COVID-19
IDWEEK 2023 Update

Jorge Mera, MD

NPAIHB ID ECHO

Outline

IDSA COVID-19 Diagnostic Guideline Updates

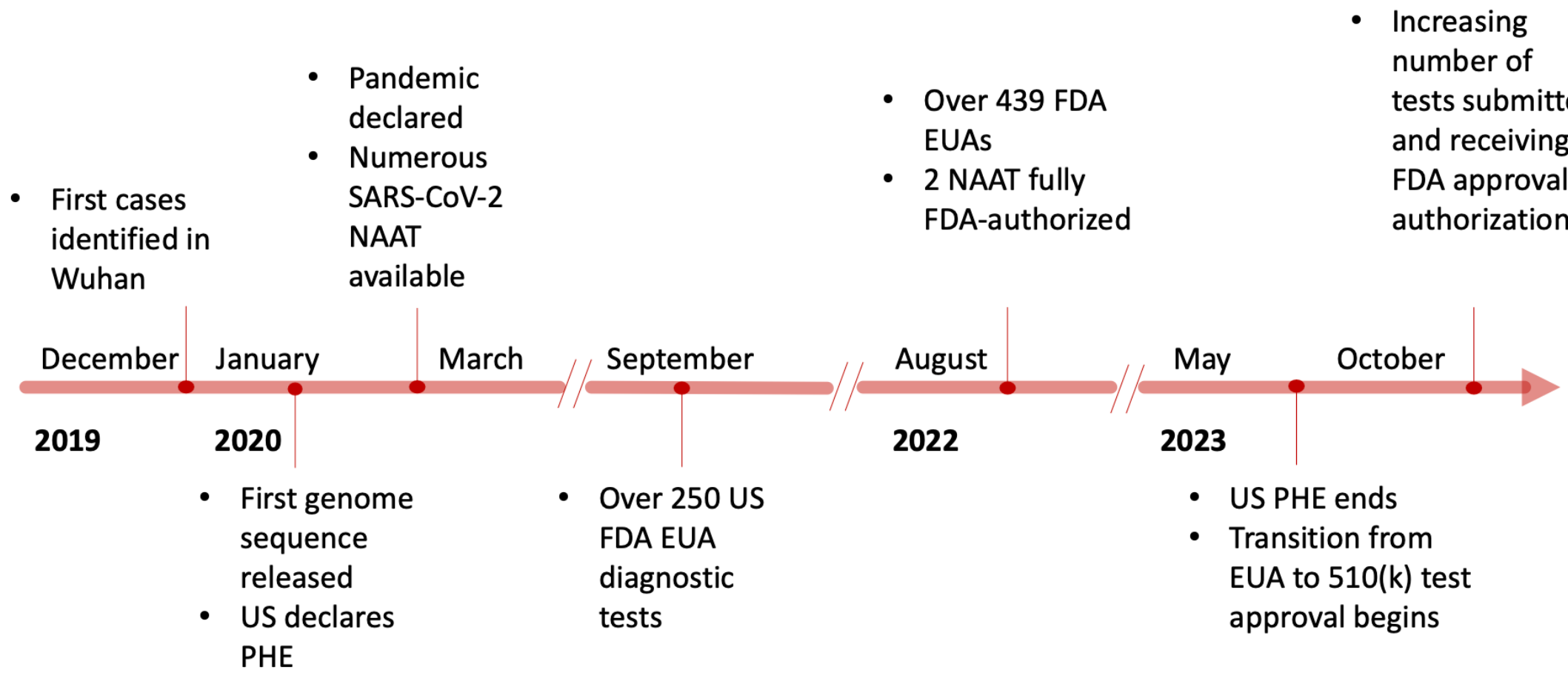
- Antigen
- Molecular
- Serology

Treatment Updates

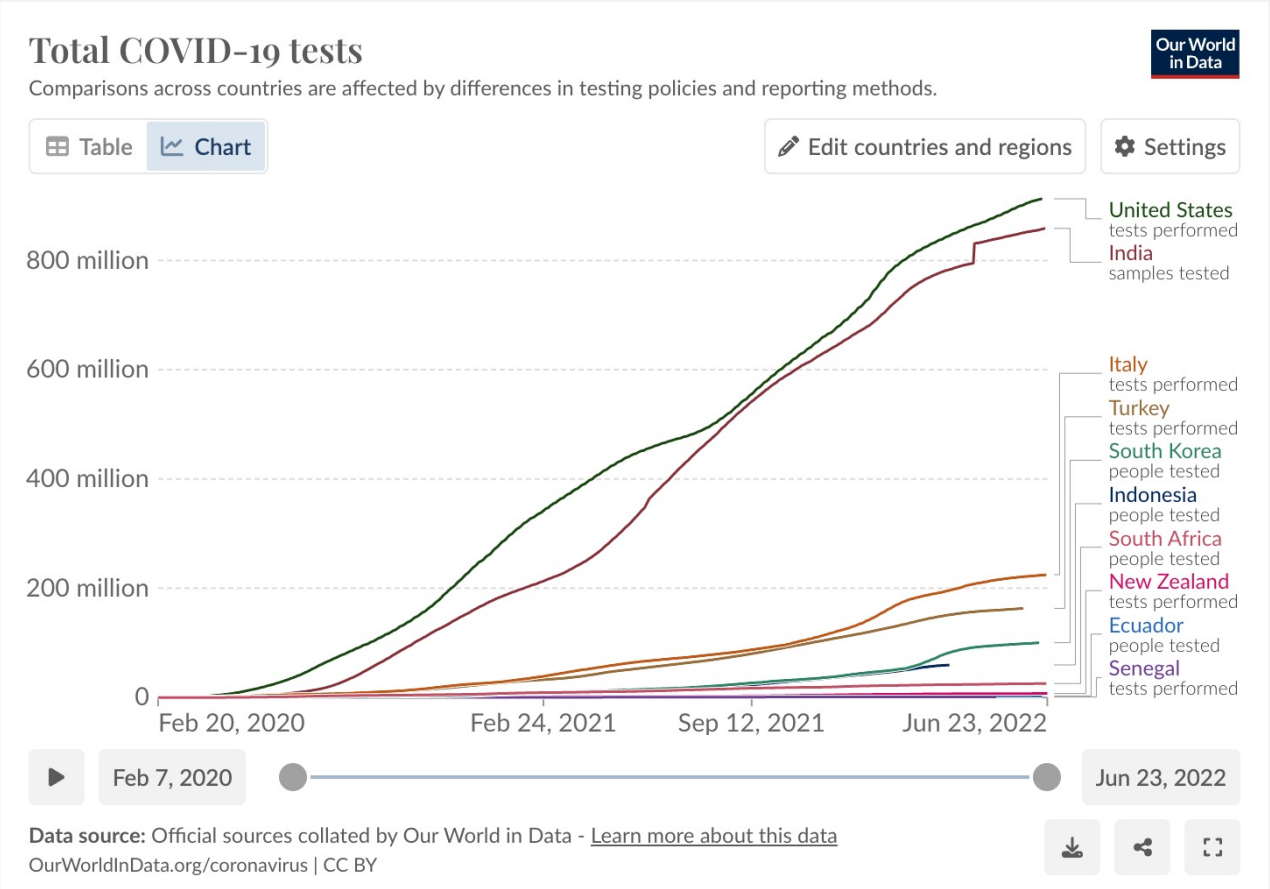
Long COVID

https://www.idsociety.org/practice- guideline/covid-19-guideline-diagnostics/

Timeline for SARS-CoV-2 Diagnostic Test Development and FDA Approval



COVID-19 Tests Worldwide



Nearly 6 billion COVID19 NAAT and antigen tests have been completed globally by mid-2022

CBC is the most performed blood test at 3.6 billion per year worldwide

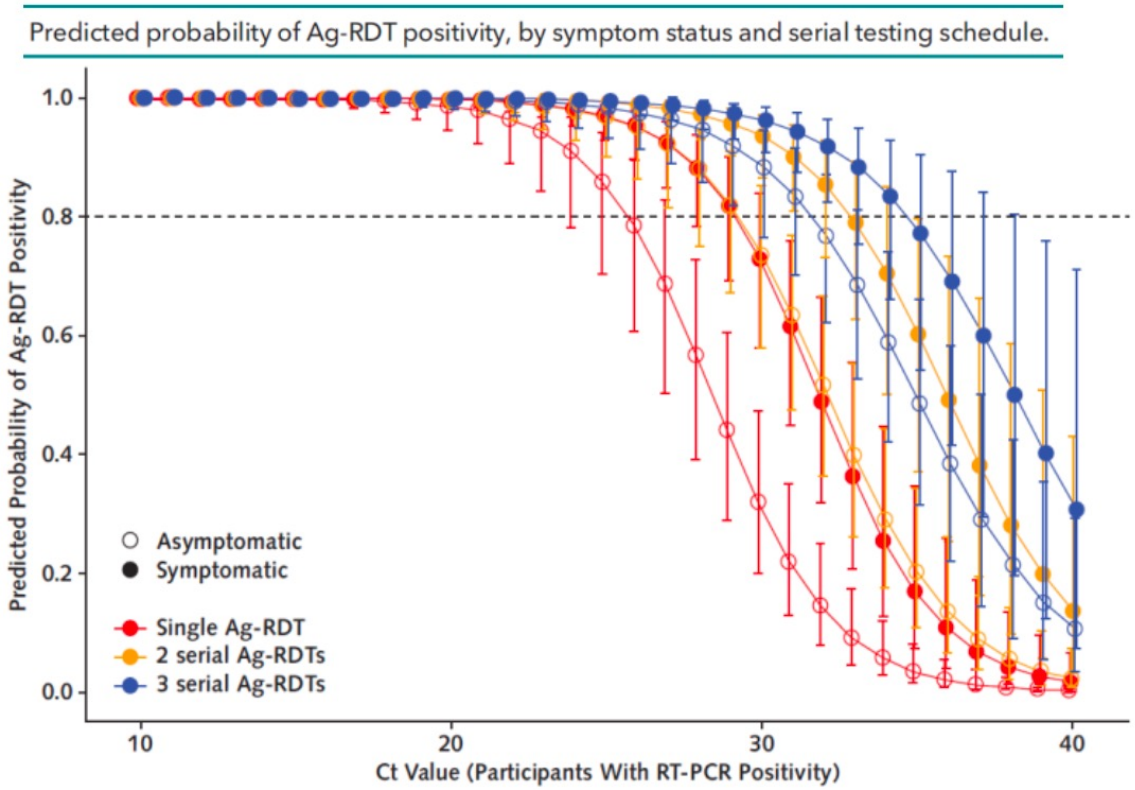
In asymptomatic individuals, performance of a COVID-19 Ag test is optimized if persons are tested:

A. X 1
B. X 2 every 48 hours
C. X 3 every 48 hours
D. X 4 every 48 hours
E. Don’t bother using an Ag test, just flip a coin

In symptomatic individuals, performance of a COVID-19 Ag test is optimized if persons are tested:

A. X 1
B. X 2 every 48 hours
C. X 3 every 48 hours
D. X 4 every 48 hours
E. Don’t bother using an Ag test, just flip a coin

