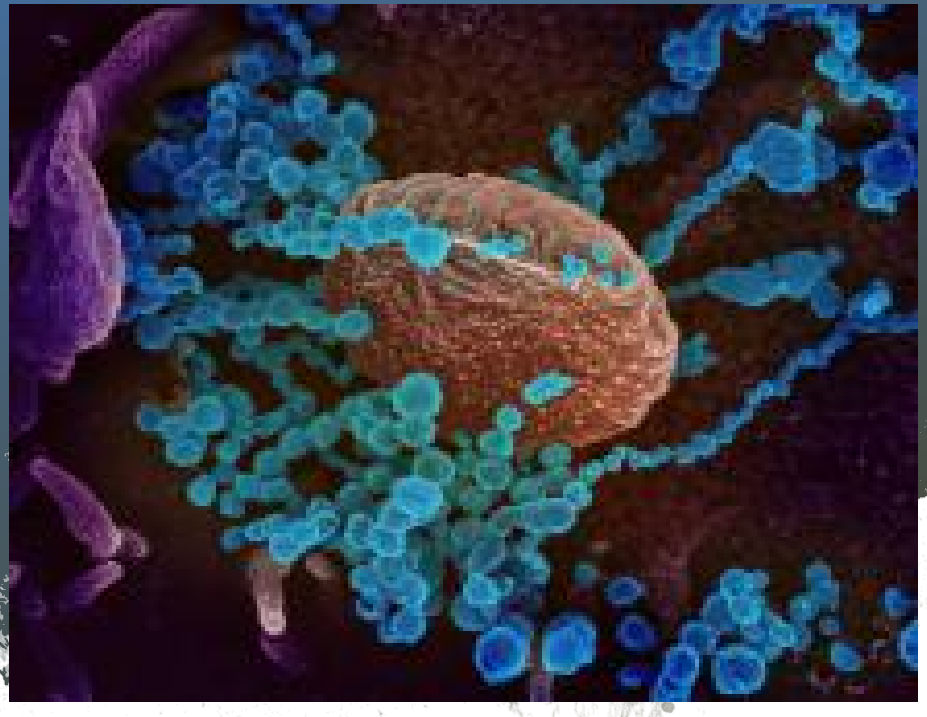
COVID-19
2020



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Disclosure

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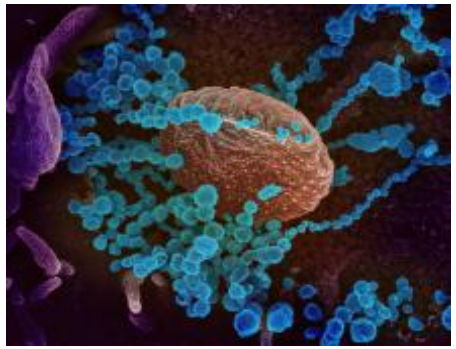
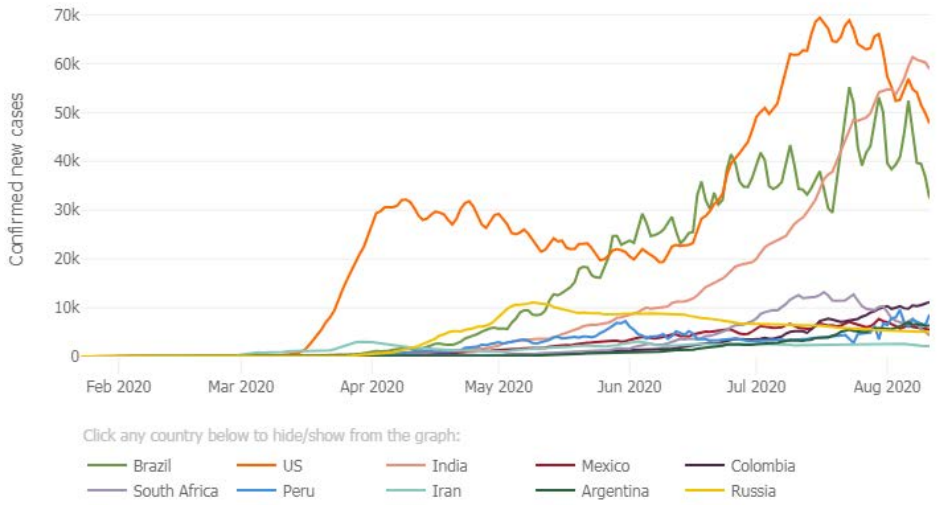
  - **Other:** Employee of Mass General Brigham Healthcare Inc (owner of MGH)



Daily confirmed new cases
Outbreak evolution for the current 10 most affected countries
Johns Hopkins Coronavirus Resource Center



CASES: >50 MILLION
DEATHS: >1,200,000
189 Countries

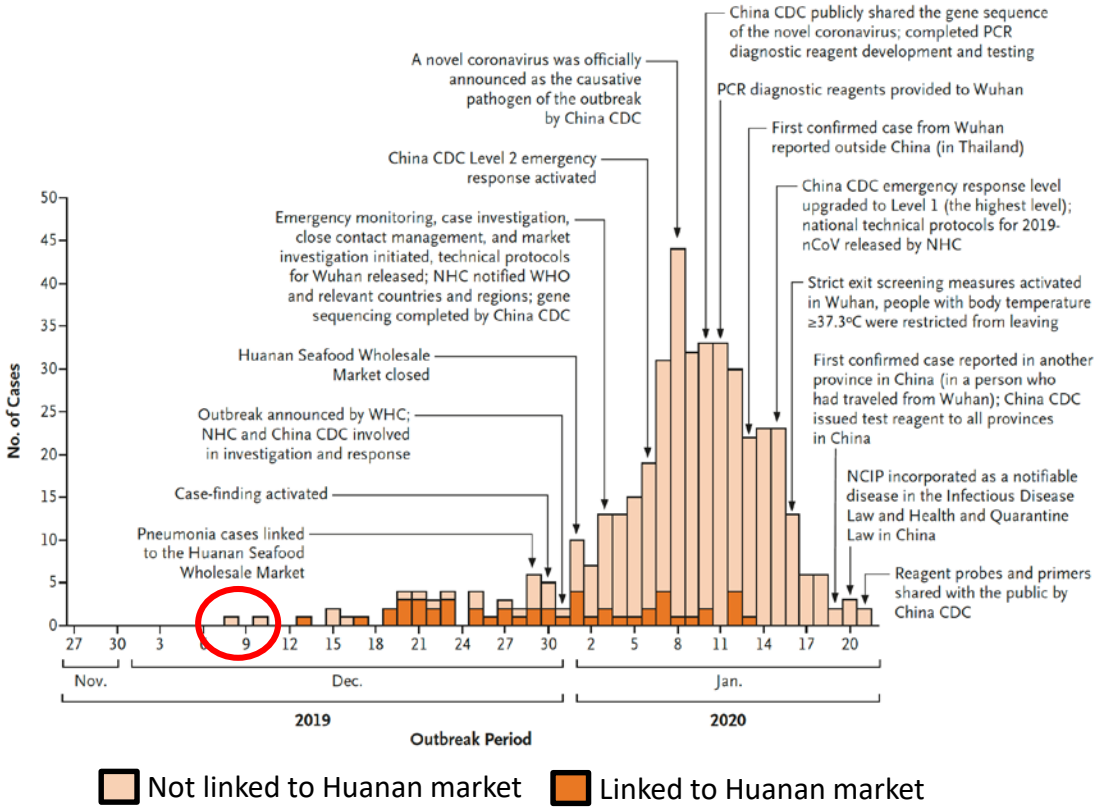
Thanks to the many healthcare workers who have dedicated themselves to caring for the thousands of COVID-19 patients.

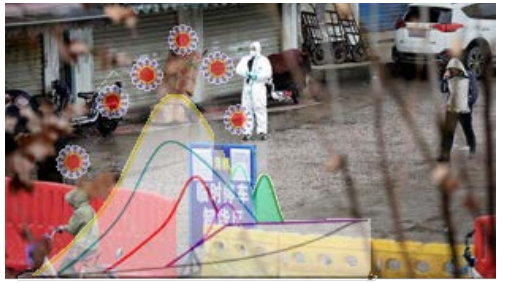
Completely (and permanently) altered many aspects of medicine

- **Many patients avoiding routine and essential care**
- **Reduced elective procedures**
- **New COVID-19 screening requirements for admissions**
- **Limitations posed by need for PPE (Facetime rounds)**
- **Overflowing ICU's (487 at MGH) -** interdisciplinary care
- **Nosocomial infections**
- **Virtual visits**
- **Remote** Medical-Surgical Screening, Bloodwork, Multidisciplinary evaluations
- **Newer technologies**: Remote PaO2, EKG, spirometry, chest examination

What is the role of the Huanan Market?

- Cluster of novel viral pneumonias from *common* source
- Crowding during preparations for festivities *synchronized* transmission
- Human-to-human transmission *at least* since 12/2019 (Patient Zero?)





Incubation time = 5.2 days (*95% CI 4.1 – 7.0*)

Doubling time t_2 = 7.4 days

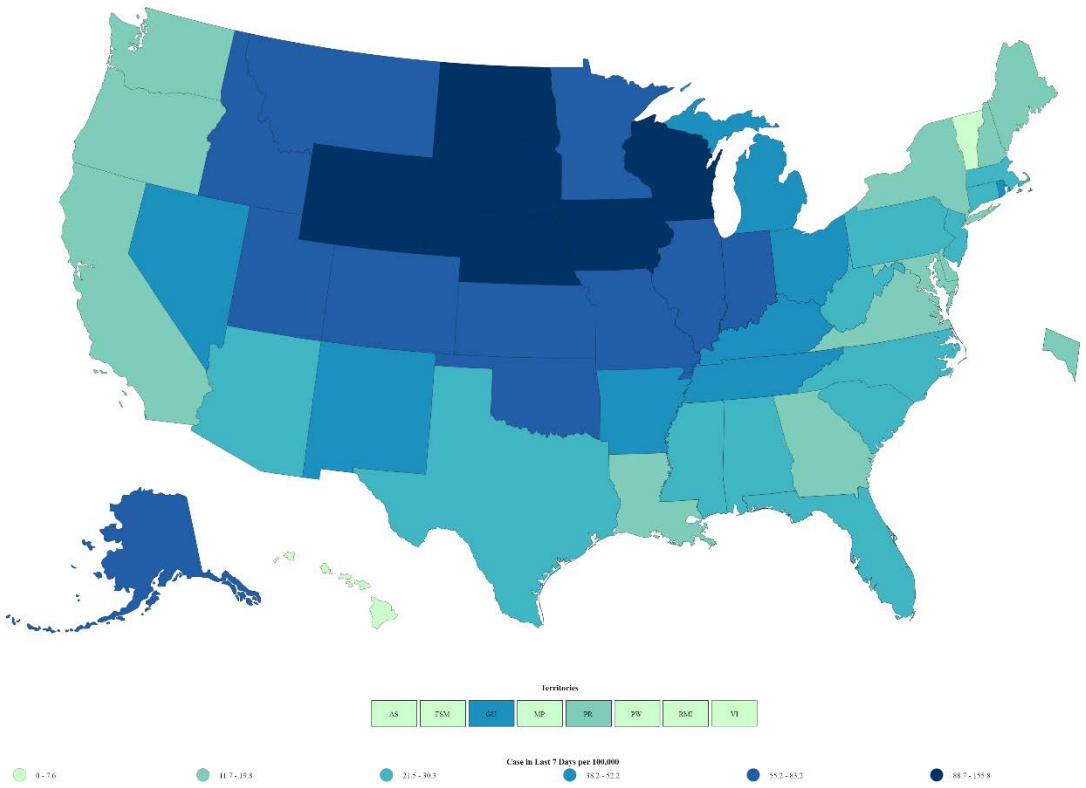
Reproductive R_0=2.2 (*95%CI 1.4 - 3.9*)

Li Q et al (2020) *Early Transmission Dynamics in Wuhan…* NEJM: doi.org/10.1056/NEJMoa2001316

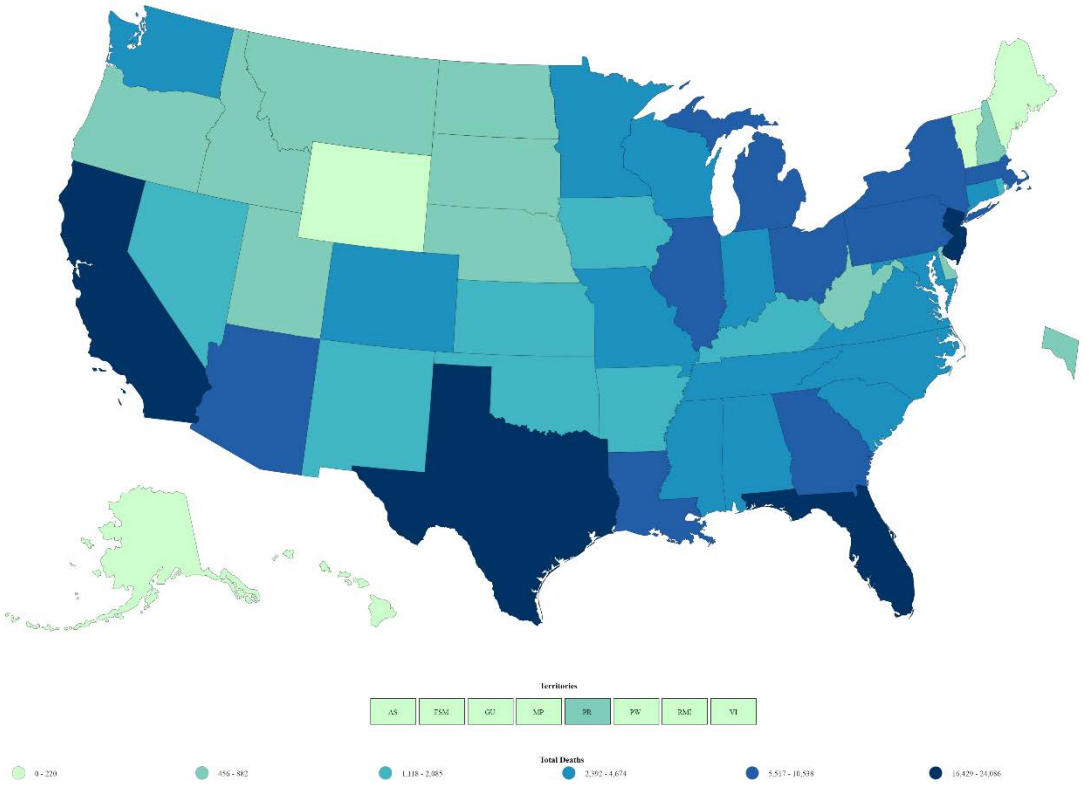
COVID-19 Worldwide

CDC: US COVID-19 Tracker

Cases (7 days)



