COVID-19 Update

02/16/22

Jim Nora, MD

Disclosures

- Employment
  - Consultants in Infectious Disease, LLC
    - Lincoln, NE
  - Bryan Health, Lincoln, NE
    - Medical Director of Infection Prevention
  - Lincoln-Lancaster County Health Dept
    - Consultative services
- No commercial interests

Objectives

- Review current recommendations for:
  - Testing
  - Vaccination
  - Outpatient treatment option
    - Tixagevimab/cilgavimab (Evusheld)
    - Nirmatrelvir / Ritonovir (Paxlovid)
    - Other MABs

Overview

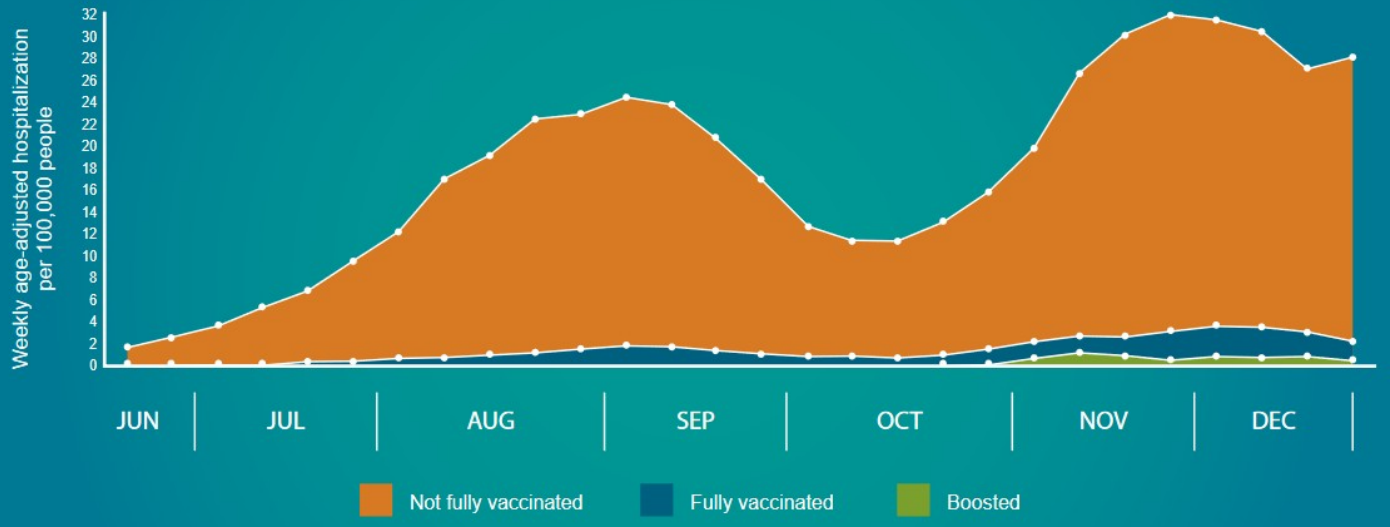
IN DECEMBER...

PEOPLE WHO WERE FULLY VACCINATED (BUT NOT YET BOOSTED) WERE ***11X LESS LIKELY*** TO BE HOSPITALIZED FOR COVID-19

PEOPLE WHO WERE BOOSTED WERE ***46X LESS LIKELY*** TO BE HOSPITALIZED FOR COVID-19

...THAN PEOPLE WHO WERE NOT FULLY VACCINATED

COVID-19 hospitalization rates by vaccination status in Nebraska, 2021



Hospitalizations: COVID-19 hospitalizations were identified from healthcare encounter data obtained from the State Health Information Exchange (CyncHealth), which were matched with Nebraska State Immunization Information System (NESIIS) vaccination data. We estimate this data source contains 60-70% of all COVID-19 hospitalizations in Nebraska.

Fully vaccinated: Fully vaccinated is defined as ≥14 days after the second dose of a two-dose vaccine or first dose of a single-dose vaccine. Not fully vaccinated includes individuals either partially vaccinated (i.e., not fully vaccinated as per the definition) or not having ever received a COVID-19 vaccine. Fully vaccinated excludes those who went on to receive a booster.

Boosted: Defined as ≥14 days after receiving a 3rd dose (for those who completed an mRNA primary series) or a 2nd dose (for those who started with J&J).

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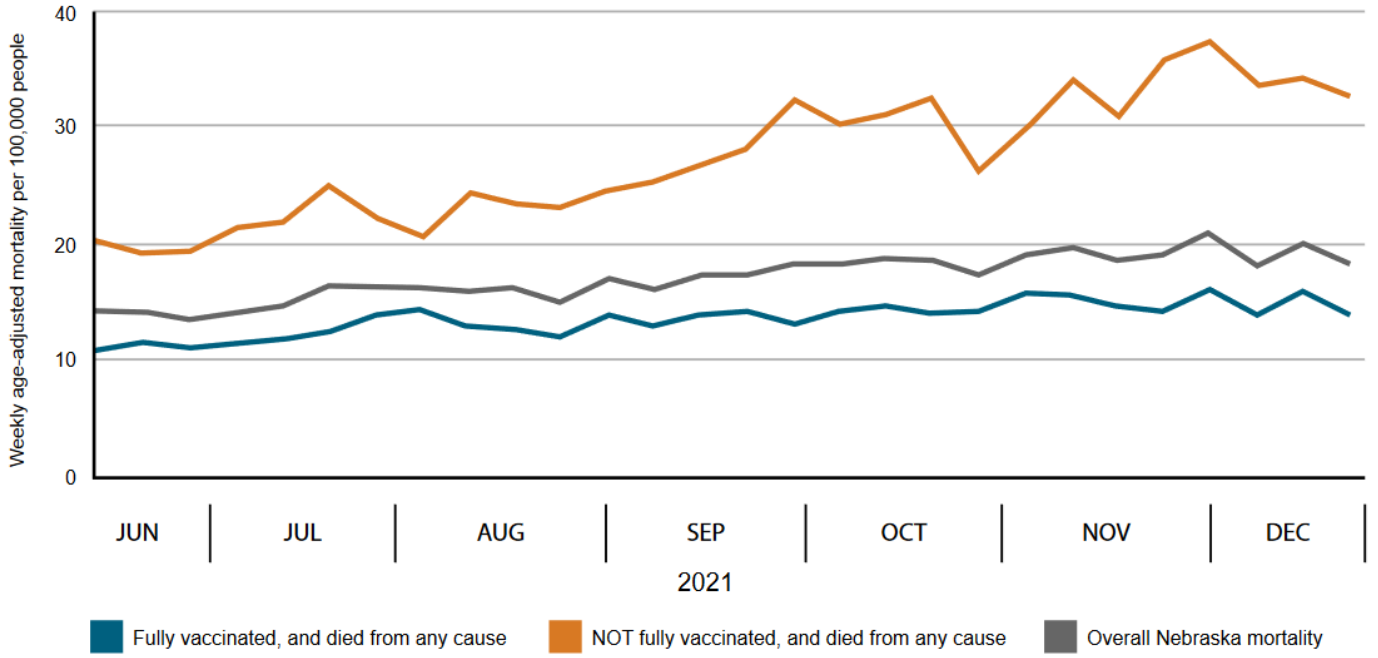
DEPT OF HEALTH AND HUMAN SERVICES

DHHS Epidemiology & Communications, Yi Du MPH MS, Sai Paritala PharmD MPH, Emily Bunch, and Matthew Donahue MD

DHHS-OTH-31 Rev. 1/11/2022

ALL-CAUSE MORTALITY AMONG NEBRASKANS, BY VACCINATION STATUS

People who are not fully vaccinated in Nebraska are dying at higher rates than fully vaccinated.
COVID-19 vaccinations are **safe** and are **preventing deaths**.



Deaths: Deaths were identified from Nebraska vital records death certificate data. A death certificate is completed for all Nebraskans who die in the state. Deaths from ANY cause were matched with Nebraska State Immunization Information System (NESIIS) vaccination data to identify mortality rates by vaccination status.

Fully vaccinated: Fully vaccinated is defined as ≥14 days after the second dose of a two-dose vaccine or first dose of a single-dose vaccine. For this analysis, boosted individuals are included. Not fully vaccinated includes individuals either partially vaccinated (i.e., not fully vaccinated as per the definition) or not having ever received a COVID-19 vaccine.

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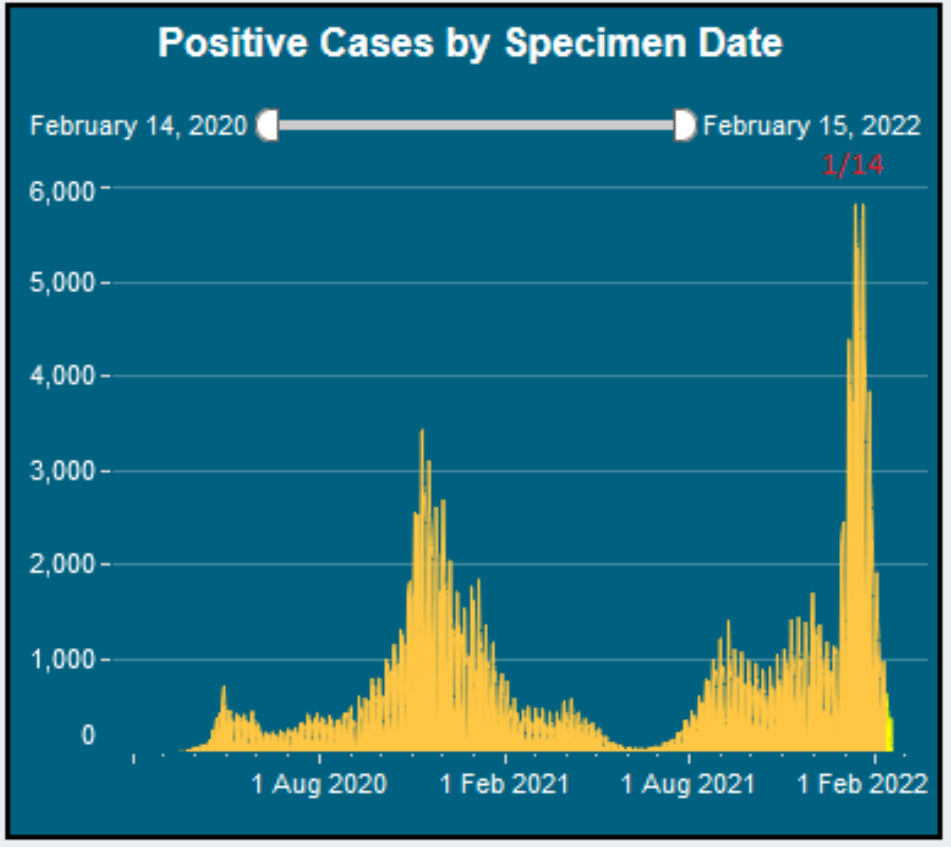
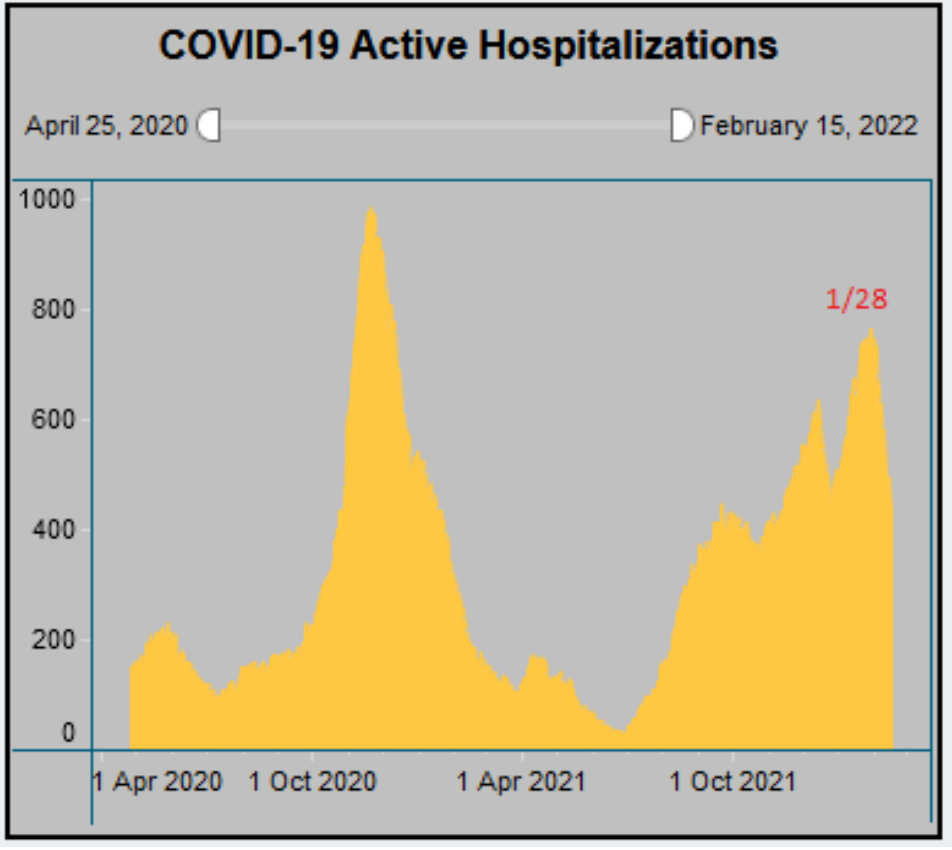
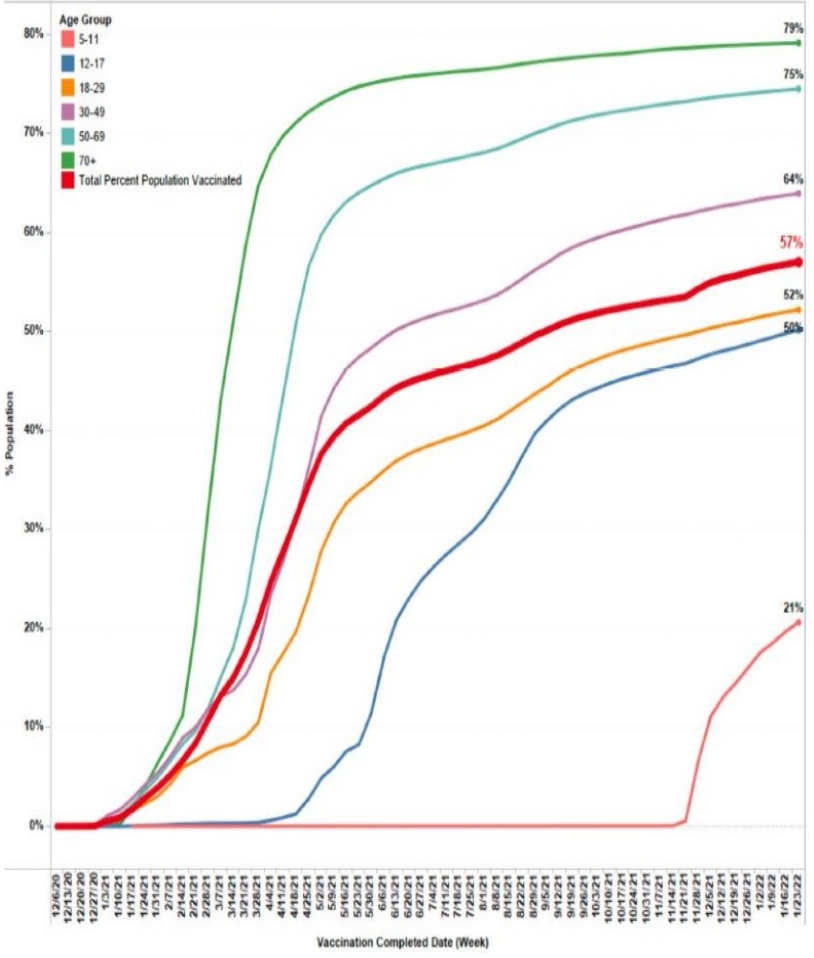
DHHS-OTH-33 1/11/2022


