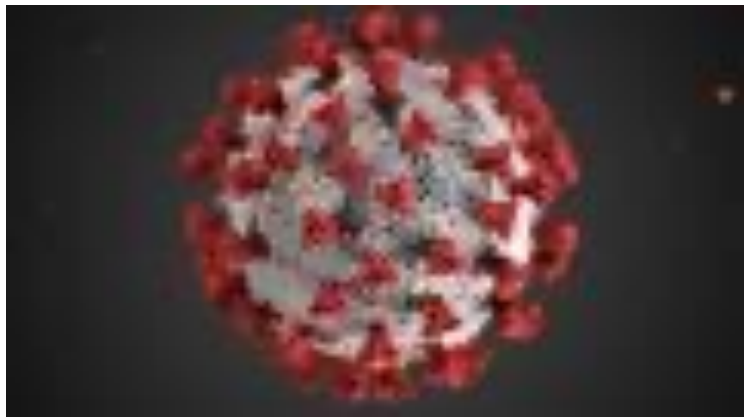

Outpatient Management of COVID-19, Practical Considerations

Jorge Mera, MD, FACP

Whitney Essex, APRN

Outline

- **Clinical Case**
- Epidemiology and Transmission
- Clinical presentation, diagnosis and treatment
- Prevention
- Long COVID
- Conclusions

Clinical Case

- **History of Present Illness:**
  - Mr. C is a 36-year-old AI/AN male patient with a PMH of well controlled HTN who comes as a walk-in patient to your clinic on a Friday at 4 pm. He complains of headache, fever and fatigue that started 4 days ago. He is fully vaccinated for COVID-19, 2 RNA vaccine doses and 1 booster (given 8 months ago). He is married, has 3 children, they are all vaccinated except for the 2-year-old who goes to day care, he denies any known COVID-19 contacts. His family is asymptomatic now, but the 2-year-old had a mild rhinitis 3 days ago.
- **Physical Exam:**
  - Vital signs reveal a HR of 92/min, RR 14/min BP 110/80 mmHg, T 38.1 C and pulse oximetry is 95% at room air. PE is normal including clear lung auscultation.
- **Labs:**
  - Comprehensive metabolic panel done 1 month ago as part of his routine lab work were normal. Today he had a COVID-19 home antigen test which was negative.

What would you tell this patient?

A. This is probably a respiratory virus, not COVID-19,

- Since he is vaccinated, antigen test is negative and has no known COVID-19 exposure.
- Supportive care and no isolation required.

B. He should be tested for SARS-CoV-2 with a molecular test

- If positive, offer him antiviral treatment and should Isolate for 5 -10 days depending on symptoms and follow-up testing results.

C. He should be tested for SARS-CoV-2 with a molecular test

- If positive, offer him antiviral treatment and he should isolate for 5 days only

D. He should be tested for SARS-CoV-2 with a molecular test

- If positive, he should not be offered antiviral treatment since he does not qualify, and should Isolate for 5 -10 days depending on symptoms and follow-up testing results

E. He should be tested for SARS-CoV-2 with a molecular test

- If molecular test is negative, he does not have COVID-19, probably a different respiratory virus infection.

Outline

- Clinical Case
- **Epidemiology and Transmission**
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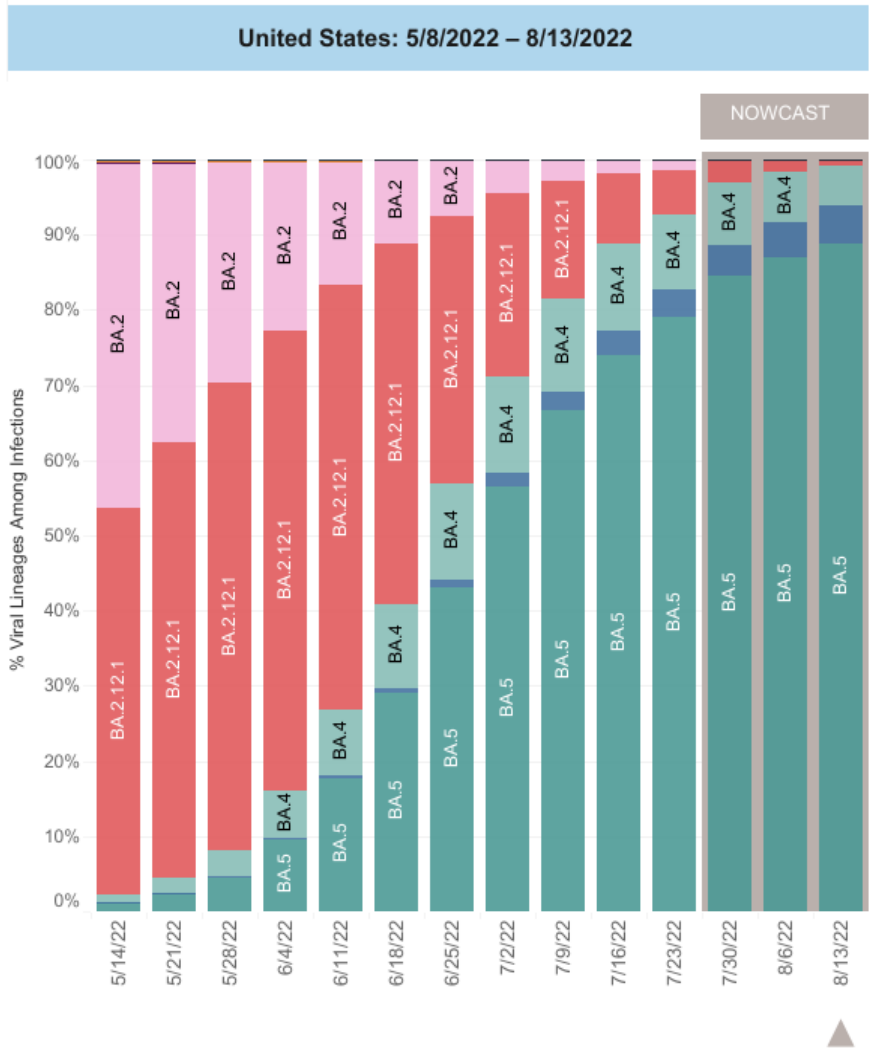


United States: 8/7/2022 – 8/13/2022 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	88.8%	87.5-90.0%
	BA.4	VOC	5.3%	4.9-5.7%
	BA.4.6	VOC	5.1%	4.1-6.4%
	BA.2.12.1	VOC	0.8%	0.7-0.9%
	BA.2	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. For regional data, BA.1.1 and its sublineages are also aggregated with B.1.1.529, as they currently cannot be reliably called in each region. Except BA.2.12.1, BA.2 sublineages are aggregated with BA.2. Sublineages of BA.4 are aggregated to BA.4. Sublineages of BA.5 are aggregated to BA.5.

- **Burden of disease**
  - Infection has spread to more than 500 million confirmed cases worldwide
  - In the US, as of Aug 6, 2022, 91.9 million cases have been reported and 1.03 million deaths
- **Omicron variant sublineages are associated with**
  - A higher risk of reinfection in individuals previously infected with other variants
  - Breakthrough infection in vaccinated individuals
  - Probably less severity

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Modes of Transmission of SARS-CoV-2

Direct person-to-person transmission is the primary means of transmission.

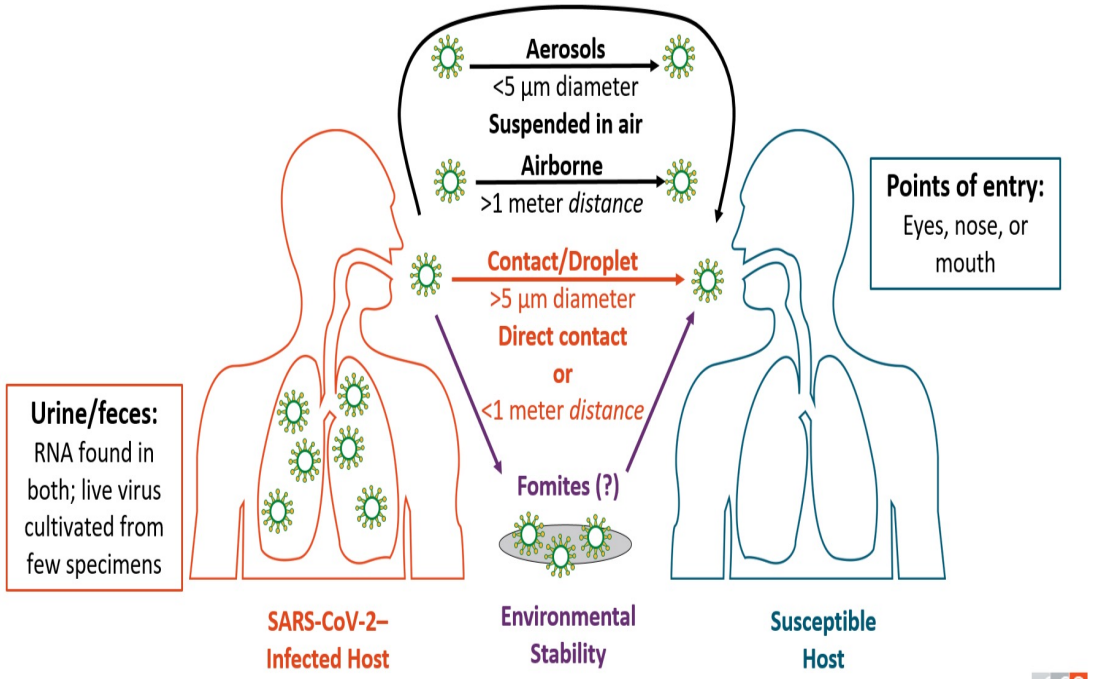
- Occur mainly through close-range contact via respiratory particles (droplets)
- Transmission over longer distances, particularly in enclosed, poorly ventilated spaces (aerosols)

Period of infectiousness

- Most infectiousness occurs a few days prior to the development of symptoms

Crowded enclosed spaces facilitate SARS-CoV-2 transmission

- Odds that a primary case transmitted SARS-CoV-2 in an enclosed environment is **18.7 x higher** compared with open-air environment (95% CI: 6.0-57.9)[1]
- Transmission rates correlate with duration of exposure.



Galbadage. Front Public Health. 2020;8:163. WHO. Scientific Brief. July 9, 2020.

Slide credit: clinicaloptions.com

1. www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html. Last updated July 10, 2022. 2. WHO. Scientific Brief. June 17, 2020.

Transmission of SARS-CoV2 (R_0)

R_0 = basic reproduction number

- The number of cases generated by a single infectious case in a population without immunity
- $R_0 \geq 2$= exponential growth

$R_{0\ of\ SARS\text{-}CoV2}$ = 2.24-3.58

$R_{0\ of\ SARS\text{-}CoV2}$ Omicron = ~ 5.08

R_0

• Measles:	15.0
• COVID-19 (omicron)	5.0
• Smallpox:	4.8
• SARS:	3.0
• Ebola:	1.9
• Seasonal Influenza:	1.3
• MERS:	0.8

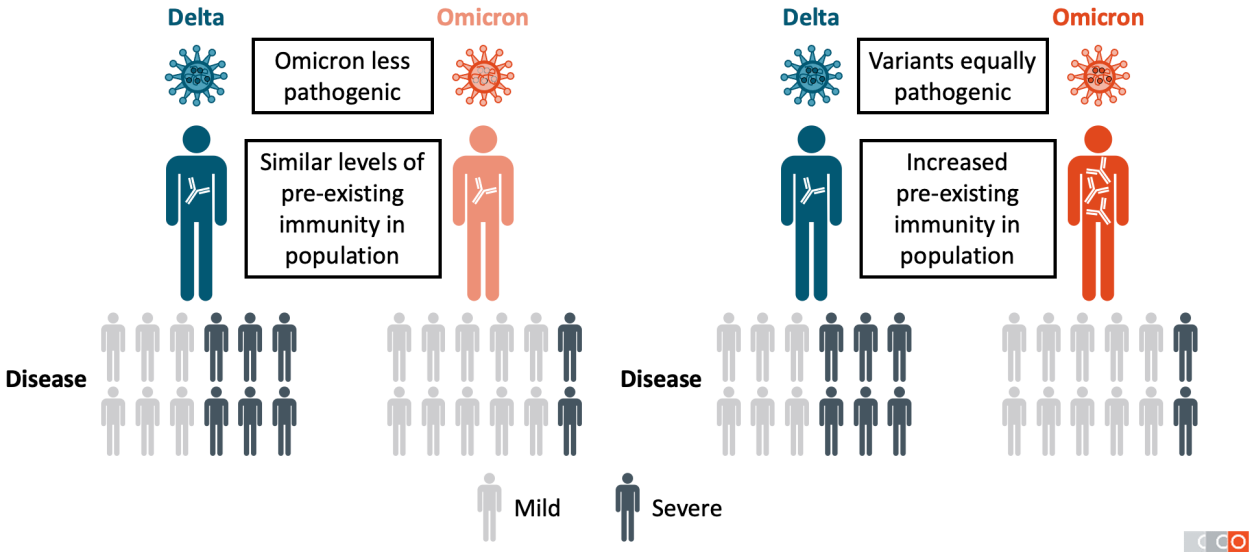
Why is SARS-COV-2 Spreading Rapidly

- Can be aerosolized
- New Variants of Concern with
  - Increased intrinsic transmissibility
  - Immune escaping ability
- Asymptomatic transmission
  - According to meta-analysis asymptomatic infections ranges from 4-40%
- Decrease enforcement of prevention measures

Li O NEJM, 2020: Rio J Eurosurveillance 2020; Zhao Int J Infect Dis 2020, Liu Y, Rocklöv J. . J Travel Med. 2022 May 31;29(3):taac037. Van Doremalen N NEJM 2020; Zou L NEJM 2020; Peiris JSM, Lancet 2003, 4 Byambasuren. JAMMI. 2020;5:223

Omicron Transmissibility and Severity

Omicron Severity Based on Reduced Pathogenicity or Increased Immunity



Sigal. Nat Rev Immunol. 2022;22:69.

