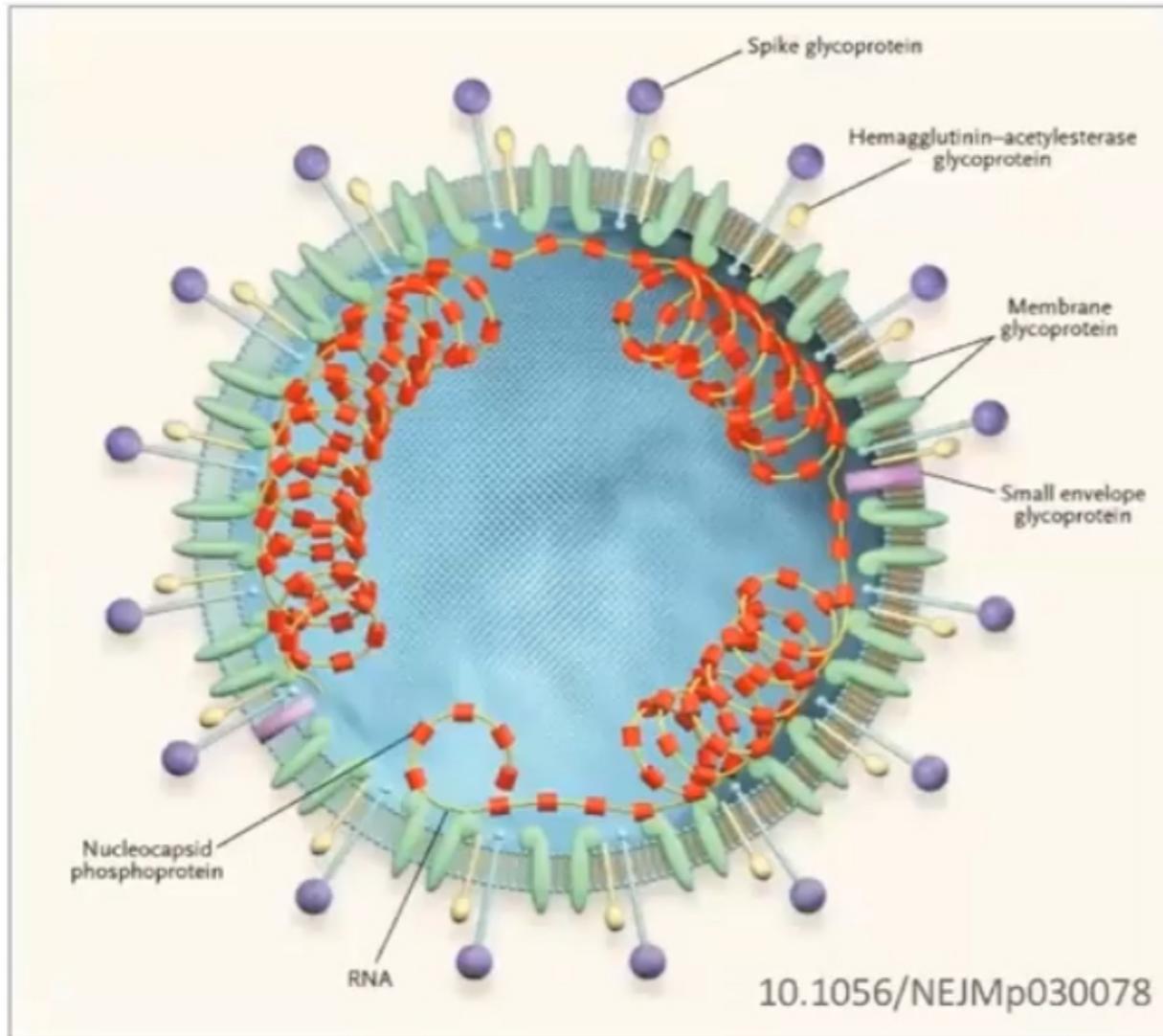


**COVID-19: ACUTE AND POST-ACUTE DIAGNOSIS AND TREATMENT
RIGHT CARE INITIATIVE**

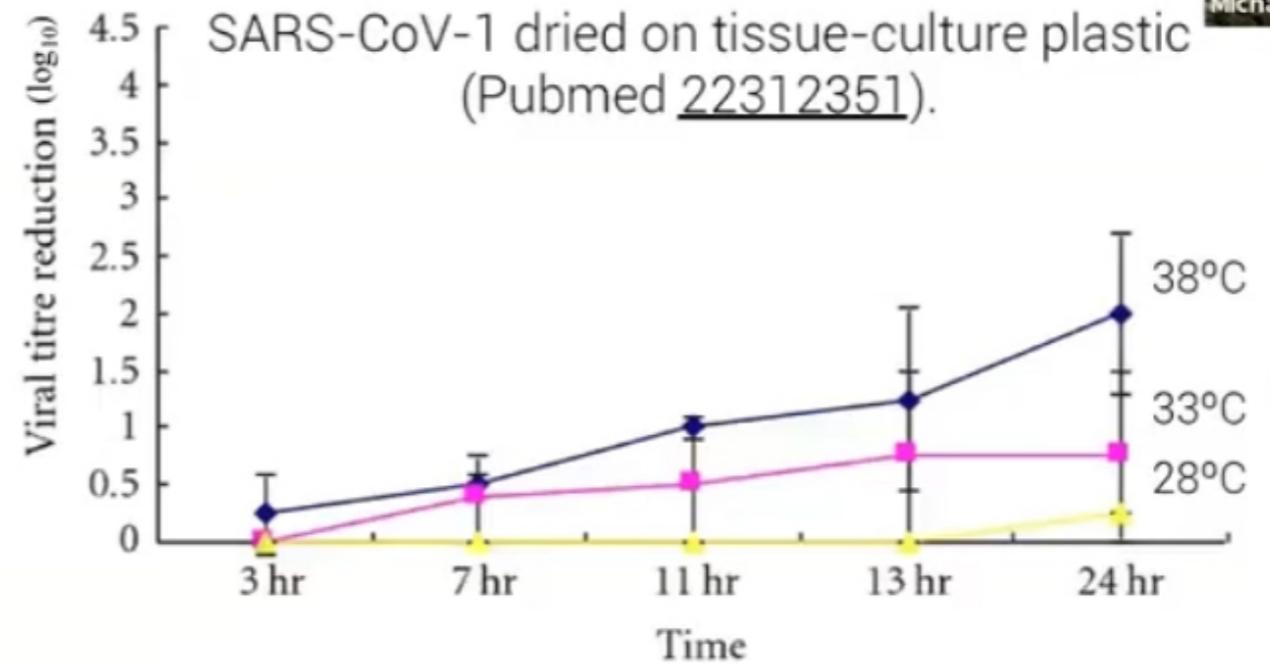
FEBRUARY 23, 2021

**WILLIAM BOMMER, MD FACC
UNIVERSITY OF CALIFORNIA, DAVIS**

SARS-CoV-1/2 environmental sensitivity



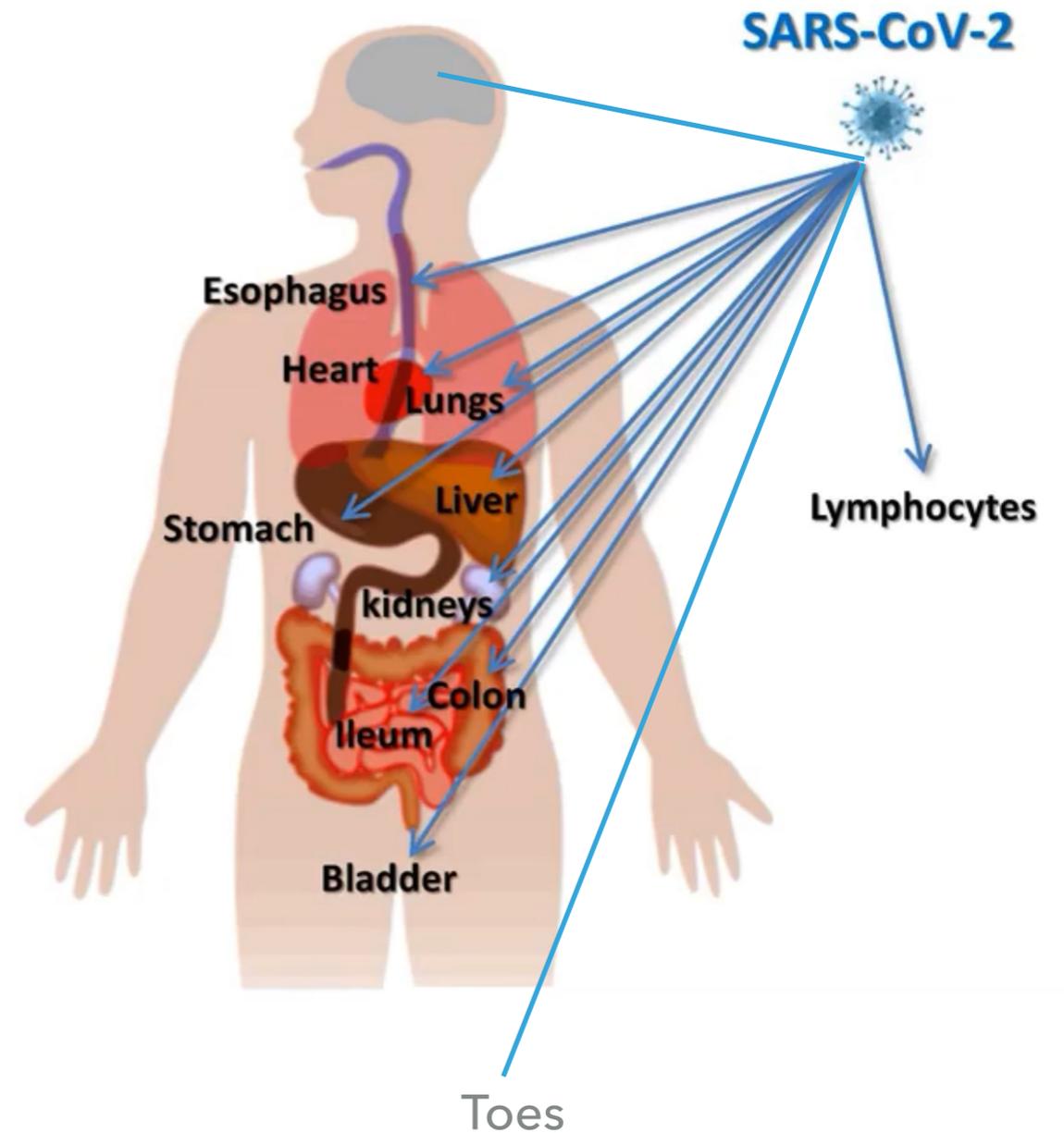
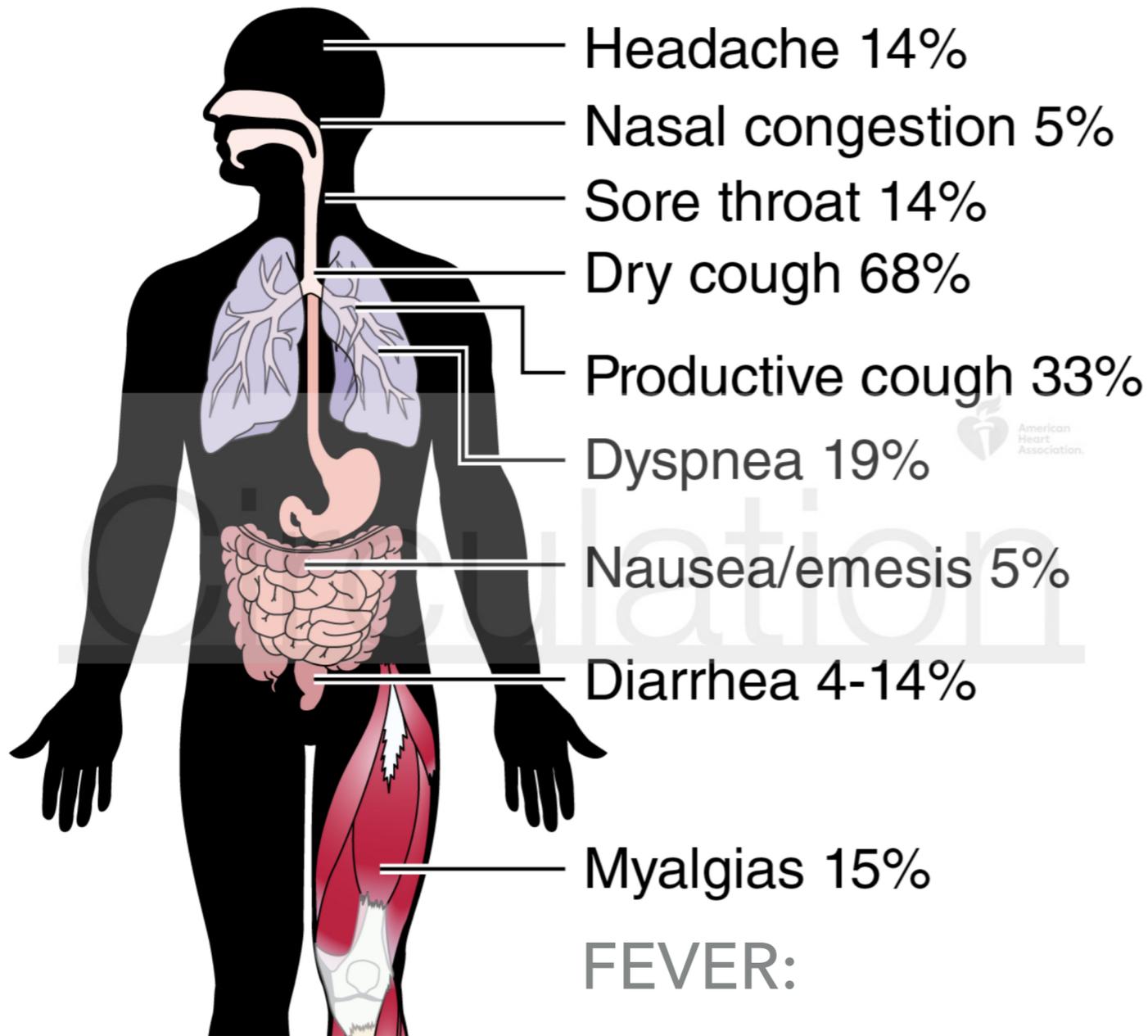
- Enveloped virus (with a plasma membrane), disrupted by surfactants/detergents, 60-80% alcohol, bleach.



- Sensitive to UV
 - 2–3x more sensitive than influenza virus to UV (Pubmed [17880524](#), [16254359](#)).
 - Estimated 10-fold survival decrease after 2–3h direct sunlight
- Sensitive to temperature
 - 10-fold survival decrease with 5°C temperature increase (Pubmed [22312351](#))
 - Killed by 30min 75°C heat (Pubmed [14631830](#)).

