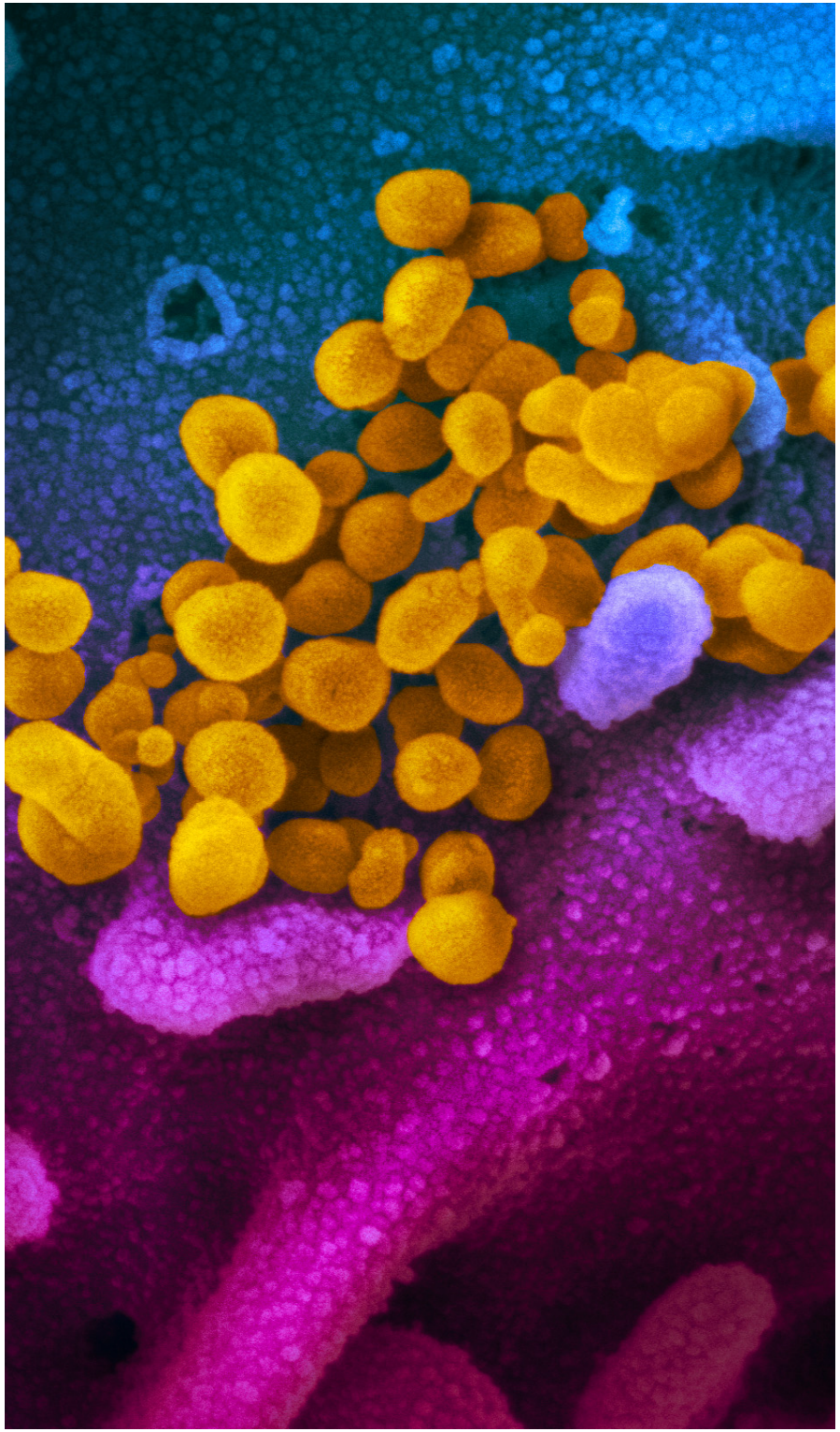


COVID-19

Updates & Key Messages

1 April 2020

AETC AIDS Education & Training Center Program Southeast

NCHTEC North Carolina HIV Training & Education Center at the UNC School of Medicine

Christopher B. Hurt, MD

Associate Professor of Medicine

Director, North Carolina HIV Training & Education Center
Site PI, Ryan White HIV/AIDS Program Part D, UNC ID Clinic
Co-Leader, UNC CFAR Collaborative HIV Epidemiology & Prevention Scientific Working Group

Institute for Global Health & Infectious Diseases
University of North Carolina at Chapel Hill
School of Medicine

As of 1 Oct 2018, Dr. Hurt receives salary support for supervising UNC site activities in a Gilead-funded study of PrEP (DISCOVER).

Dr. Hurt is supported by the Centers for Disease Control and Prevention (ELC-2017-J3), Health Resources and Services Administration (HRSA-17-039, U1OHA30535), the National Institute on Drug Abuse (UH3DA044823), and the National Institute of Allergy and Infectious Diseases (P30AI50410, UM1AI069423, UM1AI068619).

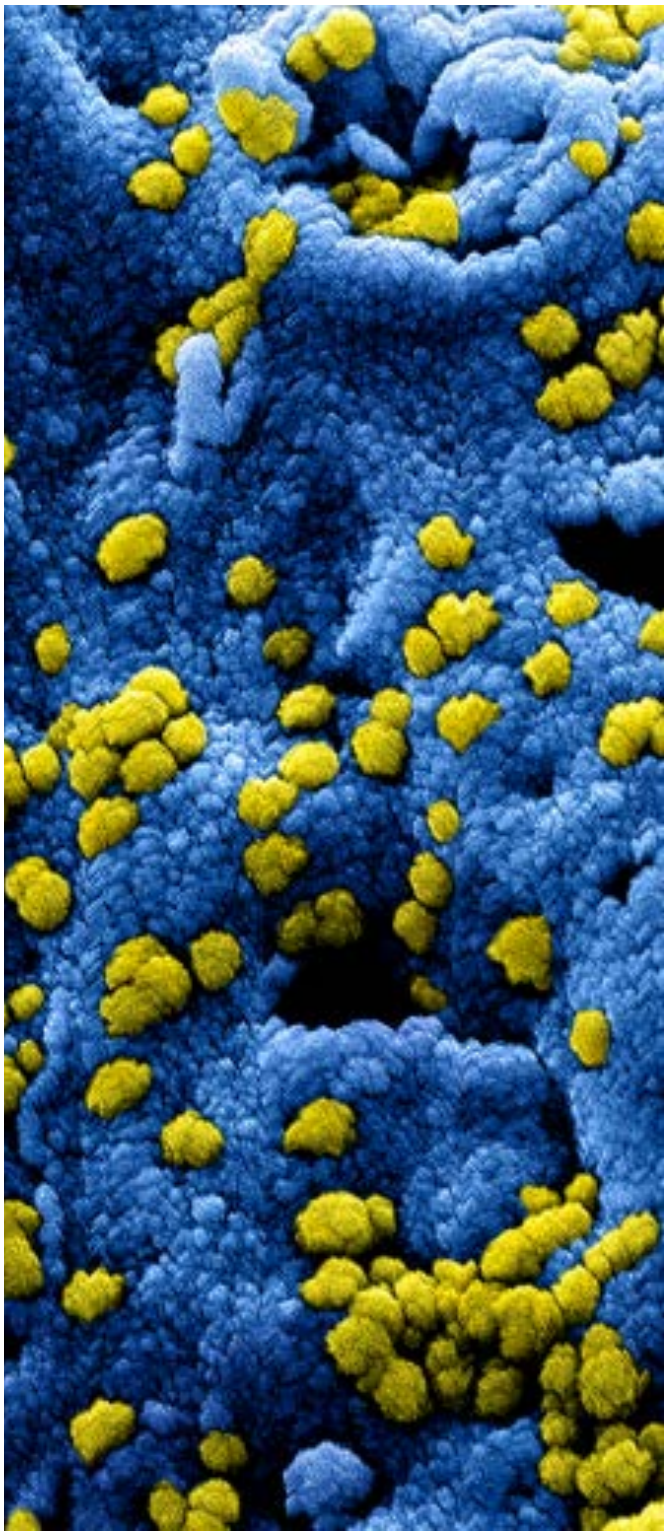
The views expressed are not necessarily those of CDC, HRSA, or the NIH.

Definitions

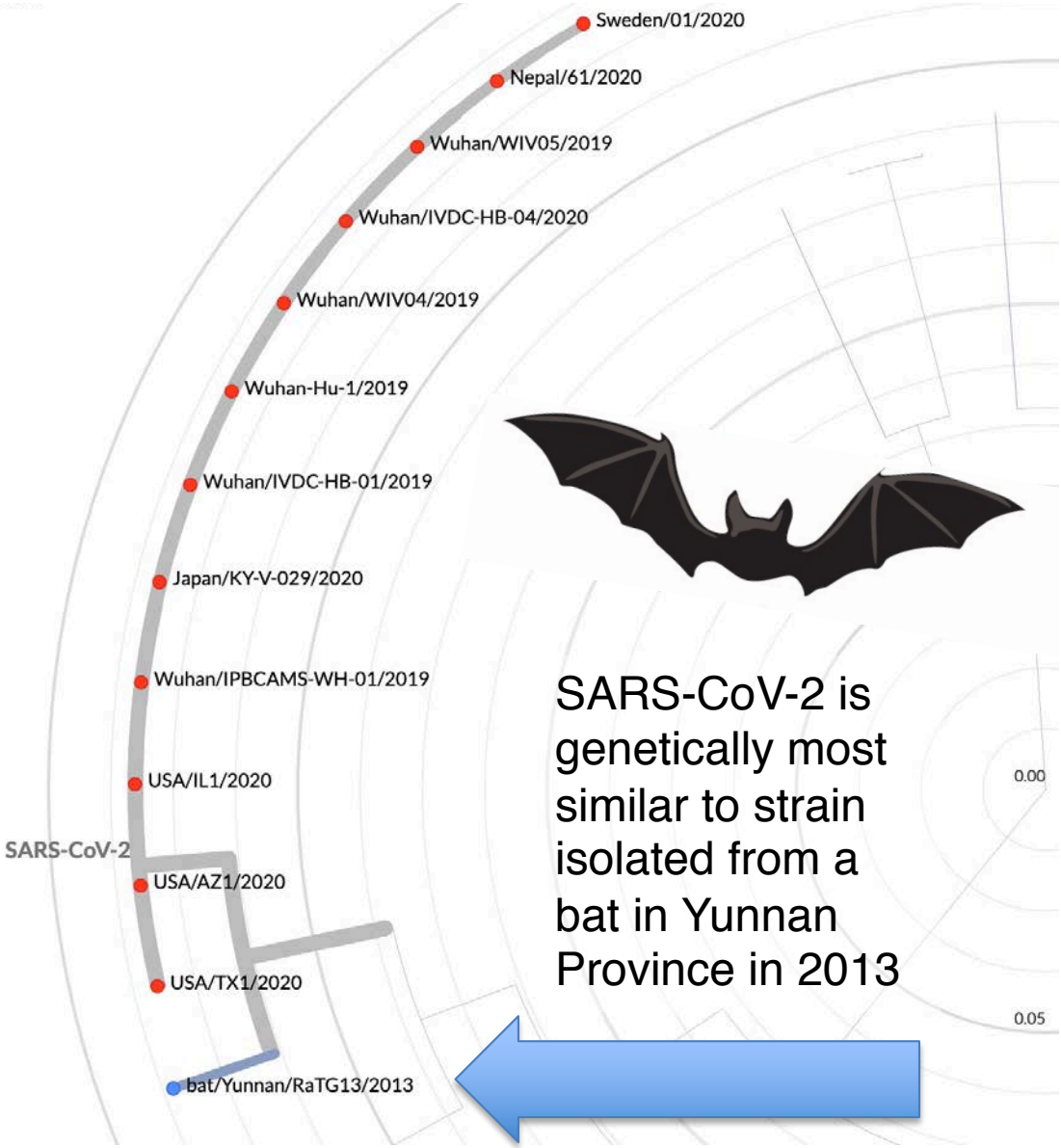
Coronavirus
Any of a group of RNA viruses that can infect animals and humans

SARS-CoV-2
Official name of novel coronavirus causing current epidemic

COVID-19
Official name of the disease resulting from infection with the SARS-CoV-2 coronavirus



Where did SARS-CoV-2 come from?



https://www.sciencemag.org/news/2020/01/mining-coronavirus-genomes-clues-outbreak-s-origins

Shang J, et al. Nature. https://doi.org/10.1038/s41586-020-2179-y https://nextstrain.org/groups/blab/sars-like-cov?c=host&l=radial&p=full

How did SARS-CoV-2 jump into people?

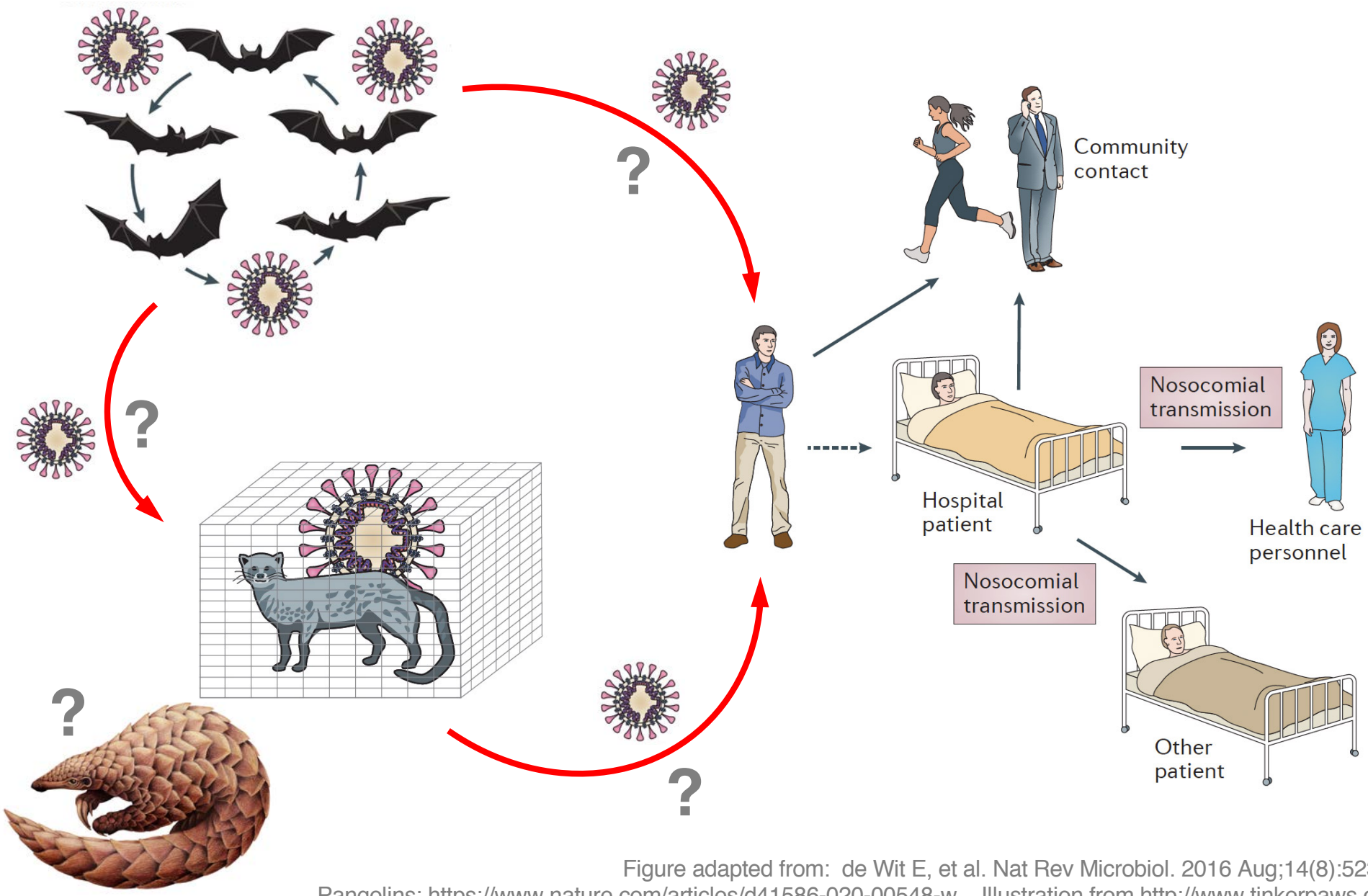
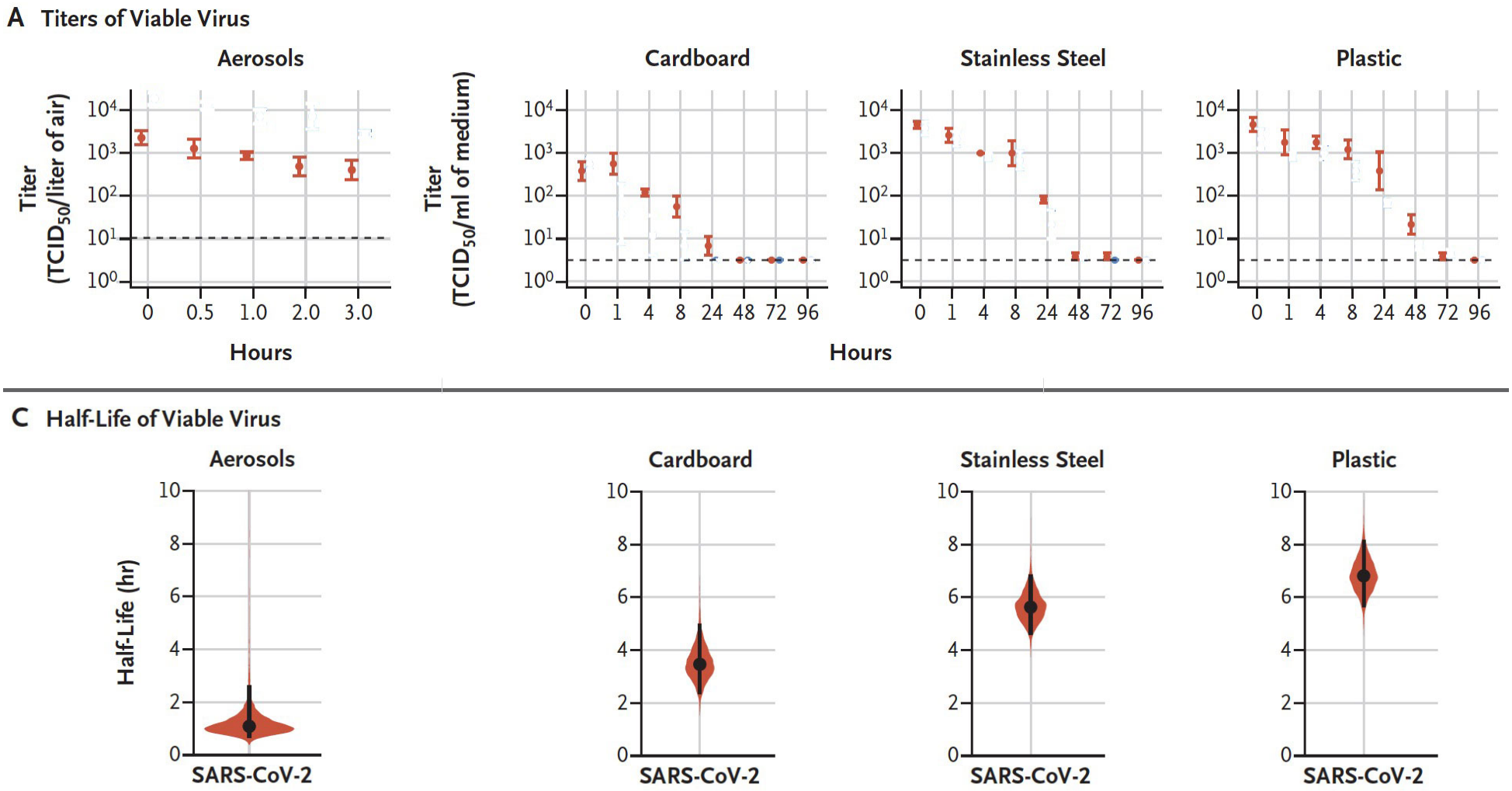


Figure adapted from: de Wit E, et al. Nat Rev Microbiol. 2016 Aug;14(8):523-34
Pangolins: https://www.nature.com/articles/d41586-020-00548-w Illustration from http://www.tinkerpaws.com/

How is SARS-CoV-2 transmitted?

