CDC/IDSA COVID-19 Clinician Call

September 11, 2021

Welcome & Introduction

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Vice President, Clinical Affairs & Guidelines
IDSA

- 74th in a series of weekly calls, initiated by CDC as a forum for information sharing among frontline clinicians caring for patients with COVID-19
- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.
- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.

Today's Call: COVID-19 Treatment Updates

Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention

Rajesh Gandhi, MD, FIDSA
Director, HIV Clinical Services and Education,
Massachusetts General Hospital
Co-Director, Harvard Center for AIDS Research and
Professor of Medicine Harvard Medical School
Chair, HIV Medicine Association

Kathryn M. Edwards, MD
Sarah H. Sell and Cornelius Vanderbilt Professor
Division of Infectious Diseases
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Ivermectin: What are the Data & What's Fueling its Use

Lindsey R. Baden, MD
Associate Professor of Medicine
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Director of Clinical Research, Division of Infectious Diseases
Brigham and Women's Hospital

Travis Stark, DPM
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Health Systems and Worker Safety Task Force
CDC COVID-19 Response

Emerging Therapies under Investigation: Focus on Fluvoxamine

Shmuel Shoham, MD
Associate Professor of Medicine
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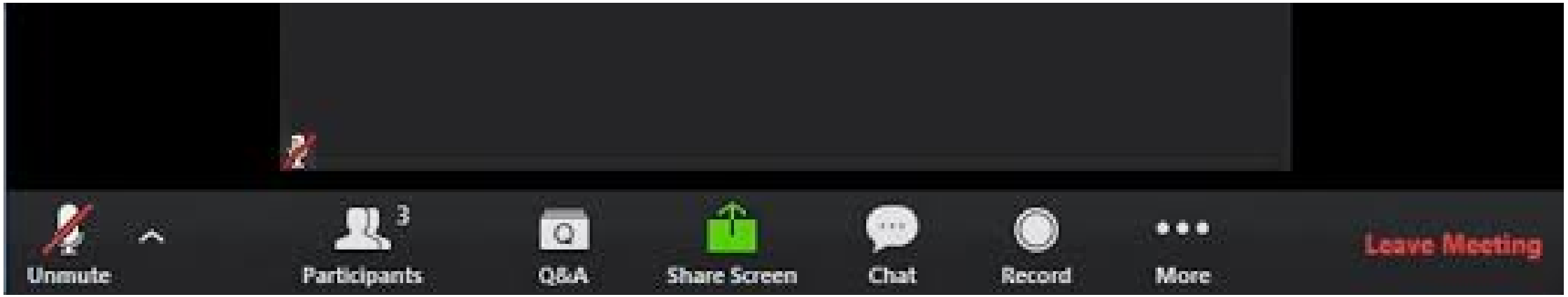
Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button



COVID-19 Treatment Updates

Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention

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Disclosures (for past two years): Member, NIH & Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels; Investigator, AIDS Clinical Trials Group and COVID-19 Prevention Network trials on anti-SARS CoV-2 monoclonal antibodies

Anti-SARS CoV-2 Monoclonal Antibodies for Treatment and Prevention

Rajesh T. Gandhi, MD

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Acknowledgments: Dr. Arthur Kim. Efe Airewele.

Outpatient Treatment Across the COVID-19 Spectrum

Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea	O_2 saturation ≥ 94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure

Disease Pathogenesis:

Viral replication

Inflammation

Hypercoagulability

Potential treatment:

Antivirals

Anticoagulation?

Antibody therapy

Decrease inflammation

Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Anti-SARS CoV-2 Monoclonal Antibodies for Treatment

- Emergency Use Authorizations (EUAs) for treatment of ambulatory patients with mild to moderate COVID-19 at high risk of progression and within 10 days of symptom onset:
  - Casirivimab + Imdevimab (600/600 mg) (IV administration preferred; subcutaneous is alternative)
  - Bamlanivimab + Etesevimab (700/1400 mg) (IV)
  - Sotrovimab (IV)

Anti-SARS CoV-2 Monoclonal Antibodies for Post-Exposure Prophylaxis

- Casirivimab/imdevimab (subcutaneous or intravenous) for post-exposure prophylaxis in individuals who are at high risk for progression to severe COVID-19 and are:
  - Not fully vaccinated or not expected to mount adequate immune response to COVID vaccination (eg immunosuppressed individuals) AND
    - Have been exposed* to individual with COVID-19

      or

    - At high risk of exposure because of occurrence of COVID-19 in same institutional setting (eg nursing home, prison)

*Within 6 feet for >=15 min, providing care at home, direct contact, exposed to respiratory droplets of infected person

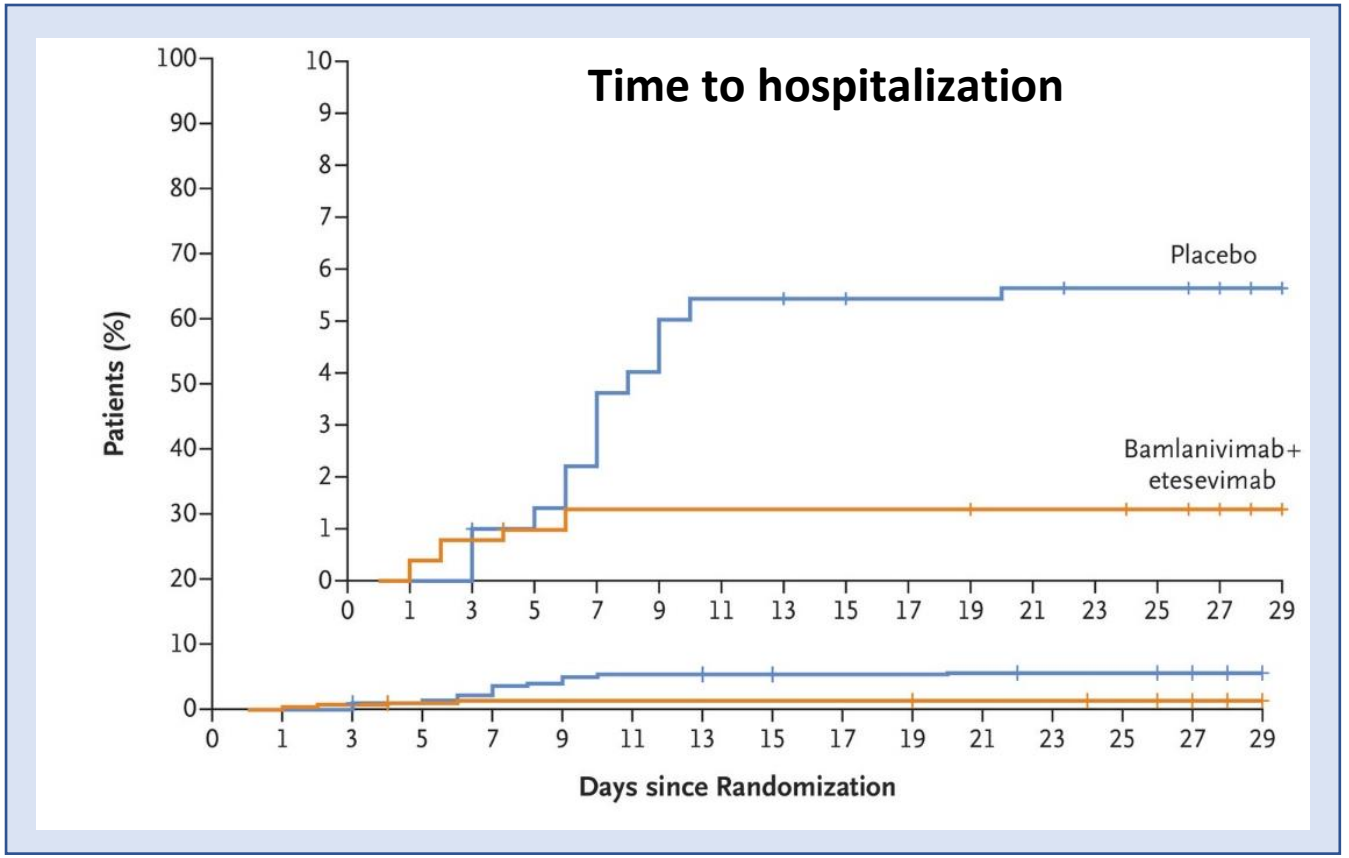
What are the Data for Use of Anti-SARS CoV-2 Antibodies for Treatment?