WHAT TO DO AND BE AWARE OF IF A HIGH-RISK INDIVIDUAL CONTRACTS THE VIRUS

ACUTE INFECTION

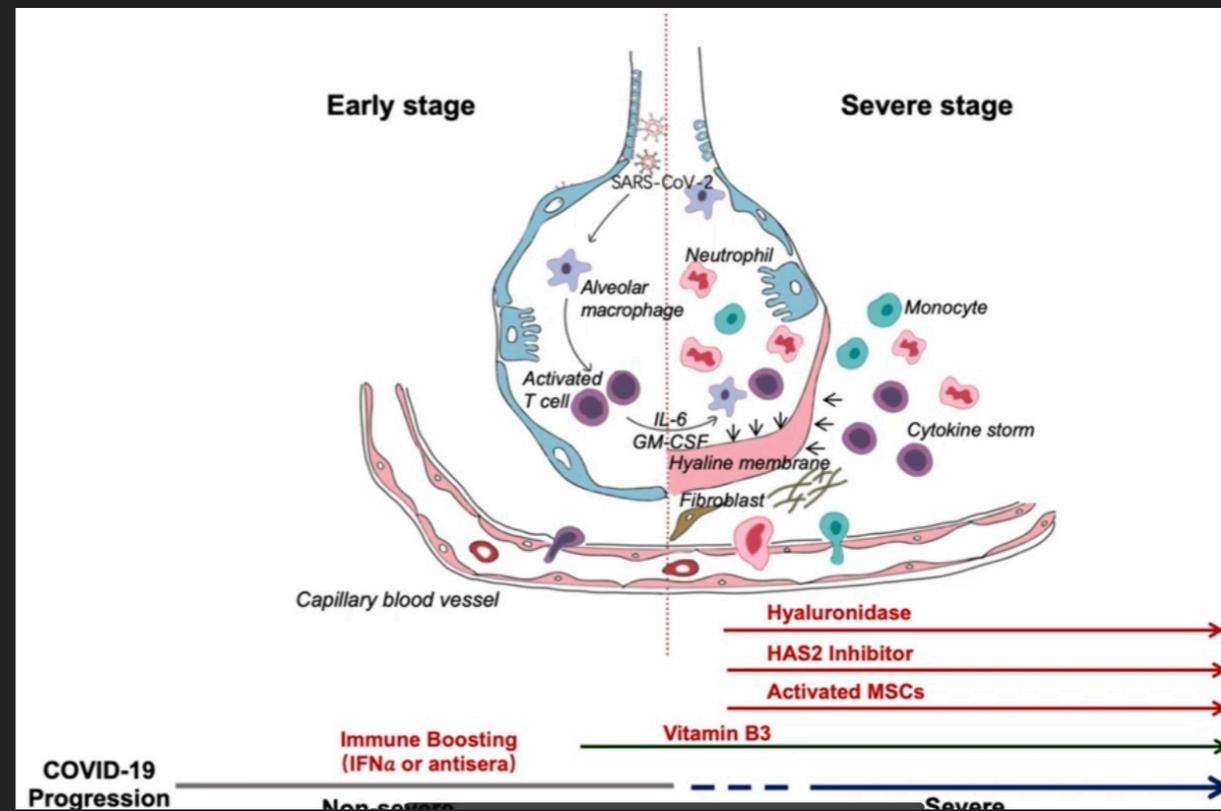


500,000 Deaths US

ACUTE INFECTION

LUNGS

Cardiovascular



Putative mechanisms of cardiac injury in COVID-19 patients

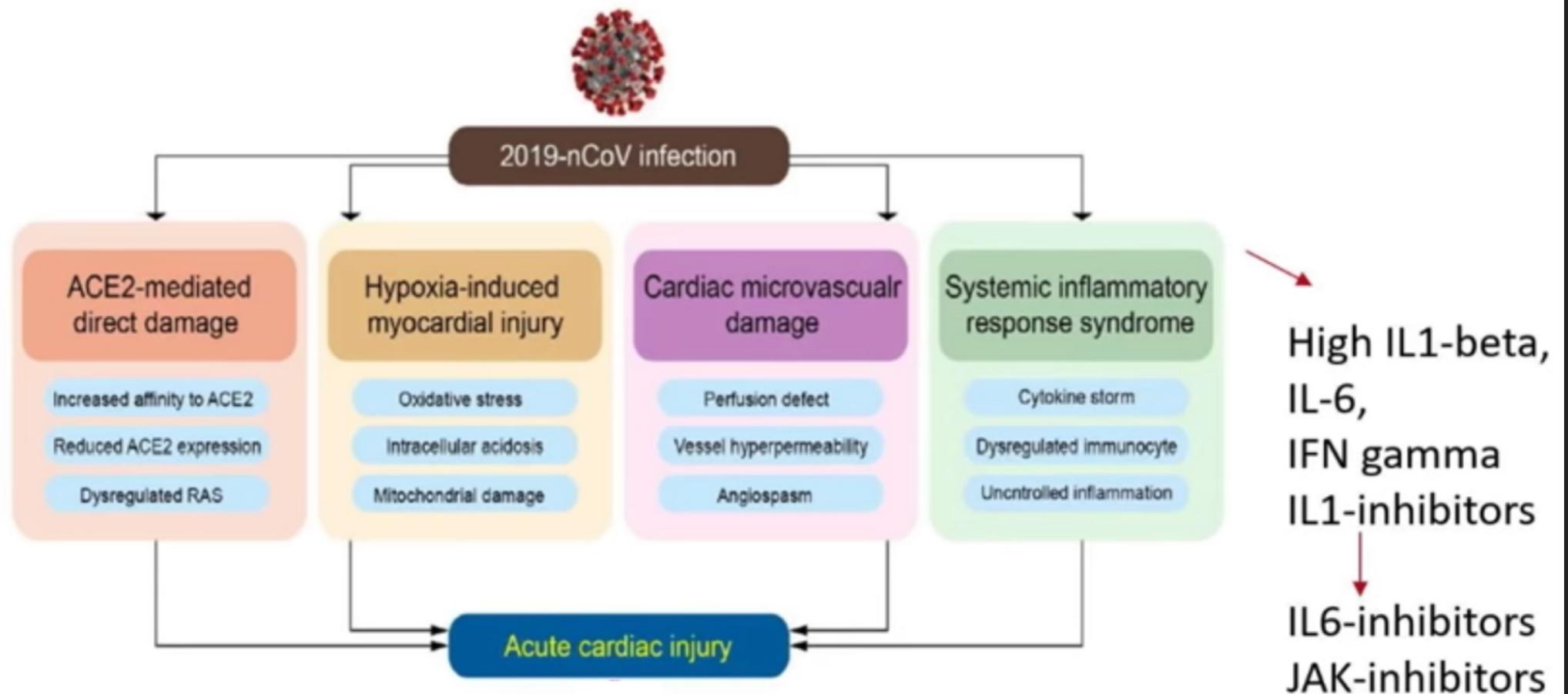
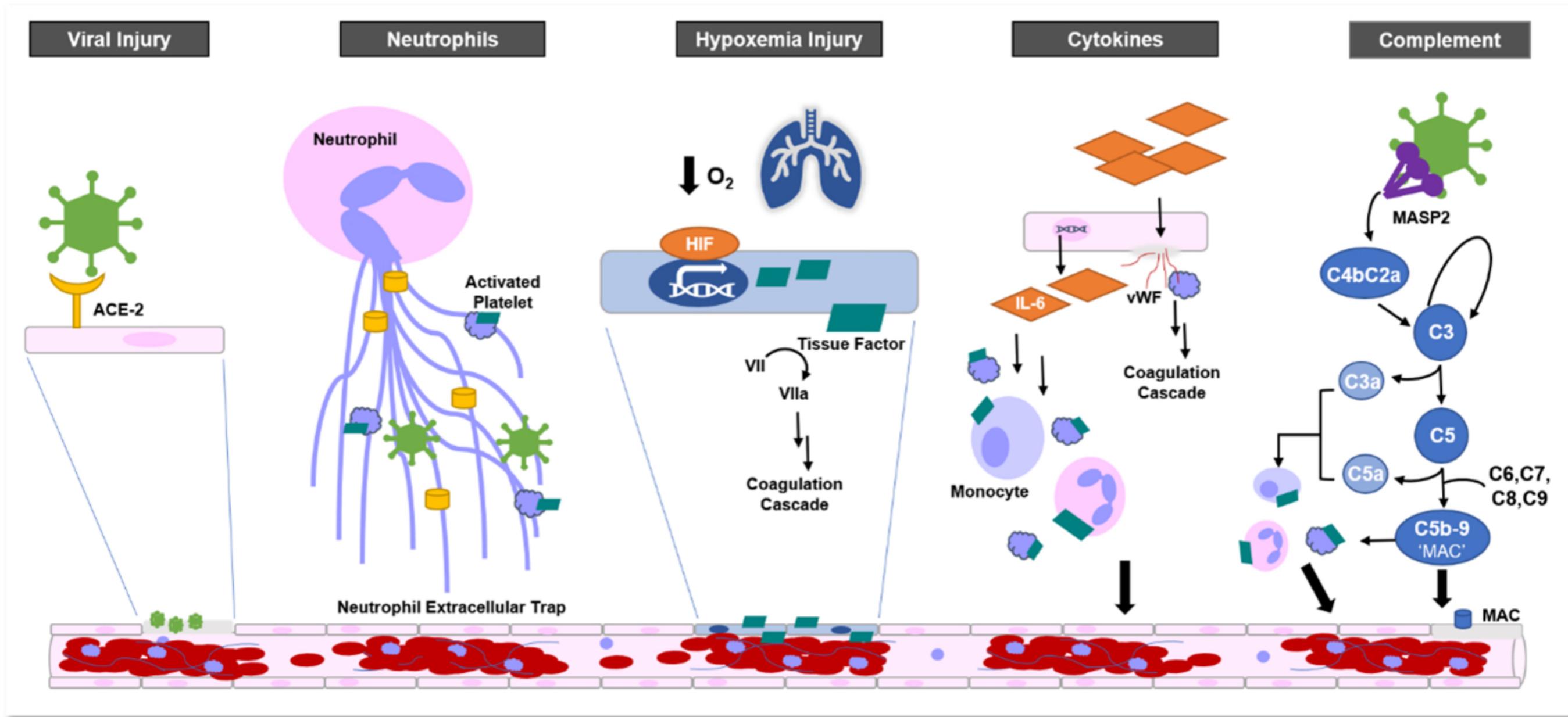


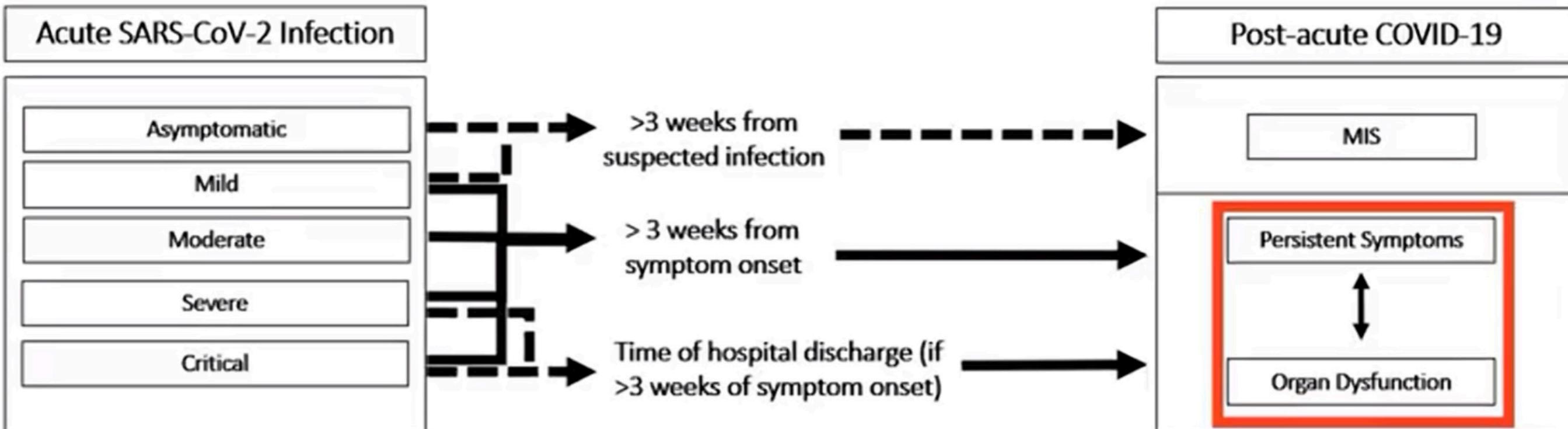
Figure 1: Hypothesized Mechanisms of Microvascular Thrombosis in COVID-19



These mechanisms include direct viral injury through infection via the angiotensin-converting enzyme 2 (ACE-2) receptor; activation of neutrophil extracellular traps that promote viral phagocytosis and thrombosis; hypoxemia injury