Therapy for Covid-19: Why Does it Matter?

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Walk through…

1. Where are we at with COVID19?
2. A quick update on what we know about COVID19 – history lesson from the US
3. Long COVID
4. Therapy for COVID, relevant to Primary Care - as recommended per WHO/international guidelines
5. Summary

Where are we at with COVID19?

The COVID19 Pandemic

- First detected in Dec 2019 & officially declared a pandemic by the WHO in March 2020 – very little was known & no targeted treatment was available
- Now more than 4 years on from when COVID19 was first declared a PHEIC
- The disease has become established and ongoing globally, and accordingly the WHO removed COVID's PHEIC classification in May 2023
- However, the pandemic is not over, even though the emergency is for now
- Let's not forget the impact that COVID19 has had (as per John Hopkins COVID resource centre – 10/3/2023):
- 676,609,955 cases
- 6,881,955 deaths
- And counting…

And Counting…

- The WHO up until now continues to collect data through country reporting
- As per the WHO's latest bulletin sentinel surveillance puts SARS COV2 PCR at 8% positivity in 69 countries (Global Influenza Surveillance and Response system)
- The current most prevalent variant is JN.1
- It's parent BA.2.86 is on the decline
- In the 28 day period from 4 March:
- 98 countries reported 275000 new cases (11%), 50 countries reported 49000 new hospital admissions (44%)
- 39 countries reported 4200 deaths (41%) , 39 countries 1200 new ICU admissions (46%)
- And remember surveillance data from wastewater surveillance suggest that clinical case reporting could underestimate cases by 2-19 fold

The Future & the Role of Primary Care

- There is now an international strategic shift from emergency management to Infection Prevention and Control
- WHO/international guidelines exist to help doctors manage all presentations of COVID19 including mild to moderate cases
- Being familiar with these guidelines forms an essential part of effective Infection Control
- Primary Care, therefore, is still very much at the forefront of dealing with the pandemic and has a vital role to play

Refresher on COVID19 & Long COVID

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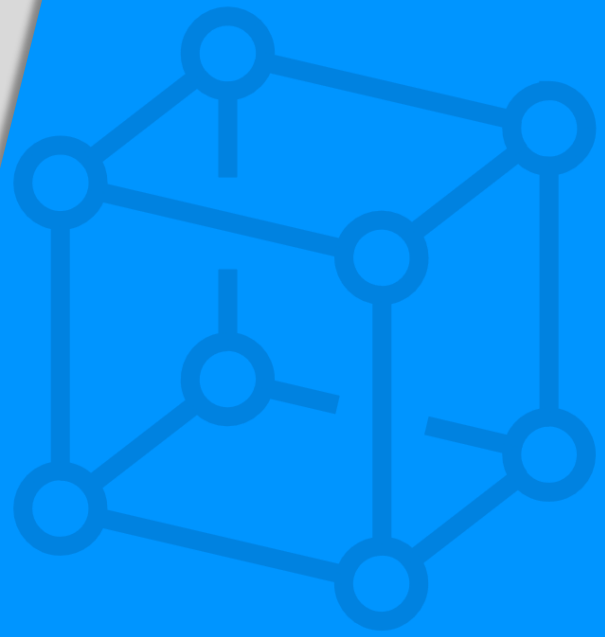
COVID-19: Severity, Symptoms, and Long-term Implications



The Spectrum of Symptomatic Coronavirus Disease (COVID-19)

Severity Level	Mild	Moderate	Severe	Critical
Definition[1]	• Constitutional symptoms (eg, fever, cough, headache, loss of taste and/or smell) • No shortness of breath	• Evidence of lower respiratory disease • Oxygen saturation ≥94%*	• Oxygen saturation <94%* or • PaO_2/FiO_2 <300 mm Hg or • Respiratory rate >30 breaths/min or • Lung infiltrates >50%	• Respiratory failure and/or • Septic shock and/or • Multiple organ dysfunction
Prevalence[2]	80%		15%	5%
Management/ prognosis[1]	Monitor patients with underlying comorbidities	Monitor all patients closely for progression	Patients may experience rapid clinical deterioration	Treat presenting condition and comorbidities, including nosocomial complications