Slide credit: clinicaloptions.com

To understand **intrinsic severity** of omicron compared with delta, need to adjust for: Vaccination status, Prior infection, Age, Comorbidity

Omicron: Transmissibility

- Omicron spreads rapidly[1,2]
  - Increased transmissibility[1]
    - Secondary attack rate in households with **omicron** vs **delta**: **31%** vs **21%**
    - Unvaccinated individuals have higher transmissibility compared with fully vaccinated individuals
    - **Omicron** is 2.7-3.7 times more transmissible than delta among vaccinated individuals[1]
  - **Immune evasion**

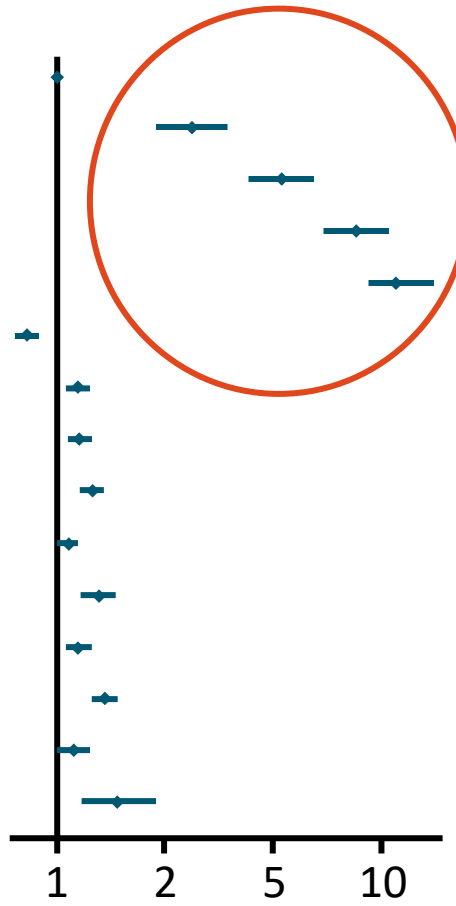
1. Lyngse. medRxiv. 2021;[Preprint]. Note: This study has not been peer reviewed.
2. cdc.gov/coronavirus/2019- ncov/variants/omicron-variant.html.
3. covid.cdc.gov/covid-data-tracker/#variant-proportions.

Slide credit: clinicaloptions.com

Predictors of Mortality Among COVID-19–Positive Hospitalized Patients in the UK

- Prospective observational cohort study of hospital admissions in England, Wales, and Scotland during February 6 - April 19, 2020 (N = 20,133)
  - Significantly increased risk of mortality among **older patients, men, and those with chronic comorbidities**

Multivariate Survival Analysis

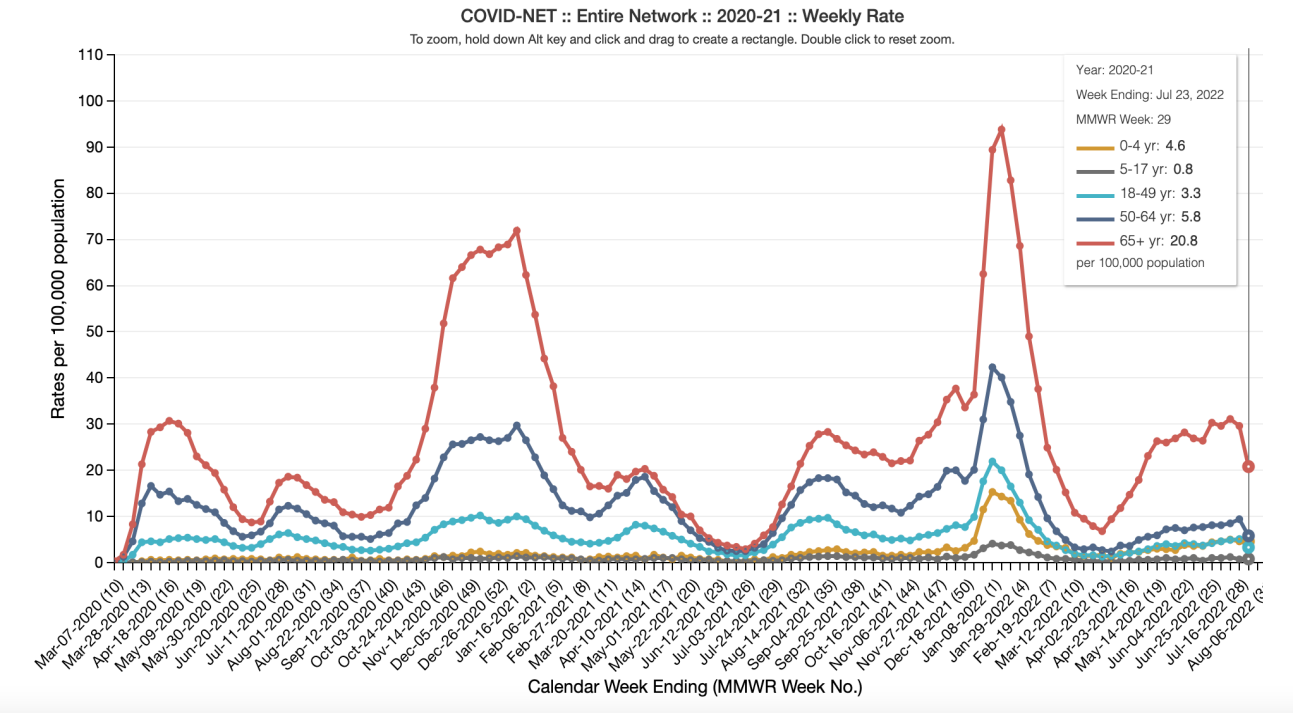


Characteristic	HR (95% CI)	*P* Value
<50 yr		
50-59 yr	2.63 (2.06-3.35)	<.001
60-69 yr	4.99 (3.99-6.25)	<.001
70-79 yr	8.51 (6.85-10.57)	<.001
≥80 yr	11.09 (8.93-13.77)	<.001
Female sex	0.81 (0.75-0.86)	<.001
Chronic cardiac disease	1.16 (1.08-1.24)	<.001
Chronic pulmonary disease	1.17 (1.09-1.27)	<.001
Chronic kidney disease	1.28 (1.18-1.39)	<.001
Diabetes	1.06 (0.99-1.14)	.087
Obesity	1.33 (1.19-1.49)	<.001
Chronic neurological disorder	1.17 (1.06-1.29)	.001
Dementia	1.40 (1.28-1.52)	<.001
Malignancy	1.13 (1.02-1.24)	.017
Moderate/severe liver disease	1.51 (1.21-1.88)	<.001

Docherty. BMJ. 2020;369:m1985.

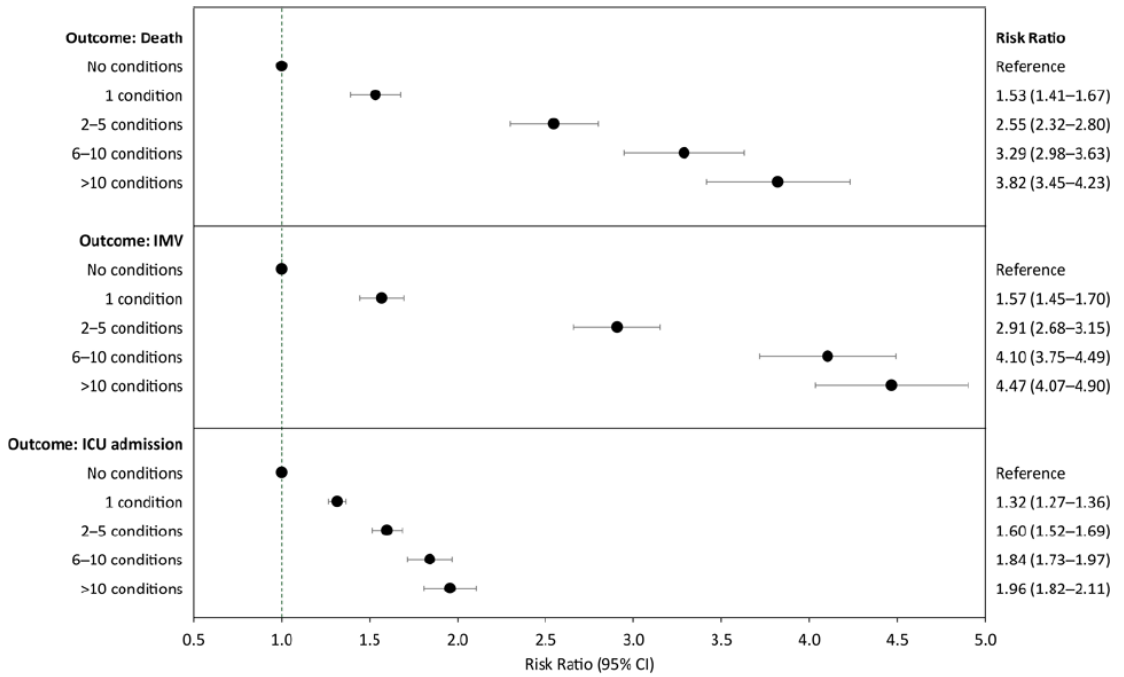
Slide credit: clinicaloptions.com

COVID-NET: Lab-Confirmed COVID-19–Associated Hospitalization Rates Stratified by Age



gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020–March 2021



Risk ratio (95% CI) of death, invasive mechanical ventilation (IMV), and admission to intensive care unit (ICU), by the number of underlying medical conditions among adults hospitalized with COVID-19 in the Premier Healthcare Database Special COVID-19 Release. Each panel contains the results of a single generalized linear model with Poisson distribution and log link function, adjusted for age group, sex, race/ethnicity, payer type, hospital urbanicity, US Census region of hospital, admission month, and admission month squared as controls. Patients who died without ICU care or IMV wereexcluded from the sample when estimating the model with the outcome of ICUcare or IMV, respectively.

Lyudmyla K et al; Preventing Chronic Disease, Public Health Research, Practice and PolicyVolume 18 — July 1, 2021

Risk for COVID-19 Infection, Hospitalization, and Death By Race/Ethnicity

Updated July 28, 2022

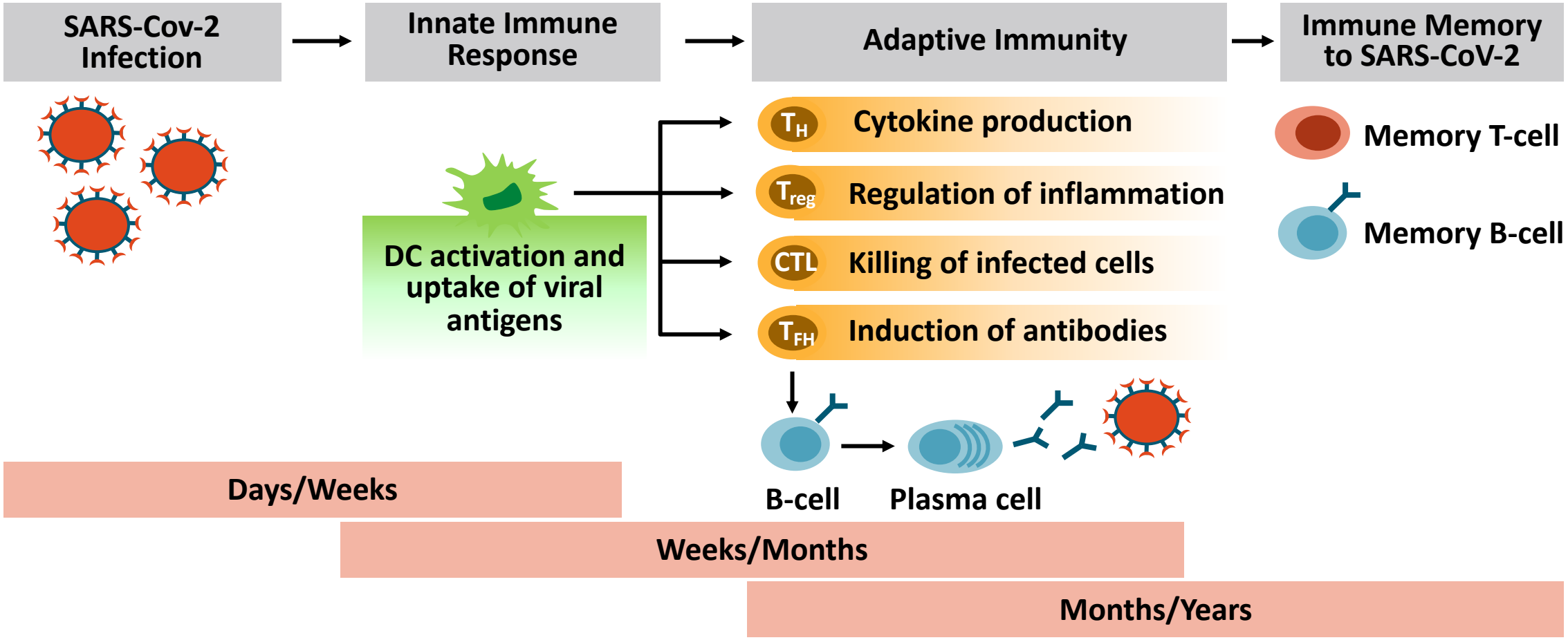
Rate ratios compared to White, Non-Hispanic persons	American Indian or Alaska Native, Non-Hispanic persons	Asian, Non-Hispanic persons	Black or African American, Non-Hispanic persons	Hispanic or Latino persons
Cases[1]	1.5x	0.8x	1.1x	1.5x
Hospitalization[2]	2.8x	0.8x	2.2x	2.1x
Death[3, 4]	2.1x	0.8x	1.7x	1.8x

Race and ethnicity are risk markers for other underlying conditions that affect health, including socioeconomic status, access to health care, and exposure to the virus related to occupation, e.g., frontline, essential, and critical infrastructure workers.