Bamlanivimab/Etesevimab: Outpatient Treatment

- Outpatients with mild to moderate COVID within 3 days of first positive test; 1 or more risk factors for developing severe COVID-19 (n=1035)
- IV bamlanivimab 2800 mg/ etesevimab 2800 mg or placebo

Results:

- 70% reduction in COVID hospitalization or any cause of death by day 29 (P<0.001)
- Similar results with bamlanivimab/etesevimab 700/1400 mg (authorized dose)



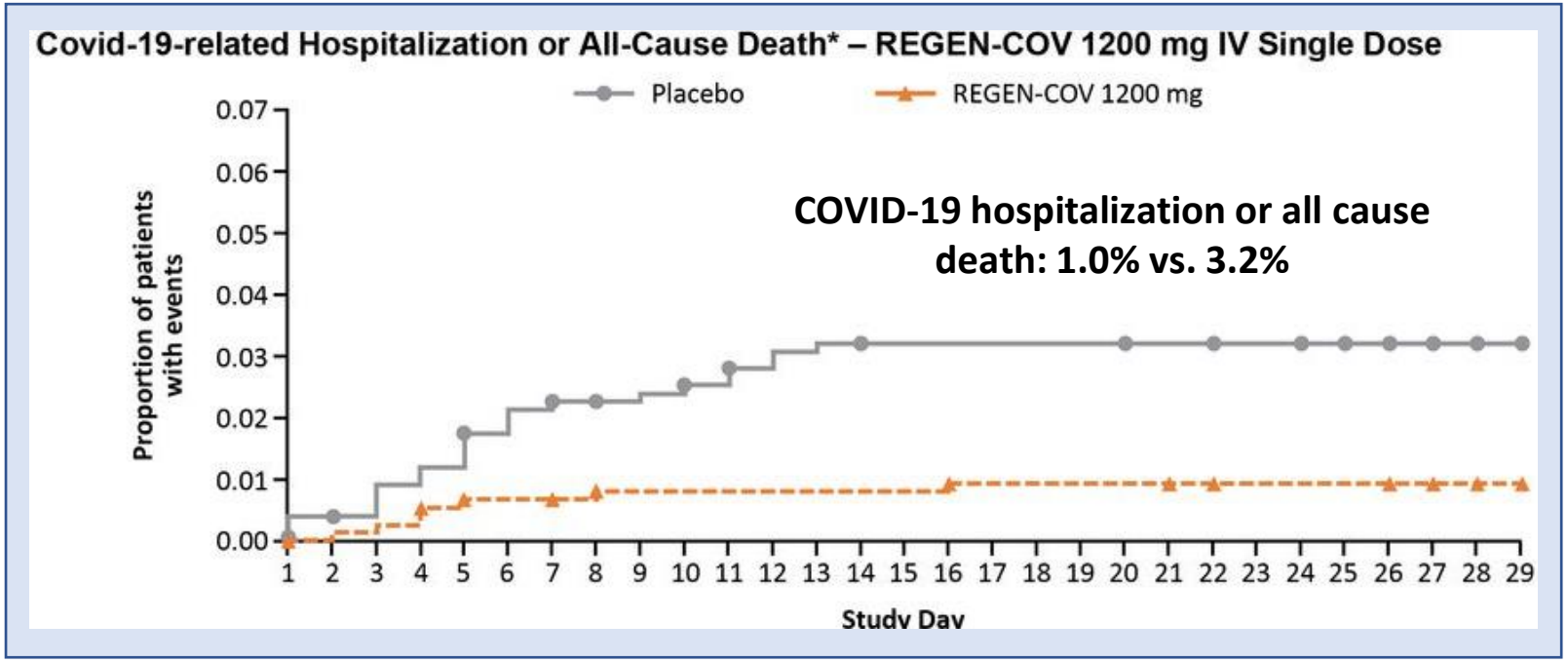
Dougan M et al, NEjM, 2021; https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced

Casirivimab/Imdevimab: Outpatient Treatment

- Outpatients (n=4057) with mild to moderate COVID: placebo or intravenous casirivimab/imdevimab (various doses)
- Modified full analysis set: +PCR; ≥1 risk factor for severe COVID

Results:

- In 600/600 mg group, 70% reduction in COVID hospitalizations or death
- More rapid resolution in symptoms in antibodies group: 10 vs. 14 days



Weinreich et al., REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients, https://doi.org/10.1101/2021.05.19.21257469

Sotrovimab: Outpatient Treatment

- Outpatients with mild to moderate COVID-19 at high risk of hospitalization (n=583)
- Randomized to receive sotrovimab or placebo

Result:

- 85% reduction in hospitalization or death

	N	Hospitalized/ death	Percent Reduction
Sotrovimab	**291**	**3 (1%)**	**85% (p=0.002)**
Placebo	**292**	**21 (7%)**	

Gupta A et al, medRxiv preprint, 2021; https://doi.org/10.1101/2021.05.27.21257096

What about SARS-CoV-2 Variants?

Variants and Anti-SARS-CoV-2 Antibodies: In Vitro Studies

- Alpha (B.1.1.7): susceptible to the authorized antibodies

- Beta (B.1.351), Gamma (P.1)
  - Marked reduction in susceptibility to bam/ete
  - Casirivimab/imdevimab, sotrovimab expected to retain activity

- Delta (B.1.617.2)
  - Bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab expected to have activity

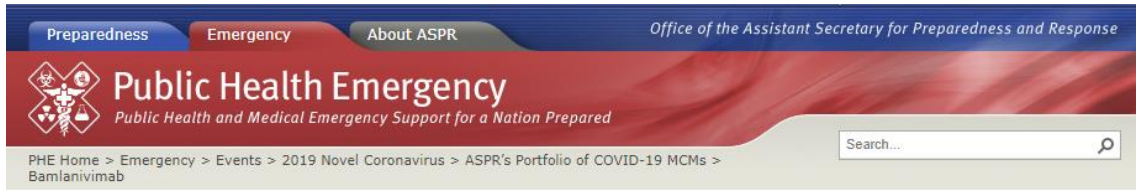
https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variants with Bamlanivimab/Etesevimab

Lineage	Country 1st Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.351	South Africa	Beta	K417N + E484K + N501Y	431
P.1	Brazil	Gamma	K417T + E484K + N501Y	252
B.1.617.2/ AY.3	**India**	**Delta**	**L452R + T478K**	**no change**
AY.1/AY.2 (B.1.617.2 sub-lineages)	India	Delta [+K417N]	L452R + T478K + K417N	1,235
B.1.427/ B.1.429	USA (California)	Epsilon	L452R	9

FDA, FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB, https://www.fda.gov/media/145802/download

Resumption in Distribution of Bamlanivimab/Etesevimab



Important Updates

September 3, 2021 - HHS is immediately implementing changes to help promote optimal and equitable use of the available supply of monoclonal antibodies while efforts to procure additional product. Learn More >>

September 2, 2021 - FDA and ASPR announce resumption in use and distribution of bamlanivimab/etesevimab in all U.S states, territories, and jurisdictions under the conditions of authorization for EUA 94. Learn More >>

August 27, 2021 - FDA and ASPR announce resumption in use and distribution of bamlanivimab/etesevimab in certain states. Learn More >>

https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx

What about people who develop COVID-19 after vaccination?

- *For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including use of and timing of treatment with monoclonal antibodies.*

What are the Data for Use of anti-SARS CoV-2 Antibodies for Post-exposure Prophylaxis?

Casirivimab/Imdevimab: Post-exposure prophylaxis

- Phase 3 placebo-controlled trial among household contacts of person with positive SARS CoV-2 test within past 96 hours
- Casi/imdev (600/600 mg) or placebo given subcutaneously

Symptomatic SARS CoV-2 Infection in Participants who were PCR and antibody negative at baseline				
	N	Events	Proportion	Risk Reduction
Placebo	752	59	7.8%	81% (p<0.0001)
Antibodies	753	11	1.5%	

Results:

- Among participants who were PCR-negative and seronegative at baseline (n=1505), 81% reduction in symptomatic SARS CoV-2 infection in casirivimab/imdevimab group (P<0.0001)
- Among infected participants, antibody group had shorter duration of symptoms (1.2 vs. 3.2 weeks) and shorter duration of high viral loads (0.4 vs 1.3 weeks)

O'Brien M et al, NEJM 2021

IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 9/3/2021

Adarsh Bhimraj*, Rebecca L. Morgan**, Amy Hirsch Shumaker, Valery Lavergne**, Lindsey Baden, Vincent Chi-Chung Cheng, Kathryn M. Edwards, Rajesh Gandhi, Jason Gallagher, William J. Muller, John C. O'Horo, Shmuel Shoham, M. Hassan Murad**, Reem A. Mustafa**, Shahnaz Sultan**, Yngve Falck-Ytter**

	Ambulatory care: mild-to-moderate disease	Hospitalized: mild-to-moderate disease	Hospitalized: severe but non-critical disease	Hospitalized: critical disease
Post-exposure casirivimab/ imdevimab	Suggest use ⊕⊕◯◯	NA	NA	NA
Bamlanivimab/ etesevimab **Casirivimab/ imdevimab** **Sotrovimab**	Suggest use ⊕⊕⊕◯	NA	NA	NA
Bamlanivimab monotherapy	NA	NA	Recommend against use ⊕⊕⊕◯	NA

See guidelines for details

Casirivimab/imdevimab recommended for post-exposure prophylaxis in people who are at high risk for progression if infected (see guidelines for details)

Anti-SARS CoV-2 monoclonal antibody products are recommended for outpatients with mild-to-moderate COVID-19 who are at high risk of disease progression (see EUA criteria)

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/; https://www.covid19treatmentguidelines.nih.gov