that initiates expression of hypoxia-induced transcription factors (HIFs) that promote tissue factor expression; cytokines that promote tissue factor expression in inflammatory cells and platelets and can induce VWF release by endothelial cells; and complement pathway activated by mannose-binding lectin-associated serine protease 2 (MASP2), C3a and C5a recruitment and activation of inflammatory cells, and membrane attack complex (MAC) platelet activation and endothelial injury.

ACUTE INFECTION

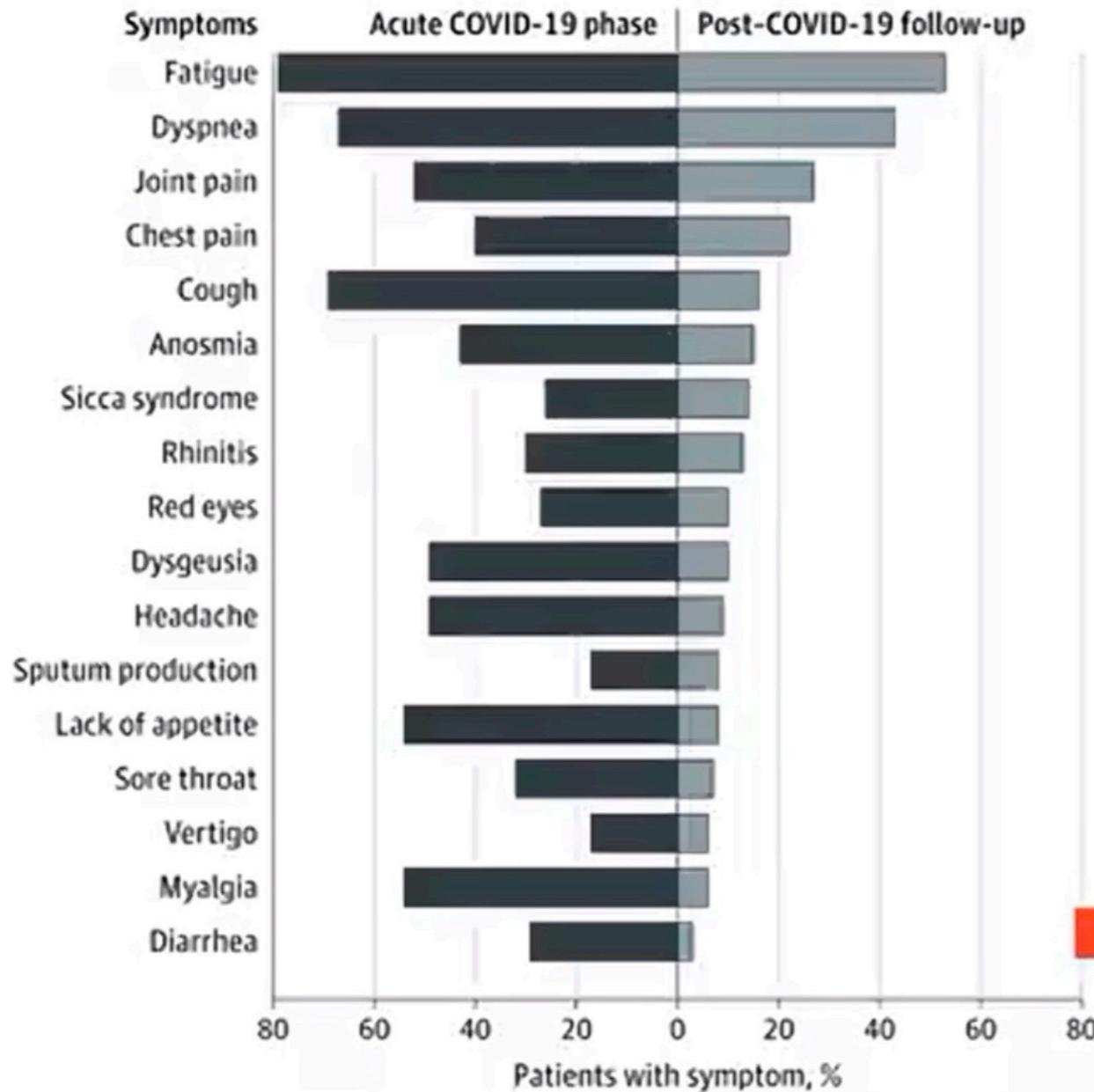
POST-ACUTE INFECTION



There is likely a relationship between organ dysfunction and persistent symptoms that is not yet completely understood.

