no. (%)	12 (1.1)	1 (0.1)	11 (6.4)	9 (13.4)	3 (0.3)
Acute respiratory distress syndrome — no. (%)	37 (3.4)	10 (1.1)	27 (15.6)	27 (40.3)	10 (1.0)
Acute kidney injury — no. (%)	6 (0.5)	1 (0.1)	5 (2.9)	4 (6.0)	2 (0.2)
Disseminated intravascular coagulation — no. (%)	1 (0.1)	0	1 (0.6)	1 (1.5)	0
Rhabdomyolysis — no. (%)	2 (0.2)	2 (0.2)	0	0	2 (0.2)
Physician-diagnosed pneumonia — no./total no. (%)	972/1067 (91.1)	800/894 (89.5)	172/173 (99.4)	63/66 (95.5)	909/1001 (90.8)
Median time until development of pneumonia (IQR) — days*					
After initial Covid-19 diagnosis	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.0 (0.0–3.5)	0.0 (0.0–1.0)
After onset of Covid-19 symptoms	3.0 (1.0–6.0)	3.0 (1.0–6.0)	5.0 (2.0–7.0)	4.0 (0.0–7.0)	3.0 (1.0–6.0)
Treatments					
Intravenous antibiotics — no. (%)	637 (58.0)	498 (53.8)	139 (80.3)	60 (89.6)	577 (55.9)
Oseltamivir — no. (%)	393 (35.8)	313 (33.8)	80 (46.2)	36 (53.7)	357 (34.6)
Antifungal medication — no. (%)	31 (2.8)	18 (1.9)	13 (7.5)	8 (11.9)	23 (2.2)
Systemic glucocorticoids — no. (%)	204 (18.6)	127 (13.7)	77 (44.5)	35 (52.2)	169 (16.4)
Oxygen therapy — no. (%)	454 (41.3)	331 (35.7)	123 (71.1)	59 (88.1)	395 (38.3)
Mechanical ventilation — no. (%)	67 (6.1)	0	67 (38.7)	40 (59.7)	27 (2.6)
Invasive	25 (2.3)	0	25 (14.5)	25 (37.3)	0
Noninvasive	56 (5.1)	0	56 (32.4)	29 (43.3)	27 (2.6)
Use of extracorporeal membrane oxygenation — no. (%)	5 (0.5)	0	5 (2.9)	5 (7.5)	0
Use of continuous renal-replacement therapy — no. (%)	9 (0.8)	0	9 (5.2)	8 (11.9)	1 (0.1)
Use of intravenous immune globulin — no. (%)	144 (13.1)	86 (9.3)	58 (33.5)	27 (40.3)	117 (11.3)
Admission to intensive care unit — no. (%)	55 (5.0)	22 (2.4)	33 (19.1)	55 (82.1)	0
Median length of hospital stay (IQR) — days†	12.0 (10.0–14.0)	11.0 10.0–13.0)	13.0 (11.5–17.0)	14.5 (11.0–19.0)	12.0 (10.0–13.0)
Clinical outcomes at data cutoff — no. (%)					
Discharge from hospital	55 (5.0)	50 (5.4)	5 (2.9)	1 (1.5)	54 (5.2)
Death	15 (1.4)	1 (0.1)	14 (8.1)	15 (22.4)	0
Recovery	9 (0.8)	7 (0.8)	2 (1.2)	0	9 (0.9)
Hospitalization	1029 (93.6)	875 (94.5)	154 (89.0)	51 (76.1)	978 (94.8)

* For the development of pneumonia, data were missing for 347 patients (31.6%) regarding the time since the initial diagnosis and for 161 patients (14.6%) regarding the time since symptom onset.
† Data regarding the median length of hospital stay were missing for 136 patients (12.4%).

NEUROLOGIC DISORDERS ASSOCIATED WITH COVID-19

- Neurologic symptoms (40% of COVID patients): Headache, epilepsy, and disturbed consciousness, sudden loss of smell and/or taste
- Uncommon neurologic disorders
  - Viral encephalitis (sx=headache, fever, projective vomiting, convulsions, decreased consciousness)
  - Acute toxic encephalopathy (cerebral edema; sx=headache, mental disorder, delirium, disorientation, LOC, coma, paralysis)
  - Acute cerebrovascular disease (associated with cytokine storm syndromes – related to elevated D-dimer and severe platelet reduction)

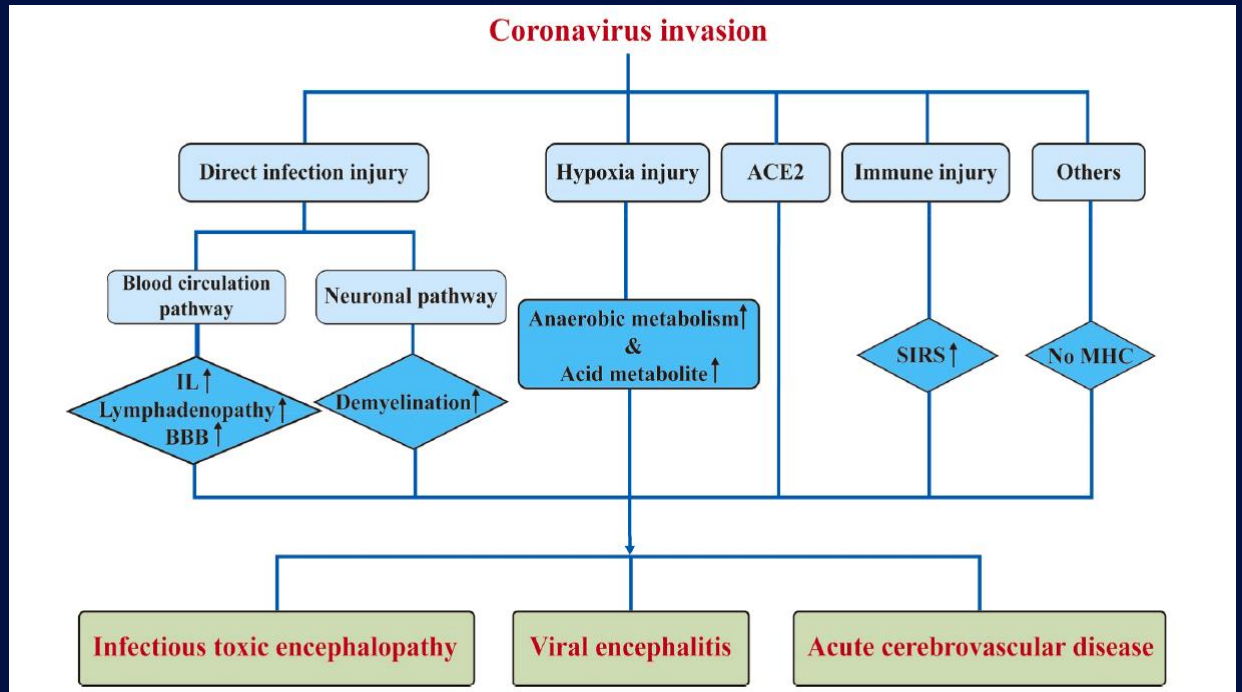


Fig. 2. Pathogenesis of nervous system injury caused by coronaviruses. ACE2: angiotensin-converting enzyme 2; BBB: blood brain barrier; IL: interleukin; MHC: major histocompatibility complexes; SIRS: systemic inflammatory response syndrome.

Wu Y, et al. Brain, Behavior, and Immunity 2020;30 March

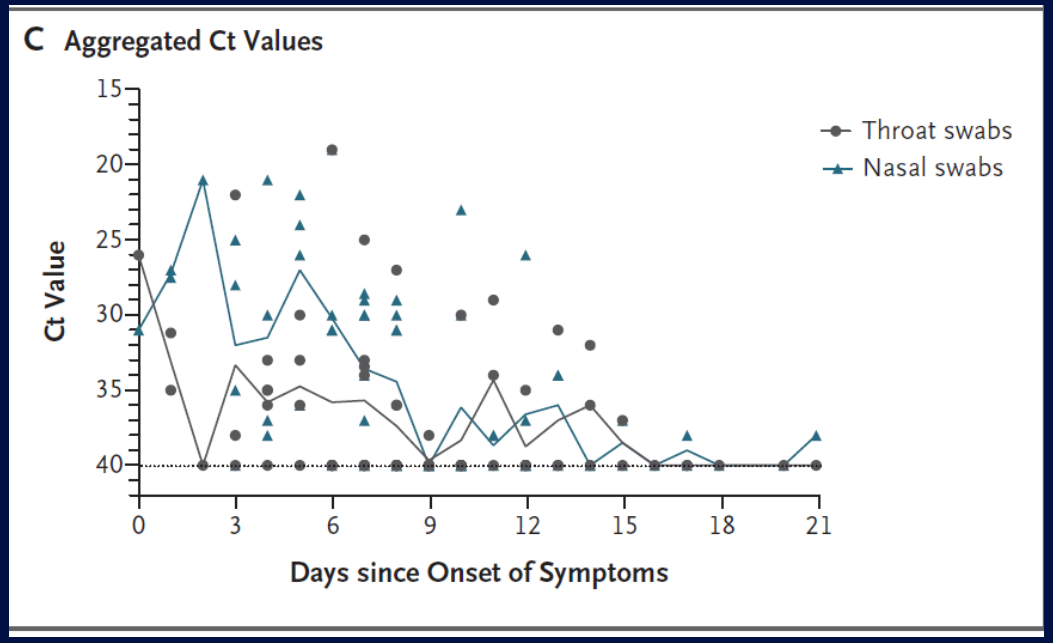
COVID-19 TESTING, UNC

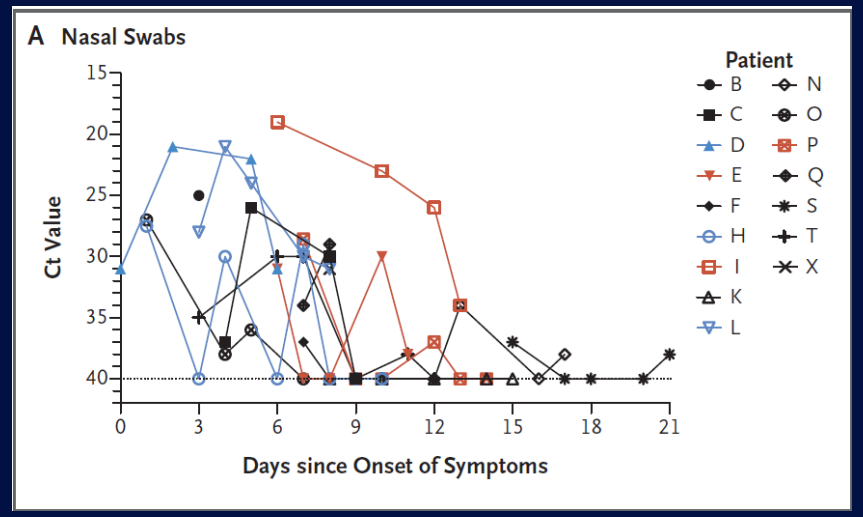
- UNC COVID testing limitations
  - Capacity ~300 per day; short term limitations = availability of swabs and reagents
  - Priorities: Symptomatic ED/inpatients > HCP > high risk outpatients
- Expansion of ED/inpatient test criteria
  - Fever AND lower respiratory symptoms (cough, SOB)
  - Changed: Fever OR lower respiratory symptoms (cough, SOB)
  - Added: Upper respiratory symptoms (sore throat, sneezing)
  - Added: Loss of sense of smell and/or taste
  - Added: GI symptoms (nausea, vomiting, diarrhea)
  - Added: If patient in critical care unit with negative NP COVID test, test of lower respiratory specimens allowed (i.e., tracheal aspirate or BAL)
- Rapid COVID test will be available later this week for ED use only: 1) Patients with above sx and no alternative dx requiring admission; 2) patients from a congregate setting with an outbreak requiring admission; 3) patients unable to provide a hx (psychotic, trauma, stroke, etc.)
- Being validated: Serologic test

