



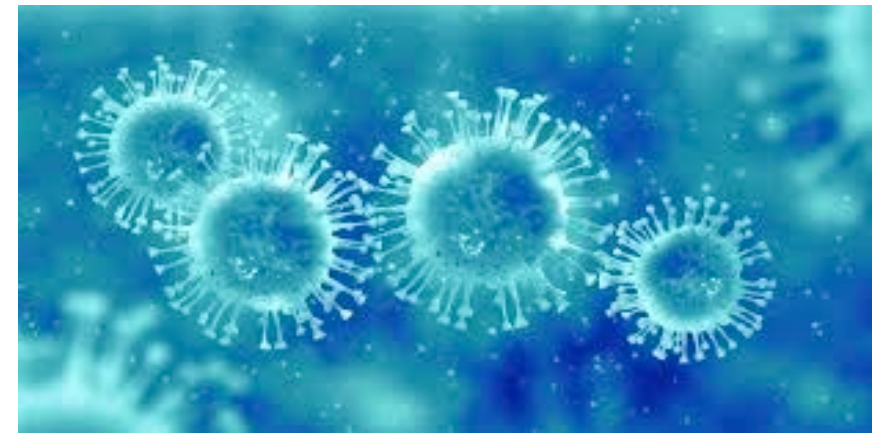
The COVID-19 Pandemic

Insights from Near the U.S. Epicenter

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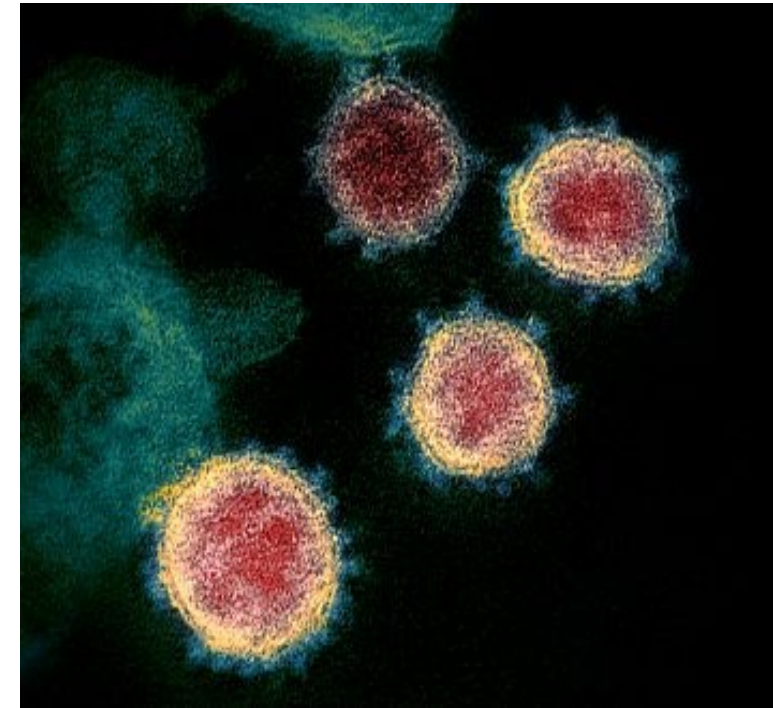
Yale University



BACKGROUND

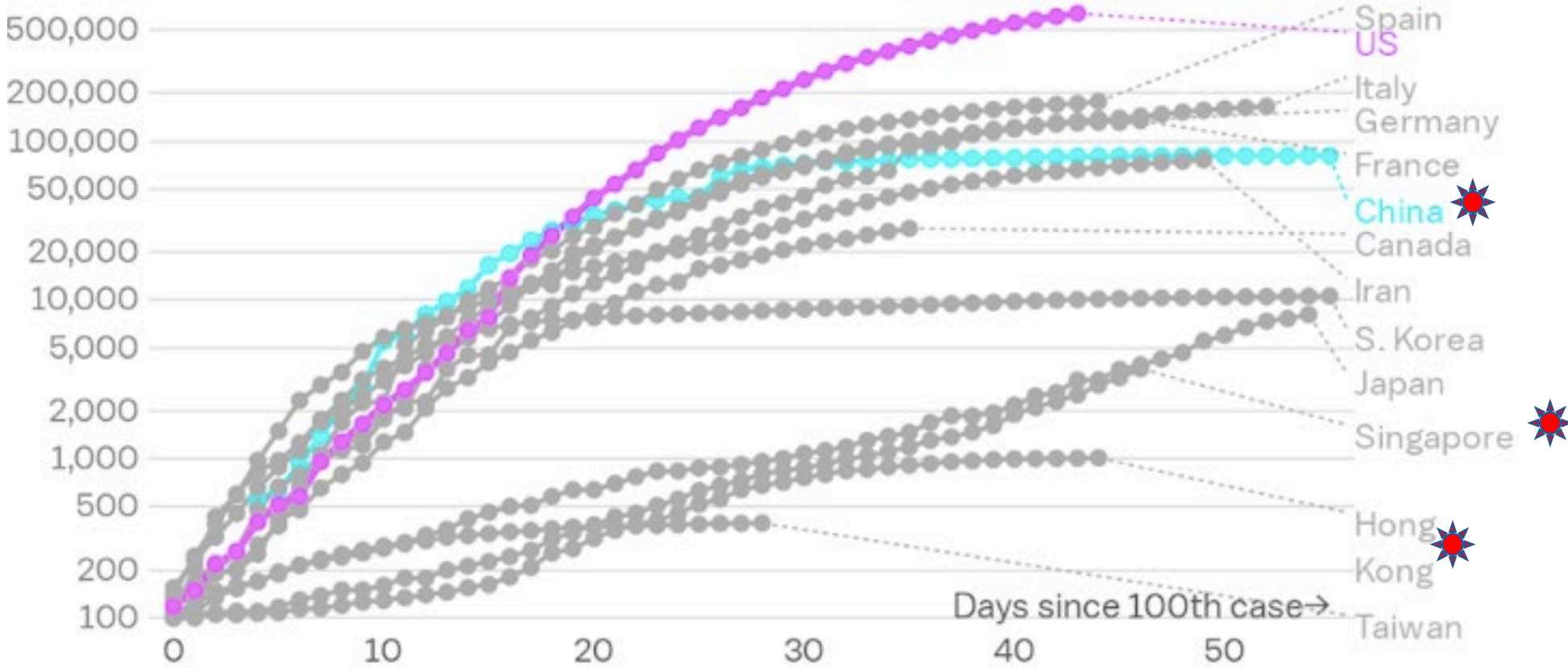
2019 Novel Coronavirus

- COVID-19 illness is due to SARS-CoV-2 virus
- SARS- CoV-2 is a *Betacoronavirus*, like MERS and SARS, most likely originated from bats
- Two human coronaviruses were described in the past and known to cause severe illness.
 - SARS- Cov: Severe Acute Respiratory Syndrome in 2002 in Southern China - 774 deaths globally
 - MERS: Middle East Respiratory Syndrome in 2012 - 858 deaths globally




Electron microscopy from a patient in the US
The National Institute of Allergy and Infectious Diseases
Rocky Mountains Laboratories (RML)

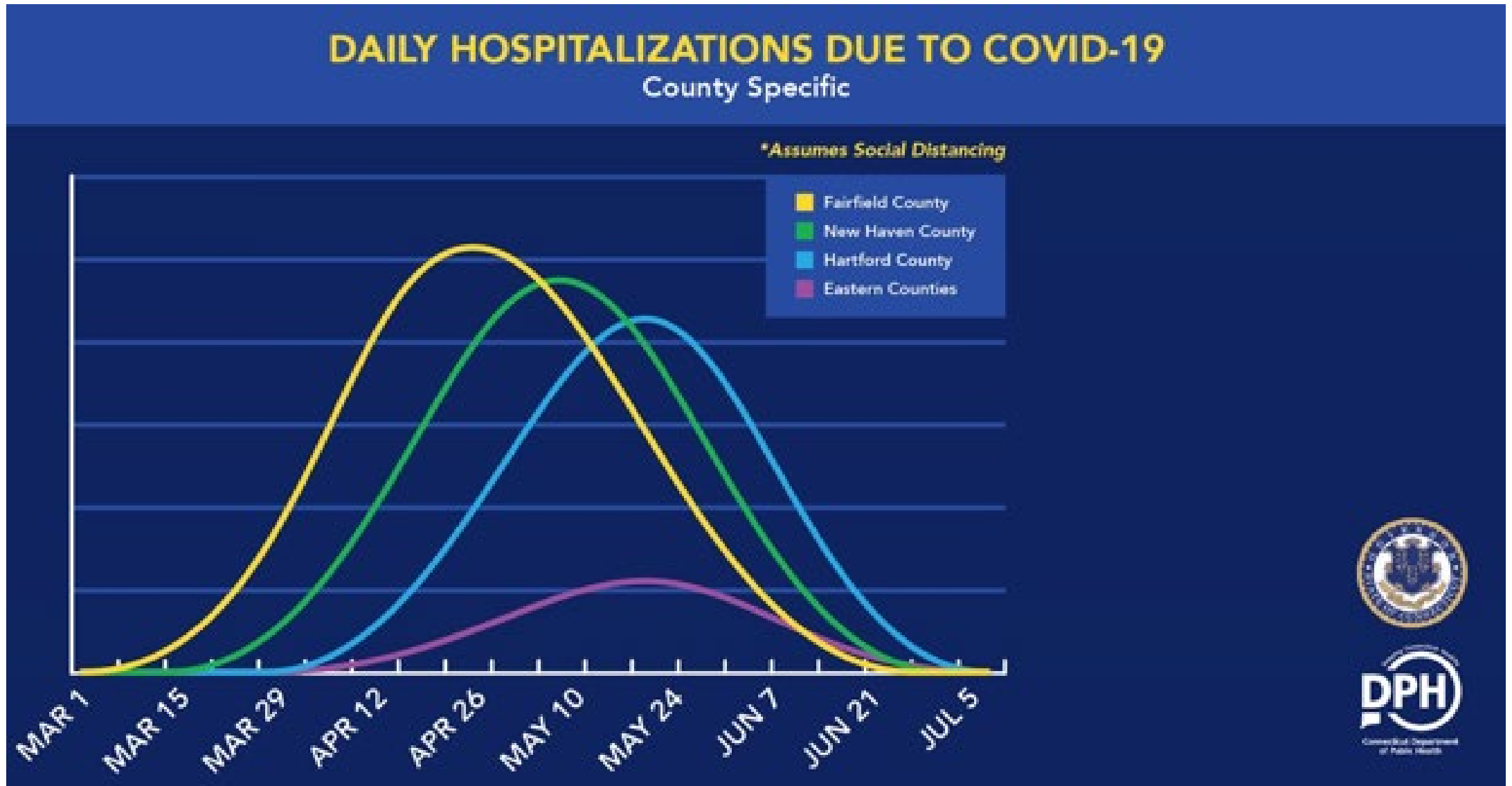
Numbers of Cases Since the First 100 Cases



China data through first 55 days. As of April 15, China had about 83,000 cases. Chart is in log scale to mimic the exponential rate at which the virus spreads.