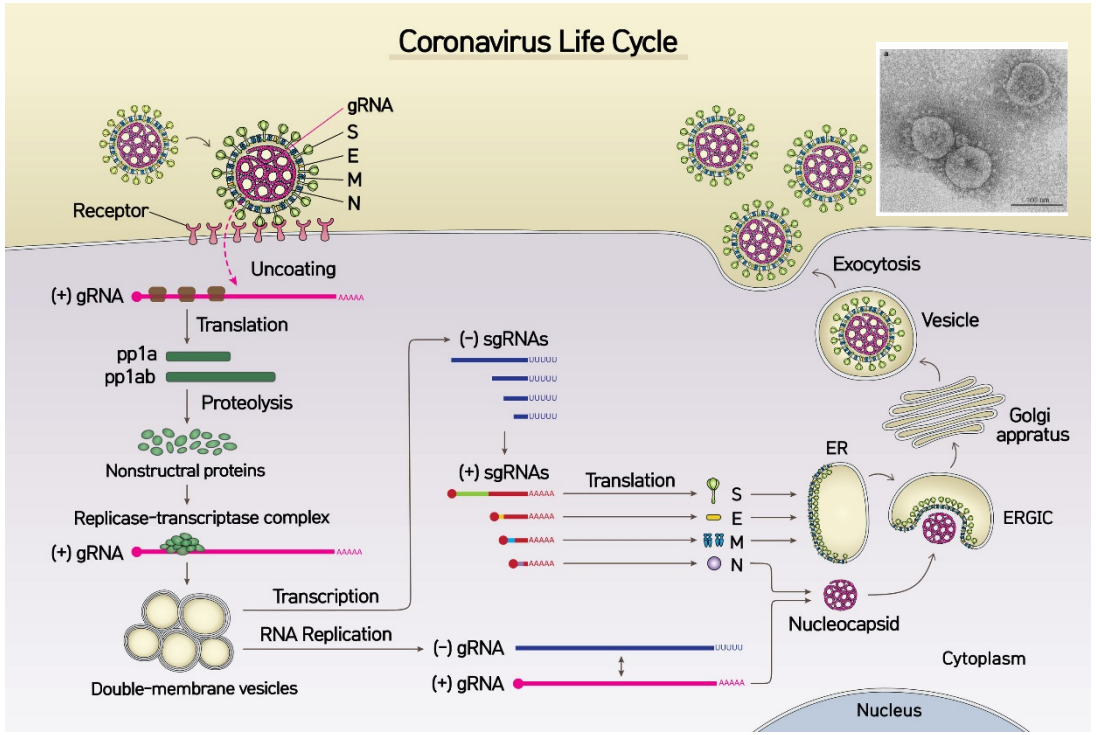
COVID-19 Deaths in the US Reported to the CDC, by State/Territory in 2020



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

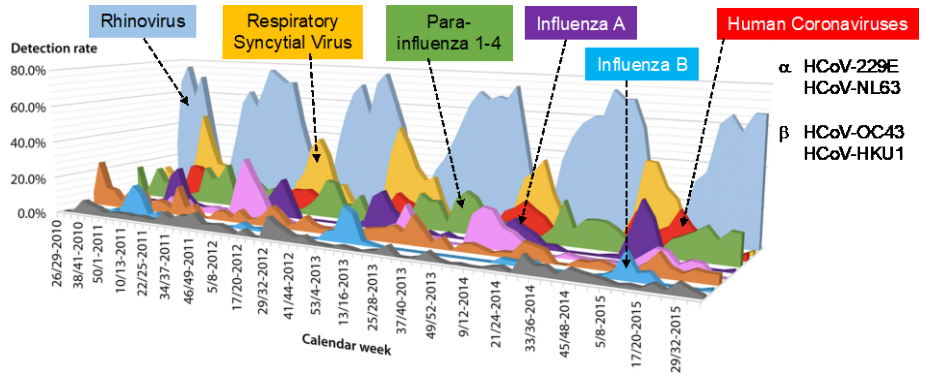
What are Coronaviruses ?

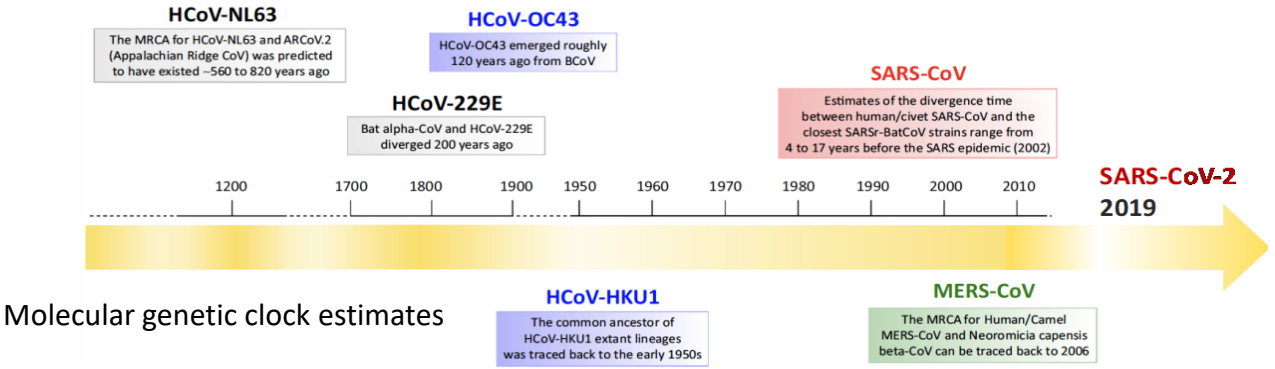
- Virions ∅ 120 nm, enveloped, **S-protein trimers ("spikes")**
- ss(+) RNA genome (g) of 30'000 nt → directly translated into polyproteins
- Proteolytic processing → *Non-structura*l proteins RNA pol complex
- Subgenomic (sg) transcripts → *Structural* and accessory proteins
- Mucosal surface infections of many vertebrates incl. humans → *jump species*



Modified after:
www.ibs.re.kr/cop/bbs/BBSMSTR_000000000738/selectBoardArticle.do?nttId=18344

What is *novel* about SARS-CoV-2?





Molecular genetic clock estimates

Furin Ewok

- NOT previously detected in humans → zoonotic origin despite multiple prior coronaviruses established in humans and other species
- SARS-CoV-2 Genome closest to bat CoV, intermediate host (Pangolin?) undefined
- **ACE2 is receptor for S-protein** → *higher* affinity than SARS-CoV-1
- **Novel 4 amino acid-insertion = target for *furin*-protease site at S1/S2 → more rapid cell entry and replication (homolog of Pangoin sequence) , high viral loads, efficient spread**
- ***No/little pre-existing immune memory; cross-reactive T-cells***
- ***Extensive innate immune activation***

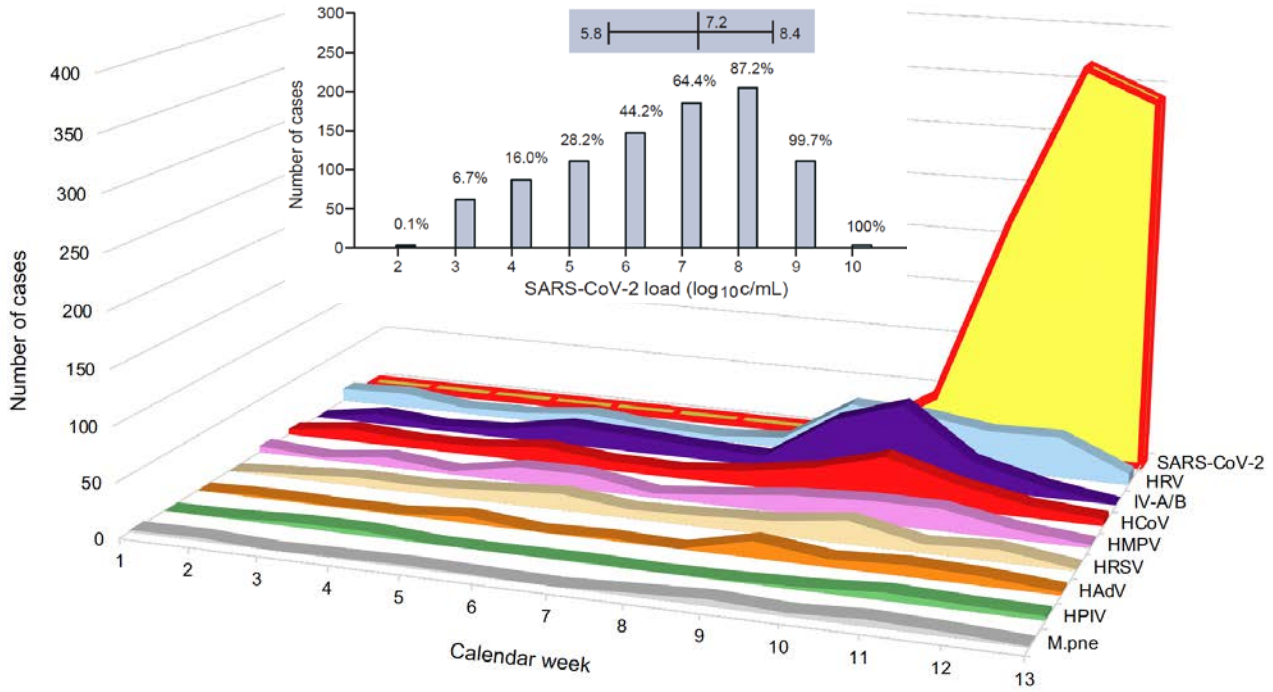
Pangolin

Courtesy of (and modified) Hans Hirsch

Forni D et al (2017) *Molecular Evolution of Human Coronavirus Genomes* Trends Microbiol 25: 35
Ison MG, Hirsch HH (2019) Community-acquired respiratory viruses in transplant patients: Diversity, impact, unmet clinical needs Clin Microbiol Rev 32: e00042-19
Grifoni A, et al (2020) *Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals* Cell 191: 1

How does this impact other respiratory viruses ?

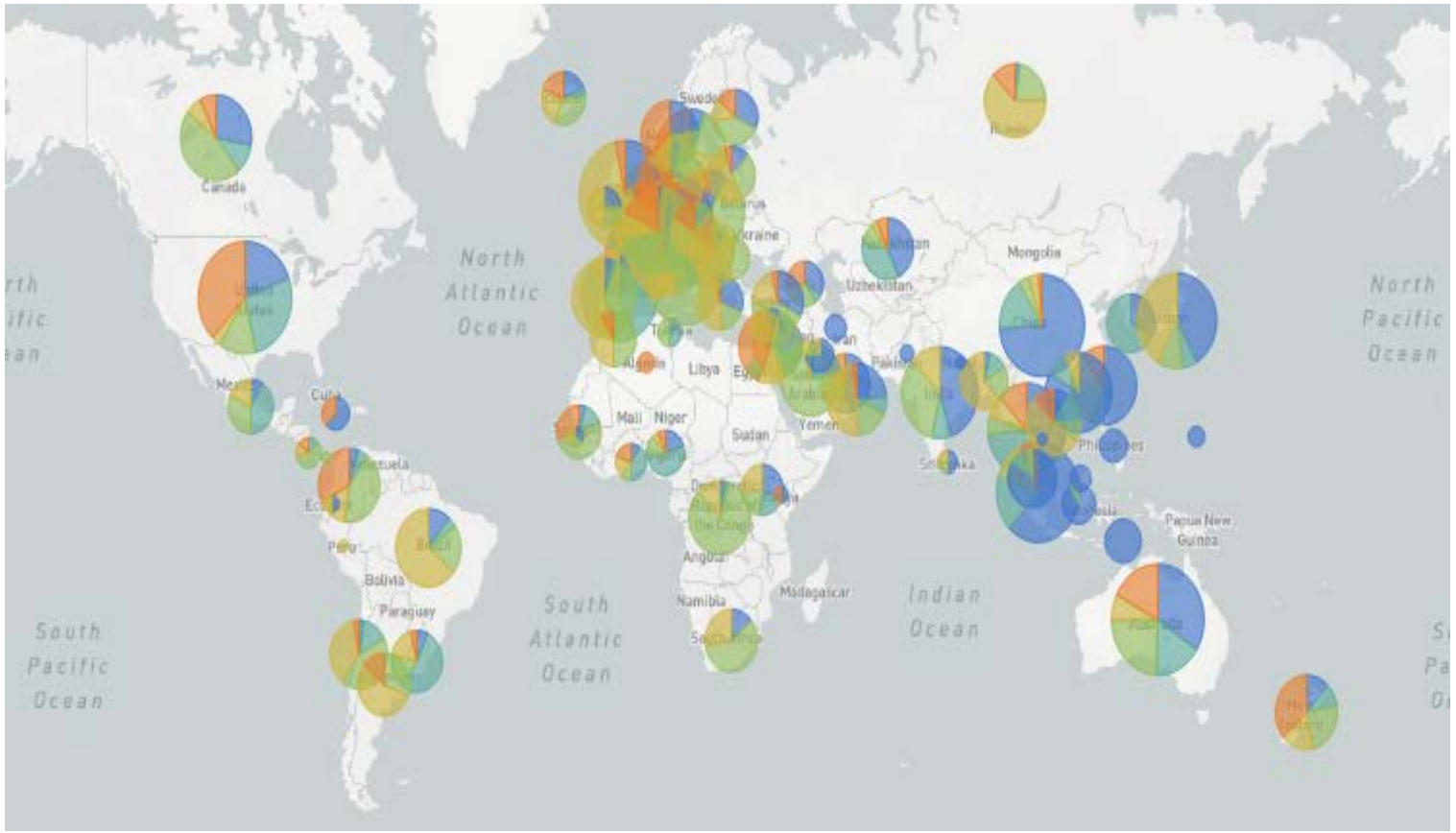
- Limited data from SARS-CoV-2 in the winter in Northern hemisphere
- **High SARS-CoV-2 loads in naso-pharyngeal swabs**
- **Community Respiratory viruses rapidly replaced among adults, but less in children**



Leuzinger K, et al. Epidemiology of SARS-CoV-2 Emergence Amidst Community-Acquired Respiratory Viruses. J Infect. Dis 2020. Courtesy of H. Hirsch.
Olsen SJ, et al. Decreased Influenza Activity During the COVID-19 Pandemic - United States, Australia, Chile, and South Africa, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1305-9.