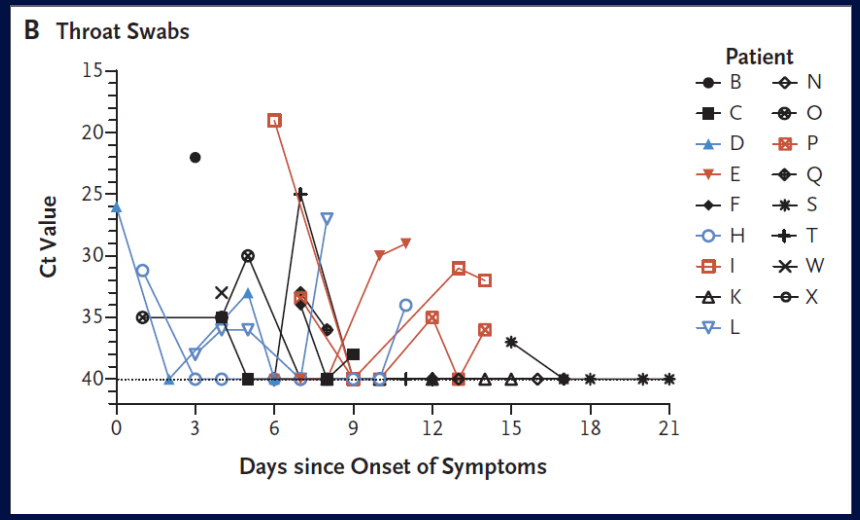
RATIONALE FOR TIME-BASED REMOVALOF ISOLATION PRECAUTONS

- Study demonstrates that NP and throat swabs detect SARS CoV-2 for up to 21 days (positivity may be lost after 7 days)
- 18 patients studied

Zhou L, et al. NEJM 382;12:19 March 2020

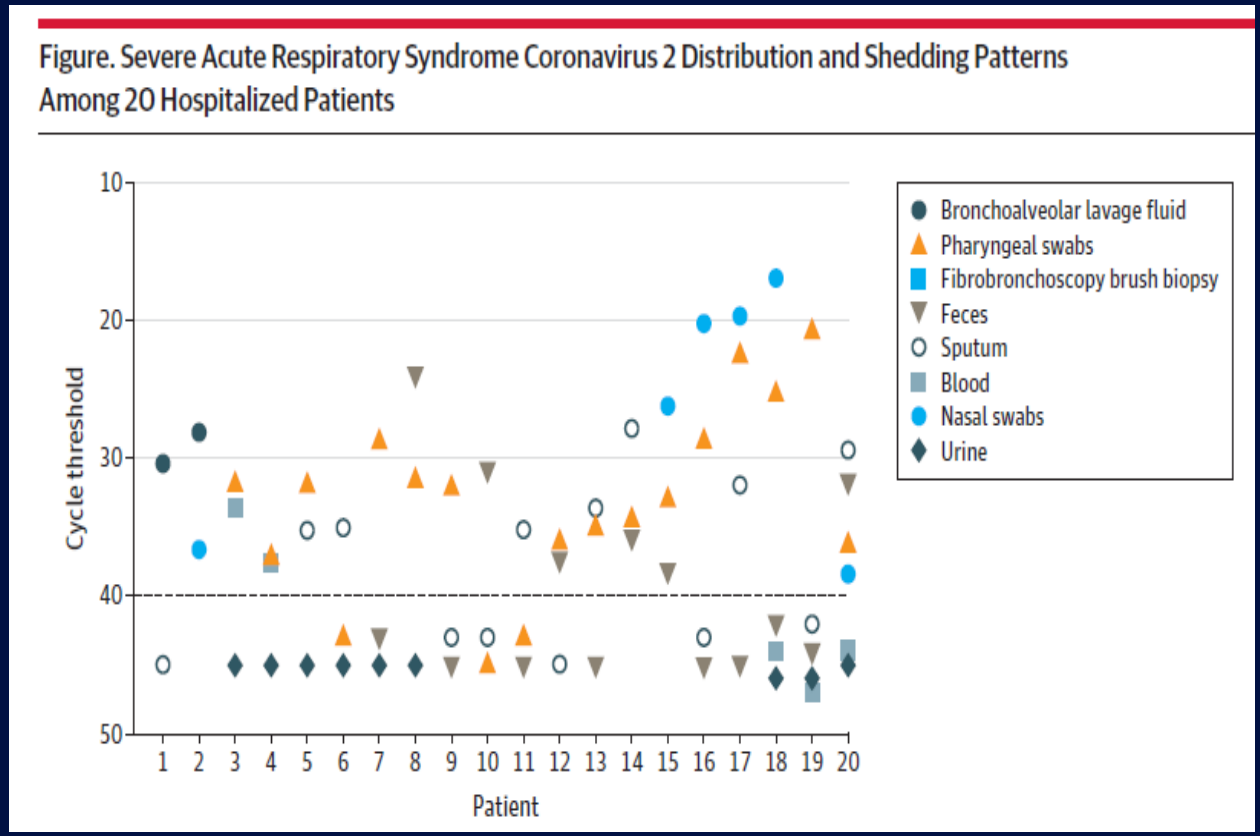






RATIONALE FOR RECOMMENDING TRACHEAL ASPIRATE/BAL SPECIMEN IN ICU PATIENTS WITH NEGATIVE NP SWAB AND COVID-19 SYMPTOMS

- Overall, 1070 specimens collected from 205 patients
- Presentation: Fever, dry cough, and fatigue; 19% had severe illness
- BAL had the highest positive rate (14/15, 93%), sputum (72/104, 72%), NP swab (5/8, 63%), fibrobronchoscope brush (126/398, 32%), feces (44/153, 29%), blood (3/307, 1%), urine (0/72, 0%)



Wang W, et al. JAMA 2020;11 March

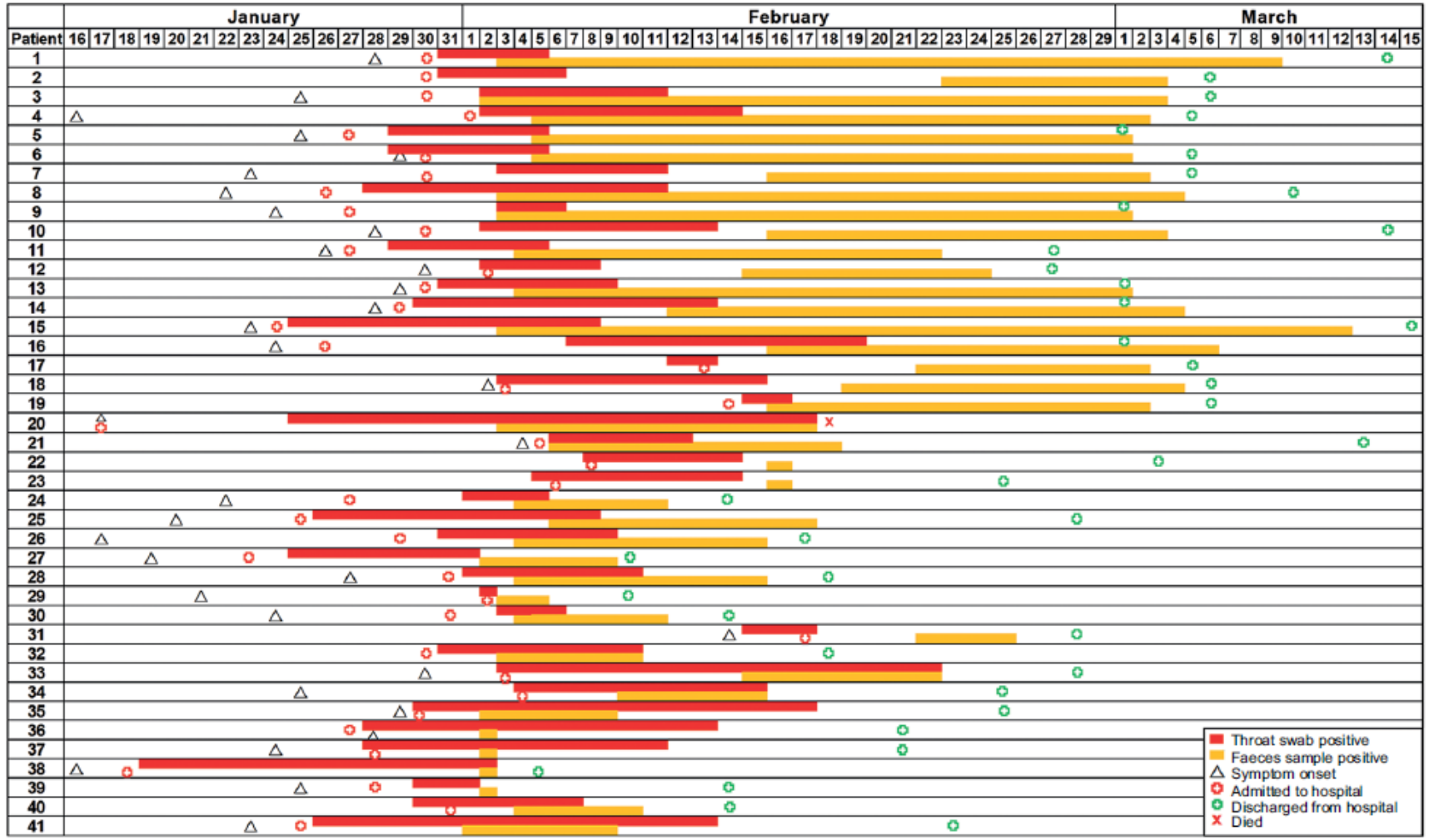


Figure: Timeline of results from throat swabs and faecal samples through the course of disease for 41 patients with SARS-CoV-2 RNA positive faecal samples, January to March, 2020