Note: Adjusting by age is important because risk of infection, hospitalization, and death is different by age, and age distribution differs by racial and ethnic group. If the effect of age is not accounted for, racial and ethnic disparities can be underestimated or overestimated.

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html

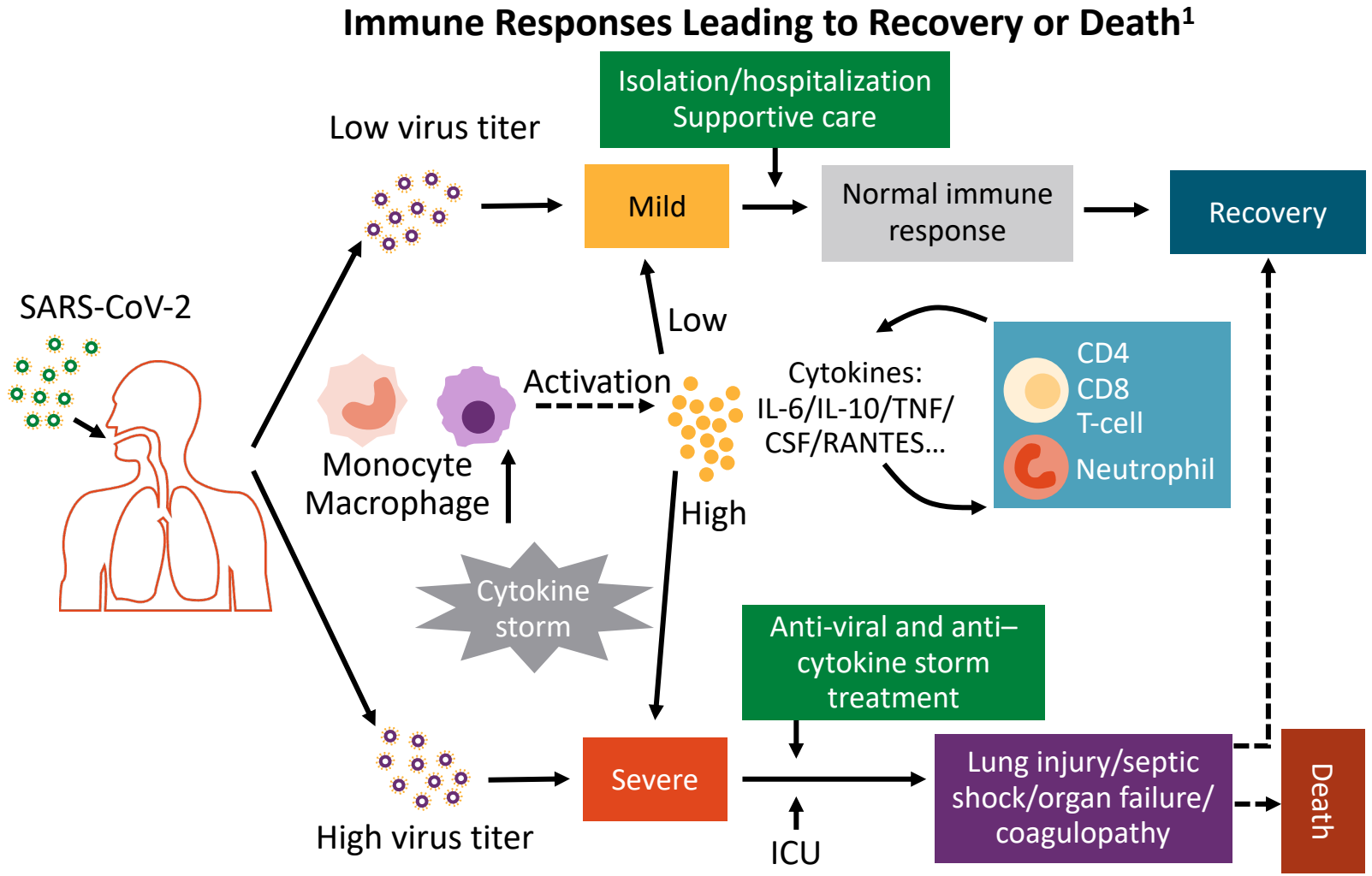
Potential Immune Correlates of Protection to SARS-CoV-2 Infection



Cox. Nat Rev Immunol. 2020;20:581.

Slide credit: clinicaloptions.com

Immune Response to SARS-CoV-2



Adequate immune responses[2]

- Timely innate/adaptive responses
- **Quick type 1 IFN response**
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

Inadequate immune responses[2]

- **Delayed/limited type 1 IFN**
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

1. Wang. J Leukoc Biol. 2020;108:17. 2. Sokolowska. Allergy. 2020;75:2445.

Slide credit: clinicaloptions.com

Outline

- Clinical Case
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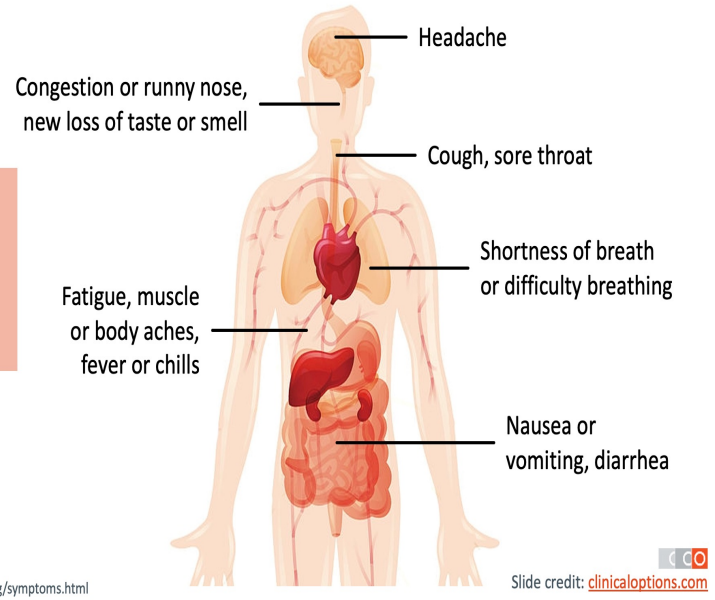
Primary Symptoms of COVID-19

"Symptoms may appear **2-14 days after exposure** to the virus"



Li. J Med Virol. 2020;92:577.
cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

Slide credit: clinicaloptions.com

Lab findings	Frequency
• Leukopenia	17%
• Leukocytosis	21%
• Lymphopenia	40%
• Thrombocytopenia	7%
• ALT > 40	31%

Radiology	
• Ground glass opacity on CT	71%
• Consolidation	59%
• Bilateral Infiltrates	75%

Zhou et al, Lancet, 2020

Common Symptoms

- **Fever** in > 75% at some point (~50% on admission)
- **Cough** 45-80% (dry > productive)
- **SOB** 20-40%
- **Myalgia** 10-50%
- **Triad of fever/Cough/SOB** in only 15%

Less Common Symptoms

- Headache, sore throat, rhinorrhea < 15%
- Nausea/Vomiting < 10%
- Diarrhea < 25%

Huang et al, Lancet; Yang et al, Lancet Resp Med; Xu et al, BMJ; Wu et al CID; Chen et al, Lancet; Wang et al JAMA; Yang et al, J Infection; Tian et al, J Infect; Li et al, NEJM; guan et al, NEJM; Qin et al, CID, Zhou et al. Lancet; Ching et al NEJM; Young et al, JAMA; Tay et al, CID; Wang et al CID; China CDC report Feb 2020, Italy Public Health Report March 2020

NIH Guidelines: Clinical Spectrum of SARS-CoV-2 Infection

Stage	Characteristics
Asymptomatic or Presymptomatic Infection:	Positive for SARS-CoV-2 virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but without symptoms consistent with COVID-19
Mild Illness	Various signs/ symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell, but no shortness of breath, dyspnea, or abnormal chest imaging.
Moderate Illness	Evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.
Severe Illness	SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2 /FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
Critical Illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

CDC: Testing Recommendations for Current SARS-CoV-2 Infection

People who have symptoms of COVID-19 or who had close contact to someone with COVID-19

- At least 5 days after known or suspected close contact to COVID-19
- A person's vaccination status does not affect the results of their viral test for SARS-CoV-2

Before and after travel

Anyone advised by healthcare professional or public health official

Point-of care serial screening testing can provide rapid results

- **This is especially important when the COVID-19 community level is high.**
- For screening (schools, workplaces, congregate settings, etc.)

https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html Updated May 3, 2022

Diagnosis of SARS-COV-2

Compared to NAAT Tests, EUA Rapid Antigen testing:

- Have high specificity and low to modest sensitivity
- Sensitivity depends on viral load and symptoms and the time of testing

Rapid RT-PCR or laboratory-based NAAT remain the diagnostic methods of choice for SARS-CoV-2

- When NAAT is not available Ag testing is an option

For symptomatic individuals either rapid RT-PCR or laboratory-based NAAT are preferred over rapid Ag tests

- Ag tests should be used within seven days of symptom onset
- If suspicion is high, negative Ag should be confirmed by standard NAAT

Virus rarely cultured in respiratory samples after 9 days of symptom onset.

- Prolonged viral RNA shedding after symptom resolution is not clearly associated with prolonged infectiousness.