From: Persistent Symptoms in Patients After Acute COVID-19

POST-ACUTE INFECTION



- N=143 patients hospitalized in Italy
- Mean age 56.5y
- 53% female
- 12.6% ICU admission

Days since symptoms onset, mean (SD)	60.3 (13.6)
Days since discharge, mean (SD)	36.1 (12.9)
Persistent symptoms, No. (%)	
None	18 (12.6)
1 or 2	46 (32.2)
≥3	79 (55.2)
Worsened quality of life, No. (%) ^b	63 (44.1)

Cardiovascular sequelae

- Acute manifestations

- Cardiac injury, myocarditis, arrhythmias, cardiogenic shock
- Thromboembolic disease

- Post-acute manifestations

- Myocardial inflammation > myocarditis > myocardial fibrosis/scar
- Arrhythmias > out-of-hospital cardiac arrest/sudden cardiac death
- Cardiomyopathy (including Takotsubo)

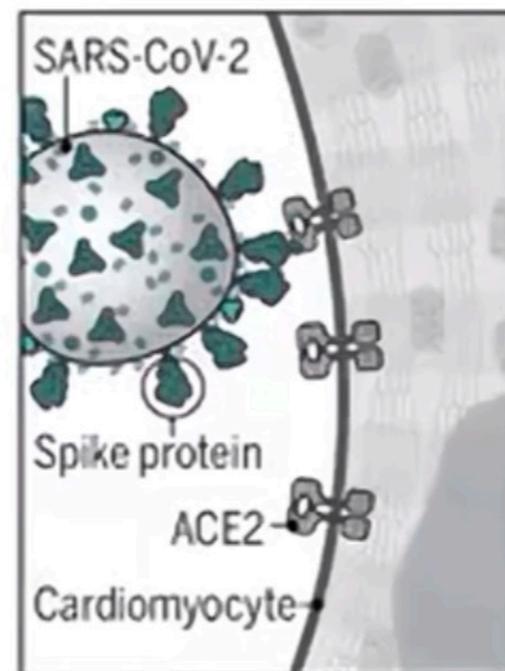
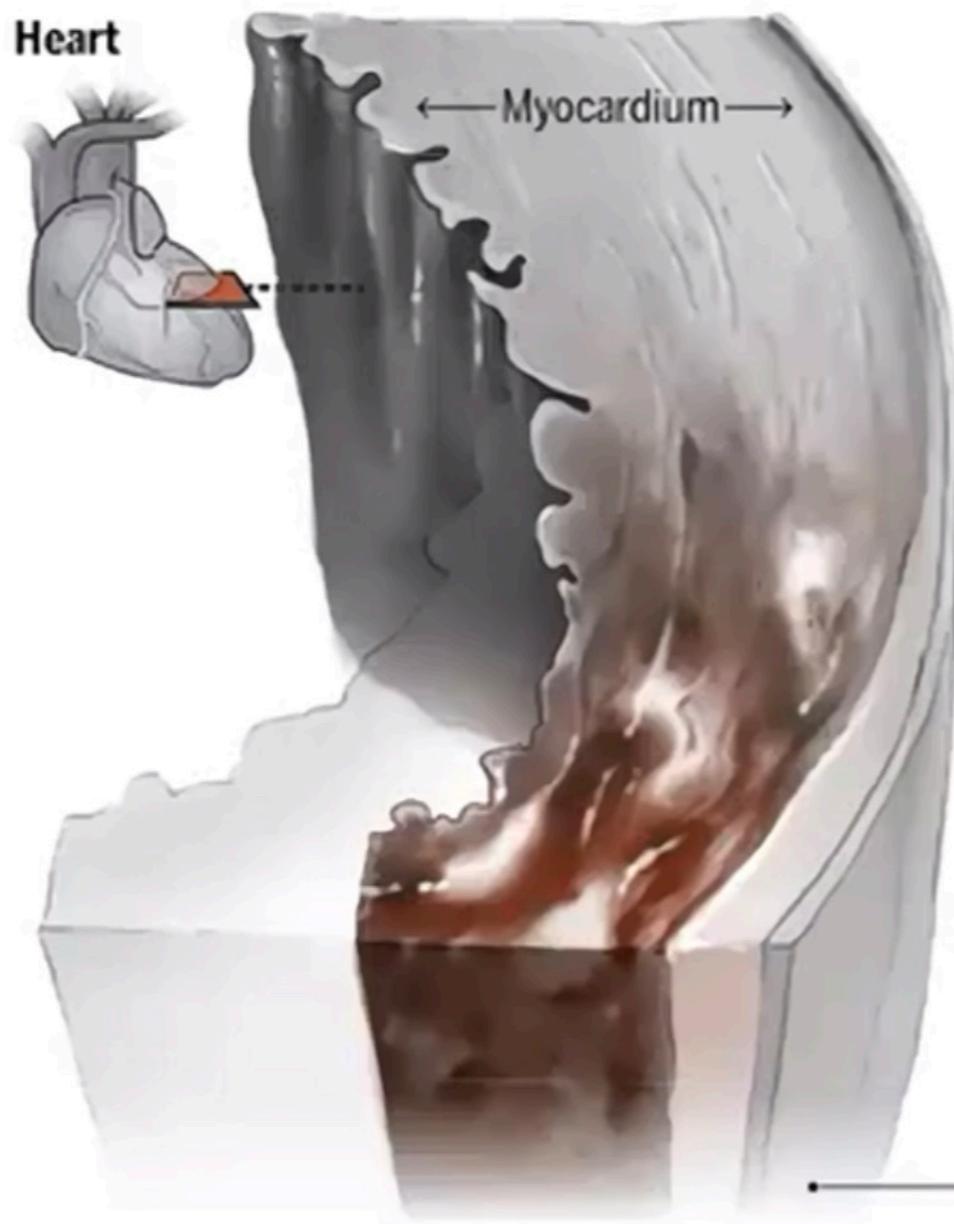
POST-ACUTE INFECTION

COVID-19 can affect the heart

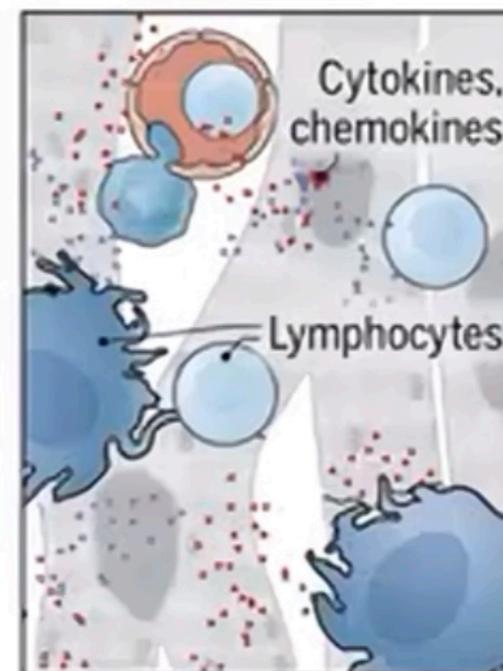
Eric J. Topol

Damaging the heart

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has the potential to directly and indirectly induce cardiac damage.



SARS-CoV-2 can **directly infect** cardiomyocytes, attaching to angiotensin-converting enzyme 2 (ACE2) through its spike protein and entering the cells by fusing viral and cellular membranes.



SARS-CoV-2 infection can **indirectly damage** cardiomyocytes through systemic inflammatory responses and diminished blood supply (e.g., from blood clots and endothelitis, not shown).

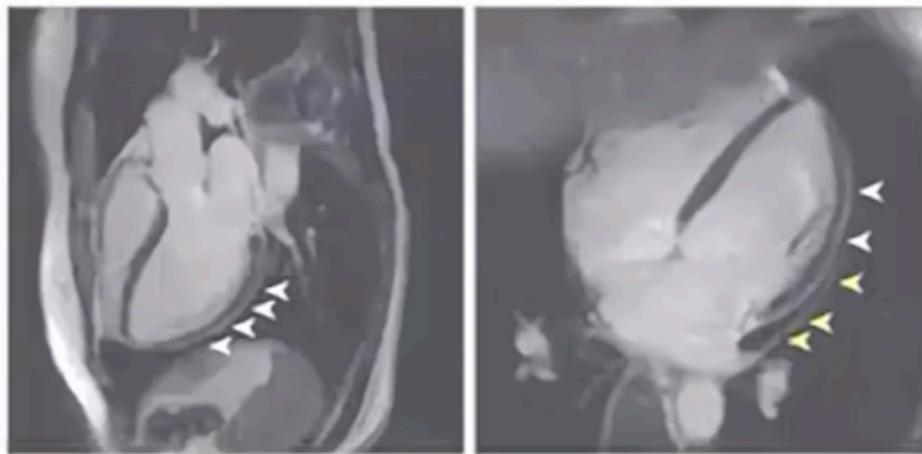
◀ Complications

Damaged cardiomyocytes, necrosis, and cardiogenic shock can result from direct and/or indirect effects of SARS-CoV-2 infection. This can lead to scarring and thinning of the myocardium, myocarditis, cardiomyopathy, arrhythmias, and potentially cardiac arrest.