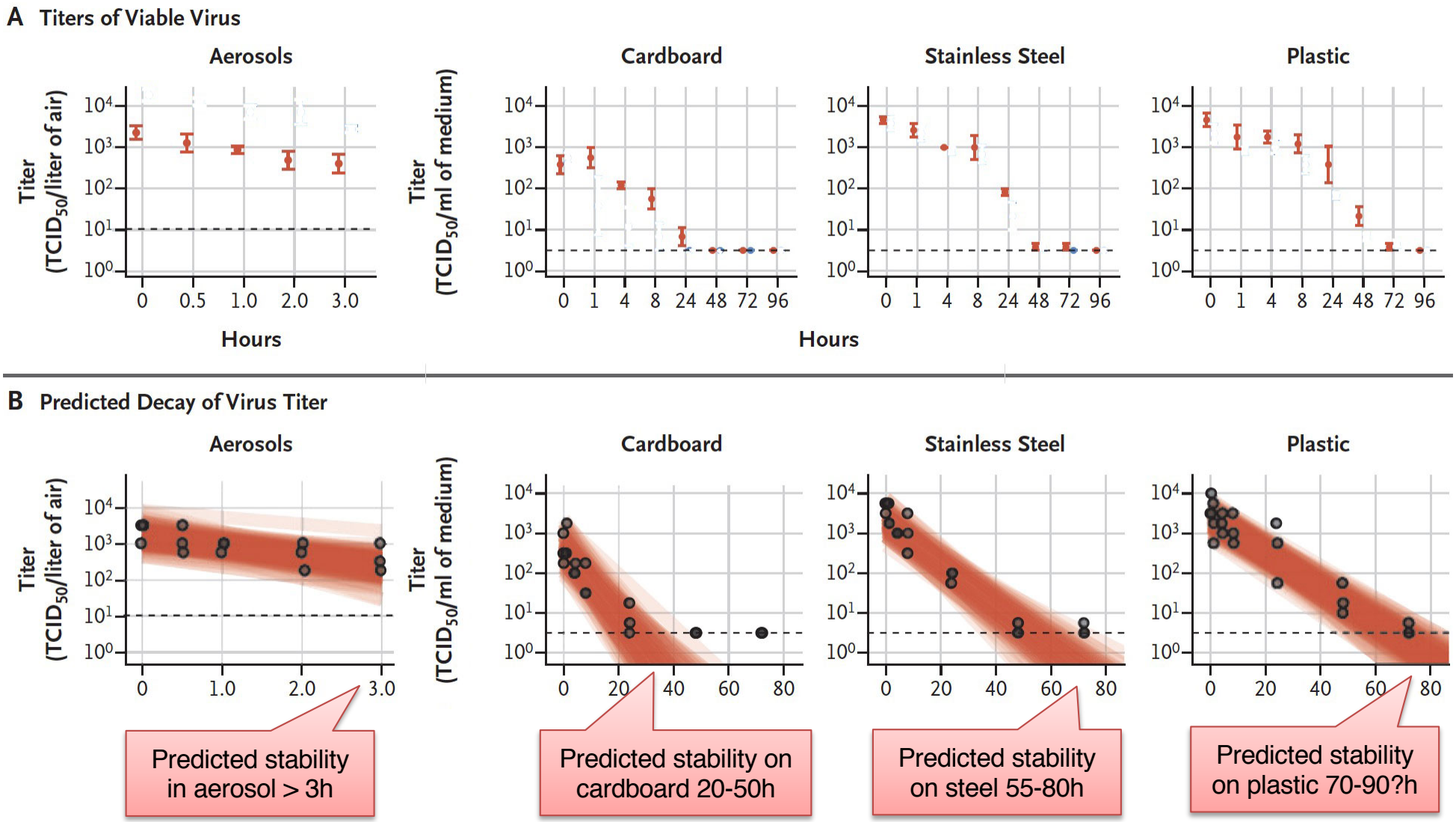
Dashed horizontal lines are lower limit of detection – CONTROLLED conditions (7d at 21-23°C, 40% humidity)



Excerpted from Figure 1 – van Doremalen N, et al. N Engl J Med. 2020 Mar 17. https://doi.org/10.1056/NEJMc2004973

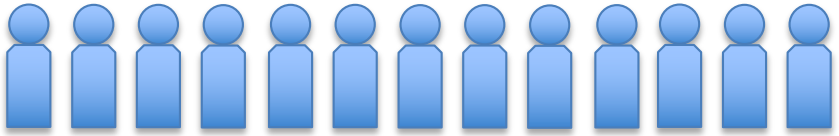
How is SARS-CoV-2 transmitted?

Dashed horizontal lines are lower limit of detection – CONTROLLED conditions (7d at 21-23°C, 40% humidity)



Excerpted from Figure 1 – van Doremalen N, et al. N Engl J Med. 2020 Mar 17. https://doi.org/10.1056/NEJMc2004973

How is SARS-CoV-2 transmitted?



13 patients with **mild-to-moderate** COVID-19 at UNMC

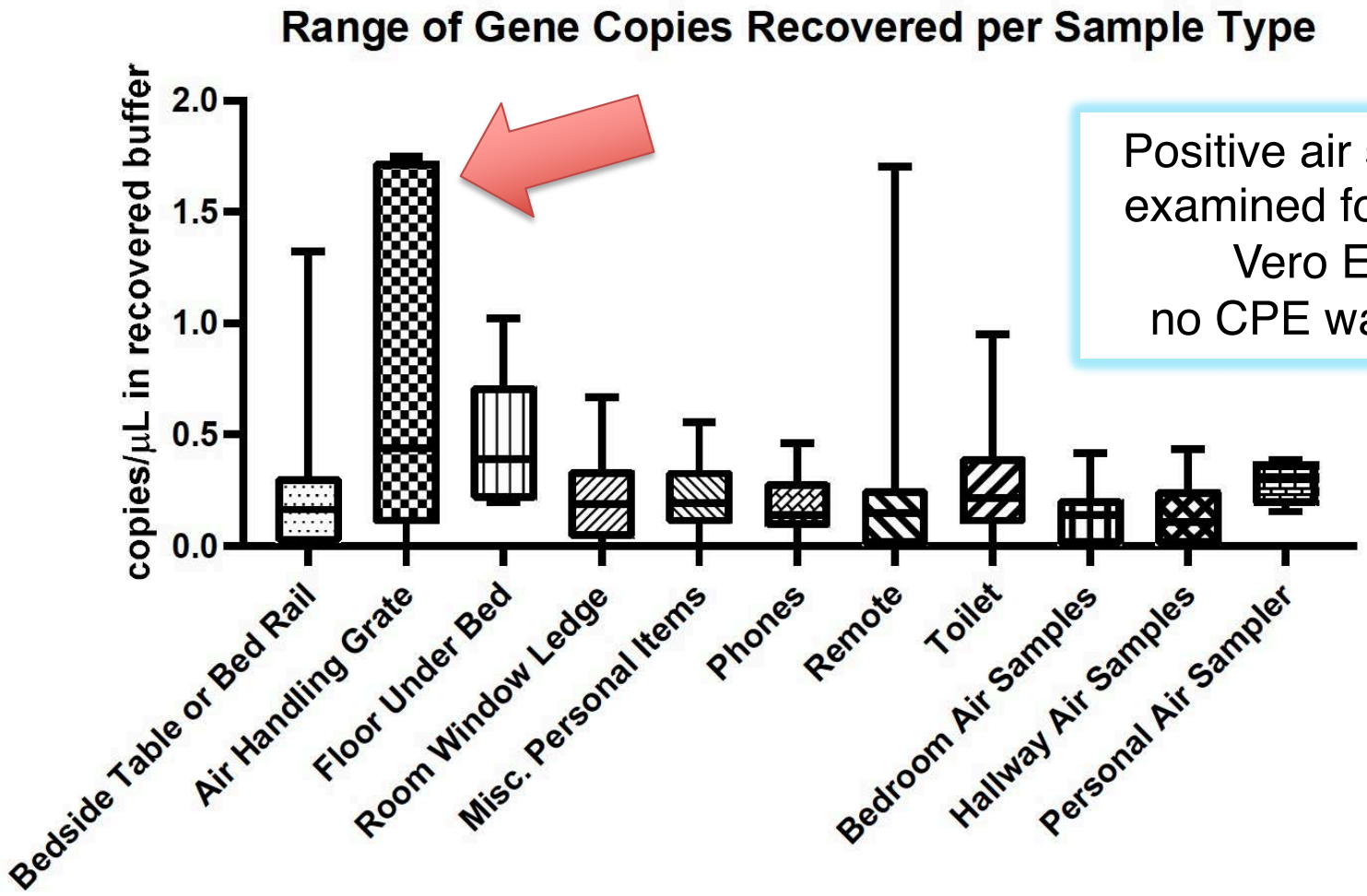
High-volume air samples	Low-volume personal air samples	Surface samples
In isolation rooms with patients present	Worn by personnel during sampling activities	Personal items
Hallways during sampling activities		Room surfaces
		Medical equipment
		Toilet

Surface and aerosol samples analyzed by RT-PCR

Remember RNA ≠ viable virus

Santarpia JL, et al. (University of Nebraska Medical Center) PREPRINT – https://doi.org/10.1101/2020.03.23.20039446

How is SARS-CoV-2 transmitted?

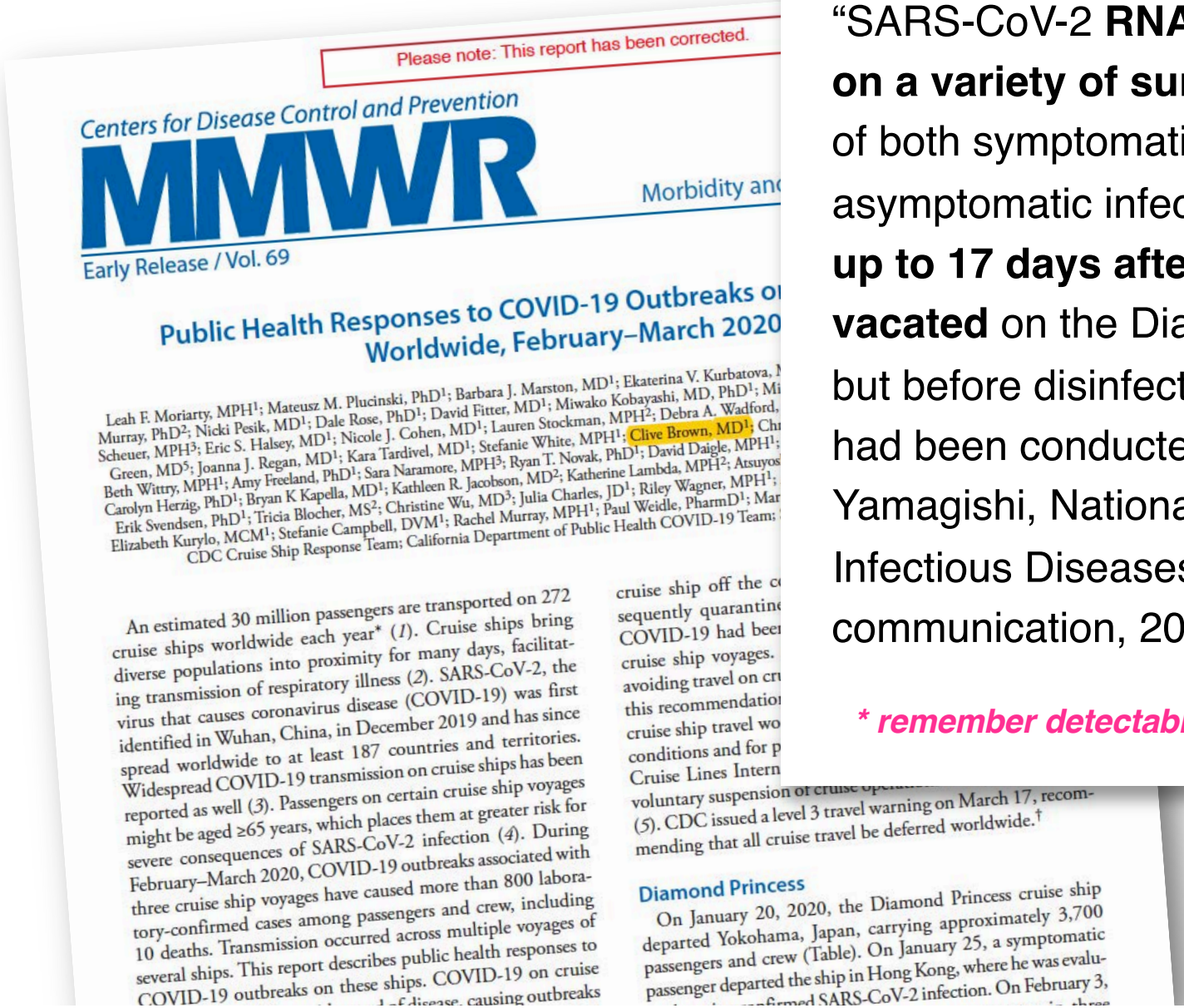


Positive air samples were examined for viral CPE in Vero E6 cells – no CPE was observed.

"…the data is [sic] suggestive that viral aerosol particles are produced by individuals that have COVID-19 disease, even in the absence of cough."

Santarpia JL, et al. (University of Nebraska Medical Center) PREPRINT – https://doi.org/10.1101/2020.03.23.20039446

How is SARS-CoV-2 transmitted?



Please note: This report has been corrected.

Centers for Disease Control and Prevention

MMWR

Morbidity and

Early Release / Vol. 69

Public Health Responses to COVID-19 Outbreaks o
Worldwide, February–March 2020

Leah F. Moriarty, MPH[1]; Mateusz M. Plucinski, PhD[1]; Barbara J. Marston, MD[1]; Ekaterina V. Kurbatova, M
Murray, PhD[2]; Nicki Pesik, MD[1]; Dale Rose, PhD[1]; David Fitter, MD[1]; Miwako Kobayashi, MD, PhD[1]; Mi
Scheuer, MPH[3]; Eric S. Halsey, MD[1]; Nicole J. Cohen, MD[1]; Lauren Stockman, MPH[2]; Debra A. Wadford,
Green, MD[5]; Joanna J. Regan, MD[1]; Kara Tardivel, MD[1]; Stefanie White, MPH[1]; Clive Brown, MD[1]; Ch
Beth Wittry, MPH[1]; Amy Freeland, PhD[1]; Sara Naramore, MPH[3]; Ryan T. Novak, PhD[1]; David Daigle, MPH[1];
Carolyn Herzig, PhD[1]; Bryan K Kapella, MD[1]; Kathleen R. Jacobson, MD[2]; Katherine Lambda, MPH[2]; Atsuyos
Erik Svendsen, PhD[1]; Tricia Blocher, MS[2]; Christine Wu, MD[3]; Julia Charles, JD[1]; Riley Wagner, MPH[1];
Elizabeth Kurylo, MCM[1]; Stefanie Campbell, DVM[1]; Rachel Murray, MPH[1]; Paul Weidle, PharmD[1]; Mar
CDC Cruise Ship Response Team; California Department of Public Health COVID-19 Team;

An estimated 30 million passengers are transported on 272 cruise ships worldwide each year* (*1*). Cruise ships bring diverse populations into proximity for many days, facilitating transmission of respiratory illness (*2*). SARS-CoV-2, the virus that causes coronavirus disease (COVID-19) was first identified in Wuhan, China, in December 2019 and has since spread worldwide to at least 187 countries and territories. Widespread COVID-19 transmission on cruise ships has been reported as well (*3*). Passengers on certain cruise ship voyages might be aged ≥65 years, which places them at greater risk for severe consequences of SARS-CoV-2 infection (*4*). During February–March 2020, COVID-19 outbreaks associated with three cruise ship voyages have caused more than 800 laboratory-confirmed cases among passengers and crew, including 10 deaths. Transmission occurred across multiple voyages of several ships. This report describes public health responses to COVID-19 outbreaks on these ships. COVID-19 on cruise

cruise ship off the c
sequently quarantine
COVID-19 had been
cruise ship voyages.
avoiding travel on cru
this recommendation
cruise ship travel wo
conditions and for p
Cruise Lines Intern
voluntary suspension of cruise
(*5*). CDC issued a level 3 travel warning on March 17, recommending that all cruise travel be deferred worldwide.†

Diamond Princess

On January 20, 2020, the Diamond Princess cruise ship departed Yokohama, Japan, carrying approximately 3,700 passengers and crew (Table). On January 25, a symptomatic passenger departed the ship in Hong Kong, where he was evalu-
passenger confirmed SARS-CoV-2 infection. On February 3,

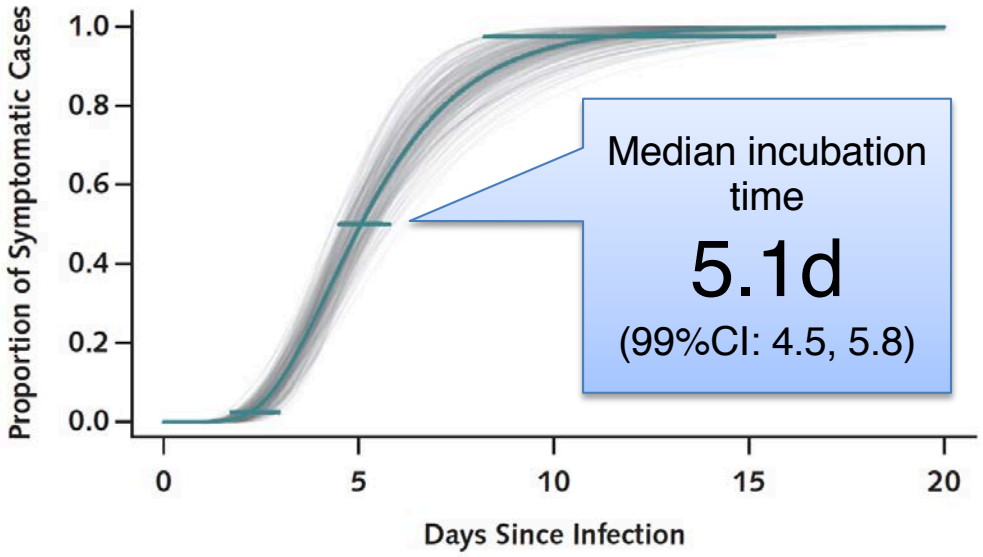
"SARS-CoV-2 **RNA was identified on a variety of surfaces*** in cabins of both symptomatic and asymptomatic infected passengers **up to 17 days after cabins were vacated** on the Diamond Princess but before disinfection procedures had been conducted (Takuya Yamagishi, National Institute of Infectious Diseases, personal communication, 2020)."