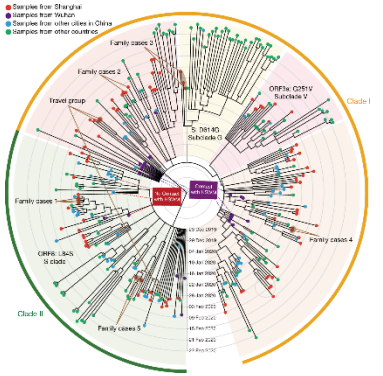
What are SARS-CoV-2 mutation rates? Does it Matter?

- **Mutations → clades and phylogenetic tree over time and regions**
- **Overall mutation rates seem rather low → little change after spillover**
- **Homogeneous sequences & clinical presentation in Wuhan**
- **Subsequent divergence – S-protein mutations -> altered membrane fusion**



https://nextstrain.org/ncov/global?c=clade_membership

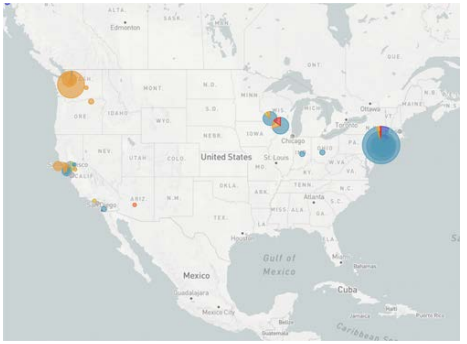
What are the clinical implications of limited mutation rates?



- Unknown but …
- The genomic sequences of SARS-CoV-2 assembled from 112 local samples and sequences in the WHO dataset showed stable evolution with two major lineages in the early phase of the outbreak in Wuhan. They exhibited *similar virulence and clinical outcomes*.
  - **Lymphocytopenia**, especially reduced $CD4^+$ and $CD8^+$ T cell counts upon hospital admission, was predictive of disease progression.
  - **High levels of interleukin (IL)-6 and IL-8** during treatment were observed in severe or critical disease (but lower level of interferons vs SARS-CoV).
  - Disease severity seemed to stem mostly from **host factors** such as age and lymphocytopenia and cytokine storm.

Zhang, X. *et al.* Viral and host factors related to the clinical outcome of COVID-19. *Nature* 583, 437–440 (2020). https://doi.org/10.1038/s41586-020-2355-0

Are there clinical implications? (2)



- SARS-CoV-2 *has* rapidly acquired mutations.
  - An S type of the virus accounted for only 3.7% of viral isolates in Wuhan compared to 96.3% of the L type while isolates outside of Wuhan were 61.3% L type and 38.4% S type.
  - B1 clade predominates on the West Coast of the United States, and the A2a clade, which apparently spread to New York through Europe and Italy predominates on the East Coast.
  - A **nonsynonymous mutation in the viral spike protein** (codon 614) resides in a highly glycosylated region of the viral spike protein. *Mutations in this region could alter membrane fusion in tissues, resulting in more pathogenicity and more human to human spread.* There are examples of mutation in this spike protein region resulting in changes in virulence.

A. Brufsky Distinct viral clades of SARS-CoV-2 J Med Virol (2020), 10.1002/jmv.25902

Comparing Coronavirus

	SARS-CoV-2	**SARS-CoV**	**MERS-CoV**
Phylogeny	Clade I, Cluster IIa	Clade I, Cluster IIb	Clade II
Intermediate Host	Pangolin ?	Palm civets	Camels
Receptor	ACE2	ACE2	DPP4
Case Fatality Rate	0.5-3%	9.5%	34.4%
R0	2-3	1.7-1.9	0.7
Extrapulmonary Clinical Features	Thrombosis, GI, renal, neurologic	GI, renal, neurologic	GI, renal, neuromuscular

Modified from D. Kumar in Fishman et al. N Engl J Med 2020; 383:1168-1180. DOI: 10.1056/NEJMcpc2004982

Adapted from Petrosillo et al., Clin Micro Infect, 2020

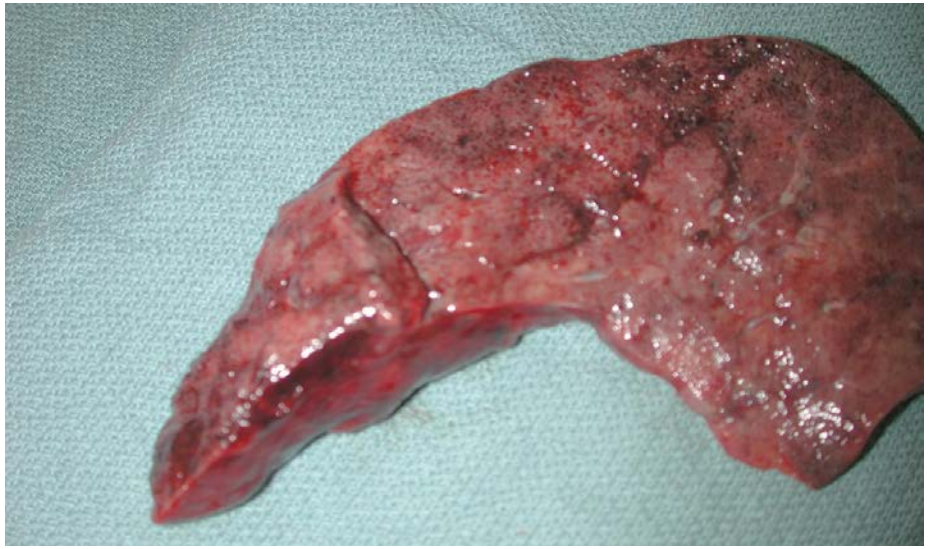
Summary of SARS-CoV-2 Transmission in Various Settings

- Crowded enclosed spaces facilitate SARS-CoV-2 transmission
- Transmission rates in enclosed spaces appear to be correlated with duration of exposure
  - Longer duration → greater risk of transmission
- Airborne transmission hypothesized
  - Biologically plausible → aerosol generated with greater than normal force or if air current moves aerosol > 1 meter and droplets remain intact
- Continued observational study and sentinel animal study required to better understand airborne transmission potential

Prior Coronavirus Outcomes - Transplant

Unlike the current pandemic, there were very few transplant patients described in past CoV outbreaks

- SARS-CoV
  - 3 transplant patients (liver, lung, kidney) and 2 deaths
  - Super-spreader event with multiple HCW infections
- MERS-CoV
  - 2 transplant patients (kidneys) with 1 death
  - Both had AKI



Tissue	Lung Transplant VL (x10^3 copies/g)	Non-transplant VL (n=21) (x10^3 copies/g)
Lung	8,760,000	360
Heart	28,000	32
Kidney	740	48
Liver	1600	18
Spleen	140	48
Lymph Node	890,000	710
Large Bowel	370,000	130
Small Bowel	240,000	270

Kumar et al., AJT, 2004; Kumar et al., Curr Op ID, 2005; AlGhamdi et al., AJT 2013

A Growing Family of Viral Pathogens

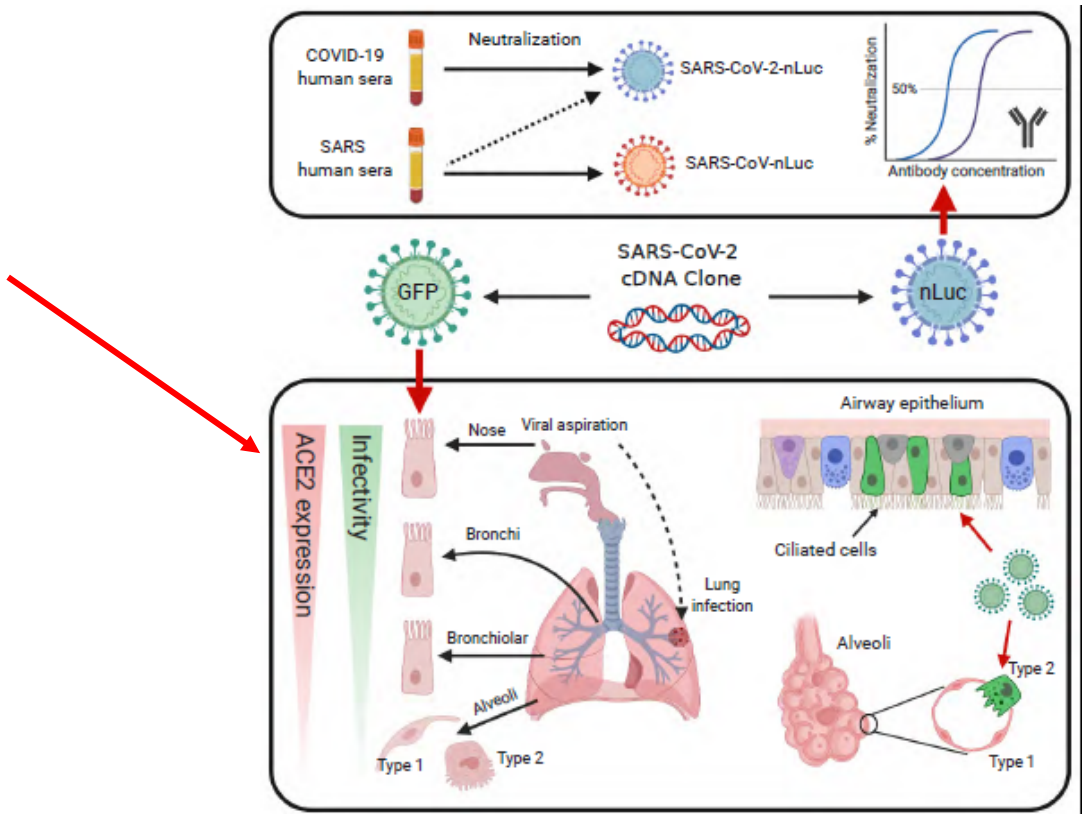
- **HERPES SIMPLEX**
- **VARICELLA ZOSTER**
- **EPSTEIN-BARR VIRUS**
- **CYTOMEGALOVIRUS**
- **HHV6**
- **HHV7**
- **HHV8/KSHV**
- **Donor-Derived: HIV, LCMV, WEST NILE, RABIES, HCV**
- **Live Vaccines (e.g., MMR, VZV)**
- **TTV (anellovirus)**

- **Hepatitis B and C**
- **Hepatitis E**
- **PAPILLOMAVIRUS**
- **POLYOMAVIRUS BK/JC**
- **PARVOVIRUS B19**
- **CARV:**
  - ADENOVIRUS
  - RSV
  - INFLUENZA
  - PARAINFLUENZA
  - METAPNEUMOVIRUS
  - ENTEROVIRUS/RHINOVIRUS
  - CORONAVIRUSES
    - **HKU1, NL63, 229E, OC43**
    - **SARS/MERS CoV**
    - **SARS CoV-2**

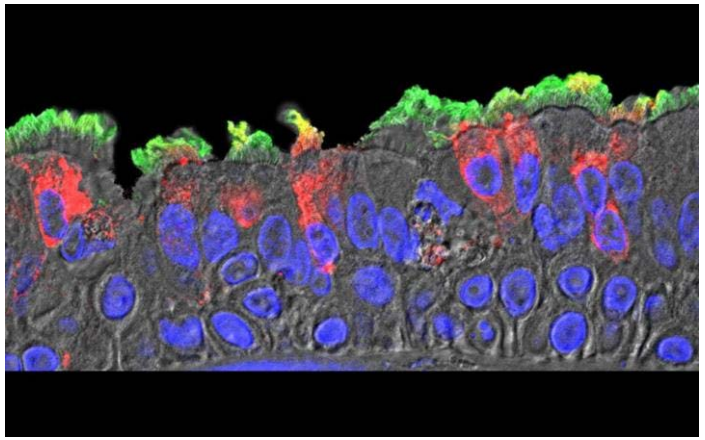
Effects of Viral Infection in Transplantation

- **"DIRECT EFFECTS" -- CAUSATION OF INFECTIOUS DISEASE SYNDROMES**
  - **Fever and neutropenia, Hepatitis, Colitis, Retinitis, Nephritis, Pancreatitis**
  - **Pneumonia, Hepatitis, Encephalitis …**
- **"INDIRECT" or IMMUNOMODULATORY EFFECTS**
  - **Systemic Immune Suppression → Opportunistic Infections (secondary)**
  - **Inflammation (local or systemic) – cytokine release syndromes**
  - **Graft Rejection, GVHD**
  - **Abrogation Of Tolerance**
- **ONCOGENESIS/CELLULAR PROLIFERATION**
  - **Hepatitis B and Hepatitis C: hepatocellular carcinoma**
  - **Epstein Barr Virus: B-cell lymphoma (PTLD)**
  - **Hepatitis C: splenic lymphoma (villous lymphocytes)**
  - **Papillomavirus: Warts, Actinic keratosis, Squamous cell & anogenital cancer**
  - **HHV8 (KSHV): Kaposi's sarcoma, effusion lymphoma**
  - **Accelerated atherogenesis, BK-ureteric obstruction**
  - **Lung Injury with Diffuse Alveolar Damage, Fibrosis and ARDS**

SARS-CoV2 Pulmonary Infection



"high-sensitivity RNA in situ mapping revealed the **highest ACE2 expression in the nose with decreasing expression throughout the lower respiratory tract**, paralleled by a striking gradient of SARS-CoV-2 infection in proximal (high) vs distal (low) pulmonary epithelial cultures."