Antigen Sensitivity Improved by Repeat Testing



- Prospective, multicenter, US cohort study Oct 2021-Jan 2022
- Asymptomatic and negative for SARS-CoV-2 day 1
- Participants had antigen test and NAAT every 48 hrs for 15 days
- 154/5353 developed COVID-19 diagnosed by NAAT
- Performance of antigen test optimized if symptomatic persons tested 2X and asymptomatic persons tested 3X

Soni A et al Ann Intern Med 2023

In asymptomatic individuals, performance of a COVID-19 Ag test is optimized if persons are tested:

A. X 1

B. X 2 every 48 hours

C. X 3 every 48 hours

D. X 4 every 48 hours

E. Don’t bother using an Ag test, just flip a coin

In symptomatic individuals, performance of a COVID-19 Ag test is optimized if persons are tested:

A. X 1

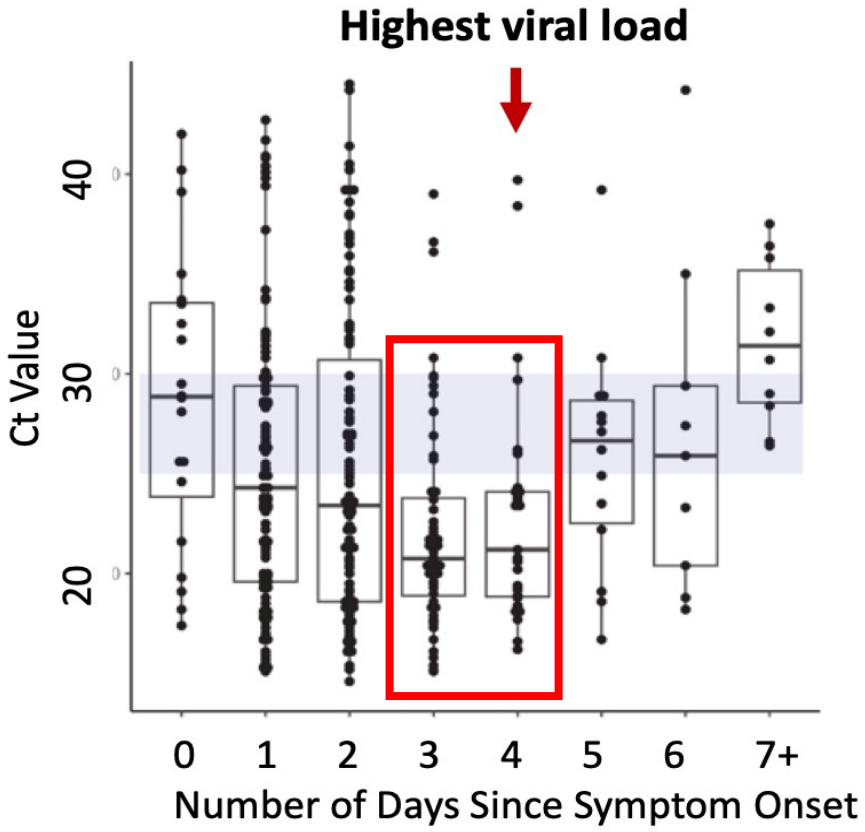
B. X 2 every 48 hours

C. X 3 every 48 hours

D. X 4 every 48 hours

E. Don’t bother using an Ag test, just flip a coin

SARS-CoV-2 viral load peaks day 4 in highly-immunized population



- Cross-sectional cohort study
- April 1, 2022, to April 13, 2023
- 348 symptomatic hospital and community-based adults in Georgia, USA with newly diagnosed COVID-19 by PCR
- 91% vaccinated and/or had prior COVID-19
- Results support repeat testing to optimize antigen sensitivity

Frediani JK et al CID, ePub ahead of print

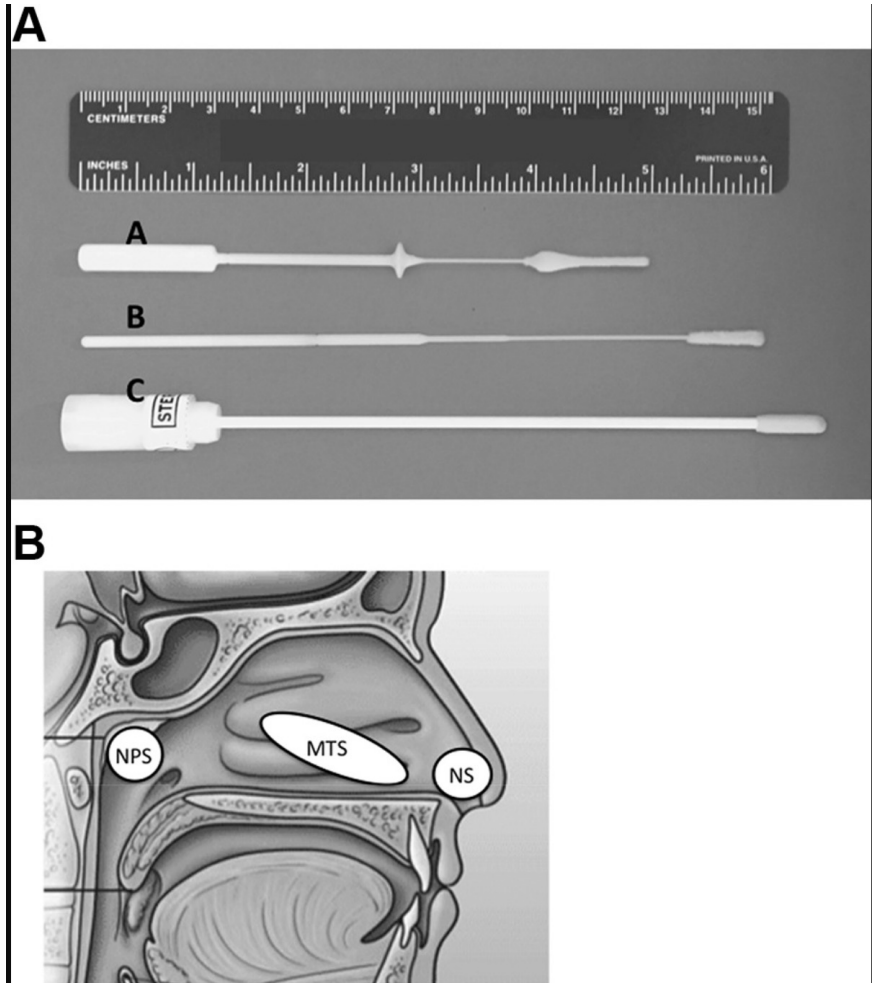
For symptomatic individuals which site has the highest performance for COVID-19 NAAT tests

A. Nasopharynx
B. Anterior nares
C. Oropharynx
D. Mid-turbinate regions
E. Saliva
F. Mouth gargle

Anatomic Site of Specimen Collection for Molecular Testing

Recommendation 2: For symptomatic individuals suspected of having COVID-19, the IDSA panel suggests collecting and testing swab specimens from either the nasopharynx, anterior nares, oropharynx, or midturbinate regions; saliva, or mouth gargle (*conditional recommendation, low certainty evidence*).

https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/



Annals of Emergency Medicine Volume 71, no. 4 : April 2018

Performance characteristics of NAAT: Nasopharyngeal swab vs other specimen types

Sample site	Saliva	Oropharyngeal (OP) swab	Anterior nares (AN) swab	Combined AN/OP swab	Midturbinate swab	Mouth gargle
	92 (89-94)	**77** (63-86)	**74** (56-87)	**87** (77-93)	**87** (78-93)	**83** (66-92)
	98 (97-99)	99 (98-100)	99 (98-100)	100 (98-100)	100 (97-100)	98 (89-100)

https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/

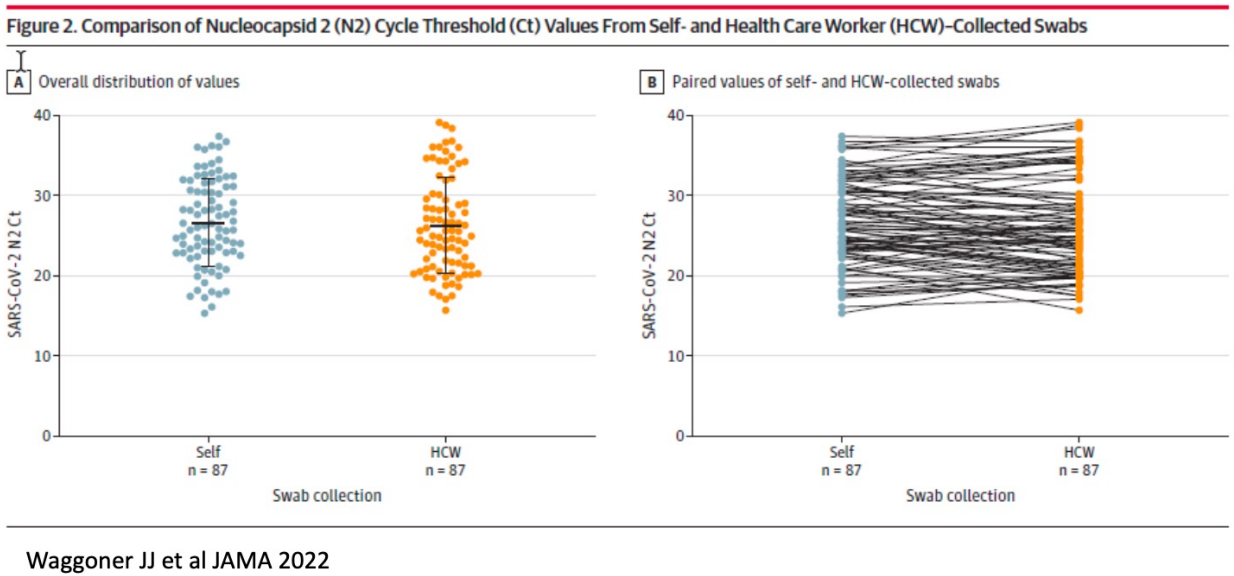
Regarding collection of specimens with nasal swab in children, which of the following individuals would have the highest yield using a NAAT test for COVID-19.

A. A healthcare worker

B. The patient

C. A and B are correct

High concordance between Ct value results of self-collected vs HCW collected nasal swabs



Waggoner JJ et al JAMA 2022

- N=194 children and adolescents
- Median age 9 yo
- Short instructional video + handout with written and visual instructions

Recommendation 3: The IDSA panel suggests that for symptomatic individuals suspected of having COVID-19, anterior nares and midturbinate swab specimens may be collected for SARS-CoV-2 NAAT by either patients or healthcare providers (*conditional recommendation, moderate certainty evidence*).