**** remember detectable RNA ≠ viable virus***

Moriarty LF, et al. MMWR. ePub: 23 March 2020. http://dx.doi.org/10.15585/mmwr.mm6912e3

What's the incubation period for COVID-19?

Figure 2. Cumulative distribution function of the COVID-19 incubation period estimate from the log-normal model.



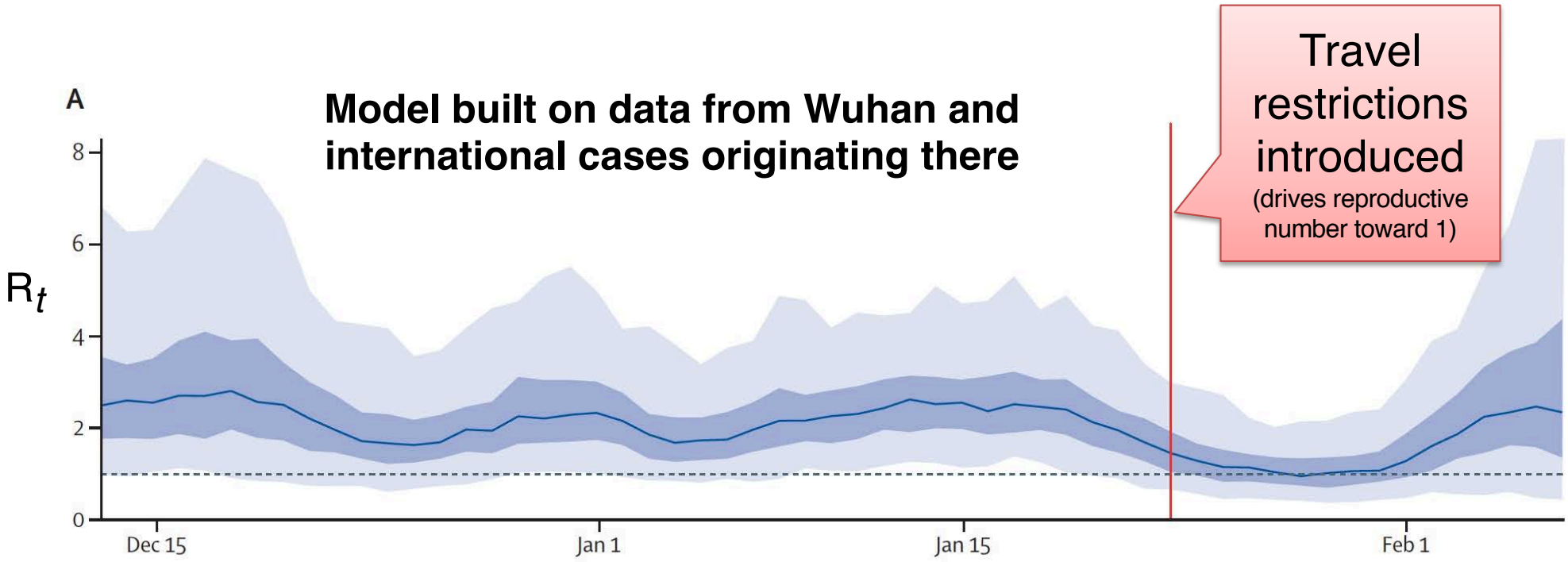
The estimated median incubation period of COVID-19 was 5.1 days (CI, 4.5 to 5.8 days). We estimated that fewer than 2.5% of infected persons will display symptoms within 2.2 days (CI, 1.8 to 2.9 days) of exposure, whereas symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons. Horizontal bars represent the 95% CIs of the 2.5th, 50th, and 97.5th percentiles of the incubation period distribution. The estimate of the dispersion parameter is 1.52 (CI, 1.32 to 1.72). COVID-19 = coronavirus disease 2019.

Using data from 181 patients, 97.5% developed **any symptom** by day 11.5
(99% CI: 8.2, 15.6)
(2.5% will develop sxs after 11.5d)

Using data from 99 patients with time to fever onset, 97.5% developed **fever** by day 12.5
(99% CI: 8.2, 17.7)
(2.5% will develop fever after 12.5d)

Lauer SA, Grantz KH, et al. Ann Intern Med. 2020 Mar 10. https://doi.org/10.7326/M20-0504

What's COVID-19's reproductive number?

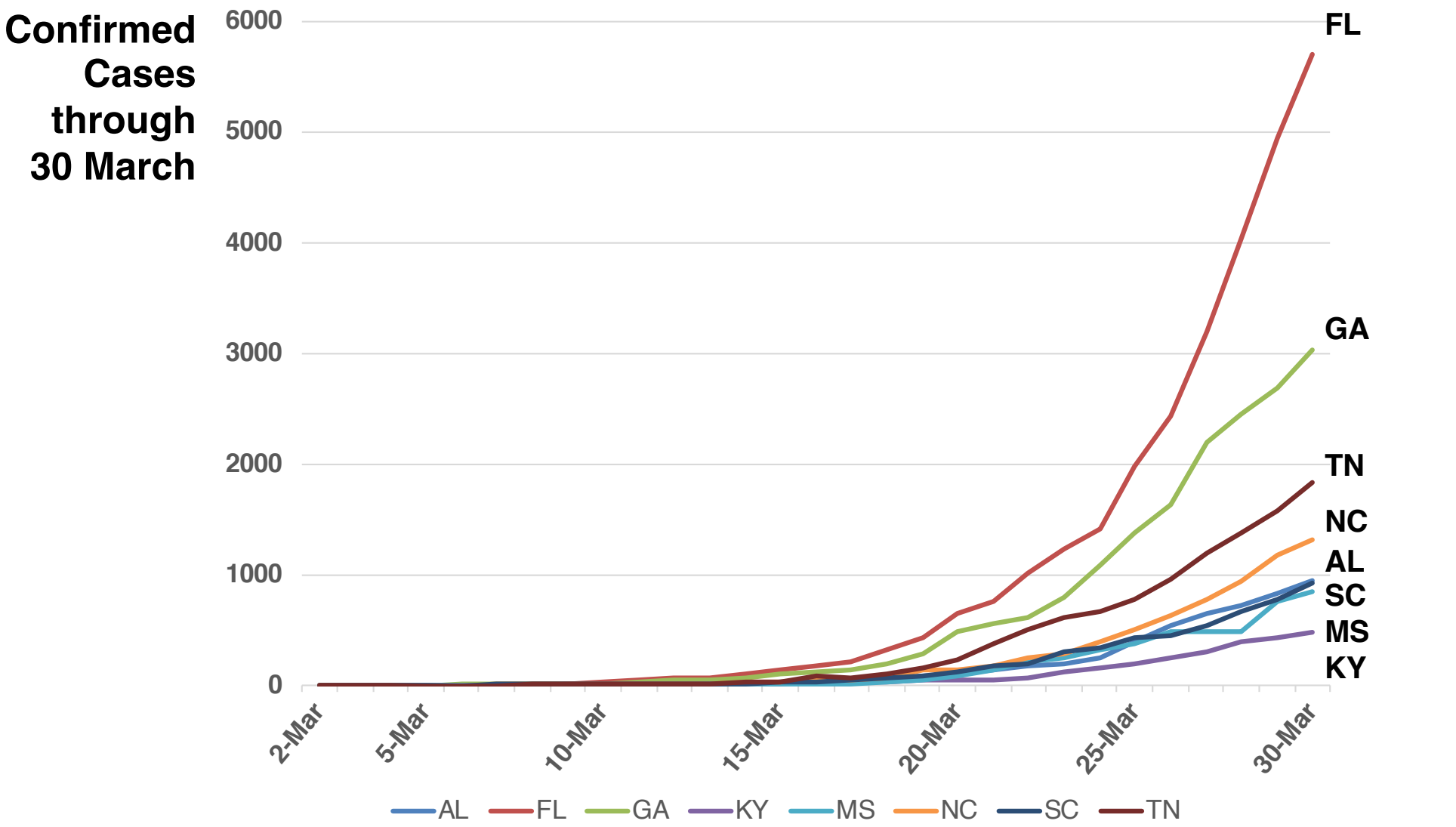


Based on early estimates, each case can be expected to produce **around 2 additional cases**

Secondary attack rate from close contacts may be as high as **35%** (95% CI: 27, 44)

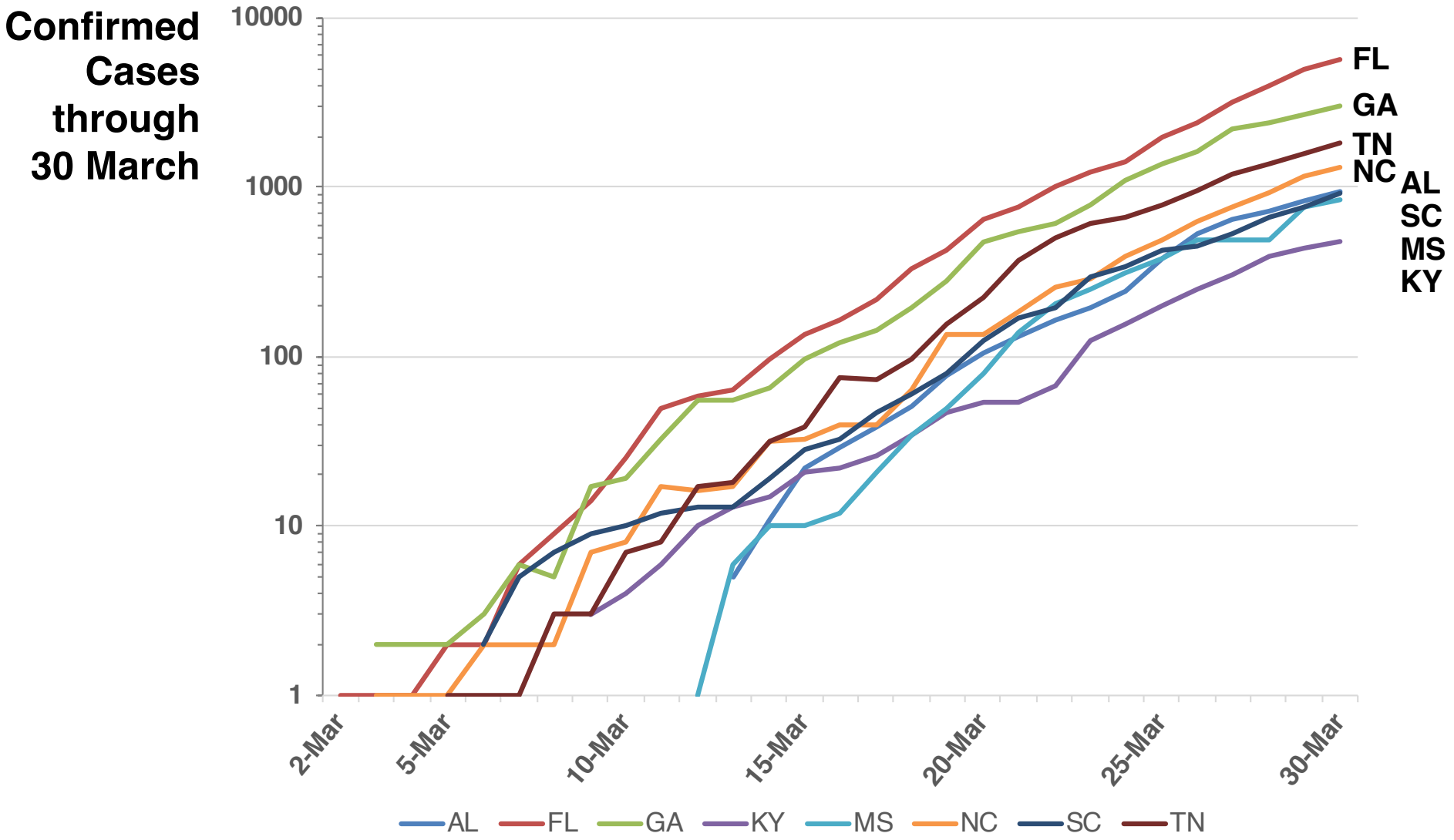
Graphic from: Kucharski AJ, et al. Lancet Infect Dis. 2020 Mar 11. pii: S1473-3099(20)30144-4
Early estimates of R_0: Li Q, et al. N Engl J Med. 2020 Mar 26;382(13):1199-1207
SAR data from: Liu Y, et al. Lancet. 2020 Mar 14;395(10227):e47

What's the current status in SE AETC states?



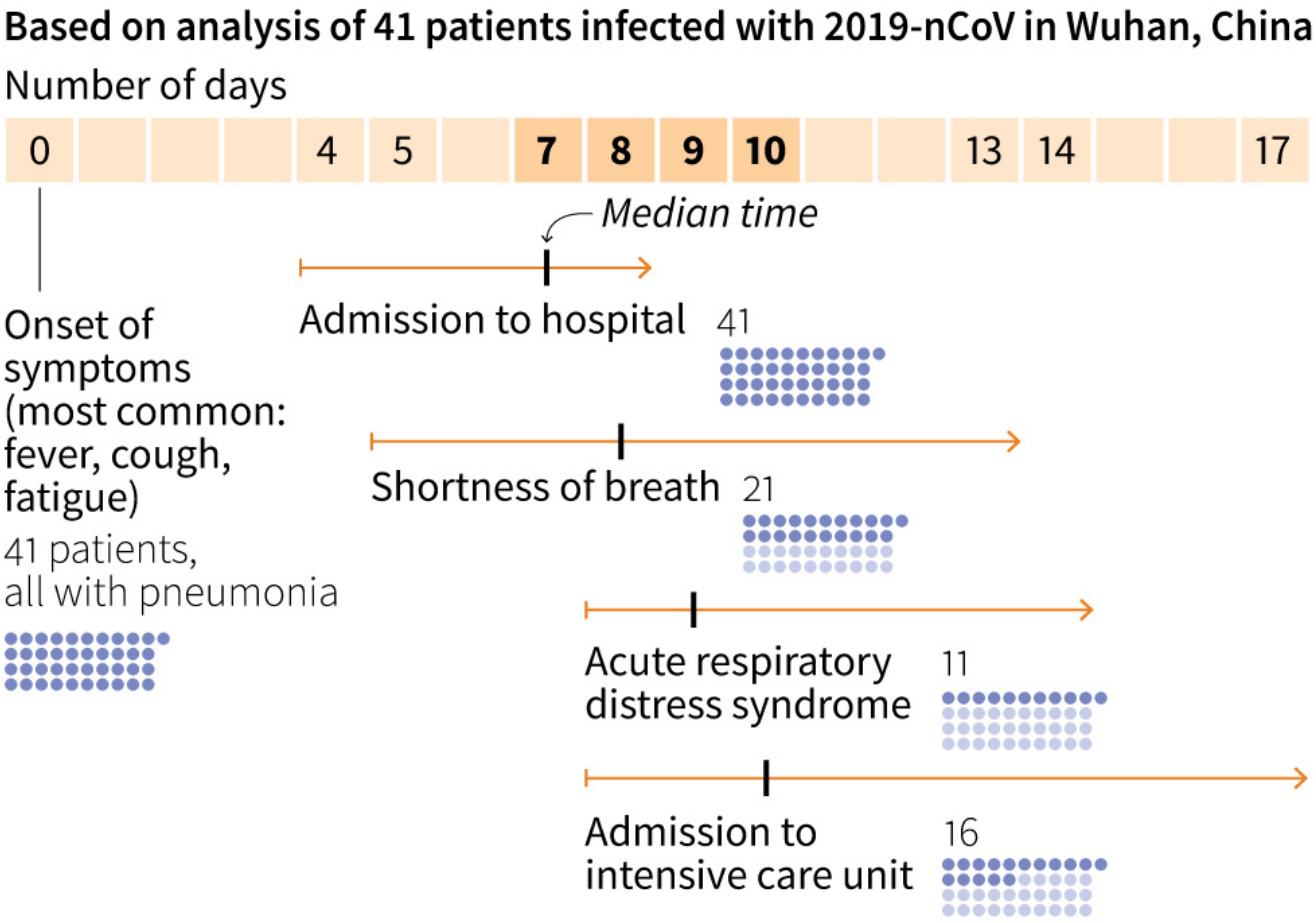
https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/

What's the current status in SE AETC states?



https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/

How does COVID-19 progress?



Huang C, et al. Lancet. 2020 Feb 15;395(10223):497-506

Admit / ED
HD#1

75yo Italian man with confirmed COVID-19
"There are bilateral large areas of ground-glass opacities with **crazy paving** → and, more evident at both bases, areas of consolidation."