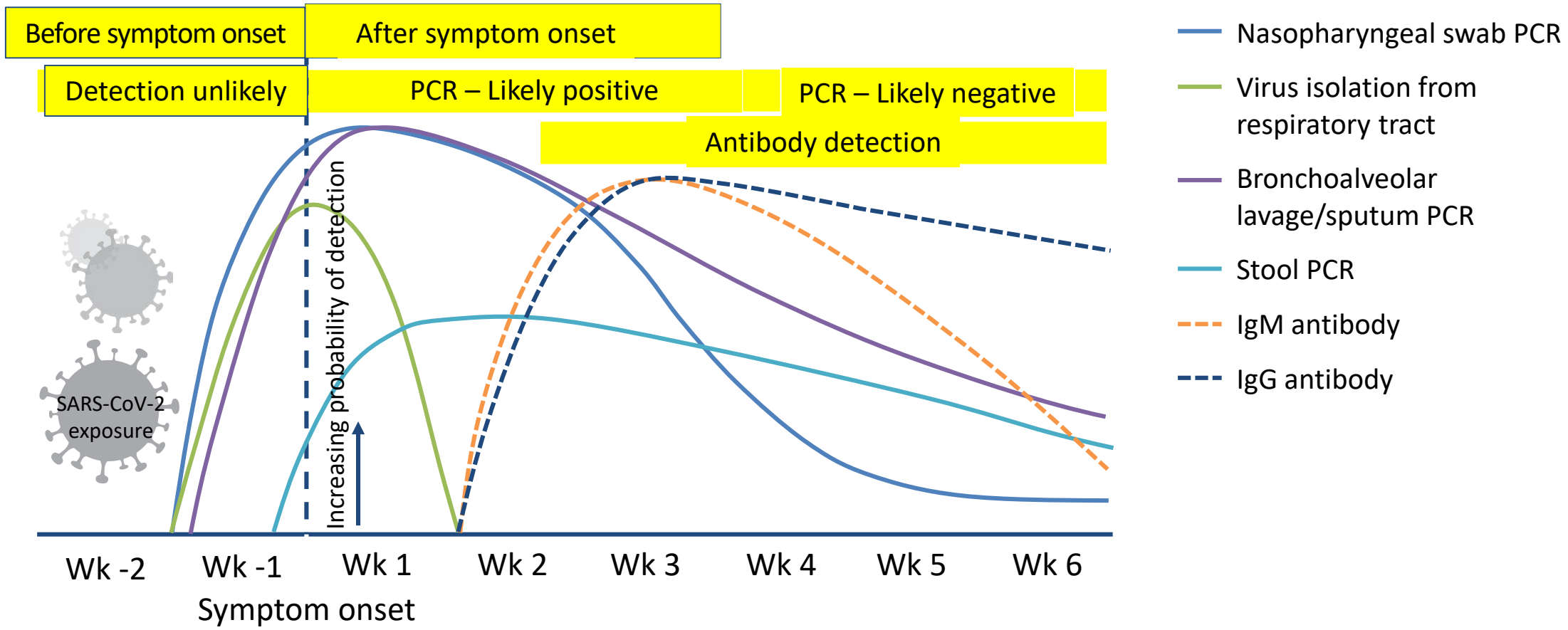


Hou et al. DOI: https://doi.org/10.1016/j.cell.2020.05.042
Cell, 2020.

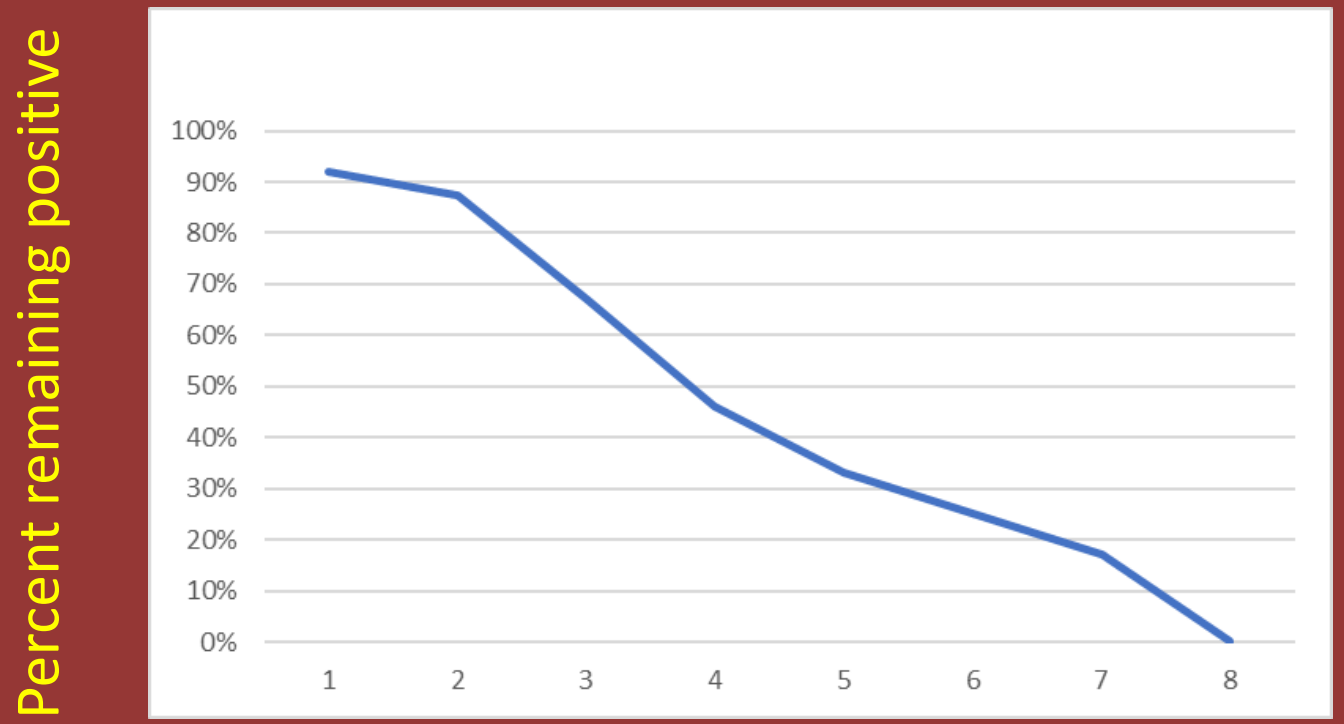
Some Testing Thoughts

- The incubation period for COVID-19—that is the time from exposure to disease onset—can range *from 2 and 14 days*; the median is *approximately 5 days*. At this point, a nasal swab for SARS CoV-2 would start to be positive. However, in some series, swabs for SARS-CoV-2 were false negative in up to ~30% of cases if they are tested too early in the course of infection (Woloshin S, et al. N Engl J Med. 2020).
- PCR (viral RNA) – most sensitive (good for hospitalized patients, symptomatic cases, healthcare workers) but requires nucleic acid extraction; can use CT (cycle threshold ~30-35) as indicator of how much RNA is present but not whether it is active virus
- Saliva test (viral RNA) 6-12 copies without extraction – faster and good for asymptomatic screening
- Antigen (viral proteins) tests – good for screening
- Antibody tests – many false – or +, but useful for thinking about donors (MANY different tests; IgG or IgM antibodies are detected in nearly all patients by Day 14-21. Pooled test of IGM/G/A may be best test (ThermoFisher) but does not tell about course of disease). Antibody production may be related to the severity of COVID-19 illness.

Temporal Considerations for Diagnosis



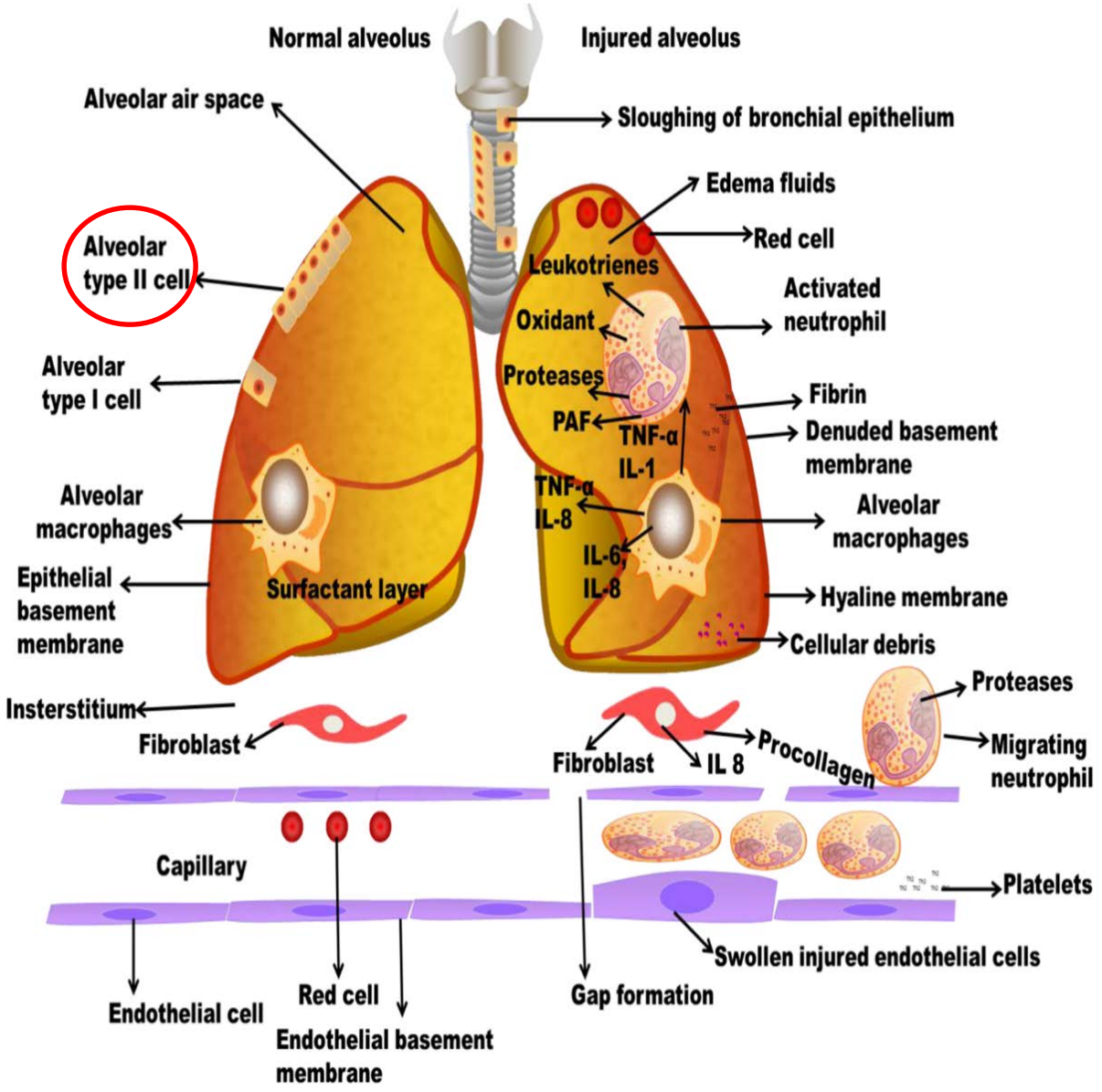
Persistent Nasopharyngeal +PCR



Prolonged, detectable viral shedding is a general phenomenon. In 378 cases, the median duration of viral RNA PCR shedding was found to be 53.5 days (interquartile range: 47.75-60.5) in respiratory samples of known COVID-19 cases, including a case in which the last positive PCR result was 83 days post-infection.[Li 2020a] The Ct value of the respiratory samples was on the high side (>30), indicating that the viral load was relatively low in this group of individuals. (Li N, Wang X, Lv T. Prolonged SARS-CoV-2 RNA shedding: not a rare phenomenon. J Med Virol. 2020a)

Pathophysiology of lung injury in COVID-19

- Type II Pneumocyte injury
- Neutrophil chemotaxis and activation
- Alveolar Macrophage activation
- Limited interferon production
- Fibrosis and edema