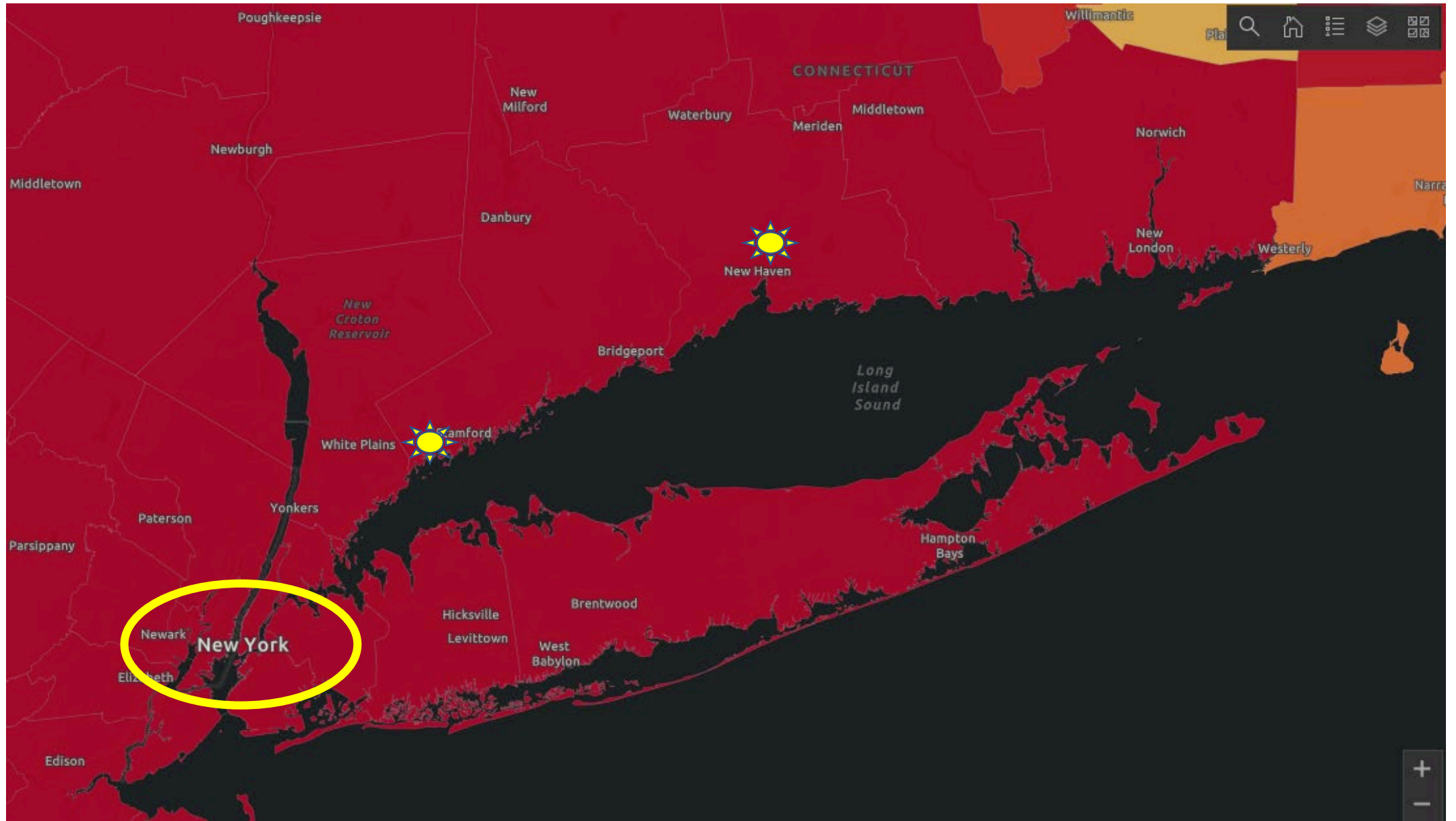
 Relaxed physical distancing, but new outbreaks

Projected CT COVID-19 Surge Timeline

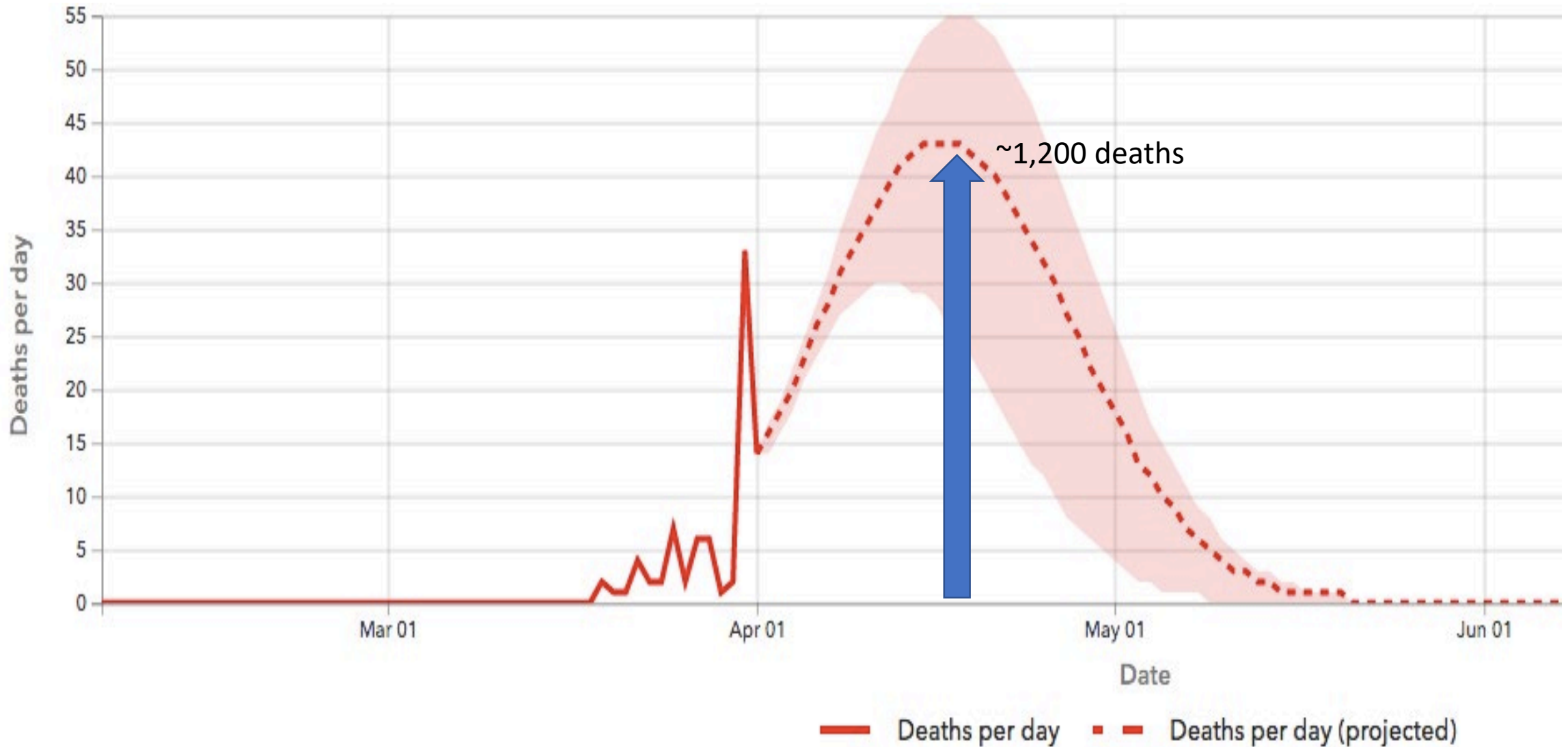


12,000 beds and 4,000 ventilators will be needed to treat COVID-19 patients.