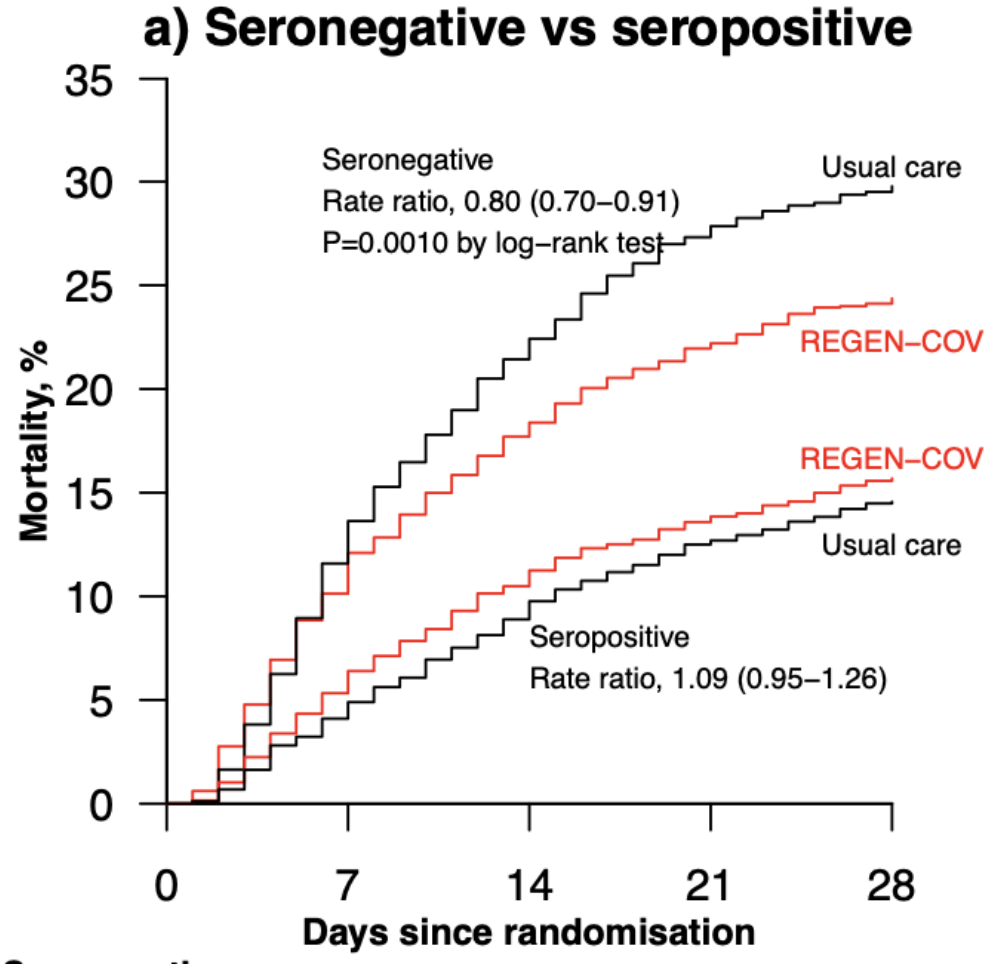
What about patients hospitalized due to COVID-19?

Casirivimab/Imdevimab in Hospitalized Patients: RECOVERY

- Hospitalized patients (n=9785) randomized to usual care with casirivimab 4,000 mg + imdevimab 4,000 mg IV or usual care alone.

Results

- 28-day all-cause mortality: 20% vs. 21% (no difference)
- In those seronegative for anti-spike protein antibody, reduction in mortality with casi/imdev: 24% vs. 30% (rate ratio 0.80; 95% CI, 0.70–0.91; P = 0.001)



https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf

Casirivimab/Imdevimab in Hospitalized Patients

- Casirivimab/imdevimab not yet authorized for treatment of hospitalized patients
- We need rapid and reliable serology test to identify seronegative individuals
- Casirivimab/imdevimab only available through expanded access program for hospitalized patients who are not on high flow oxygen or mechanically ventilated

Rapidly evolving information with more to come ….

Anti-SARS CoV-2 Monoclonal Antibodies: Summary

Treatment:

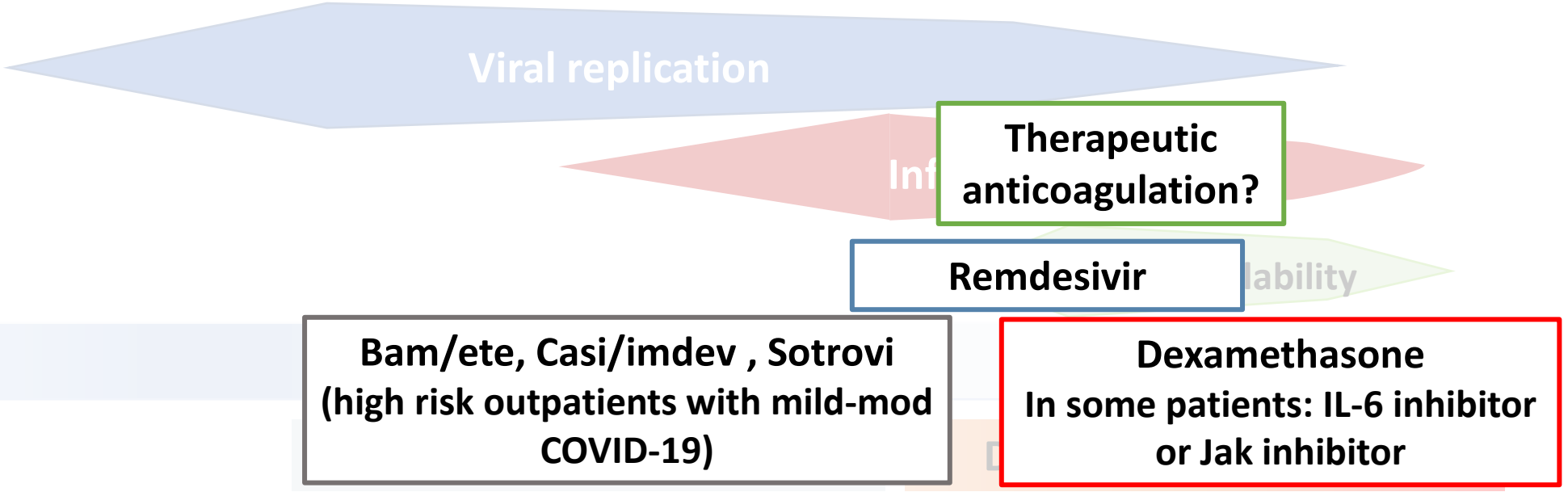
- mAbs authorized to treat high-risk outpatients with mild-moderate COVID-19
  - Not authorized for use in people hospitalized due to COVID-19; may be used in people hospitalized for reasons other than COVID-19 (see FDA FAQ)
  - In the future, mAbs may have role in seronegative hospitalized patients but need rapid and reliable serologic test

Post-exposure prophylaxis:

- Casirivimab/imdevimab authorized for post-exposure prophylaxis for people who are at higher risk for severe COVID-19 who are not fully vaccinated or who are not expected to mount an immune response (eg immunocompromised hosts)

Post-Exposure Prophylaxis and Treatment Across the COVID-19 Spectrum

Exposure	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea	O_2 saturation ≥ 94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

COVID-19 Treatment Updates

Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention: Pediatric Considerations

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Sarah H. Sell and Cornelius Vanderbilt Professor
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Department of Pediatrics
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Disclosures: Dr. Edwards is a consultant to Bio-Net and IBM and serves as a member of Data Safety and Monitoring Boards for NIAID, Sanofi, X-4 Pharma, Seqirus, Moderna, Roche, and Pfizer.

Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention: Pediatric Considerations