Wu Y, et al. Lancet;May 2020:434-435

TEMPORAL PROFILE OF SERIAL VIRAL LOADS IN COVID-19 PATIENTS

- Study design: Cohort analysis (N=30)
- Samples = posterior oropharyngeal saliva and other respiratory tract specimens (mean viral load = 5.2 $\log_{10}$ copies per mL)
- Salivary viral load highest during first week after symptom onset with decline over time (slope = 0.15)
- Older age correlated with higher viral load
- Confirms that viral load highest in early stage of disease
- Demonstrates time course of development of antibodies

Kai-Wang K, et al. Lancet ID;2020:23 March

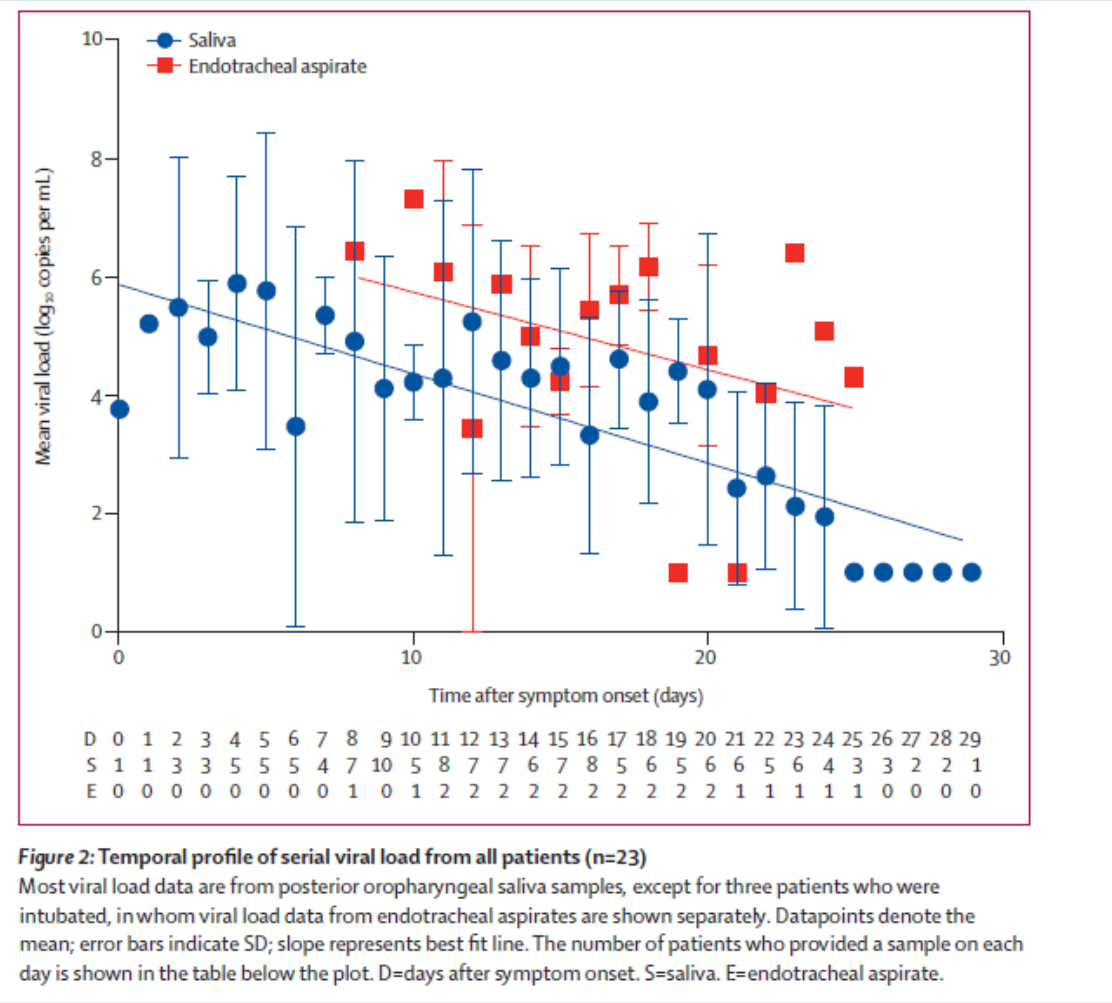


Figure 2: **Temporal profile of serial viral load from all patients (n=23)**
Most viral load data are from posterior oropharyngeal saliva samples, except for three patients who were intubated, in whom viral load data from endotracheal aspirates are shown separately. Datapoints denote the mean; error bars indicate SD; slope represents best fit line. The number of patients who provided a sample on each day is shown in the table below the plot. D=days after symptom onset. S=saliva. E=endotracheal aspirate.

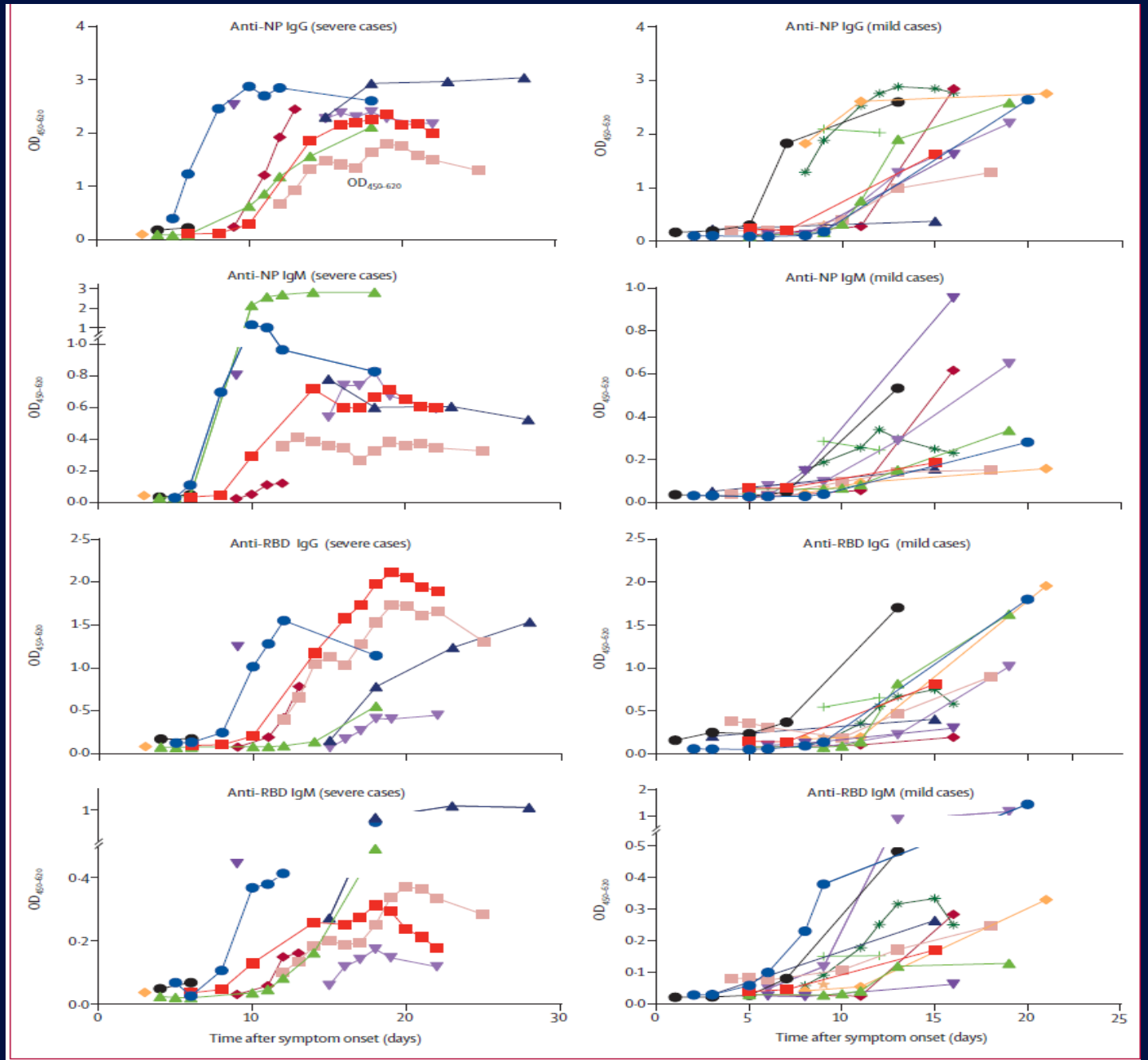


Figure 4: **Temporal profiles of serum IgM and IgG against NP and spike protein RBD, as ascertained by EIA**
Each line represents an individual patient. NP=nucleoprotein. RBD=receptor-binding domain. $OD_{450-620}$=optical density at 450–620 nm.

