NEW VACCINES *and* NOVEL MONOCLONAL ANTIBODY TREATMENTS *on the* FRONTLINE *of* COVID-19
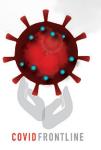
FRIDAY, JULY 23, 2021

FACULTY

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COVID FRONTLINE

Public Health Foundation

AGENDA

1. **Vaccine and Non-vaccine Therapeutic Options for COVID-19**
    a. Current treatment guidelines
    b. Vaccines for COVID-19
    c. Management of recently diagnosed COVID-19 patients
    d. Clinical trial data on the efficacy and safety of agents authorized for emergency use in the treatment and prevention of COVID-19
    e. Emerging vaccine and non-vaccine therapeutic options

2. **Resources for Providers**
    a. NICA COVID-19 Guidance and Resource Toolkit
    b. New partnerships with health systems to establish infusion centers for COVID-19 antibody treatments

3. **Patient Education**
    a. Educating patients on symptoms of COVID-19 and when to seek medical attention
    b. What are the potential short-term and long-term complications of COVID-19?
    c. Strategies to prevent the spread of COVID-19
    d. How vaccines work and the efficacy and safety of approved vaccines
    e. Weighing the benefits and risks of non-vaccine treatment options

4. **Efforts to Lessen the Impact of COVID-19 on Underserved Communities**
    a. Strategies to improve COVID-19 care and prevention in underserved populations
    b. Programs and initiatives to improve COVID-19 testing and treatment

5. **Case studies**

6. **Conclusions**

New Vaccines and Novel Monoclonal Antibody Treatments on the Frontline of COVID-19

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PROGRAM OVERVIEW

This live activity will review clinical trial data on the efficacy and safety of monoclonal antibodies and vaccines authorized for use in the treatment and prevention of COVID-19, and highlight and address healthcare disparities during the COVID-19 pandemic.

TARGET AUDIENCE

This CME initiative is designed for HCPs who are involved in the care and treatment of patients with COVID-19, including physicians, NPs, PAs, nurses, and pharmacists who treat and manage underserved patient populations.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Evaluate clinical trial data of vaccines and monoclonal antibody therapies for the prevention and treatment of COVID-19.

- Select appropriate treatment for managing mild-to-moderate COVID-19 for people with certain pre-existing conditions.

- Explain the efficacy and safety of approved vaccinations and monoclonal antibody treatments to patients

- Incorporate tools and resources developed to promote safe and responsible use of infusion therapies for the treatment of patients with COVID-19.

- Explain COVID-19 related initiatives and programs aimed at lessening health disparities in underserved communities.

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Purpose: This program would be beneficial for nurses involved in the treatment of patients with COVID-19. Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Shyama Kottilil, MD, PhD	Discloses that the University of Maryland has received funds to participate in clinical trials, and he has received research funds paid to the university from Merck, Gilead Sciences, and Arbutus Biopharma. He has served on the advisory boards of Merck Inc and Regeneron Pharmaceuticals.
William A. Fischer II, MD	Discloses that he has been contracted for research for Ridgeback Biopharmaceuticals for COVID-19 research, as well as consulted for Merck and Roche. He also worked for Syneos and Janssen for adjudication of AE in RSV and influenza studies respectively, and served as the site PI for the Phase I Lilly study of bamlanivimab and for the Phase II study of casirivimab/imdevimab at University of North Carolina.

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

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2. Participate in the web-based live activity.
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This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

COVID-19 FRONTLINE

New Vaccines and Novel Monoclonal Antibody Treatments on the Frontline of COVID-19

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Disclosures
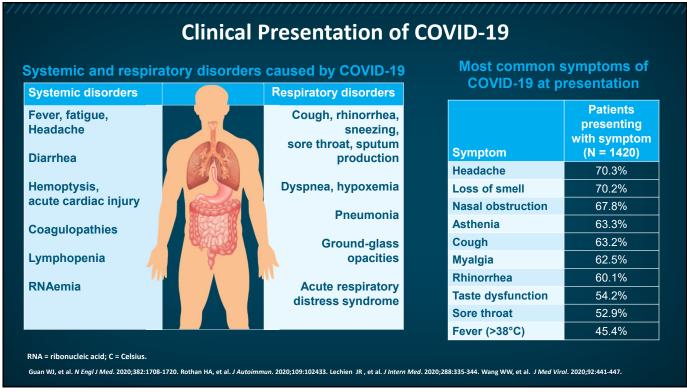
- Dr Kottilil discloses the University of Maryland has received funds to participate in clinical trials, and he has received research funds paid to the university from Merck, Gilead Sciences, and Arbutus Biopharma. He has served on the advisory boards of Merck Inc and Regeneron Pharmaceuticals.

- Dr. Fischer discloses he has been contracted by Ridgeback Biotherapeutics for coronavirus disease 2019 (COVID-19) research, and has consulted for Merck and Roche. He also worked for Syneos Health and Janssen Pharmaceuticals on the adjudication of adverse events in respiratory syncytial virus and influenza studies, respectively; he served as the site principal investigator for the phase I Lilly study of bamlanivimab and the phase II study of casirivimab/imdevimab at The University of North Carolina

- During this lecture Dr. Kottilil and Dr. Fischer may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

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Learning Objectives

- Evaluate clinical trial data of vaccines and monoclonal antibody (mAb) therapies for the prevention and treatment of COVID-19

- Select appropriate treatment for managing mild to moderate COVID-19 for people with certain preexisting conditions

- Explain the efficacy and safety of FDA emergency use authorization (EUA) vaccinations for COVID-19 and mAb treatments for patients

- Incorporate tools and resources developed to promote the safe and responsible use of infusion therapies for the treatment of patients with COVID-19

- Explain COVID-19 related initiatives and programs aimed at lessening health disparities in underserved communities

3

Clinical Presentation of COVID-19

Systemic and respiratory disorders caused by COVID-19

Systemic disorders	Respiratory disorders
Fever, fatigue, Headache	Cough, rhinorrhea, sneezing, sore throat, sputum production
Diarrhea	
Hemoptysis, acute cardiac injury	Dyspnea, hypoxemia
	Pneumonia
Coagulopathies	
Lymphopenia	Ground-glass opacities
RNAemia	Acute respiratory distress syndrome

Most common symptoms of COVID-19 at presentation

Symptom	Patients presenting with symptom (N = 1420)
Headache	70.3%
Loss of smell	70.2%
Nasal obstruction	67.8%
Asthenia	63.3%
Cough	63.2%
Myalgia	62.5%
Rhinorrhea	60.1%
Taste dysfunction	54.2%
Sore throat	52.9%
Fever (>38°C)	45.4%

RNA = ribonucleic acid; C = Celsius.