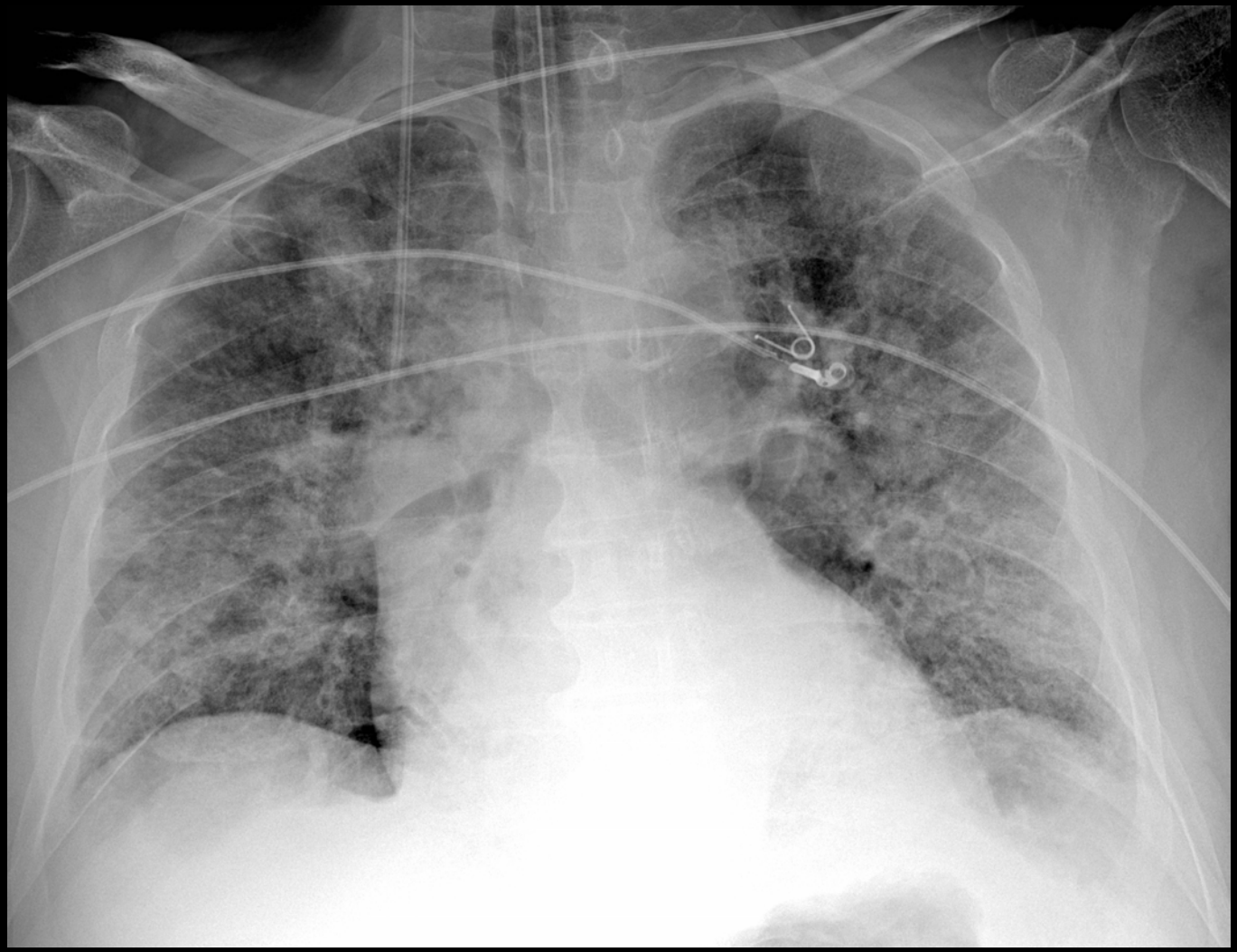
https://radiopaedia.org/cases/covid-19-pneumonia-12?lang=us

Admit / ED
HD#1

75yo Italian man with confirmed COVID-19
"There are bilateral large areas of ground-glass opacities with **crazy paving** and, more evident at both bases, areas of consolidation."

https://radiopaedia.org/cases/covid-19-pneumonia-12?lang=us

HD#2



75yo Italian man with confirmed COVID-19

“AP chest radiograph for CVC position shows the presence of extensive bilateral ground-glass opacities as demonstrated on the recent CT. Also right IJV catheter and ETT noted.”

https://radiopaedia.org/cases/covid-19-pneumonia-12?lang=us

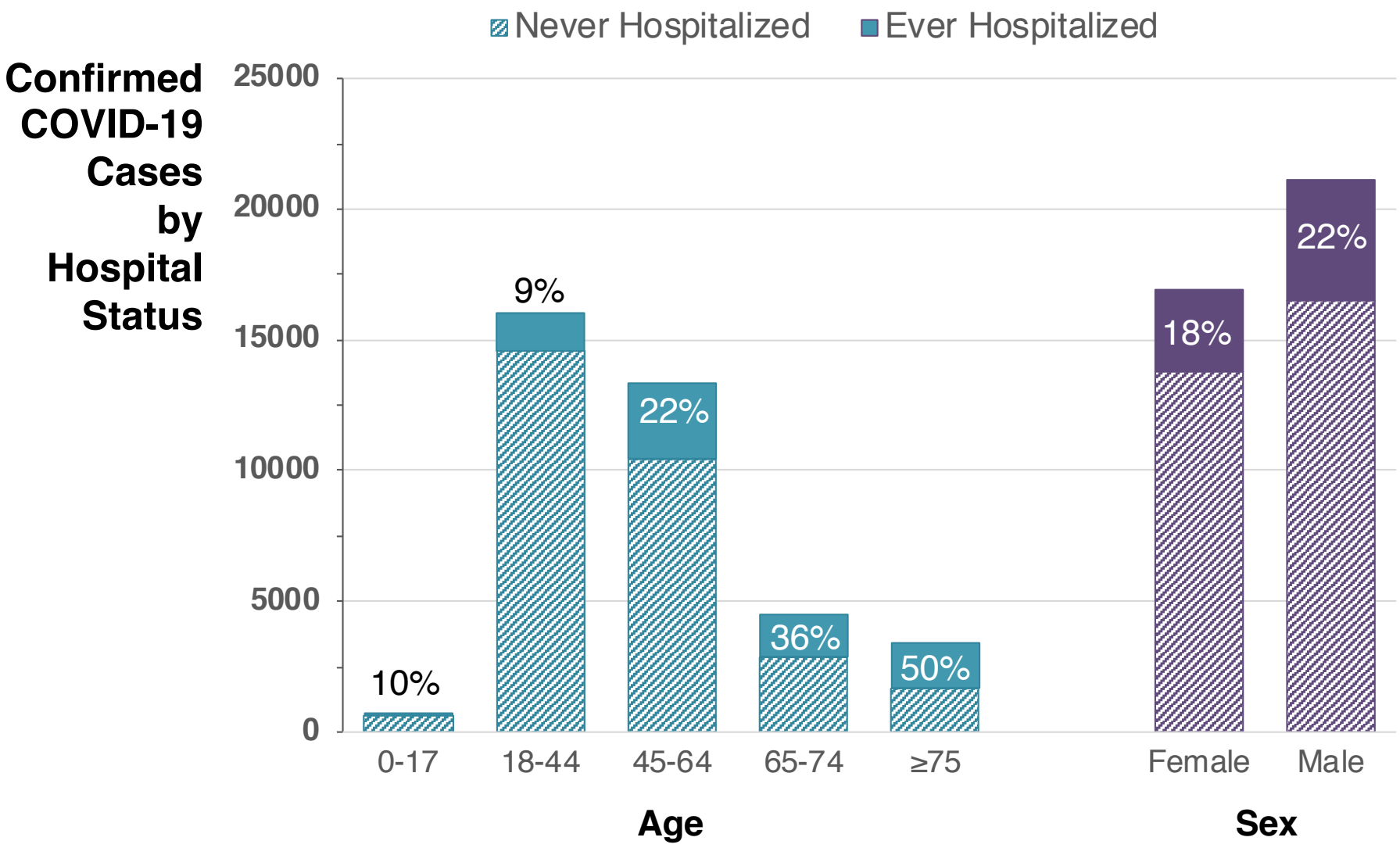
Who is at risk of dying from COVID-19?

Case Fatality Rate (%) by Age Group

Age group	Italy through 17 March	China through 11 Feb	United States through 16 March
0-9	0	0	0 0-19
10-19	0	0.2	
20-29	0	0.2	0.1-0.2 20-44
30-39	0.3	0.2	
40-49	0.4	0.4	0.5-0.8 45-54
50-59	1.0	1.3	1.4-2.6 55-64
60-69	3.5	3.6	2.7-4.9 65-74
70-79	12.8	8.0	4.3-10.5 75-84
≥80	20.2	14.8	
≥85			10.4-27.3 ≥85

US data: Lower bound = # deaths ÷ # in age group. Upper bound = # deaths ÷ # in age group w/confirmed death.
US: https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm
Italy & China: Onder G, et al. JAMA. 2020 Mar 23. https://doi.org/10.1001/jama.2020.4683

What can NYC's experience tell us?

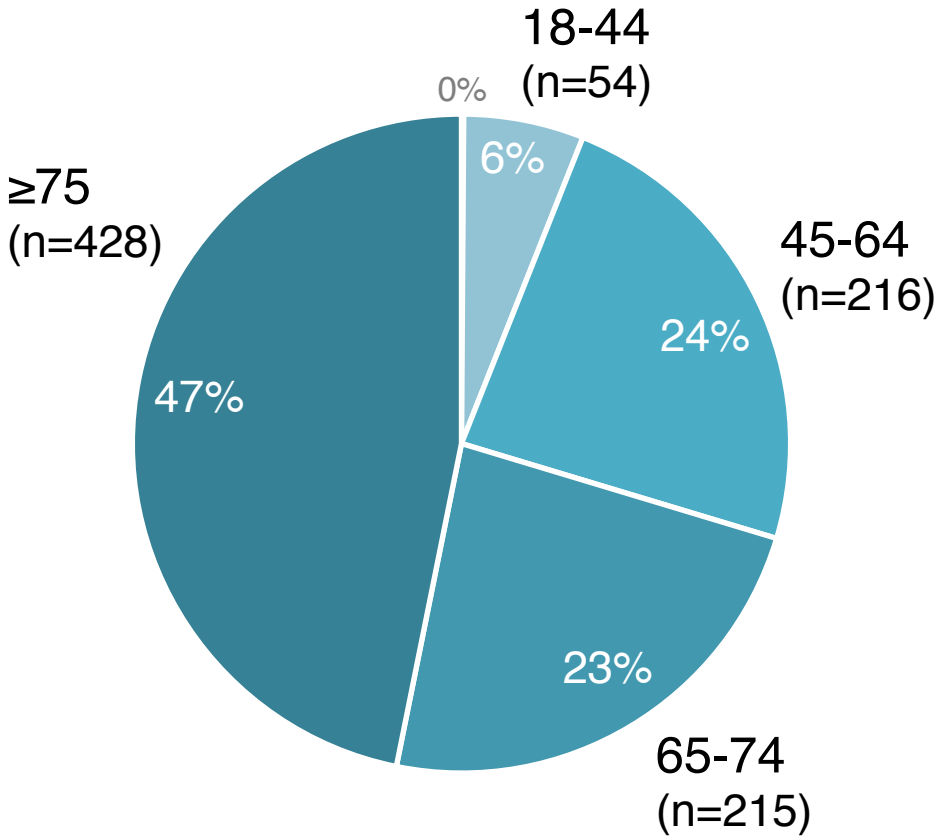


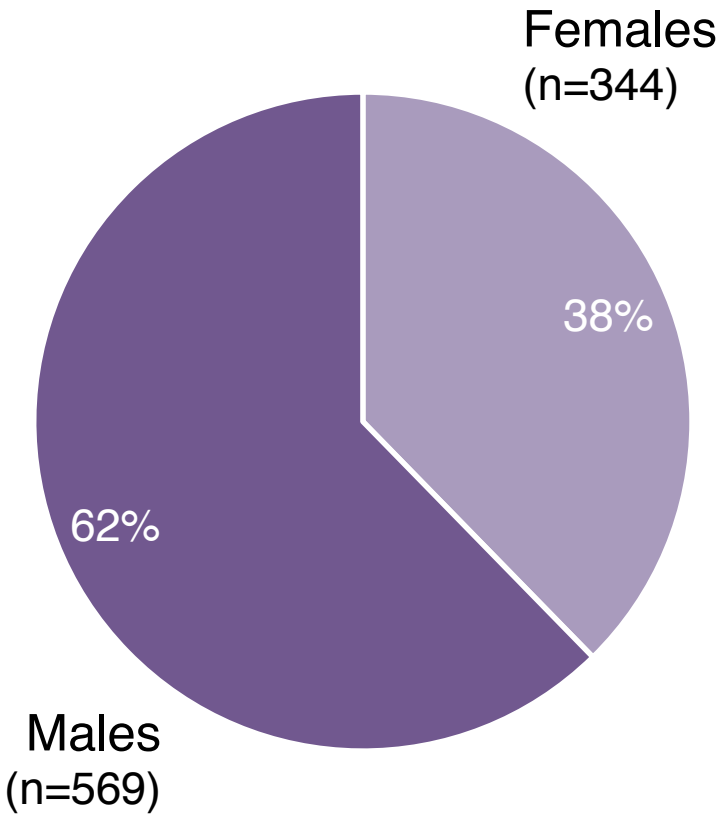
As of 1630 on 30 March

Data from: https://www1.nyc.gov/site/doh/covid/covid-19-main.page

What can NYC's experience tell us?

Cumulative COVID-19-Associated Deaths in New York City

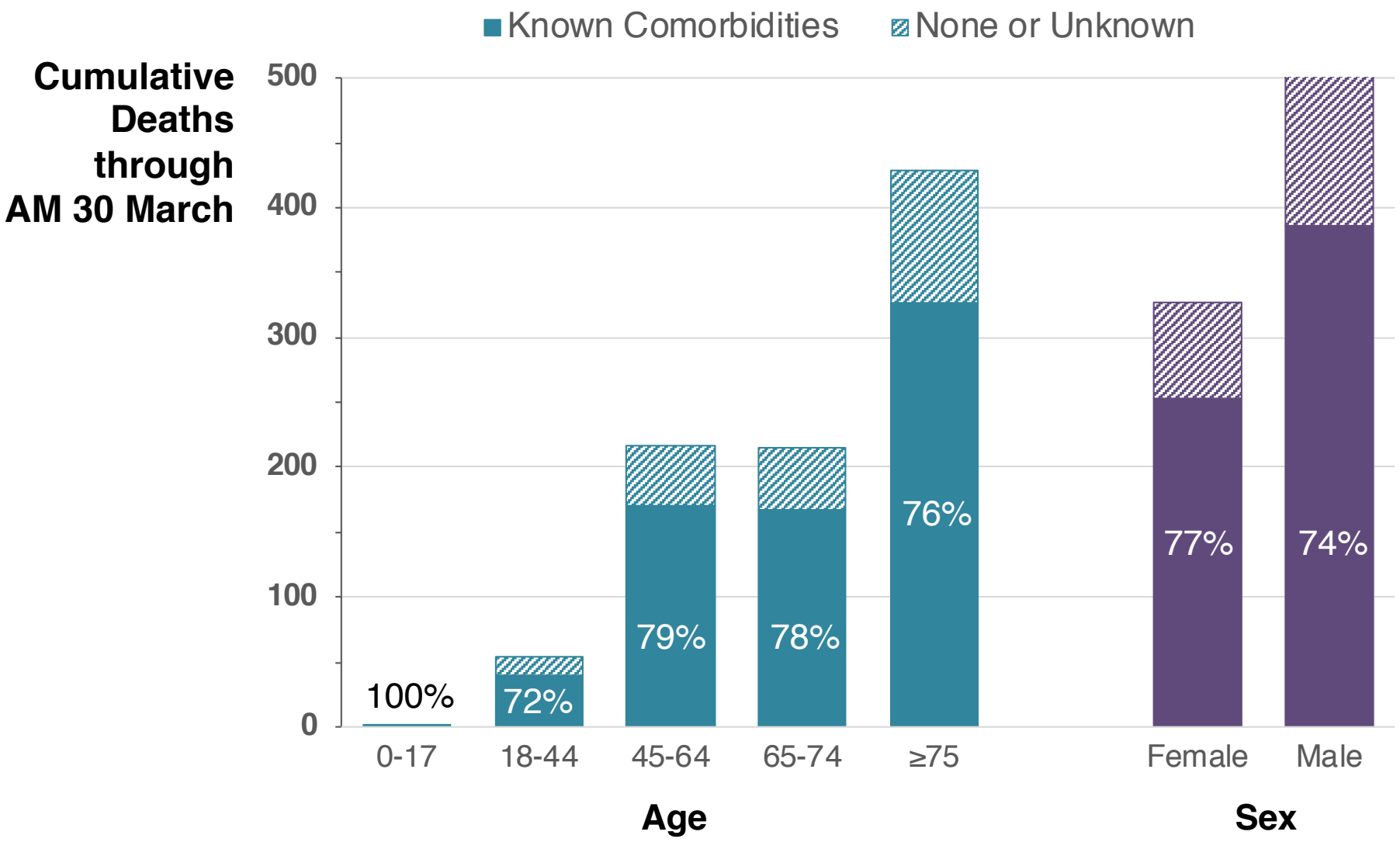




As of 1630 on 30 March

Data from: https://www1.nyc.gov/site/doh/covid/covid-19-main.page

What can NYC's experience tell us?