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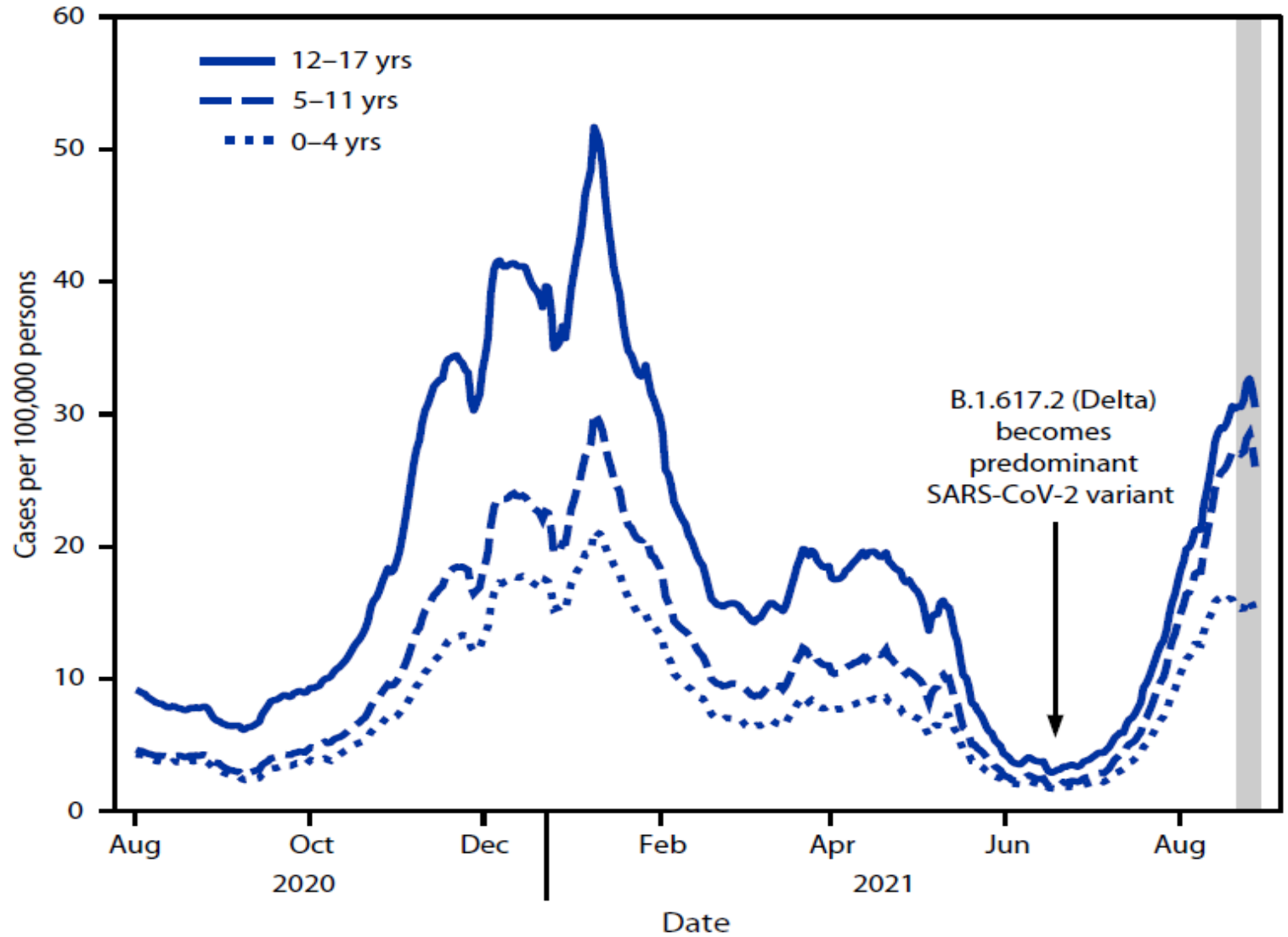
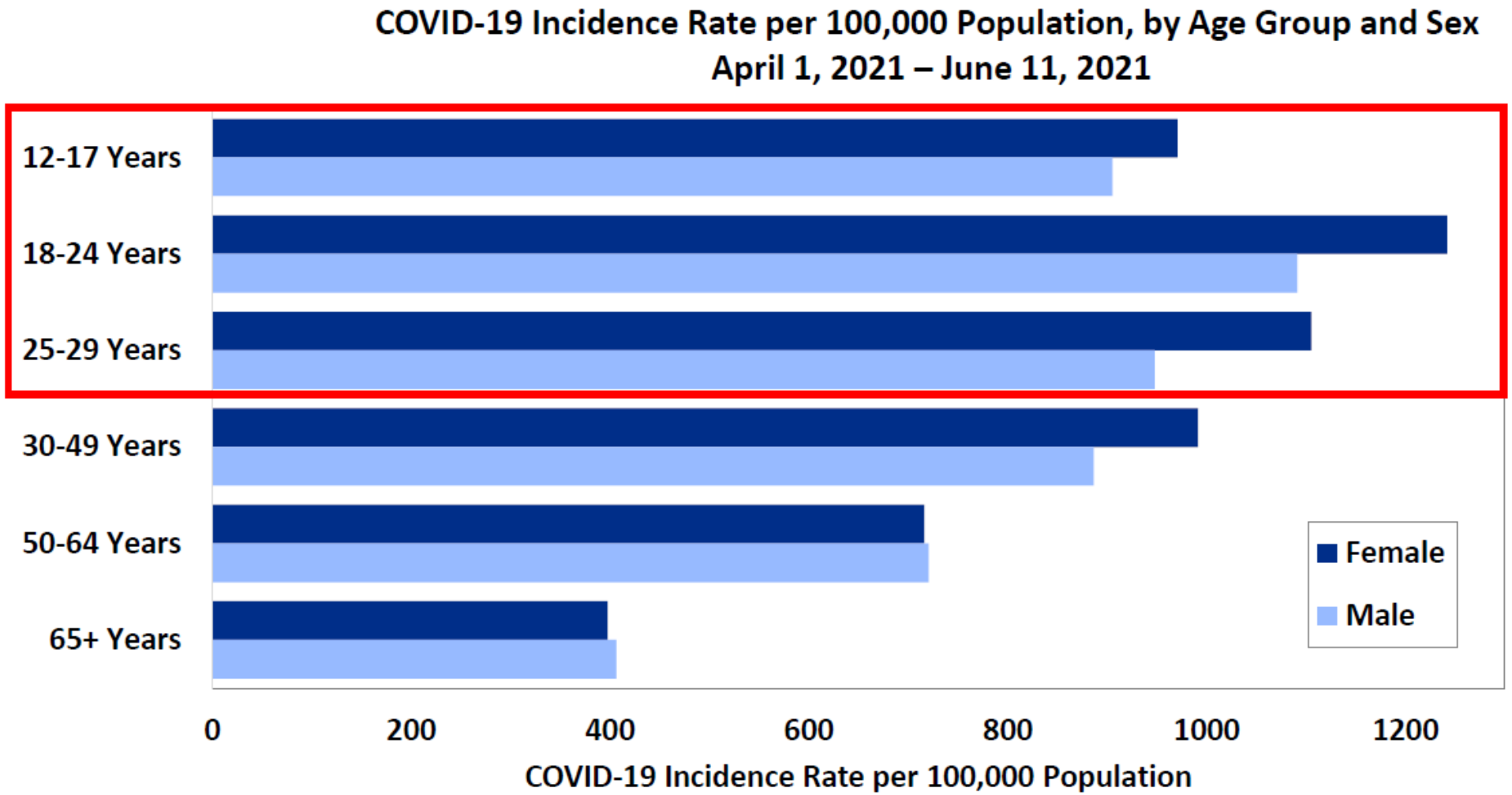
Northwestern University Feinberg School of Medicine

FIGURE 1. Average daily COVID-19 case incidence* among persons aged 0–17 years, by age group — United States, August 1, 2020–August 27, 2021



Source: CDC's case-based COVID-19 surveillance system, accessed August 30, 2021. https://www.cdc.gov/nndss/action/covid-19-response.html

Adolescents and young adults have the highest COVID-19 incidence rates



Since beginning of pandemic **at least 7.7 million** COVID-19 cases have been reported among persons aged 12–29 years

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

Severe Acute Respiratory Syndrome Coronavirus 2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth

THE JOURNAL OF PEDIATRICS • www.jpeds.com Volume 230 • March 2021

Table III. Baseline characteristics of patients hospitalized with SARS-CoV-2

Characteristics	Total, N = 281		Clinical group: Respiratory, N = 143		MIS-C, N = 69		Other, N = 69		*P* value
Coexisting conditions									
Obesity*	85/250	(34.0%)	62/134	(46.3%)	18/64	(28.1%)	5/52	(9.6%)	<.001
Respiratory*	49/281	(17.4%)	39/143	(27.3%)	6/69	(8.7%)	4/69	(5.8%)	<.001
Neurologic*	23/281	(8.2%)	22/143	(15.4%)	0/69	(0.0%)	1/69	(1.4%)	<.001
Immunosuppressed*	16/281	(5.7%)	13/143	(9.1%)	1/69	(1.4%)	2/69	(2.9%)	.052
Diabetes*	11/281	(3.9%)	8/143	(5.6%)	0/69	(0.0%)	3/69	(4.3%)	.14
Sickle cell	9/281	(3.2%)	7/143	(4.9%)	2/69	(2.9%)	0/69	(0.0%)	.21
Cardiovascular*	18/281	(6.4%)	12/143	(8.4%)	2/69	(2.9%)	4/69	(5.8%)	.30
Gastrointestinal*	10/281	(3.6%)	10/143	(7.0%)	0/69	(0.0%)	0/69	(0.0%)	.005
History of smoking*	13/228	(5.7%)	10/116	(8.6%)	0/52	(0.0%)	3/60	(5.0%)	.069
Medical complexity*	59/281	(21.0%)	45/143	(31.5%)	5/69	(7.2%)	9/69	(13.0%)	<.001

TABLE. Demographic and clinical characteristics and outcomes among adolescents aged 12–17 years with laboratory-confirmed COVID-19–associated hospitalizations, by primary reason for admission — COVID-NET, 14 states,* January 1, 2021–March 31, 2021

Characteristic	No. of hospitalizations (%)		
	Total	Primary reason for admission COVID-19–related	Primary reason for admission not clearly COVID-19–related
Total no. of hospitalized adolescents	376 (100.0)†	204 (100.0)†	172 (100.0)†
Underlying medical condition			
≥1 underlying medical condition¶	207 (55.1)	144 (70.6)	63 (36.6)
Obesity***	101 (27.9)	73 (35.8)	28 (17.7)
Chronic lung disease, including asthma	87 (24.0)	63 (30.9)	24 (15.2)
Neurologic disorders	43 (11.9)	29 (14.2)	14 (8.9)
Chronic metabolic disease, including diabetes	32 (8.8)	24 (11.8)	8 (5.1)
Immunocompromised condition	20 (5.5)	14 (6.9)	6 (3.8)
Blood disorder, including sickle cell anemia	21 (5.8)	19 (9.4)	2 (1.3)
Cardiovascular disease	15 (4.1)	9 (4.4)	6 (3.8)

Deaths in Children and Adolescents Associated With COVID-19 and MIS-C in the United States

Table 4. Underlying medical conditions for all decedents, decedents who met MIS-C criteria, and decedents who did not meet MIS-C criteria ($n = 112$)

	All Decedents ($n = 112$)		Met MIS-C Criteria ($n = 16$)		Did not Meet MIS-C Criteria ($n = 80$)	
	N	%	*N*	%	*N*	%
Number of Underlying Medical Conditions						
None	16	14%	5	31%	10	13%
1	24	21%	1	6%	17	21%
2	22	20%	4	25%	15	19%
3	15	13%	2	13%	13	16%
4	10	9%	1	6%	8	10%
≥5	25	22%	3	19%	17	21%
Metabolic and Endocrine	**51**	**46%**	**7**	**44%**	**39**	**49%**
Obesity	47	42%	5	31%	37	46%
Diabetes Mellitus*	11	10%	1	6%	9	11%
Other[a]	12	11%	2	135	9	11%
Neurologic and Developmental	**37**	**33%**	**5**	**31%**	**24**	**30%**
Developmental Disorder	25	22%	3	19%	15	19%
Seizure disorder	17	15%	3	19%	11	14%
Other[b]	20	18%	2	13%	15	19%
Respiratory	**35**	**31%**	**6**	**38%**	**24**	**30%**
Asthma or Reactive Airway Disease	33	29%	5	31%	23	29%
Other[c]	6	5%	1	6%	2	3%