Guan WJ, et al. *N Engl J Med*. 2020;382:1708-1720. Rothan HA, et al. *J Autoimmun*. 2020;109:102433. Lechien JR , et al. *J Intern Med*. 2020;288:335-344. Wang WW, et al. *J Med Virol*. 2020;92:441-447.

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COVID-19 Disease Severity

A large study of 44,672 confirmed COVID-19 cases identified by the Chinese Centers for Disease Control and Prevention found that 81% of cases were mild-to-moderate, 14% were severe, and 5% were critical.

	Disease characteristics—NIH
Asymptomatic or pre-symptomatic	Individuals who test positive using a virologic test but who have no symptoms that are consistent with COVID-19
Mild illness	Various symptoms (eg, fever, cough, sore throat, headache, malaise, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	SpO_2 ≥94% on room air and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	SpO_2 <94% on room air, PaO_2/FiO_2 <300, respiratory rate >30 breaths/min, or lung infiltrates >50%
Critical illness	Respiratory failure, septic shock, and/or multiorgan dysfunction

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Association Between Preexisting Characteristics and COVID-19 Survival

- Prospective cohort study of 20,133 patients in the UK hospitalized with COVID-19

- Increasing age, male sex, and chronic comorbidities, including obesity, were identified as independent risk factors for mortality

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

1 2 5 10

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Increased Risk of Hospitalization and Death With Certain Comorbidities

Factors that increase the risk of progressing to severe COVID-19	
• Cancer	• Overweight or obesity
• Cardiovascular disease	• Older age (≥65 years of age)
• Chronic kidney disease	• People from racial and ethnic minority groups
• Chronic lung diseases	
• Dementia or other neurologic conditions	• People with disabilities
	• Pregnancy
• Diabetes (type 1 or 2)	• Sickle cell disease or thalassemia
• Down syndrome	• Smoking, current or former
• HIV infection	• Solid-organ or blood stem-cell transplant
• Immunocompromised state	• Stroke or cerebrovascular disease
• Liver disease	• Substance use disorders

HIV = human immunodeficiency virus.

US Centers for Disease Control and Prevention (CDC). Medical conditions. (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Accessed 6.2.2021.

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Antibody Therapies
for the Management of COVID-19

William A. Fischer II, MD

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Antibody Therapy in Mild-to-Moderate COVID-19

	Asymptomatic or presymptomatic	Mild illness	Moderate illness	Severe illness	Critical illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (eg, fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94% respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed disease pathogenesis	Viral replication				
			Inflammation		
Potential treatment	Antiviral therapy			Anti-inflammatory therapy	
		Antibody therapy			
Management considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Adapted from Gandhi RT, et al. *N Engl J Med*. 2020;383:1757-1766.

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Monoclonal Antibody Therapies With EUA

These therapies must be given as soon as possible and within 10 days of symptom onset.

Casirivimab 600 mg

AND

Imdevimab 600 mg

Must be administered together as a SQ injection or a single IV infusion over a minimum of 20 to 52 minutes

Bamlanivimab 700 mg

AND

Etesevimab 1400 mg

Distribution paused

Administer together as single IV infusion over a minimum of 21 to 60 minutes

Sotrovimab 500 mg

Administer as an IV infusion over a minimum of 30 minutes

The EUA for bamlanivimab monotherapy was revoked due to prevalence of resistant SARS-CoV-2 variants.

EUA = Emergency Use Authorization; SQ = subcutaneous; IV = intravenous.

FDA. Bamlanivimab and etesevimab EUA, rev 5.2021. (www.fda.gov/media/145802/download). FDA. Casirivimab and imdevimab EUA, rev 5.2021 (www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf). FDA. Sotrovimab EUA, 2021. (www.fda.gov/media/149534/download). FDA. Bamlanivimab monotherapy EUA revoked, 4.16.2021. (www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab). URLs accessed 6.2.2021.

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EUA of COVID-19 mAb Therapy

- EUA for the treatment of **mild-to-moderate COVID-19** in patients
  - Who are at least 12 years of age and weigh at least 40 kg
  - Have positive results of direct SARS-CoV-2 viral testing and **within 10 days of symptom onset**
  - Who are at **high risk** of progressing to severe COVID-19 or hospitalization

- Not authorized for use in hospitalized patients or those who require oxygen therapy due to COVID-19

- These therapies may be associated with worse clinical outcomes in patients hospitalized due to COVID-19 requiring high-flow oxygen or mechanical ventilation

FDA. Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). FDA. Bamlanivimab EUA. (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf).

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High-Risk Factors Listed in the EUA

The following conditions place patients at higher risk for severe COVID-19.

- **Older age** (≥65 years)
- **Obesity or being overweight** (adults BMI >25 kg/m^2, or BMI ≥85th percentile for patients 12–17 years)
- **Pregnancy**
- **Chronic kidney disease**
- **Diabetes**
- **Immunosuppressive disease or immunosuppressive treatment**
- **Cardiovascular disease** (including congenital heart disease)
- **Hypertension**
- **Chronic lung diseases** (such as COPD, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- **Sickle cell disease**
- **Neurodevelopmental disorders** (eg, cerebral palsy) or other medically complex conditions (eg, genetic or metabolic syndromes and severe congenital anomalies)
- **Medical-related technological dependence** (eg, tracheostomy, gastrostomy, positive-pressure ventilation [not related to COVID-19])

BMI = body-mass index; COPD = chronic obstructive pulmonary disease.

FDA. Bamlanivimab and etesevimab EUA, rev 5.2021. (www.fda.gov/media/145802/download). FDA. Casirivimab and imdevimab EUA, rev 5.2021. (www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf). FDA. Sotrovimab EUA, 2021. (www.fda.gov/media/149534/download). URLs accessed 6.2.2021.