Positive Cases by Specimen Date
February 14, 2020
February 15, 2022
1/14
6,000
5,000
4,000
3,000
2,000
1,000
0
1 Aug 2020
1 Feb 2021
1 Aug 2021
1 Feb 2022


COVID-19 Active Hospitalizations
April 25, 2020
February 15, 2022
1000
800
600
400
200
0
1/28
1 Apr 2020
1 Oct 2020
1 Apr 2021
1 Oct 2021

Vaccinations

Cumulative % Population Fully Vaccinated Residents, by Age Group and Week, Nebraska
(Includes Pfizer 5-11 yr old fully vaccinated)



Total % Population Fully Vaccinated By LHD and Age Group
(Includes Pfizer 5-11 yr old fully vaccinated)

LHD short	5-11	12-17	18-29	30-49	50-69	70+	Grand Total
Central	13%	37%	48%	58%	73%	75%	51%
Dakota	4%	35%	47%	57%	72%	78%	48%
Douglas	29%	65%	64%	71%	80%	85%	63%
East Central	6%	26%	46%	58%	73%	78%	50%
Elkhorn Logan Valley	8%	30%	44%	56%	73%	79%	51%
Four Corners	12%	33%	38%	57%	73%	80%	52%
Lincoln/Lancaster	30%	67%	54%	76%	84%	87%	64%
Loup Basin	5%	18%	28%	39%	56%	63%	40%
North Central	5%	18%	30%	39%	54%	67%	40%
Northeast	8%	25%	30%	47%	60%	69%	40%
Panhandle	8%	24%	31%	43%	59%	68%	41%
Public Health Solutions	12%	37%	43%	54%	72%	81%	53%
Sarpy/Cass	26%	62%	60%	64%	78%	84%	60%
South Heartland	6%	24%	38%	52%	69%	77%	48%
Southeast	14%	40%	43%	55%	71%	74%	53%
Southwest	6%	17%	28%	40%	59%	67%	41%
Three Rivers	18%	43%	51%	62%	76%	80%	67%
Two Rivers	11%	37%	40%	57%	71%	78%	50%
West Central	6%	21%	31%	43%	59%	65%	41%
Grand Total	21%	50%	52%	64%	75%	79%	57%

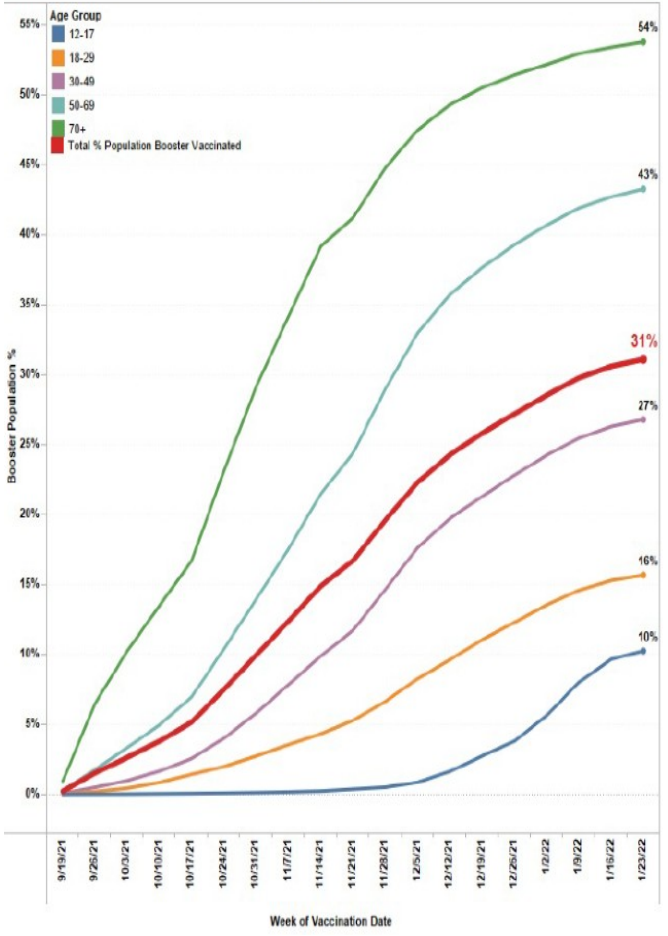
About the Data

Data Sources: Numerator is NESIIS Extract. Population data from CDC Bridged Race Population Estimates, 2019. Fully vaccinated is defined here as Nebraska residents who have received their 2nd dose of a 2 dose vaccine, or 1st dose of a 1 dose vaccine.

Note: Data are preliminary and may differ from local, state, or federal sources. Vaccinations administered outside the state of Nebraska or by federal partners (DOD, VA, IHS) are not included. Other vaccination data sources may use different population data to calculate rates. Therefore, vaccination rates here may be lower than rates posted on other sites.

Vaccinations (Boosters)

Cumulative % Population with Additional Booster Dose Administered, by Age Group and Week, Nebraska



Total % Population with Additional Booster Dose Administered, by LHD and Age Group

LHD short	12-17	18-29	30-49	50-69	70+	Grand Total
Central	5%	11%	19%	40%	51%	26%
Dakota	3%	6%	11%	32%	44%	19%
Douglas	15%	21%	32%	48%	58%	35%
East Central	2%	9%	18%	39%	51%	26%
Elkhorn Logan Valley	3%	9%	18%	39%	53%	27%
Four Corners	5%	9%	20%	41%	57%	29%
Lincoln/Lancaster	16%	19%	37%	55%	63%	38%
Loup Basin	2%	7%	13%	31%	43%	23%
North Central	2%	7%	13%	27%	42%	22%
Northeast	2%	8%	17%	32%	44%	22%
Panhandle	2%	6%	13%	29%	42%	21%
Public Health Solutions	4%	11%	20%	43%	58%	31%
Sarpy/Cass	15%	19%	28%	44%	52%	32%
South Heartland	3%	9%	19%	40%	55%	28%
Southeast	6%	10%	21%	42%	54%	30%
Southwest	1%	6%	11%	30%	44%	22%
Three Rivers	7%	14%	25%	45%	58%	33%
Two Rivers	4%	8%	19%	37%	52%	25%
West Central	2%	6%	13%	30%	43%	21%
Grand Total	10%	16%	27%	43%	54%	31%