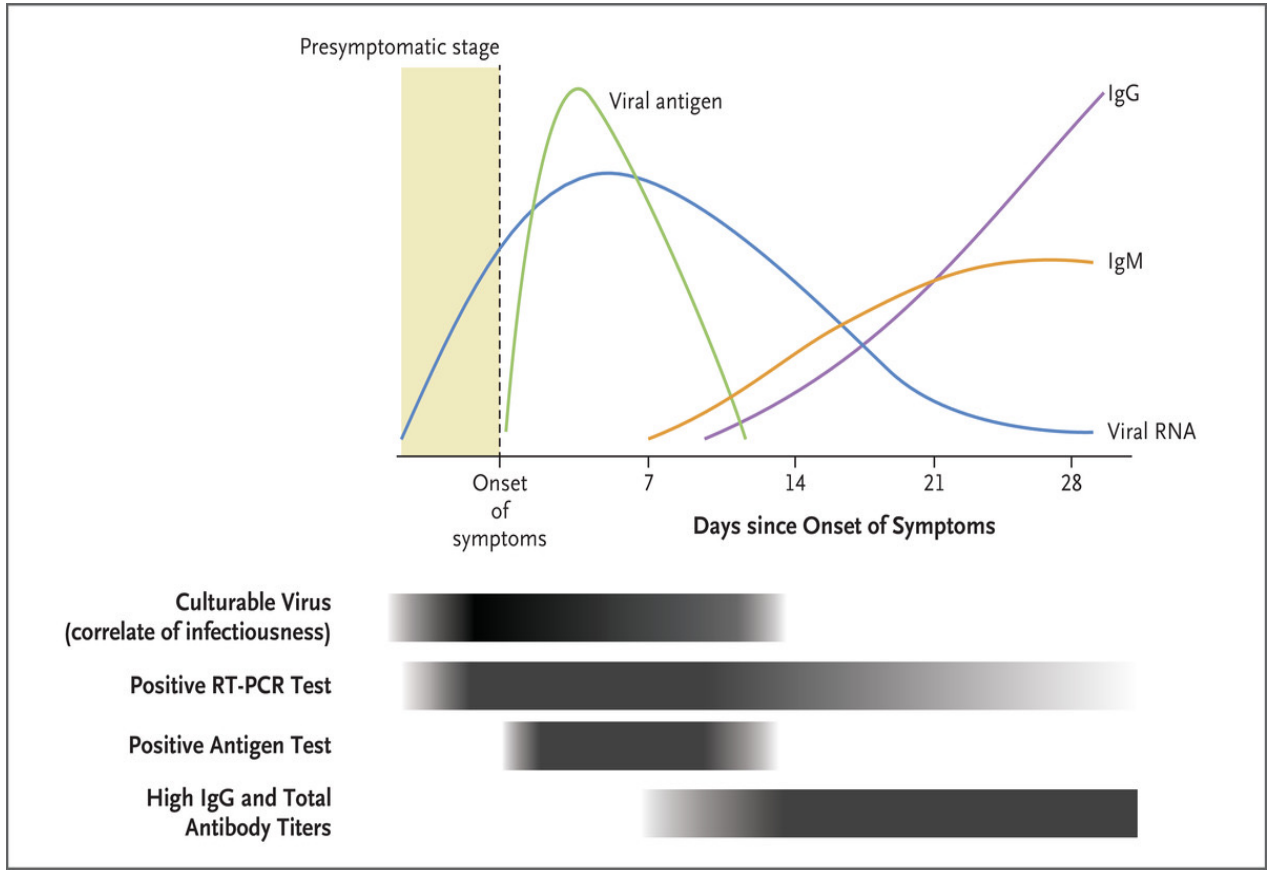


Figure 1. Pathophysiology and Timeline of Viremia, Antigenemia, and Immune Response during Acute SARS-CoV-2 Infection. In some persons, reverse-transcriptase–polymerase-chain-reaction (RT-PCR) tests can remain positive for weeks or months after initial infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but this positivity rarely indicates replication-competent virus that can result in infection. NEJM

NAAT: Nucleic Acid Amplification Test

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#

Drain PK. Rapid Diagnostic Testing for SARS-CoV-2. N Engl J Med. 2022 Jan 20;386(3):264-272.

Sensitivity and Specificity of SARS-COV-2 Detection Compared to a Reference Standard

Type of Test	Subtype of test	Example	Sensitivity	Specificity
NAAT	Laboratory Based result > 1 one hour		Reference	Reference
	Rapid Result < 1 hour	PCR (Film array)	97% (95% CI: 94-99)	96% (95% CI: 94-98)
		Isothermal (Abbot ID Now)	81% (95% CI: 56-81)	99% (95% CI, 97-99)
Antigen		Binax Now	Symptomatic < 7 days: 84% Symptomatic > 7 days: 64% Asymptomatic: 49%	99%

Sampling method did not affect the results and all NAAT methods showed high specificity (i.e., ≥97%).

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#

Community Level of SARS-CoV-2 Infection

COVID-19 Community Levels – Use the Highest Level that Applies to Your Community				
New COVID-19 Cases Per 100,000 people in the past 7 days	Indicators	Low	Medium	High
Fewer than 200	New COVID-19 admissions per 100,000 population (7-day total)	<10.0	10.0-19.9	≥20.0
	Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)	<10.0%	10.0-14.9%	≥15.0%
200 or more	New COVID-19 admissions per 100,000 population (7-day total)	NA	<10.0	≥10.0
	Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)	NA	<10.0%	≥10.0%

The COVID-19 community level is determined by the higher of the new admissions and inpatient beds metrics, based on the current level of new cases per 100,000 population in the past 7 days

Implications for Using COVID-19 Community Levels to Inform Public Health Recommendations

- COVID-19 community levels can inform recommendations for **community-level preventive strategies** and **individual preventive behaviors**
- At higher COVID-19 community levels recommendation would include:
  - Masking
  - Testing Strategies (e.g., screening testing)
  - High-risk individuals and their household or social contacts (e.g., masking, testing, and access to treatments)
  - Setting-specific recommendations (e.g., K-12 schools, healthcare)
  - High-risk congregate settings (e.g., masking and screening testing)

Summary of Guidance for Minimizing the Impact of COVID-19 on Individual Persons, Communities, and Health Care Systems — United States, August 2022

Early Release / August 11, 2022 / 71

Monitoring COVID-19 Community Levels to guide COVID-19 prevention efforts.

- Persons can use information about the current community level of COVID-19 impact to decide which prevention behaviors to use
- These recommendations have the explicit goals of reducing medically significant illness and limiting strain on the health care system.
- At all COVID-19 Community Levels (low, medium, and high), recommendations emphasize staying up to date with vaccination, improving ventilation, testing persons who are symptomatic and those who have been exposed, and isolating infected persons.

Testing for current infection.

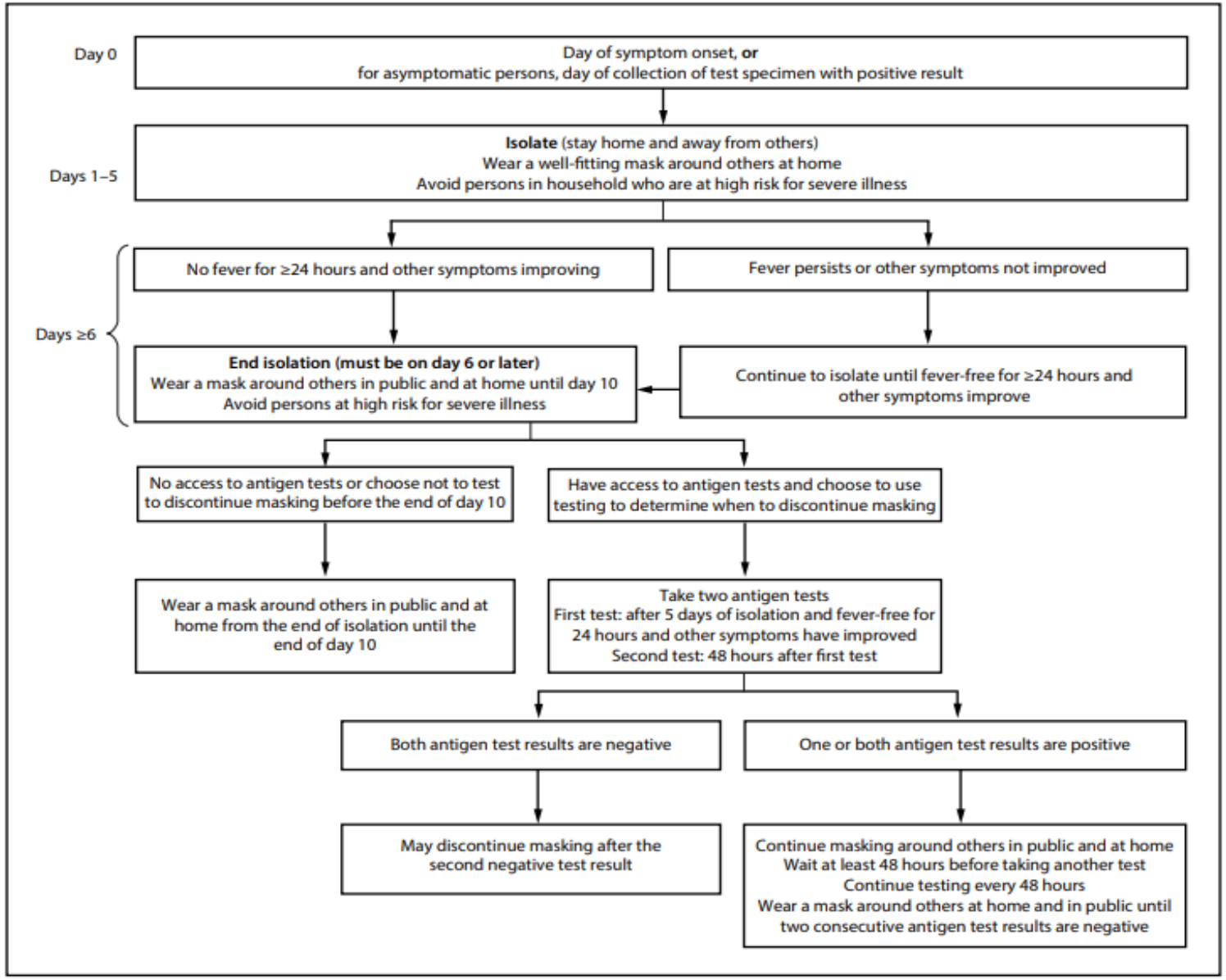
- Diagnostic testing can identify infections early so that infected persons can take action to reduce their risk for transmitting virus and receive treatment (all symptomatic individuals and exposed individuals should be tested)
- When considering whether and where to implement screening testing of asymptomatic persons with no known exposure, public health officials might consider prioritizing high-risk congregate settings, such as long-term care facilities, homeless shelters, and correctional facilities, and workplace settings that include congregate housing with limited access to medical care.
- When implemented, screening testing strategies should include all persons, irrespective of vaccination status.
- Screening testing might not be cost-effective in general community settings, especially if COVID-19 prevalence is low

Managing SARS-CoV-2 exposures.

- CDC now recommends case investigation and contact tracing **only in health care settings and certain high-risk congregate settings**

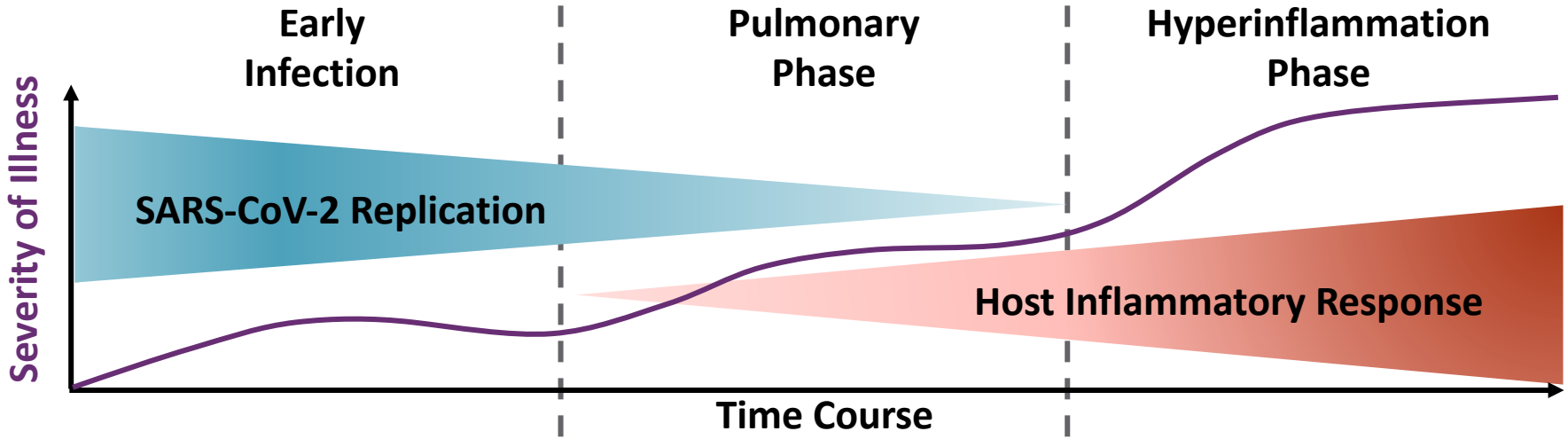
Massetti GM, Jackson BR, Brooks JT, et al. Summary of Guidance for Minimizing the Impact of COVID-19 on Individual Persons, Communities, and Health Care Systems — United States, August 2022. MMWR Morb Mortal Wkly Rep. ePub: 11 August 2022.:

FIGURE. Recommendations for isolation,* masking,† and additional precautions for persons with COVID-19 illness§ or who receive a positive SARS-CoV-2 test result¶, — United States, August 2022**



Massetti GM, Jackson BR, Brooks JT, et al. Summary of Guidance for Minimizing the Impact of COVID-19 on Individual Persons, Communities, and Health Care Systems — United States, August 2022. MMWR Morb Mortal Wkly Rep. ePub: 11 August 2022.:

Benefit of Therapeutic Classes Dictated by SARS-CoV-2 Pathogenesis



Clinical Signs/ Symptoms	Lymphopenia, mild constitutional symptoms, fever >99.6°F, dry cough	Shortness of breath ± hypoxia, abnormal chest imaging, transaminitis, low-normal procalcitonin	ARDS, SIRS/shock, cardiac failure; elevated inflammatory markers, troponin, and NT-proBNP
Treatment Goals	Reduce onward transmission	Reduce progression/ hospitalization	Reduce morbidity/ mortality
	Enhance immunity; use antivirals		**Dampen immunopathogenesis, coagulation**
	Paxlovid Remdesivir Bebtelovimab Molnupiravir	$FIO_2 \geq 94\%$ / $FIO_2 < 94\%$	Dexamethasone Tocilizumab Baricitinib

NIH COVID-19 Treatment Guidelines. Clinical management summary. January 19,2022. Siddiqi. J Heart Lung Transplant. 2020;39:405.