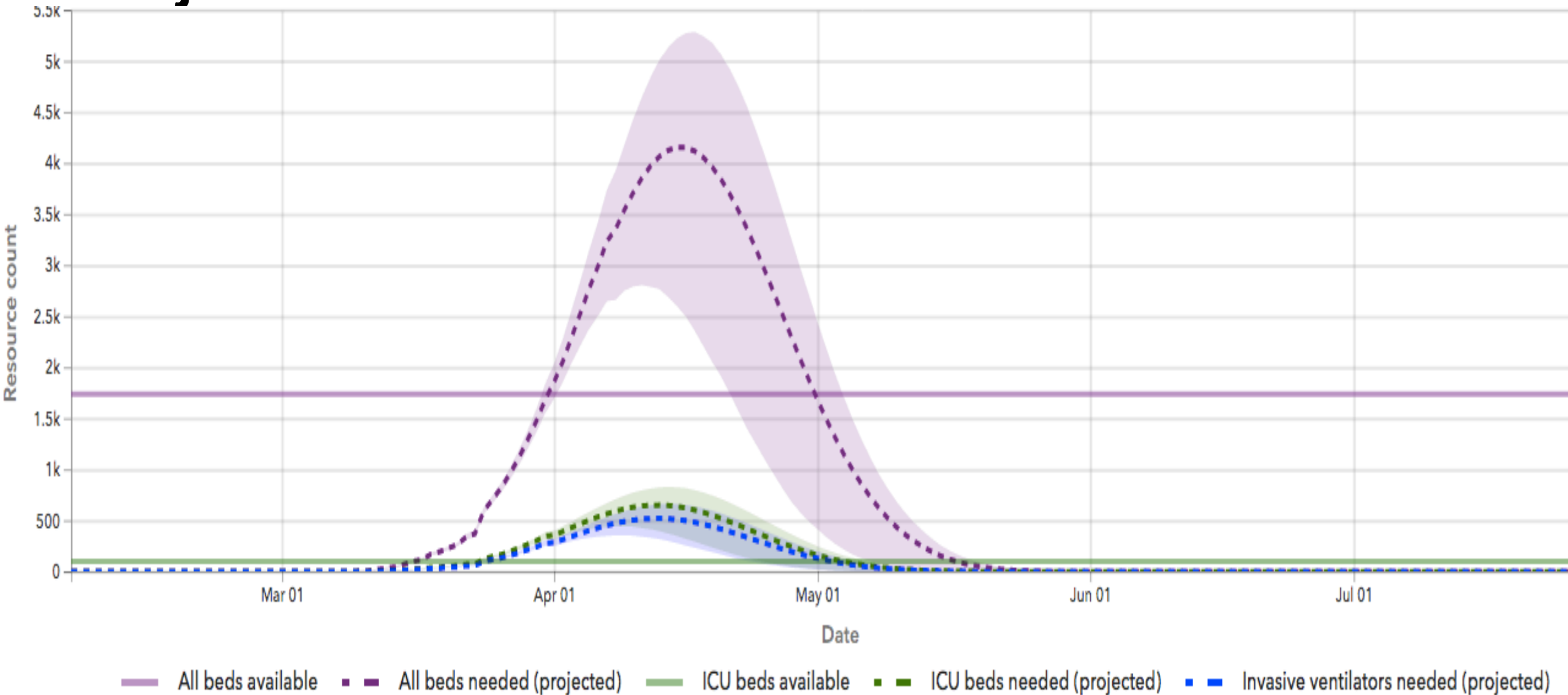
Case Density: New Haven



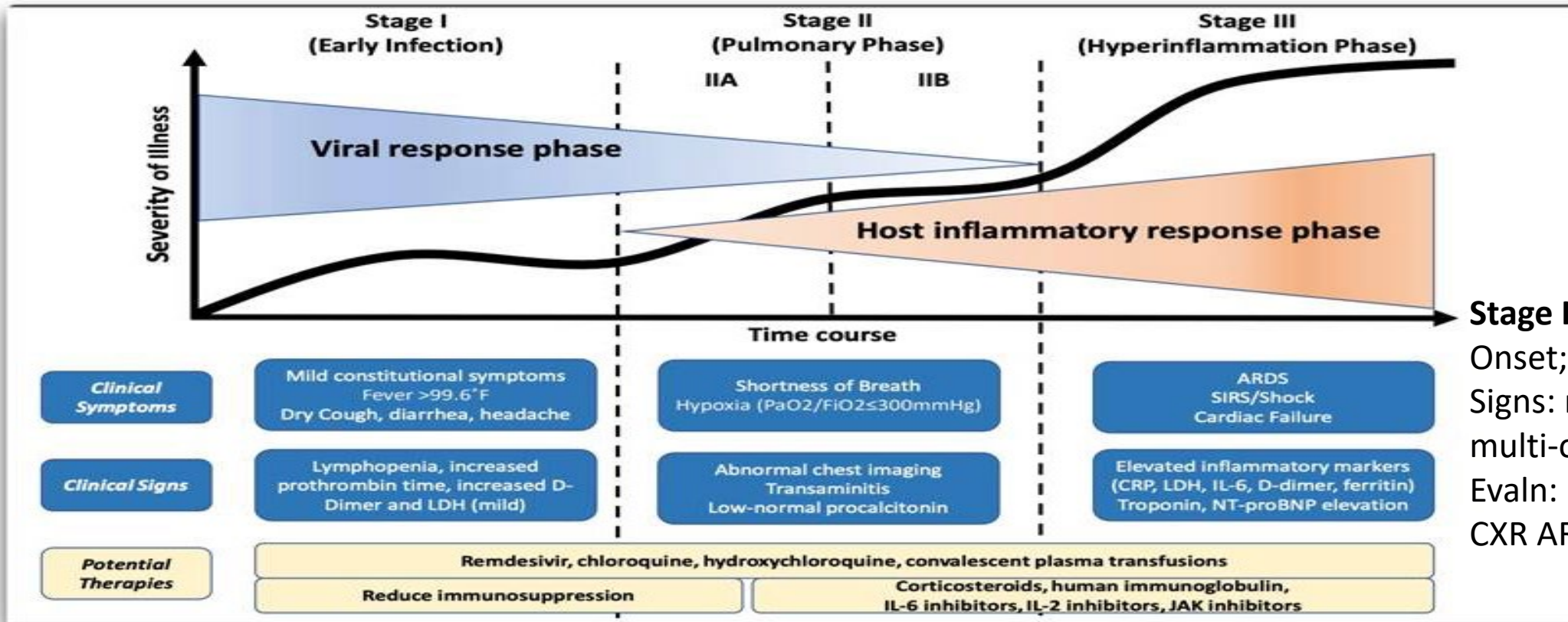
Projected COVID-19 Cases and Death: Connecticut



Projected Beds and ICU Needs: Connecticut



Pathophysiology of COVID-19



Stage III: 7-16 days after sx Onset; no COVID treatment
Signs: respiratory failure, multi-organ failure
Evaln: high CRP and ferritin, CXR ARDS

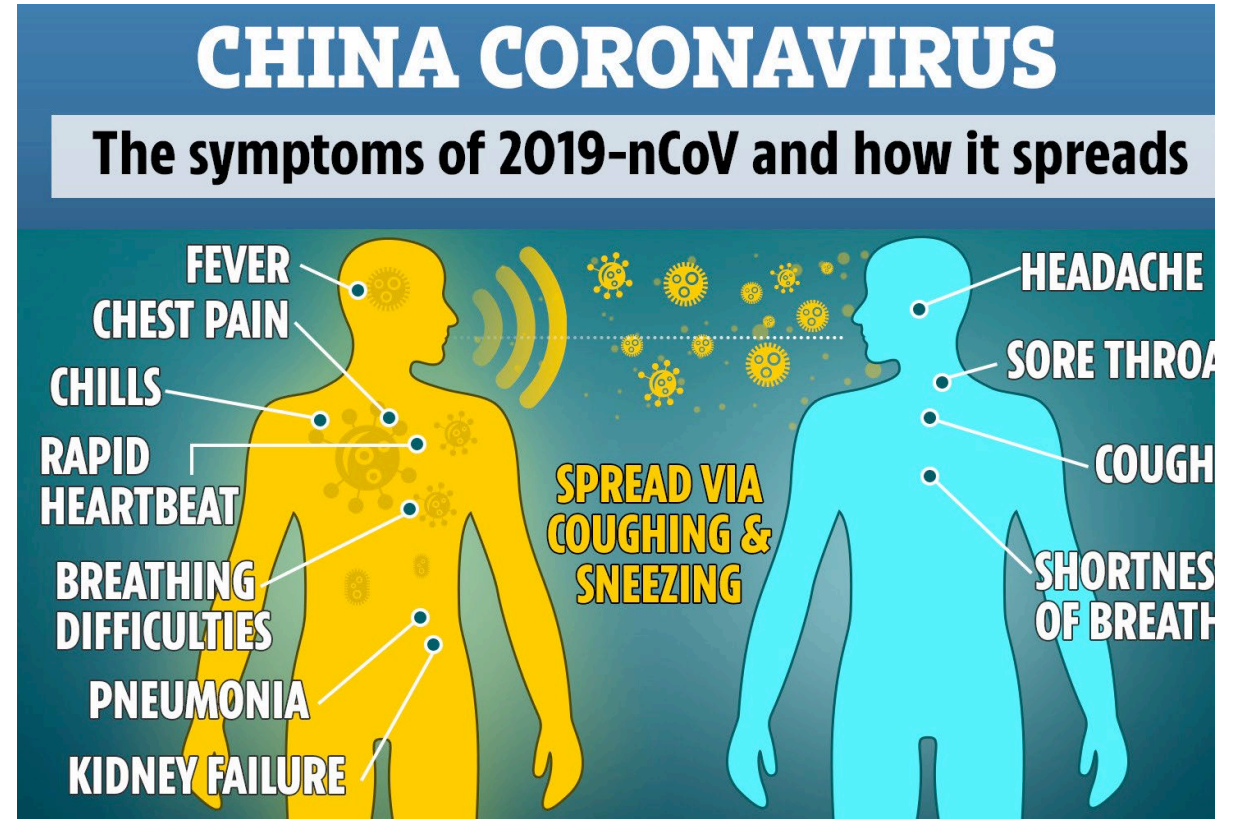
Stage I: Within 5 days symptom Onset
Monitor: fever, resp sx, O₂ satn
Risks: age >60; BMI >30; comorbidities

Stage IIA: 5-10 days after sx onset
Signs: persistent fever, O₂ sat <93% RA, tachypnea
Evaln: CRP>70, abnormal CXR, ferritin, Abs Ly Count <0.8, AST, LDH