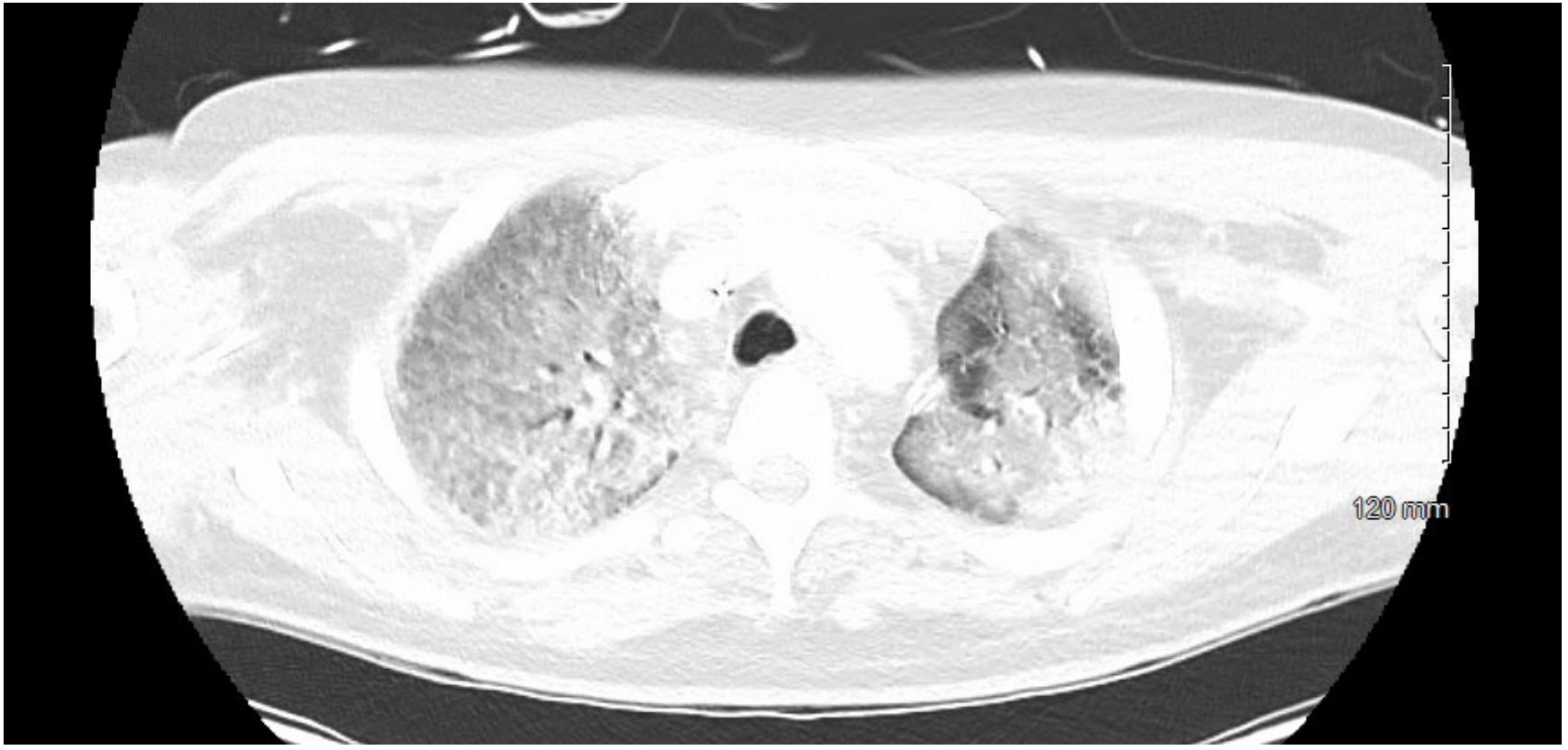
About the Data

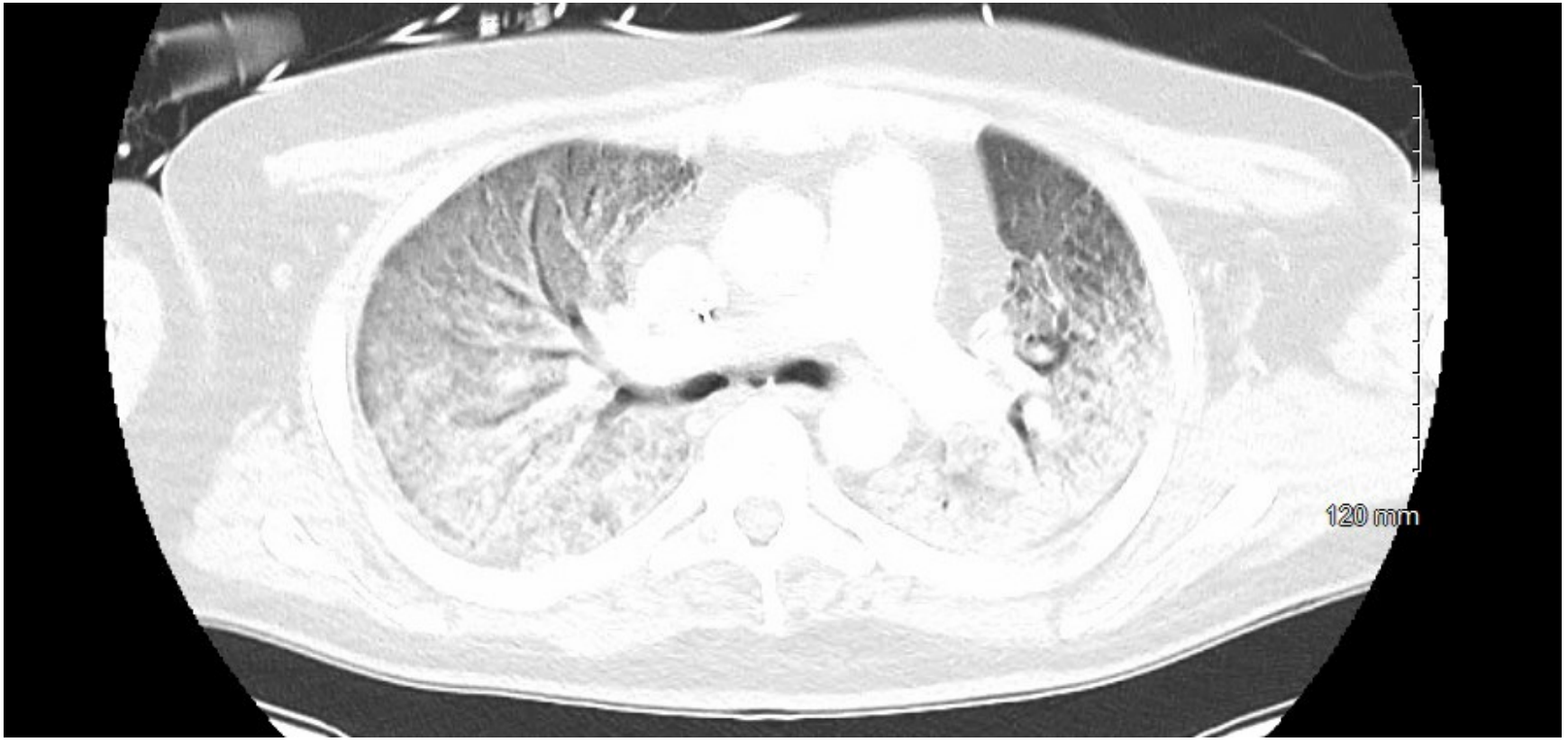
Data Sources: Numerator is NESIIS Extract. Population data from CDC Bridged Race Population Estimates, 2019. Data are preliminary and may differ from local, state, or federal sources. Vaccinations administered outside the state of Nebraska or by federal partners (DOD, VA, IHS) are not included. Other vaccination data sources may use different population data to calculate rates. Therefore, vaccination rates here may be lower than rates posted on other sites.

Booster dose is administered when a person has completed their vaccine series and protection against against virus has decreased over time. According to CDC, individuals who recieved a Pfizer-BioNTech or Moderna vaccine the following populations are eligible for a booster shot at 6 months or more after their initial series ->65 yr age group,>18 yrs living in long-term care setting, underlying medical conditons, residents in high-risk settings.For individuals, who received Janssen vaccine, booster shots are recommmended for >18 yrs who were vaccinated two months ago. The hete..

Credits

- State dashboard
  - Figure 3
- Department of HHS
  - Dr. Donahue
    - Figures 1-2, 4-5


120 mm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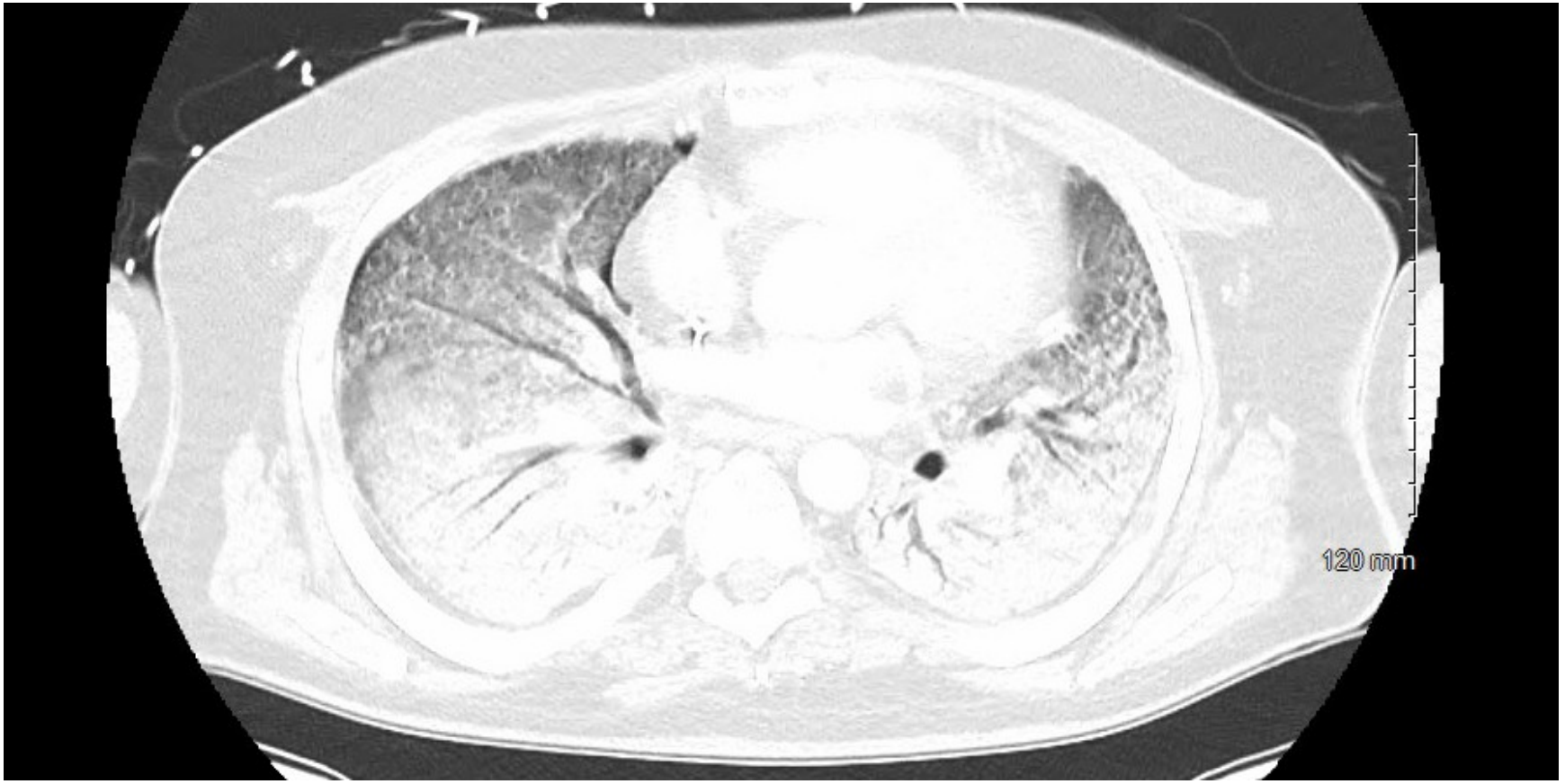

120 mm

Testing

Testing Options

- Direct viral tests
  - PCR (NAAT)
  - Antigen
- Serology tests
  - Antibody testing not typically recommended

Testing for Diagnosis

Examples of diagnostic testing include:

- Testing persons with symptoms consistent with COVID-19, whether or not they are up to date on their vaccinations.
- Testing persons as a result of contact tracing efforts.
- Testing persons who indicate that they had close contact exposure with someone suspected or confirmed as having COVID-19.

Testing for Screening

Examples of screening include:

- Testing employees in a workplace setting
- Testing students, faculty, and staff in a school or university setting
- Testing a person before or after travel
- Testing at home for someone who does not have symptoms associated with COVID-19 and no known exposures to someone with COVID-19

NAATs vs Antigen Tests

	NAATs	Antigen Tests
Intended Use	Diagnose *current* infection	Diagnose *current* infection
Analyte Detected	Viral Ribonucleic Acid (RNA)	Viral Antigens
Specimen Type(s)	Nasal, Nasopharyngeal, Oropharyngeal, Sputum, Saliva	Nasal, Nasopharyngeal

	NAATs	Antigen Tests
Sensitivity	Varies by test, but generally high for laboratory-based tests and moderate-to-high for POC tests	Varies depending on the course of infection, but generally moderate-to-high at times of peak viral load*
Specificity	High	High
Test Complexity	Varies by test	Relatively easy to use
Authorized for Use at the Point-of-Care	Most are not, some are	Most are, some are not
Turnaround Time	Most 1-3 days. Some could be rapid in 15 minutes	Ranges from 15 minutes to 30 minutes
Cost/Test^	Moderate (~$75-$100/test)	Low (~$5-$50/test)

	NAATs	Antigen Tests
Advantages	Most sensitive test method available Short turnaround time for NAAT POC tests, but few available Usually does not need to be repeated to confirm results	Short turnaround time (approximately 15 minutes)+ When performed at or near POC, allows for rapid identification of infected people, thus preventing further virus transmission in the community, workplace, etc. Comparable performance to NAATs for diagnosis in symptomatic persons and/or if culturable virus present

	NAATs	Antigen Tests
Disadvantages	Longer turnaround time for lab-based tests (1–3 days) Higher cost per test A positive NAAT diagnostic test should not be repeated within 90 days, because people may continue to have detectable RNA after risk of transmission has passed	May need confirmatory testing Less sensitive (more false negative results) compared to NAATs, especially among asymptomatic people and with some variants

Testing: Key Messages

- PCR (NAAT) testing is the most sensitive
  - May be required in some settings
- Antigen testing is rapid and convenient
  - Sensitivity fairly high in the setting of compatible illness and significant community transmission
  - Sensitivity may be improved by repeating tests

Resources

- CDC testing guidance
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html
- CDC isolation and quarantine for patients
  - https://www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html
- CDC work restrictions for HCP
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Freturn-to-work.html

Vaccines

Vaccines

- Current terminology from CDC
  - Fully vaccinated
    - When a person has received their complete primary series
  - Up to date
    - When a person has received all recommended vaccine doses including boosters
- Vaccine schedules are different for immunocompromised

FDA Status: Pfizer Vaccine

- FDA approval
  - for persons 16 and older: 2 part primary series
- EUA
  - Ages 5 to up to 16: 2 part primary series
  - Ages 5 and older for 3rd primary dose (immunocompromised)
  - Ages 12 and older booster (Pfizer primary series)
  - Ages 18 and older booster (non-Pfizer primary series)
- EUA is being sought for younger ages
  - 2 and older up to 5 years old (delayed)

FDA Status: Moderna Vaccine

- FDA approval
  - for persons 18 and older: 2 part primary series
- EUA
  - Ages 18 and older for 3rd primary dose (immunocompromised)
  - Ages 18 and older booster (Moderna primary series)
  - Ages 18 and older booster (non-Moderna primary series)

FDA Status: J & J Vaccine

- FDA approval
  - none
- EUA
  - Ages 18 and older for single primary series dose
  - Ages 18 and older as a single booster (2 or more months after primary J&J)
  - Ages 18 and older as a single booster (5 or more months after non J&J primary series)

Do I qualify for a COVID-19 vaccine booster and which one?