Citation: McCormick DW, Richardson LC, Young PR, et al. Deaths in children and adolescents associated with COVID-19 and MIS-C in the United States. *Pediatrics*. 2021; doi: 10.1542/peds.2021-052273

Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of Coronavirus Disease 2019 in Children and Adolescents

Joshua Wolf,[1,2] Mark J. Abzug,[3] Rachel L. Wattier,[4] Paul K. Sue,[5] Surabhi B. Vora,[6] Philip Zachariah,[7] Daniel E. Dulek,[8] Alpana Waghmare,[6,9] Rosemary Olivero,[10] Kevin J. Downes,[11] Scott H. James,[12] Swetha G. Pinninti,[12] April Yarbrough,[13] Margaret L. Aldrich,[14] Christine E. MacBrayne,[15] Vijaya L. Soma,[16] Steven P. Grapentine,[17] Carlos R. Oliveira,[18] Molly Hayes,[19] David W. Kimberlin,[12] Sarah B. Jones,[20] Laura L. Bio,[21] Theodore H. Morton,[1] Jane S. Hankins,[22] Gabriela M. Maron,[1] Kathryn Timberlake,[23] Jennifer L. Young,[24] Rachel C. Orscheln,[25] Hayden T. Schwenk,[26] David L. Goldman,[14] Helen E. Groves,[27] W. Charles Huskins,[28] Nipunie S. Rajapakse,[28] Gabriella S. Lamb,[29] Alison C. Tribble,[30] Elizabeth C. Lloyd,[30] Adam L. Hersh,[31] Emily A. Thorell,[31] Adam J. Ratner,[16,32] Kathleen Chiotos,[11,33] and Mari M. Nakamura[29,34]

Background. In November 2020, the US Food and Drug Administration (FDA) provided Emergency Use Authorizations (EUA) for 2 novel virus-neutralizing monoclonal antibody therapies, bamlanivimab and REGN-COV2 (casirivimab plus imdevimab), for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adolescents and adults in specified high-risk groups. This has challenged clinicians to determine the best approach to use of these products.

Methods. A panel of experts in pediatric infectious diseases, pediatric infectious diseases pharmacy, pediatric intensive care medicine, and pediatric hematology from 29 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a guidance statement was developed and refined based on review of the best available evidence and expert opinion.

Risk for severe COVID-19	Condition	Recommendation Treatment	Recommendation Prophylaxis
Severe	• Obesity • Severe Immunocompromise • Medical complexity with respiratory technology dependence	Suggest administration	Consider if high risk exposure and unvaccinated or unlikely to respond to vaccine
Moderate	• Mild to moderate immunocompromise • Chronic respiratory conditions • Congenital heart disease • Sickle Cell Disease	Consider administration	Insufficient evidence
Low	• Diabetes • Chronic kidney disease	Suggest no routine use	

COVID-19 Treatment Updates

Ivermectin: What are the Data and What's Fueling its Use

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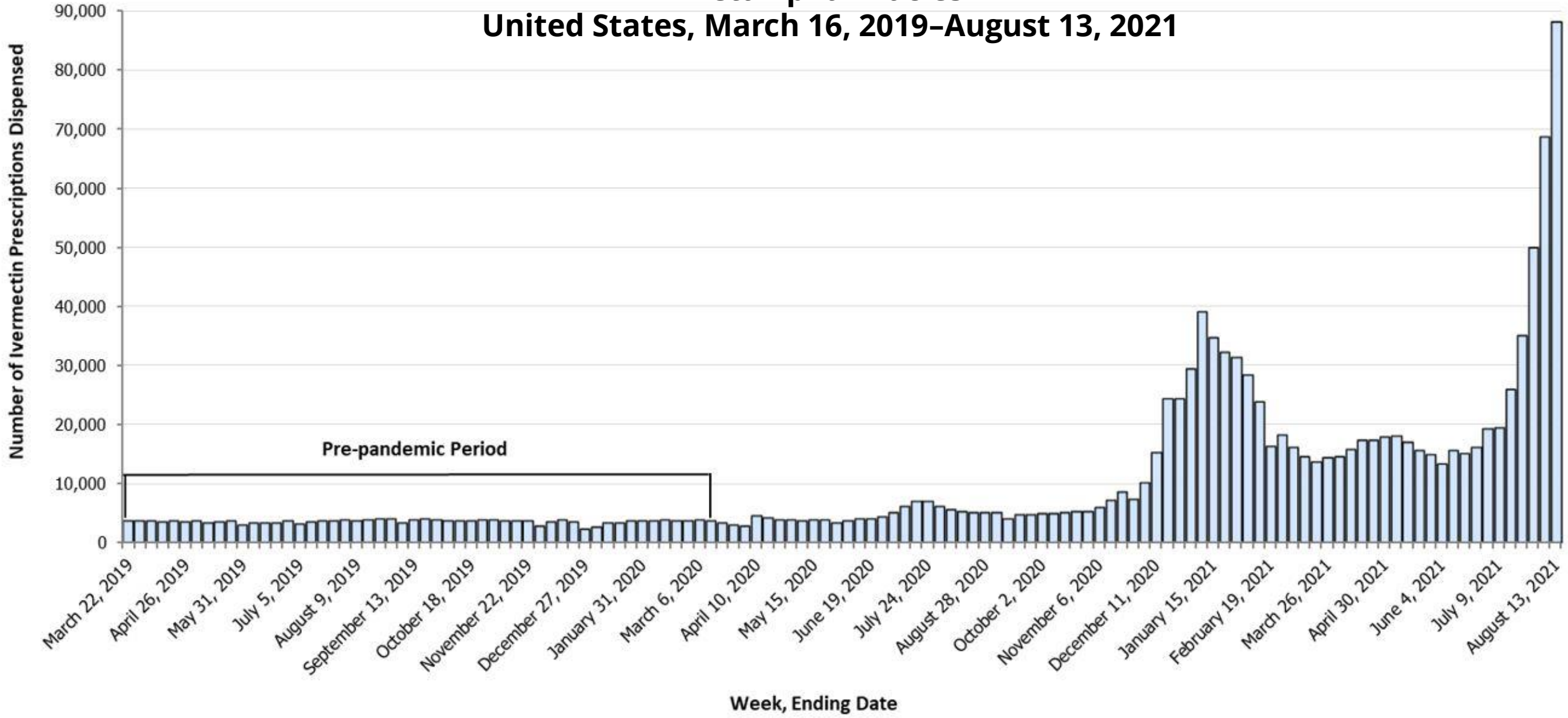
Brigham and Women's Hospital

Disclosures: Receive research support from NIH, Gates, Wellcome Trust for vaccine and therapeutics development including for SARS-CoV-2. Serve on multiple NIH SMC/DSMBs and the IDSA Covid-19 Treatment Guidelines Committee.

Why is ivermectin considered for treatment?

- Ivermectin: An anti-parasitic agent. FDA-approved for onchocerciasis and strongyloidiasis and used off-label for the treatment of many parasitic infections.
- Although it has *in vitro* activity against some viruses, including SARS-CoV-2, it has no proven therapeutic utility.
  - *In vitro* activity against SARS-CoV-2 requires concentrations considerably higher than those achieved in human plasma and lung tissue to reach the *in vitro* IC_{50} .
- Has been shown to have anti-inflammatory effects in *in vitro* and *in vivo* studies; hence hypothesized to have a mechanism beyond its anti-viral effects in the treatment of COVID-19
- Since ivermectin is generally well-tolerated, it has been empirically evaluated in uncontrolled studies for COVID-19, alone and in combination with other off-label medications.

Estimated number of outpatient ivermectin prescriptions dispensed from retail pharmacies
United States, March 16, 2019–August 13, 2021



Evidence Summary

- Systematic literature review identified 15 studies
  - Ages 8-86 years old, reported outcomes of mortality, symptom resolution, viral clearance, and AEs
  - Eligible studies compared ivermectin against a placebo or standard of care
    - 10 RCTs and 2 non-randomized informed inpatient assessment
    - 8 RCTS informed the ambulatory assessment
    - Design considerations
      - Quality of randomization process and blinding uneven
      - Dose used ranged from 100 to 400 mcg/kg/day for 1 to 7 days
  - Overall relatively small numbers and very small number of events
      - For example, assessing mortality:
        - Hospitalized patients 7 RCTs with 602 enrolled and 26 events
        - Ambulatory patients 7 studies with 1,631 enrolled and 15 events

Observations

Inpatients

- No evidence from RCTs for benefit on:
  - mortality
  - symptom resolution or
  - viral clearance

Outpatients

- No evidence for benefit on
  - mortality
  - disease progression or
  - viral clearance
- Unclear if ivermectin may reduce time to recovery among outpatients

FDA U.S. FOOD & DRUG ADMINISTRATION

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Why You Should Not Use Ivermectin to Treat or Prevent COVID-19

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AMA, APhA, ASHP statement on ending use of ivermectin to treat COVID-19

SEP 1, 2021

WASHINGTON, DC – The American Medical Association (AMA), American Pharmacists Association (APhA), and American Society of Health-System Pharmacists (ASHP) **strongly oppose the ordering, prescribing, or dispensing of ivermectin to prevent or treat COVID-19 outside of a clinical trial.**

Ivermectin is approved by the U.S. Food and Drug Administration (FDA) for human use to treat infections caused by internal and external parasites. It is not approved to prevent or treat COVID-19. Ivermectin is also available to treat certain veterinary conditions; medications formulated or intended for use in animals should not be used by humans. We are alarmed by reports that outpatient prescribing for and dispensing of ivermectin have increased 24-fold since before the pandemic and increased exponentially over the past few months. As such, we are calling for an immediate end to the prescribing, dispensing, and use of ivermectin for the prevention and treatment of COVID-19 outside of a clinical trial. In addition, we are urging physicians, pharmacists, and other prescribers—trusted health care professionals in their communities—to warn patients against the use of ivermectin outside of FDA-approved indications and guidance, whether intended for use in humans or animals, as well as purchasing ivermectin from online stores. Veterinary forms of this medication are highly concentrated for large animals and pose a significant toxicity risk for humans.

https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19

Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
August 26, 2021, 11:40 AM ET
CDCHAN-00449

Summary

Ivermectin is a U.S. Food and Drug Administration (FDA)-approved prescription medication used to treat certain infections caused by internal and external parasites. When used as prescribed for approved indications, it is generally safe and well tolerated.