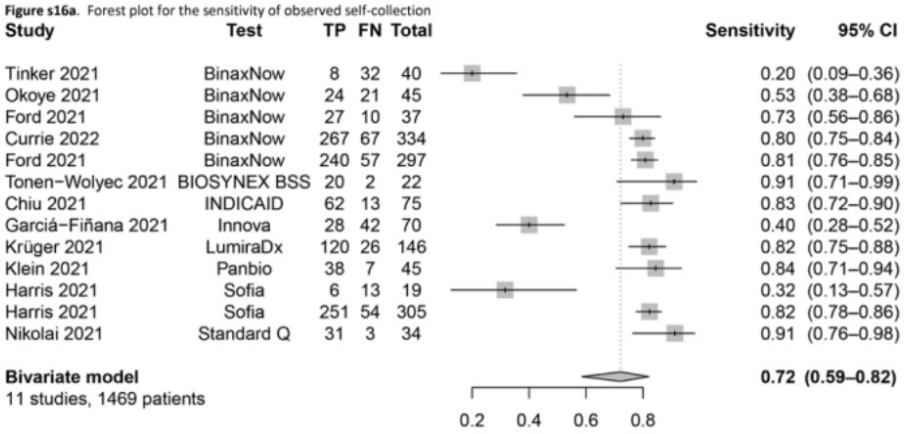
Regarding collection of specimens with nasal swab in children, which of the following individuals would have the highest yield using a NAAT test for COVID-19.

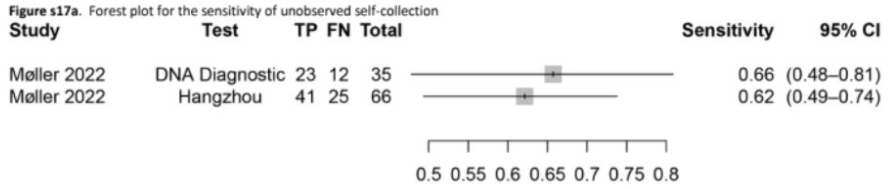
A. A healthcare worker

B. The patient

C. A and B are correct

Antigen Testing: Observed vs Unobserved Self-Collection of Anterior Nares Swab Specimens





Hayden MK et al CID 2023, ePub ahead of print

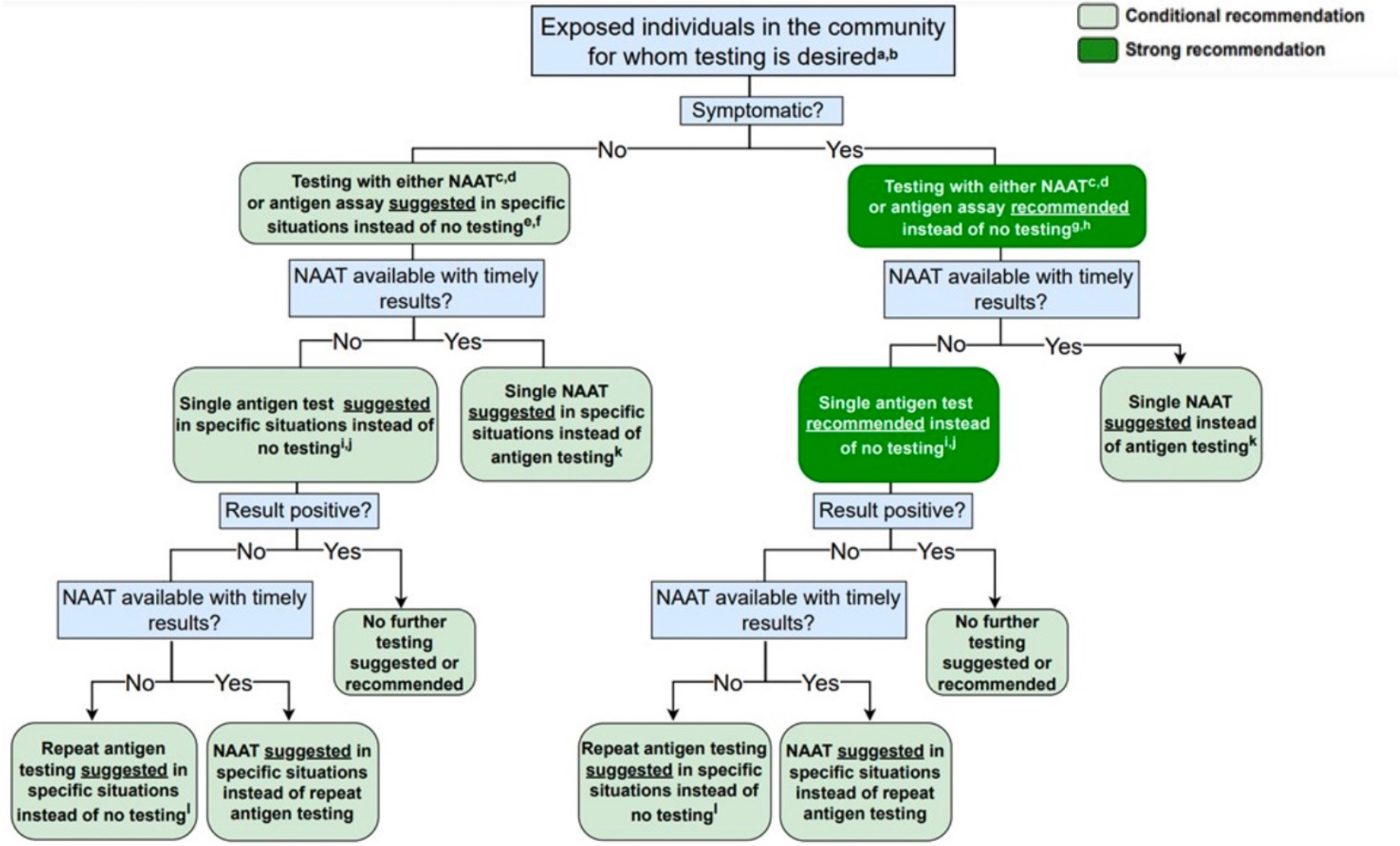
Recommendation 10: The IDSA panel suggests either observed or unobserved self-collection of swab specimens for Ag testing if self-collection is performed *(conditional recommendation, low certainty evidence).*

Use of NAAT to Reduce SARS-CoV-2 Transmission in Healthcare Settings

- **Recommendation 8**: The IDSA panel suggests against routine SARS-CoV-2 NAAT in asymptomatic individuals without a known exposure to COVID-19 who are being hospitalized *(conditional recommendation, very low certainty evidence)*.
- **Recommendation 9**: The IDSA panel suggests against routine SARS-CoV-2 NAAT of asymptomatic individuals without a known exposure to COVID-19 who are undergoing a medical or surgical procedure *(conditional recommendation, very low certainty evidence)*.

Talbot TR et al Infect Control Hosp Epidemiol 2023; Rhee C et al CID 2023.

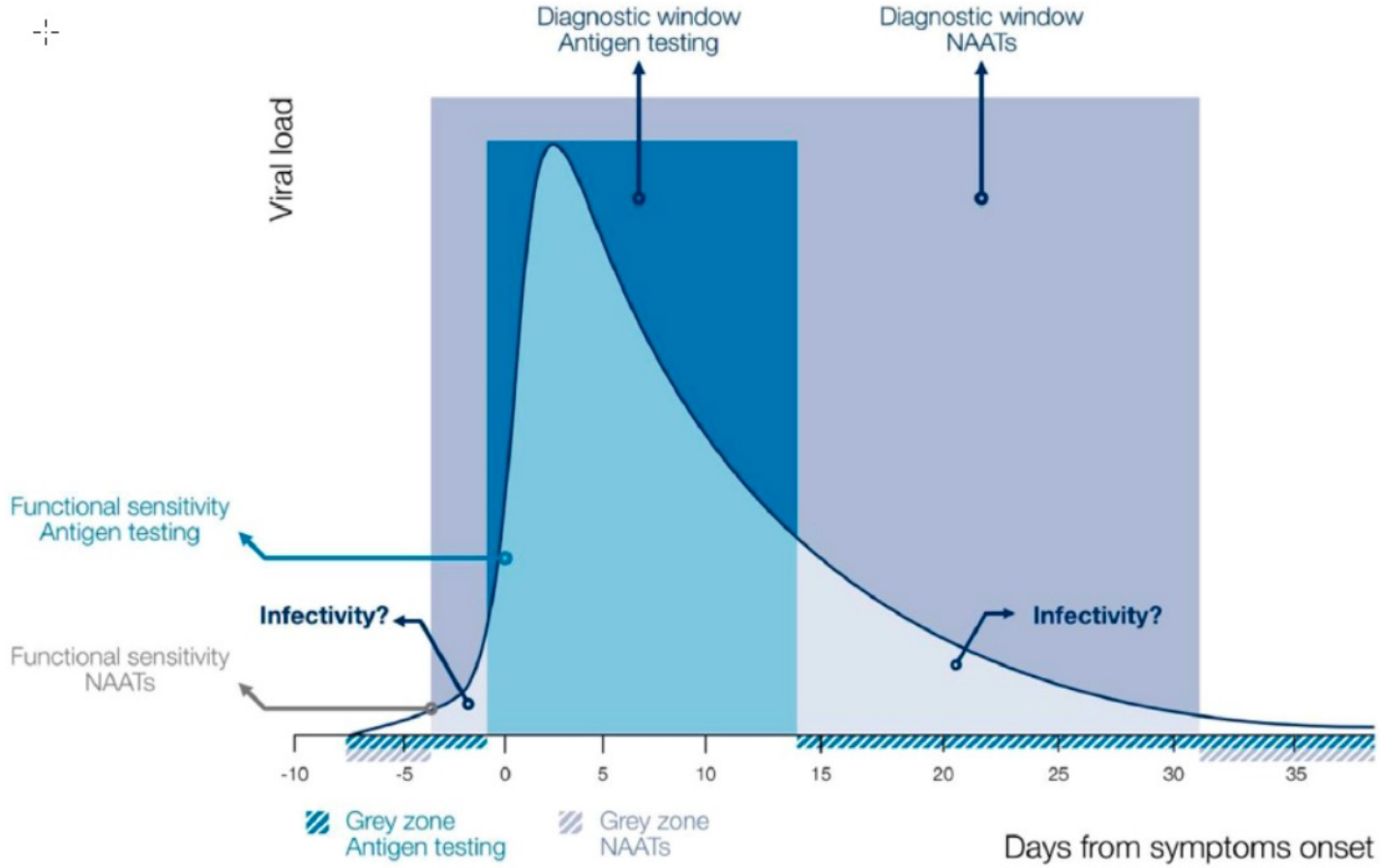
Diagnosis of SARS-CoV-2 Infection Using NAAT & Antigen Testing