Which primary vaccine series did you complete?	Pfizer-BioNTech	Moderna	Janssen (J&J)
You can get a booster if:	It's been at least 5 months since completing a primary series AND you are:	It's been at least 5 months since completing a primary series AND you are:	It's been at least 2 months since completing primary vaccination AND you are:
	Age 12+	Age 18+	Age 18+
If eligible, you can get a booster of:	Pfizer-BioNTech* Moderna Janssen (J&J) *Only Pfizer-BioNTech can be used as a booster in those age 12-17.	Moderna Pfizer-BioNTech Janssen (J&J)	Janssen (J&J) Pfizer-BioNTech Moderna

For more information, visit www.fda.gov/covid19vaccines.

FDA U.S. FOOD & DRUG ADMINISTRATION

Different COVID-19 Vaccines

Updated Jan. 21, 2022 Languages Print

Approved or Authorized Vaccines

Three COVID-19 vaccines are authorized or approved for use in the United States to prevent COVID-19. Pfizer-BioNTech or Moderna (COVID-19 mRNA vaccines) are preferred. You may get Johnson & Johnson's Janssen COVID-19 vaccine in some situations.

- Pfizer-BioNTech
- Moderna
- Johnson & Johnson's Janssen

Vaccine Series: Not immunocompromised

Pfizer-BioNTech[1]	Moderna[1]	Johnson & Johnson's Janssen[1,2]
Ages Recommended 5+ years old	**Ages Recommended** 18+ years old	**Ages Recommended** 18+ years old
Primary Series 2 doses[3,4] Given 3 weeks (21 days) apart [5]	**Primary Series** 2 doses [3] Given 4 weeks (28 days) apart [5]	**Primary Series** 1 dose
Fully Vaccinated 2 weeks after final dose in primary series	**Fully Vaccinated** 2 weeks after final dose in primary series	**Fully Vaccinated** 2 weeks after 1st dose

Vaccine Series: Not immunocompromised

Pfizer-BioNTech[1]	Moderna[1]	Johnson & Johnson's Janssen[1,2]
Booster Dose Everyone ages 12+ should get a booster dose at least 5 months after the last dose in their primary series. • Teens 12–17 should only get a Pfizer-BioNTech COVID-19 Vaccine booster • Everyone 18+ should get a booster dose of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines)	**Booster Dose** Everyone ages 18+ should get a booster dose of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) at least 5 months after the last dose in their primary series.	**Booster Dose** Everyone ages 18+ should get a booster dose of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) at least 2 months after the first dose of J&J/Janssen COVID-19 Vaccine. You may get J&J/Janssen in some situations.

Vaccine Series:
Not immunocompromised

Pfizer-BioNTech[1]	Moderna[1]	Johnson & Johnson's Janssen[1,2]
When Boosted A person is considered "boosted" and **up to date** right after getting their booster dose.	**When Boosted** A person is considered "boosted" and **up to date** right after getting their booster dose.	**When Boosted** A person is considered "boosted" and **up to date** right after getting their booster dose.

Immunocompromised

Eligible For	IF YOU RECEIVED **Pfizer-BioNTech**	IF YOU RECEIVED **Moderna**	IF YOU RECEIVED **Johnson & Johnson's Janssen**
Additional Primary Shot	People **age 5+** who are moderately or severely immunocompromised **should** get an additional primary shot of Pfizer-BioNTech COVID-19 vaccine Given 28 days after 2nd shot	People age 18+ who are moderately or severely immunocompromised **should** get an additional primary shot of Moderna COVID-19 vaccine Given 28 days after 2nd shot	No additional primary shot is recommended at this time

Immunocompromised

Eligible For	IF YOU RECEIVED **Pfizer-BioNTech**	IF YOU RECEIVED **Moderna**	IF YOU RECEIVED **Johnson & Johnson's Janssen**
Booster Shot	• Teens **ages 12–17** should only get a Pfizer-BioNTech COVID-19 vaccine booster shot • People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 5 months after additional primary shot	People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 5 months after additional primary shot	People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 2 months after 1st shot

Immunocompromised

Who Is Moderately or Severely Immunocompromised?

People are considered to be moderately or severely immunocompromised if they have:

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking medicine to suppress the immune system
- Received a stem cell transplant within the last 2 years or are taking medicine to suppress the immune system
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress your immune response

Some Benefits of Vaccination

- Greatly reduced risk of serious illness or death
  - Reduced risk of long COVID and MIS-C
- Less likely to transmit to others
- No need to quarantine after exposure (if fully up to date on vaccines)
  - Should get tested at 5 days
  - Still need to mask for 10 days

Vaccines: Future Directions

- Omicron specific vaccine
- Vaccine targeting more conserved areas
- Purified protein vaccine (Novavax)
  - Approved in UK, many European countries

Vaccines: Key Messages

- Everyone 12 and older should be boosted
  - Up to date = fully vaccinated + boosted
- Anyone immunocompromised 5 and older should get 1 additional dose as part of the primary series
- mRNA vaccines are preferred

Vaccines: Resources

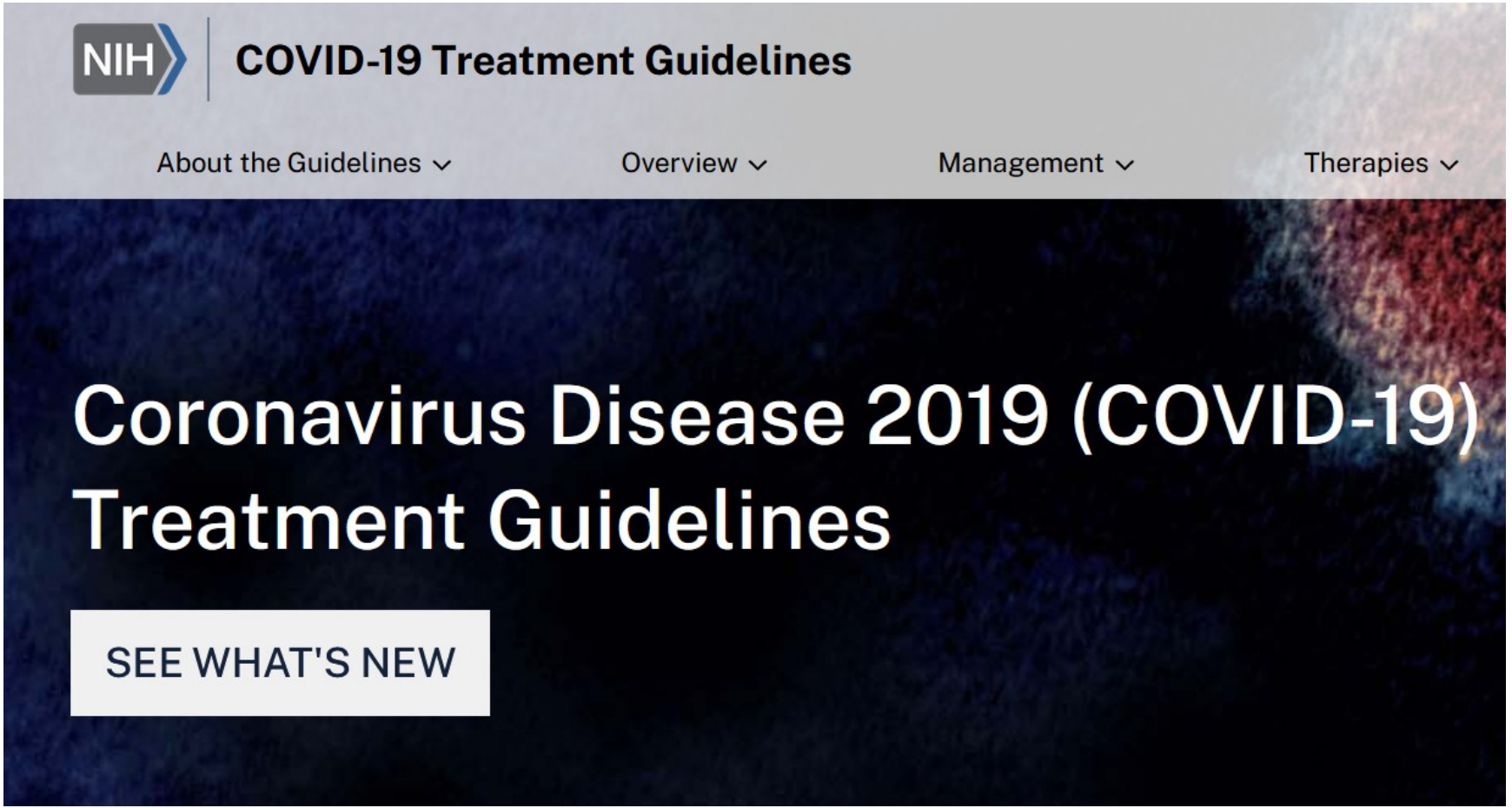
- CDC / ACIP
  - https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html
- FDA
  - https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines#authorized-vaccines

Outpatient Treatments

Outpatient Treatment Overview

- PrEP tixagevimab/cilgavimab (Evusheld)
- PEP Currently none
- Outpatient illness
  - 2 MABs sotrovimab, bebtelovimab
  - 3 ARVs remdesivir (IV only) (Veklury)
    nirmatrelvir/ritonovir (Paxlovid)
    monulpiravir

www.covid19treatmentguidelines.nih.gov



Prioritization of Treatment

- NIH guidelines have 4 tiers
  - TIER 1
    - Immunocompromised
    - Unvaccinated > 75 or > 65 with risk factors
  - TIER 2
    - Unvaccinated > 65 or < 65 with risk factors

Prioritization of Treatment

- NIH guidelines have 4 tiers
  - TIER 3
    - Vaccinated > 75 or > 65 with risk factors
  - TIER 4
    - Vaccinated > 65 or < 65 with risk factors

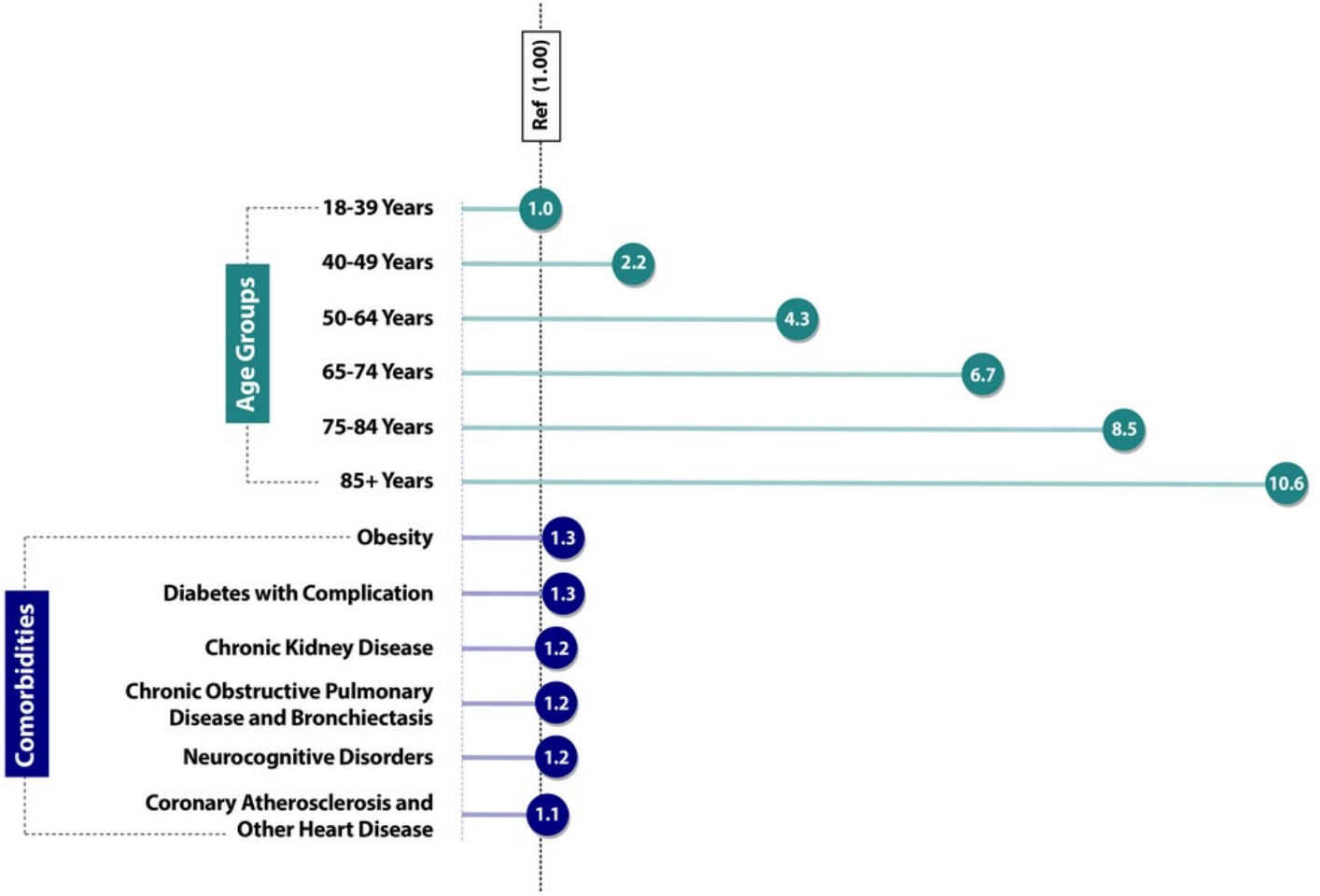
NIH Priority Immunocompromised Patients

- Patients who have received: B-cell depleting therapies (rituximab, etc), bruton tyrosine kinase inhibitors, chimeric antigen receptor T cells.
- Post-hematopoietic cell transplant recipients with GVHD or who are taking immunosuppressives for another reason. Patients with hematologic malignancies who are on active therapy.
- Lung transplant recipients. Patients within 1 year of receiving a solid-organ transplant (SOT) other than lung transplant. SOT with recent treatment for acute rejection with T or B cell depleting agents.
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV with CD4 count <50 cells/mm3
- www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies

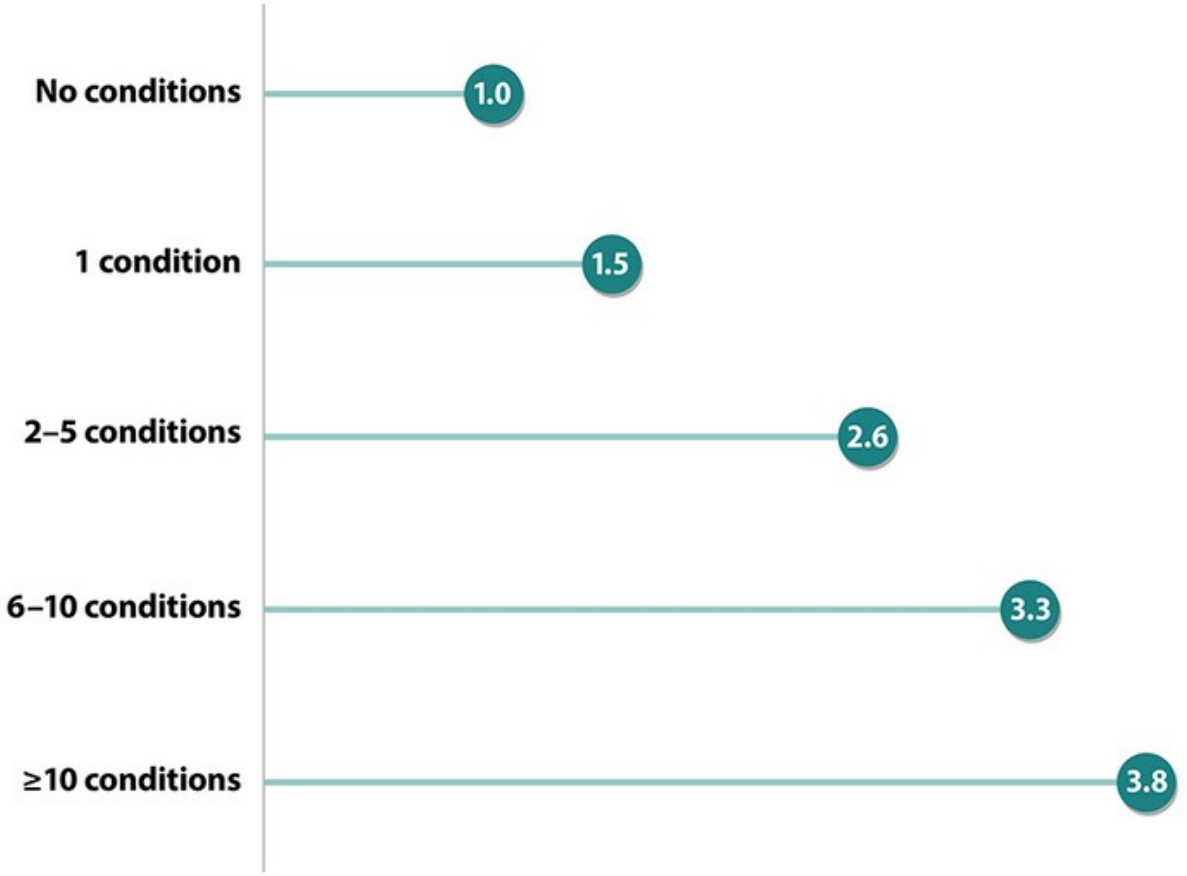
CDC COVID Risk Factors

- Cancer, cerebrovascular disease, CKD, certain chronic lung diseases, certain chronic liver diseases, diabetes type 1 or 2, certain heart conditions, certain mental health disorders, BMI >= 30, pregnancy and recent pregnancy, current of former smoking, TB
- www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

COVID-19 Death Risk Ratio (RR) for Select Age Groups and Comorbid Conditions



COVID-19 Death Risk Ratio (RR) Increases as the Number of Comorbid Conditions Increases



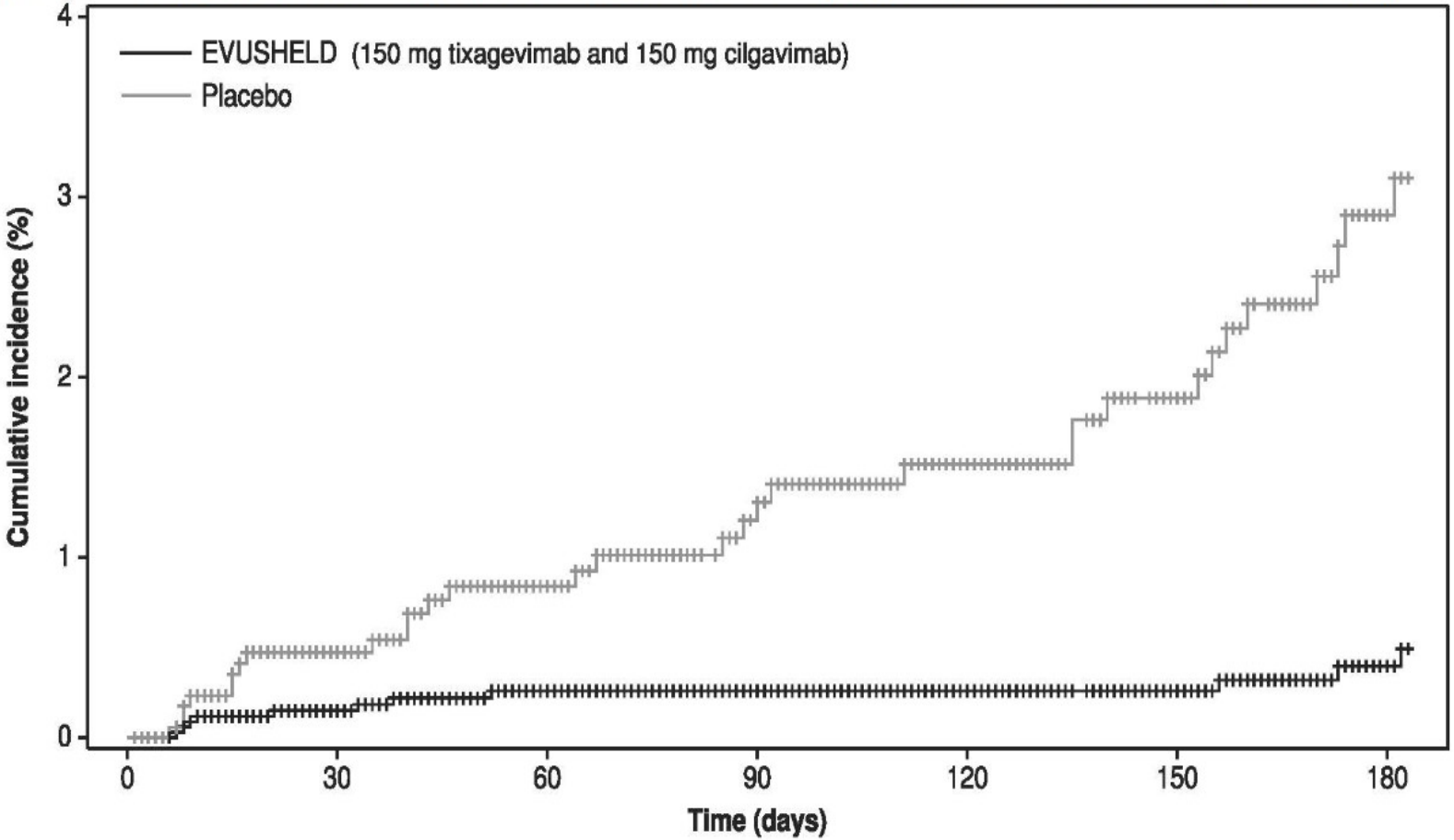
Monoclonal Antibodies

- Tixagevimab/cilgavimab (Evusheld)
  - PrEP ONLY!
- Sotrovimab
- Bebtelovimab

Tixagevimab/Cilgavimab (Evusheld)

- EUA age 12 and older, > 40 kg
- PrEP (pre-exposure prophylaxis)
- PROVENT trial (not yet published)
  - 77% reduction of symptomatic COVID
    - No severe COVID or deaths in treatment arm
      (vs 3 cases severe COVID and 2 deaths in placebo arm)
  - Active against Delta with in-vitro Omicron activity

Figure 1 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (PROVENT)



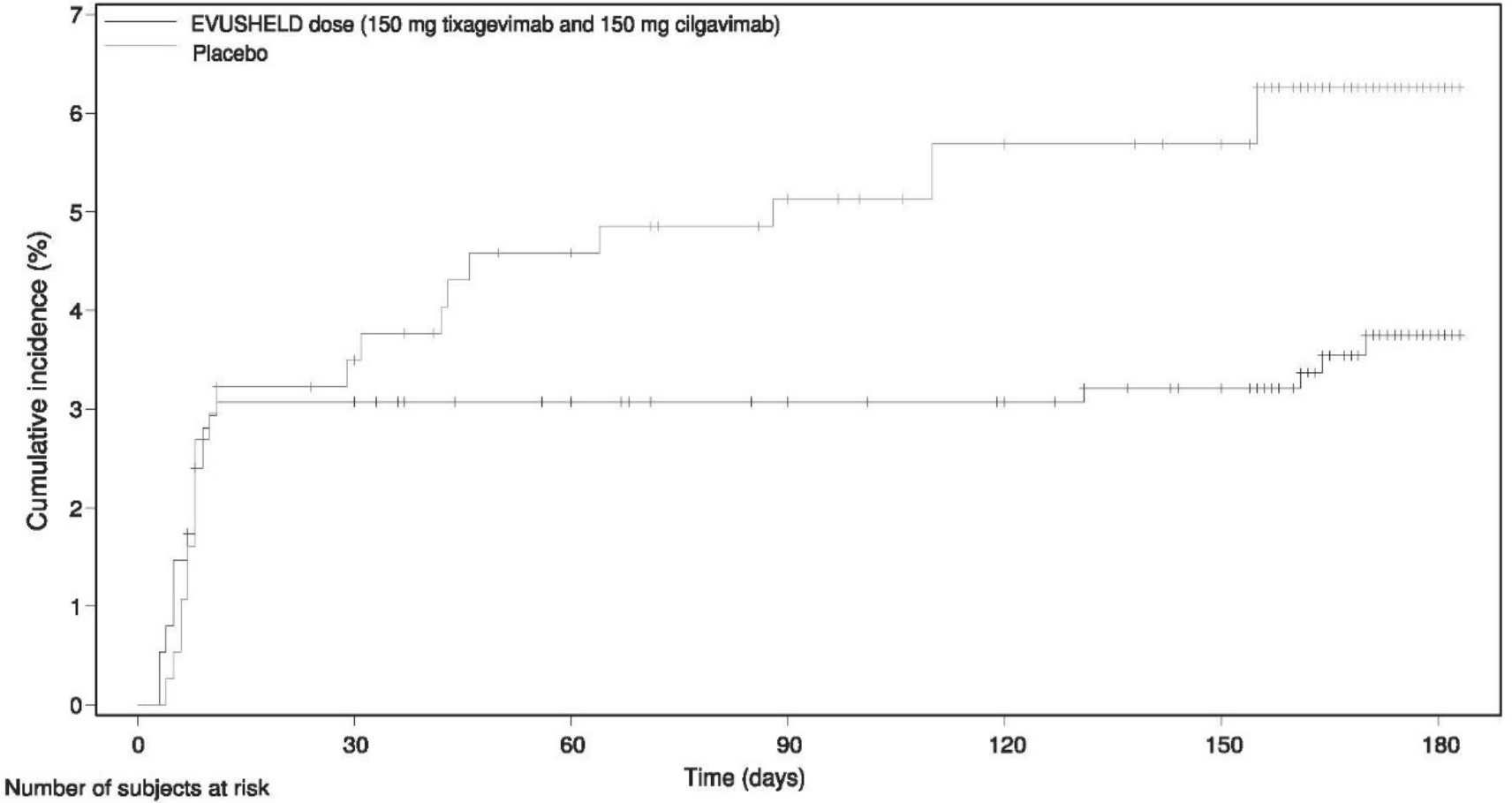
Number of participants at risk

EVUSHELD	3441	2957	2393	2054	1815	1667	1044
Placebo	1731	1483	1177	991	856	774	472