Slide credit: clinicaloptions.com

Who Qualifies?

Confirmed SARS-COV-2 positive test
- PCR (*highest sensitivity), NAAT or Antigen

Symptomatic
- Mild or Moderate Illness
- Not Hypoxic

Risk factor for progression of the disease
- Age, Comorbidities, and Race/Ethnicity

Timing
- Within 7 days of symptom onset

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options: **Preferred Therapies** *Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)** • **Remdesivir[c,d] (BIIa)** **Alternative Therapies** *For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab[e] (CIII)** • **Molnupiravir[c,f] (CIIa)** For use **ONLY** in regions where the Omicron BA.2 subvariant is not the dominant subvariant and in situations where none of the preferred or alternative options are available, feasible to use, or clinically appropriate: • **Sotrovimab[g] (CIII)** The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.[h]

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

NIH Guidelines recommendations for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression
(listed in order of preference)

88%

#1 Nirmatrelvir 300mg/ritonavir 100mg, oral (Paxlovid) **[AIIa]**

- Initiated ASAP
- Has significant

0kg

#2 Remdesivir

- Initiate ASAP **v**
- NIH recommer

a]

#3 Bebtelovima

- Initiate ASAP **v**
- Patients should be observed for at least 1 hour after infusion.

a]

kg

Efficacy of These Treatments in Randomized Clinical Trials Have Only Been Proven in Patients Who Are Not Vaccinated

30%

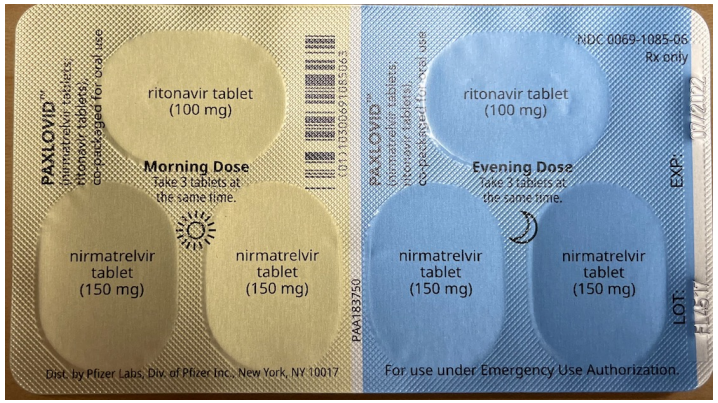
#4 Molnupiravir 800mg, oral, ONLY if other options can be used **[CIIa]**

- Initiate ASAP **within 5 days** of symptom onset, aged ≥18 years, non-pregnant

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [04/27/2022].

Nirmatrelvir 300mg/ritonavir 100mg (Paxlovid)

First-line Preferred Regimen



Allergic Reactions

- Hives, trouble breathing or swallowing, swelling, throat tightness, hoarseness, skin rash

Drug-drug interactions

- Highly dependent on CYP3A for clearance; elevated concentrations are associated with serious and/or life-threatening reactions

Other reported side effects

- – **metallic taste** or other altered taste (COMMON), diarrhea, high blood pressure, muscle aches

Authorization:

- Mild to moderate illness only – not for hospitalized persons
- Treatment only – not for pre- or post-exposure

Dosing:

- 300mg nirmatrelvir (two 150mg tablets) with 100mg ritonavir (one 100mg tablet), with all 3 tablets taken together twice daily for 5 days
  - **Renal dosing:** Dose reductions must be made for patients with moderate renal impairment (there is a renal dose pack!!!!)
- For those aged ≥12 years and weighing ≥40 kg

Timing:

- Start Paxlovid within 5 days of symptom onset
- Better outcomes if started within 3 days of symptom onset
- Reduces risk of hospitalization/death
- Has significant/complex drug-drug interactions

Outline

- Clinical Case
- Epidemiology and Transmission
- Clinical presentation, diagnosis and treatment
- **Prevention**
- Long COVID
- Conclusions

COVID-19 Prevention

Non-Pharmacologic Preventive Interventions

- Rapid identification of close contacts and infected cases and quarantine or Isolate
- Maintain social distance (~6 ft > 3ft > 1 ft)
- If you can not avoid crowds, poorly ventilated spaces or close-contact settings, minimize the time in them and wear masks indoors (N95>surgical>cloth>no mask)
- Disinfect frequent-touch surfaces regularly and wash hands frequently
- Practice proper respiratory etiquette
- PPE for health workers

Pharmacological Preventive Interventions

- Pre-exposure prophylaxis with Tixagevimab –cilgavimab in individuals 12 years and older who are expected to have suboptimal response to vaccination or have a contraindication to the vaccine.

FDA authorized COVID-19 Vaccines

Adult Series	Vaccine Type
2-dose BNT162b2 (aged ≥16 yr) and 2 Boosters*	RNA delivered in lipid nanoparticles
2-dose mRNA-1273 (aged ≥18 yr) and 2 boosters*	RNA delivered in lipid nanoparticles
1-dose Ad26.COV2.S (aged ≥18 yr)** and 1 booster	DNA in a replication incompetent adenovirus 26 vector
2-dose Novavax (aged ≥18 yr), No booster	Recombinant protein subunit

Pediatric Primary Series
2-dose BNT162b2 (aged > 6 months)
2-dose mRNA-1273(aged > 6 months)

Third Primary Series Dose (Immunocompromised)
BNT162b2 (aged ≥5 yr)
mRNA-1273 (aged ≥18 yr)

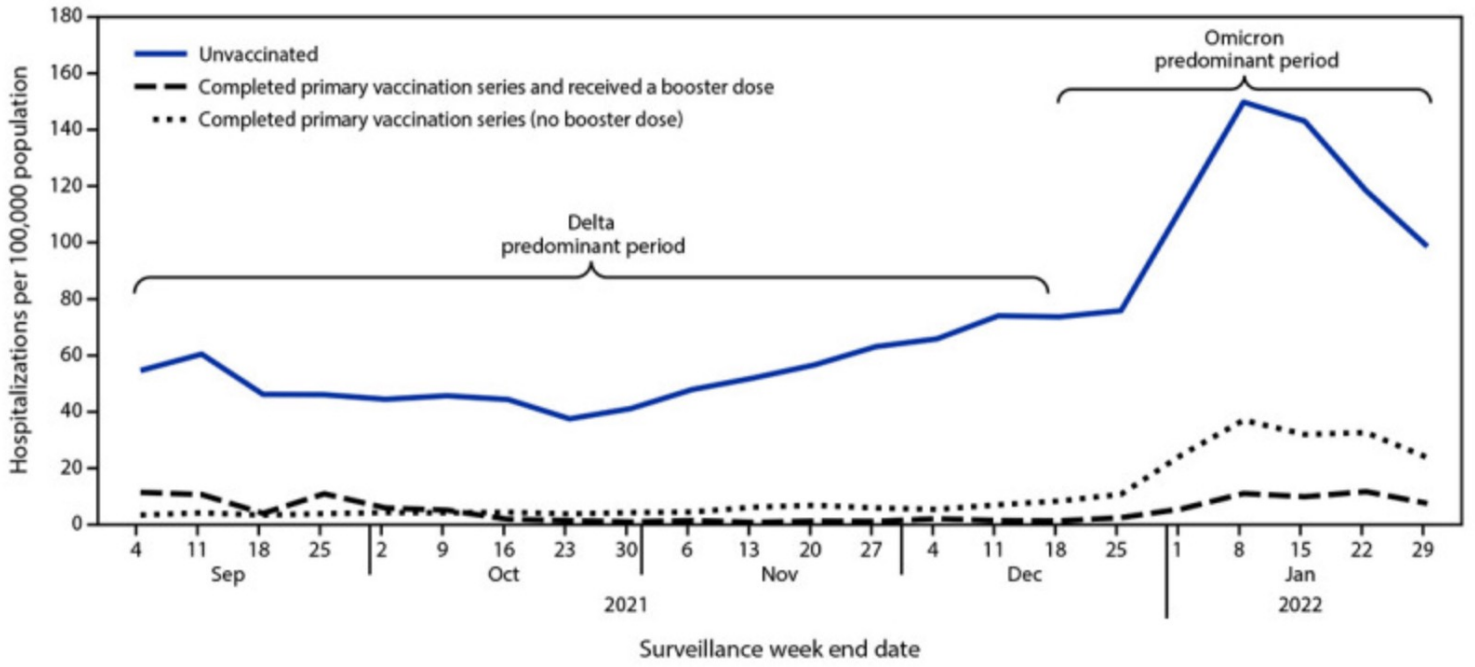
* Second booster ≥4 months after 1 st booster of any authorized COVID-19 vaccine in persons ≥50 yrs old or ≥12 yrs old who are immunocompromised. authorized heterologous boosters

** FDA limits use to only those who are not able or willing to receive an mRNA vaccine because of thrombosis with thrombocytopenia syndrome (risk

cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html.

COVID-19-Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status - COVID-NET, 14 States, July 2021-January 2022

- Taylor CA, Whitaker M, Anglin O, Milucky J, et al. MMWR Morb Mortal Wkly Rep. 2022 Mar 25;71(12):466-473.



Weekly age-adjusted rates of COVID-19–associated hospitalizations among adults aged ≥18 years, by vaccination status* — COVID-19–Associated Hospitalization Surveillance Network, 13 states,† September 4, 2021–January 29, 2022§

What would you tell this patient?

A. This is probably a respiratory virus, not COVID-19,

- Since he is vaccinated, antigen test is negative and has no known COVID-19 exposure.
- Supportive care and no isolation required.

B. He should be tested for SARS-CoV-2 with a molecular test

- If positive, offer him antiviral treatment and should Isolate for 5 -10 days depending on symptoms and follow-up testing results.

C. He should be tested for SARS-CoV-2 with a molecular test

- If positive, offer him antiviral treatment and he should isolate for 5 days only

D. He should be tested for SARS-CoV-2 with a molecular test

- If positive, he should not be offered antiviral treatment since he does not qualify, and should Isolate for 5 -10 days depending on symptoms and follow-up testing results

E. He should be tested for SARS-CoV-2 with a molecular test

- If molecular test is negative, he does not have COVID-19, probably a different respiratory virus infection.

Outline

- Clinical Case
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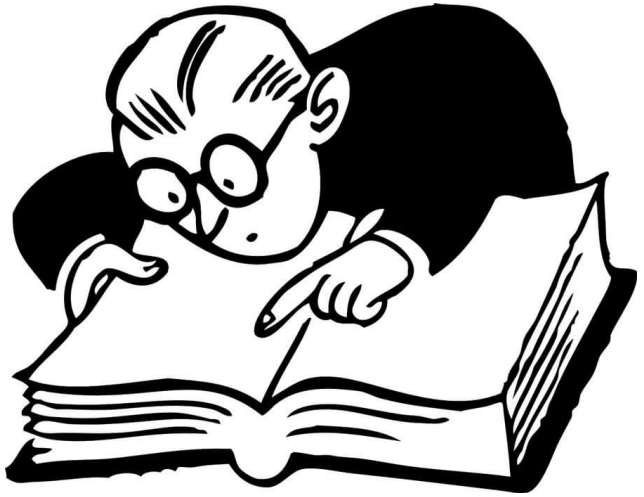
- **Long COVID**
- Conclusions

Terminology

- Many terms in used, inconsistent definitions:
  - Long Haulers
  - **Long-COVID**
  - Long-term COVID
  - Post-acute COVID-19
  - Chronic COVID-19
  - Other Post-Infectious Fatiguing Illnesses (OPIFI)
  - Post-COVID Syndrome
  - **Post-COVID Conditions (PCC)**
  - **Post-Acute Sequelae of SARS-CoV-2 (PASC)**



WHO Definition

- Broad range of symptoms (physical and mental) and symptom clusters that develop during or after COVID-19
- Continue for ≥2 months (ie, three months from the onset of illness)
- Have an impact on the patient's life
- Are not explained by an alternative diagnosis.

A clinical case definition of post COVID-19 condition by a Delphi consensus

WHO

Post COVID-19 condition occurs in individuals with **a history of probable or confirmed SARS-CoV-2** infection, **usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.** Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others, which generally have an **impact on everyday functioning.** Symptoms may be **new onset,** following initial recovery from an acute COVID-19 episode, or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time. A separate definition may be applicable for children.