TIME COURSE OF SEROLOGIC RESPONSE IN COVID-19 PATIENTS

Kai-Wang K, et al
Lancet ID 2020;

CLINICAL FACTORS THAT CORRELATE WITH INCREASED RISK OF SEVERE COVID DISEASE AND/OR DEATH

Markers

- C-Reactive Protein >125 mg/L (possibly lower)
- D-dimer >500 ng/mL
- LDH >245 U/L
- WBC >10,000 cells/mm^3
- RR >24 bpm
- Ferritin >300 mcg/mL
- Absolute Lymphocyte count (ALC) <0.8 cells/mm^3

Risk Factors

- Age >45 years; highest age >65 years*
- Co-morbidities
  - Diabetes mellitus*
  - Serious heart conditions*
  - Chronic lung disease*
  - Moderate to severe asthma*
  - Hypertension
  - Chronic kidney diseases undergoing dialysis*
  - People with liver disease*
  - Immunocompromised*: cancer treatment, organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, prolonged use of corticosteroids, and immune modulating medications

Ruan, et al. Intensive Care Med; Shi, et al. JAMA Cardiology; Wu, et al. JAMA Intern Med; Zhou, et al Lancet; Shi et al., Crit Care; CDC: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html

TABLE 1. Reported outcomes among COVID-19 patients of all ages, by hospitalization status, underlying health condition, and risk factor for severe outcome from respiratory infection — United States, February 12–March 28, 2020

Underlying health condition/Risk factor for severe outcomes from respiratory infection (no., % with condition)	No. (%)			
	Not hospitalized	Hospitalized, non-ICU	ICU admission	Hospitalization status unknown
Total with case report form (N = 74,439)	**12,217**	**5,285**	**1,069**	**55,868**
Missing or unknown status for all conditions (67,277)	**7,074**	**4,248**	**612**	**55,343**
Total with completed information (7,162)	**5,143**	**1,037**	**457**	**525**
One or more conditions (2,692, 37.6%)	1,388 (27)	732 (71)	358 (78)	214 (41)
Diabetes mellitus (784, 10.9%)	331 (6)	251 (24)	148 (32)	54 (10)
Chronic lung disease* (656, 9.2%)	363 (7)	152 (15)	94 (21)	47 (9)
Cardiovascular disease (647, 9.0%)	239 (5)	242 (23)	132 (29)	34 (6)
Immunocompromised condition (264, 3.7%)	141 (3)	63 (6)	41 (9)	19 (4)
Chronic renal disease (213, 3.0%)	51 (1)	95 (9)	56 (12)	11 (2)
Pregnancy (143, 2.0%)	72 (1)	31 (3)	4 (1)	36 (7)
Neurologic disorder, neurodevelopmental, intellectual disability (52, 0.7%)†	17 (0.3)	25 (2)	7 (2)	3 (1)
Chronic liver disease (41, 0.6%)	24 (1)	9 (1)	7 (2)	1 (0.2)
Other chronic disease (1,182, 16.5%)§	583 (11)	359 (35)	170 (37)	70 (13)
Former smoker (165, 2.3%)	80 (2)	45 (4)	33 (7)	7 (1)
Current smoker (96, 1.3%)	61 (1)	22 (2)	5 (1)	8 (2)
None of the above conditions¶ (4,470, 62.4%)	3,755 (73)	305 (29)	99 (22)	311 (59)

Abbreviation: ICU = intensive care unit.

* Includes any of the following: asthma, chronic obstructive pulmonary disease, and emphysema.

† For neurologic disorder, neurodevelopmental, and intellectual disability, the following information was specified: dementia, memory loss, or Alzheimer's disease (17); seizure disorder (5); Parkinson's disease (4); migraine/headache (4); stroke (3); autism (2); aneurysm (2); multiple sclerosis (2); neuropathy (2); hereditary spastic paraplegia (1); myasthenia gravis (1); intracranial hemorrhage (1); and altered mental status (1).

§ For other chronic disease, the following information was specified: hypertension (113); thyroid disease (37); gastrointestinal disorder (32); hyperlipidemia (29); cancer or history of cancer (29); rheumatologic disorder (19); hematologic disorder (17); obesity (17); arthritis, nonrheumatoid, including not otherwise specified (16); musculoskeletal disorder other than arthritis (10); mental health condition (9); urologic disorder (7); cerebrovascular disease (7); obstructive sleep apnea (7); fibromyalgia (7); gynecologic disorder (6); embolism, pulmonary or venous (5); ophthalmic disorder (2); hypertriglyceridemia (1); endocrine (1); substance abuse disorder (1); dermatologic disorder (1); genetic disorder (1).

¶ All listed chronic conditions, including other chronic disease, were marked as not present

CDC. MMWR 2020;69:282 (3 April)

WHO TREATMENT GUIDELINES, 28 JANUARY

- Give supplemental oxygen therapy immediately to patients with COVID-19 and respiratory distress, hypoxaemia, or shock
- Use conservative fluid management in patients with COVID-19 when there is no evidence of shock.
- Give empiric antimicrobials to treat all likely pathogens causing COVID-19. Give antimicrobials within one hour of initial patient assessment for patients with sepsis.
- Do not routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason.
- Closely monitor patients with COVID-19 for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and apply supportive care interventions immediately.
- Understand the patient's co-morbid condition(s) to tailor the management of critical illness and appreciate the prognosis. Communicate early with patient and family.

SURVIVING SEPSIS CAMPAIGN: MANAGEMENT OF COVID-19

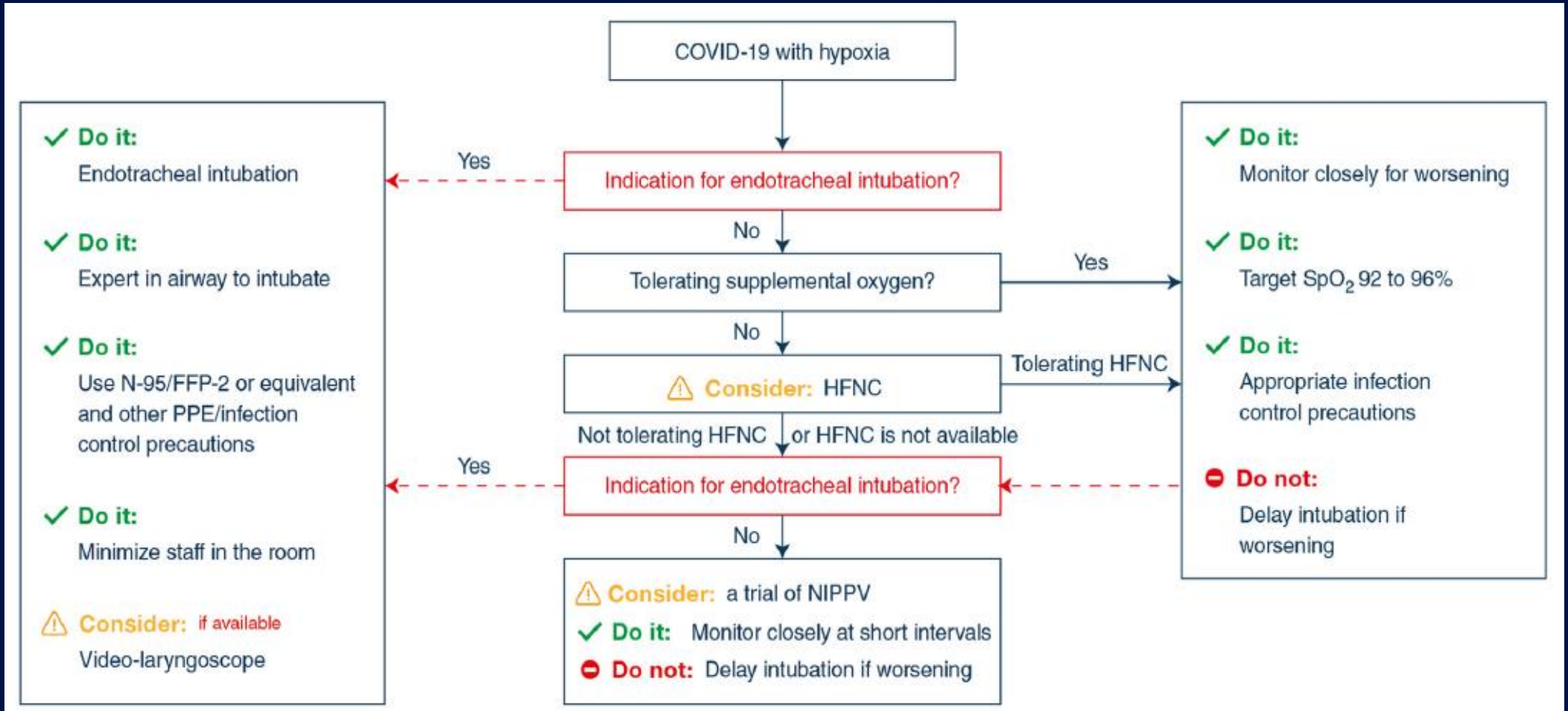


Fig. 2 Summary of recommendations on the initial management of hypoxic COVID-19 patients

Alhazzani W, et al. Intensive Care Med 2020

SURVIVING SEPSIS CAMPAIGN: MANAGEMENT OF COVID-19

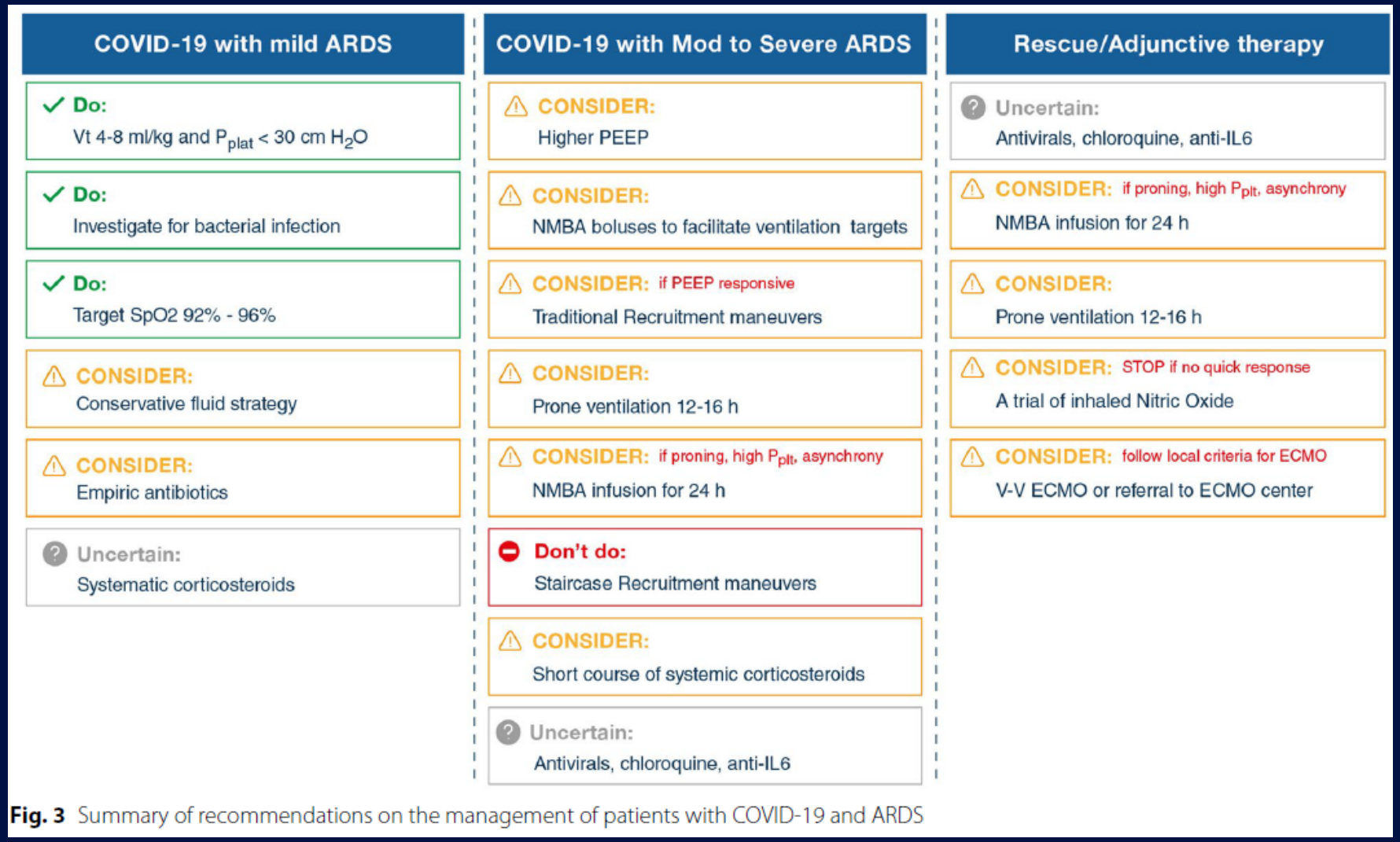


Fig. 3 Summary of recommendations on the management of patients with COVID-19 and ARDS