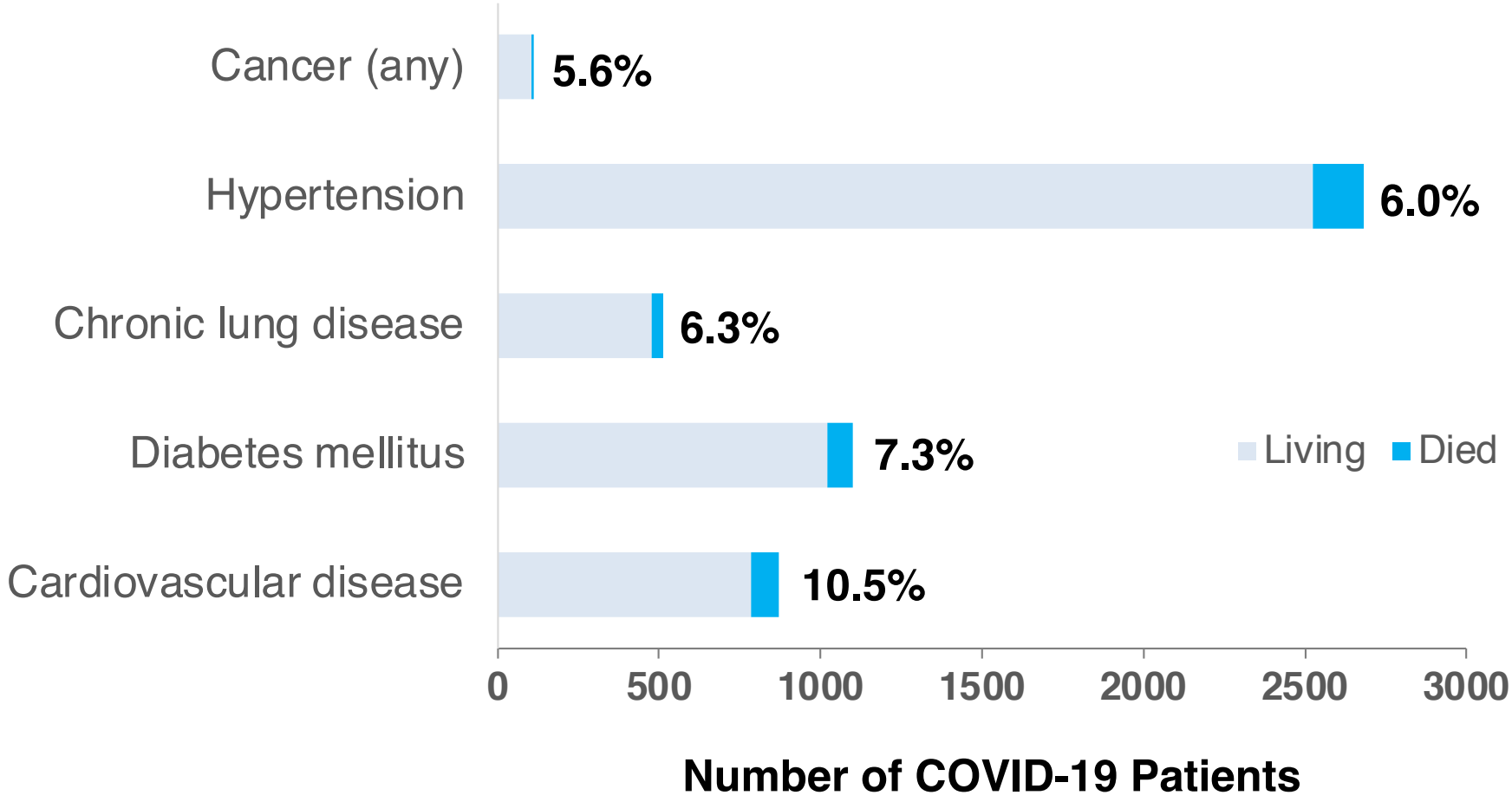


As of 1630 on 30 March

Data from: https://www1.nyc.gov/site/doh/covid/covid-19-main.page

Who is at risk of dying from COVID-19?

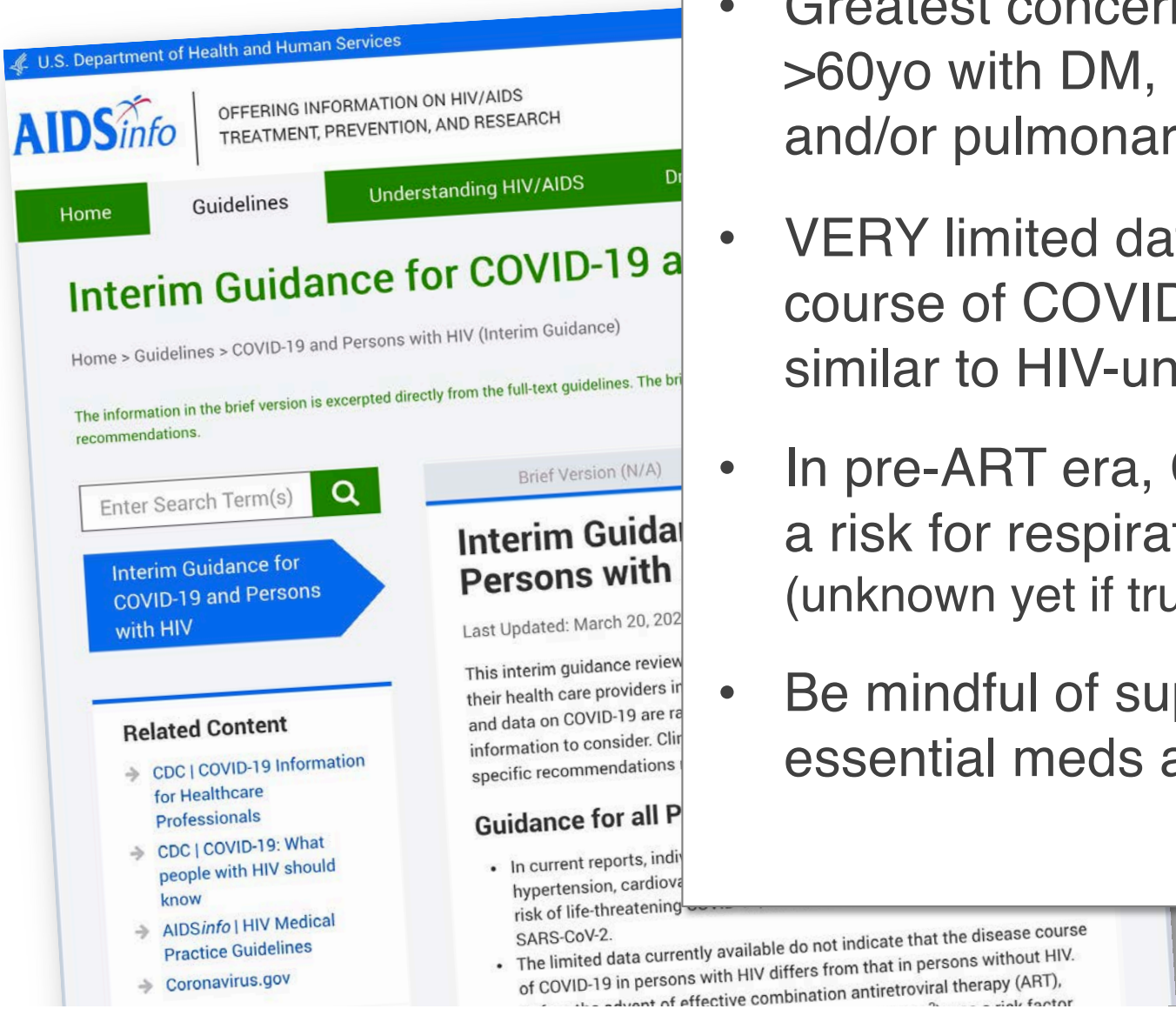
Comorbidities and Case Fatality Rates (%), China



The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020[J]. China CDC Weekly, 2020, 2(8): 113-122.

What about people with HIV?

https://aidsinfo.nih.gov/
20 March 2020



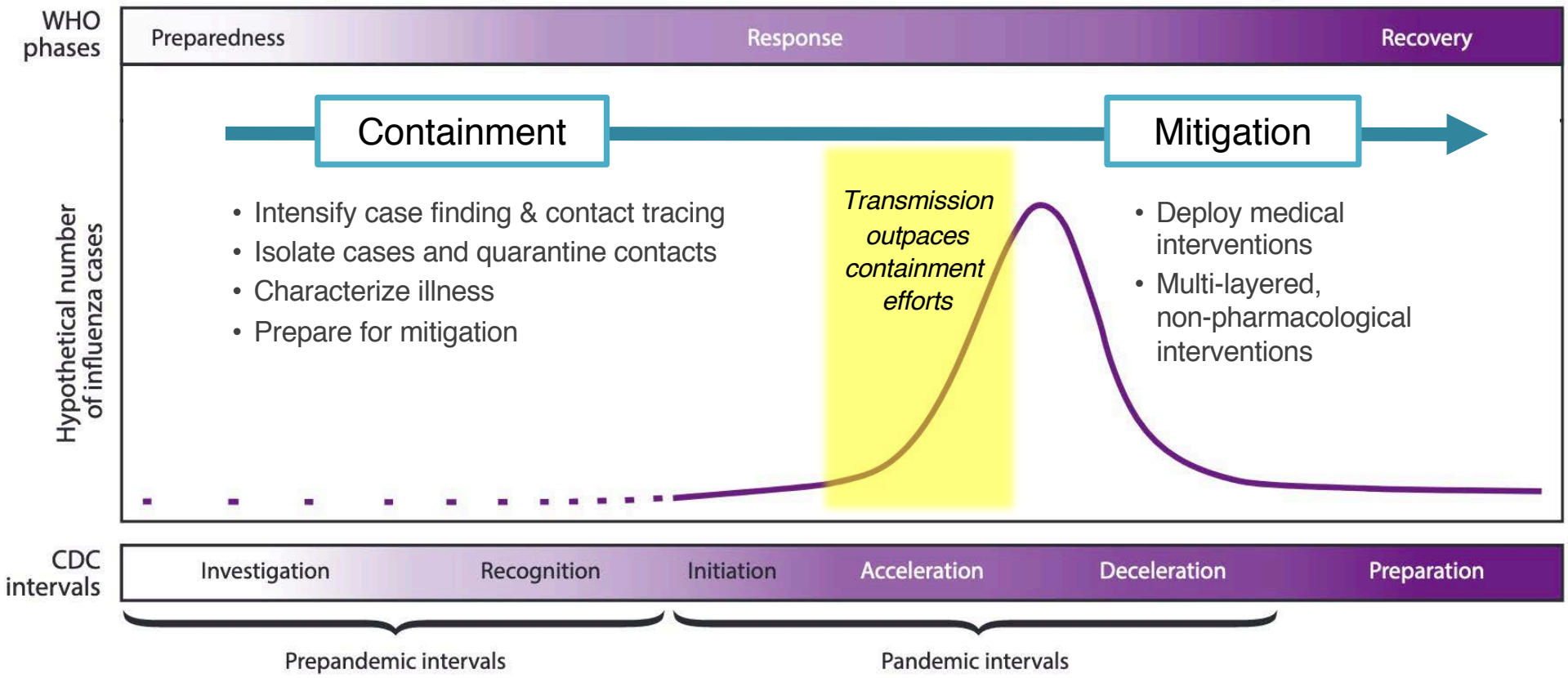
- Greatest concern is for PwH >60yo with DM, HTN, CVD, and/or pulmonary disease
- VERY limited data suggest course of COVID-19 in PwH is similar to HIV-uninfected
- In pre-ART era, CD4 <200 was a risk for respiratory infections (unknown yet if true for COVID-19)
- Be mindful of supply of ART & essential meds and avoid gaps

What about people with HIV?

http://bit.ly/covid19hiv

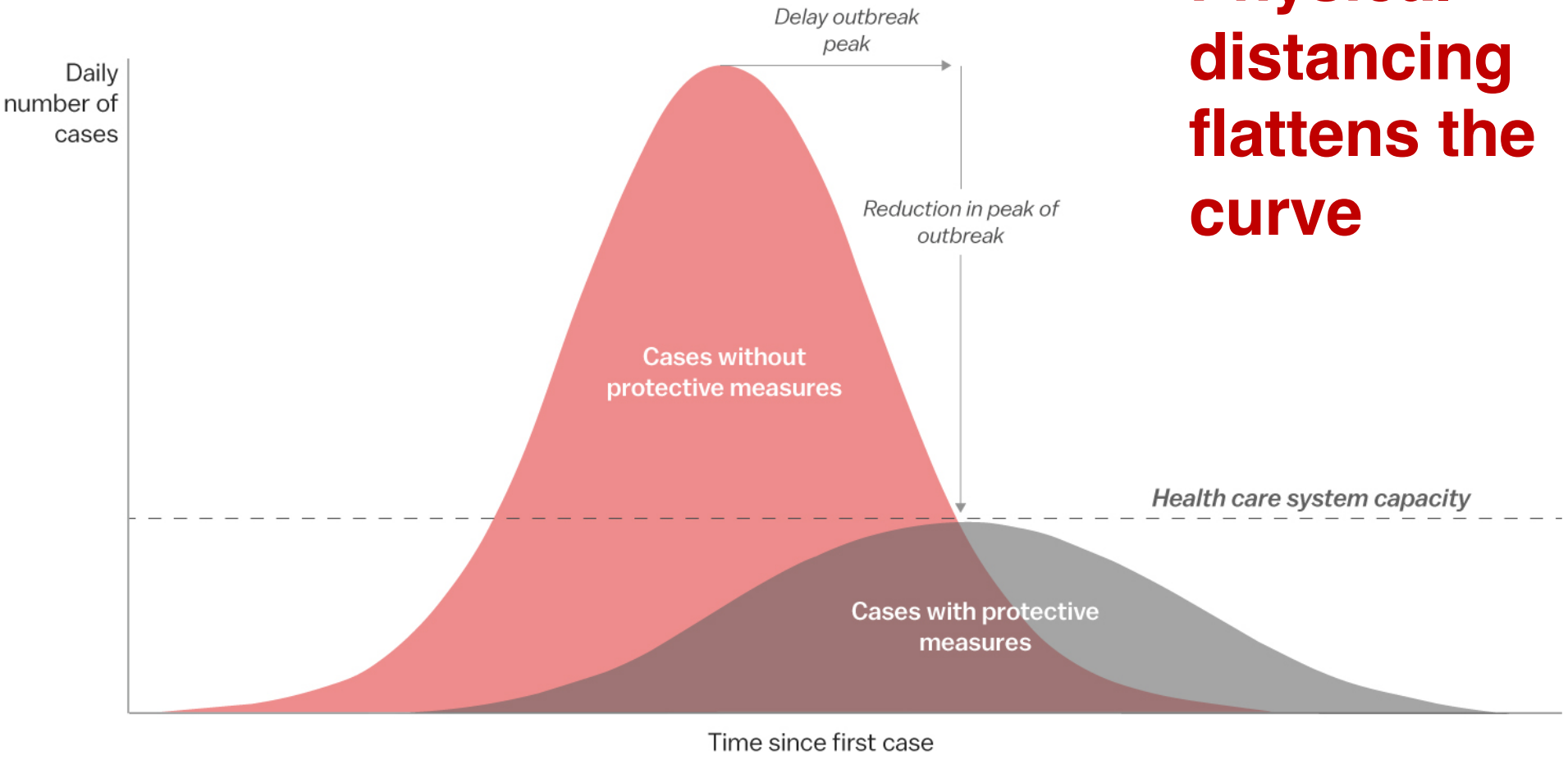
- **Emphasize common sense approaches!**
- The lower your CD4 count, the more cautious you ought to be
- Negotiate between providers & patients about spacing out visits, doing phone or video, etc. until we're through the worst of things

What's happening now?



Adapted from Brooks, J (CDC) – COVID-19 Special Session – CROI 2020
Qualls N, et al. MMWR Recomm Rep. 2017 Apr 21;66(1):1-34. https://www.cdc.gov/mmwr/volumes/66/rr/pdfs/rr6601.pdf

What's happening now?