Tixagevimab/Cilgavimab (Evusheld)

- Post exposure prophylaxis?
- STORM CHASER trial
  - Double blind, RCT with 1,142 patients enrolled
  - Possible COIVD exposure within 8 days
- No risk reduction seen in 1st 30 days

Figure 2 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (STORM CHASER)



Tixagevimab/Cilgavimab (Evusheld)

- Outpatient administration (every 6 months?)
  - 2 gluteal injections, one after the other
  - One hour wait
- Risk stratification
  - Categories 1-4
- RENAL no restrictions
- PREGNANCY risk unknown
- Give at least 2 weeks after most recent vaccine dose

Sotrovimab

- Active against Omicron
  - 85% risk reduction
  - EUA Ages 12 and older
    - Start within 10 days of symptom onset
  - RENAL no restrictions
  - PREGNANCY risk unknown
  - MAJOR PROBLEM limited availability

Bebtelovimab

- EUA granted on “totality of Phase 2 data”
- EUA requirements
  - Positive test
  - High risk of progression
  - No alternatives available or apporpriate
- 2 mL IV infusion

Babtelovimab

- Presumed to be active against Omicron
  - EUA Ages 12 and older
    - Start within 7 days of symptom onset
  - RENAL no restrictions
  - PREGNANCY risk unknown
  - MAJOR PROBLEM limited availability and data

Antiviral Therpaies

- Remdesivir
- Nirmatrelvir/Ritonovir (Paxlovid)
- Monulpiravir

Remdesivir

- Inpatient and outpatient use
  - FDA approved age 12 and older (>40 kg)
    - Outpatient off-label use acceptable
    - NIH guidelines: start within 7 days of symptom onset
  - EUA for age < 12 and weight > 3.5 kg
    - Hospitalized patients
    - Outpatients with mild to moderate COVID and high risk of progression

PINETREE Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 27, 2022 VOL. 386 NO. 4

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

The NEW ENGLAND JOURNAL of MEDICINE

Early Remdesivir to Prevent Progression to Severe Covid-19

DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

562
Outpatients with Covid-19,
<7 days from symptom onset and with
≥1 risk factor for disease progression

Covid-related hospitalization or death from any cause by day 28

N=279	N=283
Intravenous Remdesivir, 3 days	Placebo
0.7% (2 patients)	5.3% (15 patients)

HR, 0.13; 95% CI, 0.03–0.59 (P=0.008)

Remdesivir resulted in an 87% lower risk of Covid-related hospitalizations or death than placebo and had an acceptable safety profile.

R.L. Gottlieb et al. 10.1056/NEJMoa2116846

Remdesivir

- Outpatient dosing once daily x 3 days
  - Start within 7 days of symptom onset
  - 200 mg on day 1, 100 mg on days 2 and 3
  - Limited to high risk patients only at present
  - RENAL limited
  - PREGNANCY risk/benefit ratio appears favorable
  - MAJOR PROBLEMS
    - 3 days of infusions AND insurance coverage

Nirmatrelvir / Ritonovir (Paxlovid)

- EUA age 12 and older, > 40 kg
  - Start within 5 days of symptom onset
- 3 tablets BID x 5 days
  - two 150 mg nirmatrelvir + one 100 mg ritonovir
- RENAL limited
- PREGNANCY nirmatrelvir risk unknown
- MAJOR PROBLEM drug interactions

Drug Interactions

- Ritonavir is a potent CYP 3A inhibitor
  - Also a substrate
- For medications that are CYP 3A substrates
  - Ritonavir can greatly increase concentration
  - Example: amiodarone
- Beware of CYP 3A inducers
  - Will rapidly metabolize ritonavir
  - Paxlovid will never achieve therapeutic range
  - Example: rifampin

Drug Interactions

- RED LIGHT – do not use
- YELLOW LIGHT – possibly use
  NEED TO CHECK DRUG INTERACTION DATABASE
- GREEN LIGHT – safe to use

Red Light Interactions

Amiodarone, Apalutamide, Bosentan, Carbamazepine, Cisapride, Clopidogrel, Clozapine, Colchicine (patients with renal and/or hepatic impairment), Disopyramide, Dofetilide, Dronedarone, Eplerenone, Ergot derivatives, Flecainide, Flibanserin, Glecaprevir/pibrentasvir, Ivabradine, Lumateperone, Lurasidone, Mexiletine, Phenobarbital, Phenytoin, Pimozide, Propafenone, Quinidine, Ranolazine, Rifampin, Rifapentine, Rivaroxaban, Sildenafil (for pulmonary hypertension), St. John’s wort, Tadalafil(for pulmonary hypertension), Ticagrelor, Vorapaxar

Yellow Light Interactions

Alfuzosin, Alprazolam, Atorvastatin, Avanafil, Clonazepam, Codeine, Cyclosporineb, Diazepam, Everolimusb, Fentanyl, Hydrocodone, Lomitapide, Lovastatin, Meperidine (pethidine), Midazolam(oral), Oxycodone, Piroxicam, Propoxyphene, Rosuvastatin, Salmeterol, Sildenafil for erectile dysfunction, Silodosin, Simvastatin, Sirolimusb, Suvorexant, Tacrolimusb, Tadalafil for erectile dysfunction, Tamsulosin, Tramadol, Triazolam, Vardenafil

www.covid19treatmentguidelines.nih.gov

Highlighted Sections

Therapeutic Management of Nonhospitalized Adults With COVID-19

The Panel has added information from both the statement on therapies for high-risk, nonhospitalized patients and the statement on patient prioritization for outpatient therapies.

Prevention of SARS-CoV-2 Infection

This section now includes information from the Panel's statement on using tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP).

Statement on Anticoagulation in Hospitalized Patients

This statement contains the Panel's recommendations on using anticoagulation in hospitalized, nonpregnant adults with COVID-19 who are receiving supplemental oxygen.

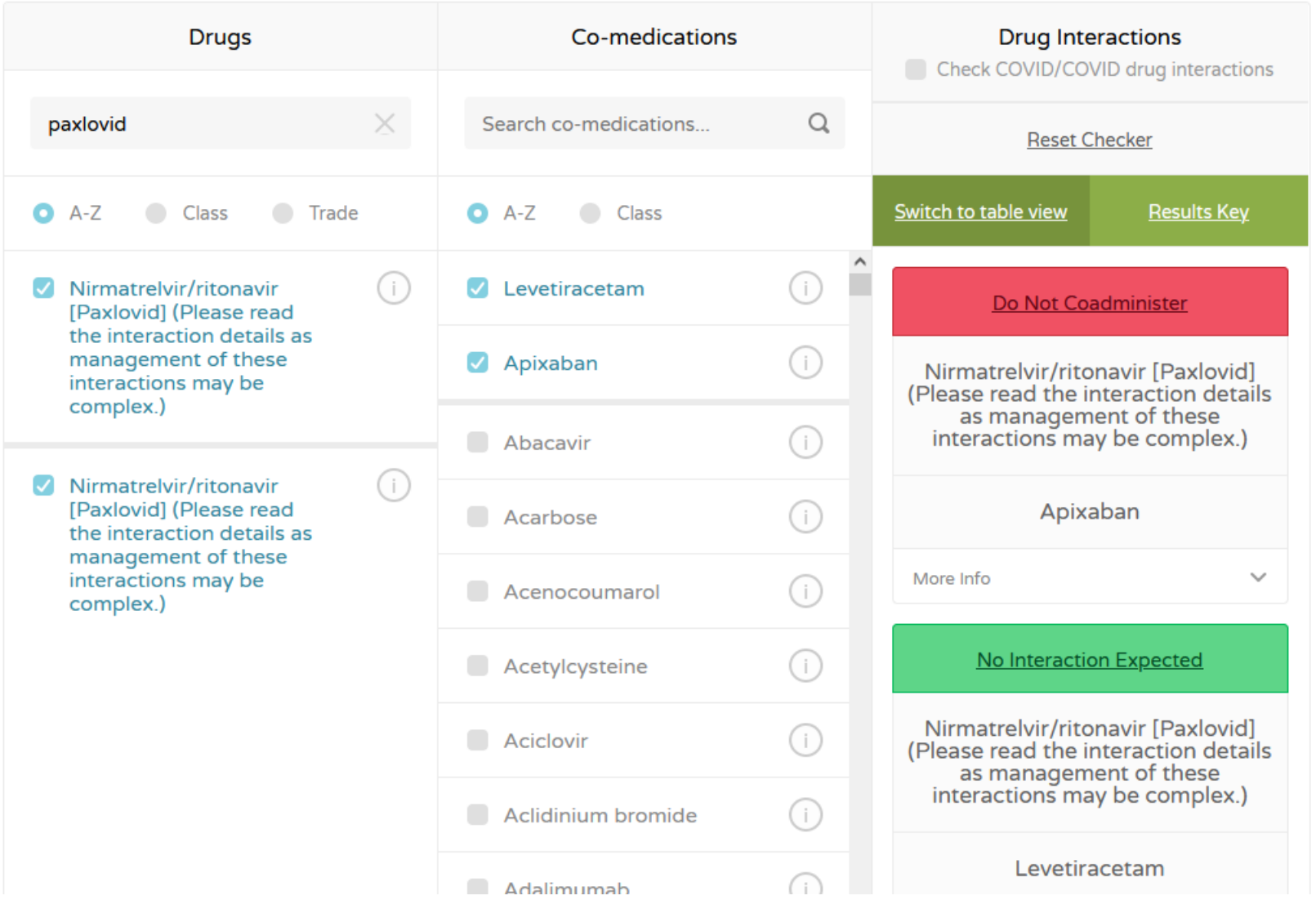
Statement on Paxlovid Drug-Drug Interactions

This statement highlights the importance of evaluating a patient's medication regimen for potentially serious drug-drug interactions before prescribing ritonavir-boosted nirmatrelvir (Paxlovid).

Prescribe an alternative COVID-19 therapy for patients who are receiving any of the medications listed.	Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid), determine whether the patient is receiving any of the medications listed. • If the patient is receiving any of these medications, withhold the medication if clinically appropriate. • If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.[a]
• Amiodarone • Apalutamide • Bosentan • Carbamazepine • Cisapride • Clopidogrel	• Alfuzosin • Alprazolam • Atorvastatin • Avanafil • Clonazepam • Codeine

Drug Interaction Checker

- UpToDate
- University of Liverpool
  - https://www.covid19-druginteractions.org/checker


Drugs
Co-medications
Drug Interactions
Check COVID/COVID drug interactions
paxlovid
Search co-medications...
Reset Checker
A-Z
Class
Trade
A-Z
Class
Switch to table view
Results Key
Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Levetiracetam
Apixaban
Abacavir
Acarbose
Acenocoumarol
Acetylcysteine
Aciclovir
Aclidinium bromide
Adalimumab
Do Not Coadminister
Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Apixaban
More Info
No Interaction Expected
Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Levetiracetam

10 Most Common US Prescriptions

- GoodRx top 10
  - Atorvastatin, lisinopril, albuterol, levothyroxine amlodipine, gabapentin, omeprazole, metformin, losartan, APAP/hydrocodone
- No significant interactions with Paxlovid
  - Lisinopril, albuterol, levothyroxine, gabapentin, omeprazole, metformin, losartan

Molnupiravir

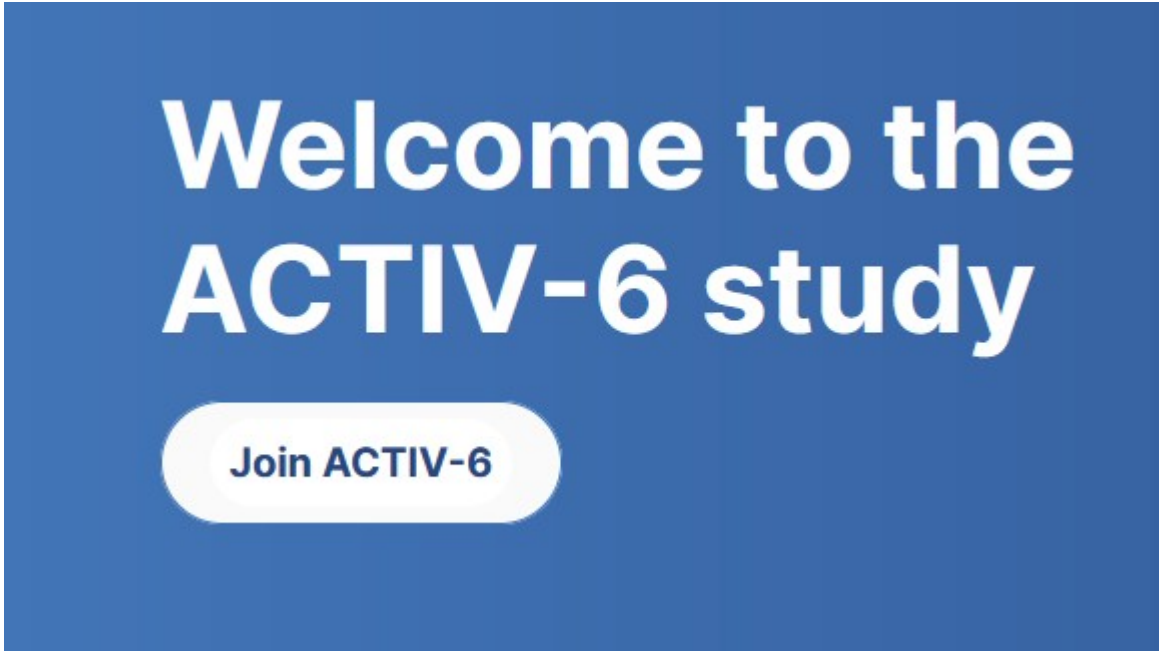
- EUA age 18 and older
  - Start within 5 days of symptom onset
- 800 mg BID x 5 days
  - four 200 mg capsules every 12 hours
- RENAL no restrictions
- PREGNANCY human risk unknown but may be harmful based on animal data
- MAJOR PROBLEMS: lower efficacy, mutagenic risk (low)

Guidelines & Obstacles

- Following NIH guidelines
  - Consistent messaging
  - Less confusion to patients
- Problems
  - Shortages
  - Mild-moderate symptoms, lower risk
    - Clinical trial

https://activ6study.org/

1-833-385-1880



You can participate from anywhere In the United States!