Alhazzani W, et al. Intensive Care Med 2020

POTENTIAL THERAPIES FOR COVID-19

Table 1. Antivirals included in the Guidelines (version 6) for treatment of COVID-19

Drug	Dosage	Method of administration	Duration of treatment
IFN-α	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	No more than 10 days
Ribavirin	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500 mg (300 mg for chloroquine) each time, 2 times/day	Oral	No more than 10 days
Arbidol	200 mg each time, 3 times/day	Oral	No more than 10 days

Other potential therapies discussed in text: remdesivir, faviparivir, darunavir; 30 total agents demonstrated to have activity in screening tests

Dong L, et al. Drug Discoveries & Therapeutics 2020;14:58-60

UNC MEDICAL CENTER: ANTIVIRAL THERAPY FOR INPATIENTS

- Remdesivir via compassionate use (available only for pregnant women or children <18 with severe disease)
- Patient intubated: Consider whether antivirals likely to have impact based on disease stage and presence of ARDS
  - Antivirals currently available have not demonstrated any benefit in severe pneumonia. However, majority of UNC ID consultants would recommend use of Remdesivir early in the course of respiratory failure
  - UNC ID consultants believe that Remdesivir (and any antiviral therapy) is unlikely to benefit patients who have established ARDS
- Does patient have contraindications to any COVID-19 antivirals available at UNC-MC
  - Comorbidity that precludes safe use
  - Critical drug-drug interactions
  - Based on above, consider off-label use of antiviral therapy: 1) Lopinavir/Ritonavir; 2) Tociluzumab (for cytokine storm and worsening respiratory status)
- UNC ID consultants do NOT recommend use of Chloroquine or Hydroxychloroquine aside of a clinical trial (substantial risk of cardiac toxicity and other potential adverse events)
- Obtain ID consult for recommendations for COVID-19 therapy

IDSA TREATMENT RECOMMENDATIONS, 13 APRIL

- Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap
- Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)
- Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)
- Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)
- Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)
- Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)
- Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap)

VACCINE STRATEGIES FOR EMERGING CORONAVIRUSES

Vaccine Strategy	Process of Production	References		Advantages	Disadvantages
		SARS	MERS		
Inactivated virus vaccines	Virus particles are inactivated by heat, chemicals, or radiation	Whole virus, with or without adjuvant (promote an effective immune response against the inactivated pathogen) [93,94]	Whole virus, with or without adjuvant (promote an effective immune response against the inactivated pathogen) [91,95]	Maintained virus particles structure; rapidly develop; easy to prepare; safety; high-titer neutralizing antibodies [93]; protection with adjuvant [96,97].	Potential inappropriate for highly immunosuppressed individuals; possible T_H2 cell-distortive immune response [98,99].
Live-attenuated virus vaccines	Attenuated the virulence, but still keeping it viable by mutagenesis or targeted deletions	Envelope protein deletion [100]; non-structural protein 14 (nsp14) and exonuclease (ExoN) inactivation [101]	Full-length infectious cDNA clone or mutant viruses [102]	Inexpensive; quick immunity; less adverse effect; activates all phases of the immune system [103]; more durable immunity; more targeted [77].	Phenotypic or genotypic reversion possible; need sufficient viral replication [77].
Viral vector vaccines	Genetically engineered unrelated viral genome with deficient packaging elements for encoding targeted gene	Spike and nucleocapsid proteins [100,104]	Spike and nucleocapsid proteins [87,88]	Safety; stronger and specific cellular and humoral immune responses [77].	Varies inoculation routes may produce different immune responses [96]; possibly incomplete protection; may fail in aged vaccinees; possible T_H2 cell-distortive immune response [105].
Subunit vaccines	Antigenic components inducing the immune system without introducing viral particles, whole or otherwise.	Spike and nucleocapsid proteins [53,59,106]	Spike and nucleocapsid proteins [85,86,107,108]	High safety; consistent production; can induce cellular and humoral immune responses; high-titer neutralizing antibodies [109].	Uncertain cost-effectiveness; relatively lower immunogenicity; need appropriate adjuvants [77].
DNA vaccines	Genetically engineered DNA for directly producing an antigen	Spike and nucleocapsid proteins [110,111]	Spike and nucleocapsid proteins [89,90]	Easier to design; high safety; high-titer neutralizing antibodies [110].	Lower immune responses; potential T_H2 cell-distortive immune response results; potential ineffective; possibly delayed-type hypersensitivity [112].

Song Z, et al. Viruses 2019;11:59

CRITERIA FOR DISCHARGE/REMOVAL OF ISOLATION PRECAUTIONS OF COVID-19 INFECTED PATIENTS

- Symptom-based strategy (≥7 days since onset of symptoms):
  AND >72 hours afebrile (off antipyretics) and substantial decrease in symptoms
  - COVID-19 infected outpatients outside UNC system
- Time-based strategy: (≥21 days since onset of symptoms)
  - COVID-19 infected outpatient seen within UNC system
- Test-based strategy: (Resolution of fever for >72 hours, improvement in respiratory symptoms AND negative results of COVID-19 PCR test x 2)
  - COVID-19 infected inpatients who would remain in the hospital
  - COVID-19 infected inpatients being discharged to a congregate setting

INFECTION PREVENTION

- Promote telemedicine
- Screening of all patients for respiratory symptoms
- Development of Respiratory Diagnostic Centers for evaluating outpatients for respiratory symptoms
- Exclusion of all visitors to the hospital (with some exceptions for end of life visits, parents of young children)
- Universal use of masks for all healthcare personnel while in healthcare facility
- Use of masks by all patients and visitors
- Use of N95 respirators for all aerosol generating procedures
- For care of patients with known or suspected COVID-19: N95 respirator, gown, face shield, gloves
- Extended use of masks/N95s unless use in care of a suspect or known COVID-19 patient
- Daily screening of all healthcare personnel for signs/symptoms of COVID-19
- COVID-19 testing of healthcare personnel with signs/symptoms of COVID-19
- Appropriate messaging regarding hand hygiene

PERSONAL PROTECTIVE EQUIPMENT (PPE)

- All HCP currently wearing a mask while in the Medical Center or clinics
  - Extended use for masks (5 work shifts maximum); HH before and after touching mask; discarded if soiled, damaged or hard to breath through; stored in a paper bag
- All patients asked to wear a surgical mask when outside their room for therapeutic purposes or being transported to a location for a test/procedure, and also whenever a HCP enters their room (regardless of COVID-19 status)
- All visitors wearing a mask at all times while in a healthcare facility
- N95 plus eye protection recommended in the following patient care situations:
  - COVID PUIs and COVID-19 infected patients
  - Aerosol generating procedures: include BiPAP/CPAP, intubation/extubation, open airway suctioning, bronchoscopy, laryngoscopy, upper endoscopy (EGD), chest PT, nebs, CPR, transesophageal echocardiography (TEE), many ENT procedures, tracheoesophageal prosthetic management)

USE OF ROUTINE MASKING OF PATIENTS AND HCP EFFECTIVE IN PREVENTING COVID ACQUISITION

- Outbreak investigation in a COVID-19 patient nursed in an open cubicle of a general hospital ward for 35 hours (patient had “severe pneumonia” and was on oxygen)
- Results: A total of 71 HCP and 49 exposed patients identified (10 patients and 7 HCP had close contact); at the end of a 28-day surveillance period, no infections among HCP or patients were identified (only tested the 30 HCP and 22 patients who developed fever and/or respiratory symptoms)
- Hospital used universal masking of HCP, patients and visitors

Wong S.C,-Y, et al.
JHI 2020;27 March

COVID-19 IN HCP

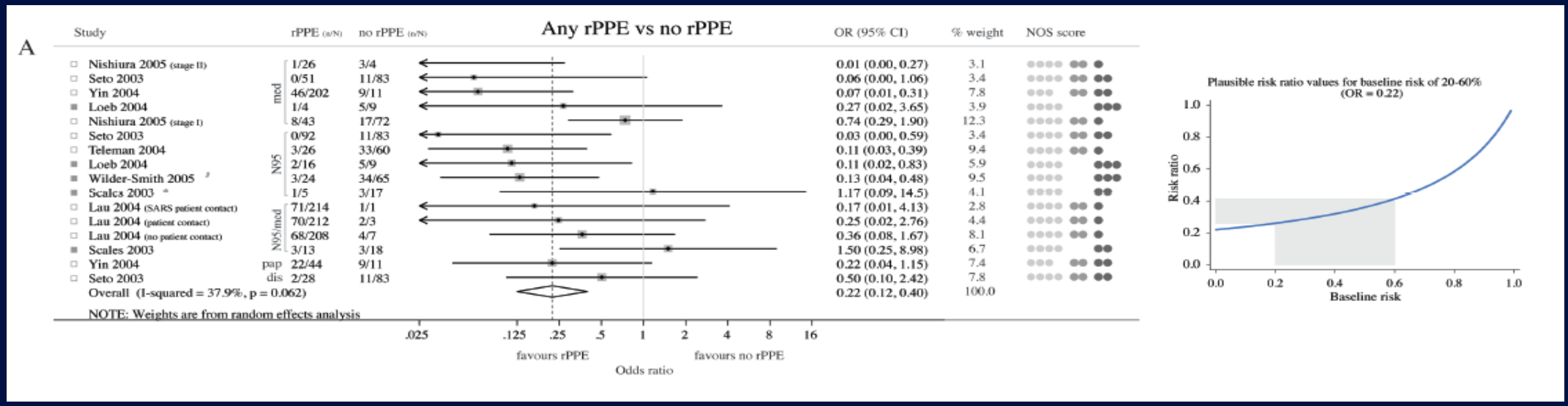
- Among HCP who developed COVID-19, age ≥65 years was a risk factor for hospitalization, ICU admission and death[1]
- HCP exposure evaluation to a COVID patient[2]
  - 121 exposed: High risk=14; medium=80; low=27; 46% of interviewed HCP had exposure during at least 1 AGP
  - 43 became symptomatic, 3 tested positive (7%) – high risk, 3; medium risk, 2 (none of the 3 used PPE)
- CDC definitions (prolonged contact)
  - Pt wearing a facemask, HCP wearing no PPE or not wearing facemask or N95 = Medium risk
  - Pt not wearing a facemask, HCP wearing no PPE or not wearing a facemask or N95 = High risk
  - Pt not wearing a facemask, HCP wearing a facemask or N95 but not wearing eye protection = Medium risk