Pericardium

Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

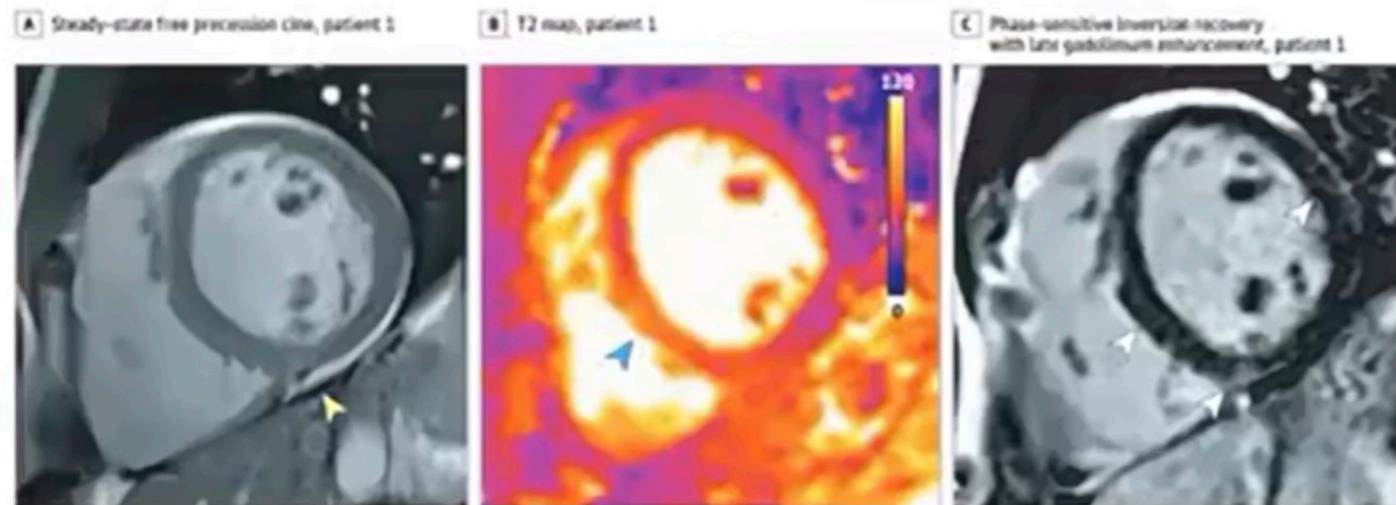
- German study, n=100 patients
- Cardiac MRI performed median 71 days after COVID-19 diagnosis
 - Cardiac involvement in 78%
 - Ongoing myocardial inflammation in 60%
- Presence of chronic comorbidities, duration and severity of acute COVID-19, time since original diagnosis did not correlate with findings



POST-ACUTE INFECTION

Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection

Figure. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From Coronavirus Disease 2019 Infection



Persistent cardiac abnormalities identified not only in the elderly with multimorbidity but also among healthy young athletes.

- 26 competitive college athletes diagnosed with COVID-19 (RT-PCR)
- None were hospitalized
- Majority did not report symptoms
- 12 (46%) had evidence of myocarditis or prior myocardial injury by cardiac magnetic resonance imaging routinely performed for positive testing results (range, 12-53 days)

Pulmonary sequelae

- Acute manifestations
 - Pneumonia, ARDS, hypoxic respiratory failure
- Post-acute manifestations = Sx/signs of restrictive lung disease
 - After hospital discharge:
 - 30d = 53% decreased DLCO, 49% diminished respiratory muscle strength
 - 3mo = 25% decreased DLCO
 - 3mo = 71% with radiographic evidence of interstitial thickening and fibrosis

POST-ACUTE INFECTION

If compounded on cardiovascular comorbidity, persistent decline in pulmonary function could have significant consequences

Neurological associations of COVID-19

Mark A Ellul, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Benedict Daniel Michael, Ava Easton, Rachel Kneen, Jim Sejvar, Tom Solomon

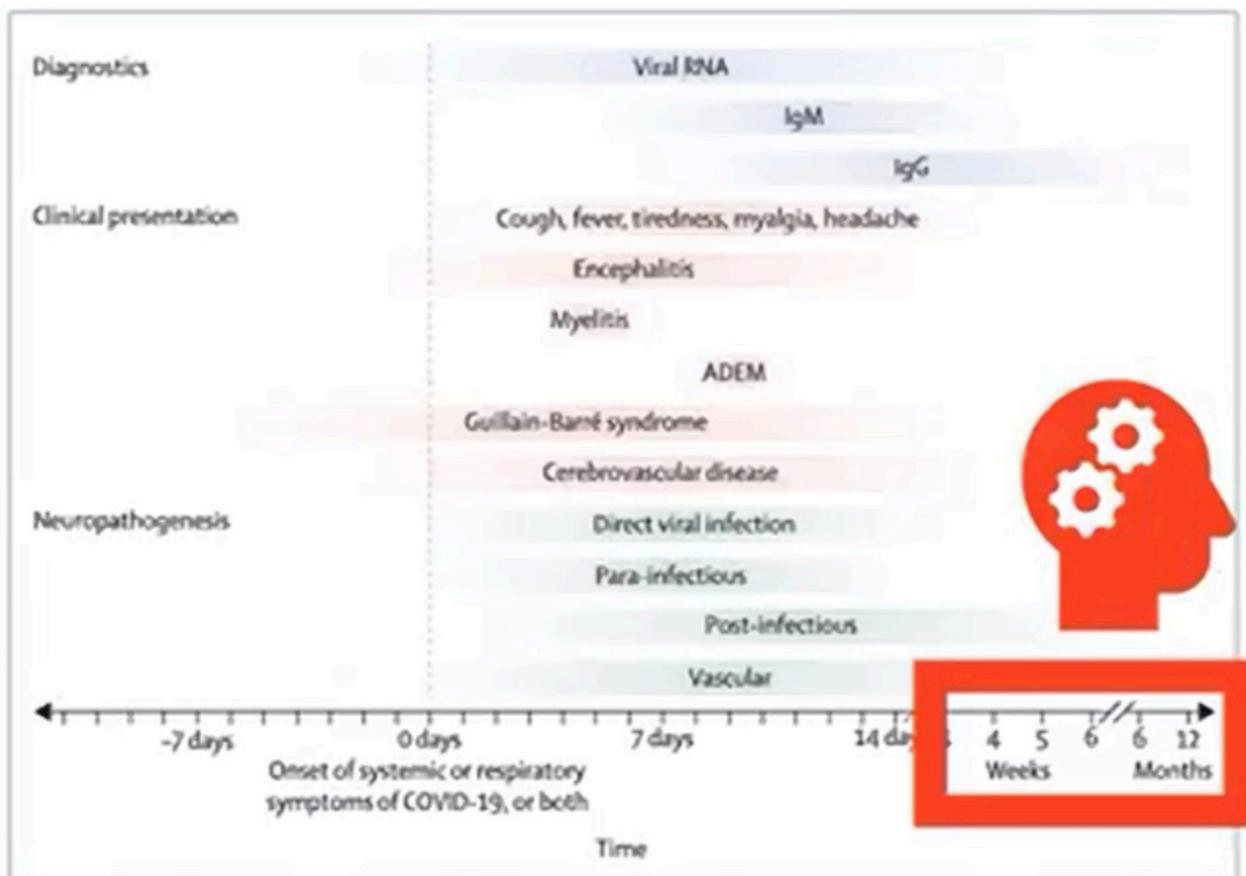


Figure 1: Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease

POST-ACUTE INFECTION

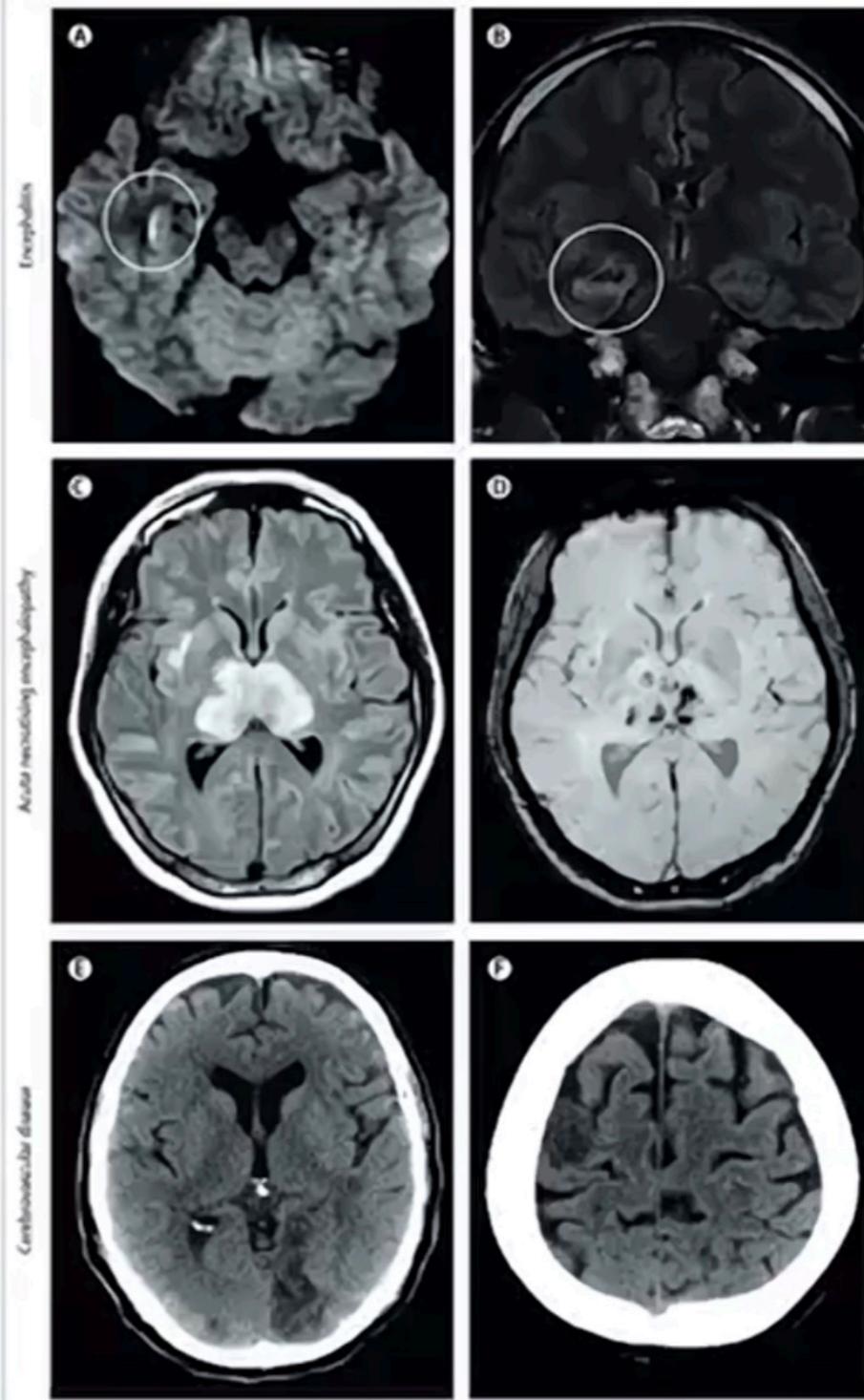


Figure 2: Brain imaging in patients with neurological disease associated with COVID-19

Renal sequelae

- Acute manifestation

- AKI (37-40% of severe COVID-19 cases in U.S.), hematuria, proteinuria
- Portends a higher risk of mortality
- Histopathology reveals ATN >> collapsing FSGS >> “COVAN” (COVID-associated nephropathy)

POST-ACUTE INFECTION

- Post-acute manifestation = prolonged kidney dysfunction

- 31% of patients requiring RRT remained on dialysis at discharge
- 37% of patients not requiring RRT continued to have kidney dysfunction

MIS-A: post-acute/infectious inflammatory syndrome

Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020



Summary

What is already known about this topic?