https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/

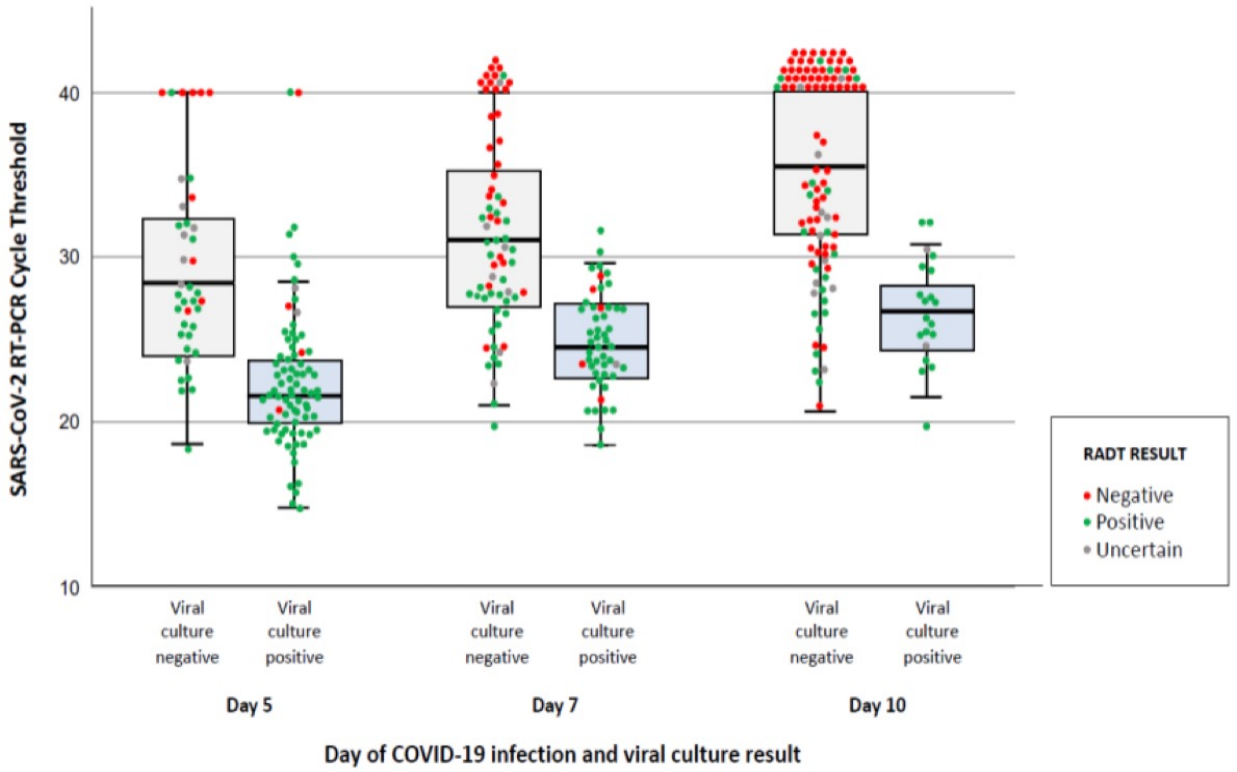
NAAT Testing to Guide Release from Isolation

- **Recommendation 11:** The IDSA panel suggests against routinely repeating NAAT in patients with COVID-19 to guide release from isolation *(conditional recommendation, very low certainty evidence)*.



Wertenauer C et al Diag Micro ID 2023

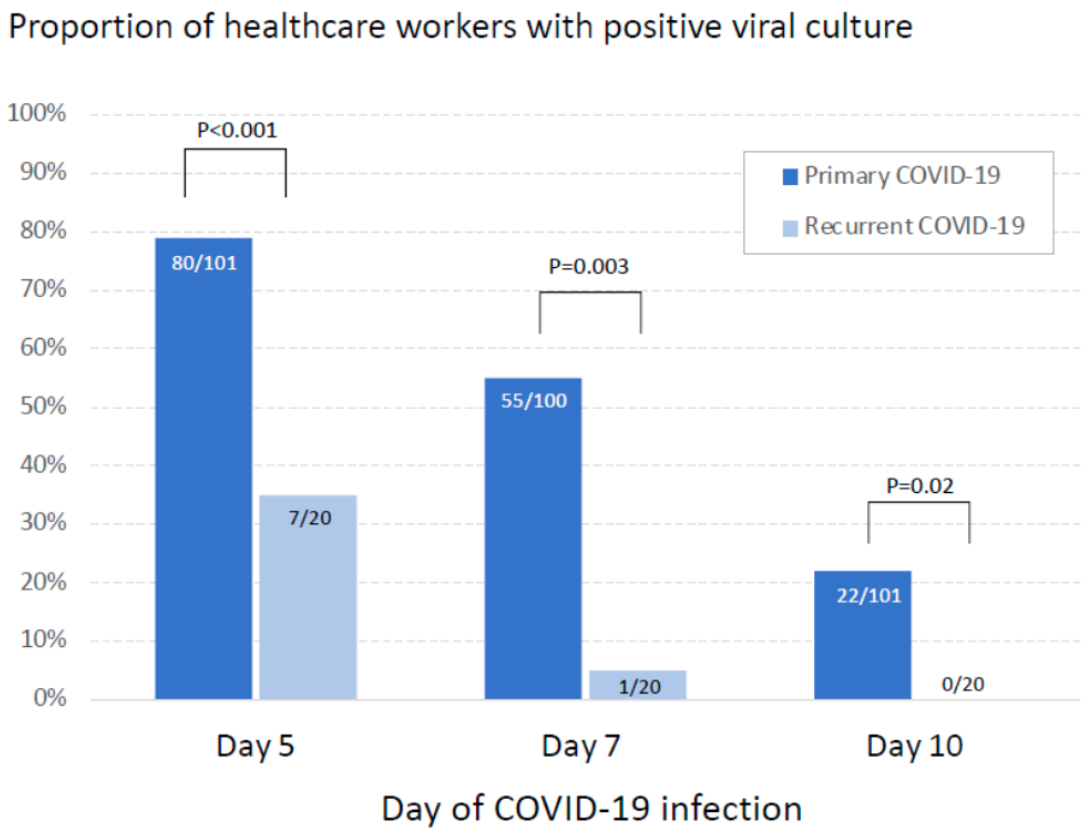
Serial Monitoring of HCWs with COVID-19 (n=121)



Dzieciolowska S et al CID 2023, ePub ahead of print

- Longitudinal, multicenter, observational cohort
- Feb 2022- March 2023
- 98% participants vaccinated
- 16% had prior COVID-19
- PCR, antigen, viral culture day 5, 7, 10
- Viral culture positivity decreased from
- 72% on day 5 to 18% on day 10
- Ct >23 and prior COVID-19 predicted non-infectivity on day 5 but symptom improvement or antigen test result did not
- **18% of those meeting all CDC criteria for release from isolation on day 7 were viral culture positive**

Serial Monitoring of HCPs with COVID-19 (n=121)

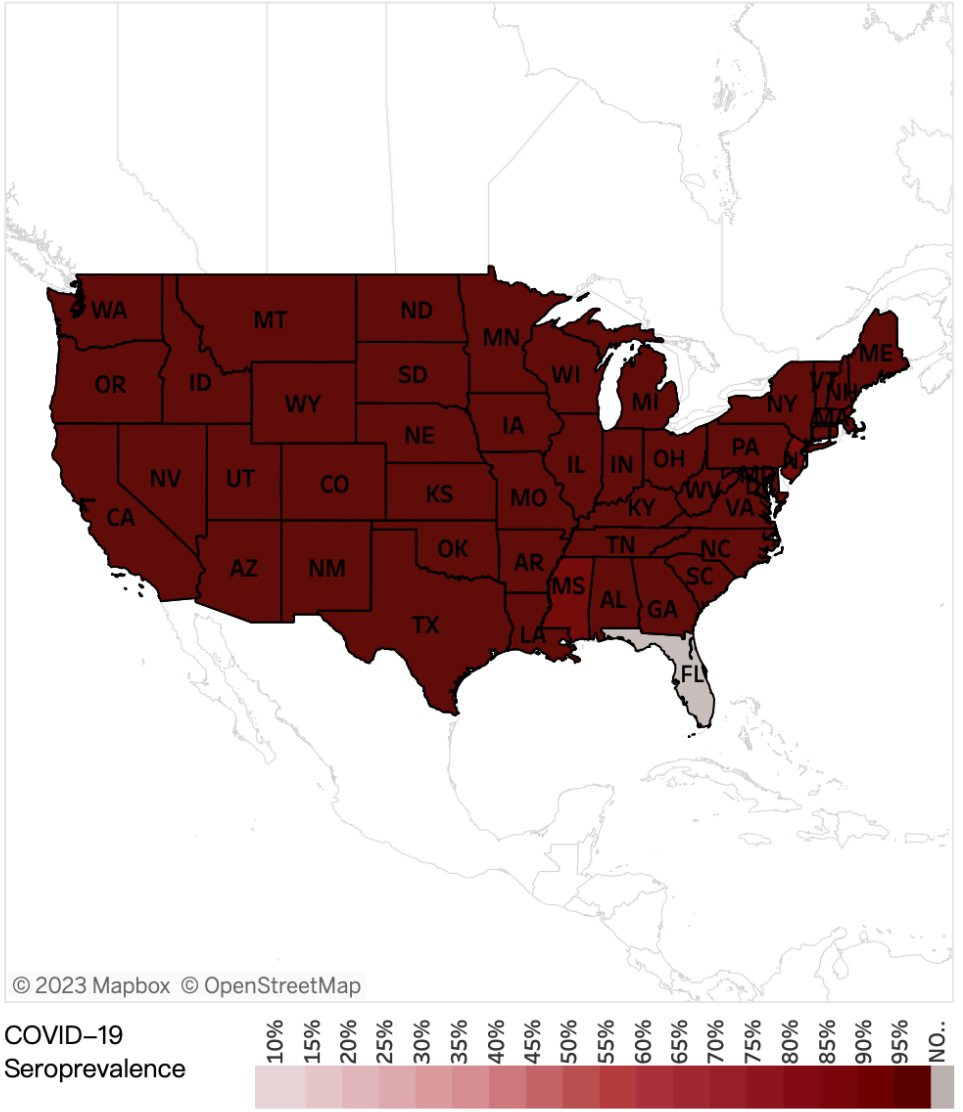


Dzieciolowska S et al CID 2023, ePub ahead of print

- Participants with recurrent COVID-19 had a lower likelihood of infectivity vs those with primary COVID-19
- Suggests that patients may become less infectious or may be infectious for a shorter period after multiple episodes of infection
- Alternative algorithms may be helpful in deciding when HCPs with COVID-19 can return to work safely

2022 Nationwide COVID-19 Infection- and Vaccination-Induced Antibody Seroprevalence (Blood donations)

Seroprevalence estimate: as of 11/15/2022	**96.7%**
95% confidence interval:	93.9% - 98.3%
Persons ≥ 16 years with ≥ 1 COVID–19 vaccine dose (%): as of 11/15/2022	66.8%
Cumulative reported COVID–19 cases per 100 population (#): as of 11/15/2022	29.6
Specimens tested (#):	68,203



Serologic Testing

Recommendation 6:
In individuals with previous SARS-CoV-2 infection or vaccination, the IDSA panel suggests against routine serologic testing given no demonstrated benefit to patient important outcomes (conditional recommendation, very low certainty of evidence).

Remarks

• Serologic testing may be useful for diagnosing MIS-C in pediatric patients, especially when NAAT or antigen testing is negative, to provide evidence of recent COVID-19 infection.

• A negative spike antibody test may identify immunocompromised patients who are candidates for immune therapy such as convalescent plasma or monoclonal antibodies, or to prioritize administration of monoclonal therapies when supplies are limited.