During the COVID-19 pandemic, ivermectin dispensing by retail pharmacies has increased, as has use of veterinary formulations available over the counter but not intended for human use. FDA has cautioned about the potential risks of use for prevention or treatment of COVID-19.

Ivermectin is not authorized or approved by FDA for prevention or treatment of COVID-19. The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel has also determined that there are currently insufficient data to recommend

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Summary
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Ivermectin is not authorized or approved by FDA for prevention or treatment of COVID-19. The National Institutes of Health's (NIH) COVID-19 Treatment Guidelines Panel has also determined that there are currently insufficient data to recommend ivermectin for treatment of COVID-19. ClinicalTrials.gov has listings of ongoing clinical trials that might provide more information about these hypothesized uses in the future.

Adverse effects associated with ivermectin misuse and overdose are increasing, as shown by a rise in calls to poison control centers reporting overdoses and more people experiencing adverse effects.

Background
The Centers for Disease Control and Prevention (CDC) confirmed with the American Association of Poison Control Centers (AAPCC) that human exposures and adverse effects associated with ivermectin reported to poison control centers have increased in 2021 compared to the pre-pandemic baseline. These reports include increased use of veterinary products not meant for human consumption.

Ivermectin is a medication that is approved by FDA in oral formulations to treat onchocerciasis (river blindness) and intestinal strongyloidiasis. Topical formulations are used to treat head lice and rosacea. Ivermectin is also used in veterinary applications to prevent or treat internal and external parasitic infections in animals. When used in appropriate doses for approved indications, ivermectin is generally well tolerated.

https://emergency.cdc.gov/han/2021/han00449.asp

COVID-19 Treatment Updates

Emerging Therapies under Investigation: Focus on Fluvoxamine

Shmuel Shoham, MD
Associate Professor of Medicine
Transplant and Oncology Infectious Disease Program
Johns Hopkins University School of Medicine

Disclosures: Grants: Ansun, F2G
Personal Fees: Celltrion, Adagio, Immunome
DSMG: Karyoharm, Intermountain Health, Adamis

CDC/IDSA Clinician Call
Emerging Therapies Under Investigation: Focus on Fluvoxamine
September 11, 2021

Shmuel Shoham, MD
Associate Professor of Medicine
Transplant and Oncology Infectious Diseases Program
Johns Hopkins University School of Medicine

JOHNS HOPKINS
MEDICINE

Fluvoxamine for COVID-19:Potential Mechanisms

- Immune modulation
  - Sigma-1 receptor activation, leading to inositol-requiring enzyme 1α-driven (IRE1) inflammation ↓
  - platelet aggregation ↓
  - mast cell degranulation ↓
  - melatonin level ↑ (Melatonin may reduce inflammation through inhibition of the NLRP3 pathway)
- Antiviral effect
  - Interference with viral entry and endolysosomal viral trafficking

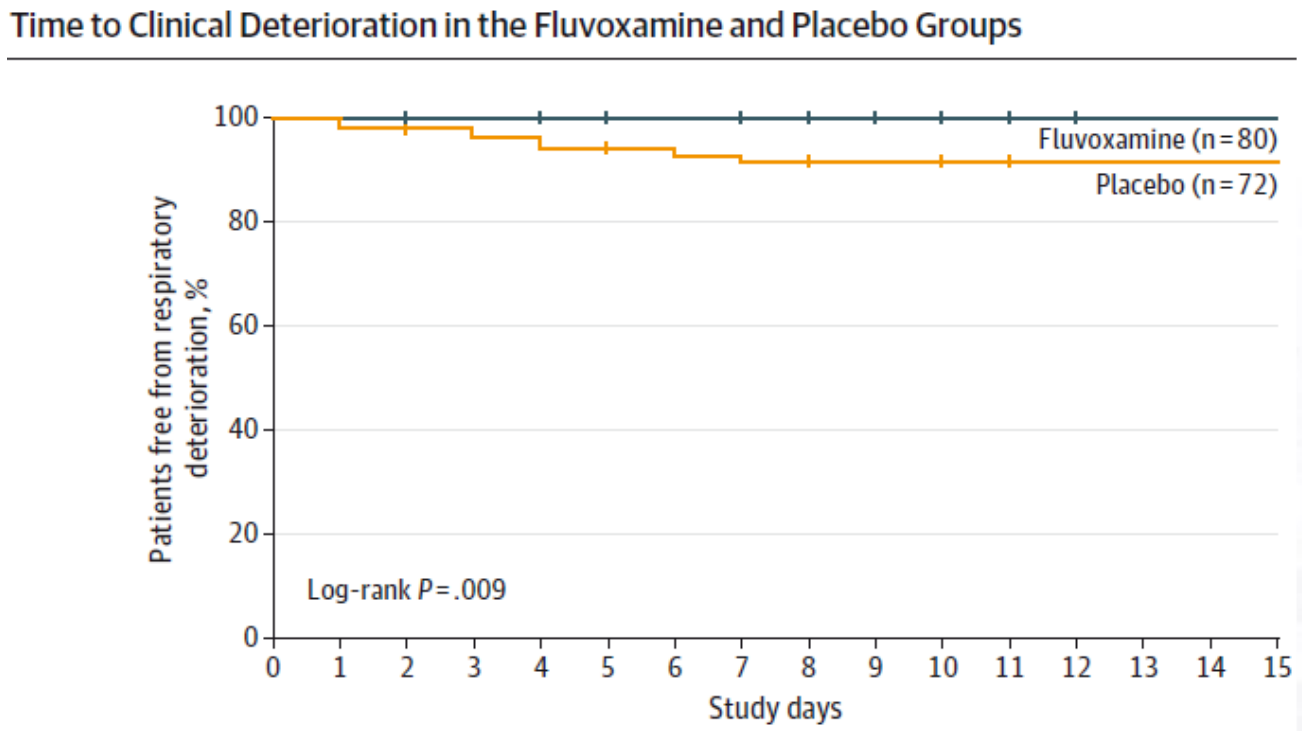
Safety of Fluvoxamine

- Safety record well-known
  - Used worldwide since 1990s
  - No fatality even in overdose
  - No cardiac QTc prolongation
- Main side effects: nausea (25%), insomnia. Mild, temporary.
- FDA warning about ALL antidepressants and increased “suicidality” in mentally ill persons age <25
- Could destabilize bipolar disorder (1% of population)
- Drug interactions:
  - **Blocks metabolism of caffeine** and rare drugs (eg theophylline)
  - 15-20% of Americans already taking an antidepressant.

Fluvoxamine vs Placebo for Outpatients With Symptomatic COVID-19

- **Lenze et al, JAMA 2020**
  - RCT (n=152); outpatient
  - Fluvoxamine 50 mg x 1 dose, then 100 mg BID x 2-3 days then 100 mg TID as feasible (only 50% got up to that dose) x 15 days
  - Clinical deterioration: 0/80 FLX patients vs 6/72 (8.3%) placebo (P = .009)

Primary endpoint: clinical deterioration (dyspnea PLUS hypoxia [O2<92%])



Fluvoxamine group:
0% (0/80)
deteriorated

Placebo group:
8.3% (6/72)
deteriorated.