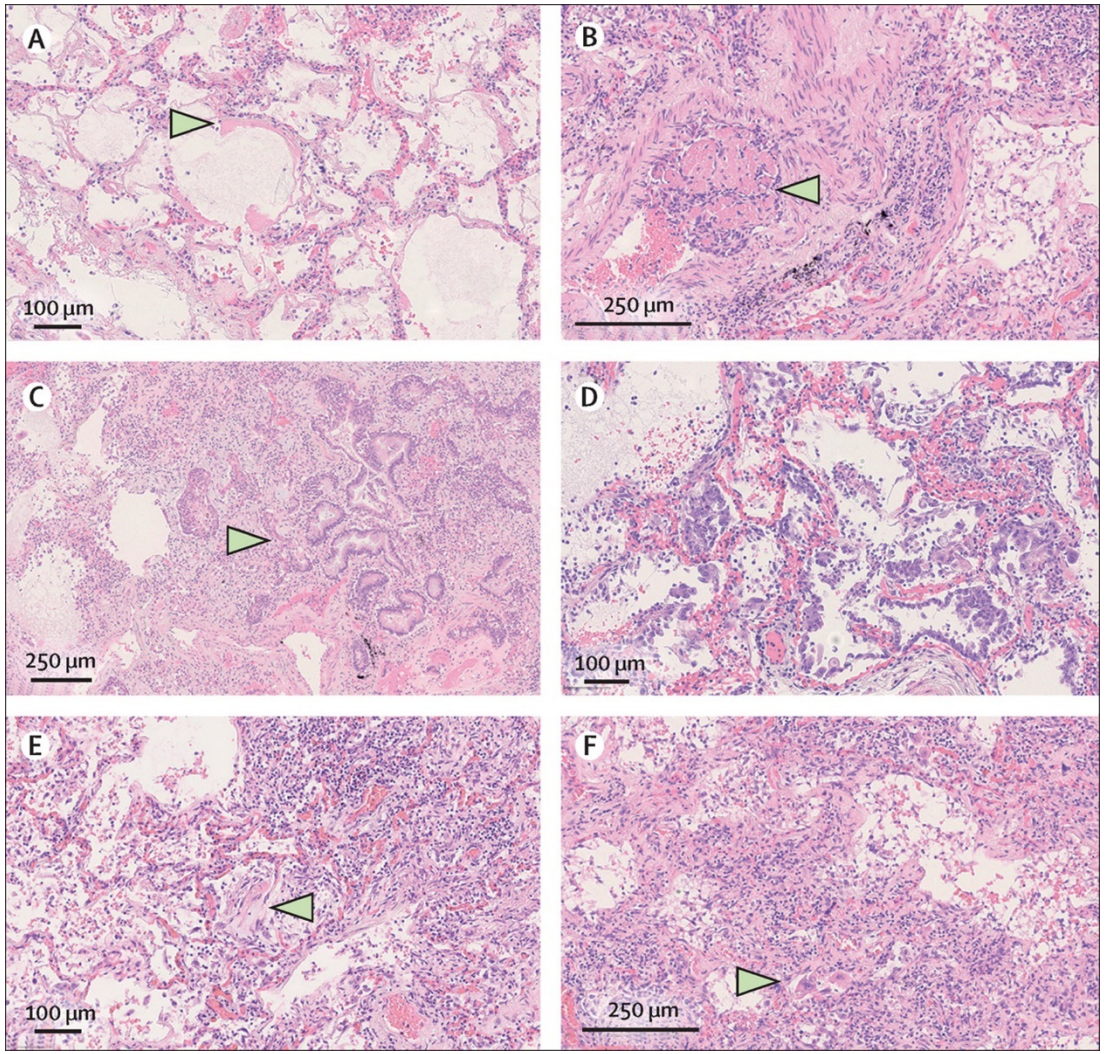


Figure 1: Haematoxylin and eosin-stained sections from representative areas of lung parenchyma with diffuse alveolar damage(A) Exudative phase of diffuse alveolar damage with hyaline membranes (arrow). (B) Organising microthrombus (arrow). (C) Concomitant interstitial pneumonia, intra-alveolar scattered multinucleated giant cells (top, left), and outstanding epithelial proliferation around a bronchiole with plurifocal squamous differentiation and mild atypia (arrow). (D) Early proliferative phase of diffuse alveolar damage with many hyperplastic, and rarely atypical, type 2 pneumocytes. (E) Intermediate phase of diffuse alveolar damage with initial organising aspects (arrow) and interstitial pneumonia with marked lymphocytic infiltrate. (F) Advanced proliferative phase of diffuse alveolar damage with interstitial myofibroblastic reaction, diffuse lymphocytic interstitial infiltrate, and residual scattered hyperplastic type 2 pneumocytes (arrow). (A, D, E) Original magnification×20. (B, C, F

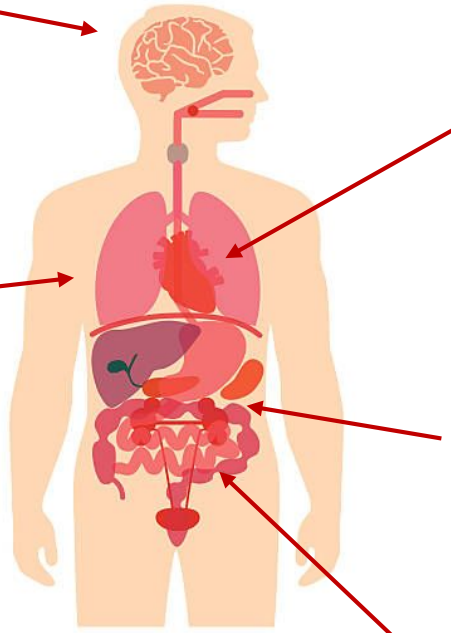
From Northern Italy: Luca Carsana et al. The Lancet Infectious Diseases 2020 201135-1140DOI: (10.1016/S1473-3099(20)30434-5)

The predominant pattern of lung lesions in patients with COVID-19 patients is **diffuse alveolar damage**, as described in patients infected with severe acute respiratory syndrome and Middle East respiratory syndrome coronaviruses. Hyaline membrane formation and **pneumocyte atypical hyperplasia** are frequent. Importantly, the presence of **platelet–fibrin thrombi in small arterial vessels** is consistent with coagulopathy,

Presentation of SARS-CoV-2 Infection

CNS/Neurological
- Stroke
- Syncope
- Anosmia
- Dysgeusia

Respiratory
- Dyspnea
- Cough
- Hypoxemia
- Pulmonary infiltrates
- Pneumonia
  - Ventilator
  - Community
  - Superinfection
- ARDS
- Pulmonary Embolus



Cardiovascular
- Elevated CK, troponin
- Myocarditis, pericarditis
- MI
- Arrhythmia
- Cardiomyopathy
- Shock

Renal
- Elevated Creatinine
- Endotheliitis
- Tubulitis

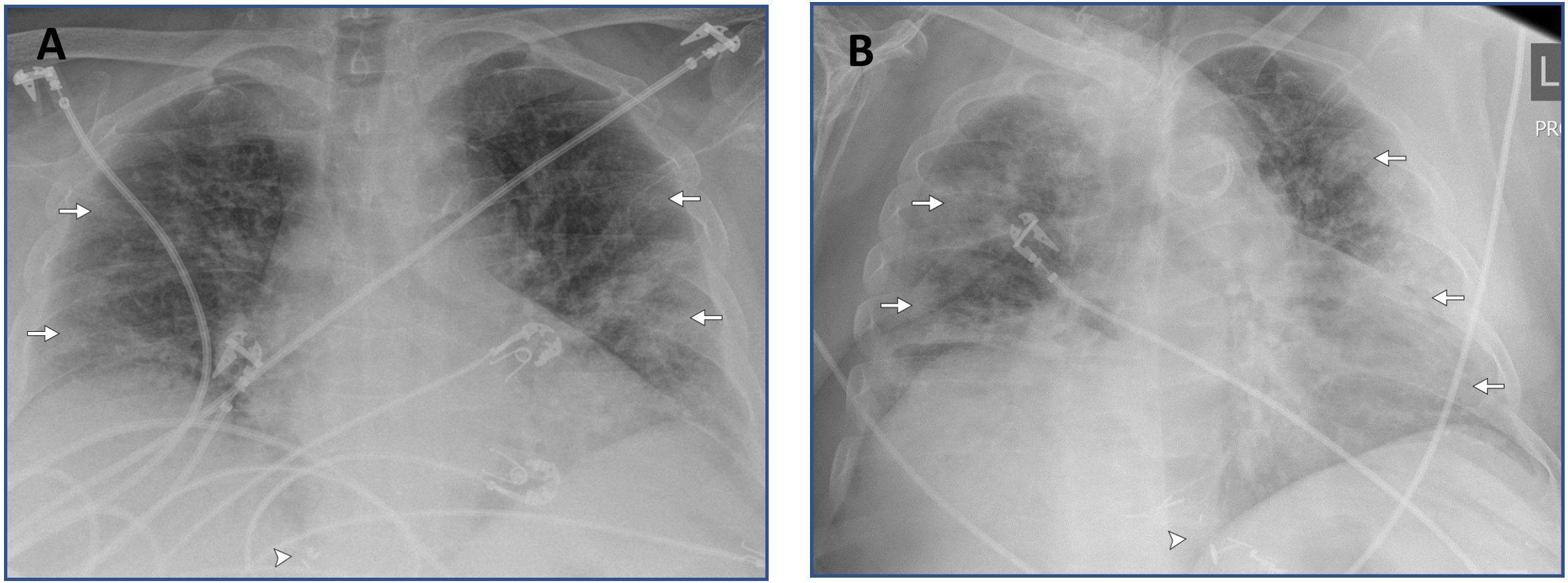
Skin
- “COVID toes” "pseudo-chilblains"
- Vesicles, pustules
- Maculopapular rash
- Urticaria
- Livedo
- Emboli
- Kawasaki
  - Conjunctivitis
  - rash

Systemic
- Neutrophilia
- Lymphopenia
- Thrombocytopenia
- Inflammation
- Viremia
- Coagulopathy (DVT)

Gastrointestinal
- Nausea
- Diarrhea
- Loss of appetite
- Elevated liver function tests

Endocrine
- Hyperglycemia
- Diabetic Ketoacidosis

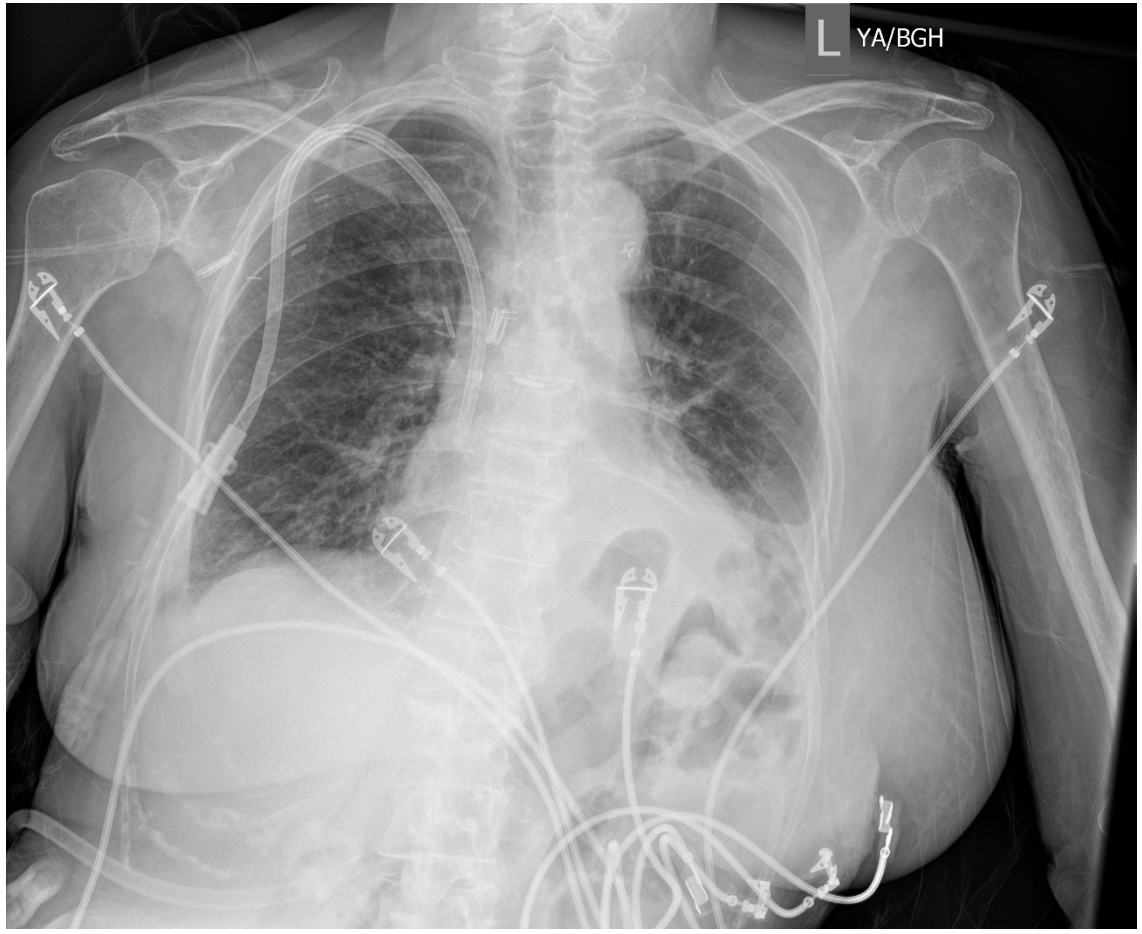
Symptoms appear 2-14 days (median ~4 days) after exposure to virus



Liver recipient: A. Portable AP view chest radiograph demonstrated low lung volumes with bilateral peripheral predominant airspace opacities in the mid-to-lower lung zones, left greater than right (arrows). B. Persistent low lung volumes with interval increase in the bilateral now diffuse consolidative airspace opacities (arrows). Post-transplantation surgical clips are demonstrated (arrowhead).

COVID-19 Variability

61 y.o. female with type A aortic dissection (10/2018) secondary to biopsy-proven GCA, s/p CABG (on VA ECMO f/b BiVAD) c/b bacteremia and renal failure now on HD (MWF, tunneled line) and s/p heart transplant (2/25/19; on prednisone/tacrolimus) with severe donor recipient mismatch requiring left hemi-sternectomy and rib resection with flap closure with post-op course c/b fungemia, bacteremia (lifelong Fluconazole), respiratory failure (s/p trach w/ hx of PsA pneumonia, decannulated), s/p PEG placement (4/30/19), recent C diff colitis on PO vancomycin, LIJ thrombus (on warfarin), presenting from her rehab facility with shortness of breath. Found to be COVID-19 + D1 sx 5/5 . Currently stable on 1L O2.



Stable left pleural effusion
Retrocardiac pulmonary opacity which could represent any combination of atelectasis, aspiration or pneumonia.