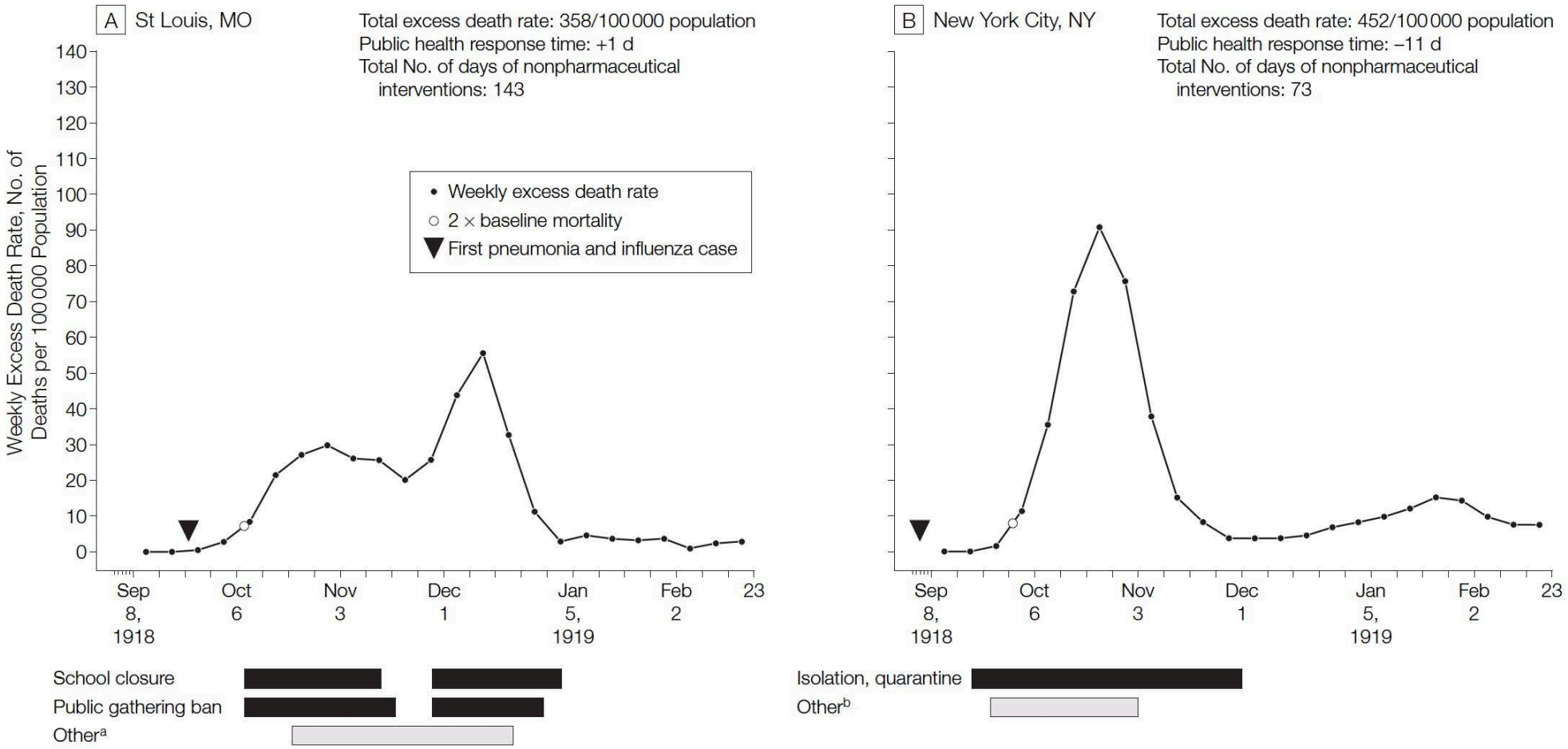


Physical distancing flattens the curve

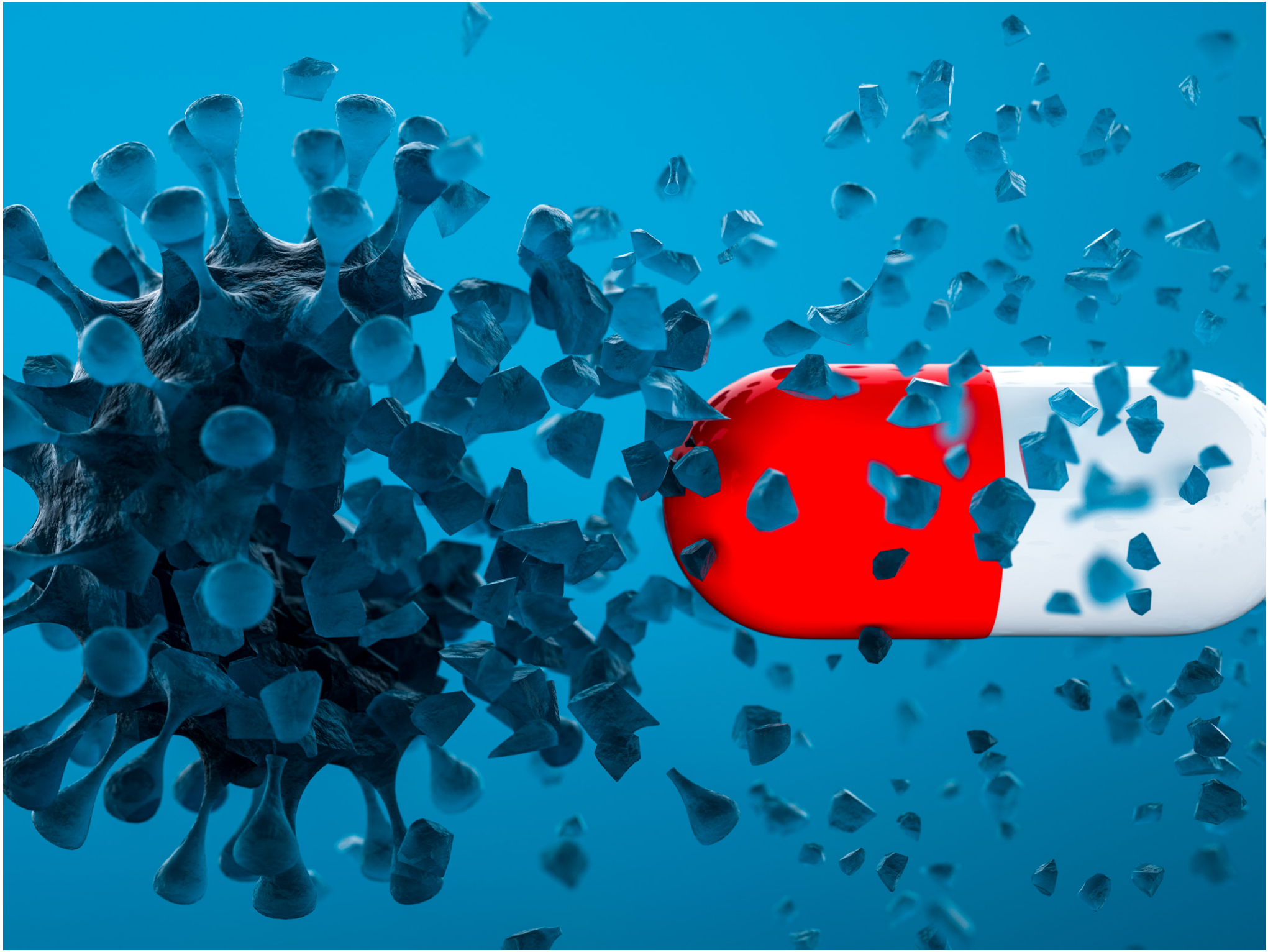
https://www.vox.com/2020/3/10/21171481/coronavirus-us-cases-quarantine-cancellation

Physical distancing works

Figure 3. Weekly Excess Death Rates From September 8, 1918, Through February 22, 1919



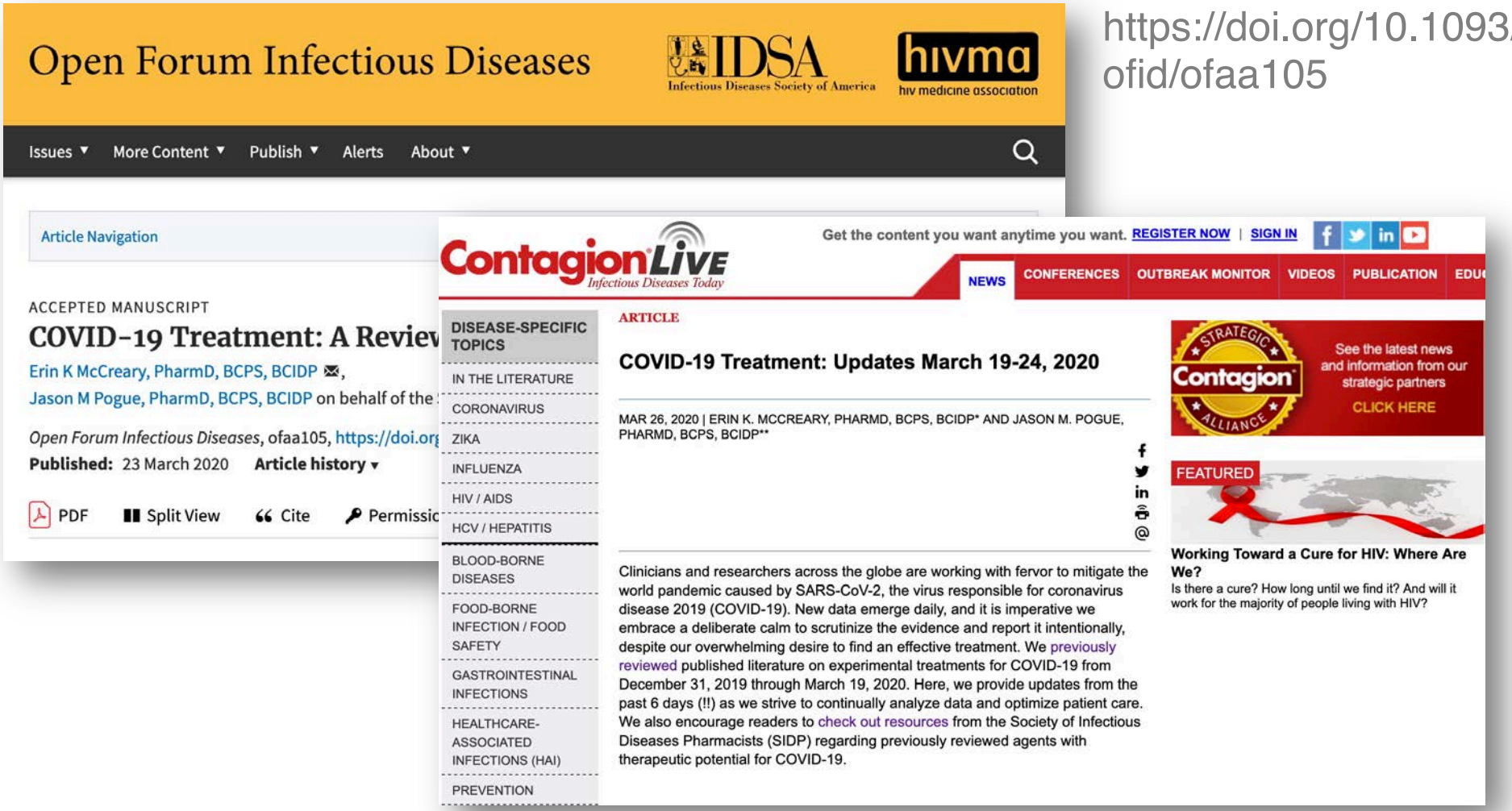
Markel H, et al. JAMA. 2007 Aug 8;298(6):644-54. https://doi.org/10.1001/jama.298.6.644



Resources from Society of ID Pharmacists

https://www.sidp.org/COVID19

McCreary & Pogue SIDP reviews



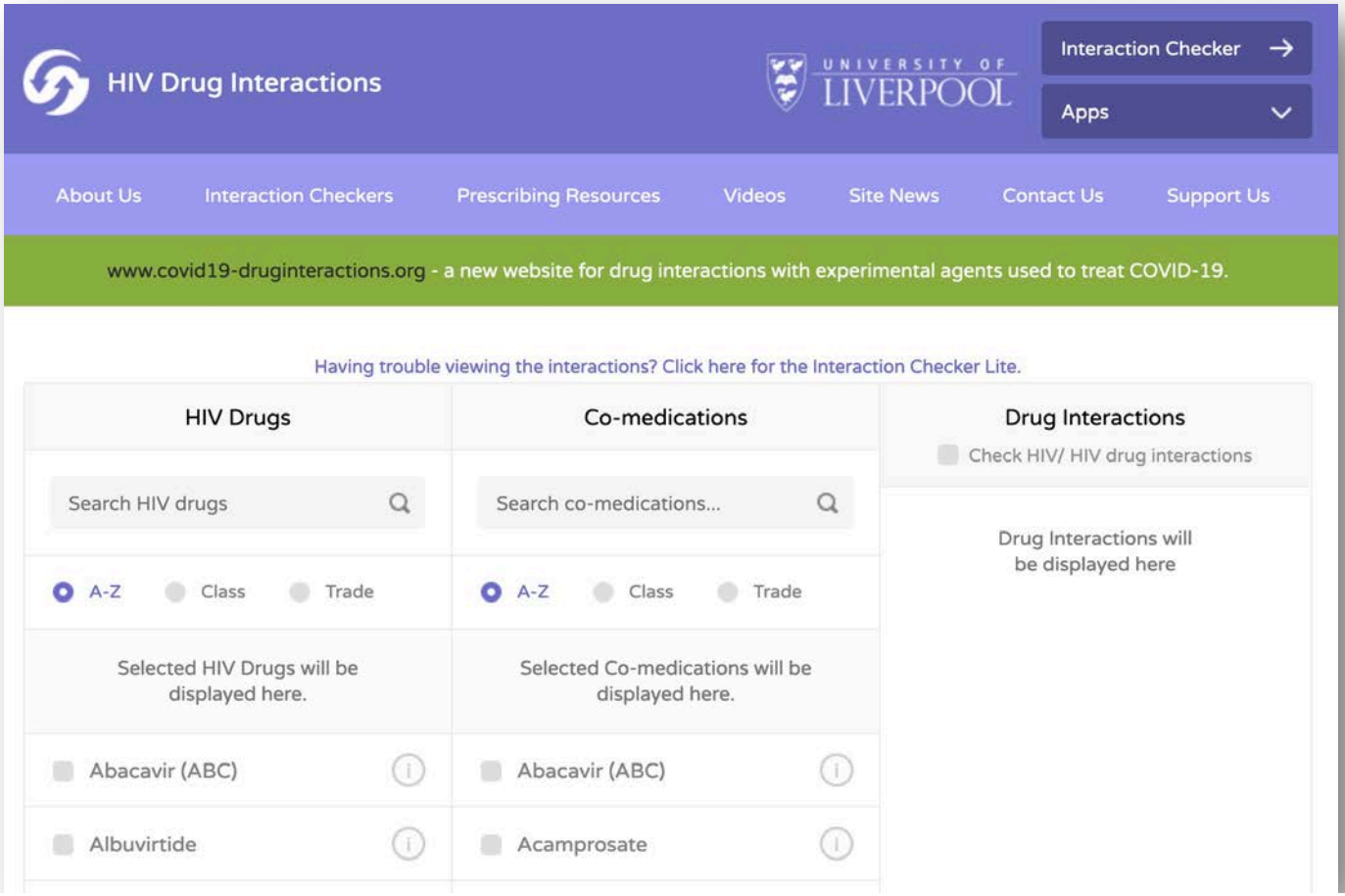
https://doi.org/10.1093/ofid/ofaa105

https://www.contagionlive.com/news/covid19-treatment-updates-march-19-24-2020

University of Liverpool interaction refs

https://www.covid19-druginteractions.org/

https://hiv-druginteractions.org/checker



Chloroquine & Hydroxychloroquine

72 BioScience Trends. 2020; 14(1):72-73.

Letter

DOI: 10.5582/bst.2020.01047

Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies

Jianjun Gao[1,*], Zhenxue Tian[2], Xu Yang[2]

[1] Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, China;
[2] Department of Pharmacy, Qingdao Municipal Hospital, Qingdao, China.

Who were the patients?

What was the control treatment?

How long were they treated?

At what point in their disease course was therapy introduced?

Author Conclusions:

"Results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course…."

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

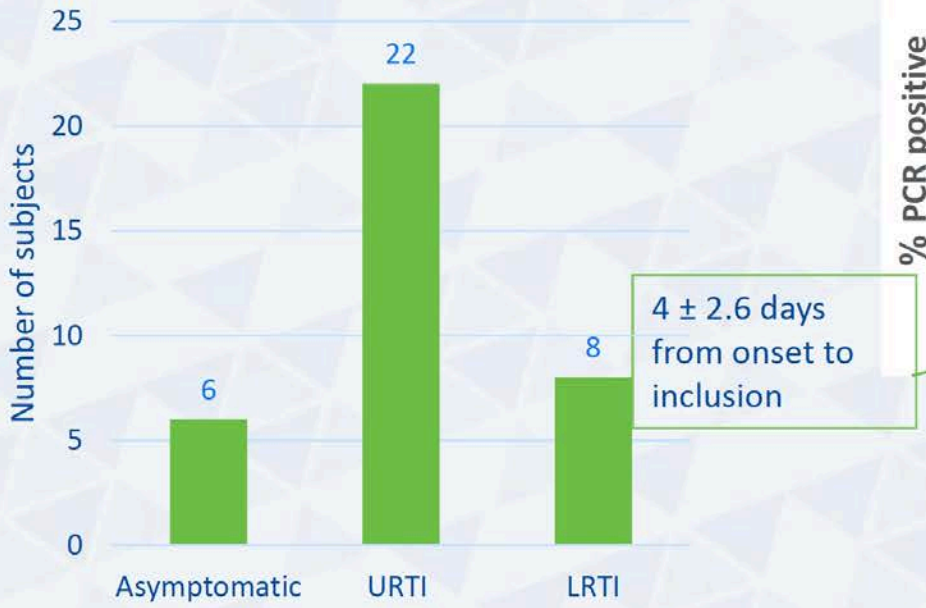
Gao J, Tian Z, Yang X. Biosci Trends Feb 19 [Epub ahead of print] Available at: https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/_article

https://sidp.org/covid19

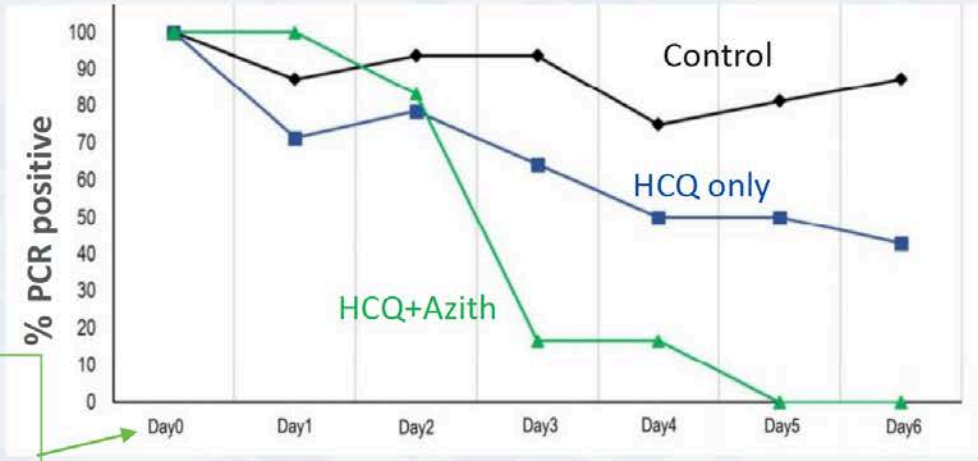
Chloroquine & Hydroxychloroquine

What about Hydroxychloroquine + Azithromycin

36 Hospitalized patients 45 ± 22 years old with COVID19



Primary outcome: Viral suppression 6 days after inclusion



N = 16: Controls
N = 14: HCQ 200 mg PO TID x10 days
N = 6: HCQ + Azithromycin 500 day 1 then 250mg x 4 days

**Exclusion criteria: Allergy, G6PD deficient, prolonged QTc, retinopathy*

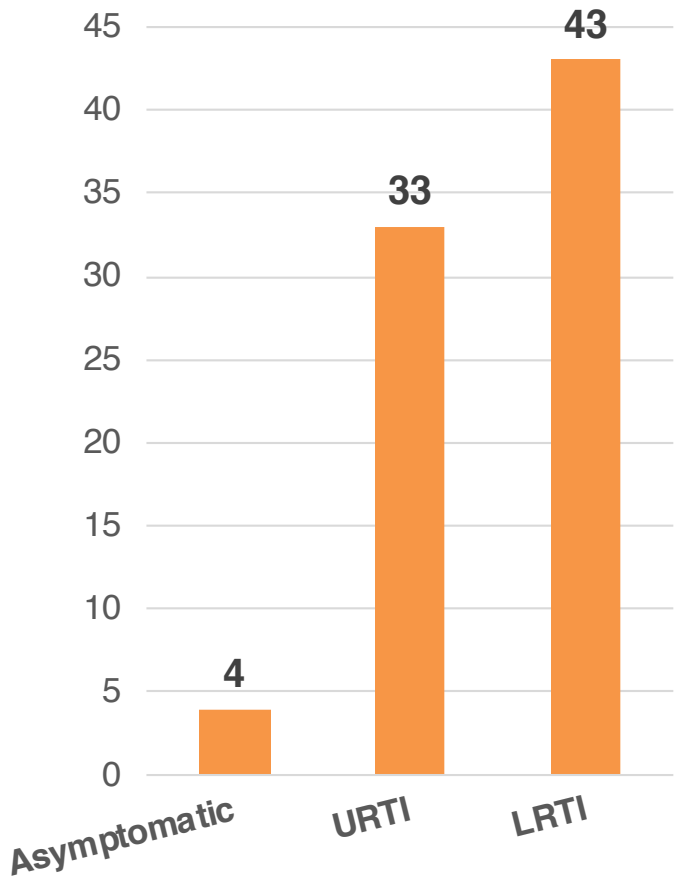
International Journal of Antimicrobial Agents – In Press 17 March 2020
DOI : 10.1016/j.ijantimicag.2020.105949