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Identifying Other High-Risk Candidates for mAb Therapy

- Other medical conditions or factors can increase a person's risk of progression to severe COVID-19

- Authorization of mAbs is not limited to medical conditions listed in the EUA

- Healthcare providers (HCPs) should consider the benefit-risk for each patient

- List of additional high-risk factors can be found on the CDC website:
  www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Additional risk factors for progression to severe COVID-19

- Cancer
- Dementia
- Down syndrome
- HIV infection
- Liver disease
- Smoking, current or former
- Stroke or cerebrovascular disease

- Thalassemia
- Substance use disorders
- Racial and ethnic minority groups
- People with disabilities
- Other factors increasing risk of progression to COVID-19

FDA. Bamlanivimab and etesevimab EUA, rev 5.2021. (www.fda.gov/media/145802/download). FDA. Casirivimab and imdevimab EUA, rev 5.2021. (www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf). FDA. Sotrovimab EUA, 2021. (www.fda.gov/media/149534/download). CDC. Medical conditions. (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). URLs accessed 6.2.2021.

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Case Study 1: Nora
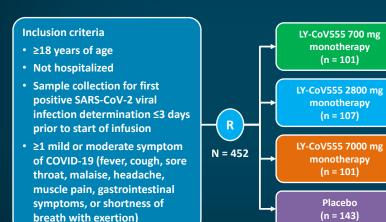
- Nora is a 45-year-old woman who presents with shortness of breath and cough that began 3 days ago. Her SpO_2 is 95% with a heart rate of 98 bpm. Her PCR test is positive for SARS-CoV-2

- Nora's prior medical history is significant for hypertension and depression. Her BMI is 26 kg/m^2, and she has elevated triglycerides

- **Is Nora a candidate for treatment with a monoclonal antibody therapy?**

  A. Yes, she should receive monoclonal antibody therapy

  B. No, she should not receive monoclonal antibody therapy

bpm = beats per minute; PCR = polymerase-chain reaction; SpO_2 = oxygen saturation.

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BLAZE-1: Phase 2 Trial of Bamlanivimab (LY-CoV555)

- Interim results from phase 2 trial of bamlanivimab in patients with mild-to-moderate COVID-19
- Risk factors for severe COVID-19 in 70% of bamlanivimab and 66% of placebo patients at baseline

Inclusion criteria
- ≥18 years of age
- Not hospitalized
- Sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of infusion
- ≥1 mild or moderate symptom of COVID-19 (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath with exertion)

R

N = 452

LY-CoV555 700 mg monotherapy (n = 101)

LY-CoV555 2800 mg monotherapy (n = 107)

LY-CoV555 7000 mg monotherapy (n = 101)

Placebo (n = 143)

Interim analysis
- Positive SARS-CoV-2 test ≤3 days before infusion
- Mild or moderate COVID-19 symptoms
- Primary endpoint: change from baseline to Day 11 (±4 days) in SARS CoV-2 viral load
- Secondary endpoints include safety, symptom severity, hospitalization, and time points for viral clearance

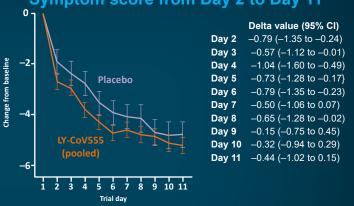Chen P, et al. *N Engl J Med*. 2021;384:229-237.

BLAZE-1 Interim Results

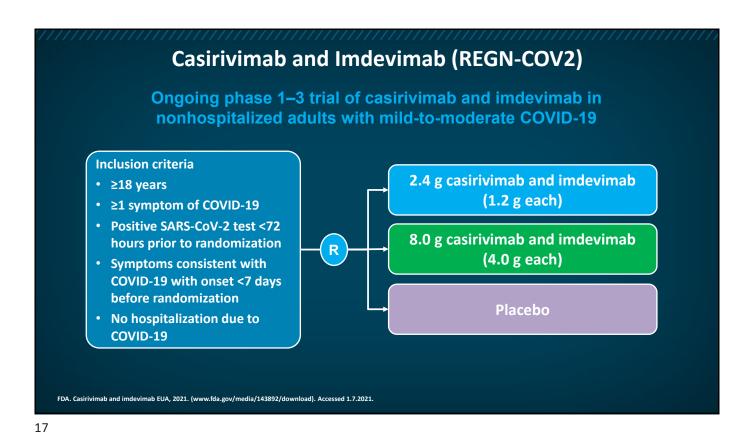| Treatment	Patients hospitalized/ total no.	Incidence of hospitalization (%)
Placebo	9/143	6.3
Bamlanivimab 700 mg	1/101	1.0
Bamlanivimab 2800 mg	2/107	1.9
Bamlanivimab 7000 mg	2/101	2.0
Bamlanivimab pooled doses	5/309	1.6

- In subjects ≥65 years and/or with a BMI ≥35, Day 29 hospitalization was 4% in treated patients and 15% in those receiving placebo

Symptom score from Day 2 to Day 11

	Delta value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

- Symptom scores ranged from 0 to 24 and included 8 domains, each of **which** was graded on a scale of 0 (no symptoms) to 3 (severe symptoms)

Chen P, et al. *N Engl J Med*. 2021;384:229-237.

Casirivimab and Imdevimab (REGN-COV2)

Ongoing phase 1–3 trial of casirivimab and imdevimab in nonhospitalized adults with mild-to-moderate COVID-19

Inclusion criteria
- ≥18 years
- ≥1 symptom of COVID-19
- Positive SARS-CoV-2 test <72 hours prior to randomization
- Symptoms consistent with COVID-19 with onset <7 days before randomization
- No hospitalization due to COVID-19

R

- 2.4 g casirivimab and imdevimab (1.2 g each)
- 8.0 g casirivimab and imdevimab (4.0 g each)
- Placebo

FDA. Casirivimab and imdevimab EUA, 2021. (www.fda.gov/media/143892/download). Accessed 1.7.2021.