Transplant: Characteristics at Admission

Characteristic	Admitted (%)	ICU (%)	Non-ICU (%)	p-value
n	32 (100%)	11 (35%)	21 (65%)	
Symptoms				
Fever	24 (75%)	9 (82%)	15 (71%)	0.681
Dyspnea	18 (56%)	8 (73%)	10 (48%)	0.266
Cough	20 (63%)	7 (64%)	13 (62%)	>0.99
Sore throat	3 (9%)	3 (27%)	0 (0%)	0.033
Myalgias	13 (41%)	6 (55%)	7 (33%)	0.283
Fatigue	19 (59%)	6 (55%)	13 (62%)	0.687
Nausea/vomiting	10 (31%)	4 (36%)	6 (29%)	0.703
Diarrhea	9 (28%)	3 (27%)	6 (29%)	
Chest pain	6 (19%)	4 (36%)	2 (10%)	0.148
Time course				
Symptom onset to admission (median, d)	7	5	7	0.128
Range (days)	1-18	1-18	2-16	
Initial observations				
Febrile >37.9	4 (13%)	2 (18%)	2 10%)	0.593
Supplemental O_2 requirement on admission	12 (38%)	11 (100%)	8 (38%)	0.001
FiO2 Range	24%-100%	24%-100%	24%-44%	
Chest x-ray findings				
None	10 (31%)	2 (18%)	8 (38%)	0.425
Unilateral	5 (16%)	1 (9%)	4 (19%)	0.637
Bilateral	17 (53%)	8 (73%)	9 (43%)	0.148

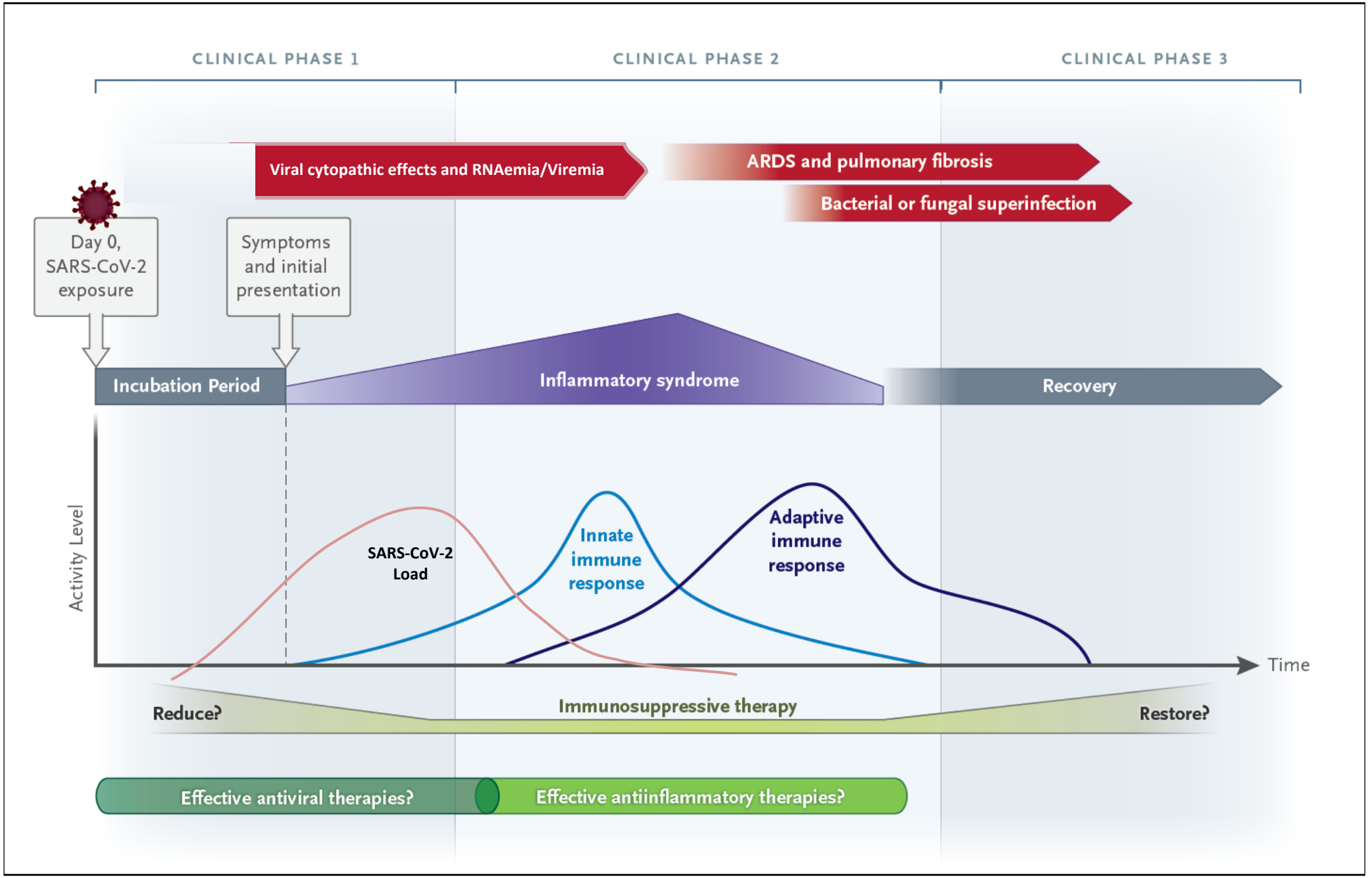
From M. Roberts et al.
Transplant Infect Dis, doi:10.1111/tid.13407

Common Biomarkers of Inflammation in SARS-CoV-2 Infection

- Hypoxemia
- White Blood Cell count (variable) and differential (low lymphocyte counts)
- Lyphocyte counts (relative lymphopenia)
- T-cell subsets and markers (e.g., PD-1, exhaustion phenotype)
- SARS-CoV-2 Viral Load (RNA)
- IgM/IgG to SARS-CoV-2
- Procalcitonin (often normal with late rise common)
- D-dimer (elevated)
- Ferritin (elevated)
- Lactic dehydrogenase (LDH, elevated)
- Interleukin-1β (IL-1β) IL-2, IL-6, IL-7 (elevated)
- Tumor necrosis factor-α (TNF-α) (elevated)
- Serum creatinine (GFR reduced)
- Creatine kinase (CK elevated)/cardiac troponin I (elevated)
- Liver function tests (variable transaminitis)
- Erythrocyte Sedimentation rate (ESR, variable)
- C-reactive protein (CRP, variable)
- Granulocyte-Macrophage colony stimulating factor (GM-CSF, elevated)
- Monocyte Chemoattractant Protein 1 (MCP-1/CC Ligand 2)
- Macrophage inflammatory protein 1A (MIP-1A/CCL3)
- MIP-1B (CCL4)

Risk factors for Severe COVID-19 Infection

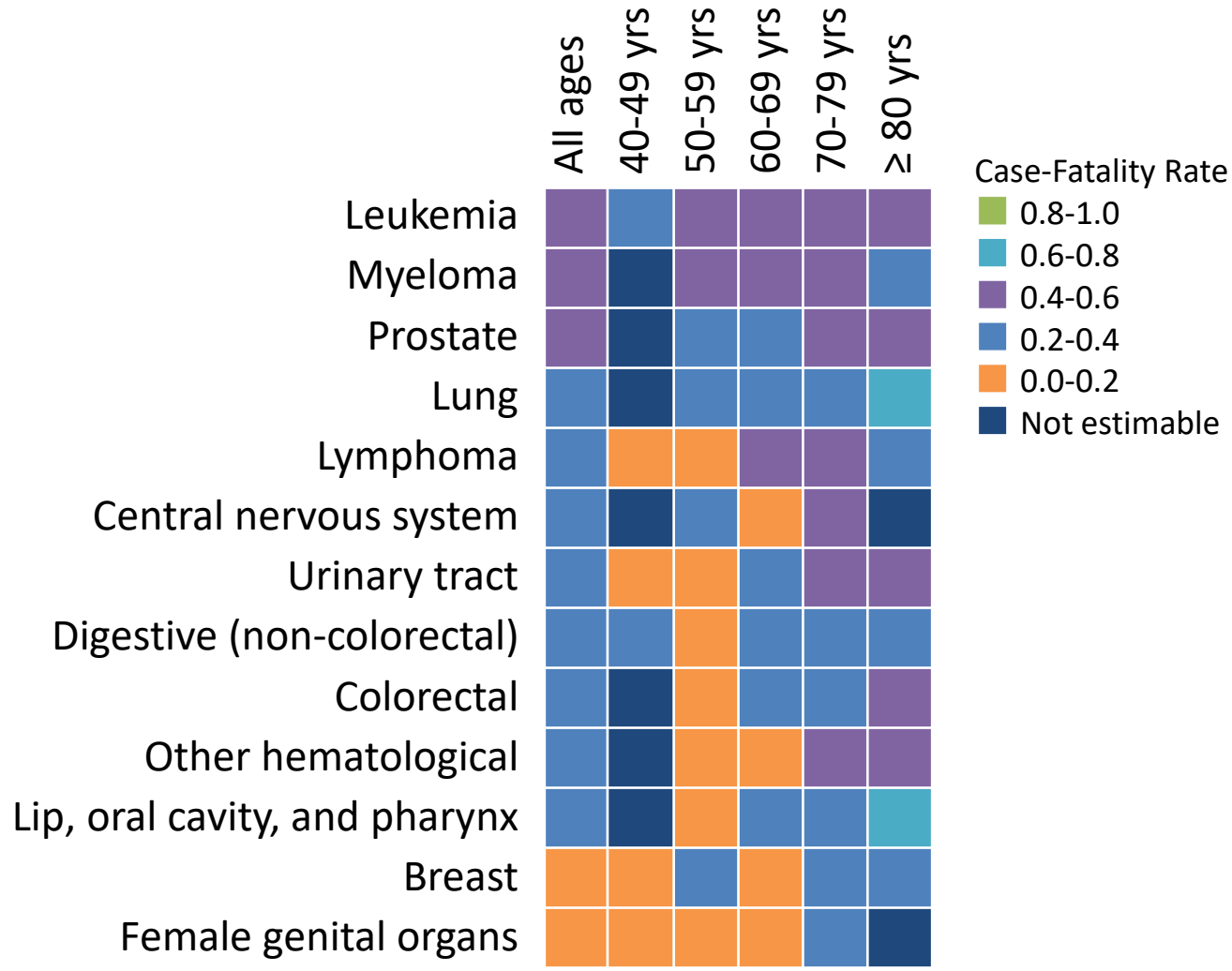
Comorbid Conditions	Labs
Advanced Age > 65 (rises with decade)	D-dimer > 1000 ng/mL
	Ferritin > 500 ug/L
Pre-existing pulmonary disease	CPK > twice upper limit of normal
Chronic kidney disease	CRP > 100
Diabetes with A1c > 7.6%	LDH > 245 U/L
	Albumin (rapid decline)
History of hypertension	Elevated troponin
Cardiovascular disease	Admission absolute lymphocyte count < 0.8
Obesity (BMI ≥ 30 kg/m2)	Elevated Interleukin-6
Organ Transplantation	ABO Blood Types (A>O risk)
Hematopoietic Malignancy	



Fishman et al. NEJM, CPC, 2020

COVID-19 Mortality in Patients With Cancer

- Prospective study evaluating the effect of primary tumor subtype, age, and sex on SARS-COV-2 prevalence and CFR during hospitalization among cancer patients in the UKCCMP cohort (N = 1044)
- All-cause CFR significantly increased with **age** from 0.10 for subset aged 40-49 yrs vs 0.48 if ≥ 80 yrs
- **COVID-19 trajectory more severe in patients with hematologic malignancies vs solid organ tumors (OR: 1.57, *P* < .0043)**
  - Patients with leukemia had highest CFR

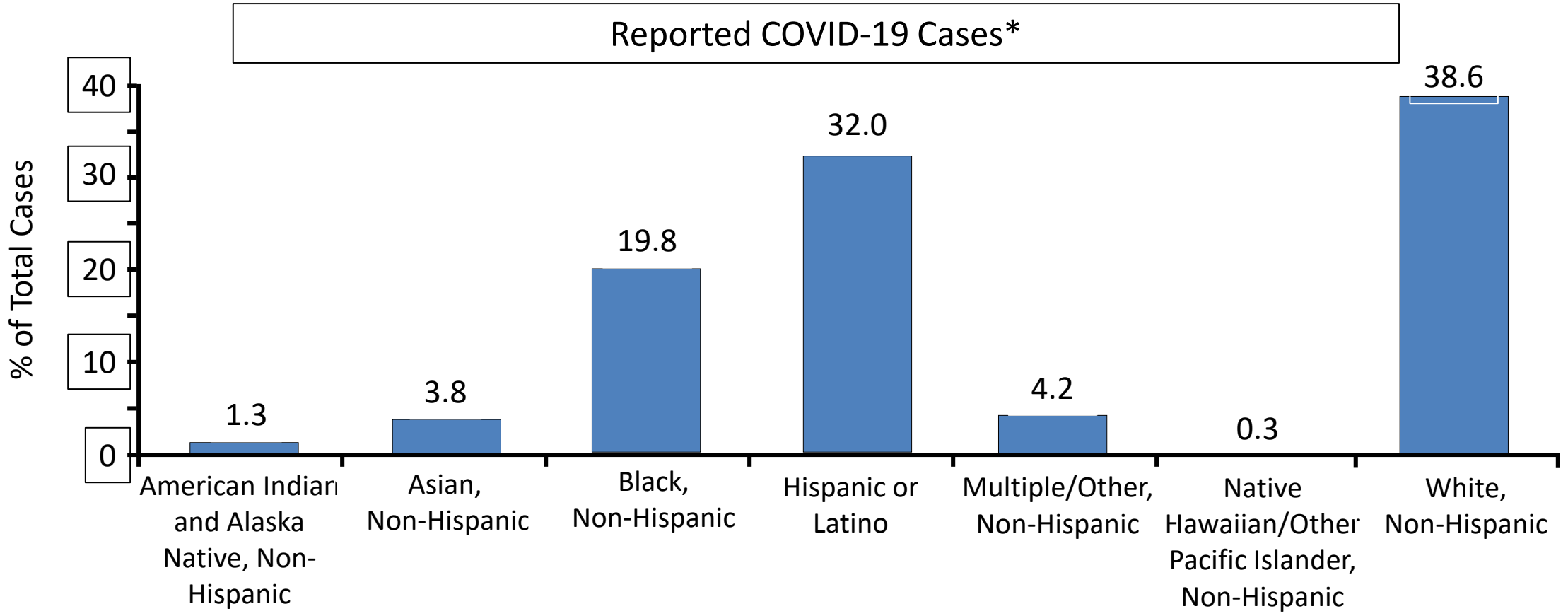


Lee. Lancet Oncol 2020;21:1309.