Serologic Testing

Recommendation	Strength & Certainty of Evidence
2. The IDSA panel recommends against using IgG antibodies to provide evidence of COVID-19 infection in symptomatic patients with a high clinical suspicion and repeatedly negative NAAT	Strong recommendation, very low certainty of evidence
3. To assist with the diagnosis of multisystem inflammatory syndrome in children (MIS-C), the IDSA panel recommends using both IgG antibody testing and NAAT to provide evidence of current or recent past COVID-19 infection	Strong recommendation, very low certainty of evidence
4. When evidence of previous SARS-CoV-2 infection is desired, the IDSA panel suggests testing for SARS-CoV-2 IgG, IgG/IgM, or total antibodies three to five weeks after symptom onset and against testing for SARS-CoV-2 IgM	Conditional recommendation, low certainty of evidence
5. When evidence of prior SARS-CoV-2 infection is desired, the IDSA panel suggests using serologic assays that target nucleocapsid protein rather than spike protein	Conditional recommendation, low certainty of evidence

Diagnostics Summary

NAATs remain the most sensitive tests for diagnosing COVID-19

- Antigen sensitivity can be improved by repeat testing

For molecular testing, anterior nares and oropharynx alone acceptable specimens

- But they have lower sensitivity than other sources
- Optimal testing algorithms likely to continue to evolve as population immunity increases

Given high global seroprevalence of SARS-CoV-2 antibodies

- Serology has limited utility
- Higher anti-spike bAbs and nAbs correlate with protection from infection but an absolute correlate of immunity not yet identified

FDA EUAs for COVID-19 tests remain in effect

- Keep an eye for FDA full approval

Outline

IDSA COVID-19 Diagnostic Guideline Updates

- Antigen
- Molecular
- Serology

Treatment Updates

Long COVID

https://www.idsociety.org/practice- guideline/covid-19-guideline-diagnostics/

Which of the following statements are true regarding treatment of patients with COVID-19

A. No dosage adjustment is required for remdesivir regardless of renal function including patients on dialysis

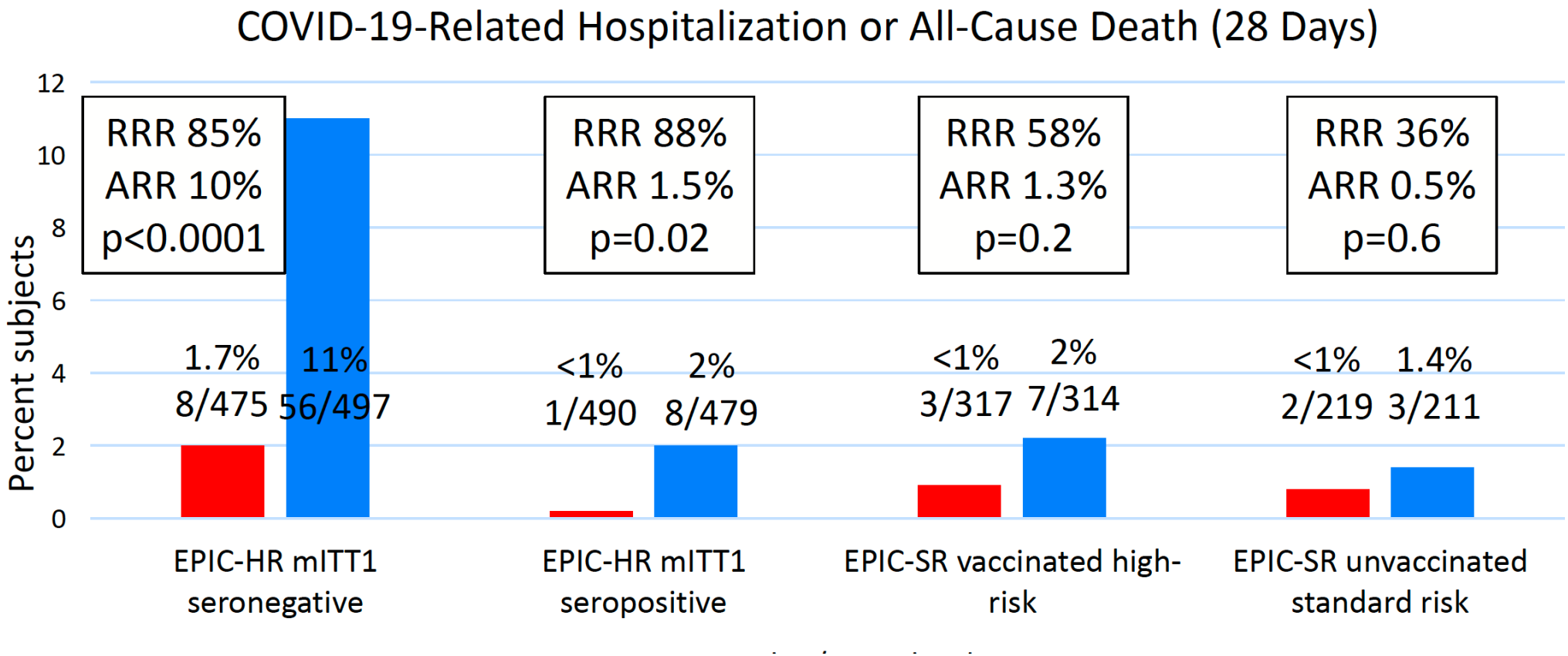
B. In patients with COVID-19 hospitalized with hypoxemia, 20 mg of Dexamethasone decreases mortality compared to 6 mg of Dexamethasone

C. The impact on hospitalization and death of nirmatrelvir/ritonavir or molnupiravir decreases in patients vaccinated for COVID-19 compared to the unvaccinated patients

D. All are correct

E. Only A and C are correct

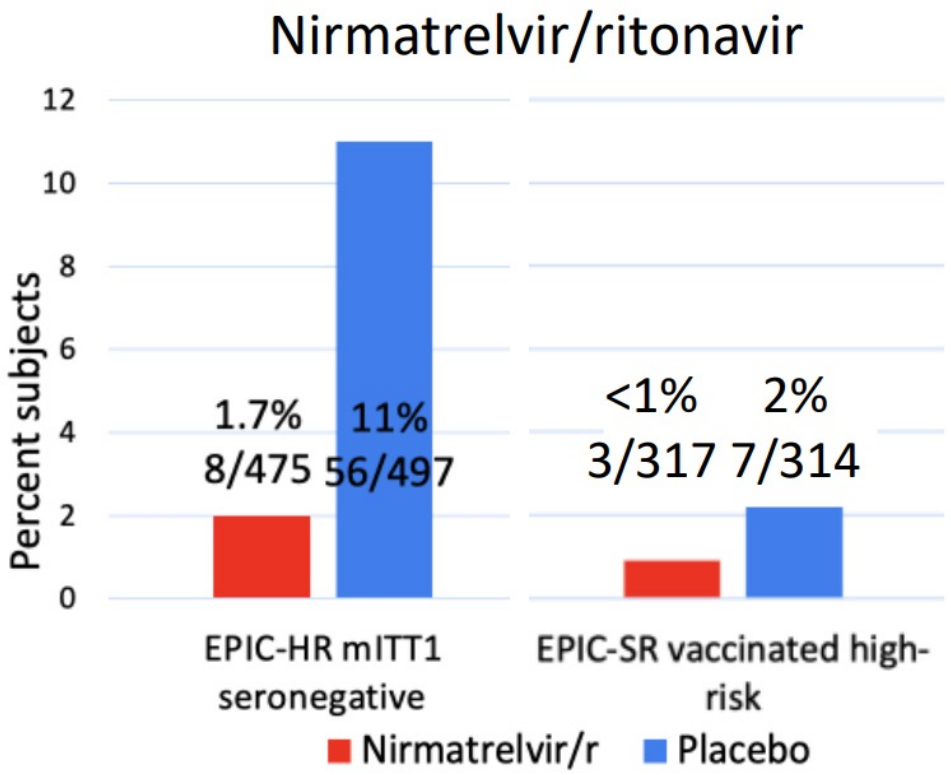
Nirmatrelvir/Ritonavir Impact on Vaccinated High Risk Patients and Unvaccinated Standard Risk Patients



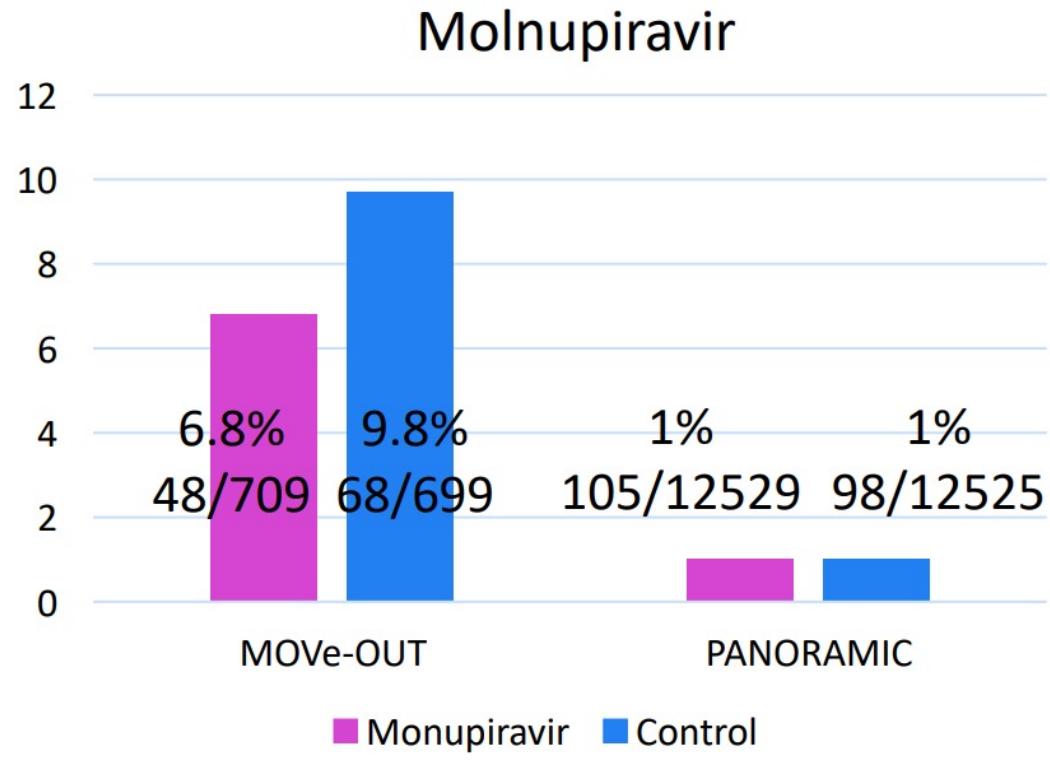
https://www.fda.gov/media/166237/download https://www.fda.gov/media/166238/download

Endpoints Need to Evolve

Percent of Hospitalization or Death in Vaccinated vs Not Vaccinated Outpatients with COVID-19



0% vaccinated 100% vaccinated



0% vaccinated 99% vaccinated

https://www.fda.gov/media/166237/download https://www.fda.gov/media/166238/download

Butler CC et al. *Lancet* 2023;401:281-93. Bernal AJ et al. *N Engl J Med* 2022;386:509-20.