Lenze et al., JAMA 2020

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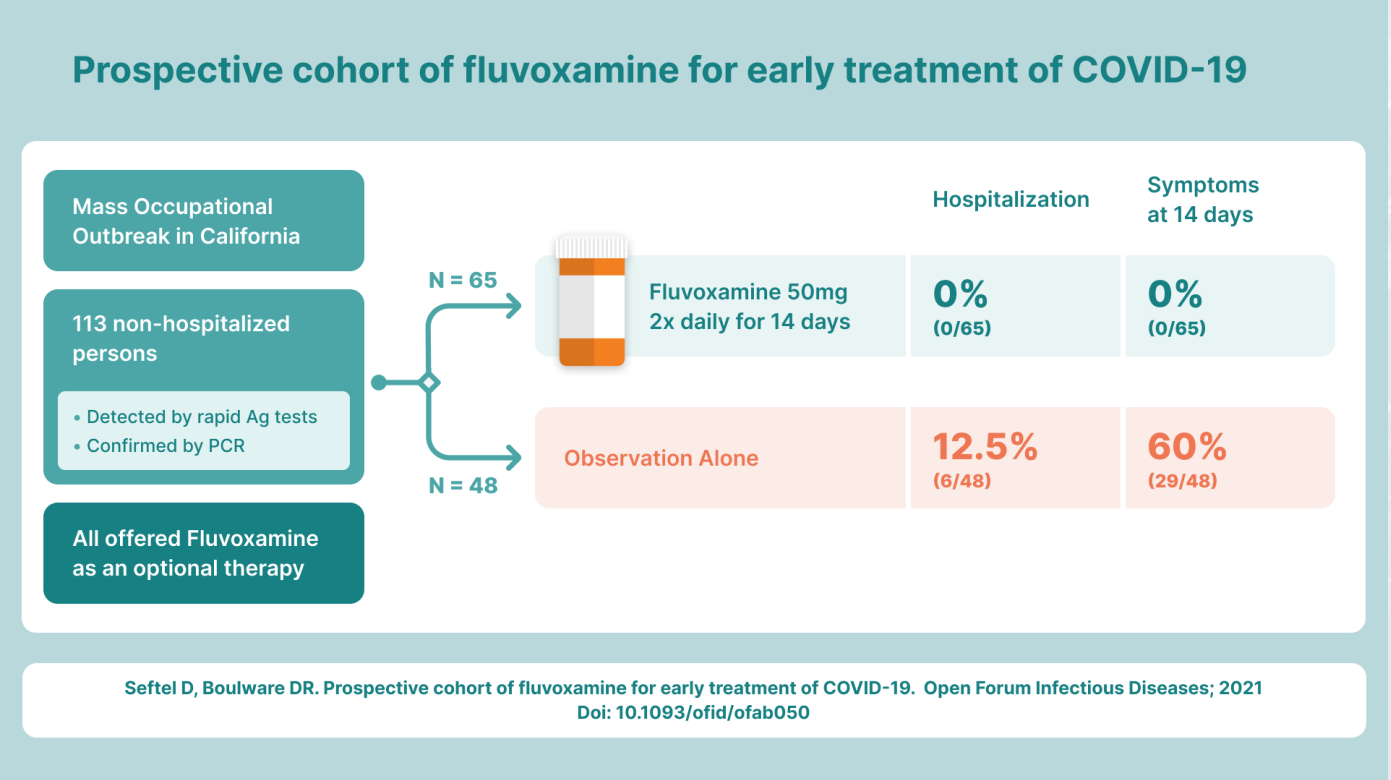
Prospective Cohort of Fluvoxamine for Early Treatment of COVID-19

- **Seftel et al, OFID 2021**
  - Prospective self selected cohort in the setting of a mass outbreak (n=65 FLX, 48 usual care)
  - Fluvoxamine 50 mg twice daily
  - Hospitalization 0/65 FLX vs. 6/48 (12.5%) for observation alone
  - Residual symptoms at 14 days 0/65 FLX vs. 29/48 (60%) with observation.

Observational Cohort



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Together Clinical Trials: Brazil

- Multicenter RCT (n=1472)
- Fluvoxamine n=739, Placebo n=733
- Reduced need for hospitalization or an extended ED visit >6 hr
  - Fluvoxamine 10.4% (77/739) vs. 14.7% (108/733) placebo
  - Relative Risk = 0.71; 95% CI: 0.54 - 0.93
- No differences
  - Viral clearance at day 7 — OR= 0.75; 95%CI: 0.53 - 1.07
  - Mortality (Outpatient trial) — OR= 0.70; 95% CI: 0.36 - 1.30
  - Length of hospitalization. — Mean Δ = 1.22 days; 95% CI: 0.98 - 1.53
  - Ventilator days — Mean Δ = 1.10; 95% CI: 0.70 - 1.73

STOP COVID 2: design summary
StopCovidTrial.com

Participants:
n=1100
enriched sample*
SARS-CoV-2+
community-dwelling
symptomatic (<7d)

Fluvoxamine 100mg twice daily (x15d)

Placebo

Outcomes:
Primary:
clinical deterioration over 15 days (definition: SOB and/or hospitalization, plus O2 <92%)

Secondary:
-15-day and 3 month function (Global Health Scale)

* one or more of: African-Am, Latinx, Native-Am, age ≥40, obesity, diabetes, HTN, heart disease (CAD/MI/CHF), lung disease, or immune condition

Ongoing trials

- COVID OUT
  - https://covidout.umn.edu
- ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications
  - https://clinicaltrials.gov/ct2/show/NCT04885530

Patients Already Taking Antidepressants

If taking Monoamine Oxidase Inhibitor (MAOI):

- Do NOT give fluvoxamine.

If taking an SSRI/SNRI:

- If psychiatrically stable, consider switching to fluvoxamine x 15 days, then switch back to original medication.
- If taking low-dose SSRI/SNRI, could keep current medication and add fluvoxamine.

Thank you

Thank you to **Eric Lenze** and **Angela Reiersen** (WUSTL) and **David Boulware** (UMN) for their expert review, guidance and for generously sharing slides.

Email: sshoham1@jhmi.edu

Twitter: @ShohamTxID

Q&A and Discussion

Links and References

Slide 14: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

Slide 15: FDA, FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB https://www.fda.gov/media/145802/download

Slide 16: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx

Slide 20: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
https://www.covid19treatmentguidelines.nih.gov

Slide 22: https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf

Slide 28: https://www.cdc.gov/nndss/action/covid-19-response.html

Slide 29: https://cdc.gov/covid-data-tracker/#demographics

Slide 37: https://emergency.cdc.gov/han/2021/han00449.asp

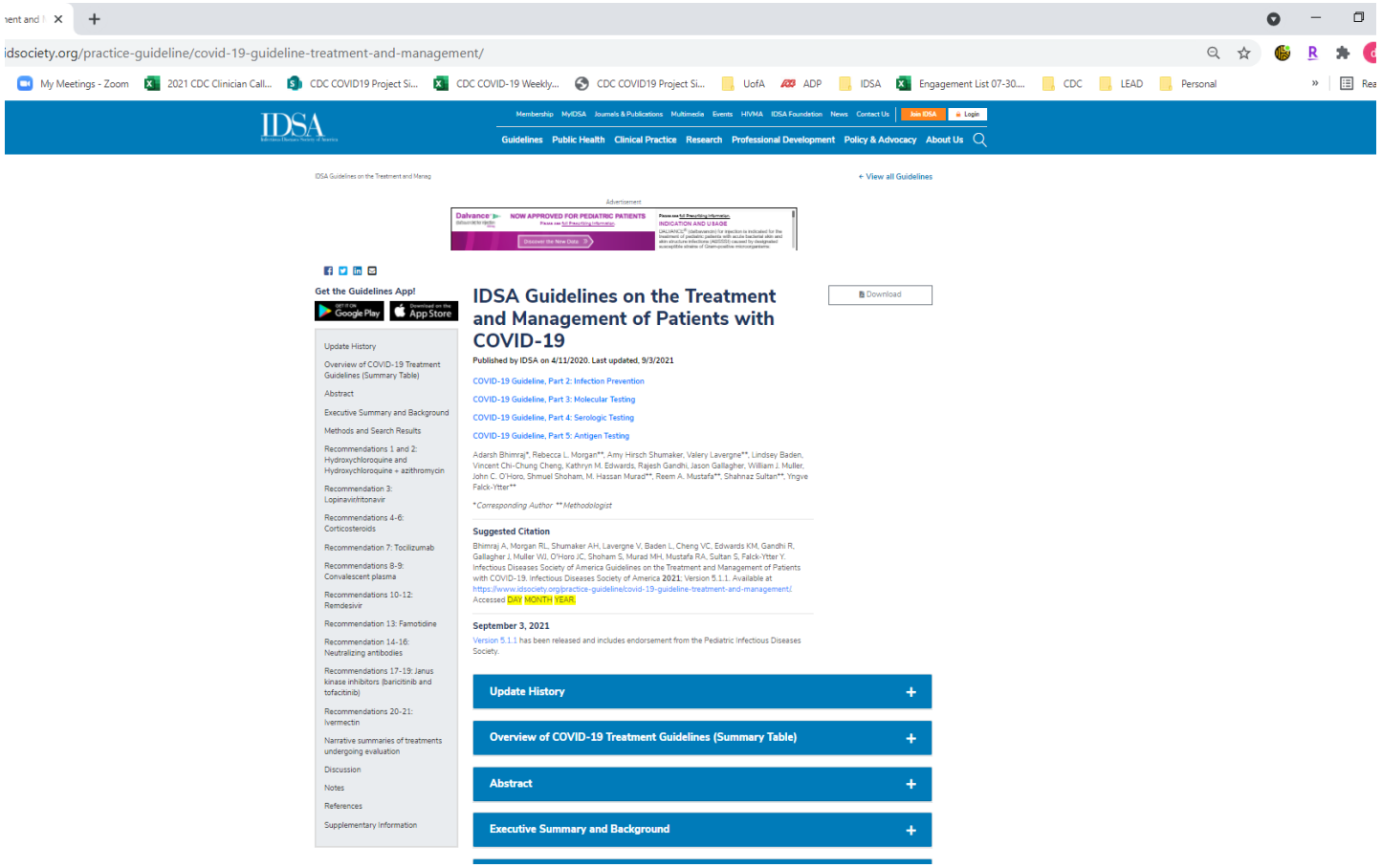
Slide 40: https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19