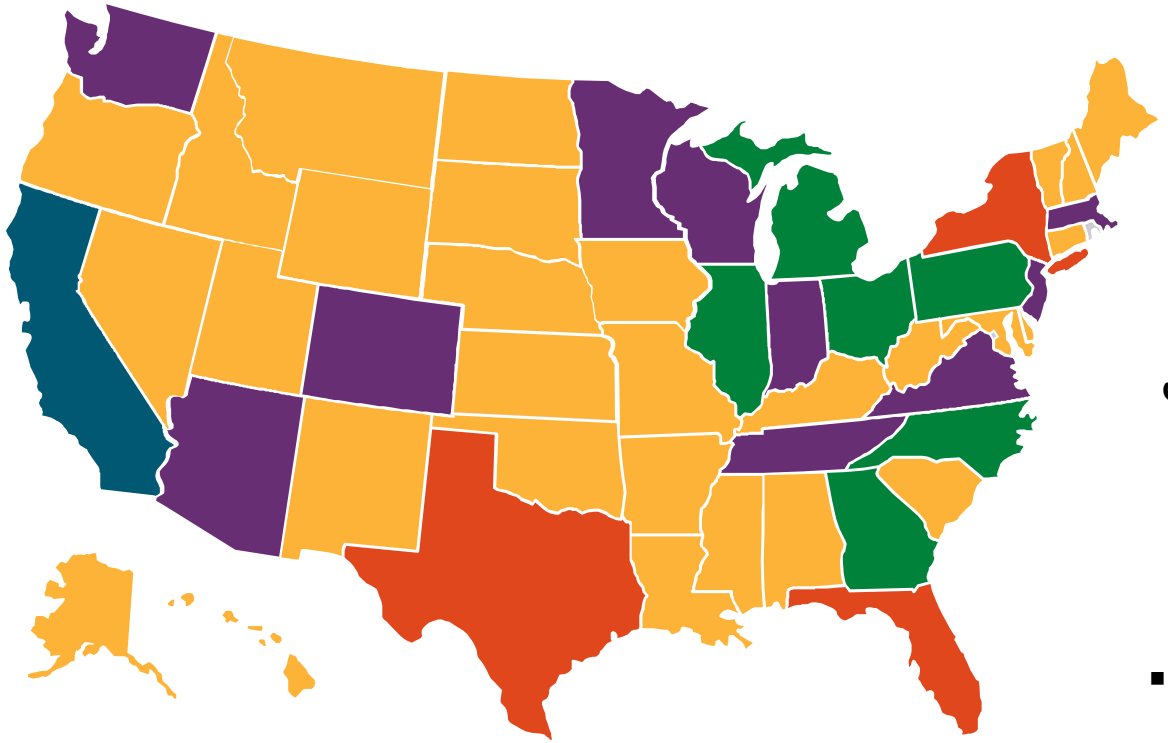
CDC

We use **post-COVID conditions** as an umbrella term for the wide range of health consequences that are present **four or more weeks** after infection with SARS-CoV-2. The time frame of four or more weeks provides a rough approximation of effects that occur beyond the acute period, but the timeframe might change as we learn more

Post-COVID Conditions: Information for Healthcare Providers (cdc.gov)

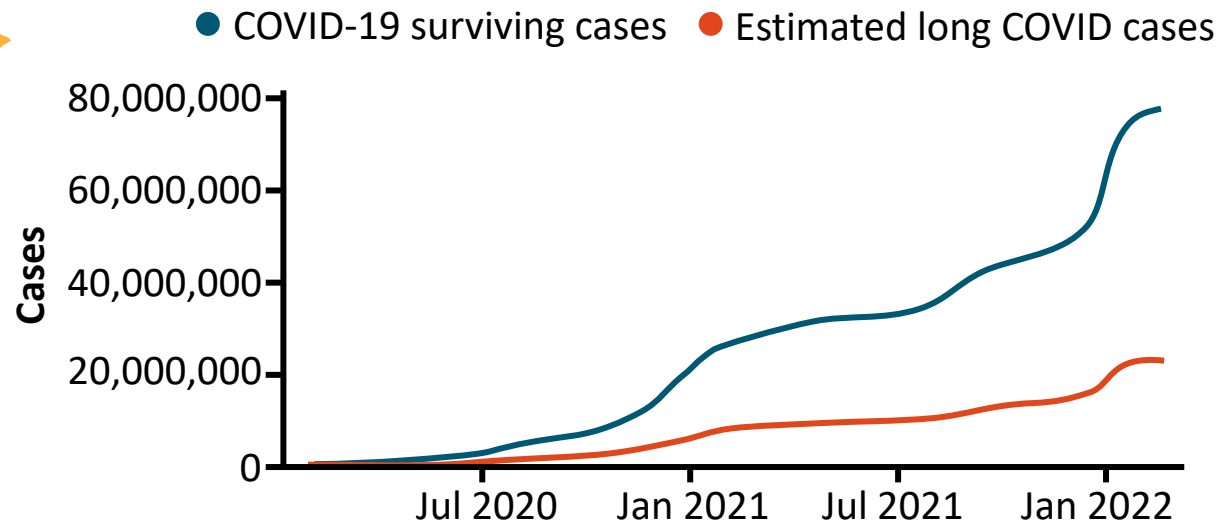
US Prevalence of Long COVID

Estimated Long COVID Cases



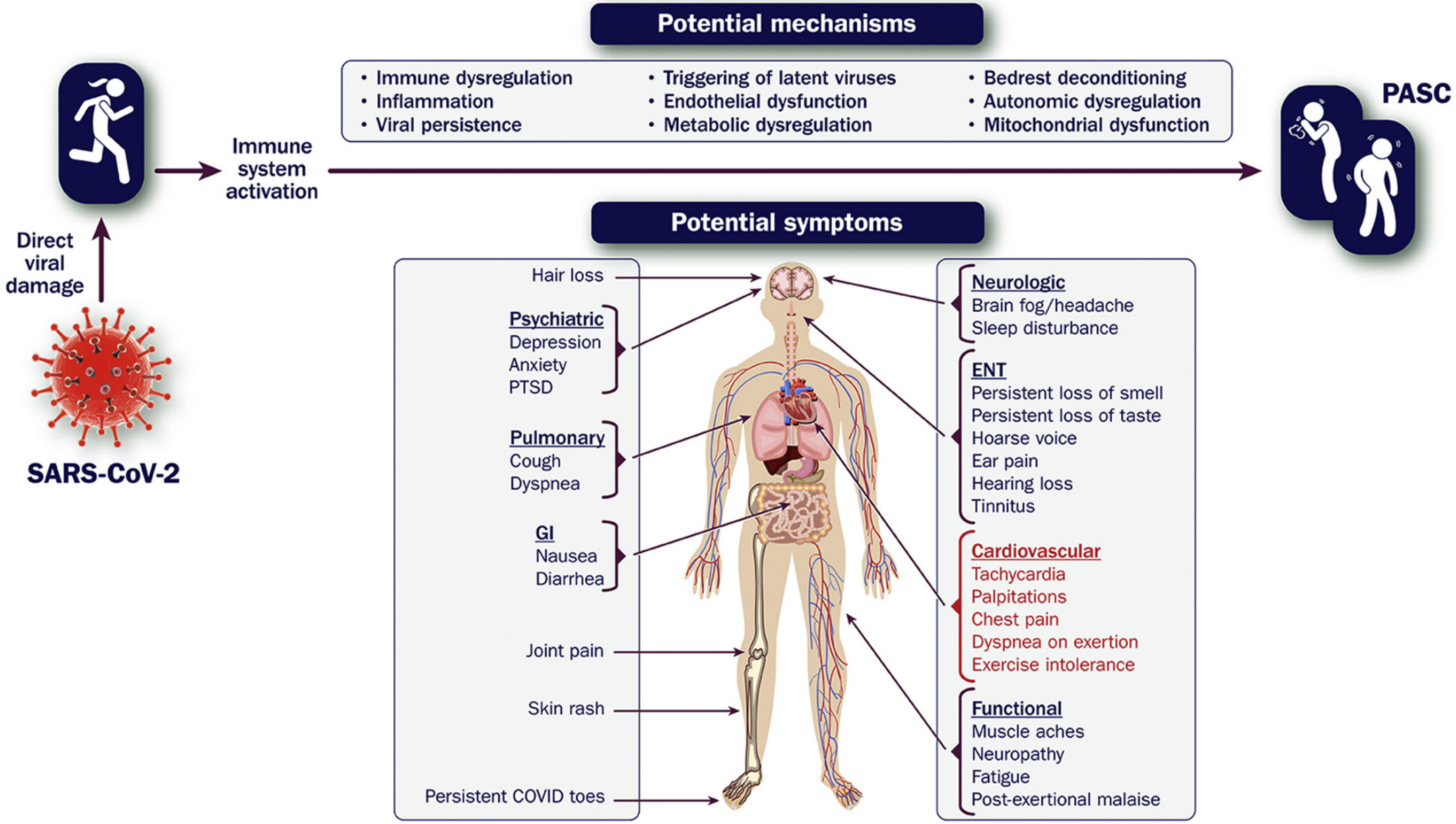
- >2,000,000 cases
- >1,000,000-2,000,000 cases
- >500,000-1,000,000 cases
- >100,000-500,000 cases
- <100,000 cases

Estimated and Cumulative Long COVID Cases



- Most patients improve over 6 mo
- Number of chronically ill patients is smaller (1%-5% of all people with COVID-19)
- **US Government & Accountability Office:** estimates 7.7 – 23 million persons with long COVID in US

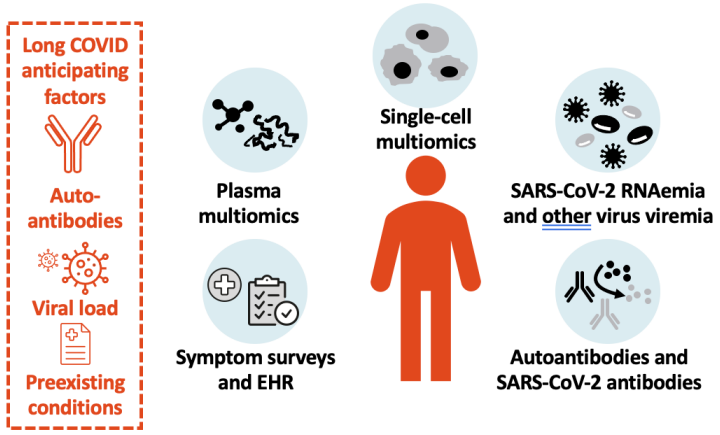
American Association of Physical Medicine and Rehabilitation. pascdashboard.aapmr.org/.



Gluckman, *JACC* 2022 (PMID: 35307156)

Risk Factors for Long COVID

Risk Factors for Long COVID



- Risk factors for long COVID at the time of COVID-19 diagnosis:
  - Type 2 diabetes
  - Circulating SARS-CoV-2 viremia
  - Epstein-Barr virus reactivation
  - Certain autoantibodies
    - Type I interferons
    - Associated with SLE

Su. Cell. 2022;185:881.