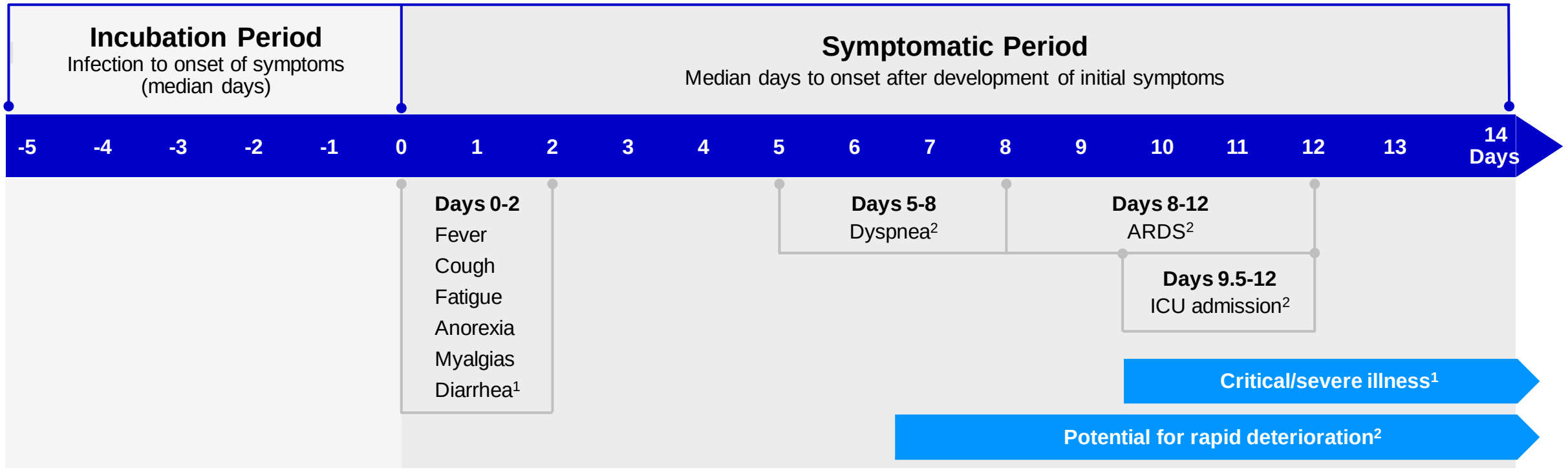
*On room air at sea level.

Most COVID-19 patients will experience mild-to-moderate respiratory illness and recover without requiring treatment, but some will become seriously ill and require treatment[3]

PaO_2/FiO_2 = arterial partial pressure of oxygen to fraction of inspired oxygen.

1. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated April 8, 2022. Accessed April 8, 2022. https://www.covid19treatmentguidelines.nih.gov 2. World Health Organization (WHO). Coronavirus disease (COVID-19). Q&A. May 13, 2021. Accessed March 3, 2022. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19 3. WHO. Coronavirus disease (COVID-19). Accessed March 3, 2022. https://www.who.int/health-topics/coronavirus#tab=tab_1