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Casirivimab and Imdevimab: Interim Results

Interim analysis of 275 nonhospitalized patients with mild-to-moderate COVID-19

At least 1 COVID-19-related medical visit within 29 days		
Treatment	**Events/total patients**	**Incidence**
All patients		
Placebo	6/93	6%
Casirivimab and imdevimab 2.4 g	3/92	3%
Casirivimab and imdevimab 8.0 g	3/90	3%
All doses casirivimab and imdevimab	6/182	3%
Seronegative patients		
Placebo	5/33	15%
Casirivimab and imdevimab 2.4 g	2/41	5%
Casirivimab and imdevimab 8.0 g	3/39	8%
All doses casirivimab and imdevimab	5/80	6%

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

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Casirivimab/Imdevimab: Efficacy by Baseline Viral Load

Casirivimab/imdevimab (REGN-COV2) provided a greater reduction in viral load in those patients with higher viral load at baseline.

Viral load over time according to baseline viral load category

>10^4 copies/mL	Difference in change from baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	−0.36	−0.64
8.0 g vs PBO	−0.59	−0.90

>10^5 copies/mL	Difference in change from baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	−0.59	−0.83
8.0 g vs PBO	−0.75	−1.12

>10^6 copies/mL	Difference in change from baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	−0.81	−1.46
8.0 g vs PBO	−1.14	−1.54

>10^7 copies/mL	Difference in change from baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	−1.03	−1.84
8.0 g vs PBO	−1.32	−1.75

Chart 1 (>10^4): PBO (n = 56); REGN-COV2, 2.4 g (n = 60); REGN-COV2, 8.0 g (n = 54). Y-axis: Mean viral load (log$_{10}$ copies/mL). X-axis: Baseline, 3, 5, 7 Days.

Chart 2 (>10^5): PBO (n = 41); REGN-COV2, 2.4 g (n = 52); REGN-COV2, 8.0 g (n = 45).

Chart 3 (>10^6): PBO (n = 27); REGN-COV2, 2.4 g (n = 34); REGN-COV2, 8.0 g (n = 34).

Chart 4 (>10^7): PBO (n = 22); REGN-COV2, 2.4 g (n = 21); REGN-COV2, 8.0 g (n = 28).

TWA = time-weighted average; LS = least-squares; PBO = placebo.

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

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Casirivimab/Imdevimab Safety

Event	REGN-COV2			Placebo (n = 93)
	2.4 g (n = 88)	8.0 g (n = 88)	Combined (n = 176)	
	Number of patients (%)			
Any serious adverse event	1 (1)	0	1 (1)	2 (2)
Any adverse event of special interest* (Grade 2 or higher hypersensitivity or infusion-related reactions)	0	2 (2)	2 (1)	2 (2)
Any serious adverse event of special interest*	0	0	0	0
Grade ≥2 infusion-related reaction within 4 days	0	2 (2)	2 (1)	1 (1)
Grade ≥2 hypersensitivity reaction within 29 days	0	1 (1)	1 (1)	2 (2)
Adverse events that occurred or worsened during the observation period†				
Grade 3 or 4 event	1 (1)	0	1 (1)	1 (1)
Event that led to death	0	0	0	0
Event that led to withdrawal from the trial	0	0	0	0
Event that led to infusion interruption*	0	1 (1)	1 (1)	1 (1)

*Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions.
†Events listed here were not present at baseline or were an exacerbation of a preexisting condition that occurred during the observation period, which is defined as the time from administration of REGN-COV2 or placebo to the last study visit.

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

20

Bamlanivimab Plus Etesevimab

- Etesevimab is a neutralizing mAb that binds to a different epitope on the spike protein than bamlanivimab

- 577 nonhospitalized patients with mild-to-moderate COVID-19 were randomized to bamlanivimab (700 mg, 2800 mg, or 7000 mg), combination therapy (bamlanivimab 2800 mg + etesevimab 2800 mg), or placebo

	Bamlanivimab 700 mg	Bamlanivimab 2800 mg	Bamlanivimab 7000 mg	Bamlanivimab 2800 mg + Etesevimab 2800 mg	Placebo
Change in log viral load from baseline to Day 11	−3.72 P= .69	−4.08 P= .21	−3.49 P= .16	−4.37 P= .01	−3.80
COVID-19-related hospitalizations or ED visits	1.0%	1.9%	2.0%	0.9%	5.8%

ED = emergency department.

Gottlieb RL, et al. *JAMA*. 2021;325:632-644.

21

COMET-ICE Trial: Sotrovimab

Interim analysis of 583 patients with mild-to-moderate COVID-19 at high risk of progressing to severe COVID-19

- 58% of subjects received sotrovimab within 3 days of COVID-19 symptom onset and 42% within 4 to 5 days

	Sotrovimab n = 291	Placebo n = 292
Progression of COVID-19 at Day 29 (hospitalization for >24 hours for acute management of any illness or death from any cause)		
Proportion, n (%)	3 (1%)	21 (7%)
Adjusted relative risk reduction (97.24% CI)	85% (44–96)	
P-value	.002	
All-cause mortality (up to day 29)		
Proportion, n (%)	0	1 (<1%)

FDA. Sotrovimab EUA, 2021 (www.fda.gov/media/149534/download). Accessed 6.2.2021.

22

Case Study 2: Ellie

- Ellie is a 29-year-old woman who was tested for SARS-CoV-2 after her husband began to experience symptoms. She initially developed a cough and headache 13 days ago and complains of worsening shortness of breath over the last week. Her SpO$_2$ is 93%

- She is 32 weeks pregnant with her second child

- **Is Sandy a candidate for therapy with monoclonal antibodies?**
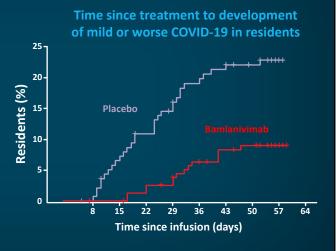 - A. Yes, she should receive monoclonal antibody therapy
  - B. No, she should not receive monoclonal antibodies

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Bamlanivimab in the Nursing Home Setting

- 966 participants, including 299 nursing home residents considered at high risk for severe COVID-19, were administered a single-dose of bamlanivimab or placebo if a case of SARS-CoV-2 was confirmed in nursing home

- Compared with placebo, bamlanivimab was associated with
  - Significantly lower proportion of residents with mild or worse COVID-19 by Day 57 (OR = 0.20; 95% CI, 0.08–0.49; *P*<.001)
  - Significant reductions in incidence of SARS-CoV-2 infection by Day 29 (OR = 0.23; CI, 0.11–0.48; *P*<.001)

- 5 COVID-19-related deaths (all in placebo group)

Time since treatment to development of mild or worse COVID-19 in residents

OR = odds ratio.