Outcomes of SARS-CoV-2 in Transplantation

	COVID-19 General	COVID-19 Transplant	Comments
Hospitalization	3-5%	77%	
ICU Admission		35%	
Intubation	12.2%	22-35%	
Mortality – Intubated		67-75%	
Overall US Mortality (published)	1-5%	~20.5-36% (11% MGH)	HR=4.27 (UK) Renal 22.8% (France)

CDC COVID Data Tracker: Reported COVID-19 Cases by Race/Ethnicity



*Last updated July 29, 2020, 5:45 PM EDT. Includes race/ethnicity data available for 1,578,696 cases.

https://www.cdc.gov/covid-data-tracker/index.html#demographics

Key Therapeutic Classes Under Investigation for Treatment of COVID-19

Antivirals

Baloxivir
Convalescent plasma
Favipiravir
(Hydroxy)chloroquine
Interferon
Lopinavir/ritonavir
Nitazoxanide
Oseltamivir
Remdesivir
Ribavirin

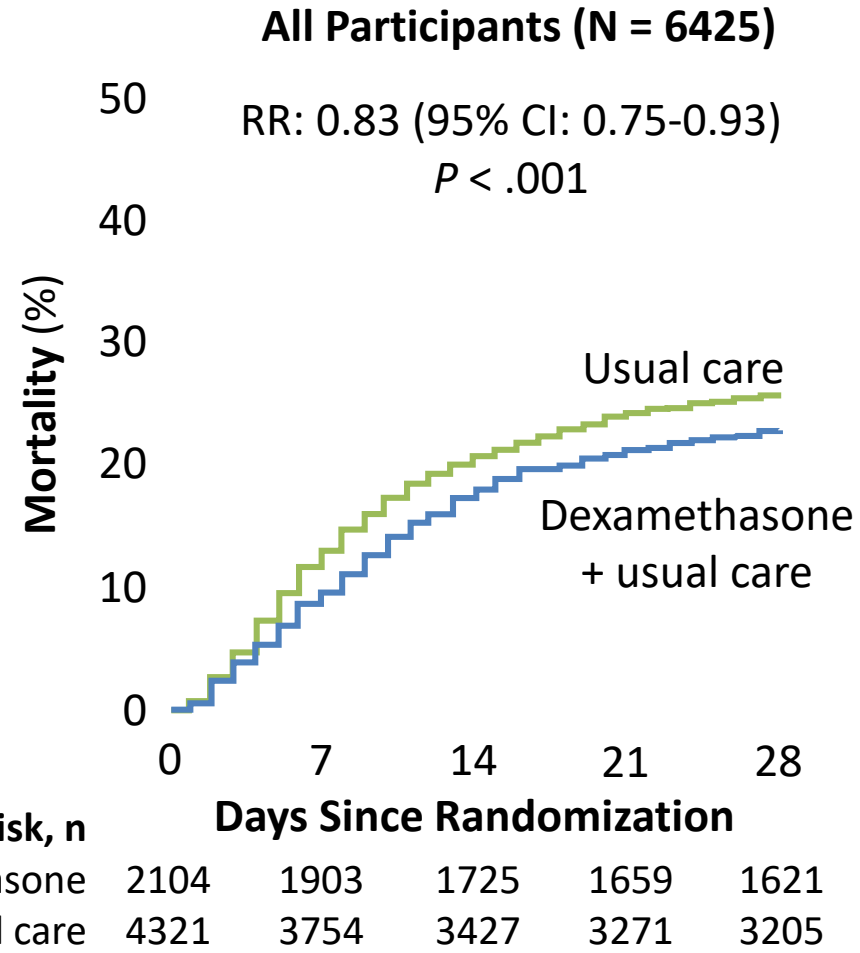
Immunomodulators

Corticosteroids, eg, dexamethasone
IL-1 inhibitors (eg, anakinra)
IL-6 inhibitors (eg, tocilizumab)
Intravenous immunoglobulin
JAK inhibitors (eg, baricitinib)

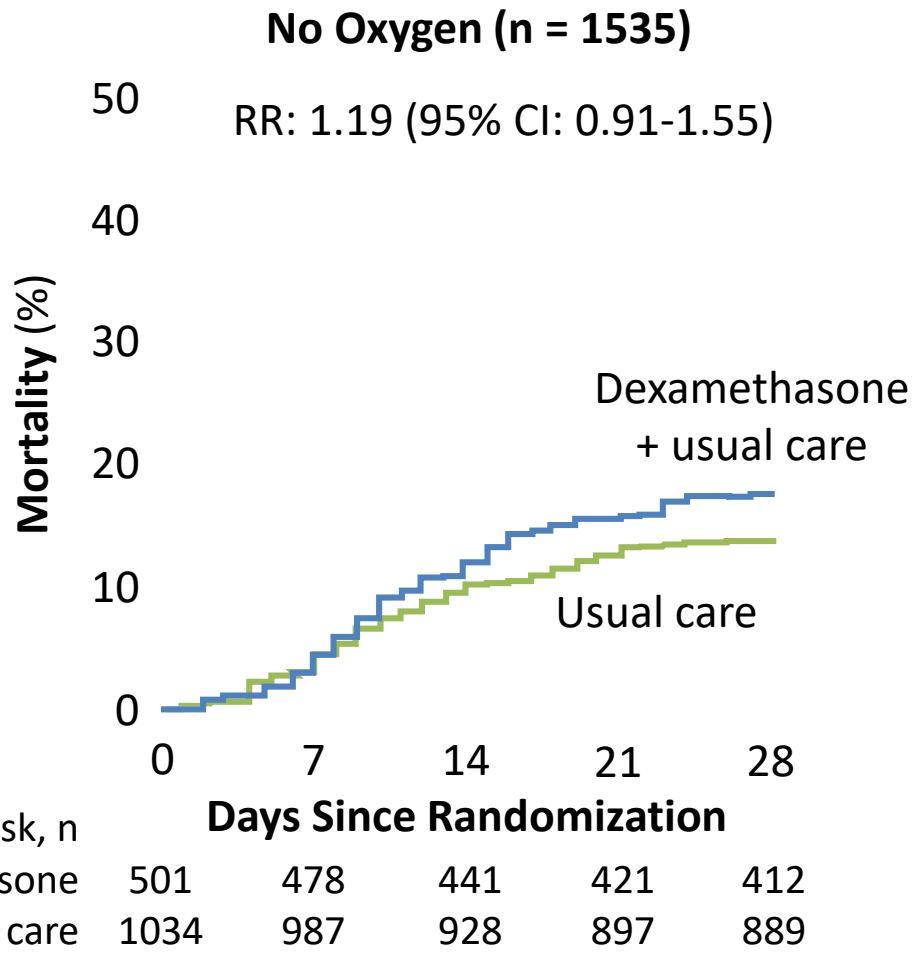
Barlow. Pharmacotherapy. 2020;40:416. McCreary. Open Forum Infect Dis. 2020;7:ofaa105. Sanders. JAMA. 2020;323:1824.

Slide credit: clinicaloptions.com

RECOVERY Trial: Mortality With Dexamethasone + Usual Care vs Usual Care Alone



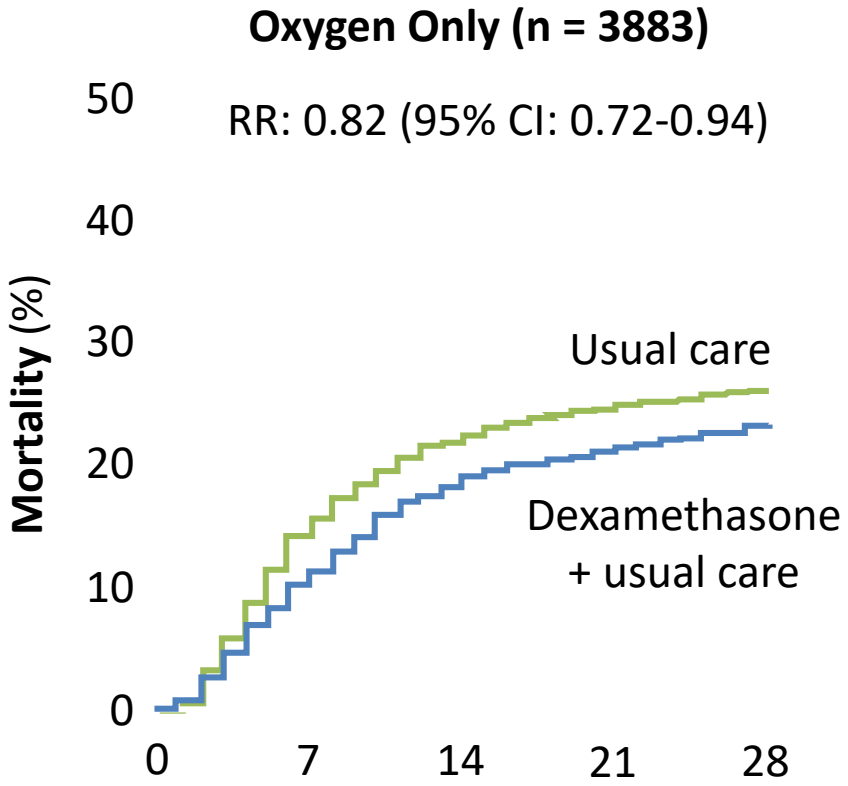
Patients at **Risk, n**					
Dexamethasone	2104	1903	1725	1659	1621
Usual care	4321	3754	3427	3271	3205



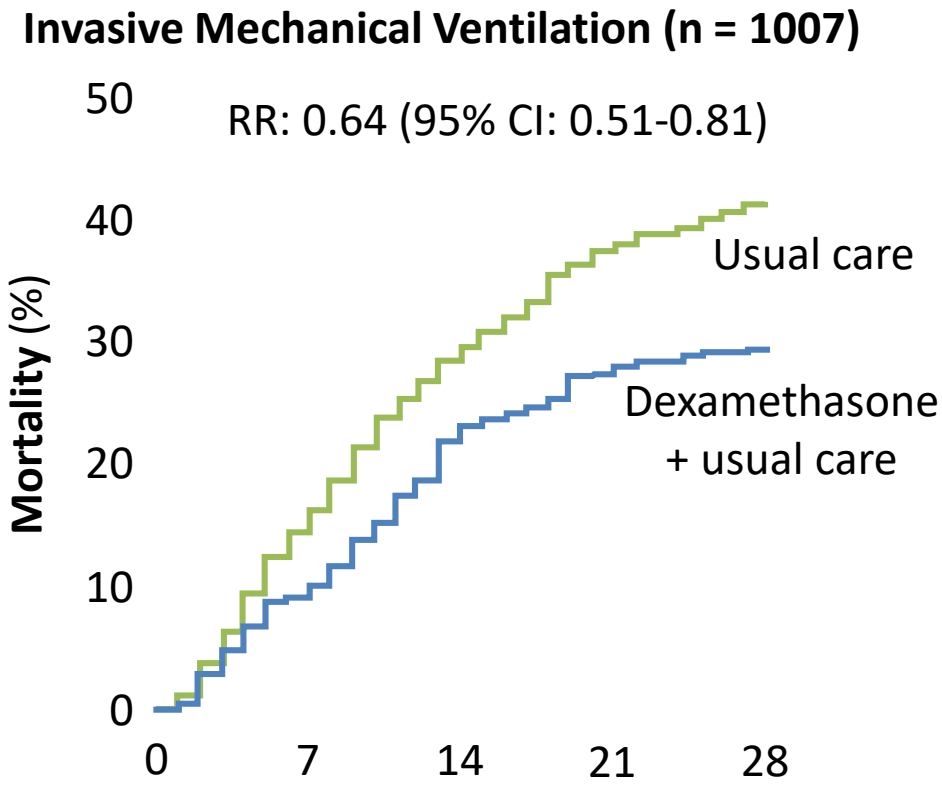
Patients at Risk, n					
Dexamethasone	501	478	441	421	412
Usual care	1034	987	928	897	889

RECOVERY Collaborative Group. NEJM. 2020;[Epub].

RECOVERY Trial: Mortality in Patients on Oxygen or Mechanical Ventilation ± Dexamethasone



Patients at Risk, n					
Dexamethasone	1279	1135	1036	1006	981
Usual care	2604	2195	2018	1950	1916



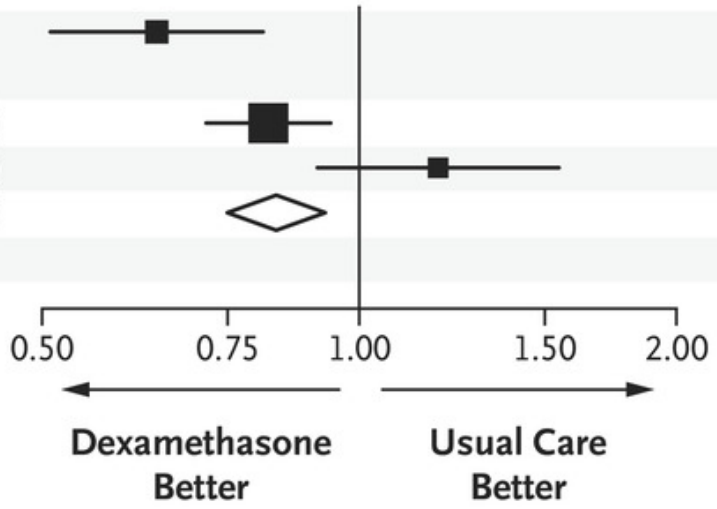
Patients at Risk, n					
Dexamethasone	324	290	248	232	228
Usual care	683	572	481	424	400

RECOVERY Collaborative Group. NEJM. 2020;[Epub].