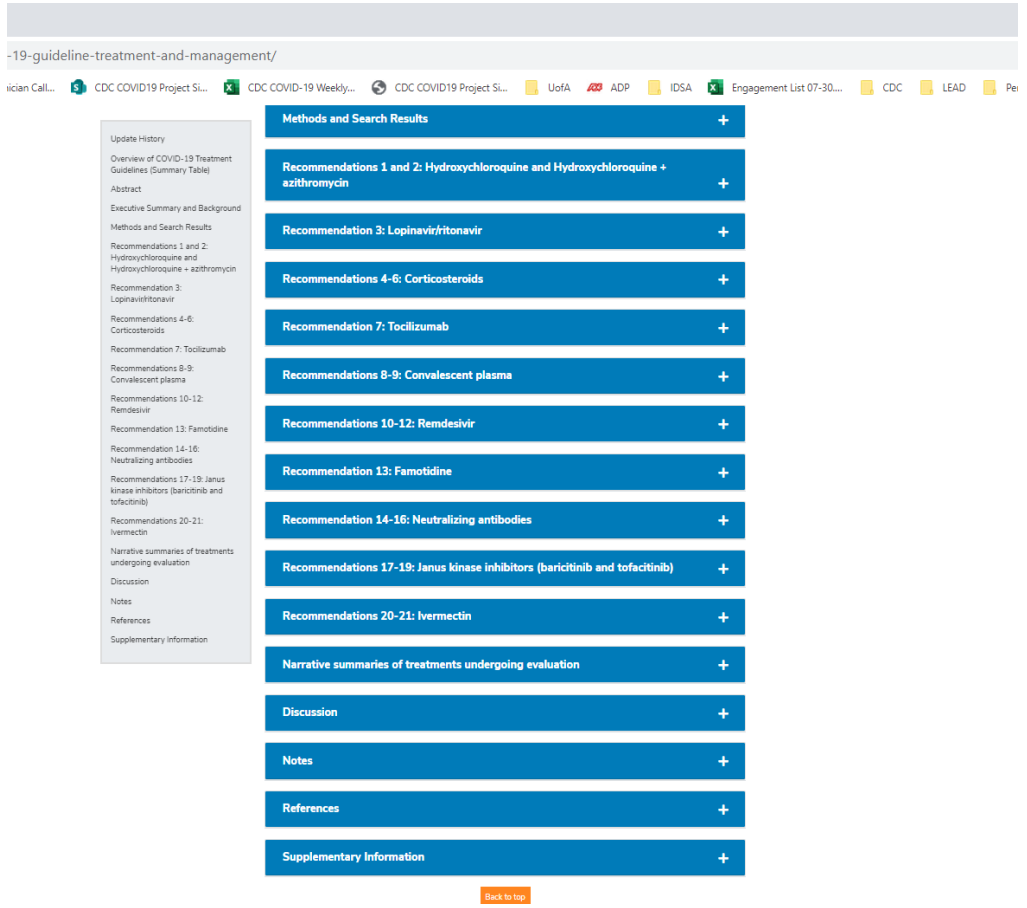
Slide 41: https://emergency.cdc.gov/han/2021/han00449.asp

Slide 52: COVID OUT - https://covidout.umn.edu

ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications: https://clinicaltrials.gov/ct2/show/NCT04885530

IDSA Guidelines on the Treatment and Management of Patients with COVID-19



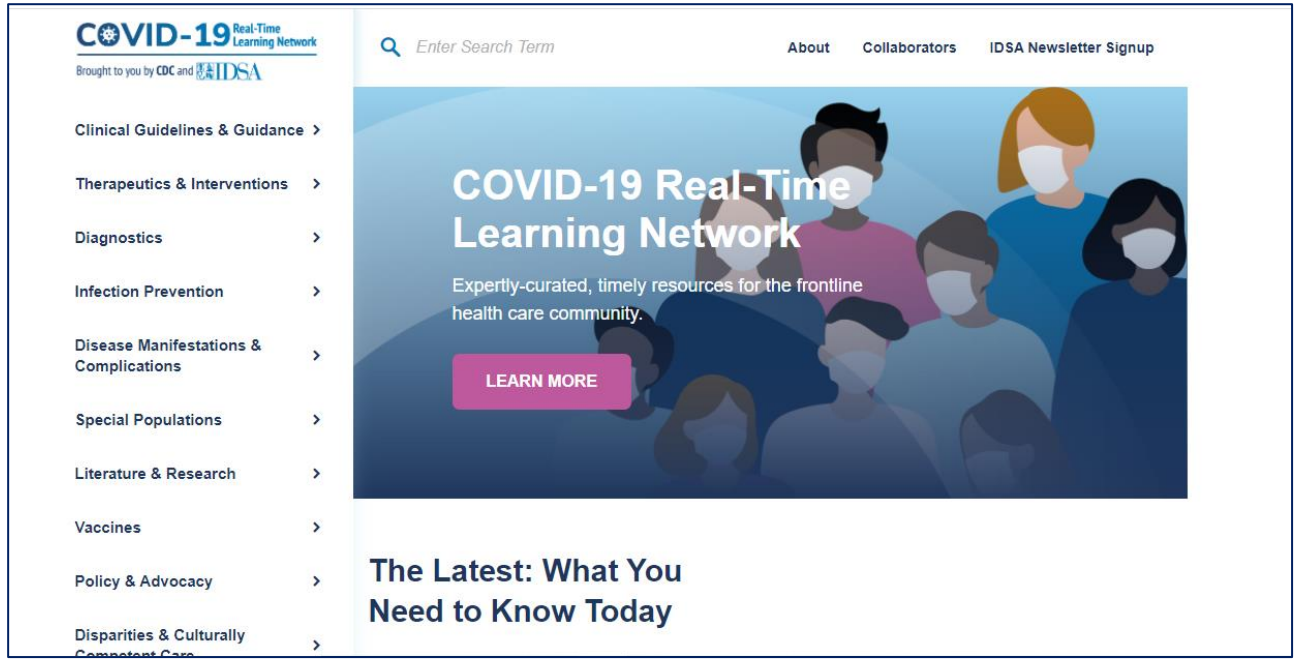


https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

COVID-19 Real-Time Learning Network

Brought to you by CDC and IDSA

An online community bringing together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.



Specialty Society Collaborators

American Academy of Family Physicians
American Academy of Pediatrics
American College of Emergency Physicians
American College of Physicians
American Geriatrics Society
American Thoracic Society
Pediatric Infectious Diseases Society
Society for Critical Care Medicine
Society for Healthcare Epidemiology of America
Society of Hospital Medicine
Society of Infectious Diseases Pharmacists

www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID19

10th Anniversary IDWeek

Sept. 29 – Oct. 3, 2021

Virtual Conference

Register by Aug. 27 to Save!

idweek.org

Chasing the Sun: COVID-19

Beyond the Horizon

Attend, Learn & Collaborate.

Advancing Science, Improving Care

Join the event and access COVID-19 content at no charge!

CDC-IDSA Partnership: Clinical Management Call Support

FOR WHOM?

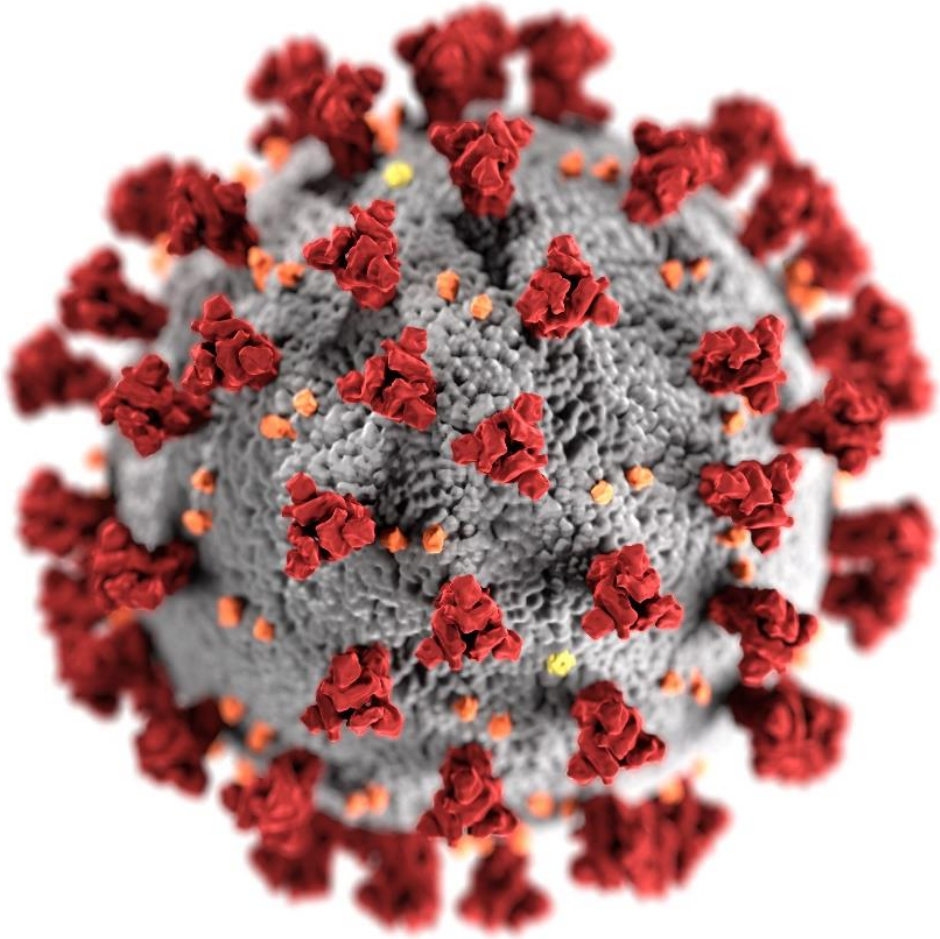
- Clinicians who have questions about the clinical management of COVID-19

WHAT?

- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

HOW?

- Clinicians may call the main CDC information line at 800-CDC-INFO (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form



IDSA
Infectious Diseases Society of America

cdc.gov/coronavirus

Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID19

We want to hear from you!

Please complete the post-call survey.

Clinician calls are now twice a month:

Next Call

Saturday, Sept. 25

A recording of this call will be posted Monday at
www.idsociety.org/cliniciancalls

-- library of all past calls available --

Contact Us:

Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)