Cohen M, et al. Conference on Retroviruses and Opportunistic Infections (CROI)2021; Abstract 121. Lilly BLAZE-2 press release, 1.21.2121. (https://investor.lilly.com/node/44291/pdf). Accessed 3.25.2021.

24

Top-Line Results on mAb Therapies

- **UK RECOVERY trial in hospitalized patients**
  - Casirivimab plus imdevimab reduced risk of death by 20% in hospitalized patients who did not develop antibodies to SARS-CoV-2
- **Casirivimab and imdevimab for COVID-19 treatment**
  - 70% reduction in risk of hospitalization or death in 4567 high-risk, nonhospitalized patients with COVID-19
- **Casirivimab and imdevimab for COVID-19 prevention**
  - Interim analysis found 100% prevention of symptomatic infection and 50% reduction in rate of COVID-19 infection in a phase 3 trial of 400 individuals with household exposure to COVID-19
- **BLAZE-1: Bamlanivimab plus etesevimab**
  - Phase 3 trial of 769 high-risk patients recently diagnosed COVID-19 showed that therapy with bamlanivimab and etesevimab reduced hospitalizations and deaths by **87%** (P= .0001)

Regeneron press release, 6.16.2021. (https://newsroom.regeneron.com/index.php/news-releases/news-release-details/regen-covtm-casirivimab-and-imdevimab-phase-3-recovery-trial). Lilly press release, 3.10.2021. (https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced). Regeneron press release, 1.26.2021. (https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-reports-positive-interim-data-regen-covtm-antibody). Regeneron press release, 3.23.2021. (https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody). URLs accessed 3.25.2021.

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COVID-19 Antibody Treatment Resource Guide
National Infusion Center Association

- Infusion center locator
- Resources for providers
  - Bamlanivimab playbook
  - Casirivimab + imdevimab guidebook
- Patient education resources
- Treatment indication checklist
- Plus other resources

National Infusion Center Association (NICA). (https://infusioncenter.org/infusion_resources/covid-19-antibody-treatment-resource-center/).

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Case Study 3: Gary

- Gary is a 67-year-old man who presents to the emergency department with cough, nausea, and shortness of breath. His SpO_2 is 94% on room air

- His past medical history is significant for diabetes and a prior myocardial infarction. After receiving an infusion of bamlanivimab/etesevimab, his symptoms improve over the next 2 days

- Gary received his first COVID-19 vaccine 3 weeks before his mAb infusion and is scheduled to receive a second dose of the vaccine in 1 week

- **Should Gary receive his second vaccine dose next week?**
    - A. Yes, he should receive his vaccine dose as scheduled
    - B. No, he should wait 1 month after mAbs to receive a vaccine dose
    - C. No, he should wait 3 months after mAbs to receive a vaccine dose
    - D. A second vaccine dose is not needed in patients who test positive for SARS-CoV-2

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Decision-Making With mAb Infusions and SARS-CoV-2 Vaccination

- For people who develop COVID-19 after SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use and timing of treatment with mAbs

- SARS-CoV-2 vaccination should be deferred for ≥90 days after receipt of anti-SARS-CoV-2 mAbs
    - mAb infusions may interfere with the immune response to vaccines
    - If patient receives mAbs after receipt of first vaccine (but before second dose), second dose should be deferred for at least 90 days
    - "Receipt of passive antibody therapy in the past 90 days is not a contraindication to receipt of COVID-19 vaccine"
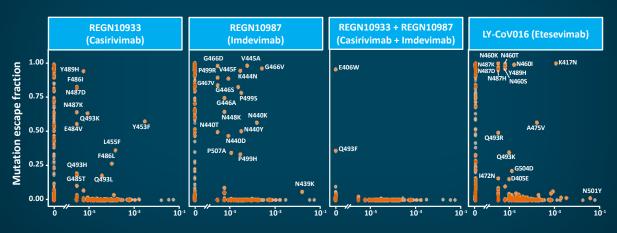   - COVID-19 vaccine doses that are given within 90 days after receipt of mAb therapy do not need to be repeated

CDC. Monoclonal antibody COVID-19 infusion, 2021. (www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html). Accessed 6.2.2021.

28

SARS-CoV-2 Resistance

Shyam Kottilil MD, PhD

Whiteboard animation on the development of resistance to mAb therapy

Antibody Escape Mutations in Circulating SARS-CoV-2

Many variants that can escape a single mAb are currently in circulation

Mutation frequency among all SARS-CoV-2 sequences in GISAID (log 10 scale)

GISAID = Global Initiative on Sharing Avian Influenza Data.

Starr TN, et al. *Science.* 2021;371:850-854.

31

Casirivimab and Imdevimab Retain Activity Against SARS-CoV-2 Variants

It is not known how pseudovirus data correlate with clinical outcomes.

Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with casirivimab and imdevimab together		
COVID-19 variants (origin)	**Substitution tested**	**Fold reduction in susceptibility**
B.1.1.7 (UK)	N501Y	No change
B.1.351 (South Africa)	K417N, E484K, N501Y	No change
P.1 (Brazil)	K417T, E484K	No change
B.1.427/B.1.429 (California)	L452R	No change
B.1.526 (New York)	E484K	No change

- Pseudoviruses of B.1.1.7 expressing entire variant spike protein were tested and include del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H
- Pseudoviruses of B.1.351 expressing entire variant spike protein were tested and include changes D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, and A701V
- No change is defined as <2-fold reduction in susceptibility
- Not all isolates of B.1.526 have the E484K mutation (as of February 2021)

FDA. Casirivimab with imdevimab EUA, 6.2021. (www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf). Accessed 5.1.2021.

32

Diminished In Vitro Activity With Bamlanivimab and Etesevimab

It is not known how pseudovirus data correlate with clinical outcomes.

Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with bamlanivimab and etesevimab together (1:2 molar ratio)		
COVID-19 variants (origin)	**Substitution tested**	**Fold reduction in susceptibility**
B.1.1.7 (UK)	N501Y	No change
B.1.351 (South Africa)	K417N, E484K, N501Y	215
P.1 (Brazil)	K417T, E484K, N501Y	>46
B.1.427/B.1.429 (California)	L452R	9
B.1.526 (New York)	E484K	31

- E484K mutation associated with significant reduction in susceptibility to bamlanivimab plus etesevimab
- Given the similarities between substitutions of B.1.351 (South Africa) and P.1 (Brazil), it is unlikely that bamlanivimab and etesevimab together will be active against these variants
- For variants with more than 1 substitution of concern, only those with the greatest impact on activity are listed
- No change = <5-fold reduction in susceptibility
- Not all isolates of New York lineage harbor E484K substitution (as of February 2021)

FDA. Bamlanivimab and etesevimab EUA, 5.2021. (www.fda.gov/media/145802/download). Accessed 5.1.2021.

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Prevention With Vaccination

34

Summary of Phase 3 Vaccine Trials

Pfizer-BioNTech mRNA vaccine (BNT162b2)

- Authorized for individuals **12** years of age and older
- Administer **2 doses three** weeks apart

Moderna mRNA vaccine (mRNA-1273)

- Authorized for individuals **18** years of age and older
- Administer **2 doses four** weeks apart
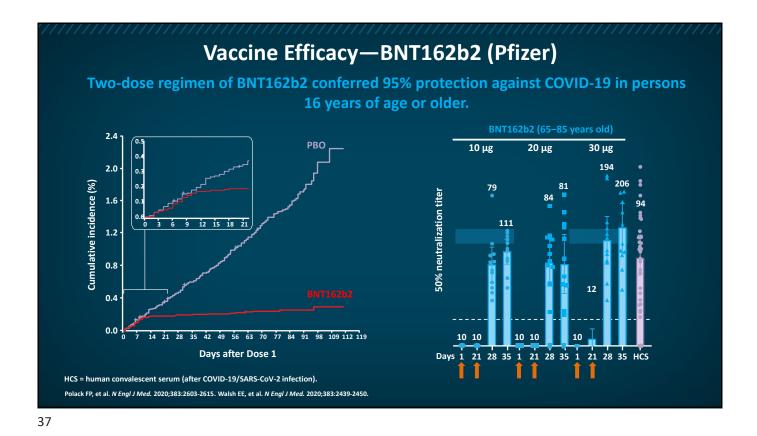
Janssen/Johnson & Johnson adenovirus vaccine (Ad26.COV2.S)
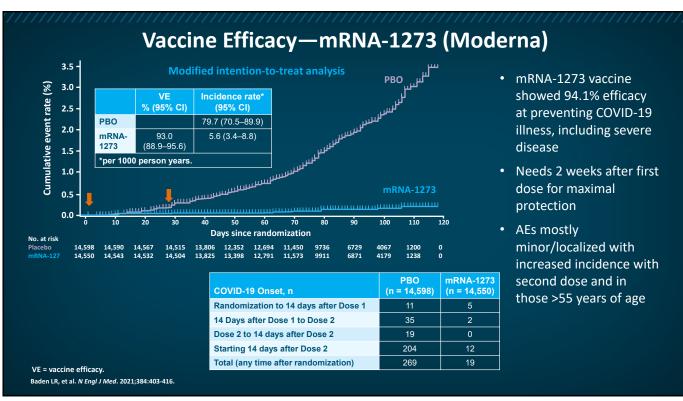
- Authorized for individuals **18** years of age and older
- Administered as a **single dose**

Oliver SE, et al. *MMWR.* 2020;69:1922-1924. Oliver SE, et al. *MMWR.* 2021;69:1653-1656. Oliver SE, et al. *MMWR.* 2021;70:329-332. Infectious Diseases Society of America (IDSA). Vaccines overview, updated 6.26.2021. (https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/vaccines-overview/).

35
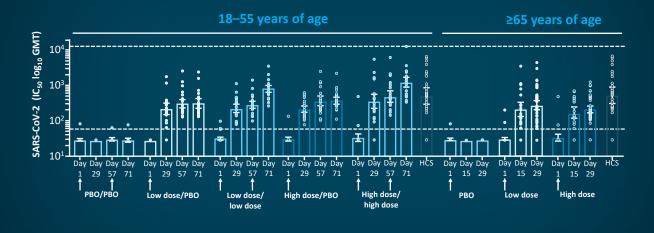
Whiteboard animation on the MOA of mRNA vaccines

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Vaccine Efficacy—BNT162b2 (Pfizer)

Two-dose regimen of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older.

HCS = human convalescent serum (after COVID-19/SARS-CoV-2 infection).

Polack FP, et al. *N Engl J Med.* 2020;383:2603-2615. Walsh EE, et al. *N Engl J Med.* 2020;383:2439-2450.

Vaccine Efficacy—mRNA-1273 (Moderna)

Modified intention-to-treat analysis

	VE % (95% CI)	Incidence rate* (95% CI)
PBO		79.7 (70.5–89.9)
mRNA-1273	93.0 (88.9–95.6)	5.6 (3.4–8.8)

*per 1000 person years.

No. at risk

Placebo	14,598	14,590	14,567	14,515	13,806	12,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-127	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

COVID-19 Onset, n	PBO (n = 14,598)	mRNA-1273 (n = 14,550)
Randomization to 14 days after Dose 1	11	5
14 Days after Dose 1 to Dose 2	35	2
Dose 2 to 14 days after Dose 2	19	0
Starting 14 days after Dose 2	204	12
Total (any time after randomization)	269	19

- mRNA-1273 vaccine showed 94.1% efficacy at preventing COVID-19 illness, including severe disease
- Needs 2 weeks after first dose for maximal protection
- AEs mostly minor/localized with increased incidence with second dose and in those >55 years of age

VE = vaccine efficacy.

Baden LR, et al. *N Engl J Med.* 2021;384:403-416.

Ad26.COV2.S: Neutralizing Antibodies (Janssen)

By Day 29 after first dose, incidence of neutralization was ≥88% across groups.

GMT = geometric mean titer.
Sadoff J, et al. *N Engl J Med*. 2021;384:1824-1835.