ACTIV-6 is a nationwide double-blind study expected to enroll nearly 15,000 participants. People can participate in ACTIV-6 from anywhere in the United States via the ACTIV-6 website or call center, 833-385-1880.

Researchers at sites across the United States are participating in study, with new sites being added each week.

Locate a site near me:

ZIP / Address: 68506

Search

Please note: You may participate from anywhere in the United States, even if there is no site near your location.

Resources

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

Key Messages: Therapies

- Preferred outpatient options
  - Sotrovimab (IV)
  - Nirmatrelvir / Ritonovir (Paxlovid) (oral)
- PrEP for at risk patients
  - Tixagevimab/Cilgavimab (Evusheld)

Final Comments

Post-COVID Anosmia

- Meta-analysis of 27,000 patients found 48% had periods of olfactory dysfunction
  - Rarely the only COVID symptom
- Recovery may take months
  - Full recovery at 4 months (84%) and 8 months (96%)

Post-COVID Anosmia

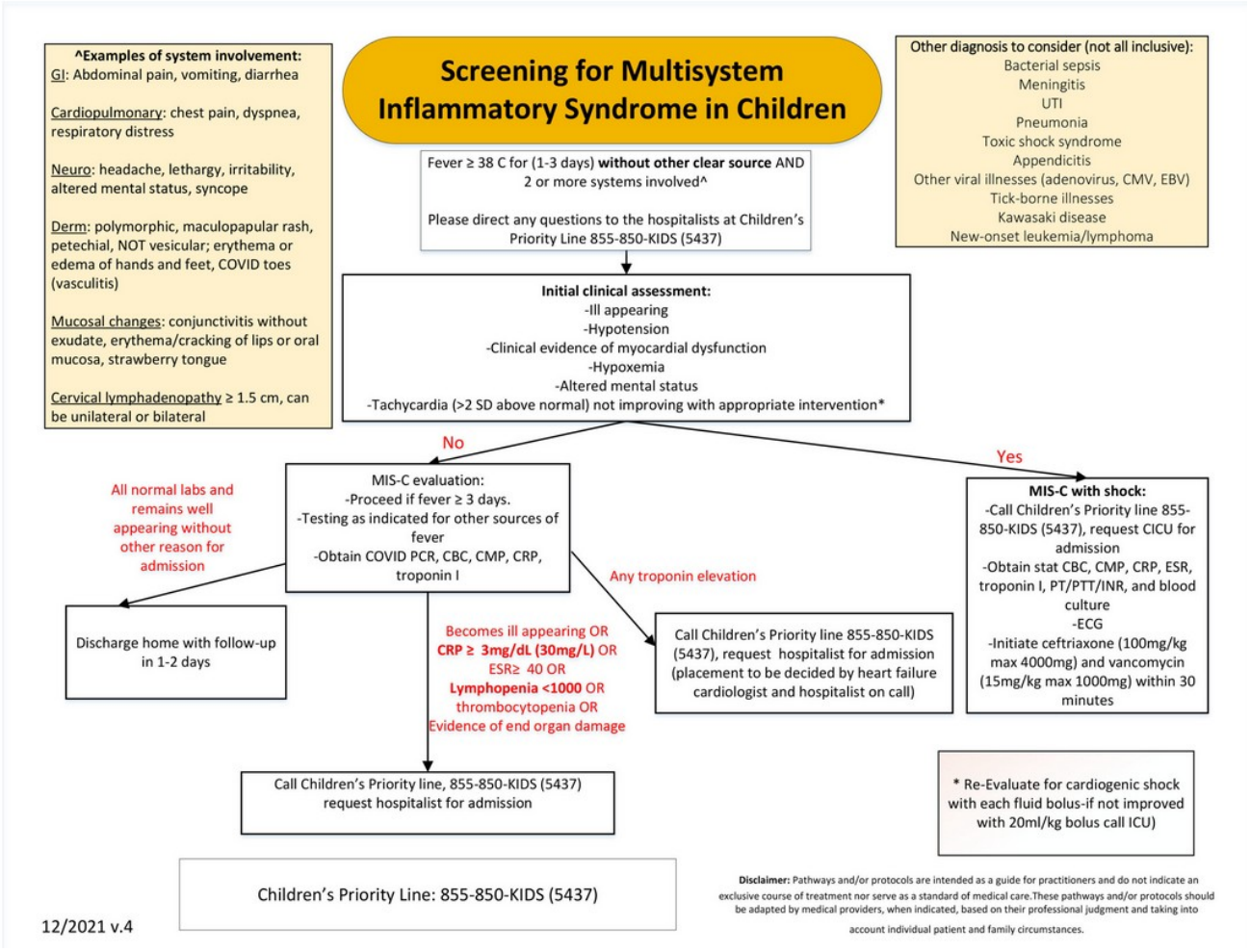
- Smell Retraining Therapy (SRT) may help to speed up recovery
  - Rose, lemon, cloves, eucalyptus scents
  - 1-2 times per day, 10-20 seconds per scent
    12 weeks
- Links
  - https://www.enthealth.org/be_ent_smart/smell-retraining-therapy/
  - Web search for “Smell training kits”

MIS-C

- Multisystem Inflammatory Syndrome in Children
  - Incomplete Kawasaki disease / toxic shock
- US statistics
  - Over 7,000 children, 59 deaths
  - 1 in 3200 childhood cases
  - 98% of hospitalized MIS-C cases were unvaccinated

MIS-C

- Children’s Hospital in Omaha
  - MIS-C Screening algorithm
  - https://www.childrensomaha.org/for-providers/for-providers-covid-19-mis-c-testing-at-childrens/
- CDC COCA call 2/10/22
  - https://emergency.cdc.gov/coca/calls/2022/callinfo_021022.asp


^Examples of system involvement:
GI: Abdominal pain, vomiting, diarrhea
Cardiopulmonary: chest pain, dyspnea, respiratory distress
Neuro: headache, lethargy, irritability, altered mental status, syncope
Derm: polymorphic, maculopapular rash, petechial, NOT vesicular; erythema or edema of hands and feet, COVID toes (vasculitis)
Mucosal changes: conjunctivitis without exudate, erythema/cracking of lips or oral mucosa, strawberry tongue
Cervical lymphadenopathy ≥ 1.5 cm, can be unilateral or bilateral
Screening for Multisystem Inflammatory Syndrome in Children
Other diagnosis to consider (not all inclusive):
Bacterial sepsis
Meningitis
UTI
Pneumonia
Toxic shock syndrome
Appendicitis
Other viral illnesses (adenovirus, CMV, EBV)
Tick-borne illnesses
Kawasaki disease
New-onset leukemia/lymphoma
Fever ≥ 38 C for (1-3 days) without other clear source AND 2 or more systems involved^
Please direct any questions to the hospitalists at Children's Priority Line 855-850-KIDS (5437)
Initial clinical assessment:
-Ill appearing
-Hypotension
-Clinical evidence of myocardial dysfunction
-Hypoxemia
-Altered mental status
-Tachycardia (>2 SD above normal) not improving with appropriate intervention*
No
Yes
All normal labs and remains well appearing without other reason for admission
MIS-C evaluation:
-Proceed if fever ≥ 3 days.
-Testing as indicated for other sources of fever
-Obtain COVID PCR, CBC, CMP, CRP, troponin I
Any troponin elevation
MIS-C with shock:
-Call Children's Priority line 855-850-KIDS (5437), request CICU for admission
-Obtain stat CBC, CMP, CRP, ESR, troponin I, PT/PTT/INR, and blood culture
-ECG
-Initiate ceftriaxone (100mg/kg max 4000mg) and vancomycin (15mg/kg max 1000mg) within 30 minutes
Discharge home with follow-up in 1-2 days
Becomes ill appearing OR
CRP ≥ 3mg/dL (30mg/L) OR
ESR≥ 40 OR
Lymphopenia <1000 OR
thrombocytopenia OR
Evidence of end organ damage
Call Children's Priority line 855-850-KIDS (5437), request hospitalist for admission (placement to be decided by heart failure cardiologist and hospitalist on call)
Call Children's Priority line, 855-850-KIDS (5437) request hospitalist for admission
* Re-Evaluate for cardiogenic shock with each fluid bolus-if not improved with 20ml/kg bolus call ICU)
Children's Priority Line: 855-850-KIDS (5437)
Disclaimer: Pathways and/or protocols are intended as a guide for practitioners and do not indicate an exclusive course of treatment nor serve as a standard of medical care.These pathways and/or protocols should be adapted by medical providers, when indicated, based on their professional judgment and taking into account individual patient and family circumstances.
12/2021 v.4

Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12–18 Years — United States, July–December 2021

Weekly / January 14, 2022 / 71(2);52–58

On January 7, 2022, this report was posted online as an MMWR *Early Release.*

Laura D. Zambrano, PhD[1,*]; Margaret M. Newhams, MPH[2,*]; Samantha M. Olson, MPH[1]; Natasha B. Halasa, MD[3]; Ashley M. Price, MPH[1]; Julie A. Boom, MD[4]; Leila C. Sahni, PhD[4]; Satoshi Kamidani, MD[5]; Keiko M. Tarquinio, MD[6]; Aline B. Maddux, MD[7]; Sabrina M. Heidemann, MD[8]; Samina S. Bhumbra, MD[9]; Katherine E. Bline, MD[10]; Ryan A. Nofziger, MD[11]; Charlotte V. Hobbs, MD[12]; Tamara T. Bradford, MD[13]; Natalie Z. Cvijanovich, MD[14]; Katherine Irby, MD[15]; Elizabeth H. Mack, MD[16]; Melissa L. Cullimore, MD[17]; Pia S. Pannaraj, MD[18]; Michele Kong, MD[19]; Tracie C. Walker, MD[20]; Shira J. Gertz, MD[21]; Kelly N. Michelson, MD[22]; Melissa A. Cameron, MD[23]; Kathleen Chiotos, MD[24]; Mia Maamari, MD[25]; Jennifer E. Schuster, MD[26]; Amber O. Orzel, MPH[2]; Manish M. Patel, MD[1]; Angela P. Campbell, MD[1,†]; Adrienne G. Randolph, MD[2,27,†]; Overcoming COVID-19

COVID-19 vaccination protects against multisystem inflammatory syndrome in children (MIS-C) among 12–18 year-olds hospitalized during July–December 2021

Vaccination reduced likelihood of MIS-C by:

ADOLESCENTS HOSPITALIZED WITH MIS-C

95% unvaccinated

No vaccinated MIS-C patients required life support

COVID-19 VACCINATION IS THE BEST PROTECTION AGAINST MIS-C

* Case-control study, 238 patients in 24 pediatric hospitals—30 U.S. states
† 2 doses of Pfizer-BioNTech vaccine received ≥28 days before hospital admission

bit.ly/MMWR7102

MMWR

Mask Effectiveness

Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Effectiveness of Face Mask or Respirator Use in Indoor Public Settings for Prevention of SARS-CoV-2 Infection — California, February–December 2021

Weekly / February 11, 2022 / 71(6);212–216

On February 4, 2022, this report was posted online as an MMWR *Early Release.*

Kristin L. Andrejko[1,2,*]; Jake M. Pry, PhD[2,*]; Jennifer F. Myers, MPH[2]; Nozomi Fukui[2]; Jennifer L. DeGuzman, MPH[2]; John Openshaw, MD[2]; James P. Watt, MD[2]; Joseph A. Lewnard, PhD[1,3,4]; Seema Jain, MD[2]; California COVID-19 Case-Control Study Team (View author affiliations)