Lower Doses of Steroids are Better

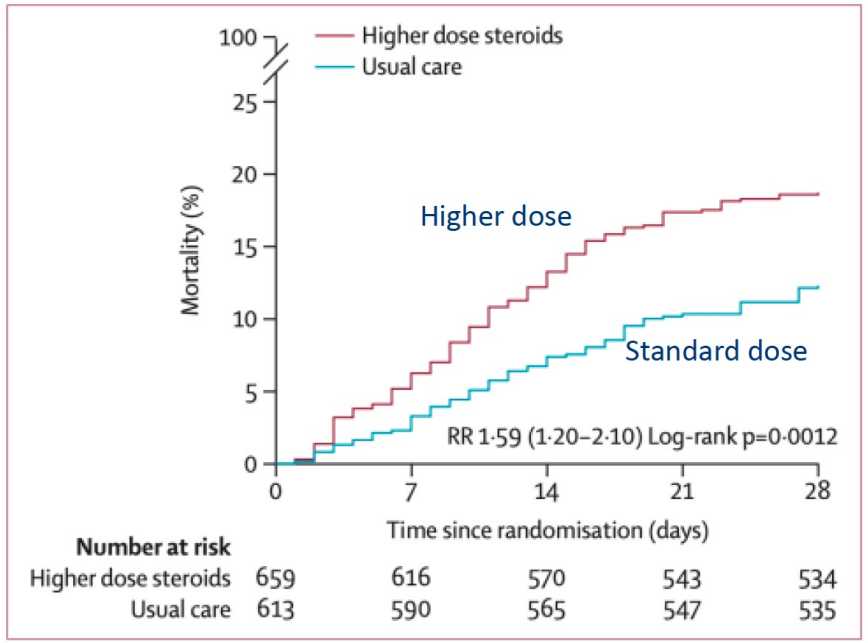


Figure 2: **Effect of allocation to higher dose corticosteroids or usual care (lower dose corticosteroids) on 28-day mortality in patients receiving no oxygen or simple oxygen only**
RR=rate ratio.

Outcome	Dex 20 mg (n=659)	Dex 6 mg (n=613)	Rate/Risk Ratio (95%CI)
28d mortality	123 (19%)	75 (12%)	1.59 (1.2-2.1)
Hospitalization, median (IQR)	9 (5-17)	9 (5/19)	NA
DC alive in 28d	526 (80%)	504 (82%)	0.92 (0.81-1.05)
Mech vent or death in 28d	131 (20%)	80 (13%)	1.52 (1.18-1.97)
Use of vent	119 (18%)	85 (14%)	1.30 (1.01-1.68)
Renal replacement therapy	11/658 (2%)	8/613 (1%)	1.28 (0.52-3.16)

RECOVERY group. Lancet 2023;401-1499-507.

Complications of Higher Dose Steroids Vs Usual Care in Hospitalized Patients With COVID-19

	Higher dose steroids (n=659)	Usual care (n=613)	Absolute difference (95% CI)
Non-SARS-CoV-2 infection			
Pneumonia	64 (10%)	37 (6%)	3·7% (0·7 to 6·6)
Urinary tract	12 (2%)	9 (1%)	0·4% (–1·0 to 1·7)
Biliary	0	0	..
Other intra-abdominal	0	1 (<1%)	–0·2% (–0·5 to 0·2)
Blood stream	7 (1%)	3 (<1%)	0·6% (–0·4 to 1·5)
Skin	1 (<1%)	3 (<1%)	–0·3% (–1·0 to 0·3)
Other	9 (1%)	13 (2%)	–0·8% (–2·2 to 0·7)
Any non-SARS-CoV-2 infection	81 (12%)	58 (9%)	2·8% (–0·6 to 6·2)
Metabolic complications*			
Ketoacidosis	1 (<1%)	1 (<1%)	0·0% (–0·4 to 0·4)
Hyperglycaemic hyperosmolar state	5 (1%)	2 (<1%)	0·4% (–0·4 to 1·2)
Other hyperglycaemia requiring new use of insulin	138 (21%)	86 (14%)	6·9% (2·8 to 11·1)
Any clinically significant hyperglycaemia	142 (22%)	87 (14%)	7·4% (3·2 to 11·5)
Severe hypoglycaemia	2 (<1%)	2 (<1%)	0·0% (–0·6 to 0·6)
New cardiac arrhythmia†	13 (2%)	8 (1%)	0·7% (–0·7 to 2·1)
Thrombotic events†	8 (1%)	13 (2%)	–0·9% (–2·3 to 0·5)
Clinically significant bleeds†	8 (1%)	4 (1%)	0·6% (–0·5 to 1·6)

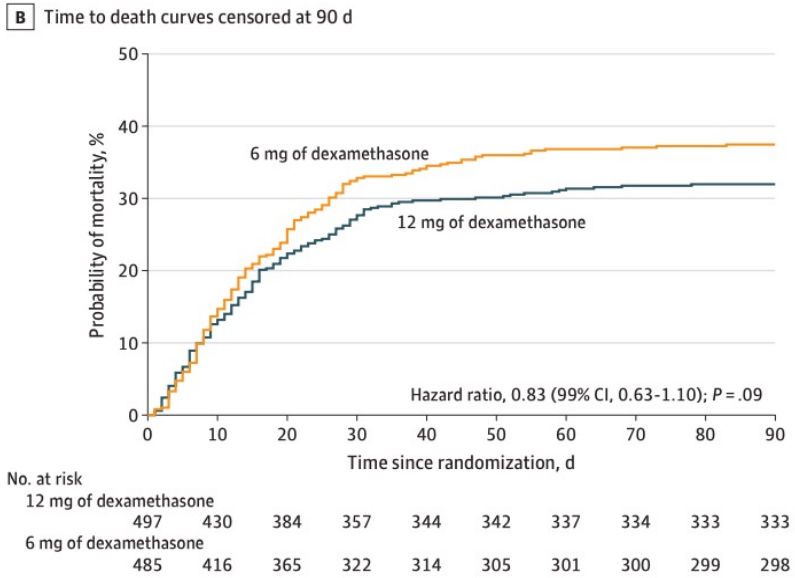
*Information on metabolic complications was added to the follow up form on July 28, 2021. Of the 1267 (>99%) randomly assigned participants with a follow-up form completed, 1062 (84%) had information on metabolic complications recorded. †Details of these events are presented in the appendix (p 65).

***Table 3:* Effect of allocation to higher dose corticosteroid on non-SARS-CoV-2 infection, metabolic complications, new cardiac arrhythmia, thrombotic events, and clinically significant bleeds**

RECOVERY group. Lancet 2023;401-1499-507.

How Low Not Defined Yet

RCT of 12mg vs 6 mg dexamethasone in patients with COVID-19 with severe hypoxemia receiving O_2 >10L/min or mechanical ventilation Conducted 8/2020-5/2021



A, Life support was defined as invasive mechanical ventilation, circulatory support, or kidney replacement therapy. There were missing data in 11 patients for the primary outcome. Red represents the worse outcomes and blue represents better outcomes. B, There were 14 patients who were not followed up for the full 90 days (7 patients in each intervention group) and who were included until the last day they were known to be alive. The median follow-up time was 90 days (IQR, 24-90 days) in the 12 mg of dexamethasone group and 90 days (IQR, 20-90 days) in the 6 mg of dexamethasone group. The time to death was compared post hoc using unadjusted Cox regression.

Characteristic	Dex 12 mg (n=497)	Dex 6 mg (n=485)
O2 by mask or nasal cannula	272 (55%)	258 (53%)
NIMV or CPAP	118 (24%)	128 (26%)
IMV	107 (22%)	99 (20%)

GFF< 30 mL/min? Remdesivir is Fine

- Sulfobutylether-b-Cyclodextrin (SBECD) is toxic in some animal models at doses much higher (~50x) than those given to humans
- Most damage was reversible
- SBECD is used in intravenous voriconazole and remdesivir
  Voriconazole – 3.2gm per 200 mg vial Remdesivir – 3-6 gm per 100 mg

Package insert has been changed (again)- no mention of avoidance in renal dysfunction

VEKLURY must be diluted prior to intravenous infusion. Refer to Dosage and Administration (2.5, 2.6) for detailed preparation and administration instructions.

2.4 Renal Impairment

No dosage adjustment of VEKLURY is recommended in patients with any degree of renal impairment, including patients on dialysis. VEKLURY may be administered without regard to the timing of dialysis *[see Dosage and Administration (2.3) and Use in Specific Populations (8.4, 8.6)]*.

2.5 Dosage Preparation and Administration in Adults and Pediatric Patients Weighing at Least 40 kg

Luke D et al. J Pharm Sci 2010;99:3291–3301. VFEND (voriconazole for injection) package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf]

GFF< 30 mL/min? Remdesivir is Fine

Subgroup of CATCO RCT with eGFR <30 mL/min

Study	RDV (n=34)	No RDV (n=25)
Hospital death, n (%)	13 (40.6)	13 (52.0)
Baseline eGFR, med (IQR)	18.9 (10.2-24.2)	22.7 (10.5-26.6)
Day 5 eGFR, med (IQR)	29.2 (14.2-45)	16.5 (8.5-30.9)
Day 5 ALT, med (IQR)	32.5 (15-47)	16.5 (8.5-30.9)
New HD, n (%)	5 (20.0)	4 (21.1)

Neofytos D et al. Clin Infect Dis 2012;54(7):913–21. Cheng M et al. JAMA Network Open 2022;5(8):e2229236

Which of the following statements are true regarding treatment of patients with COVID-19

A. No dosage adjustment is required for remdesivir regardless of renal function including patients on dialysis

B. In patients with COVID-19 hospitalized with hypoxemia, 20 mg of Dexamethasone decreases mortality compared to 6 mg of Dexamethasone

C. The impact on hospitalization and death of nirmatrelvir/ritonavir or molnupiravir decreases in patients vaccinated for COVID-19 compared to the unvaccinated patients

D. All are correct

E. Only A and C are correct

Other COVID-19 treatments

Fluvoxamine data did not hold

Metformin ?

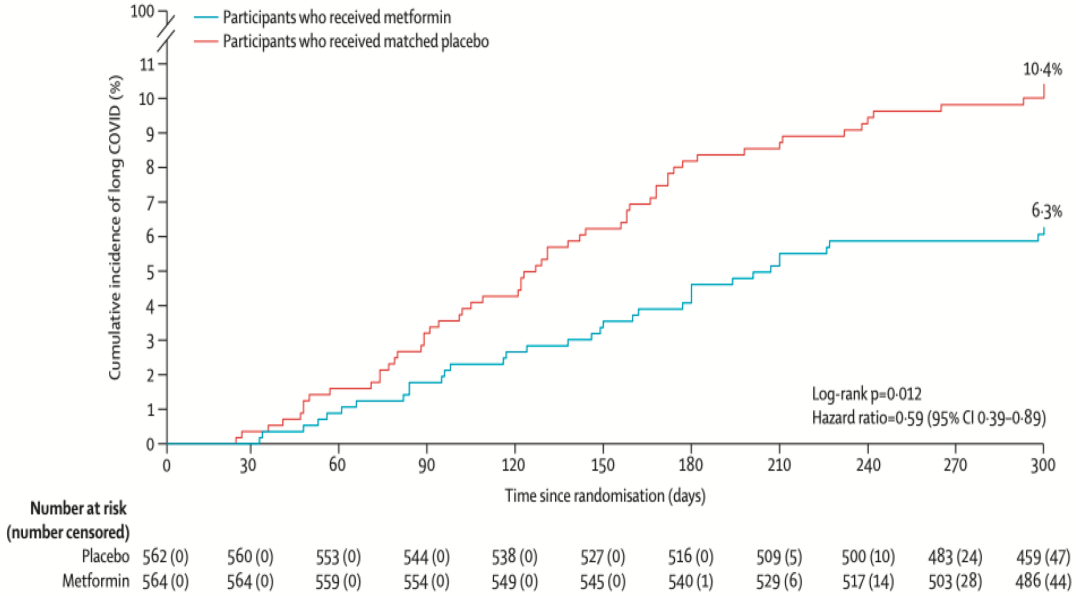
Immunomodulators, tocilizumab, baricitinib work

Metformin?