Slide credit: clinicaloptions.com

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

Chi-square trend across three categories: 11.5



The RECOVERY Collaborative Group. N Engl J Med 2020. DOI: 10.1056/NEJMoa2021436

IDSA Recommendations on Treatment and Management of Patients With COVID-19

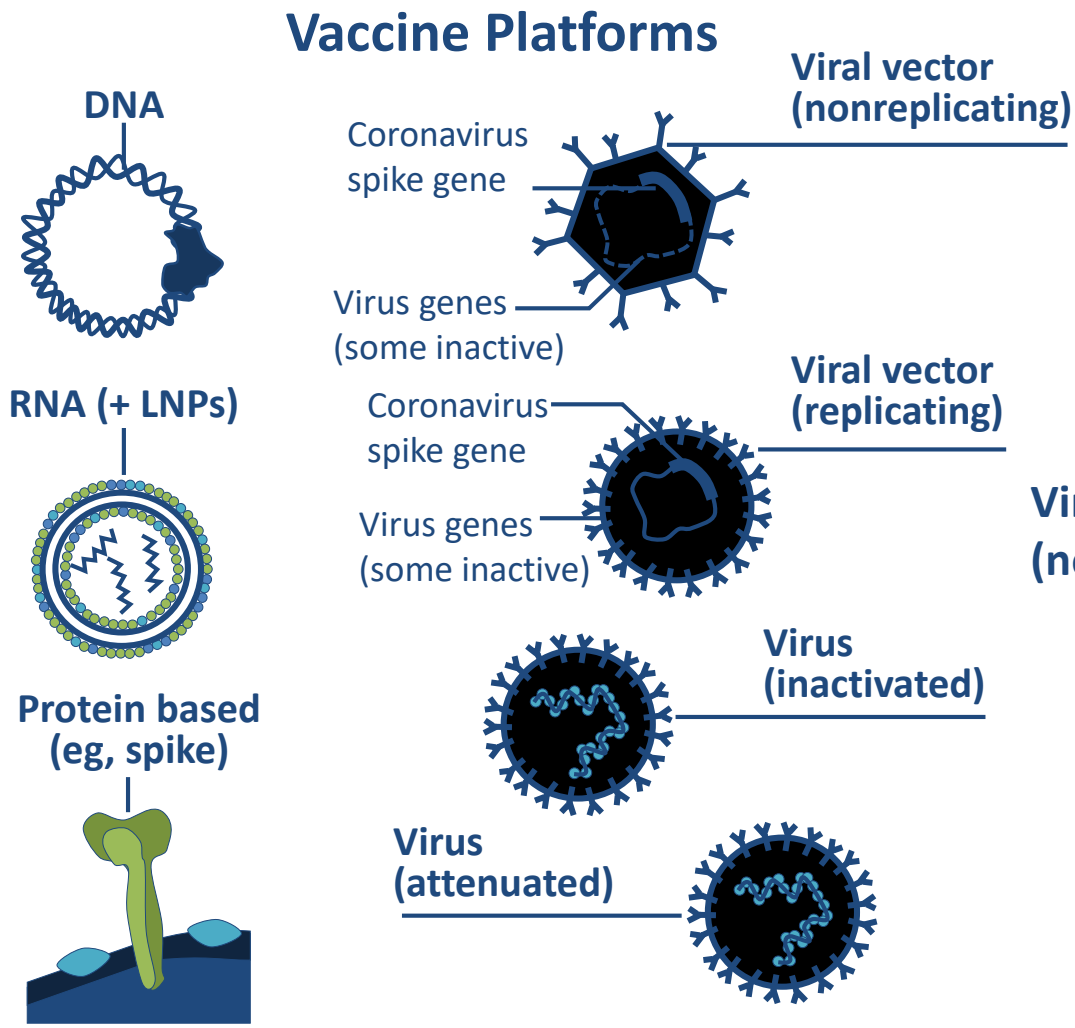
- Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

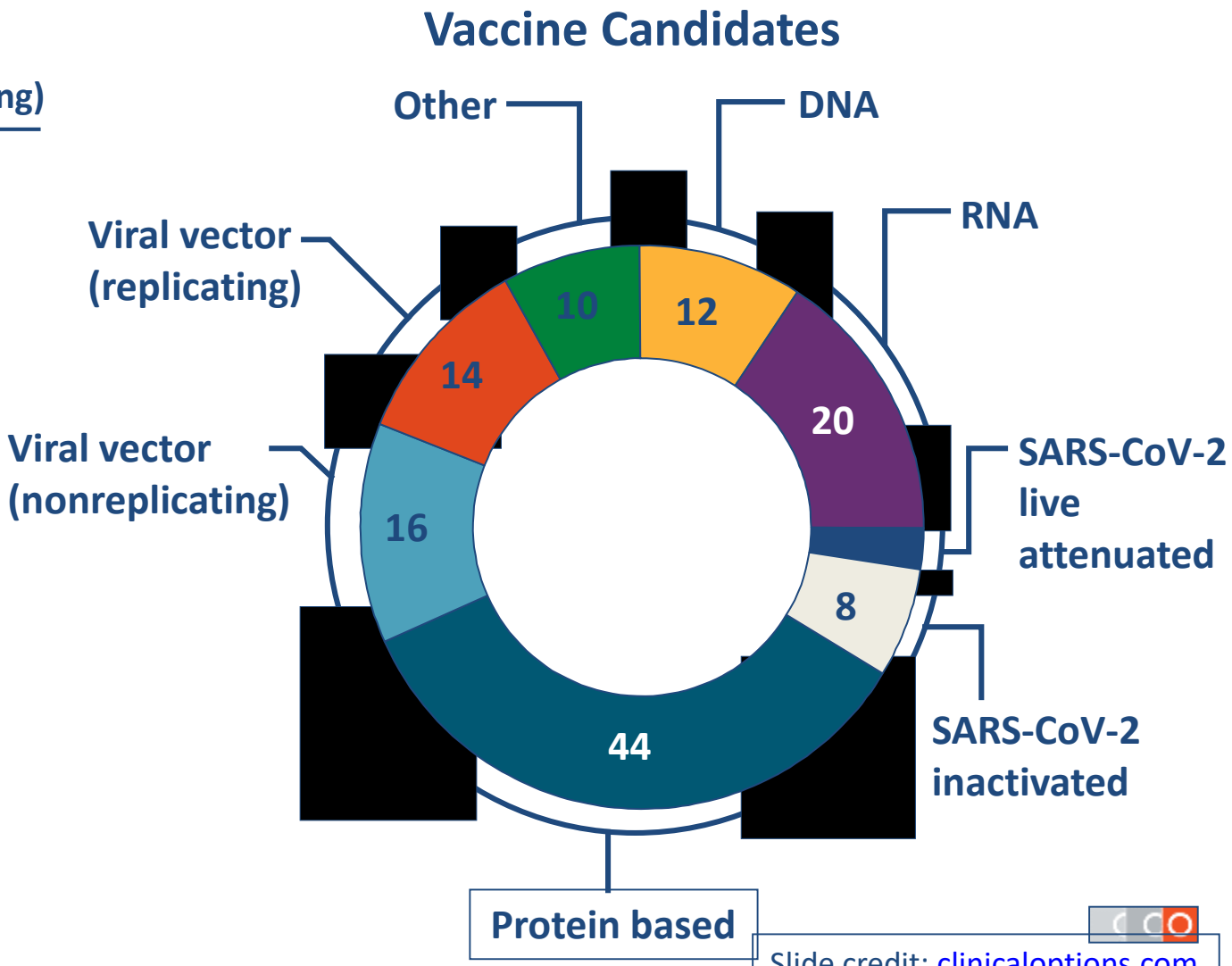
IDSA Guidance	Patient Population	Treatment
Recommends	▪ Hospitalized with critical* COVID-19	▪ Dexamethasone[†]
Suggests	▪ Hospitalized with severe[‡] COVID-19 ▪ Hospitalized with severe*[‡] COVID-19	▪ Dexamethasone[†] ▪ Remdesivir[‖]
Recommends only in clinical trial	▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19	▪ Lopinavir/ritonavir ▪ Convalescent plasma
Recommends against	▪ COVID-19 ▪ Hospitalized with COVID-19	▪ (Hydroxy)chloroquine ▪ (Hydroxy)chloroquine + azithromycin
Suggests against	▪ Hospitalized with nonsevere[§] COVID-19 ▪ Hospitalized with COVID-19	▪ Glucocorticoids ▪ Tocilizumab
Suggests against outside clinical trial	▪ Hospitalized with severe COVID-19	▪ Famotidine

*Mechanical ventilation or ECMO. [†]If unavailable, methylprednisolone and prednisone acceptable at equivalent total daily doses. $SpO_2 \leq 94\%$ on room air, including those on supplemental oxygen. [§] $SpO_2 > 94\%$, no supplemental [‖] patients on supplemental oxygen, 5 days suggested; for patients on mechanical ventilation or ECMO, 10 days.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 3.3.0.

Vaccine Candidates in Development for SARS-Cov-2



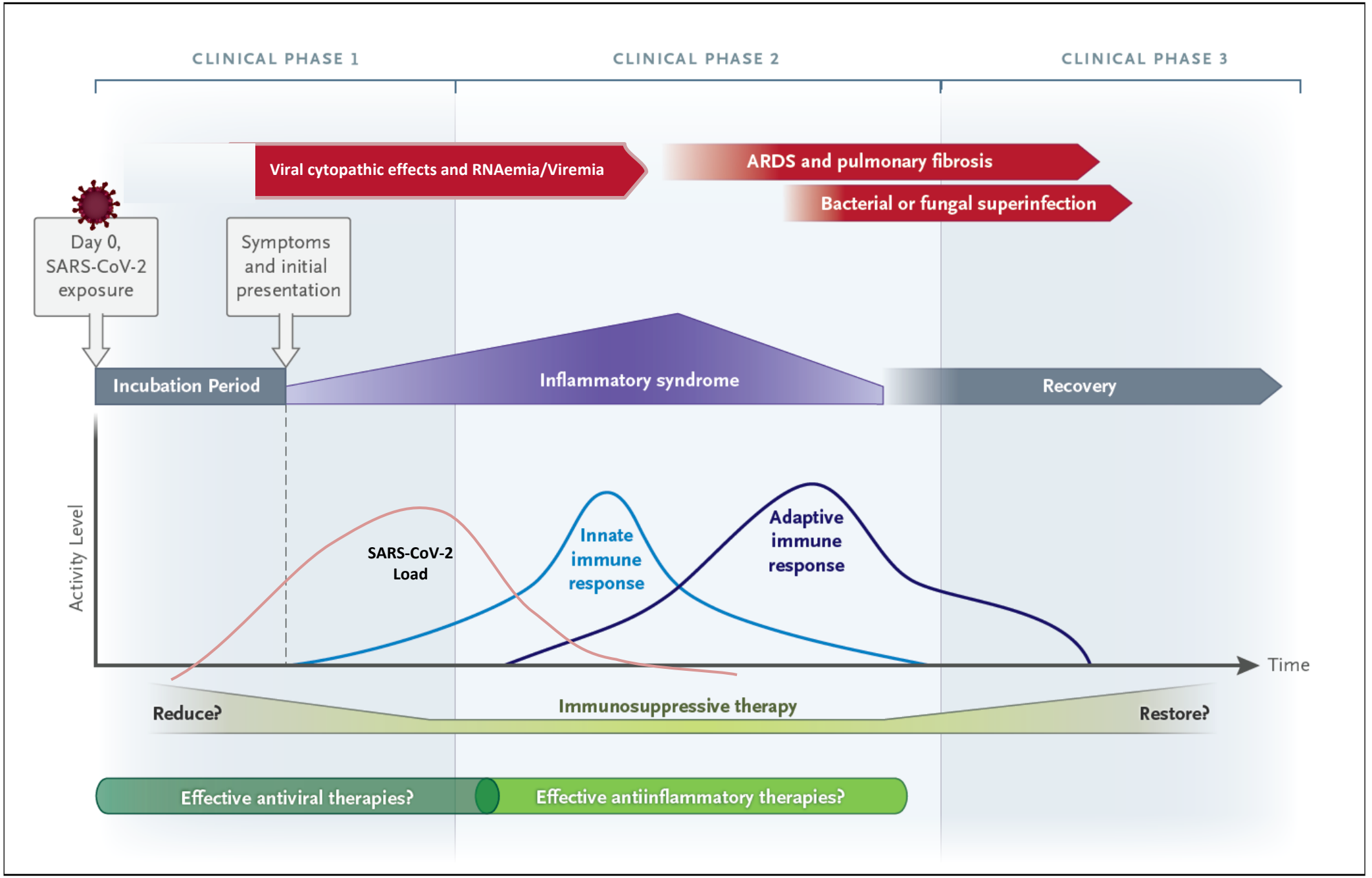


Funk. Frontiers in Pharmacology. 2020;[Epub].

Slide credit: clinicaloptions.com

Reinfection?

- Incomplete data
- Healthy person from Hong Kong – two distinct genetic sequences
- Nevada – 25 yo man 2 mos after initial case contracted severe COVID-19 caring for his parents.
- >10 cases so far (Hong Kong, the United States, India, Ecuador, Netherlands, and Belgium)



Fishman et al. NEJM, CPC, 2020

Stay Safe

Thanks!

If I can help:
Fishman.jay@mgh.harvard.edu