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe complication of SARS-CoV-2 infection in children and adolescents. Since June 2020, several case reports and series have been published reporting a similar multisystem inflammatory syndrome in adults (MIS-A).

What is added by this report?

Cases reported to CDC and published case reports and series identify MIS-A in adults, who usually require intensive care and can have fatal outcomes. Antibody testing was required to identify SARS-CoV-2 infection in approximately one third of 27 cases.

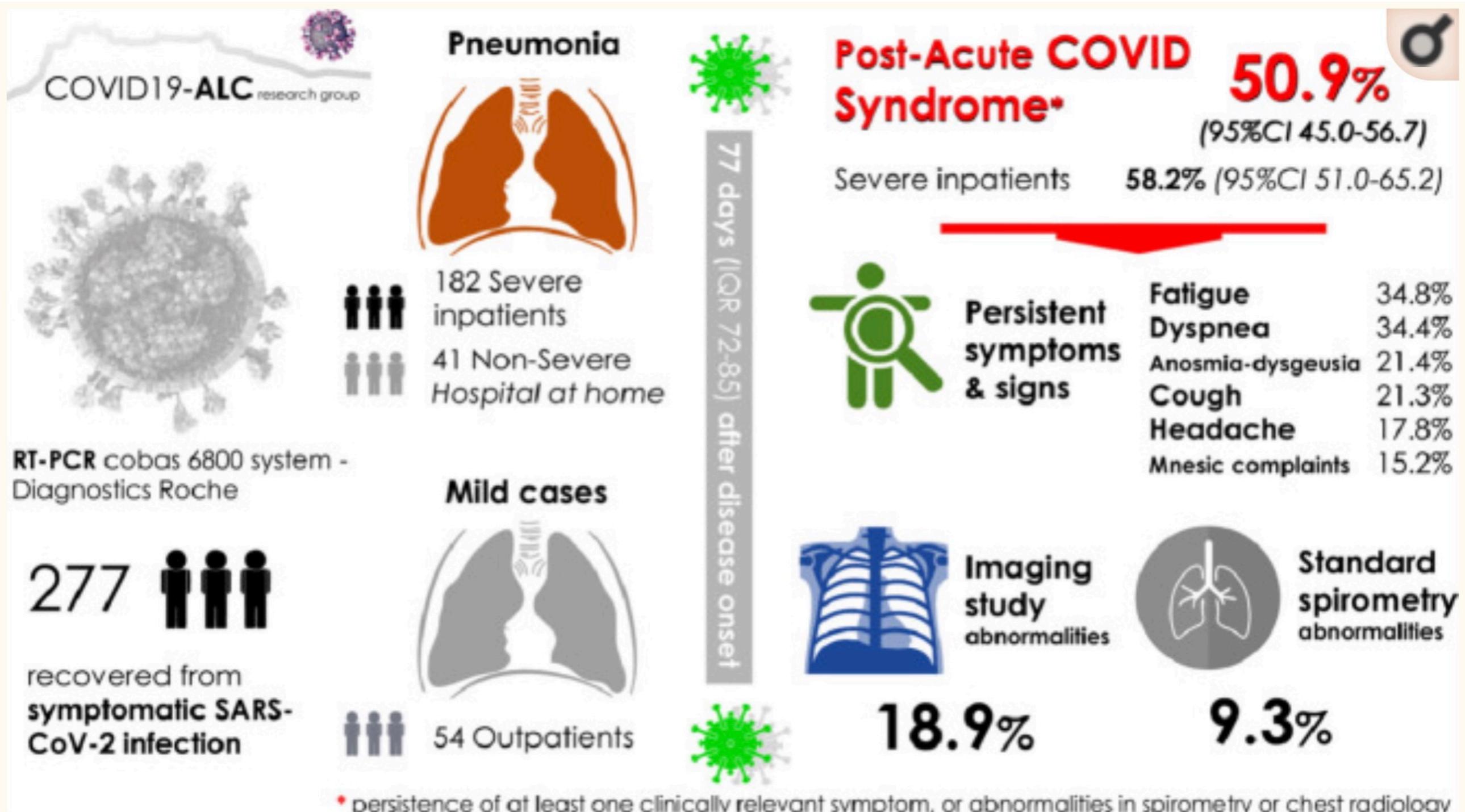
What are the implications for public health practice?

Clinical suspicion and indicated SARS-CoV-2 testing, including antibody testing, might be needed to recognize and treat adults with MIS-A. Further research is needed to understand the pathogenesis and long-term effects of this condition.

Ultimately, the recognition of MIS-A reinforces the need for prevention efforts to limit spread of SARS-CoV-2.

Post-acute COVID-19 Syndrome. Incidence and risk factors: a Mediterranean cohort study.

[Oscar Moreno-Pérez](#), MD, PhD,^{a,b,#} [Esperanza Merino](#),^{c,#*} [Jose-Manuel Leon-Ramirez](#), MD,^d [Mariano Andres](#),



Pneumological features**Pneumologist***

Dyspnea, %

Persistence

34.4 (95/277)

11.1 (31/277)

Cough, %

Persistence

21.3 (59/277)

2.1 (6/277)

Neurological features**Neurologist***

Headache, %

17.8 (49/277)

Moderate-Severe*, %

53 (26/49)

Persistence, %

2.9 (8/277)¹

De novo, %

2.5 (7/277)

Pathological CT or MR, %

0.3 (1/277)

Mnesic complaints, %

15.2 (42/277)

Clinical relevance*, %

57.1(24/42)

Persistence, %

5.0 (14/277)²

De novo, %

3.6 (10/277)

Pathological CT or MRI, %

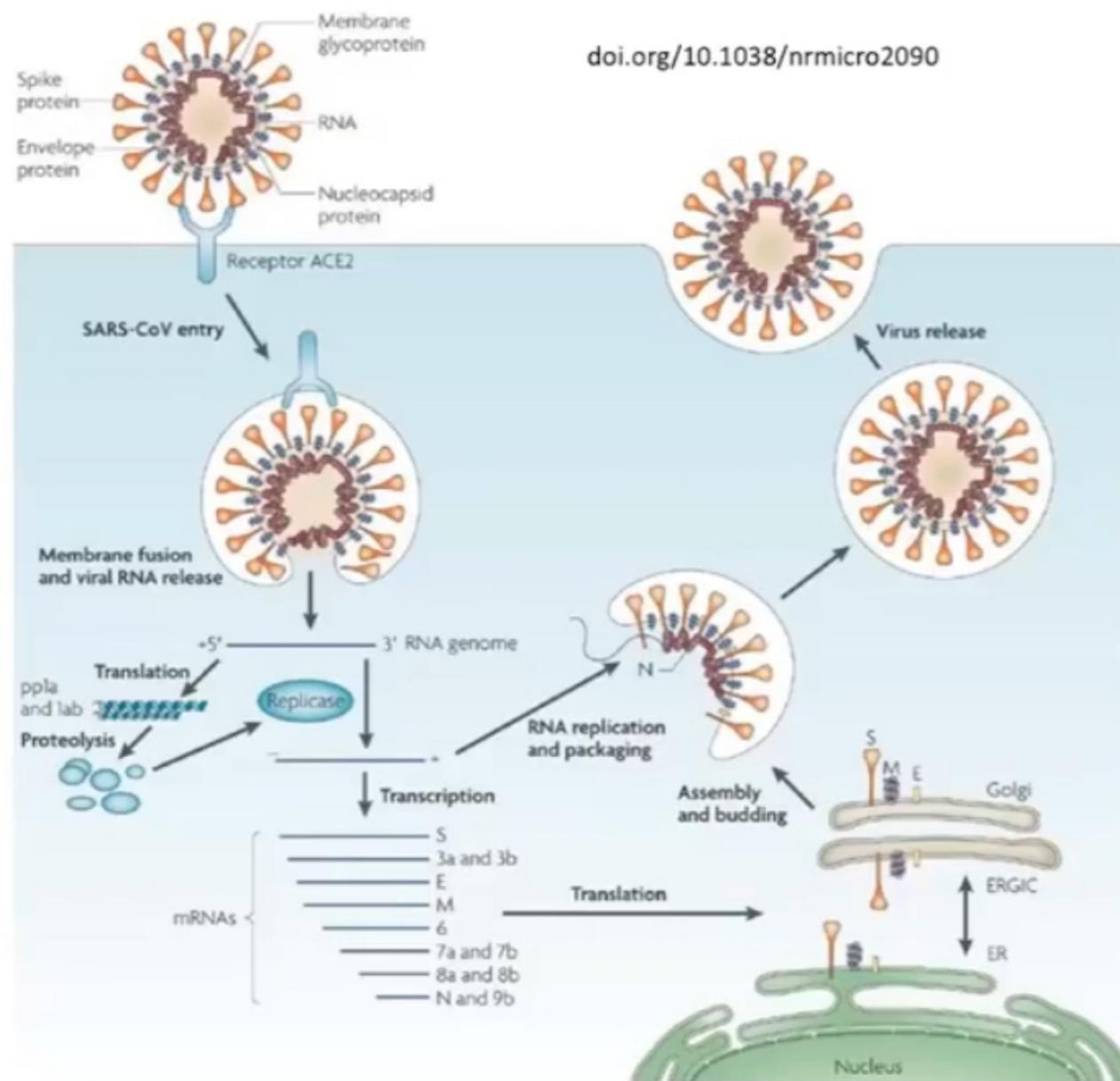
1.4 (4/277)