39

Ad26.COV2.S Vaccine

- Top-line results from the phase 3 ENSEMBLE trial found 66% overall efficacy
  - 72% efficacy in the United States, 66% in Latin America, 57% in South Africa
  - 85% effective in preventing severe/critical disease
  - Complete protection against COVID-19-related death

- CDC and FDA recommend use of Ad26.COV2.S vaccine after temporary pause to assess reports of rare adverse event

- Increased risk of rare thrombosis with thrombocytopenia syndrome (TTS)

- All cases of blood clots with low platelets occurred in women younger than 50 years

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mRNA Vaccine Real-World Efficacy

Person-days, SARS-CoV-2 infections, and vaccine effectiveness among healthcare personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status—8 US locations, December 14, 2020–March 13, 2021

| COVID-19 immunization status | Person-days | SARS-CoV-2 infections | | Unadjusted vaccine effectiveness* | Adjusted vaccine effectiveness*† |
		No.	Incidence rate per 1000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized ≥14 days after receiving first dose only‡ ≥14 days after first dose through receipt of second dose	41,856 15,868 25,988	8 5 3	0.19 0.32 0.12	82 (62–91)	80 (59–90)
Fully immunized ≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

*Vaccine effectiveness was estimated using a Cox proportional hazards model accounting for time-varying immunization status.
†Hazard ratio is adjusted for study site.
‡Participants received first dose but had not received second dose by end of study period.

N/A = not applicable.

Thompson MG, et al. *MMWR* . 2021;70:495-500. (https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7013e3-H.pdf). Accessed 5.1.2021.

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Patient Education

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Quality of Patient Education Materials (PEMs)

- NIH and US Department of Health and Human Services (DHHS) recommend patient education materials should be written at or below a **sixth grade** reading level

- Study of web-based PEMs about COVID-19 from 145 medical centers associated with US medical schools found:
  - Only 1 (0.7%) was at or below a sixth grade reading level
  - 62% discussed seeking immediate medical care, but few referred to specific symptoms that warranted medical care
  - At-risk populations were often omitted from PEMs
  - Only 16% of PEMs discussed asymptomatic spread of disease

High-risk factor for severe COVID-19	% of websites that listed high-risk factor
>65 years	63%
Serious heart condition	52%
Chronic lung disease	47%
Diabetes	46%
Immunocompromised	35%
Patients with cancer	29%
Immunosuppressants	23%
Immune deficiencies	22%
Pregnancy	16%
Transplant patients	16%
Obesity	15%
Chronic kidney disease	15%
Asthma	14%
Long-term care patients	11%
HIV/AIDS	9%
Liver disease	8%
Dialysis	8%

Kruse J, et al. *Am J Infect Control.* 2021;49:690-693.

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Points Often Missed in Patient Education

When to seek emergency care

- Trouble breathing
- Persistent pain or pressure in chest
- New confusion
- Inability to wake or stay awake
- Pale, gray, or blue-colored skin, lips, or nail beds, depending on skin tone

Mild-to-moderate disease can rapidly progress to severe COVID-19.

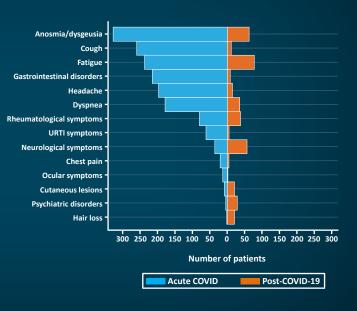**How to prevent the spread of COVID-19**

- Stay home except to get medical care
- Wear a mask over your nose and mouth
- Separate yourself as much as possible from people you live with
- Tell your close contacts they may have been exposed
- Wash your hands and disinfect surfaces

CDC. What to do if you are sick, 3.17.2021. (https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html).
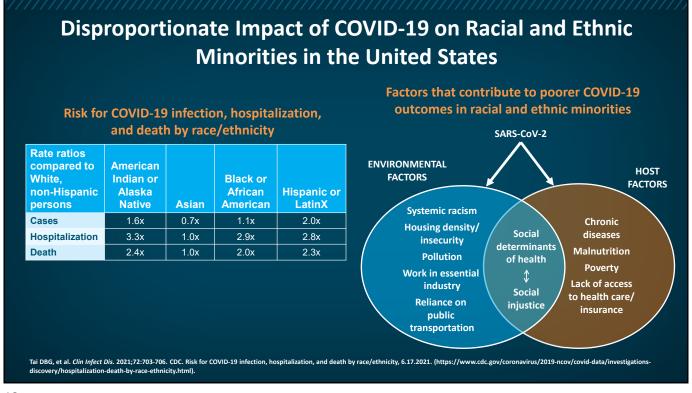
44

Many Patients Unaware of "Long-Haul" COVID-19

- Symptoms that last weeks or months can appear after SARS-CoV-2 infection or weeks after infection

- Symptoms may appear in patients with any disease severity, including asymptomatic patients

- A study of 599 individuals evaluated 6 months after the onset of symptoms found
  - 40.2% had post-COVID-19 syndrome
  - 17.3% had 2 or more sequelae

URTI = upper respiratory tract infections.
Peghin M, et al. *Clin Microbiol Infect*. 2021. (doi: 10.1016/j.cmi.2021.05.033).

A bar chart showing number of patients with Acute COVID and Post-COVID-19 symptoms:
Anosmia/dysgeusia, Cough, Fatigue, Gastrointestinal disorders, Headache, Dyspnea, Rheumatological symptoms, URTI symptoms, Neurological symptoms, Chest pain, Ocular symptoms, Cutaneous lesions, Psychiatric disorders, Hair loss. X-axis: Number of patients (300 250 200 150 100 50 0 50 100 150 200 250 300). Legend: Acute COVID, Post-COVID-19.

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Disproportionate Impact of COVID-19 on Racial and Ethnic Minorities in the United States

Risk for COVID-19 infection, hospitalization, and death by race/ethnicity

Rate ratios compared to White, non-Hispanic persons	American Indian or Alaska Native	Asian	Black or African American	Hispanic or LatinX
Cases	1.6x	0.7x	1.1x	2.0x
Hospitalization	3.3x	1.0x	2.9x	2.8x
Death	2.4x	1.0x	2.0x	2.3x

Factors that contribute to poorer COVID-19 outcomes in racial and ethnic minorities

SARS-CoV-2

ENVIRONMENTAL FACTORS
- Systemic racism
- Housing density/insecurity
- Pollution
- Work in essential industry
- Reliance on public transportation

Social determinants of health
↕
Social injustice

HOST FACTORS
- Chronic diseases
- Malnutrition
- Poverty
- Lack of access to health care/insurance

Tai DBG, et al. *Clin Infect Dis.* 2021;72:703-706. CDC. Risk for COVID-19 infection, hospitalization, and death by race/ethnicity, 6.17.2021. (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html).