Acute COVID-19

Trial	Outcome	Active (Metformin)	Placebo	Analysis
COVID-OUT	Composite of: hypoxemia, ED visit, hospitalization, death	154/652 (23.6%)	179/653 (27.4%)	aOR 0.84 (0.66-1.09)
TOGETHER	Hospitalizations, O_2 sat <92%, ER visit >6 hours	34/215 (15.8%)	28/203 (13.8%)	RR 1.14 (0.73-1.81)

Long COVID-19

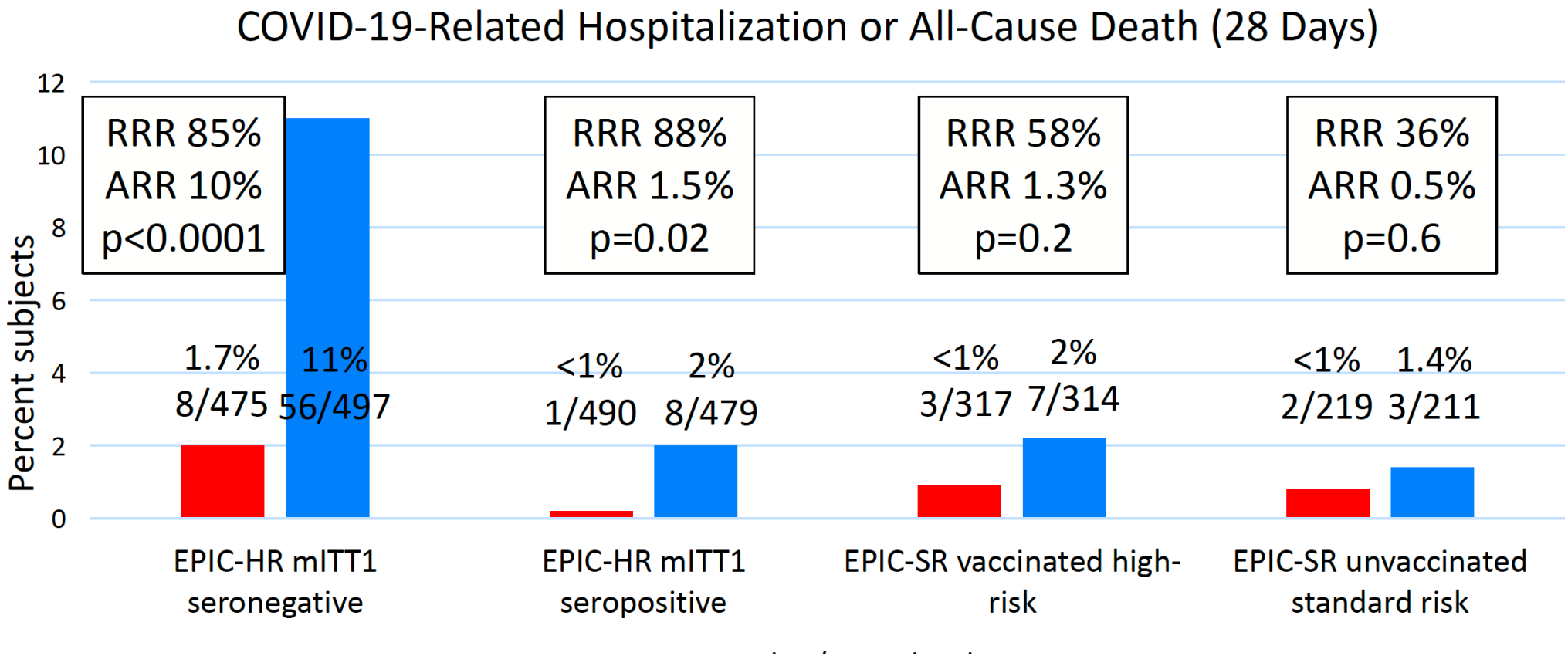


Pipeline

- Pegylated interferon gamma
  - Showed efficacy in TOGETHER trial in 2000 pts (83% vaccinated)
- Entrelsivir`
  - Oral protease inhibitor, approved in Japan
- Bofultrelvir (FB001)`
  - Oral protease inhibitor in phase 3
- Vilobelimab
  - Anti-C5a antibody for critical COVID, FDA authorized
- Oral remdesivir (VV116, ATV006, GS-621763)`
  - VV116 had similar results to nirmatrelvir/r in phase 3 study of time to improvement
- Obeldesivir in 2 phase 3 studies`
  - OAKTREE continues (SR), BIRCH discontinued (HR)
- Bemnifosbuvir
  - Oral RNA polymerase inhibitor in phase 3

Mukae H et al. Clin Infect Dis 2023;76:1403-11. Boffito M et al. Microb Spectrum https://doi.org/10.1128/spectrum.00077-23. Vlaar APJ et al. Lancet Respir Med 2022;10:1137-46. Reis G et al. N Engl J Med 2023:388:518-28. Cao Z et al. N Engl J Med 2023;388:407-17.

Outcomes Endpoints Will Probably Need to Be Changed in Future Studies

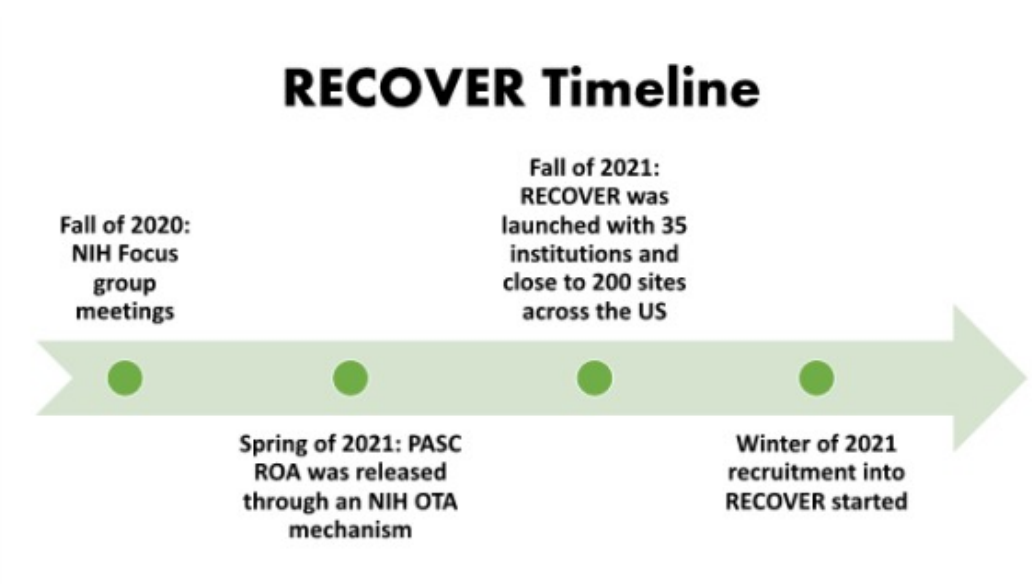


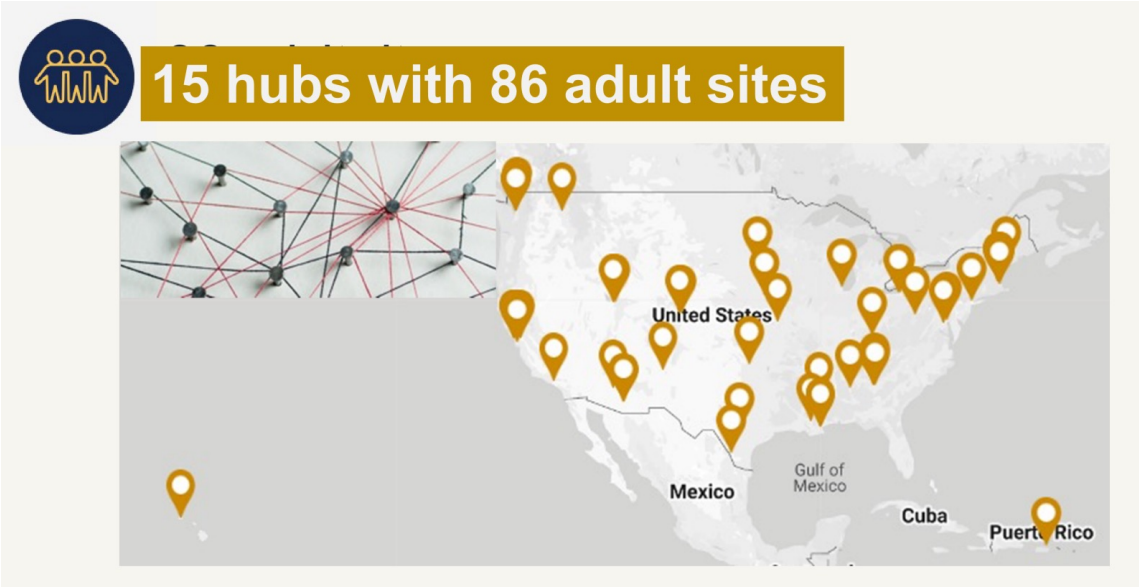
https://www.fda.gov/media/166237/download https://www.fda.gov/media/166238/download

Long-COVID update

- What question was the NIH committee asked to answer
  - Characterize the incidence and prevalence of sequelae of SARS-CoV-2 infection
  - Characterize the spectrum of clinical symptoms, subclinical organ dysfunction, natural history, and distinct phenotypes identified as sequelae of SARS-CoV-2 infection
  - Define the biological mechanisms underpinning pathogenesis of the sequelae of SARS-CoV-2 infection.