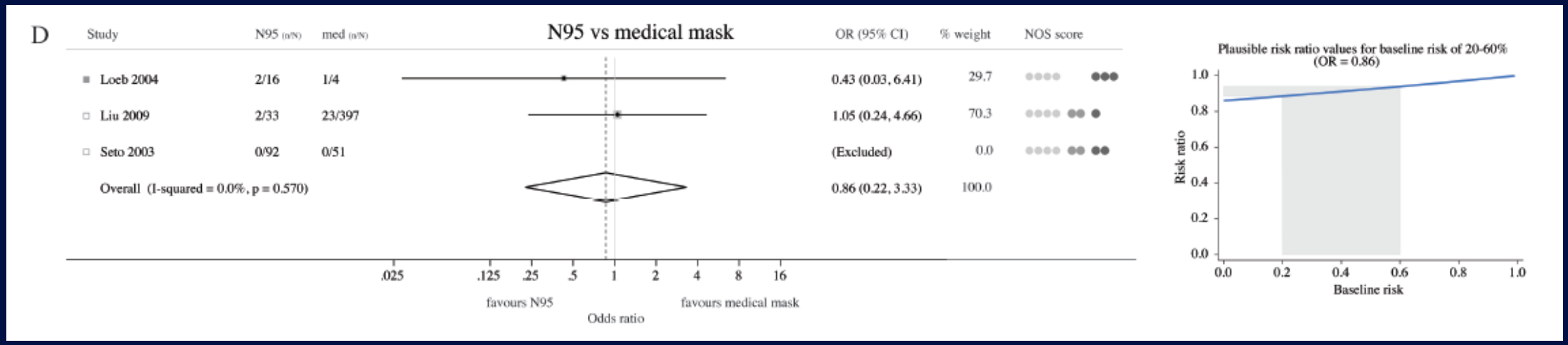
Symptoms reported[§,] (4,707)**	
Fever, cough, or shortness of breath[††]	4,336 (92)
Cough	3,694 (78)
Fever[§§]	3,196 (68)
Muscle aches	3,122 (66)
Headache	3,048 (65)
Shortness of breath	1,930 (41)
Sore throat	1,790 (38)
Diarrhea	1,507 (32)
Nausea or vomiting	923 (20)
Loss of smell or taste[¶¶]	750 (16)
Abdominal pain	612 (13)
Runny nose	583 (12)
Any underlying health condition[§,*] (4,733)**	1,779 (38)

[1]CDC, MMWR 2020;69:14 April; [2]CDC, MMWR 2020;69:14 April

META-ANALYSIS OF PROTECTIVE EFFECTS OF MASKS AND N95s AGAINST SARS INFECTION

Meta-analysis of observational studies provided evidence of a protective effect of masks (OR = 0.13; 95% CI: 0.03–0.62) and respirators (OR = 0.12; 95% CI: 0.06–0.26) against severe acute respiratory syndrome (SARS)





Offeddu V, et al. Clin Infect Dis 2017;65:1934-42

CLUSTER RCT OF CLOTH MASKS COMPARED TO MEDICAL MASKS IN HCP

- Study design: Hospital wards randomized to medical masks, cloth masks or control group (usual practice, that included mask wearing)
- Methods:
  - 14 secondary-level/tertiary-level hospitals in Hanoi, Vietnam
  - 1607 hospital HCP aged ≥18 years
- Results: The rates of all infection outcomes were highest in the cloth mask arm, with the rate of ILI statistically significantly higher in the cloth mask arm (relative risk (RR)=13.00, 95% CI 1.69 to 100.07) compared with the medical mask arm. Cloth masks also had significantly higher rates of ILI compared with the control arm. An analysis by mask use showed ILI (RR=6.64, 95% CI 1.45 to 28.65) and laboratory-confirmed virus (RR=1.72, 95% CI 1.01 to 2.94) were significantly higher in the cloth masks group compared with the medical masks group. Penetration of cloth masks by particles was almost 97% and medical masks 44%.

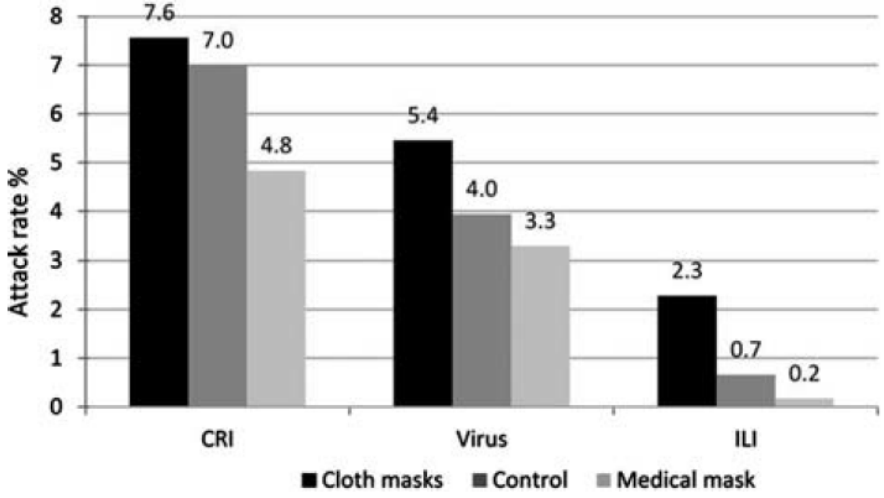


Figure 2 Outcomes in trial arms (CRI, clinical respiratory illness; ILI, influenza-like illness; Virus, laboratory-confirmed viruses).

Table 2 Intention-to-treat analysis

	CRI N (%)	RR (95% CI)	ILI N (%)	RR (95% CI)	Laboratory-confirmed viruses N (%)	RR (95% CI)
Medical mask*	28/580 (4.83)	Ref	1/580 (0.17)	Ref	19/580 (3.28)	Ref
Cloth masks†	43/569 (7.56)	1.57 (0.99 to 2.48)	13/569 (2.28)	**13.25 (1.74 to 100.97)**	31/569 (5.45)	1.66 (0.95 to 2.91)
Control‡	32/458 (6.99)	1.45 (0.88 to 2.37)	3/458 (0.66)	3.80 (0.40 to 36.40)	18/458 (3.94)	1.20 (0.64 to 2.26)

MacIntyre CR, et al. BMJ Open 2015;5:e006577

Decontamination and Reuse of Filtering Facepiece Respirators, CDC

- Disposable filtering facepiece respirators (FFRs) are not approved for routine decontamination and reuse as standard of care. However, FFR decontamination and reuse may need to be considered as a crisis capacity strategy to ensure continued availability. Based on the limited research available, ultraviolet germicidal irradiation, vaporous hydrogen peroxide, and moist heat showed the most promise as potential methods to decontaminate FFRs.
- HCPs should take the following precautionary measures prior to using a decontaminated FFR:
  - Clean hands with soap and water or an alcohol-based hand sanitizer before and after touching or adjusting the FFR.
  - Avoid touching the inside of the FFR.
  - Use a pair of clean (non-sterile) gloves when donning and performing a user seal check.
  - Visually inspect the FFR to determine if its integrity has been compromised.
  - Check that components such as the straps, nose bridge, and nose foam material did not degrade, which can affect the quality of the fit, and seal.
  - If the integrity of any part of the FFR is compromised, or if a successful user seal check cannot be performed, discard the FFR and try another FFR.
  - Users should perform a user seal check immediately after they don each FFR and should not use an FFR on which they cannot perform a successful user seal check.

https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/decontamination-reuse-respirators.html

REPROCESSING MASKS, FDA GUIDEANCE, MARCH 2020

- A description of the process for disinfection/reprocessing controls, including: critical cycle parameters (e.g,. concentration, time, heat, relative humidity) required for appropriate bioburden AND information on chemical and biological indicators (UNC monitors all cycle parameters)
- Validation of bioburden reduction/disinfection (UNC uses an appropriate BI in each run)
- Description of chair of custody and safeguards for scale-up process, if applicable (UNC has a defined method for safely collecting used masks including PPE for handlers)
- Material compatibility (Number of reprocessing cycles determined by labeling the N95s band; each N95 assessed for damage after reprocessing and discarded if damaged)
- Filtration performance (Tested at UNC by our engineers/aerosol)
- Fit test data (Tested at UNC by our engineers/aerosol experts using a dummy)
- A copy of the reprocessed device product labeling

COLLECTION AND DISTRIBUTION OF REPROCESSED N95 RESPIRATORS

- Reprocessed N95 respirators will be used, when our supply of new N95s is diminished
- Healthcare personnel asked NOT to wear makeup or fragrances (e.g., cologne, perfume)
- Collection
  - Bins located in high use areas: ICUs, ED, OR, RDC, 6BT and other locations
  - Used masks collected by EVS; inspected, sorted and packaged for sterilization
- At reprocessing location (School of Dentistry or UNCH CPD, N95 placed in ETO sterilizer
- Post-reprocessing
  - N95 discarded if soiled or damaged
  - N95s inventoried by type and size, and then packaged for distribution
- Reprocessed N95 currently stored in Central Distribution; will be made available for ordering
- HCP using a reprocessed mask should perform a user seal check

N95 SEAL CHECK

In accordance with *CDC Contingency Capacity Strategies for N95 respirators*, we are transitioning from formal fit-testing to a user-seal check process.

How to Perform an N95 Seal Check

Place both hands over the respirator, take a quick breath in to check whether the respirator seals tightly to the face.