Stage IIB: 7-14 days after sx onset
Signs: increasing O₂ requirement, fever
Evaln: CRP jump >20; increasing ferritin, LDH, ALC, CXR worse

Clinical Presentation (EARLY)

Symptoms and complications	N%
Fever	98%
Cough	76%
Myalgia or fatigue	44%
Sputum production	28%
Diarrhea	3%
WBC $\leq 10 \times 10^9/L$	70%
Lymphocytopenia	63%
ALT > 40 U/L	37%
Cr > 133 mmol/L	10%
LDH > 243 U/L	73%
Hypersensitive troponin I > 28 pg/ml	12%
Procalcitonin < 0.1 ng/ml	69%
Acute respiratory distress syndrome	29%



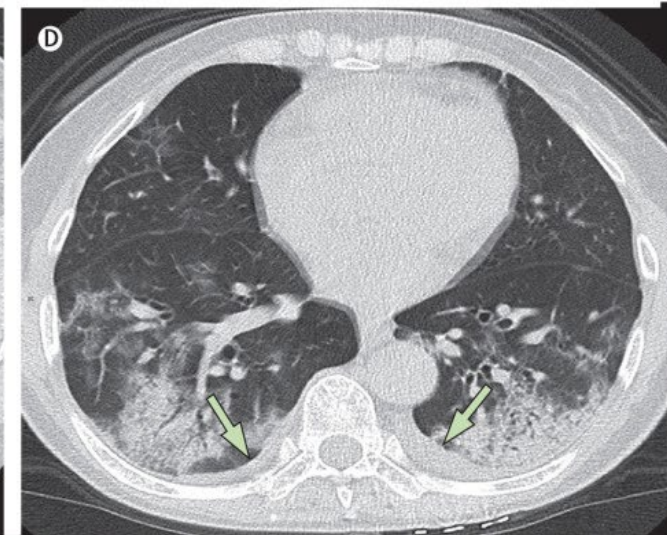
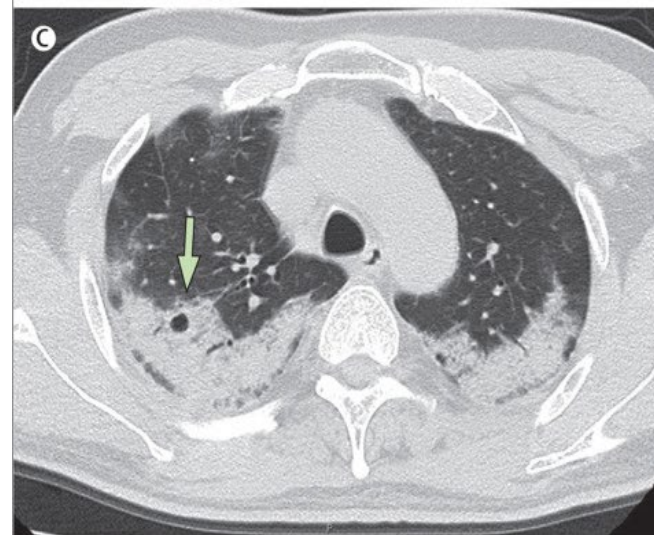
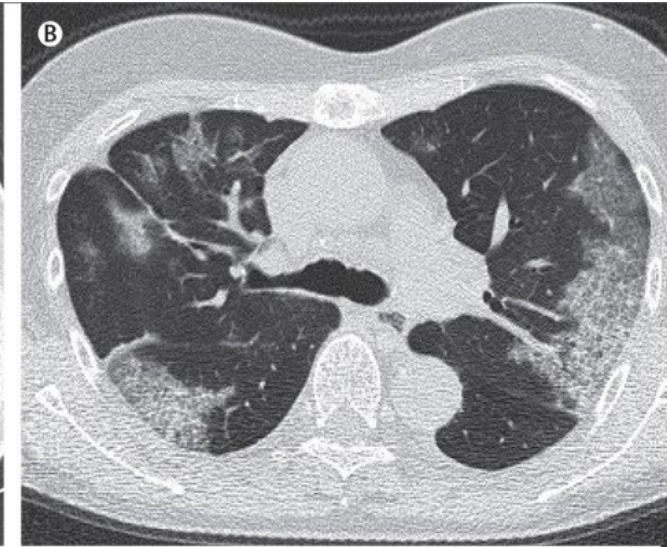
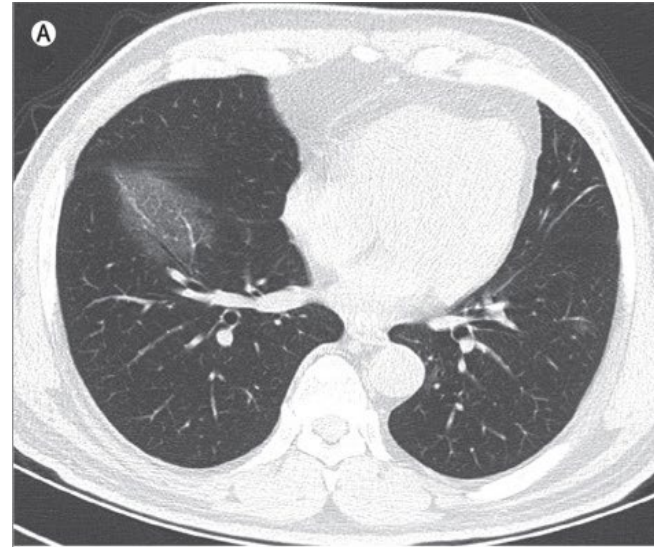
US Experience

- Symptoms vary from the early (viral) and later (CRS) phases
- Fever is present in 50-60% upon presentation, but may get to 85-90% eventually over the course of disease
- GI presentation more common than thought
- Anosmia is very common
- More medical comorbidity in the US
 - Elevated BMI appears to play a major role
 - Diabetes likely major contributor to outcome



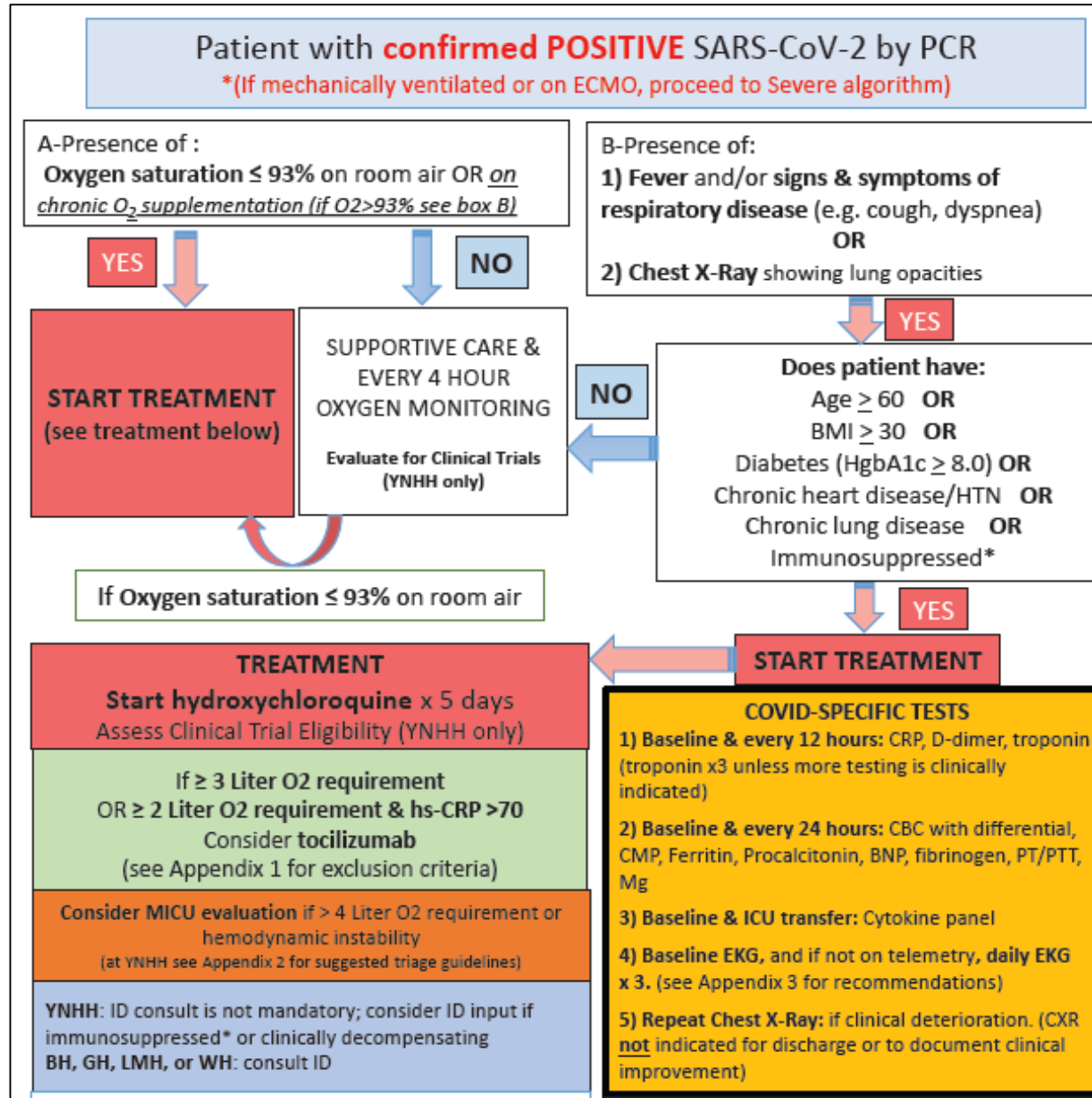
Radiologic Findings

- Peripheral Interstitial changes
- Patchy infiltration
- Bilateral multifocal ground glass opacities
- Lung consolidations
- B-lines