SLIDE IMAGE FROM SIDP

Gautret et al. Int J Antimicrob Agents 2020. https://doi.org/10.1016/j.ijantimicag.2020.105949

Hydroxychloroquine

80 Hospitalized Patients
Median Age 52 (range 18-88)
with NP swab PCR+ for SARS-CoV-2



Intervention:
- HCQ 200mg PO TID x10d **AND**
- Azithromycin 500mg PO x1 on day 1, then 250mg PO x4d

Mean duration of symptoms at admit: 4.9 ± 3.6 days

43 / 80 (53.8%) had CT consistent with pneumonia

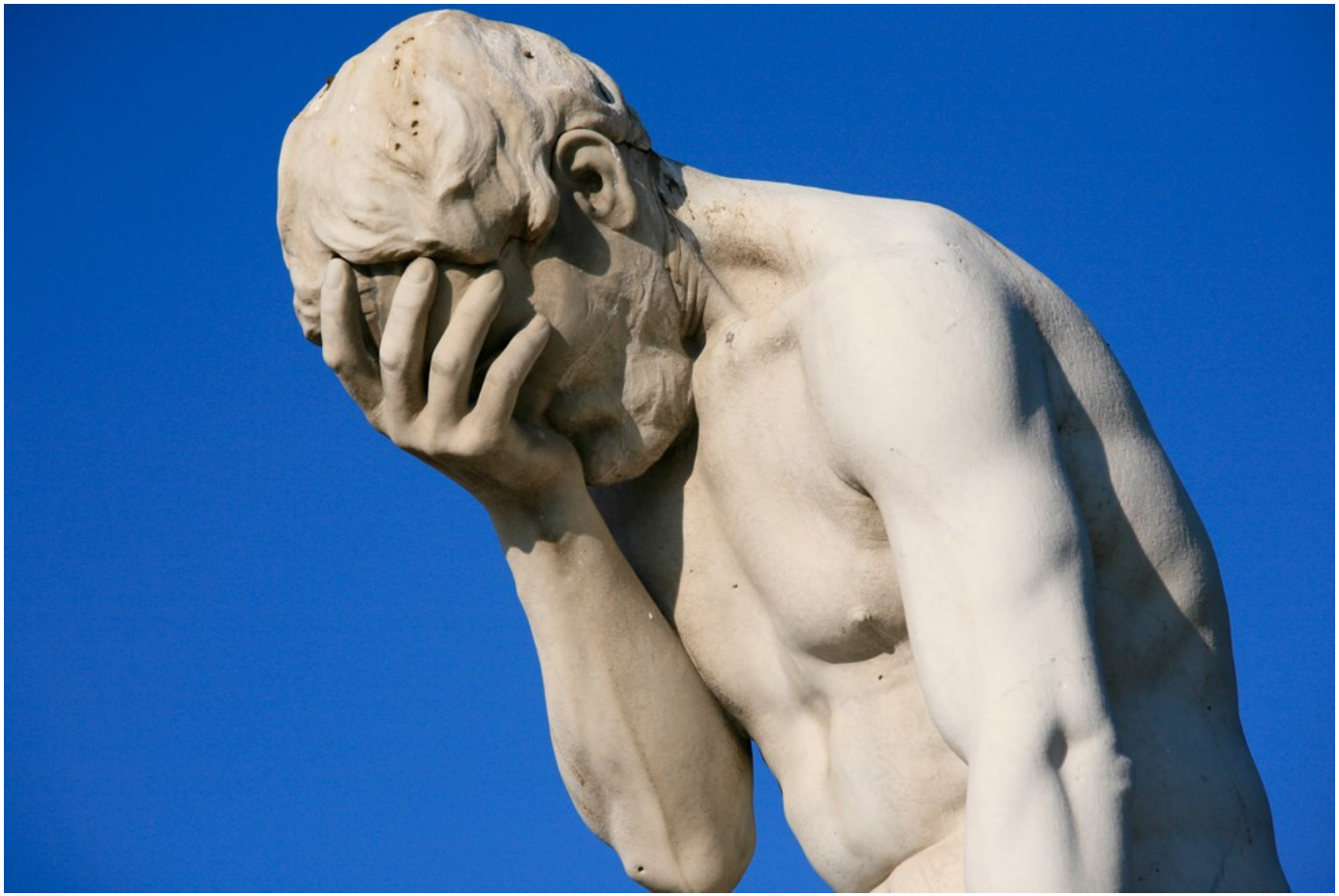
69 / 75 (92%) had NEWS score 0-4 (low) at baseline – *5 of the 80 had missing data (!?!)*

79 / 80 (98.8%) alive

- 12 / 80 (15%) needed oxygen
- 14 / 79 (17.7%) still admitted at writing
- 3 / 79 (3.8%) went to ICU → 2 went back to floor
- 65 / 79 (82.3%) were discharged home
  - 61 / 65 (93.8%) had NEWS score 0-4 (low) at time of discharge home

FROM PRE-PRINT OF THE *SECOND* FRENCH PAPER
https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf

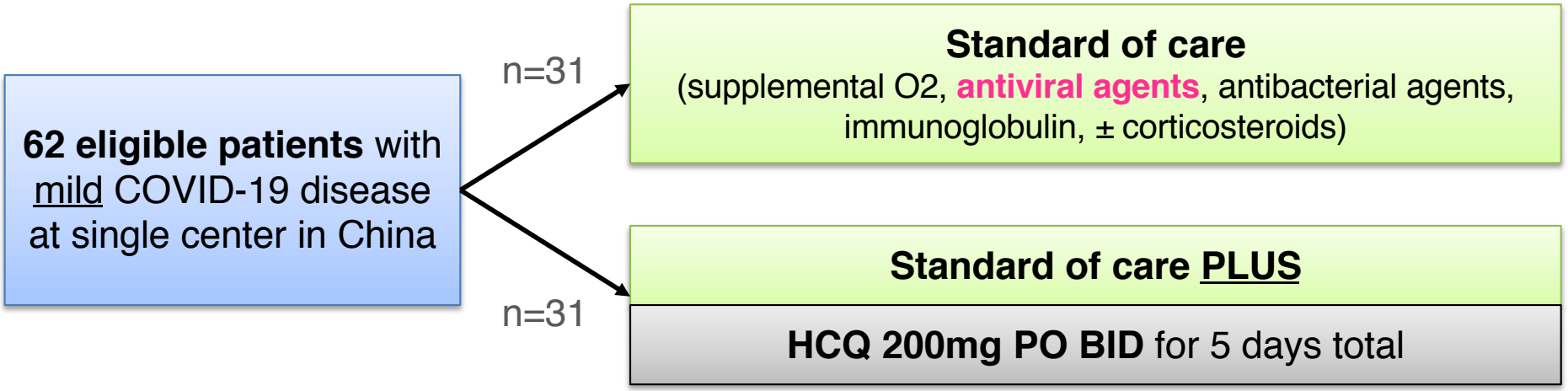
Hydroxychloroquine



https://blogs.sciencemag.org/pipeline/archives/2020/03/29/more-on-cloroquine-azithromycin-and-on-dr-raoult

Caïn by Henri Vidal, Jardin des Tuileries, Paris (1896)

Hydroxychloroquine



Baseline Characteristics

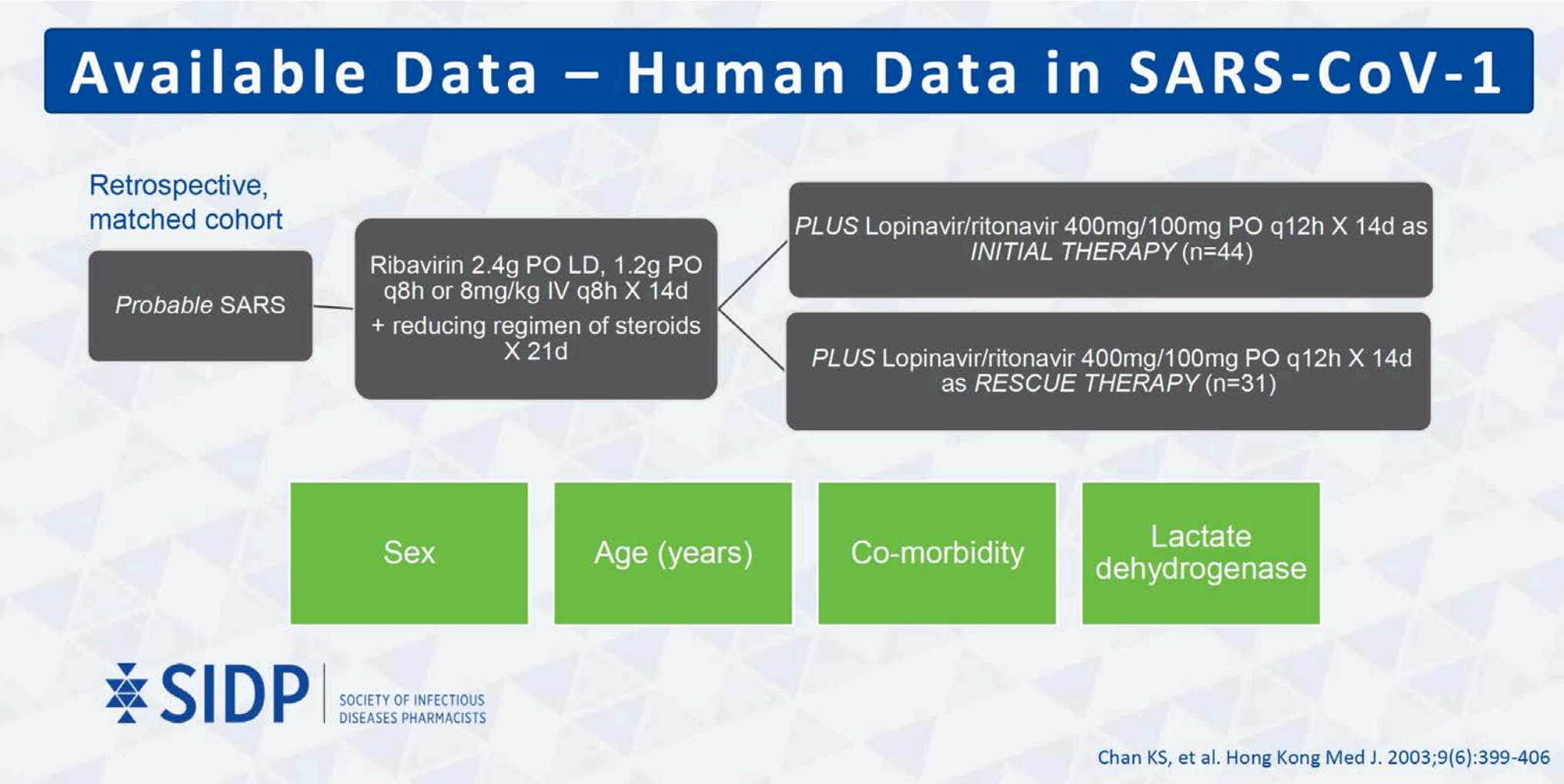
	Control (n=31)	HCQ (n=31)	*P*
Age, mean (SD)	45.2 (14.7)	44.1 (16.1)	0.88
Male, n (%)	16 (52)	17 (55)	0.80
Febrile day before randomized, n (%)	17 (55)	22 (71)	
Cough day before randomized, n (%)	15 (48)	22 (71)	

Outcomes

	Control (n=31)	HCQ (n=31)	*P*
Days to becoming afebrile, mean (SD)	3.2 (1.3)	2.2 (0.4)	0.0008
Days to cough remission, mean (SD)	3.1 (1.5)	2.0 (0.2)	0.0016
Progression to severe, n (%)	4 (12.9)	0 (0%)	–
CT improved, n (%)	17 (55)	25 (81)	0.048

Chen Z, et al. PREPRINT https://doi.org/10.1101/2020.03.22.20040758

Lopinavir/ritonavir



Chan KS, et al. Hong Kong Med J. 2003 Dec;9(6):399-406

Lopinavir/ritonavir

NOTE: Only 576 (90.9%) of these 634 had microbiologically confirmed SARS infection – but to get LPV/r, pts had to have confirmed SARS-CoV

Table 3. Comparison of outcomes for the group given LPV/r as initial treatment and a matched cohort*

	LPV/r as initial treatment, n=44 Crude rate or mean (95% CI)	Matched cohort, n=634 Standardised rate or mean† (95% CI)	P value
Death rate (%)	2.3 (0-6.8)	15.6 (9.8-22.8)	<0.05
Intubation rate (%)	0	11.0 (7.7-15.3)	<0.05
Desaturation rate (SaO2≤95%) [%]	68.2 (52.3-81.8)	84.5 (74.4-95.2)	NS‡
Proportion requiring pulse methylprednisolone rescue (%)	27.3 (11.4-40.9)	55.4 (47.6-63.9)	<0.05
Mean pulse methylprednisolone dose (g)	1.6 (1.1-2.0)	3.0 (2.8-3.2)	<0.05

* Matched on age, sex, presence/absence of co-morbidity, and initial lactate dehydrogenase level
† Standardised based on the percentage distribution of subjects of the treated group across the prognostic strata in Table 1
‡ NS not significant

NOTE: Only 329 (95.6%) of these 634 had microbiologically confirmed SARS infection – but to get LPV/r, pts had to have confirmed SARS-CoV

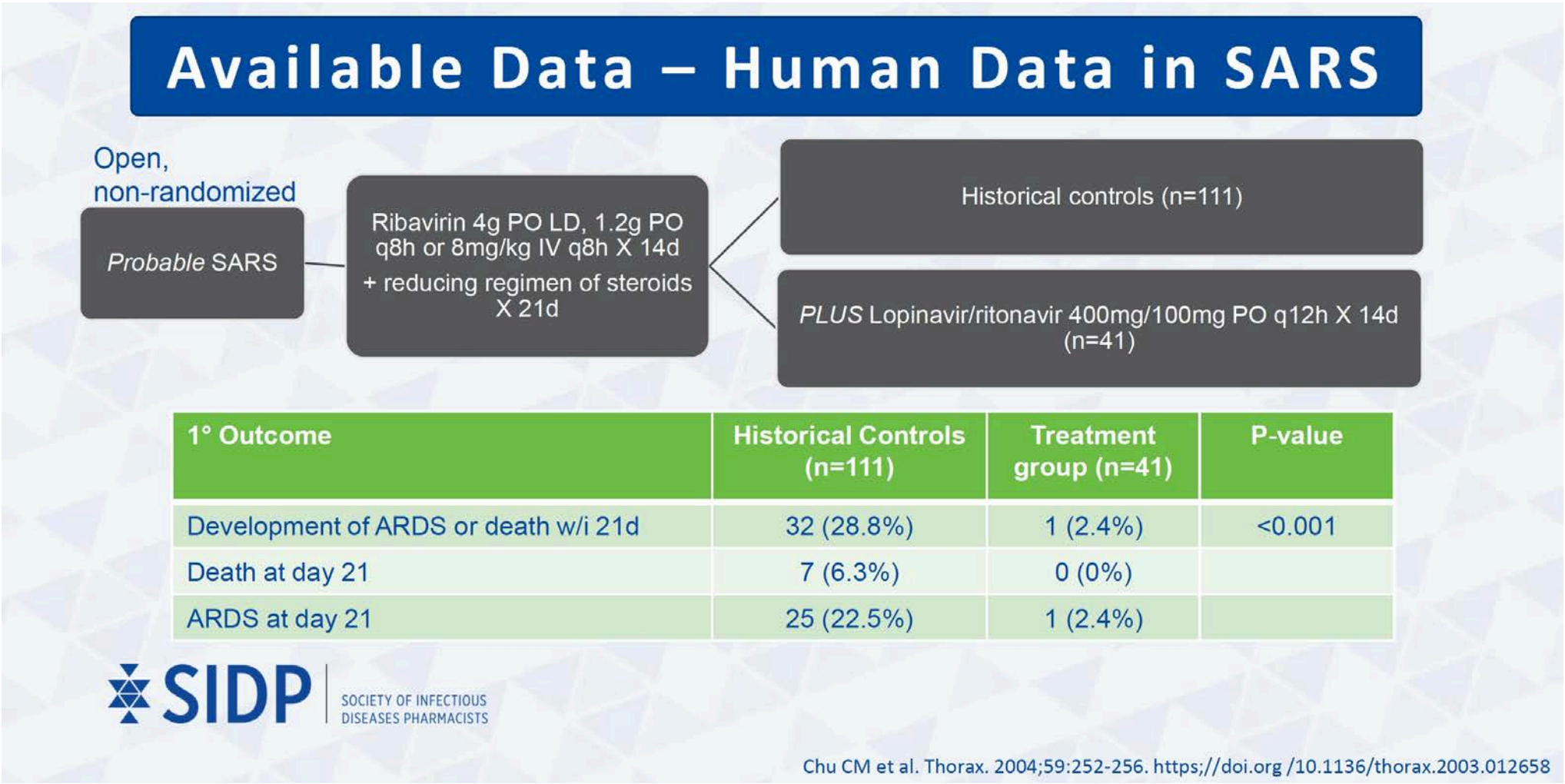
Table 4. Comparison of outcomes of the group given LPV/r as rescue treatment and a matched cohort*

	LPV/r as rescue, n=31 Crude rate or mean (95% CI)	Matched cohort, n=343 Standardised rate or mean† (95% CI)	P value
Death rate (%)	12.9 (0-25.8)	14.0 (5.2-26.3)	NS‡
Intubation rate (%)	9.7 (0-22.6)	18.1 (9.0-29.7)	NS
Desaturation rate (SaO2≤95%) [%]	93.5 (80.6-100)	92.1 (75.9-100)	NS
Mean pulse methylprednisolone dose (g)	3.8 (3.5-4.2)	3.0 (2.9-3.2)	<0.05

* Matched on age, sex, presence/absence of co-morbidity, lactate dehydrogenase level before pulse methylprednisolone, and use of pulse methylprednisolone
† Standardised based on the percentage distribution of subjects of the treated group across the prognostic strata in Table 1
‡ NS not significant