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Overcoming Vaccine Hesitancy

- Provide assurance of vaccine safety and efficacy
- Highlight collective and individual benefits of vaccination
- Explain the vaccine development, FDA EUA, monitoring, and distribution process
- Address vaccine hesitancy and respond to dominant concerns without judgment or overly directive language
- Monitor misinformation and develop counter messages
- Acknowledge people's concerns
- Identify the needs and perspectives of the intended audience

Vaccine hesitancy over time by race/ethnicity

Race/ethnicity	January 2021	March 2021	Net change
White	21%	16%	-5%
Black	34%	18%	-16%
Asian	7%	5%	-3%
LatinX	19%	13%	-5%
Other/multiple race	32%	24%	-8%

NIH. COVID-19 vaccination communication. (https://obssr.od.nih.gov/wp-content/uploads/2020/12/COVIDReport_Final.pdf). Assistant Secretary for Planning and Evaluation (ASPE). COVID-19 vaccine hesitancy: demographic factors, geographic patterns, and changes over time. (https://aspe.hhs.gov/system/files/pdf/265341/aspe-ib-vaccine-hesitancy.pdf).

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Resources to Engage Underserved Populations

- Patient education resources in English, Spanish, and other languages
  - Patients with limited English proficiency have an increased incidence of medical errors resulting in serious harm, worse understanding of their condition, and high rates of ED recidivism
  - Use of interpreter services and appropriate education materials may improve outcomes
- Communication guides to promote community engagement
- Testing resources and more

NIH Community Engagement Alliance
https://covid19community.nih.gov/resources/learning-about-vaccines

RADx-UP (NIH initiative to reduce disparities in underserved populations)
https://radx-up.org/learning-resources/

CDC health equity resources
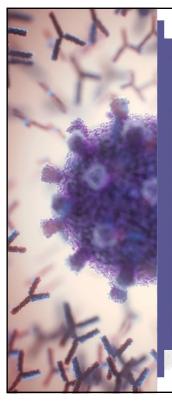https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/index.html

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Summary of Agents Authorized for EUA for COVID-19

- Several neutralizing mAb therapies are authorized for treatment of mild-to-moderate COVID-19 in patients at high risk of progressing to severe COVID-19 or hospitalization
  - mAbs against SARS-CoV-2 reduced the risk of COVID-19-related hospitalization
  - Therapy should be provided as soon as possible and within 10 days of symptoms onset

- Authorized vaccines are effective in preventing COVID-19
  - Adverse events are generally mild and are most common after the second vaccine dose

- To improve patient outcomes and limit the pandemic
  - Patient education is required on preventing SARS-CoV-2 spread and identifying severe symptoms that warrant medical care
  - Providers must address vaccine hesitancy and systemic barriers to care (eg, limited English proficiency)
  - Access to vaccines and mAb therapies must be improved

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Thank you!

Q & A

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NEW VACCINES *and* NOVEL MONOCLONAL ANTIBODY TREATMENTS *on the*

FRONTLINE *of* COVID-19

For more information and activities, visit:
https://covidfrontline.posterprogram.com

For more information on National Infusion Centers Association, visit:
https://infusioncenter.org/

Learn more about how COVID-19 can be treated with monoclonal antibodies, visit: **https://covidfrontline.posterprogram.com**

View the Treatment Reveal Card at:
https://treatmentreveal.covid-frontline.com/index.html

Access the COVID Frontline Patient Resource Portal at:
https://www.covidfrontlineresource.com/activation

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM) .
This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

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NEW VACCINES *and* NOVEL MONOCLONAL ANTIBODY TREATMENTS *on the*

FRONTLINE *of* COVID-19

For more information and additional resources please visit
https://covidfrontline.posterprogram.com

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This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM) .
This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

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New Vaccines and Novel Monoclonal Antibody Treatments on the Frontline of COVID-19

Resource	Address
Amanat F, Krammer F. SARS-CoV-2 vaccines: Status report. *Immunity*. 2020;52:583-589.	https://pubmed.ncbi.nlm.nih.gov/32259480/
Baden LR, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.	https://www.nejm.org/doi/full/10.1056/nejmoa2035389
Baum A, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science*. 2020;369:1014-1018.	https://pubmed.ncbi.nlm.nih.gov/32540904/
Castelli MS, et al. The pharmacology and therapeutic applications of monoclonal antibodies. *Pharmacol Res Perspect*. 2019;7:e00535.	https://pubmed.ncbi.nlm.nih.gov/31859459/
Centers for Disease Control and Prevention (CDC). CDC Recommends Use of Johnson & Johnson's Janssen COVID-19 Vaccine Resume. **Updated May 6, 2021.**	https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/JJUpdate.html
Centers for Disease Control and Prevention (CDC). COVID Data Tracker. **Accessed July 2, 2021.**	https://covid.cdc.gov/covid-data-tracker/#datatracker-home
Centers for Disease Control and Prevention (CDC). Health Equity. **Accessed July 2, 2021.**	https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/index.html
Centers for Disease Control and Prevention (CDC). SARS-CoV-2 Variant Classifications and Definitions. **Updated June 29, 2021.**	https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html
Gandhi RT, et al. Mild or moderate Covid-19. *N Engl J Med.* 2020;383:1757-1766.	https://pubmed.ncbi.nlm.nih.gov/32329974/
Gottlieb RL, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. *JAMA.* 2021;325:632-644.	https://pubmed.ncbi.nlm.nih.gov/33475701/
Hansen J, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science*. 2020;369:1010-1014.	https://pubmed.ncbi.nlm.nih.gov/32540901/
Infectious Disease Society of America (IDSA). **IDSA Guidelines on the Treatment and Management of Patients with COVID-19.** Last updated June 25, 2021.	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
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