Pathological neurocognitive test,

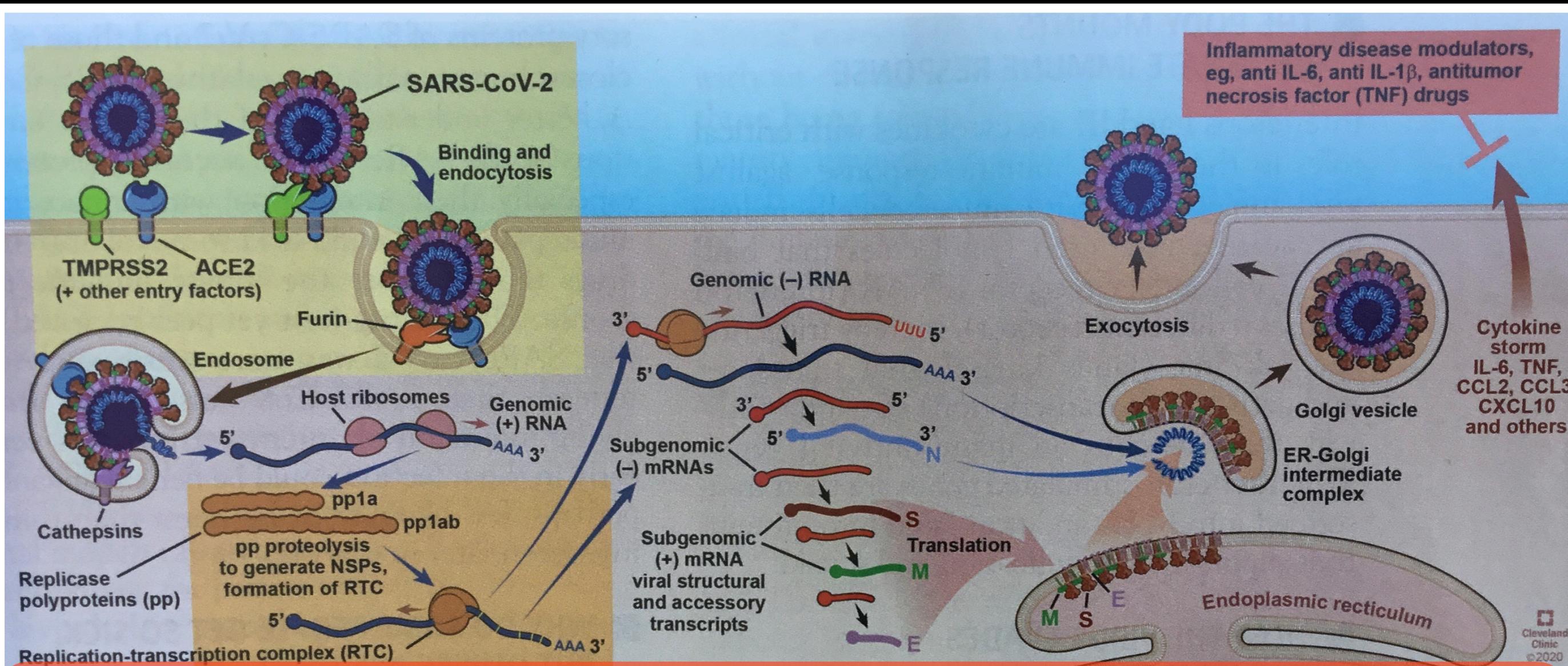
1.8 (5/277)³

WHAT ARE SOME OF THE ACUTE TREATMENT OPTIONS ?

SARS-CoV-1/2 life cycle



1. Spike protein (S) binds to ACE2.
2. The transmembrane protease TMPRSS or endosomal cathepsin L cleaves S to activate membrane fusion.
3. Cellular ribosomes translate a nonstructural polyprotein from the positive-strand RNA.
4. Embedded viral proteases process the polyprotein to create the replicase.
5. The replicase produces full-length copies of both strands and subgenomic mRNAs.
6. Ribosomes translate the subgenomic mRNAs to produce structural proteins.
7. Structural proteins package the positive-strand RNA and bud off into exocytic vesicles.



Blockade of entry

- | | |
|-------------------------------------|------------------------|
| Antispikes antibody | Endocytosis inhibitors |
| Convalescent serum | Chloroquine |
| Vaccine against spike | Hydroxychloroquine |
| Inhibition of S1/S2 cleavage | |
| Anti-TMPRSS2 agents | |

Blockade of replication

- Interference with RdRP (replicase)
- Remdesivir (GS-5734)
- EIDD-1931
- Viral protease inhibitor
- Ribavirin

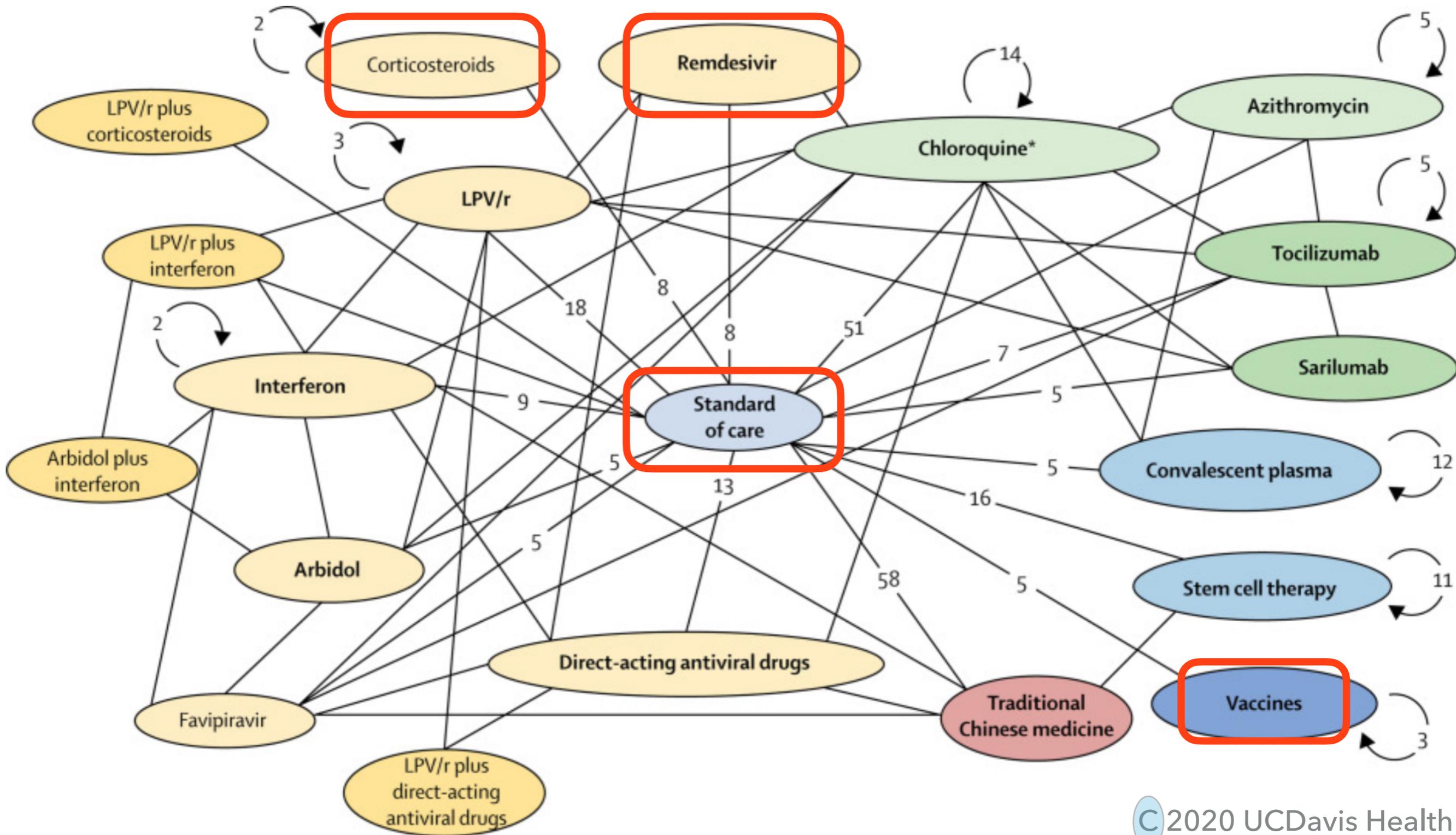
Boosters of innate immune response

- MDA5
- IFN-I, IFN-III
- ISG effectors
- OAS, PKR

Enhancers of antiviral innate immunity

- Early treatment with IFN or IFN inducers
- Blockade of IFN antagonists

ACUTE TREATMENT OPTIONS: EARLY TRIALS



Coronavirus Disease 2019 Treatment Guidelines

VIEW GUIDELINES

Credit NIAID-RML

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnote.

DISEASE SEVERITY

PANEL'S RECOMMENDATIONS

Not Hospitalized,
Mild to Moderate COVID-19

There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who are at high risk of disease progression.^a

The Panel recommends against the use of **dexamethasone** or **other corticosteroids (AIII)**.^b

Hospitalized but Does Not Require
Supplemental Oxygen

The Panel recommends against the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.^b

There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.