Chan KS, et al. Hong Kong Med J. 2003 Dec;9(6):399-406

Lopinavir/ritonavir



1° Outcome	Historical Controls (n=111)	Treatment group (n=41)	P-value
Development of ARDS or death w/i 21d	32 (28.8%)	1 (2.4%)	<0.001
Death at day 21	7 (6.3%)	0 (0%)	
ARDS at day 21	25 (22.5%)	1 (2.4%)	

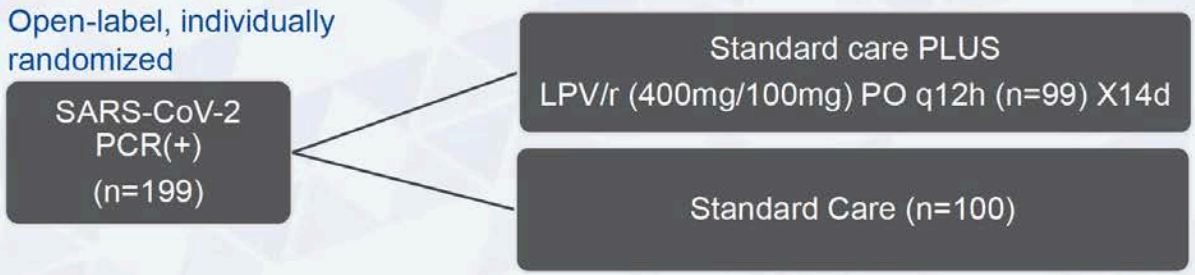
SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Chu CM et al. Thorax. 2004;59:252-256. https;//doi.org /10.1136/thorax.2003.012658

Chu CM, et al. Thorax. 2004 Mar;59(3):252-6

Lopinavir/ritonavir

Available Data – COVID-19 in China



Standard Care: Supplemental O_2, noninvasive and invasive ventilation, abx, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO)

1° Outcome	LPV/r (n=99)	Standard Care (n=100)	Difference
Time from illness onset to randomization, median days (IQR)	13 (11–17)	13 (10–16)	-
Time to clinical improvement, median days (IQR)	16.0 (13.0 to 17.0)	16.0 (15.0 to 18.0)	1.31 (0.95 to 1.80)
ITT 28d mortality, n (%)	19 (19.2)	25 (25.0)	−5.8 (−17.3 to 5.7)
mITT 28d mortality, n (%)	16 (16.7)	25 (25.0)	-8.3 (-19.6 to 3.0)
Time from randomization to d/c, median days (IQR)	12 (10 to 16)	14 (11 to 16)	1 (0 to 3)
Pts w/ clinical improvement at 14d, n (%)	45 (45.5)	30 (30.0)	15.5 (2.2 to 28.8)

Cao B, et al. NEJM, 2020. https://doi.org/10.1056/NEJMoa2001282

Cao B, et al. N Engl J Med. 2020 Mar 18. https://doi.org/10.1056/NEJMoa2001282

Lopinavir/ritonavir

Available Data – COVID-19 in China

Author Conclusions:

LPV/r treatment added to standard txt was **not associated w/ clinical improvements or mortality in seriously ill patients** with COVID-19 vs. standard care alone. Decrease in viral loads over time **did not differ** between the two groups

*high overall mortality, numerical benefits in early txt group and post-hoc groups

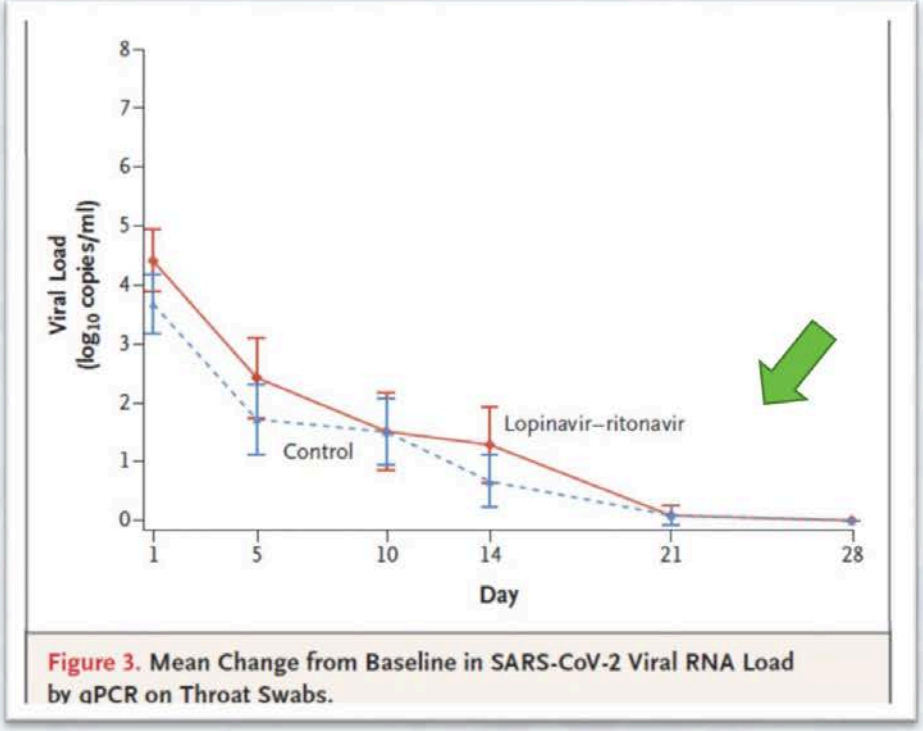


Figure 3. Mean Change from Baseline in SARS-CoV-2 Viral RNA Load by qPCR on Throat Swabs.

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Cao B, et al. NEJM, 2020. https://doi.org/10.1056/NEJMoa2001282

https://sidp.org/covid19

Remdesivir

Remdesivir (GS-5734)

Mechanism of Action: Interference with viral RNA-dependent RNA polymerase; premature termination of viral RNA transcription

Status: Investigational, COVID-19 Phase III trials ongoing

Formulation: Intravenous only

Dosing: 200 mg IV loading dose, then 100 mg IV daily for 5-10 days
Pediatric Dosing: 5 mg/kg IV loading dose (max 200 mg), then 2.5 mg/kg IV daily (max 100 mg)

Manufacturer: Gilead Sciences

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

*Optimal duration currently under investigation

Tchesnokov; Viruses 2019.

https://sidp.org/covid19

Remdesivir

In vitro Activity

Virus	EC50 (cells)	CC50 (cells)	Selectivity Index
SARS-CoV-2	**0.77 µM (Vero E6)**	>100 µM (Vero E6)	>130
SARS-CoV-1	0.069 µM (HAE)	> 10 µM (HAE)	>144
MERS	0.074 µM (HAE)	> 10 µM (HAE)	>135
Ebola	0.086 µM (MCr)	6.1 (Hep-2)	N/A

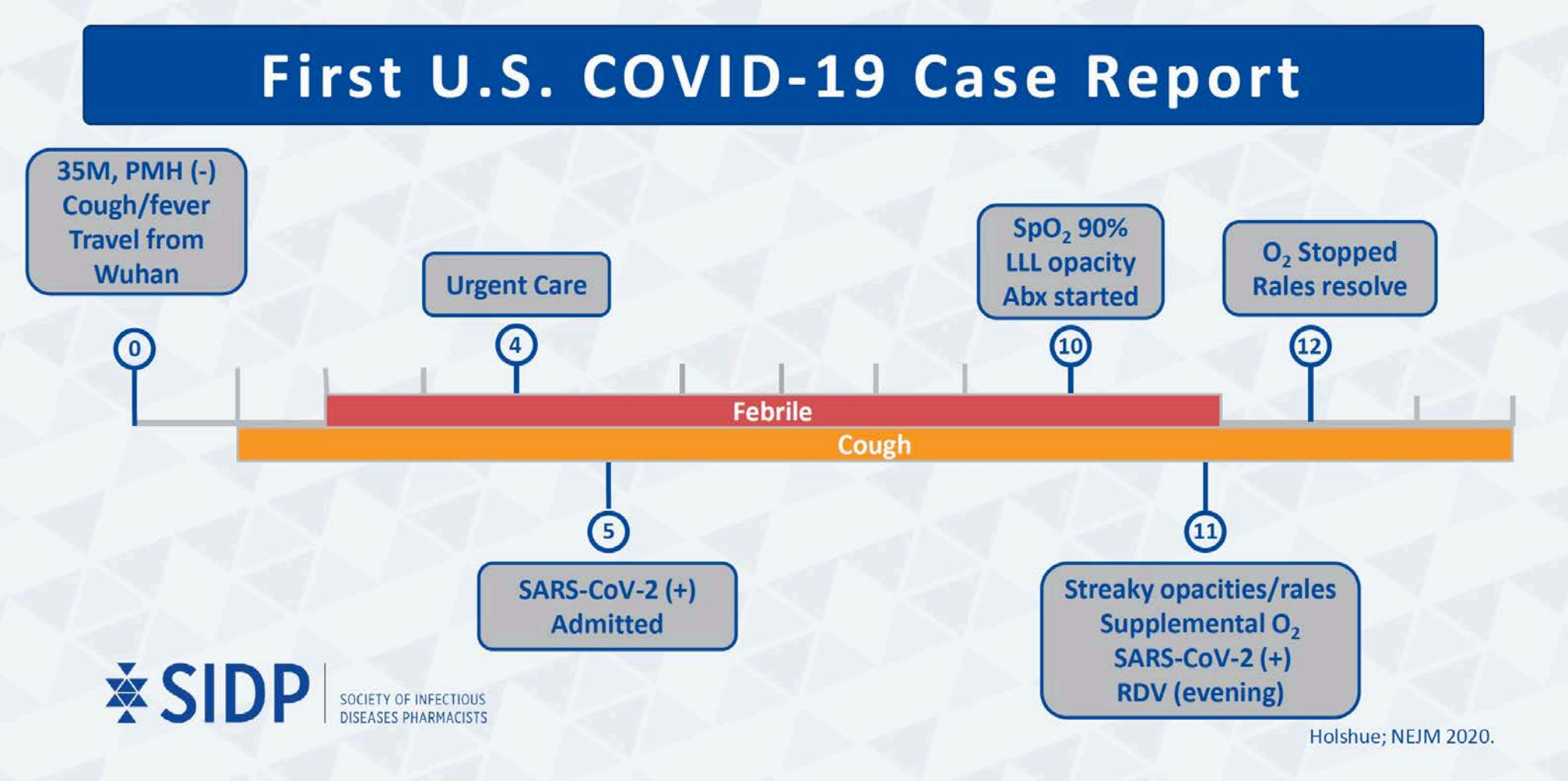
EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; Vero E6 = African monkey kidney cells; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Gordon; J Bio Chem 2020.
Sheahan; Sci Transl Med 2017.
Agostini; Am Soc Micro 2018.
Yao; *CID* 2020.

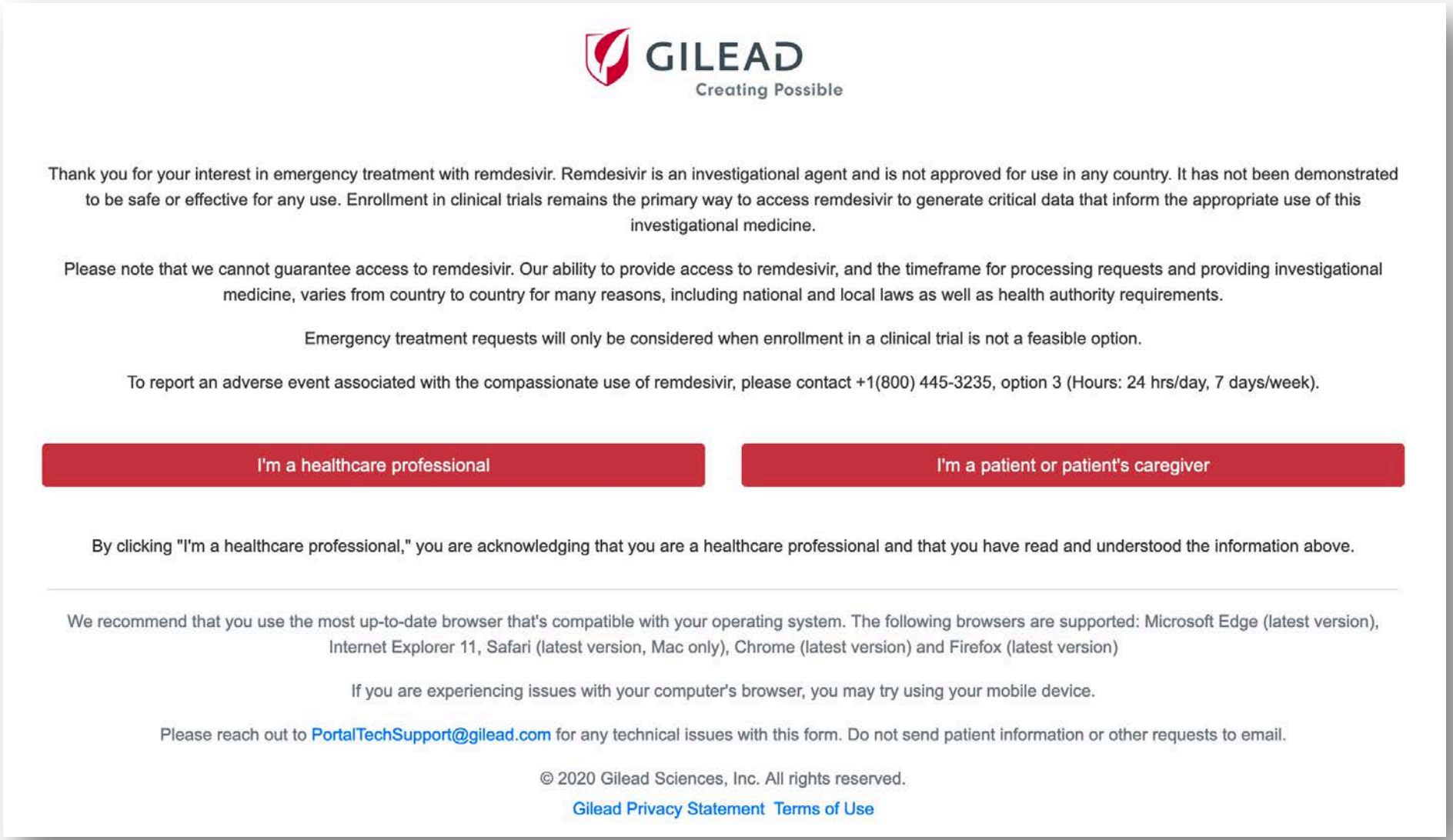
https://sidp.org/covid19

Remdesivir



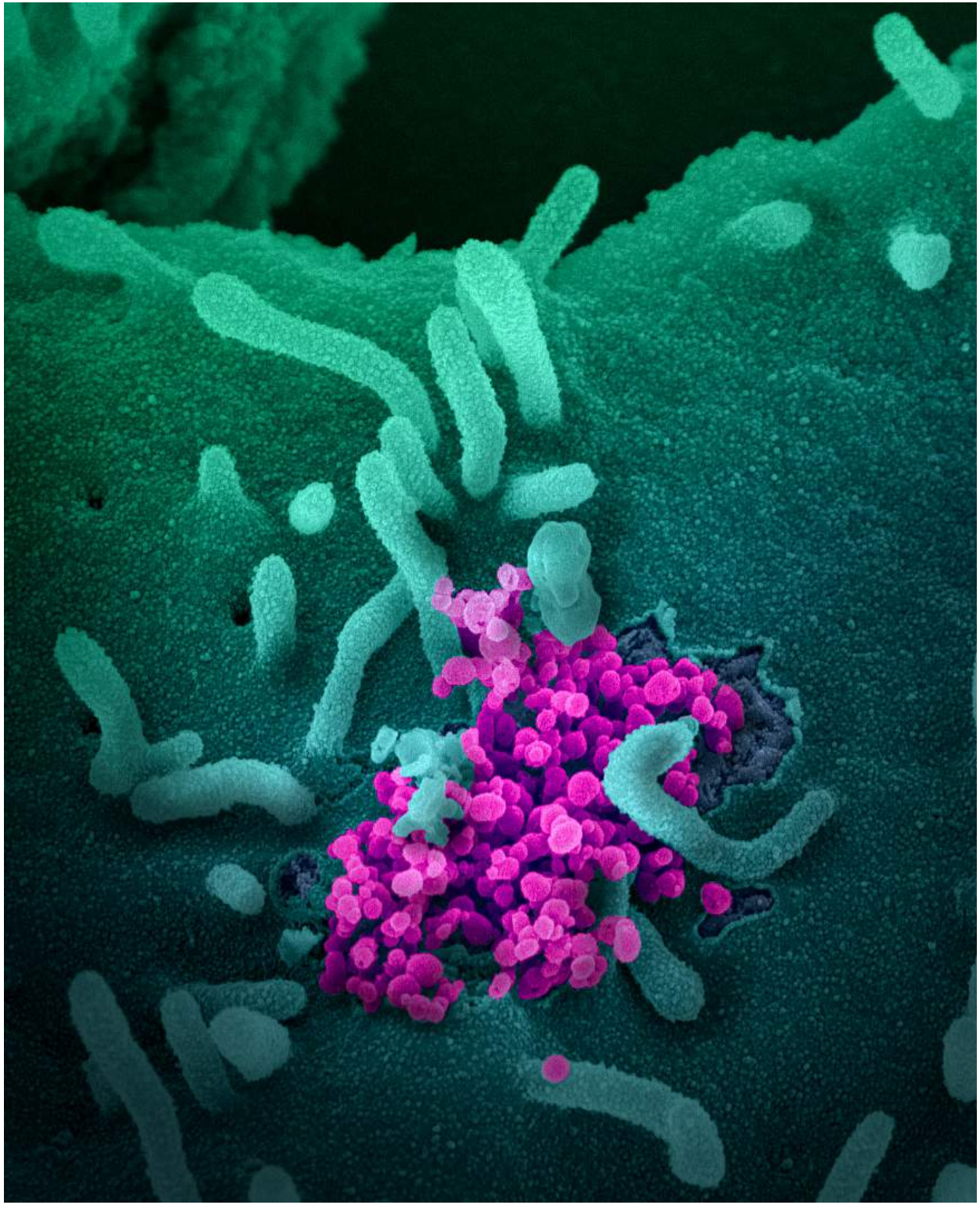
https://sidp.org/covid19

Remdesivir



https://rdvcu.gilead.com

Remdesivir



What are your centers using?

Questions?

Please email me!

Christopher Hurt, MD

churt@med.unc.edu