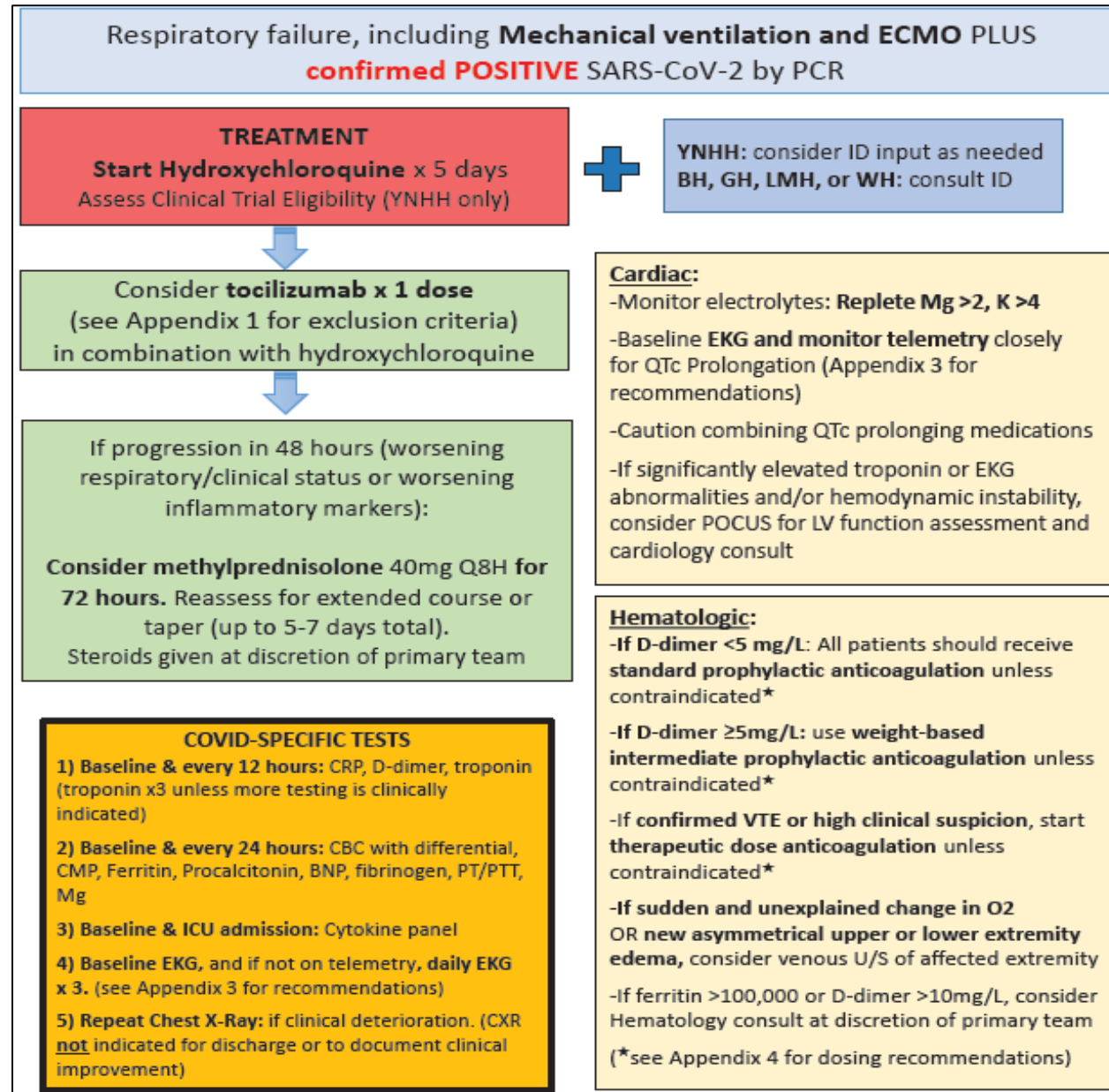


Treatment Strategies

YNHH Treatment Protocol – Non ICU Patients



YNHH Treatment Protocol – ICU Patients



YNHH Recommended Agents

Currently recommended medications for COVID-19 (Subject to change as more data becomes available and based on medication availability)					
Drug	Dose	Mechanism	Rationale for use	Notable Adverse Reactions	Other considerations
Hydroxy-chloroquine (HCQ) ¹⁻⁹	400mg PO q12h x 24h followed by 200mg q12h x 4 days for a 5 day total duration then re-assess	<ul style="list-style-type: none"> Prevents acidification of endosomes interrupting cellular functions and replication Prevents viral entry via ACE2 binding Reduction of viral infectivity Immunomodulator 	<ul style="list-style-type: none"> In-vitro data shows potent SARS-COV-2 inhibition and early clinical data shows possible benefit HCQ was found more potent than chloroquine in inhibiting SARS-CoV-2 in vitro 	<ul style="list-style-type: none"> QTc prolongation Rash Retinopathy is rare (Baseline eye exam is not required for use for COVID-19) 	<ul style="list-style-type: none"> There is a theoretical potential for an increase in hydroxychloroquine levels when used with atazanavir therefore <i>monitor for possible QTc prolongation</i> For patients with NG/OG/NT hydroxychloroquine can be crushed for enteral administration Therapy can be extended past 5 days based on patient's clinical response, but should not exceed 10 total days
IMMUNOMODULATING AGENTS					
Tocilizumab ¹⁰⁻¹³	8mg/kg IV x 1 dose (actual body weight); dose max 800 mg)	<ul style="list-style-type: none"> Monoclonal antibody to IL6 receptor 	<ul style="list-style-type: none"> IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease Retrospective data suggest possible benefit (clinical trials ongoing) 	<ul style="list-style-type: none"> Headache Elevated liver enzymes Infusion reactions (e.g. flushing, chills) 	<ul style="list-style-type: none"> The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time Additional doses not indicated at this time

Efficacy of hydroxychloroquine in patients with COVID-19: Results of a randomized clinical trial (N=62)

Group	All	Exacerbated	Unchanged	Improved		
				Moderate	Significant	Total
All	62	11 (17.7 %)	9 (14.5 %)	18 (29.0 %)	24 (38.7 %)	42 (67.7 %)
Control, n (%)	31	9 (29.0 %)	5 (16.1%)	12 (38.7 %)	5 (16.1%)	17 (54.8%)
HCQ, n (%)	31	2 (6.5 %)	4 (12.9 %)	6 (19.4%)	19 (61.3%)	25 (80.6%)
P value	0.0476					

Hospitalized Patients with confirmed COVID-19 with mild pneumonia or non-severe infection treated with HCQ for 5 days

- Decrease clinical progression and pneumonia (radiological progression on CT scan)
- Decrease time to clinical recovery

Note: all 62 pts received SOC (antivirals, steroids, Igs, O2, abx) +/- additional HQ

No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial

Table 2: Primary and secondary outcomes. Weighted proportions, RRs and 95% CIs were obtained by inverse probability treatment weighting. *two missing data were removed from analysis. Abbreviations: CI, confidence interval; ICU, intensive care unit.

	HCQ (n=84)		No HCQ (n=97)		RR (95% IC)
	Raw	Weighted proportion	Raw	Weighted proportion	
Death or transfer to ICU	16/84 (19.0)	20.5	21/97 (21.6)	22.1	0.93 (0.48 to 1.81)
Day 7 mortality	3/84 (3.6)	2.8	4/97 (4.1)	4.6	0.61 (0.13 to 2.90)
Occurrence of acute respiratory distress syndrome*	24/84 (28.6)	27.7	23/95 (24.2)	24.1	1.15 (0.66 to 2.01)



QTc monitoring for COVID-19 Patients

1. Baseline

- a. Discontinue and avoid all other non-critical QT prolonging agents.
- b. Assess a baseline ECG, renal function, hepatic function, serum potassium and serum magnesium.
- c. When possible, have an experienced cardiologist/electrophysiologist measure QTc, and seek pharmacist input in the setting of acute renal or hepatic failure.