Place both hands completely over the respirator and exhale. If you feel leakage, there is not a proper seal.

*** Skip this step if using an N95 with a valve**

If air leaks around the nose, readjust the nosepiece as described.

If air leaks at the mask edges, re-adjust the straps along the sides of your head until a proper seal is maximized.

*N95 with an Exhalation Valve: What is different?

You may receive an N95 with a valve. These N95 respirators will protect you the same as a regular, un-valved N95 but should NOT be used in sterile procedures or worn by a person who is exhibiting respiratory symptoms because the air you exhale comes out of the valve unfiltered.

Steps to Safely Removing your N95

Decontamination and Reuse of Filtering Facepiece Respirators: ETO

- Summary of crisis standards of care decontamination recommendations: Ethylene oxide (ET0)
  - Manufacturer or 3rd party guidance or procedures available: No
  - Recommendation for use after decontamination: None by CDC
- Summary of the decontamination method and effect on FFR performance: ETO*
  - Treatment level: 1 hour at 55°C; conc. range: 725–833/L
  - FFR filtration performance: Passed (also verified at UNC)
  - FFR fit performance: Evaluated at UNC = Passed
  - ETO levels post-reprocessing at UNC = Substantially below EPA limits
- Summary: Ethylene oxide (EtO) was shown to not harm filtration performance for the nine tested FFR models. All tests were conducted for one hour at 55˚C with EtO gas concentrations ranging from 725 to 833 g/L. Six models that were exposed to three cycles of 736 mg/L EtO all passed the filtration performance assessment [3]. Data is not available for the effect that EtO treatment may have on FFR fit. However, EtO treatment does not cause visible physical changes to the appearance of FFRs. Any use of ethylene oxide (EtO) should be accompanied by studies to ensure no off-gassing into the breathing zone of the wearer as EtO is carcinogenic and teratogenic.

*Viscusi, D.J., et al., Evaluation of five decontamination methods for filtering facepiece respirators. Annals of occupational hygiene, 2009. 53(8): p. 815-827; Bergman, M., et al., Evaluation of Multiple (3-Cycle) Decontamination Processing for Filtering Facepiece Respirators. Journal of Engineered Fibers and Fabrics, 2010. 5(4): p. 33-41; Viscusi, D.J., King, W.P., Shaffer, R.E., Effect of decontamination on the filtration efficiency of two filtering facepiece respirator models. Journal of the International Society for Respiratory Protection, 2007. 24: p. 93-107.

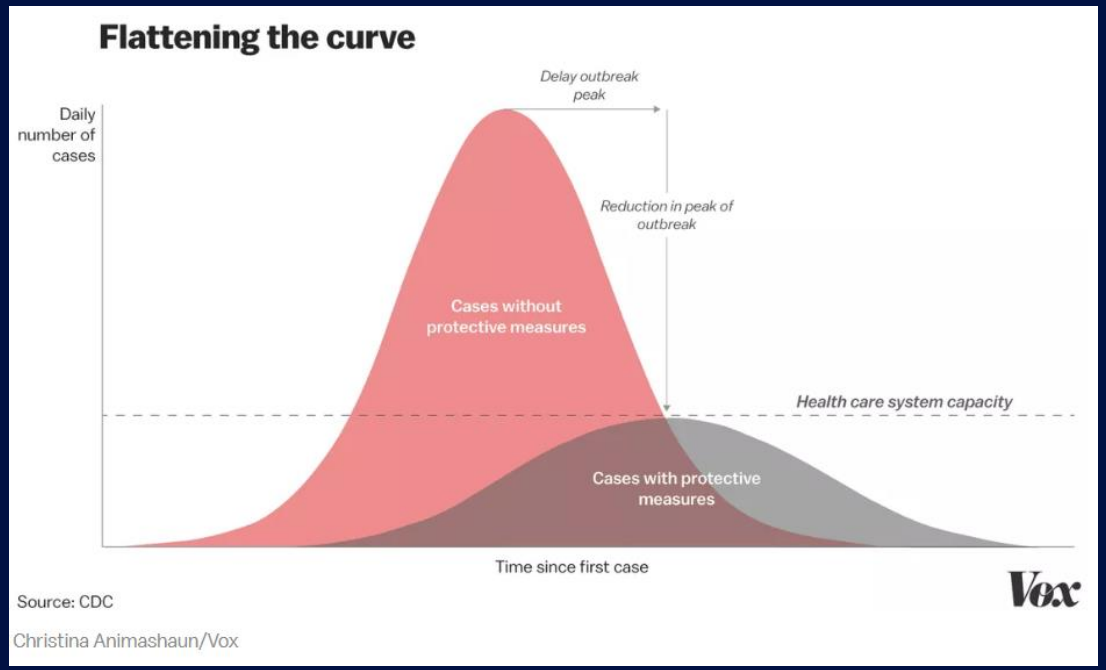
Decontamination and Reuse of Filtering Facepiece Respirators, CDC: VHP

- Summary of crisis standards of care decontamination recommendations: Vaporized hydrogen peroxide
  - Manufacturer or 3rd party guidance or procedures available: Yes
  - Recommendation for use after decontamination: Can be worn for any patient care activities
- Summary of the decontamination method and effect on FFR performance: Vaporized hydrogen peroxide*
  - Battelle report: Bioquell Clarus C HPV generator; The HPV cycle included a 10 min conditioning phase, 20 min gassing phase at 2 g/min, 150 min dwell phase at 0.5 g/min, and 300 min of aeration
  - Bergman et al: Room Bio-Decontamination Service (RBDS™, BIOQUELL UK Ltd, Andover, UK), which utilizes four portable modules: the Clarus® R HPV generator (utilizing 30% H2O2), the Clarus R20 aeration unit, an instrumentation module and a control computer. Room concentration = 8 g/m3, 15 min dwell, 125 min total cycle time.
  - FFR filtration performance: Passes
  - FFR fit performance: FFR fit was shown to be unaffected for up to 20 VHP treatments cycles using a head form
  - Other observations: Degradation of straps after 30 cycles (Battelle report)
- Summary: Investigations into VHP decontamination of FFRs provides evidence of minimal effect to filtration and fit while demonstrating 99.9999% efficiency in killing bacterial spores. VHP did not reduce the filtration performance of the ten N95 FFR models tested while showing a 6-log reduction in Geobacillus stearothermophilus spores. Bergman et al. found that three cycles of VHP treatment using the STERRAD 100S H2O2 Gas Plasma Sterilizer negatively affected filtration performance

*mBergman, M., et al., Evaluation of Multiple (3-Cycle) Decontamination Processing for Filtering Facepiece Respirators. Journal of Engineered Fibers and Fabrics, 2010. 5(4): p. 33-41. Battelle. Final Report for the Bioquell Hydrogen Peroxide Vapor (HPV) Decontamination for Reuse of N95 Respirators. 2016; Available from: https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/investigating-decontamination-and-reuse-respirators-public-health-emergenciesm

KEYS TO COVID-19 MITIGATION: PHYSICAL DISTANCING AND DIAGNOSTIC TESTING

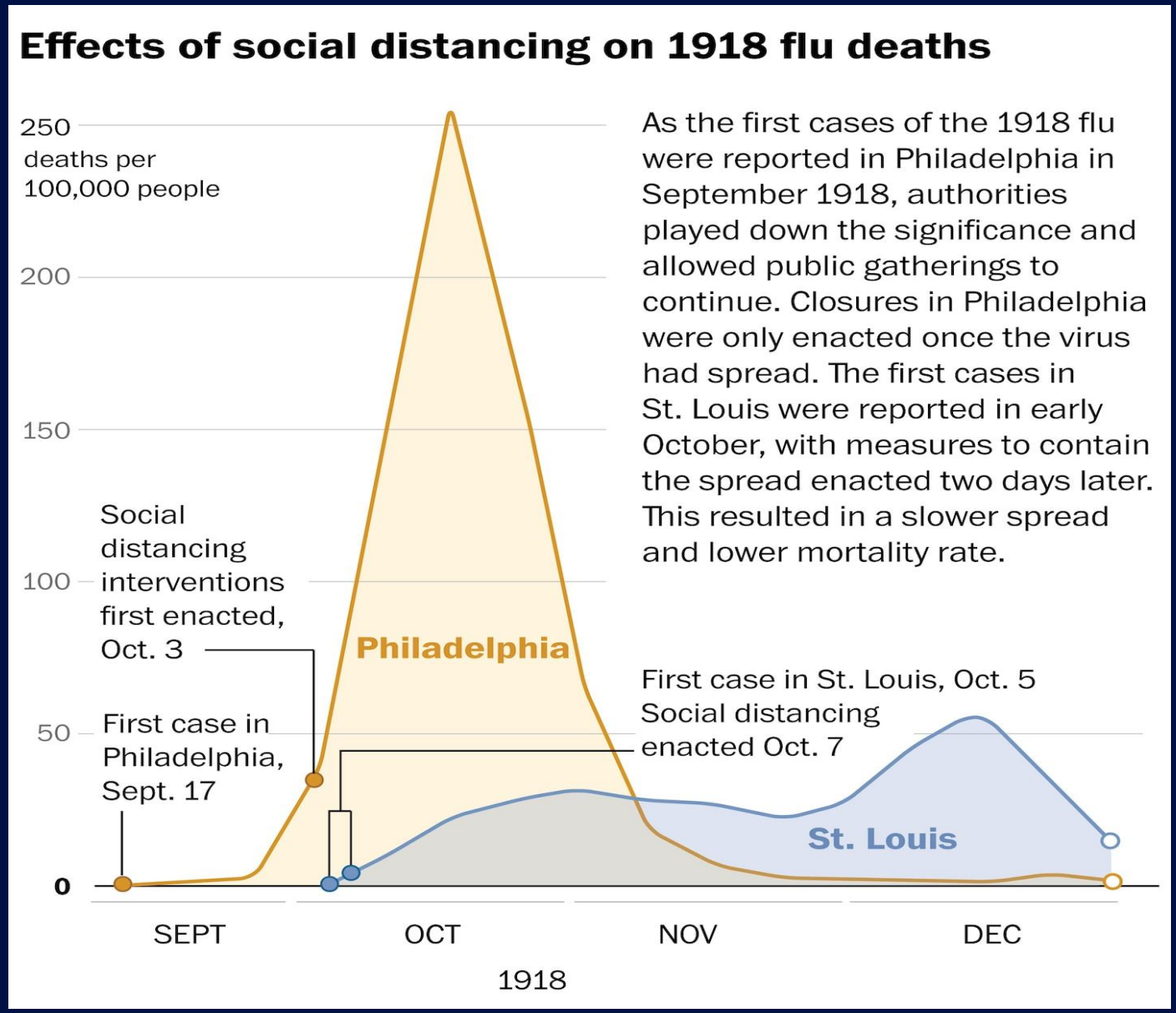
SOCIAL DISTANCING FLATTENS THE CURVE!!