MMWR Feb 2022

- Randomly selected CA residents tested for SARS-CoV-2 during a 9.5 month period in 2021
- Mask use was assessed among cases (positive tests) and matched controls (negative tests)
- Primary analysis compared self-reported mask use in indoor public settings 14 days before testing

Frequency of Use vs Risk

TABLE 2. Face mask or respirator use in indoor public settings among persons with positive and negative SARS-CoV-2 test results — California, February–December 2021

Return

Mask type and use*	SARS-CoV-2 infection status, no. (%)		Odds ratio (95% CI)	
	Positive (case-participant) N = 652	Negative (control-participant) N = 1,176	Unadjusted† [p-value]	Adjusted§ [p-value]
None (Ref)	44 (6.7)	42 (3.6)	—	—
Any use¶	608 (93.3)	1,134 (96.4)	0.57 (0.37–0.90) [0.02]	0.51 (0.29–0.93) [0.03]
Some of the time	62 (9.5)	76 (6.5)	0.81 (0.47–1.41) [0.49]	0.71 (0.35–1.46) [0.36]
Most of the time	153 (23.5)	239 (20.3)	0.64 (0.40–1.05) [0.08]	0.55 (0.29–1.05) [0.07]
All of the time	393 (60.3)	819 (69.6)	0.49 (0.31–0.78) [<0.01]	0.44 (0.24–0.82) [<0.01]

Type of Mask vs Risk

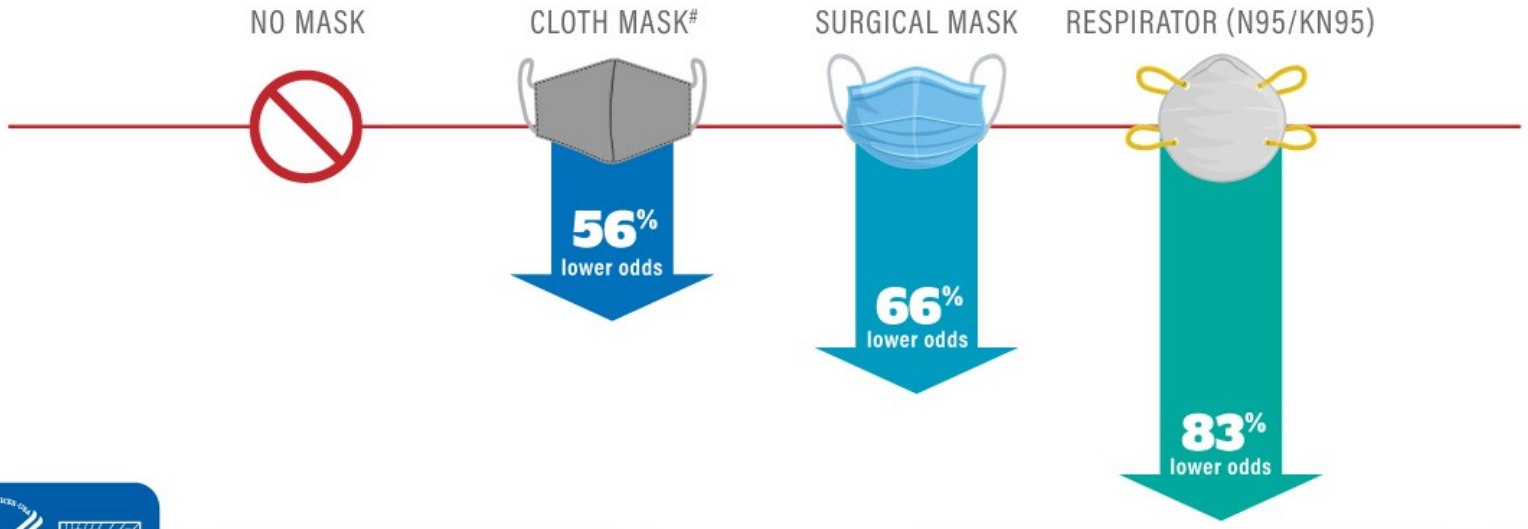
TABLE 3. Types of face mask or respirator worn in indoor public settings among persons with positive or negative SARS-CoV-2 test results — California, September–December 2021

Mask type*	SARS-CoV-2 infection status, no. (%)		Odds ratio (95% CI)	
	Positive (case-participant) N = 259	Negative (control-participant) N = 275	Unadjusted† [p-value]	Adjusted§ [p-value]
None (Ref)	24 (9.3)	11 (4.0)	—	—
Cloth mask	112 (43.2)	104 (37.8)	0.50 (0.23–1.06) [0.07]	0.44 (0.17–1.17) [0.10]
Surgical mask	113 (43.6)	139 (50.5)	0.38 (0.18–0.81) [0.01]	0.34 (0.13–0.90) [0.03]
N95/KN95 respirator	10 (3.9)	21 (7.6)	0.22 (0.08–0.62) [<0.01]	0.17 (0.05–0.64) [<0.01]

People who reported always wearing a mask in indoor public settings were less likely to test positive for COVID-19 than people who didn't*

WEARING A MASK LOWERED THE ODDS OF TESTING POSITIVE

Among 534 participants reporting mask type†



bit.ly/MMWR7106

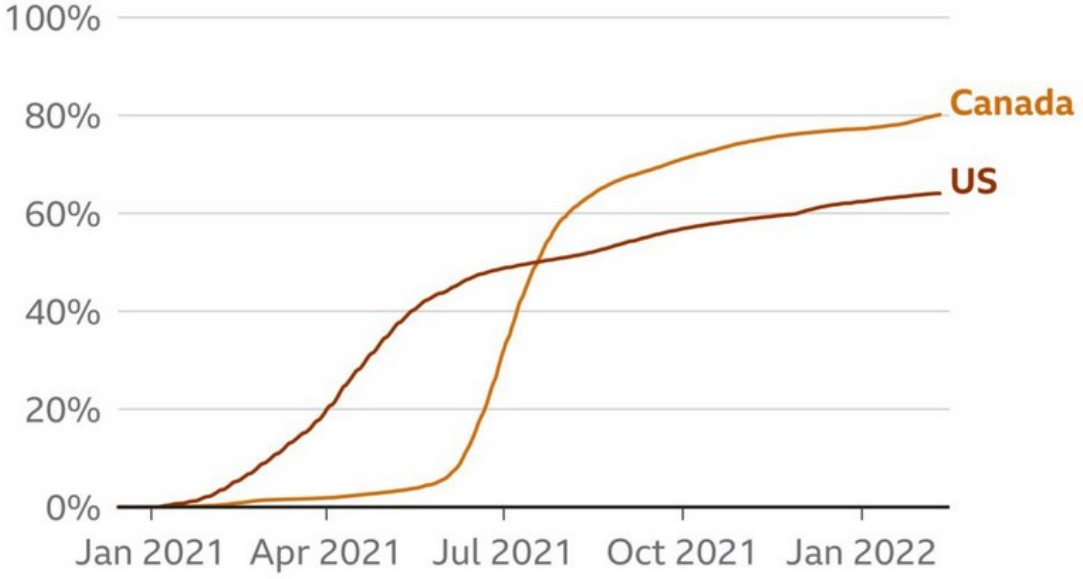
* Matched case-control study, 1,828 people, Feb 10–Dec 1, 2021
† Compared people with similar characteristics (e.g., vaccination)
# Not statistically significant

MMWR

Team USA vs Canada

Share of population fully vaccinated

Proportion of people fully vaccinated by date since Dec 2020

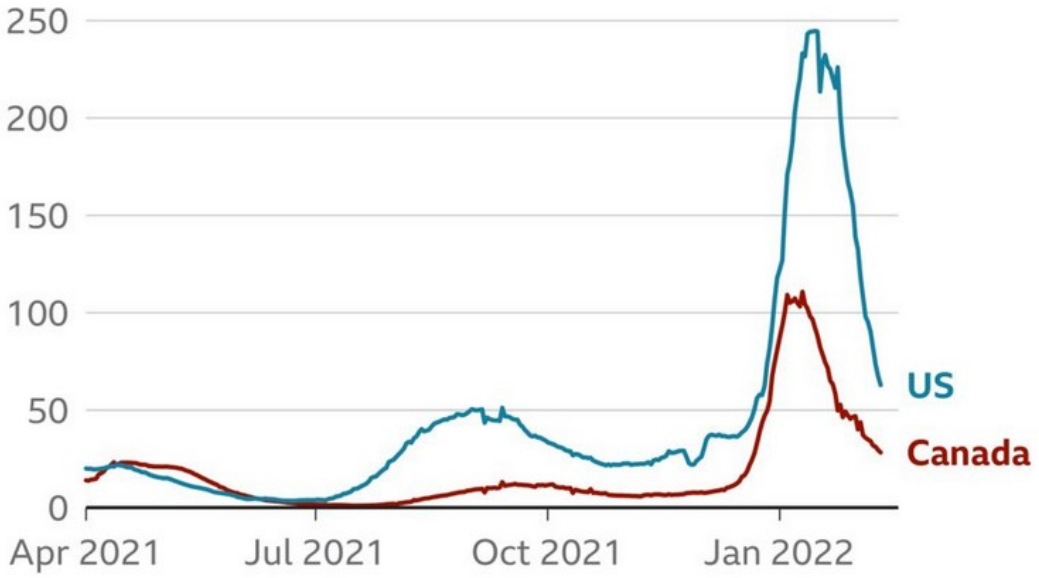


Source: Our World in Data, 09:30 GMT on 11 Feb

BBC

Case rates in US outpaced Canada's

Daily confirmed cases per 100,000, rolling seven-day average



Note: Countries do not always release data every day, which may explain some of the sharp changes in the trendlines

Source: Johns Hopkins University, gov.uk dashboard, data to 10 Feb

BBC

Reported deaths much higher in the US

Recorded coronavirus deaths, total and per capita

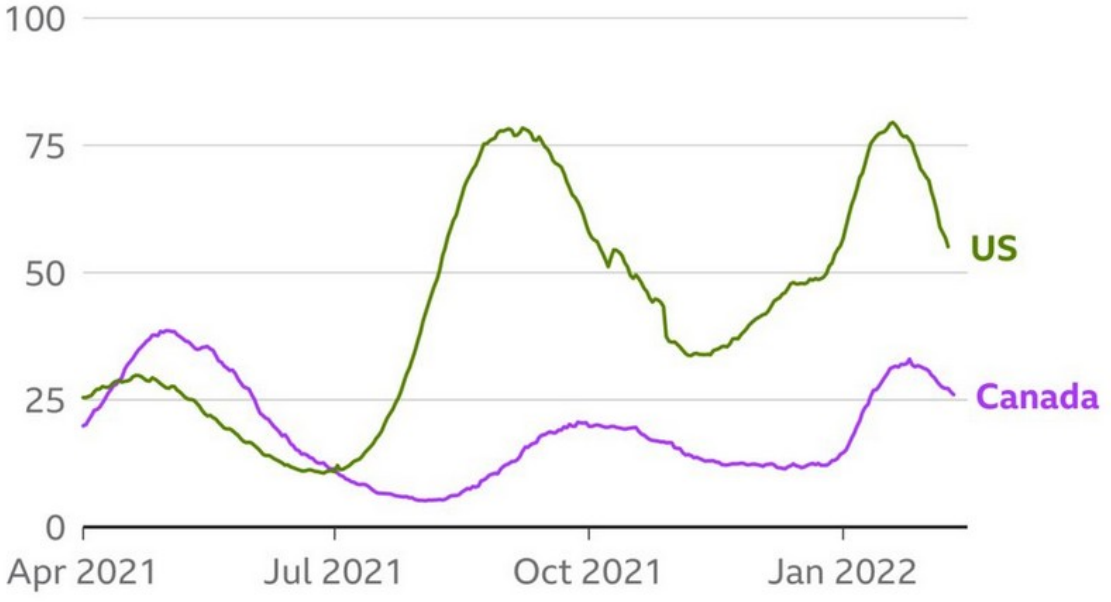
Note: Country death totals have been rounded down to the nearest 1,000

Source: Johns Hopkins University, Gov.uk dashboard, 11 Feb

BBC

ICU patients in US and Canada

Daily rate of people in ICU with Covid per million



Source: Our World in Data, 11 Feb

BBC

Summary

- Keep COVID-19 vaccines up to date
  - Boosters for those 12 and older
- Encourage PrEP in vulnerable populations
- Use available outpatient treatments
  - Sotrovimab
  - Nirmatrelvir / Ritonovir (Paxlovid)

Other Nebraska Resources

- UNMC Global Center for Health Security
  - https://www.unmc.edu/healthsecurity/covid-19/biweekly-updates.html
- Nebraska ICAP
  - https://icap.nebraskamed.com/

Thank You!