Hospitalized and Requires
Supplemental Oxygen
(But Does Not Require Oxygen Delivery
Through a High-Flow Device,
Noninvasive Ventilation, Invasive
Mechanical Ventilation, or ECMO)

- Use one of the following options:
- **Remdesivir^{c,d}** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**
 - **Dexamethasone^e plus remdesivir^{c,d}** (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)^{f,g}**
 - **Dexamethasone^e** (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**

Hospitalized and Requires Oxygen
Delivery Through a High-Flow Device
or Noninvasive Ventilation

Use one of the following options:

- **Dexamethasone^{e,g} (AI)**
- **Dexamethasone^e plus remdesivir^{c,d} (BIII)^{f,g}**

Hospitalized and Requires Invasive
Mechanical Ventilation or ECMO

Dexamethasone^e (AI)^h

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

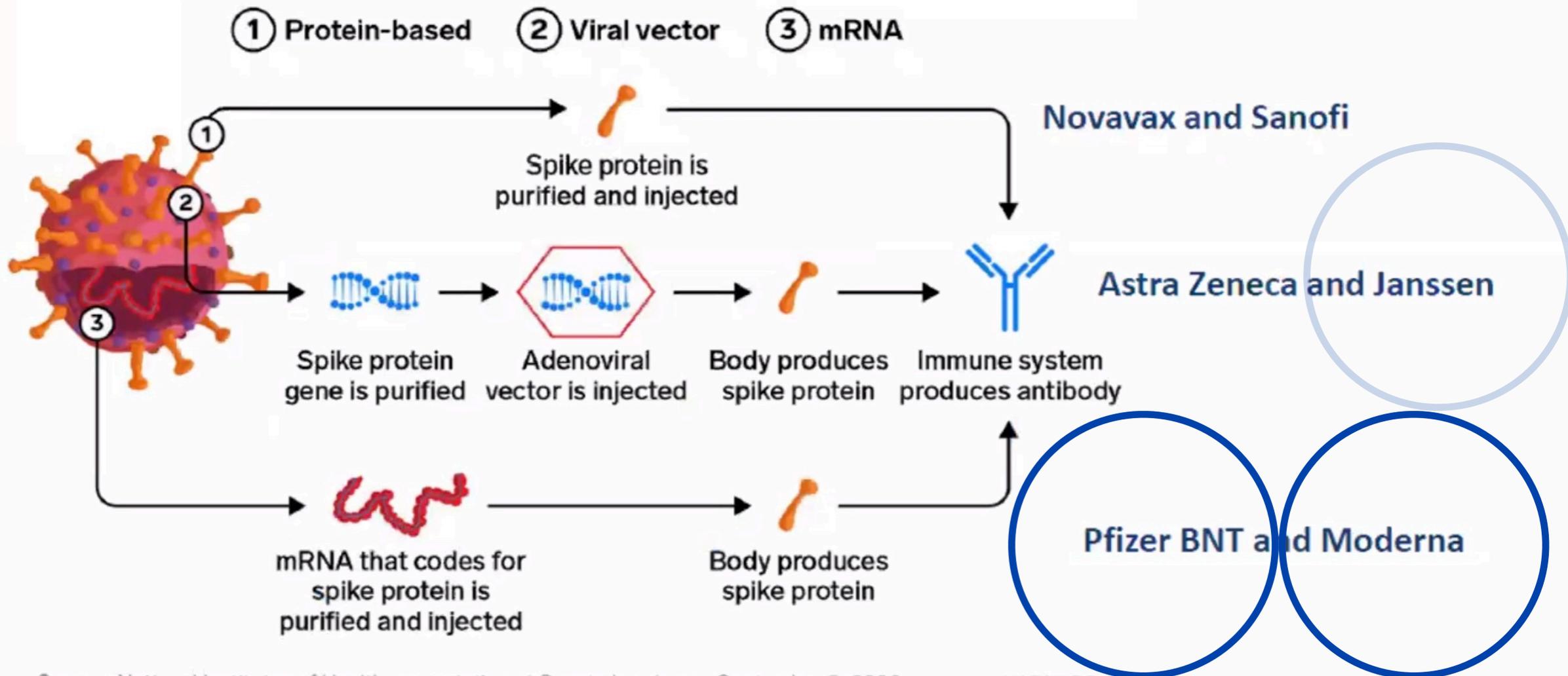
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

^a See the Anti-SARS-CoV-2 Monoclonal Antibodies section for more information on using bamlanivimab and casirivimab plus imdevimab in patients with mild to moderate COVID-19.

^b Patients who are receiving corticosteroids for other indications should continue therapy for their underlying conditions as directed by their health care providers.

Types of Vaccines in Development for COVID-19

Three types of coronavirus vaccines in development



Source: National Institutes of Health presentation at Senate hearing on September 9, 2020

INSIDER

CHRISTIAN SANDROCK, MD, MPH, FCCP

**POST ACUTE COVID 19: DIAGNOSIS,
TREATMENT, MANAGEMENT**

QUESTIONS AND ANSWERS BACKUP SLIDES

https://www.dhs.gov/sites/default/files/publications/mql_sars-cov-2_-_cleared_for_public_release_20200630.pdf

QUESTIONS?

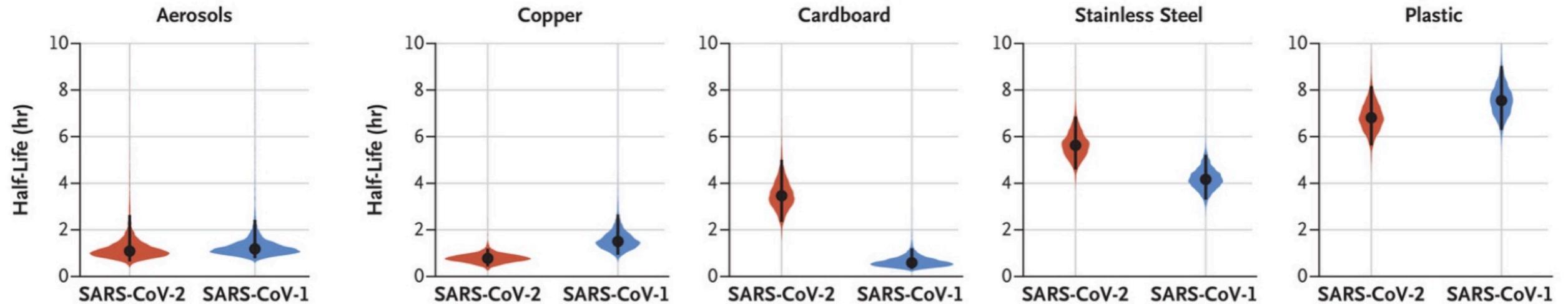
- ▶ **Who can catch SARS-CoV 2(Covid 19)?** Bats, pangolins, primates, ferrets, mink, hamsters, domestic cats, and tigers, and possibly sheep, cows, and goats can be infected, but not dogs, ducks, chickens, turkeys, or quail.
- ▶ **How many different coronaviruses are there?**
Coronaviruses have been around for centuries, perhaps thousands of years and may have co-evolved with bats over millions of years. There are thousands of different varieties. Four types cause about 35% of common colds, and 3 types are deadly. SARS killed almost 800 in 2002 before burning out, and MERS has killed over 800 so far, while SARS CoV 2 has killed 750,000.

QUESTIONS?

- ▶ **How does our body fight the virus?** Virus infected cells induce and secrete interferon I and III that trigger and activate many antiviral genes–RNA–proteins that suppress viral replication and spread (Oligoadenylate synthetase and ribonuclease L degrade viral RNA).
- ▶ **How does the virus evade this defense?** Coronaviruses interfere with interferon production and antiviral response with multiple accessory proteins. The virus blocks host sensor proteins and degrade host messenger RNA. The virus spikes flex and bend and are camouflaged in Glycan(sugar molecules) to avoid host blocking antibodies.

HOW LONG DOES COVID SURVIVE ON SURFACES

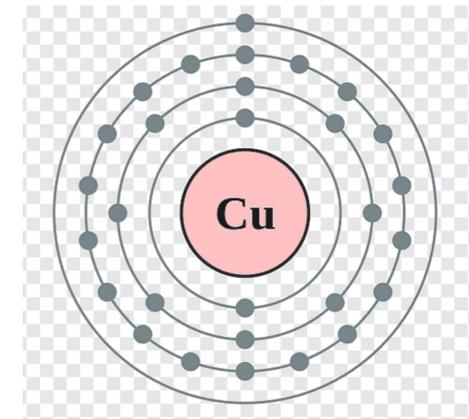
C Half-Life of Viable Virus



The virus's survival depends on the type of surface it lands on. The live virus can survive anywhere between three hours and seven days, depending on the material.

Here's how long the virus typically lasts on common surfaces:

- Glass – 5 days.
- Wood – 4 days.
- Plastic & stainless-steel – 3 days.
- Cardboard – 24 hours.
- Copper surfaces – 4 hours.



It's important to note that the amount of live virus decreases over time on surfaces. So the risk of infection from touching something that had the virus on it for a few days would lessen.

ARE FACE MASKS EFFECTIVE PREVENTION?

- ▶ Masks are effective at slowing transmission.
- ▶ The WHO recommends that the general population wear non-medical masks when in public settings and when physical distancing is difficult, and that vulnerable populations (e.g., elderly) wear medical masks when close contact is likely. Infected individuals wearing facemasks in the home before the onset of symptoms was associated with a reduction in household transmission.
- ▶ Modeling suggests that widespread use of facemasks is effective at reducing transmission.
- ▶ A meta-analysis of SARS, MERS, and COVID-19 transmission events found evidence that wearing face masks and eye protection were each associated with lower risk of transmission. N95 respirators were associated with a larger reduction in transmission risk compared to surgical face masks. Physical distance (>1 or 2 meters) was also associated with lower transmission risk.
- ▶ In a separate meta-analysis, N95 respirators were found to be beneficial for reducing the occurrence of respiratory illness in health care professionals including influenza, though surgical masks were similarly effective for influenza. N95 respirators were associated with large reductions (up to 80%) in SARS-CoV-1 infections.
- ▶ Surgical face masks, respirators and homemade face masks may prevent transmission of coronaviruses from infectious individuals (with or without symptoms) to other individuals. Surgical masks were associated with a significant reduction in the amount of seasonal coronavirus (not SARS-CoV-2) expressed as aerosol particles (<5 μm) compared to not wearing a mask.
- ▶ The efficacy of homemade PPE, made with T-shirts, bandanas, or similar materials, is less than standard PPE, but may offer some protection if no other options are available. The filtering efficiency of homemade mask materials is variable. Some non-standard materials (e.g., cotton, Colton hybrids) may be able to filter out >90% of simulant particles >0.3 μm , while other materials (e.g., T-shirt, vacuum cleaner bag, towels) appear to have lower filtration efficacy (~35-62%). Of 42 homemade materials tested, the three with the greatest filtration efficiencies were layered cotton with raised visible fibers, though homemade materials were not as effective as surgical or N95 masks.

QUESTIONS?

- ▶ **If you survive the virus are you immune for life?** The innate immune system CD4 and CD8 T-cell memory for SARS CoV appear to last for up to 11 years. Although antibody levels may drop at 3-12 months, immune memory should allow a much faster viral response in the future.
- ▶ **Will we see another Corona virus pandemic?** We have seen 3 highly pathogenic human coronaviruses in just 20 years. Continued exposure to animals, worldwide travel, and new variants of coronavirus mean not if but when will we see the next pandemic.

IS IT SAFE FOR CHILDREN TO RETURN TO SCHOOL

- ▶ Although most children have a mild Covid 19 infection, 90 children have died and 570 children have developed multisystem inflammatory syndrome.
- ▶ Schools often have a lower rate of contagion than adjacent communities
- ▶ School systems with strict restrictions in very low incidence counties may have a low risk of infection.