MITIGATION STRATEGIES

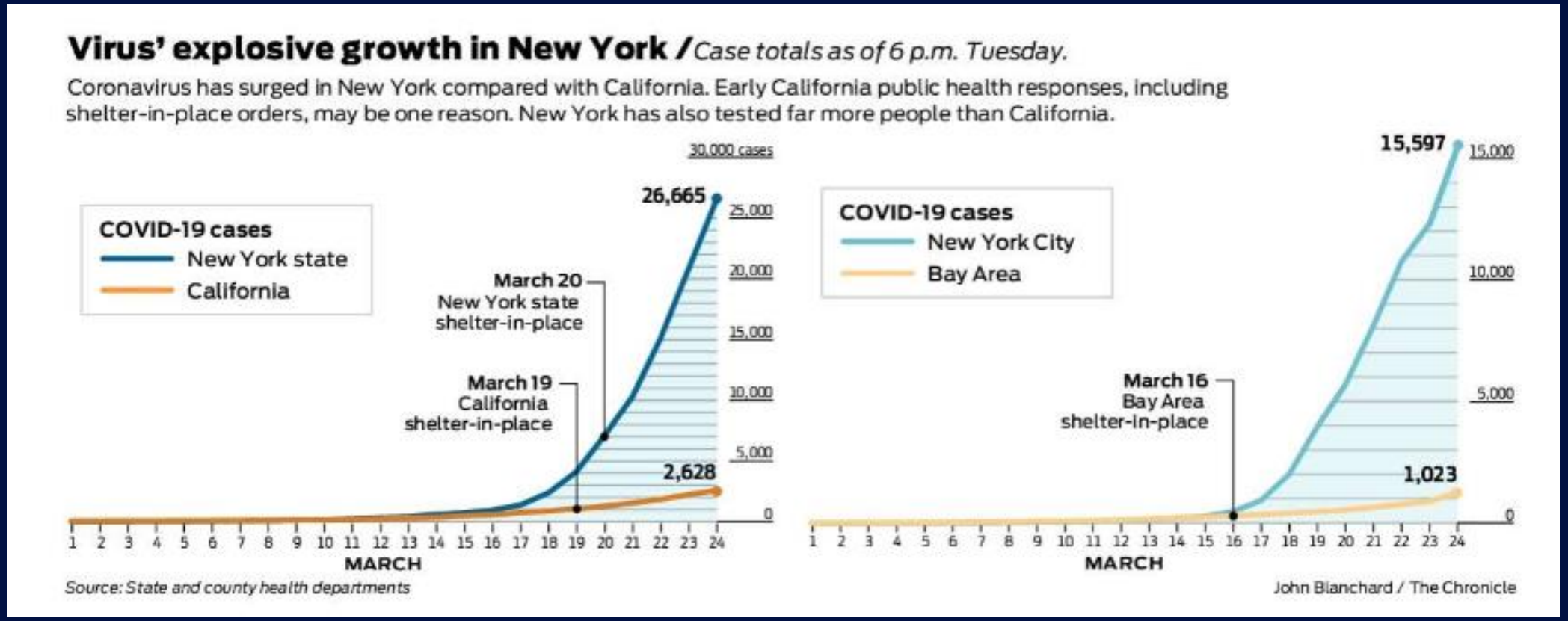
- Public health interventions
  - Quarantine: Separates and restricts persons exposed to an infectious disease
  - Isolation: Separates and restricts persons who have an infectious disease
  - Case finding: Used by Public Health Departments to locate persons exposed to a known case
  - All of above are dependent on have availability of access to a rapid, sensitive and specific diagnosis test
- Physical distancing
  - Must be maintained for 2-3 incubation periods after community acquisition has ceased

https://www.vox.com/2020/3/10/21171481/coronavirus-us-cases-quarantine-cancellation



Graphic from Washington Post: https://www.washingtonpost.com/health/2020/03/10/social-distancing-coronavirus/
Data from: Hatchett RJ, Mecher CE, Lipsitch M. Proc Natl Acad Sci U S A. 2007 May 1;104(18):7582-7

INITIATION OF PHYSICAL DISTANCING ON COVID-19 GROWTH

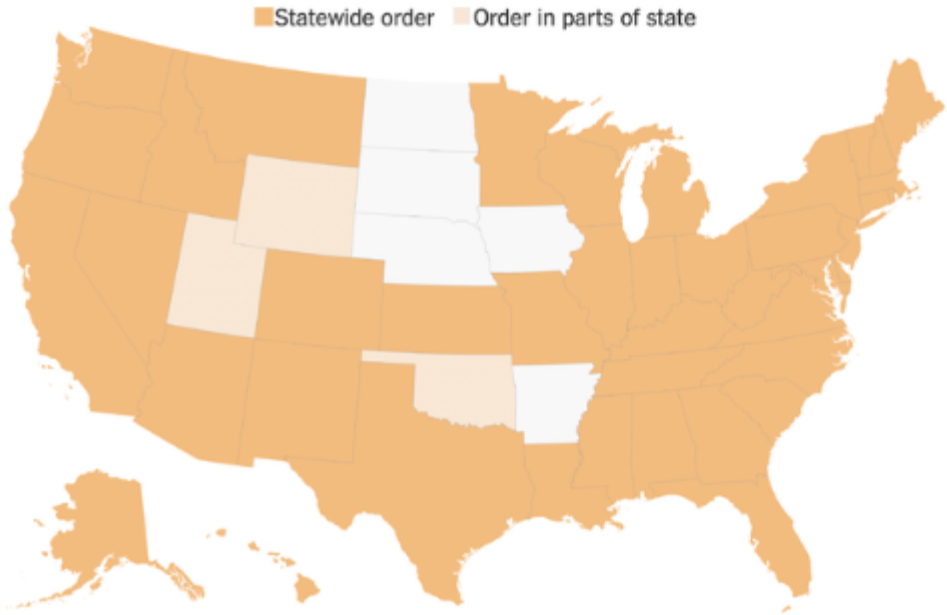


https://www.sfchronicle.com/health/article/NY-has-10-times-the-coronavirus-cases-CA-has-Why-15154692.php#

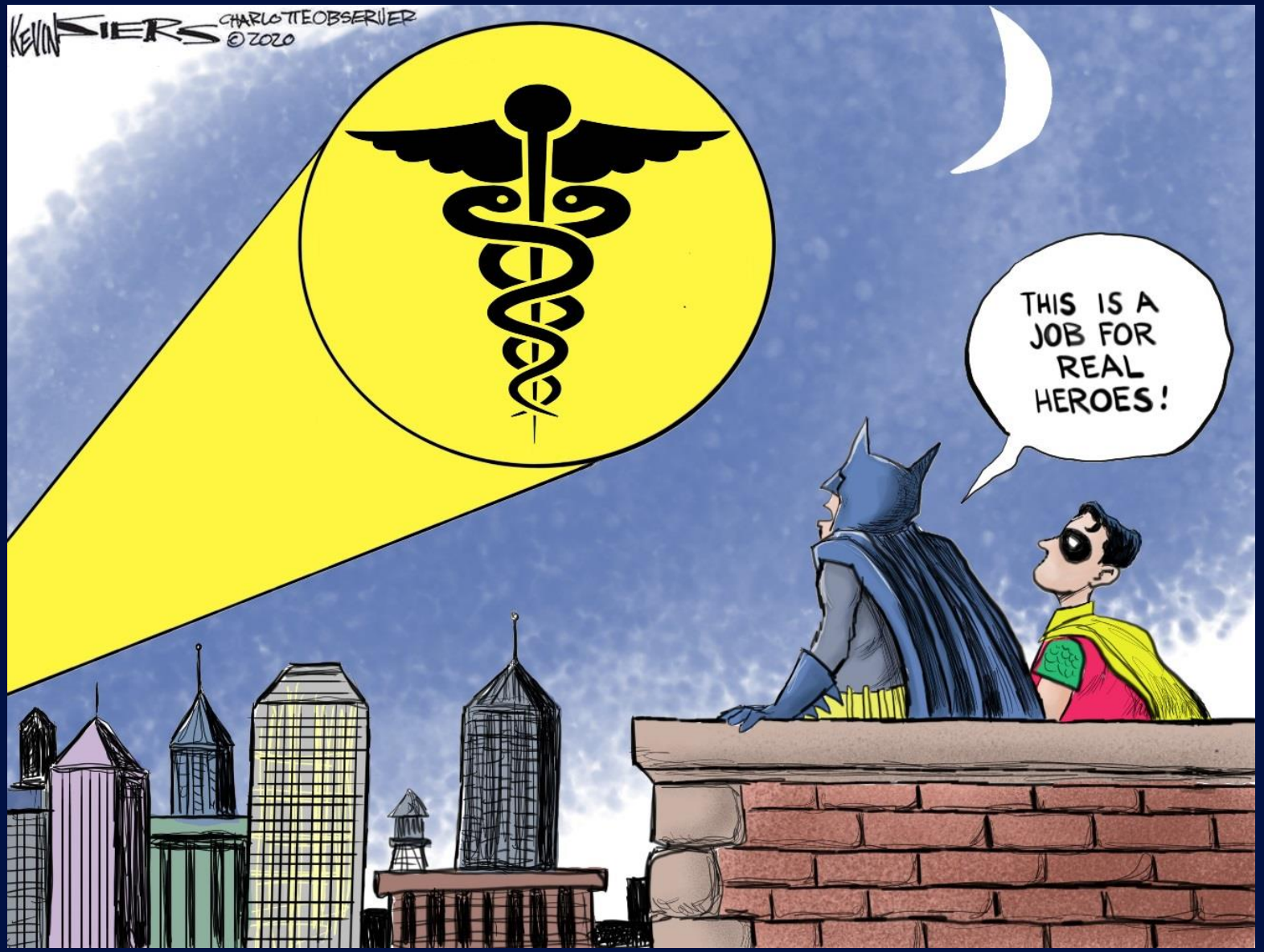
PHYSICAL DISTANCING, US

See Which States and Cities Have Told Residents to Stay at Home

In an attempt to stop the spread of the coronavirus, a vast majority of states and the Navajo Nation have given directives, affecting about nine in 10 U.S. residents.



https://www.nytimes.com/2020/03/30/world/coronavirus-news.html



You are ALL critical to the response to epidemics and pandemics