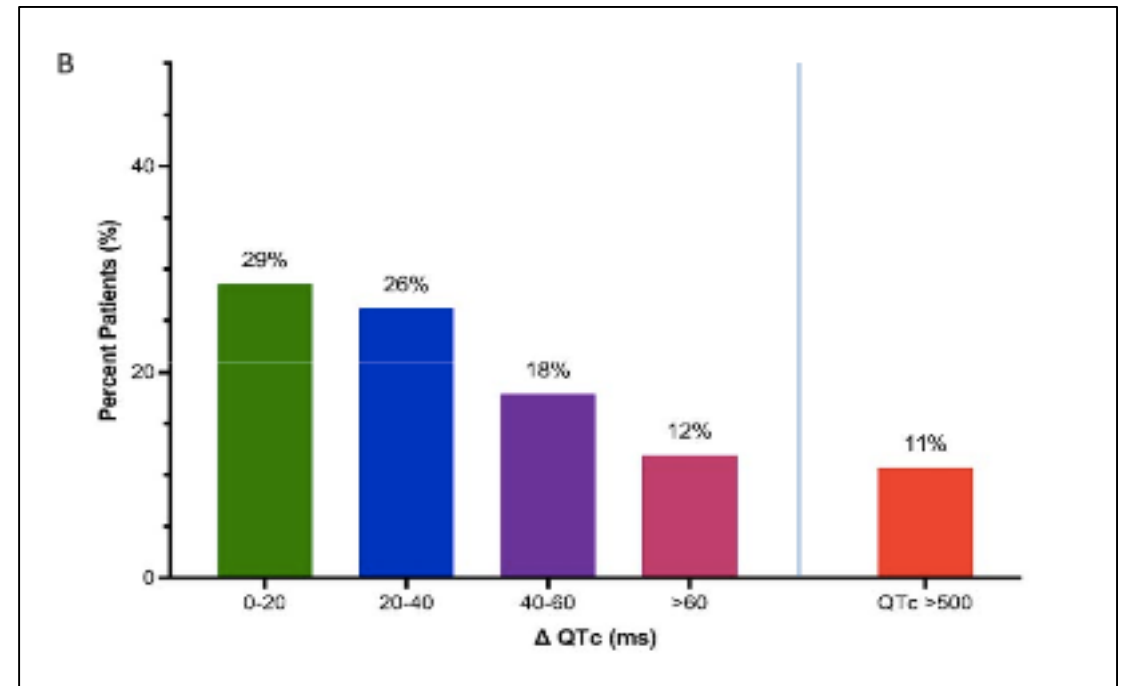
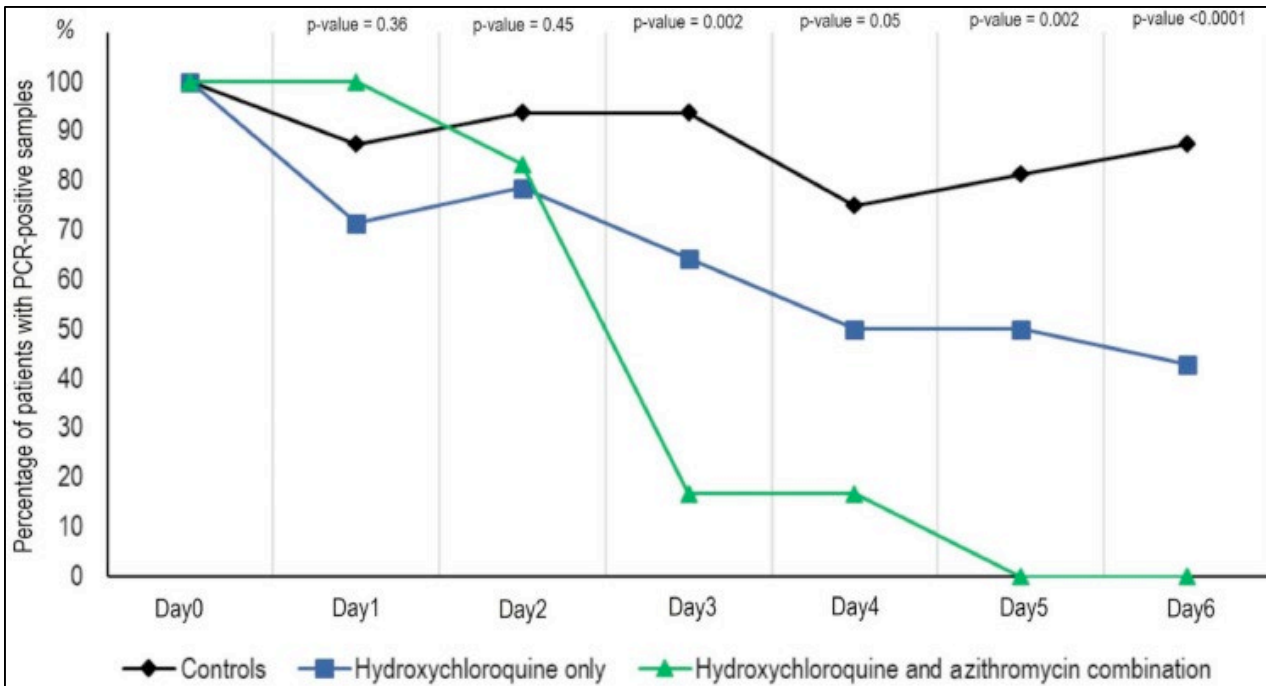
2. Relative contraindications (subject to modification based on potential benefits of therapy)

- a. History of long QT syndrome, or
- b. Baseline QTc >500 msec (or >530-550 msec in patients with QRS greater than >120 msec)

3. Ongoing monitoring, dose adjustment and drug discontinuation

- a. Place on telemetry prior to start of therapy.
- b. Monitor and optimize serum potassium daily.
- c. Acquire an ECG 2-3 hours after the second dose of hydroxychloroquine, and daily thereafter.
- d. If QTc increases by >60 msec or absolute QTc >500msec (or >530-550 msec if QRS >120 msec), discontinue azithromycin (if used) and/or reduce dose of hydroxychloroquine and repeat ECG daily.
- e. If QTc remains increased >60 msec and/or absolute QTc >500 msec (or >530-550 msec if QRS >120 msec), reevaluate the risk/benefit of ongoing therapy, consider consultation with an electrophysiologist, and consider discontinuation of hydroxychloroquine.

Efficacy of HCQ + Azithromycin in patients with COVID-19: Results of a small clinical trial



Hospitalized Patients with confirmed COVID-19

- Decrease viral carriage
- Concern for prolonged QTc

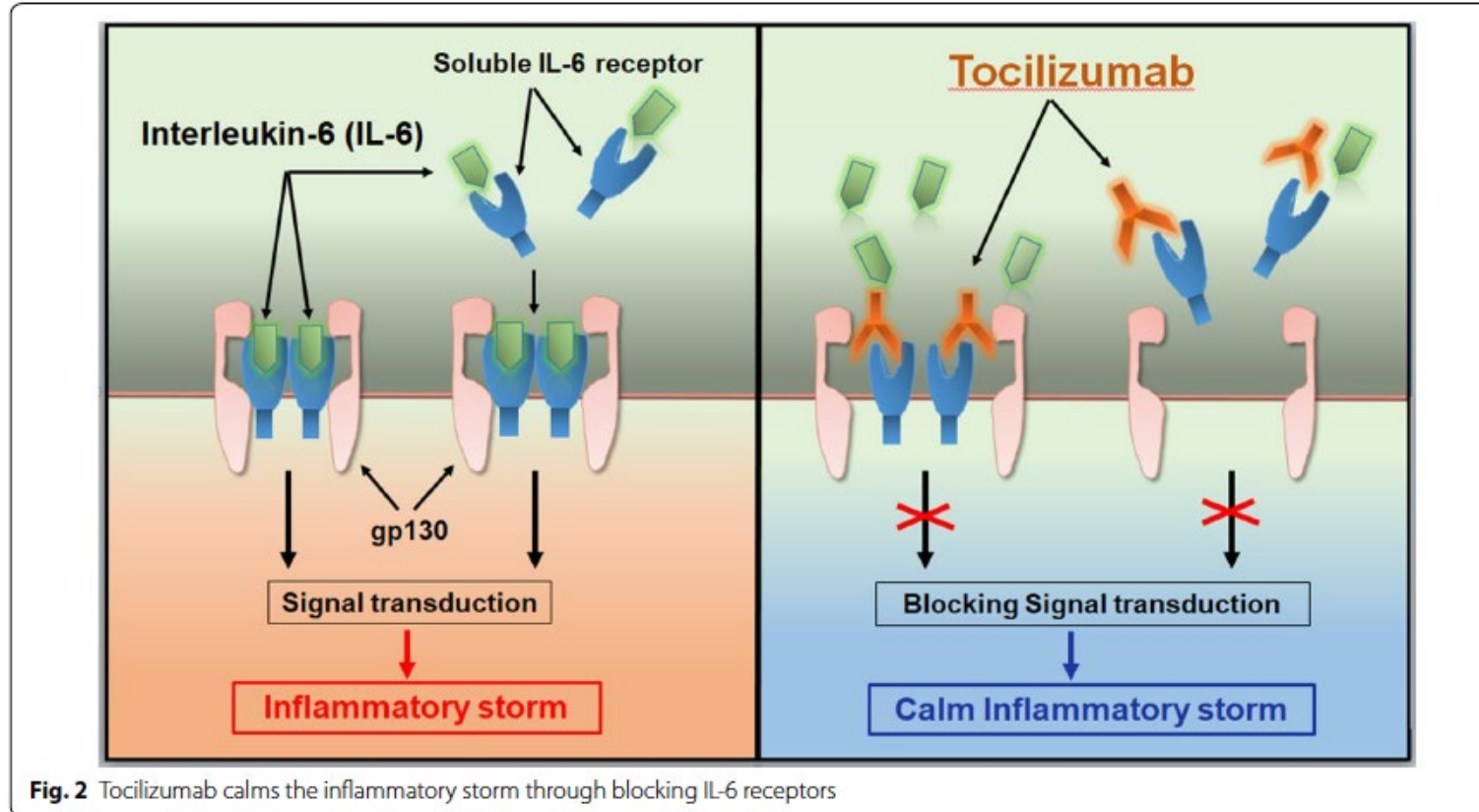
Efficacy of HCQ and AZ in patients with COVID-19: Summary of clinical trial

	Study type (number of patients)	Treatment	Duration	Control group (number of patients)	Primary outcome	Clinical outcomes	ICU patients (n/N)	Adverse events (n/N)	Mortality (n/N)
Gautret et al ⁸	Prospective open-label, non-randomised trial (n=42)	Hydroxychloroquine (200 mg every 8 h) alone (n=14) or with azithromycin (500 mg on day 1, 250 mg on days 2-5; n=6)	10 days	Yes (n=16)	Viral load (nasopharyngeal swab): presence or absence of SARS-CoV-2 at day 6	NR	0/36	NR	0/36
Gautret et al ⁹	Prospective observational study (n=80)	Hydroxychloroquine (200 mg every 8 h) and azithromycin (500 mg on day 1, 250 mg on days 2-5)	10 days	No	Disease progression: need for oxygen or ICU admission	Viral load, hospital length of stay	3/80	7/80	1/80
Chen et al ¹²	RCT (n=30)	Hydroxychloroquine (200 mg every 12 h)	7 days	Yes (n=15)	Viral load (nasopharyngeal swab): presence of SARS-CoV-2 at day 7	NR	0/30	4/15	0/30
Chen et al ¹³	RCT (n=62)	Hydroxychloroquine (200 mg every 12 h)	5 days	Yes (n=31)	Time to clinical recovery	Pulmonary recovery, adverse events	0/62	2/31	0/62
Molina et al ¹⁴	Prospective observational study (n=11)	Hydroxychloroquine (200 mg every 8 h) and azithromycin (500 mg on day 1, 250 mg on days 2-5)	10 days	No	Viral load (nasopharyngeal swab): presence of SARS-CoV-2 on days 5-6	NR	2/11	1/11	1/11