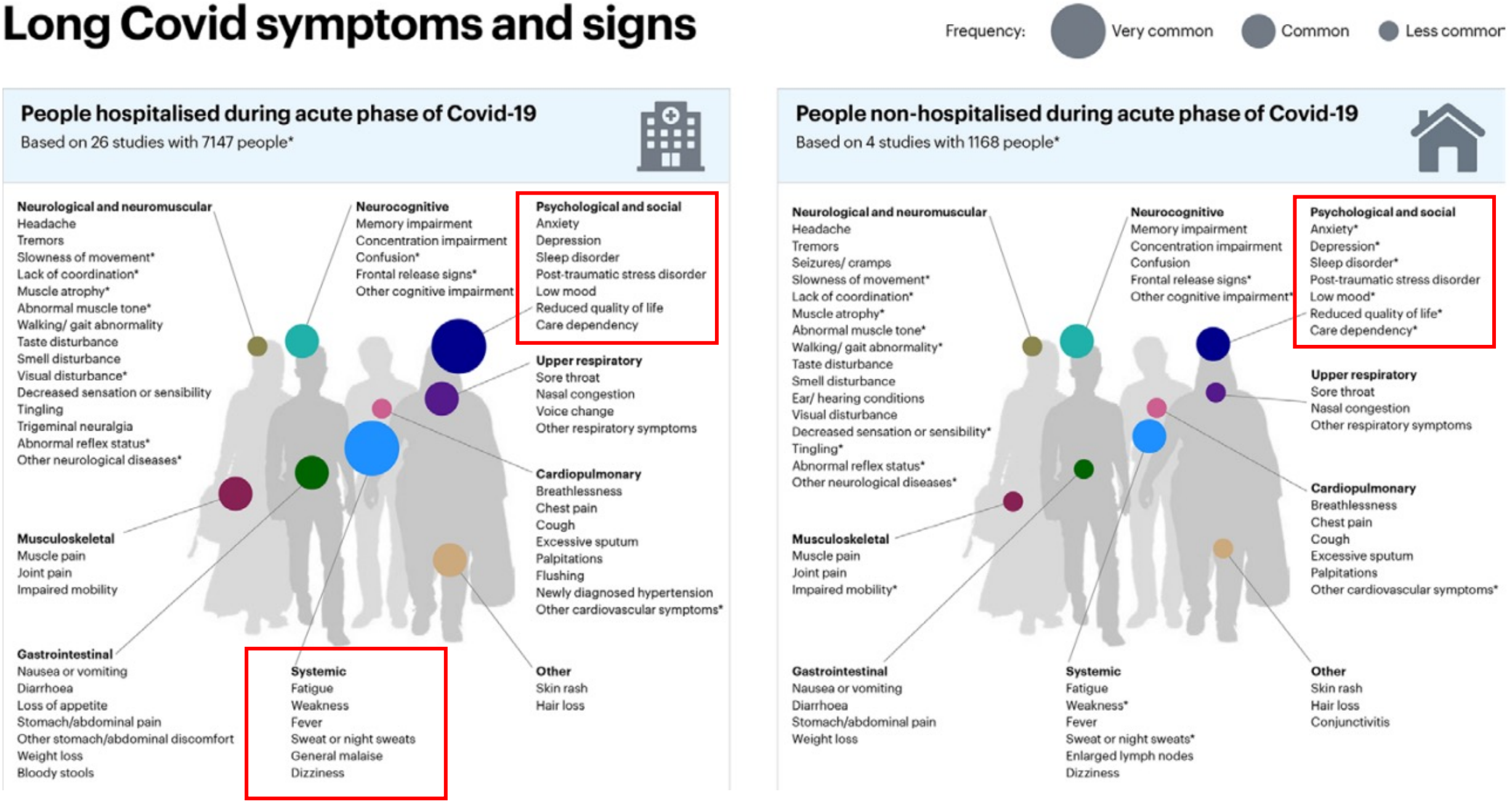
Slide credit: clinicaloptions.com

- **Gender**
  - Female 1.5 higher odds of long-COVID
  - Penn Post-COVID Clinic: 66.3% female, 31.3% male
- **Age**
  - Linear increase up to age 70 than a decrease after
  - Penn Post-COVID Clinic: 18-34 (18%), 35-49 (33.8%), 50-69 (39.4%), >70 years (8.3%)
- **Health**
  - More likely in older patients with more comorbid conditions such as hypertension, obesity, psychiatric conditions, poor general health, asthma, or immunosuppressed
- **Severity of Initial Illness**
  - Number of initial symptoms and prolonged hospitalization/ICU admission likely predictive

doi: https://doi.org/10.1101/2021.06.24.21259277, doi: 10.15585/mmwr.mm6930e1

doi: 10.1016/j.cmi.2021.11.002

Long Covid symptoms and signs



Michelen M, Manoharan L, Elkheir N*, et al* Characterising long COVID: a living systematic review *BMJ Global Health* 2021;**6:**e005427.

Laboratory Testing in Patients with Post COVID-19 Conditions

Basic diagnostic laboratory testing to consider

CATEGORY	LAB TESTS
Blood count, electrolytes, and renal function	Complete blood count with possible iron studies to follow, basic metabolic panel, urinalysis
Liver function	Liver function tests or complete metabolic panel
Inflammatory markers	C-reactive protein, erythrocyte sedimentation rate, ferritin
Thyroid function	TSH and free T4
Vitamin deficiencies	Vitamin D, vitamin B12

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-assessment-testing.html

More specialized diagnostic laboratory

BNP and troponin

- In patients whose course was complicated by CHF or myocarditis
- In patients with new onset cardiac symptoms

D-dimer

- In patients with unexplained persistent or new dyspnea, or in any patient in whom there is a concern for thromboembolic disease.

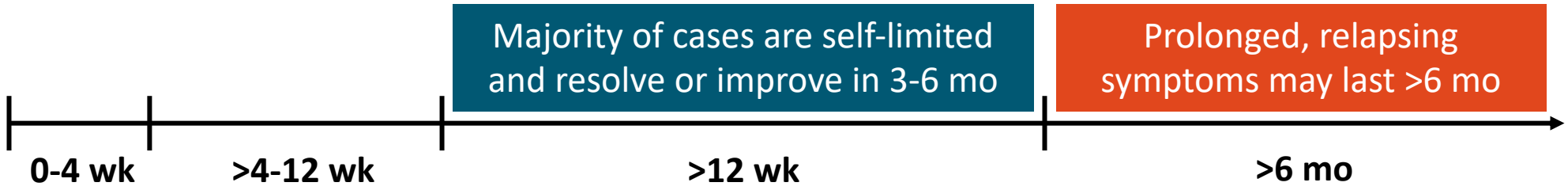
Antinuclear antibody and creatinine kinase

- In patients with arthralgias, myalgias, or other symptoms concerning for rheumatologic disorders.

SARS-CoV-2 Serology

- For patients with prior COVID-19 based upon symptoms, but without a documented positive molecular antigen test, the value of obtaining SARS-CoV-2 serology is unclear but may be helpful

Long COVID Symptoms: Timelines



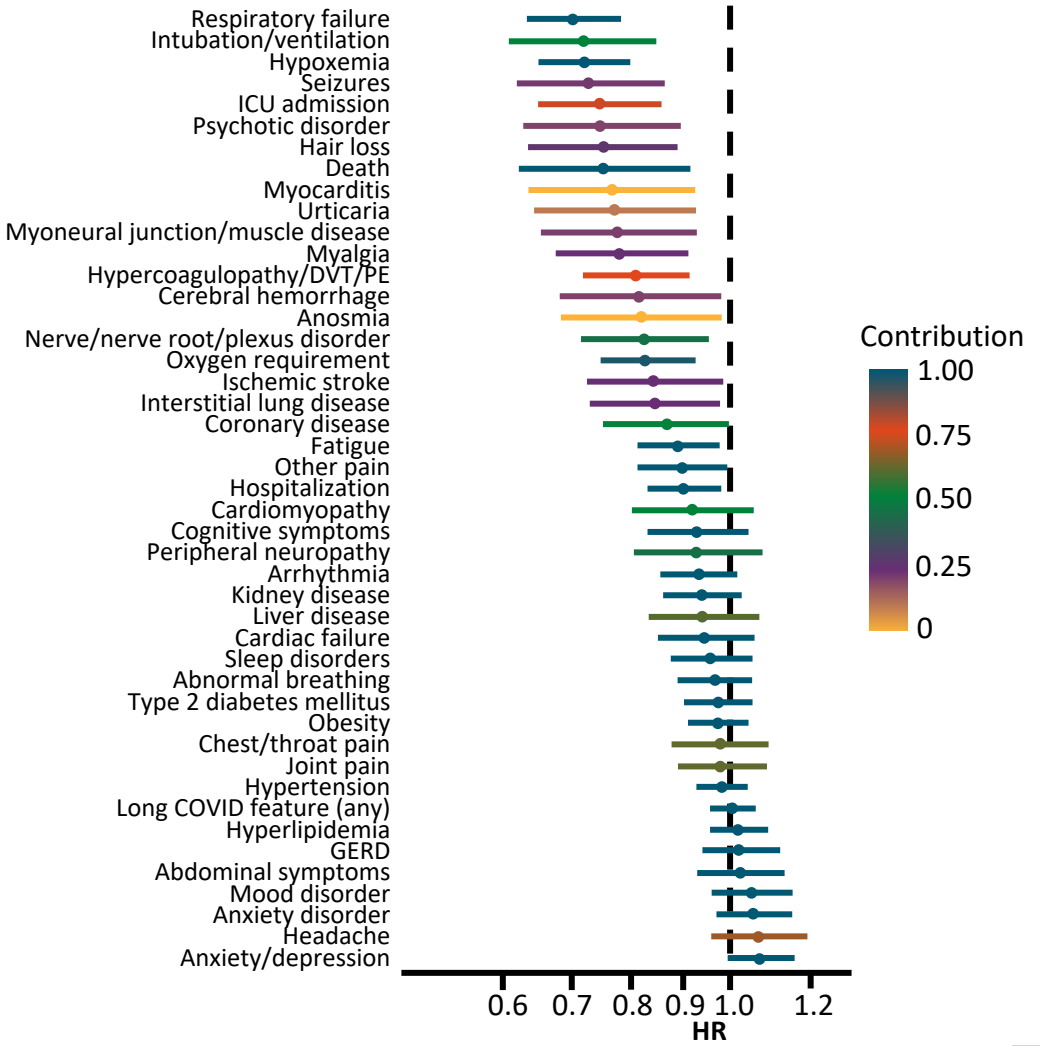
- 10%-30% of COVID-19 patients have chronic symptoms
  - More common in younger female patients with mild initial illness
- More severe: post-hospitalization with major end-organ injury
  - ARDS, AKI or CKD, PE or DVT, myocardial injury

Schmidt. Nat Biotechnol. 2021; Epub online.

Slide credit: clinicaloptions.com

Long COVID and COVID-19 Vaccination

- Long COVID can occur after a breakthrough infection, but rates are consistently lower in vaccinated vs unvaccinated persons
- 2 doses of SARS-CoV-2 vaccine is protective against *some* postacute sequelae of COVID-19, but not all



Kuodi. medRxiv. 2022;[Preprint]. Note: this study has not been peer reviewed.
Taquet. medRxiv. 2021;[Preprint]. Note: this study has not been peer reviewed.

Slide credit: clinicaloptions.com

General Management Approach

Long COVID conditions can and should be managed by primary care providers

Normal laboratory test results and imaging do not rule out Long COVID

There are still many things about Long COVID that we do not understand and can not measure

Provide understanding and support

Identify and treat "comorbid conditions" that could have been undiagnosed but present before acute COVID-19

Address severe symptoms sensibly, especially those that are "stressors"

Pain and headaches

Sleep disturbances

Orthostatic intolerance

Cognitive impairment

Anxiety, grief/loss (especially in the first 1-2 years of illness)

Help patients build a "toolbox" of rescue medications and strategies to manage symptom flares and maintain some physical conditioning

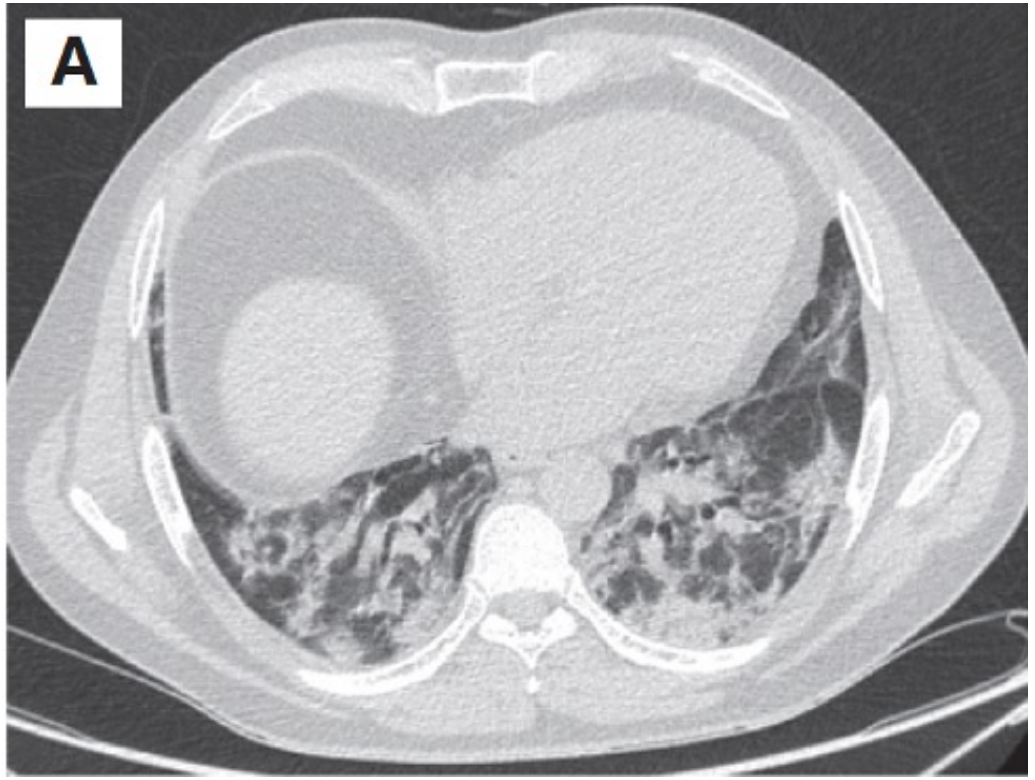
Post COVID-19 Cardiopulmonary Conditions You Do Not Want to Miss