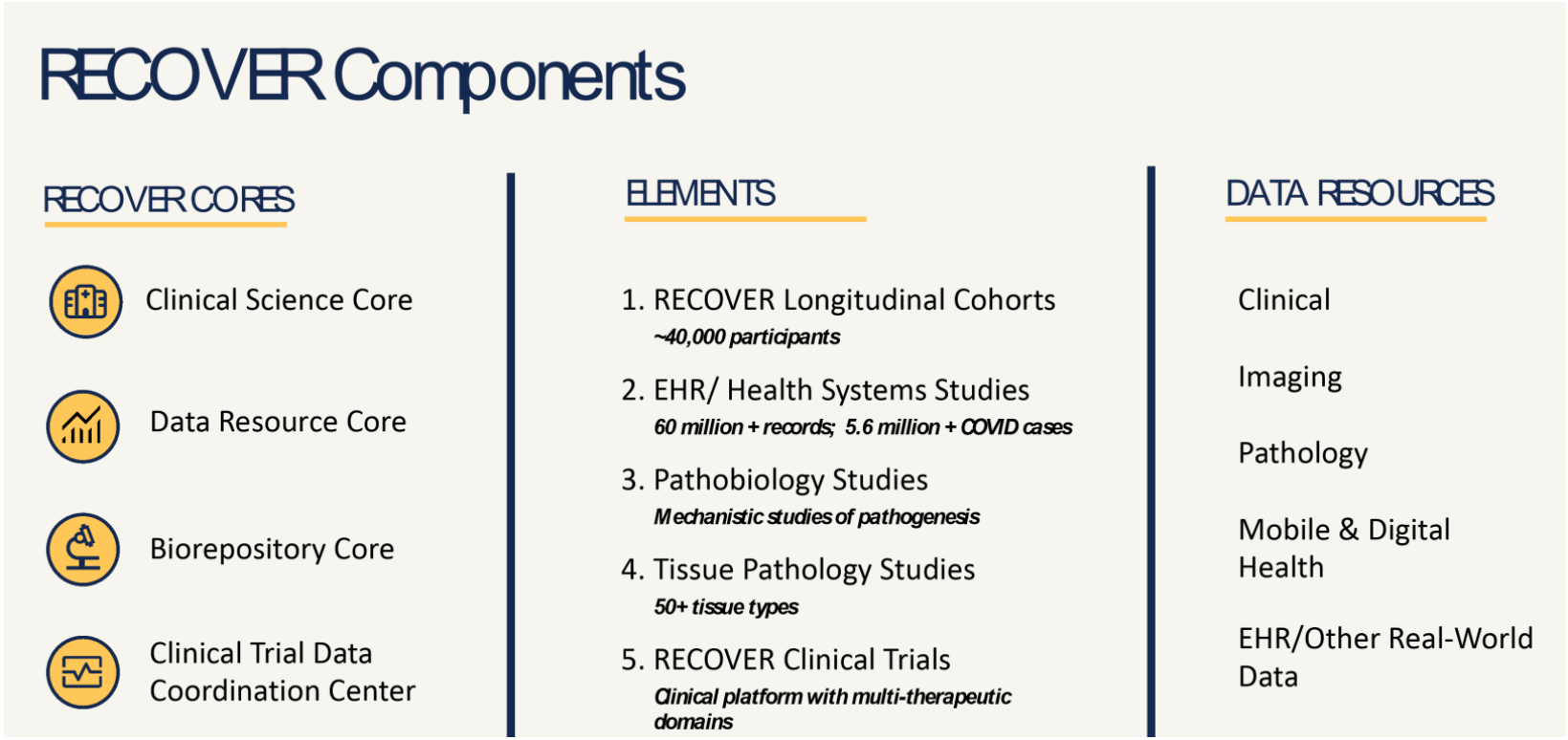
Long COVID: RECOVER





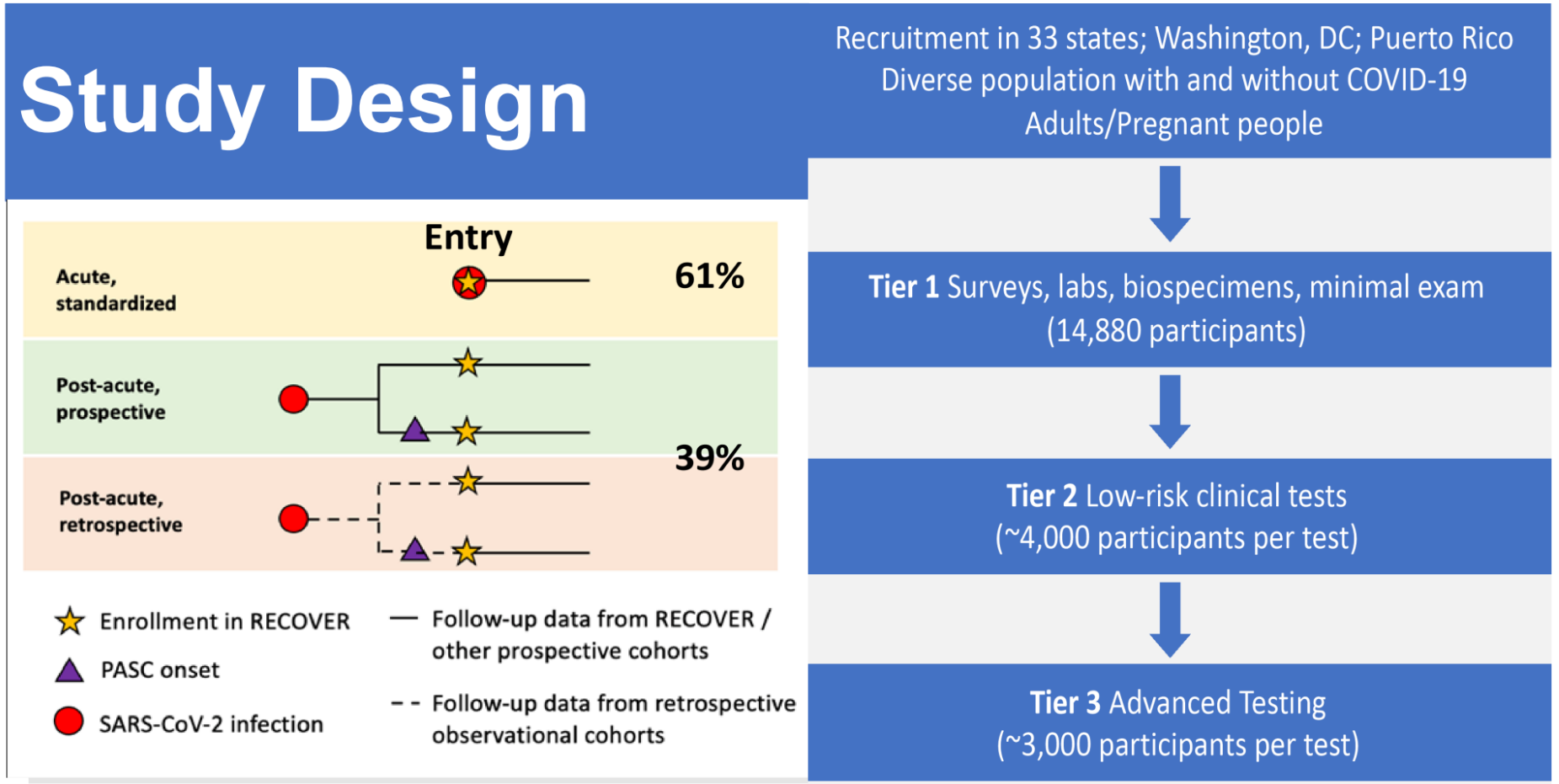
IDWEEK 2023. Igor Ofotokun, MD. Emory University School of Medicine. Chair Recover Adult Cohort Coordinating Committee

Long COVID: RECOVER



IDWEEK 2023. Igor Ofotokun, MD. Emory University School of Medicine. Chair Recover Adult Cohort Coordinating Committee

Long COVID: RECOVER

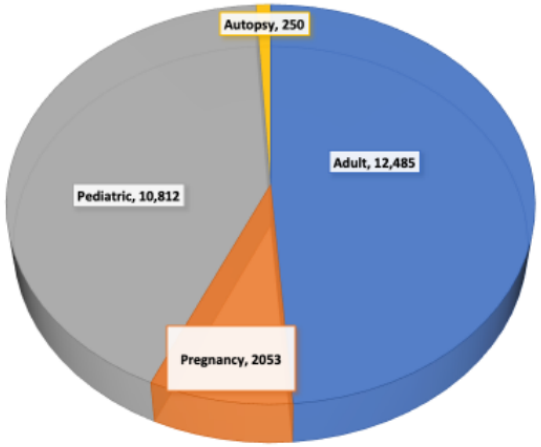


Ambi-directional longitudinal meta-cohort study of individuals **with and without** COVID-19

Long COVID: RECOVER

Enrollment: adult

Participant category	Enrolled to date	% of total target
Acute cases (enrolled within 30 days of infection)	4,842	97%
Post Acute Cases (Infected, enrolled >30 days after infection)	6,968	97%
Control (Uninfected at the time of enrollment)	2,318	87%
Total	**14,128**	**95%**



Demographics

Identity group	Enrolled %	US adult population
American Indian/Alaska Natives, Native Hawaiian /Other Pacific Islander	2%	1%
Asian, non-Hispanic	7%	6%
Black, non-Hispanic	16%	13%
Hispanic	17%	19%
White, non-Hispanic	56%	59%

Long COVID: RECOVER

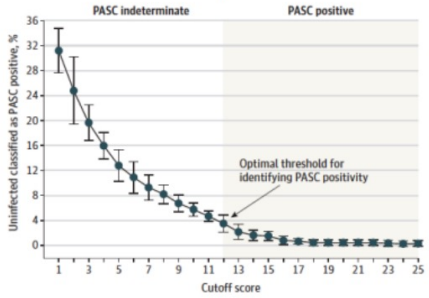
Development of a Definition of Post-acute Sequelae of SARS-CoV-2 Infection

1 Symptom selection (LASSO) 2 Score assignment and calculation 3 Optimal threshold identification

Model-selected symptoms that define PASC and their corresponding scores

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

Optimal score cutoff for classifying a participant as PASC positive using cross-validation



- The PASC score was calculated by adding up the scores for each symptom an individual has

  Score < 12 → PASC-indeterminate

  Score ≥ 12 → PASC-positive

Symptom frequencies among PASC+ participants for symptoms that contribute to the PASC score

	Symptoms	Frequency (%)
1	Post exertional malaise	87
2	Fatigue	85
3	Brain fog	64
4	Dizziness	62
5	GI symptoms	59
6	Palpitations	57
7	Sexual desire or capacity	42
8	Small or taste	41
9	Thirst	40
10	Chronic cough	33
11	Chest pain	26
12	Abnormal movements	15

JAMA. 2023;329(22)

Long COVID: RECOVER

Development of a Definition of Post-acute Sequelae of SARS-CoV-2 Infection

Estimated prevalence of PASC in the overall study population was ~10%

PASC positivity was more common and associated with more severe manifestation in participants infected in the pre-Omicron era.

The proportion of PASC positivity was lower among fully vaccinated than unvaccinated participants

PASC positivity was more common among reinfected participants compared with participants with 1 reported infection

Long-term symptoms associated with SARS-CoV-2 infection spanned multiple organ systems

JAMA. 2023;329(22)

Summary

Our understanding of PASC (Long COVID) is expanding

The burden appears to be high, with estimated prevalence of 10%

Almost every organ system is affected

12 symptoms are consistently present in majority of affected individuals

Several subtypes or phenotypes may exist depending on the organ most impacted

Ongoing analyses will unravel the pathobiology


Questions?