COVID-19=coronavirus disease 2019. ICU=intensive care unit. NR=not reported. RCT=randomised controlled trial. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table: Clinical studies of hydroxychloroquine in patients with COVID-19

Tocilizumab for the Treatment of SARS-CoV-2

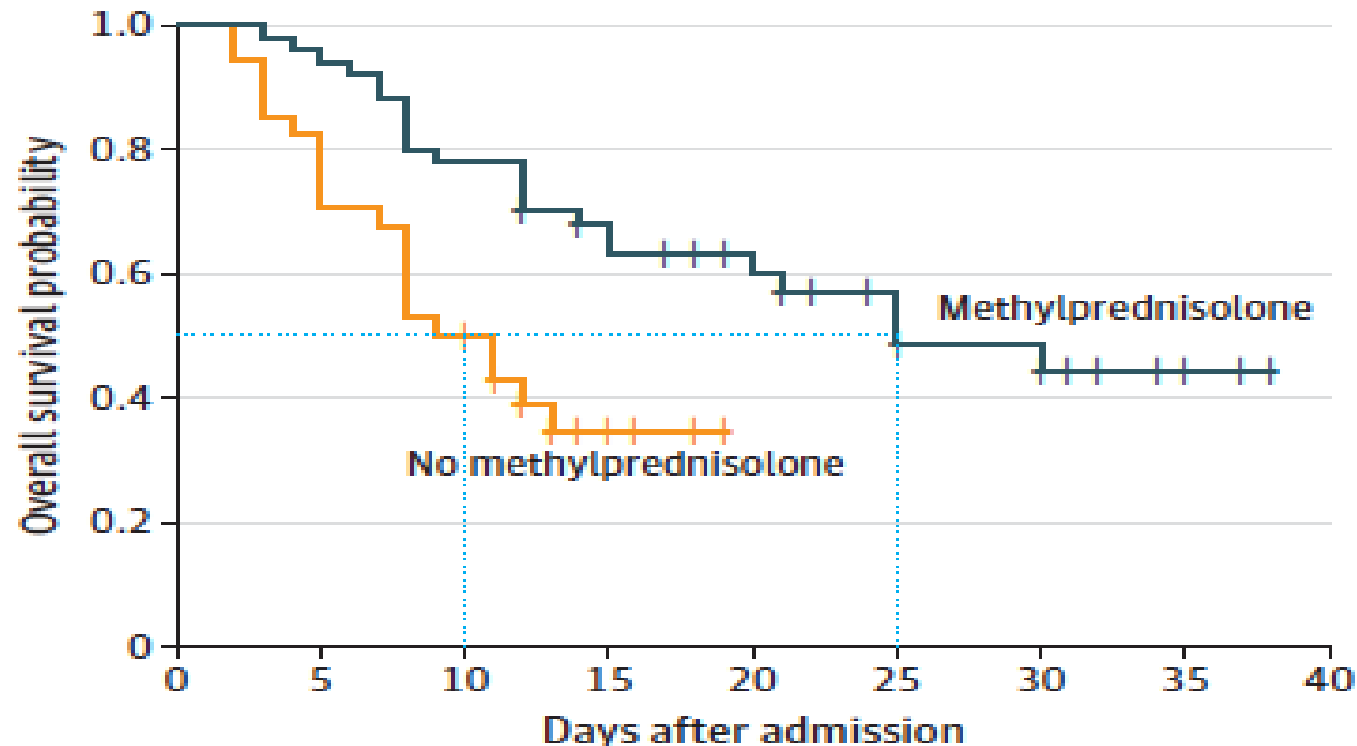


Small study 21 severe or critical patients with COVID-19 treated with tocilizumab, an IL-6 blocker

- 20/21 requiring O₂
- 19 (90.5%) survival rate

Methylprednisolone in Patients with Severe Disease

Figure. Survival Curve in Patients With Acute Respiratory Distress Syndrome Who Did and Did Not Receive Methylprednisolone Treatment



62%
reduction
in
mortality

No. at risk

No methylprednisolone	34	28	17	4	0	0	0	0	0
Methylprednisolone	50	48	39	29	20	14	11	4	0

WORKFLOW ISSUES

Strategies

- Cohorting COVID-19 patients
- Limiting staff who enter rooms – consultations!
- Opening up non-essential rooms
- Early DNR/CMO discussions
- Mechanically ventilated patients do not get CPR
- Proning of patients to reduce intubation risk

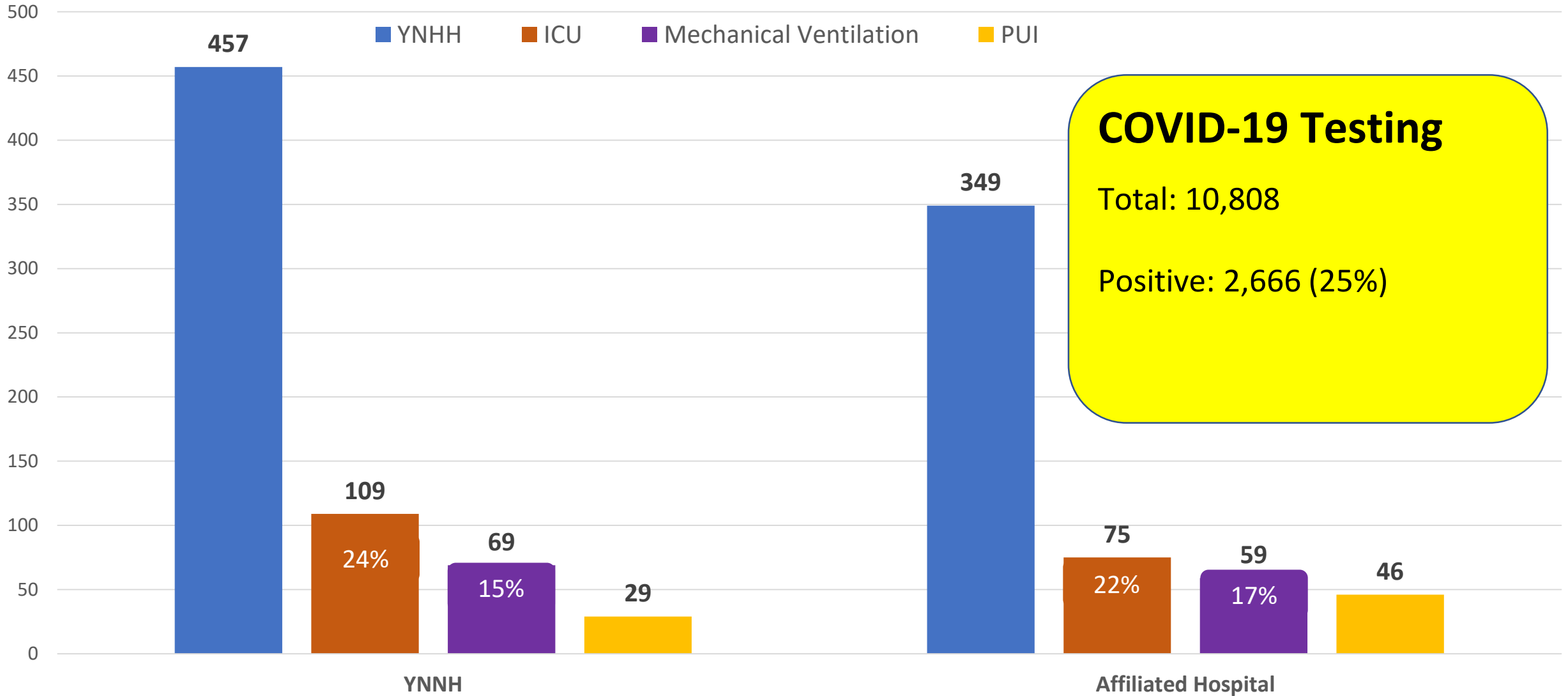
YNHH Discharge Guidelines- Clinical Criteria

Clinical Criteria:

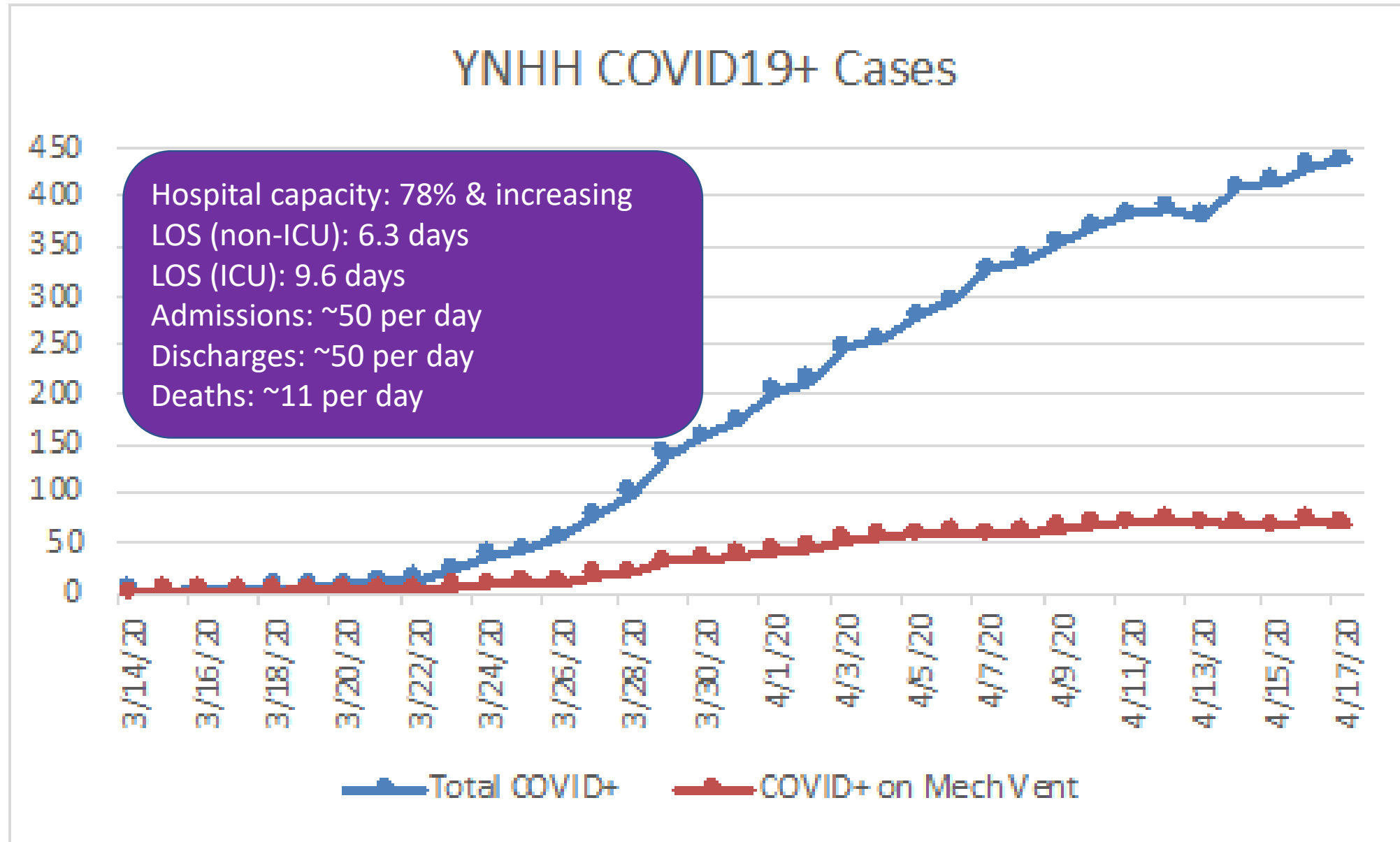
- 1) Afebrile > 48 hours prior to discharge, OFF of anti-pyretics
- 2) Stable oxygen saturation x 48h, on no more than 2LPM of O2 continuous
 - a. If on O2 at baseline, should be within 1-2LPM of baseline rate; no more than 5LPM continuous
- 3) Stable or improving inflammatory markers (CRP, absolute lymphocyte count are priorities; Other markers like Ferritin may lag). Values do NOT need to have normalized prior to discharge.
- 4) Other clinical variables improved as relevant
- 5) Access to prompt outpatient follow up
 - a. Utilization of PCP
 - b. Utilization of COVID Tele Inpatient Follow Up clinic as available
- 6) Home care/Self Isolation instructions reviewed with patient, understanding verbalized. Written instructions (from Epic Clinical References) provided as well.

YNHH Experience

Inpatient Case-Load: April 17, 2020



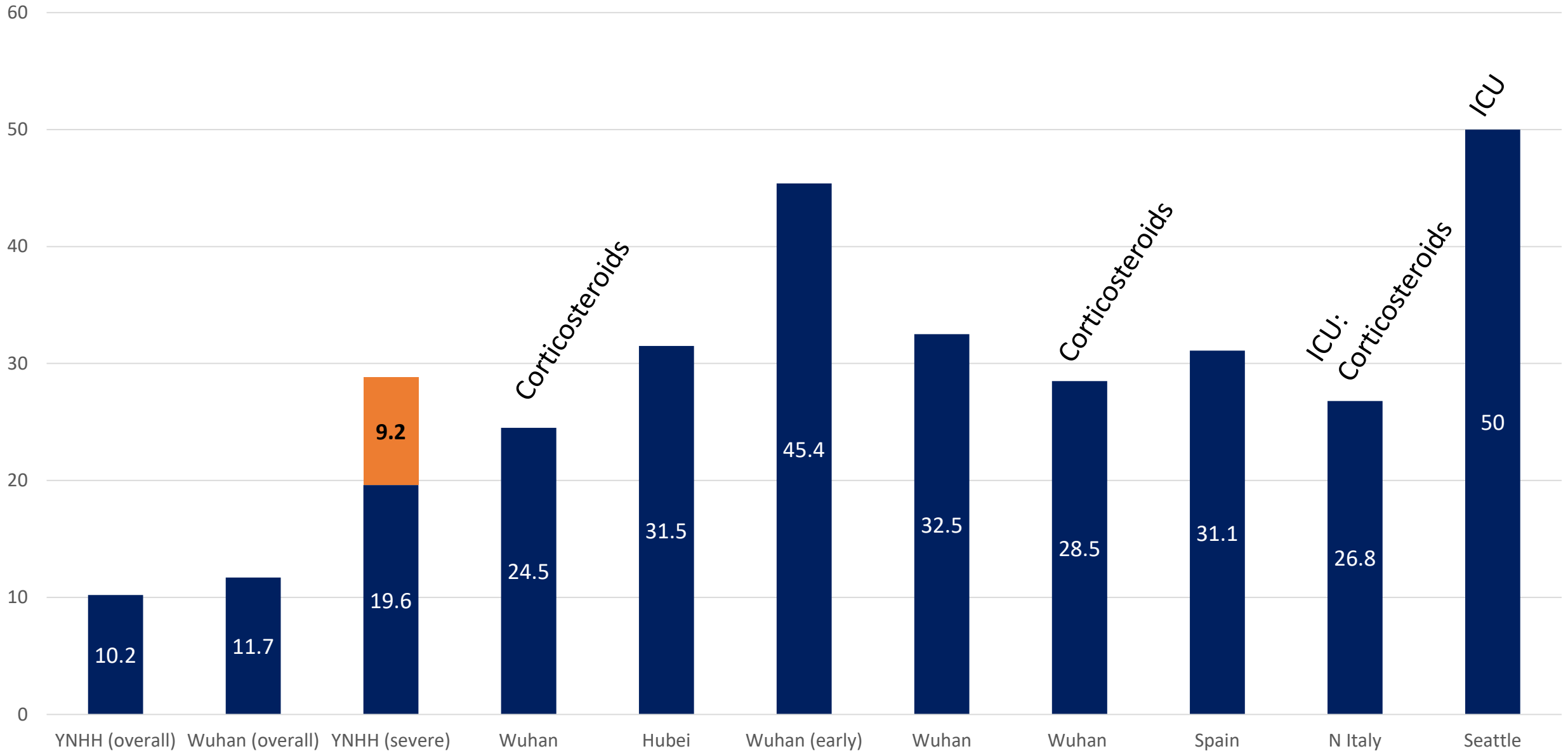
Daily Snapshot at YNHH



Patient Characteristics (N=257)

- Stratification
 - Severe: 112 (44%) → 90 (80%) received tocilizumab
 - Moderate: 145 (56%) → 57 (39%) received tocilizumab
- Mean age: 64 years
- Mortality: 25 (9.7%) died (10.9 vs 8.2%; p=ns)
- No differences in mortality based on race or medical comorbidity
- There were changes in response based on age – higher mortality reductions with age >70 years
- Survival reductions in patients with more severe disease

Mortality in Patients with Severe COVID-19

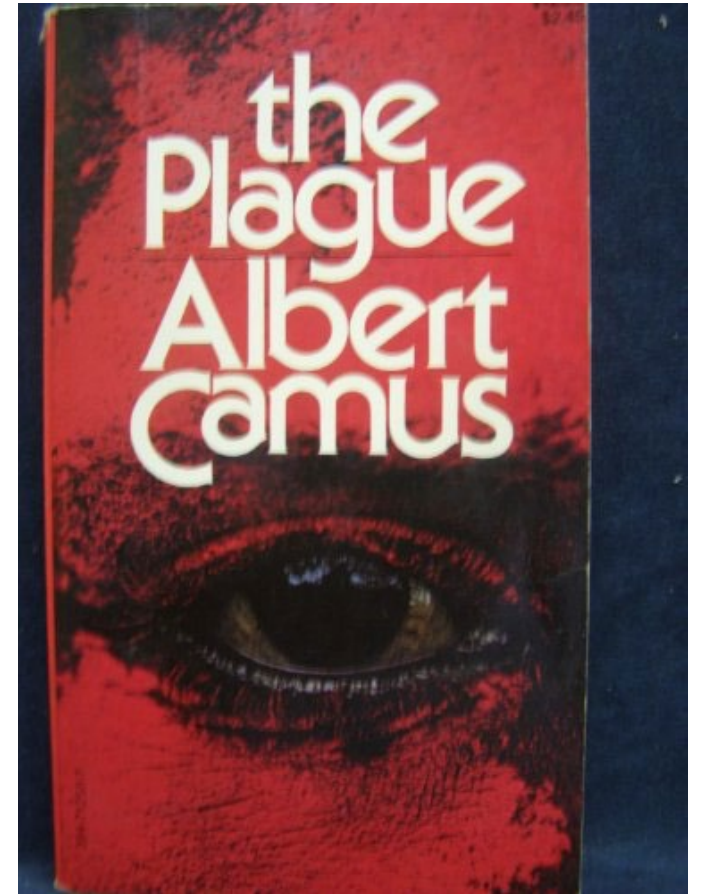


Reflections on the Pandemic?



What a long strange
trip it's been.

Jerry Garcia



Thoughts from the Plague - Camus

- Recall from sabbatical: “Nothing in the world is worth turning one's back on what one loves.”
- First few days on service: “I have no idea what's awaiting me, or what will happen when this all ends. For the moment I know this: there are sick people and they need curing.”
- Watching my colleagues and watching the news: “There are more things to admire in men [and women] than to despise.”
- As the number of patients burgeons: “What’s true of all the evils in the world is true of plague as well. It helps men [and women] to rise above themselves.”
- Every morning: “I was very fond of you, but now I’m so, so tired. I’m not happy to go, but one needn't be happy to make another start.”