Identify early the most serious and potentially life-limiting complications

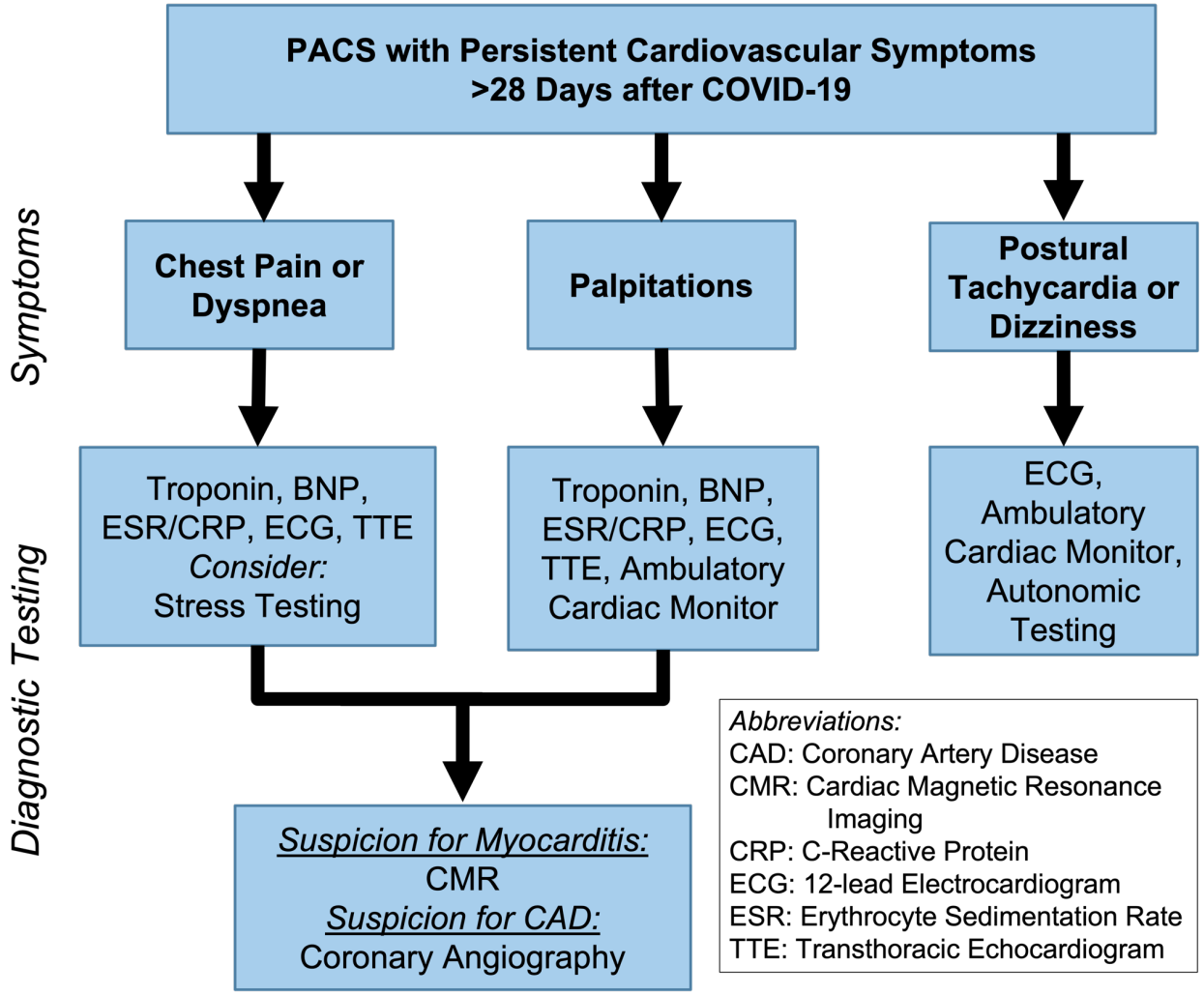
- Organizing Pneumonia
- Pulmonary fibrosis
- Pulmonary thromboembolism
- Pulmonary Hypertension
- Bacterial/fungal Infectious complications (Pneumonia)

Tests

- Chest CT w or wo contrast
- Pulmonary function tests
- 6 min walk or similar
- EKG/Echocardiogram



Approach to CV complications



When to Refer to Cardiology?

- Abnormal cardiac test results
- Known CV disease with new/worsening symptoms/signs
- Documented cardiac complications during acute COVID-19 illness
- Persistent unexplained cardiopulmonary symptoms

Gluckman, *JACC* 2022 (PMID: 35307156)

Dixit, …, Hsu, *Am Heart J Plus* 2021 (PMID: 34192289)

Definitions

- **Orthostatic Intolerance:**
  - Development of symptoms (cerebral hypoperfusion, sympathetic overactivation) during standing that clears upon recumbence
- **Orthostatic Hypotension:**
  - ↓ SBP >20 mmHg or DBP >10mm Hg within 3 mins of standing
- **Postural Orthostatic Tachycardia Syndrome (POTS):**
  - ↑ HR >30 bpm (>40 bpm adolescents) within 10 minutes of standing
  - Absence of Orthostatic Hypotension
  - Development of symptoms triggered by standing
    - Lightheadedness, Dizziness, Palpitations, Tremulousness, Generalized Weakness, Blurred Vision, Exercise Intolerance, Dyspnea, Fatigue

POTS = Orthostatic Intolerance
Orthostatic Intolerance ≠ POTS

Lecture, Dr. M. Kazamel, UAB Neurology

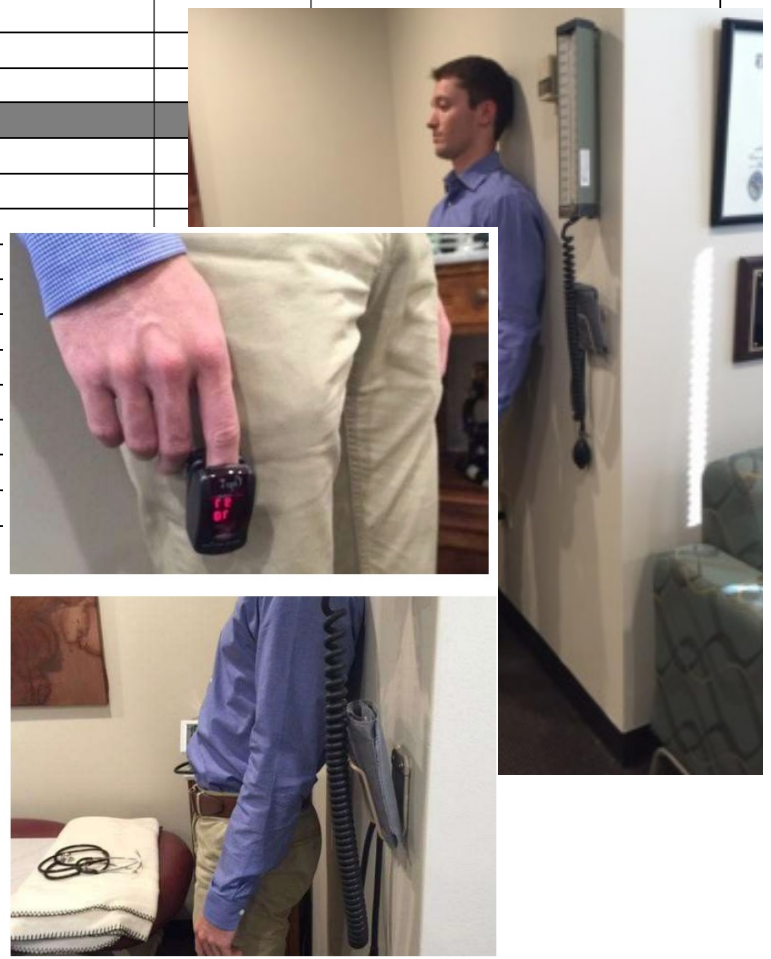
Active Stand Test / NASA Lean Test

1. **Supine, quiet x 10-15 minutes**
   - BP & HR measurements (x2)
2. **Standing x 10 minutes**
   - 1min, 3 min, 5min, 10min: BP & HR measurements

- Morning (ideally); No compression garments
- Limit water/fluid intake <1L in 24 hrs prior
- Withhold meds/supplements that may interfere with accurate results
  - Beta-blockers, Stimulants (caffeine, methylphenidate), tricyclic antidepressants, SSRI/SNRI, fludrocortisone, midodrine, antihypertensives

Orthostatic Vital Signs/The 10-Minute NASA Lean Test

	Blood Pressure (BP)		Heart Rate	
	Systolic	Diastolic	bpm	Comments/Symptoms
Supine 1 minute				
Supine 2 minute				
Standing 0 minute				
Standing 1 minute				
Standing 2 minute				
Standing 3 minute				
Standing 4 minute				
Standing 5 minute				
Standing 6 minute				
Standing 7 minute				
Standing 8 minute				
Standing 9 minute				
Standing 10 minute				



- **Orthostatic hypotension (OH)** ↓ SBP by 20 mm Hg or more, or ↓ DBP by 10 mm Hg or more in the first 3 minutes.
- **Postural orthostatic tachycardia syndrome (POTS)** was defined as ↑HR by >30 beats per minute (bpm) upon standing or any HR > 120 bpm

Bryarly, JACC 2019 (PMID: 30871704) https://batemanhornecenter.org/wp-content/uploads/filebase/providers/mecfs/10-Minute-NASA-Lean-Test-Clinician-Instructions-06_2021.pdf

Treatment Strategies

Non-Pharmacological:

Avoid Triggers

- Carbohydrate heavy meals
- Heat
- Minimize/avoid caffeine and alcohol

Hydration

- >3 liters water/day

Salt Intake

- 5-10 grams sodium/day

Bryarly, JACC 2019 (PMID: 30871704)

Treatment Strategies

Pharmacological:

- *Beta-Blockers (propranolol)*
- *Ivabradine (I_f blocker)*
- *Clonidine (central sympatholytic)*

} Hyperadrenergic

- *Midodrine (α1 agonist)*
- *Fludrocortisone (aldosterone analog)*

} Hypotensive / Orthostatic Hypotension

- *Anti-histamines:* Mast Cell Activation Disorder overlap?
- *Pyridostigmine (acetylcholinesterase inhibitor):* Cardiovagal dysfunction?

- Caution:
  - Sympathomimetics (SSRI, SNRI, amphetamines) in hyperadrenergic patients

Fu, Hypertension 2011 (PMID: 21690484)
Taub, JACC 2021 (PMID: 33602468)
Bryarly, JACC 2019 (PMID: 30871704)

Conclusions

- COVID-19 is here to stay
- AI/AN are disproportionately affected by COVID-19
- The most effective way to curb the COVID-19 pandemic will be though vaccination
  - Contact tracing, testing, isolation and quarantine are also important interventions
- Effective treatments to decrease hospitalization and death are available, but more data is needed in their impact on fully vaccinated individuals
- A very large wave of Long COVID likely to follow each surge
  - Will require enormous effort, compassion, multi-disciplinary care, and a thoughtful, symptom-based approach to management

Two Vaccines May be Used for the Prevention of Monkeypox Disease:

- **JYNNEOS is a third-generation vaccine based on a live, attenuated non-replicating orthopoxvirus**
  - Modified Vaccinia Ankara (MVA). MVA is a live virus that does not replicate efficiently in humans. It has FDA EUA for
  - JYNNEOS vaccine is used for the prevention of smallpox and monkeypox disease among people at high risk for infection
  - Active immunization by **intradermal** injection for prevention of monkeypox disease in individuals 18 years of age and older determined to be at high risk for monkeypox infection.
  - Active immunization by subcutaneous injection for prevention of monkeypox disease in individuals less than 18 years of age determined to be at high risk for monkeypox infection.
- **ACAM2000 is a second-generation vaccine indicated for the prevention of smallpox disease**.
  - It has been made available for use against monkeypox under an Expanded Access Investigational New Drug (EA-IND) protocol, which requires informed consent along with completing additional forms.
  - ACAM2000 vaccine is approved for immunization against smallpox disease for people at high risk for infection.
  - ACAM2000 contains a live vaccinia virus that is replication-competent in humans.
  - Available evidence supporting the use of smallpox vaccine for monkeypox prevention is derived from the vaccine used during smallpox eradication,
- In the context of limited vaccine supply, JYNNEOS
  - Vaccine doses should be prioritized for people who are at high risk for severe disease caused by infection with the *Monkeypox virus* (including, but not limited to, people with HIV infection or other immunocompromising conditions, who are pregnant, or who are at increased risk for serious adverse events following ACAM2000 vaccination).

https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html

Table 1. Vaccination Strategies Used in the 2022 U.S. Monkeypox Outbreak

Strategy	Definition	Criteria
Post-Exposure Prophylaxis (PEP)	Vaccination **after known exposure** to monkeypox	• People who are known contacts to someone with monkeypox who are identified by public health authorities, for example via case investigation, contact tracing, or risk exposure assessment
Expanded Post-Exposure Prophylaxis (PEP++)	Vaccination **after known or presumed** exposure to monkeypox	Any of the following: • People who are known contacts to someone with monkeypox who are identified by public health authorities, for example via case investigation, contact tracing, or risk exposure assessment • People who are aware that a recent sex partner within the past 14 days was diagnosed with monkeypox • Certain gay, bisexual, or other men who have sex with men, or transgender people, who have had any of the following within the past 14 days: sex with multiple partners (or group sex); sex at a commercial sex venue; or sex in association with an event, venue, or defined geographic area where monkeypox transmission is occurring
Pre-Exposure Prophylaxis (PrEP)	Vaccination **before exposure** to monkeypox	• People in certain occupational risk groups*

*People at risk for occupational exposure to orthopoxviruses include research laboratory workers performing diagnostic testing for *Monkeypox virus,* and members of health care worker response teams designated by appropriate public health and antiterror authorities (see ACIP recommendations).

https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html