COVID-19 Symptoms and Severity Emerge After Infection



ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

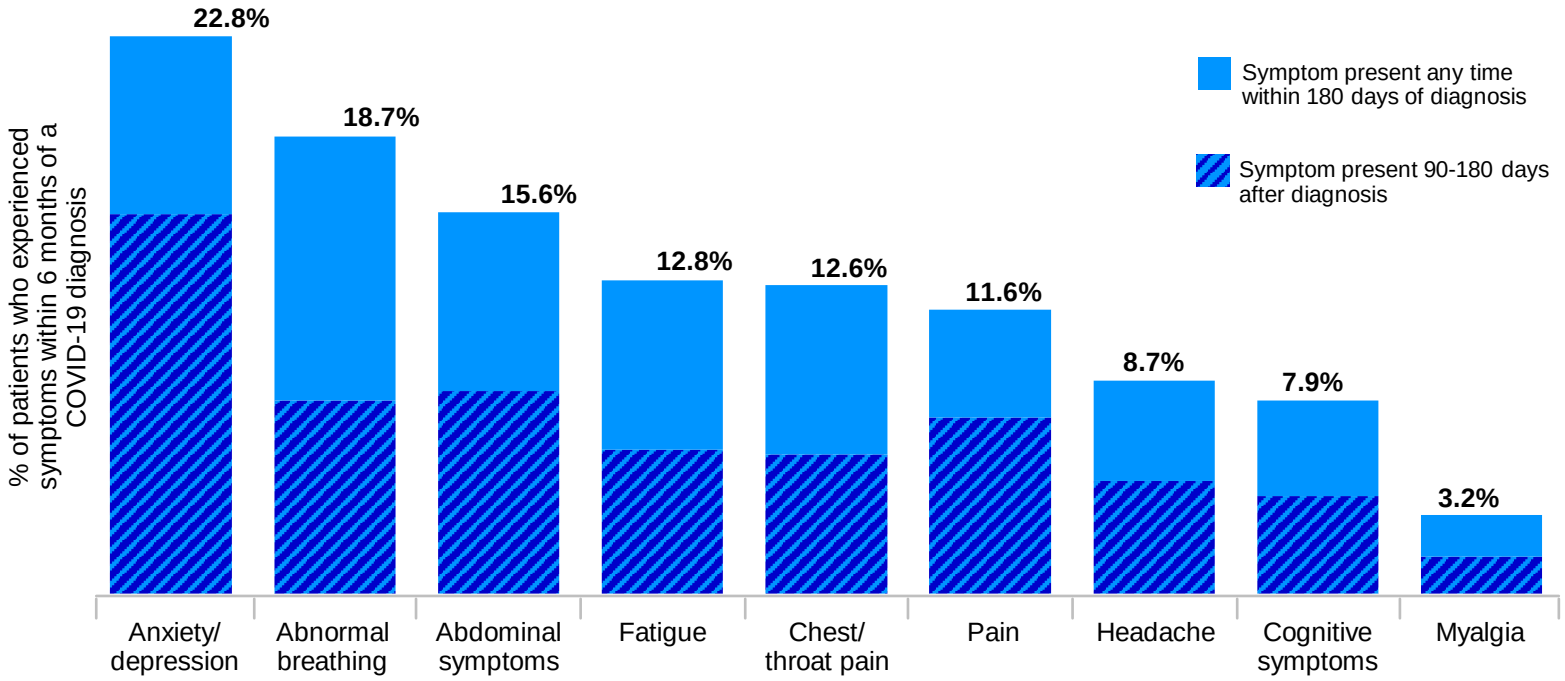
1. Berlin DA, et al. *N Engl J Med*. 2020;383(25):2451-2460. 2. Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Updated February 16, 2021. Accessed March 3, 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

Patients May Experience “Long COVID” Symptoms for Months After Onset

Long COVID-19: a range of new, returning, or ongoing health problems experienced ≥4 weeks after infection. Symptoms can occur regardless of COVID-19 severity[1,2]

Systemic symptom examples[3]	Emotion/mood-related symptom examples[3]
• Fatigue • Post-exertional malaise • Elevated temperature • Chills • Flushing • Sweats • Weakness • Coldness • Heat intolerance • Low temperature	• Anxiety • Irritability • Depression • Sense of doom • Anger • Suicidality • Aggression • Hypomania • Delusions • Mania

Incidence of Long COVID-19 Features[4]*

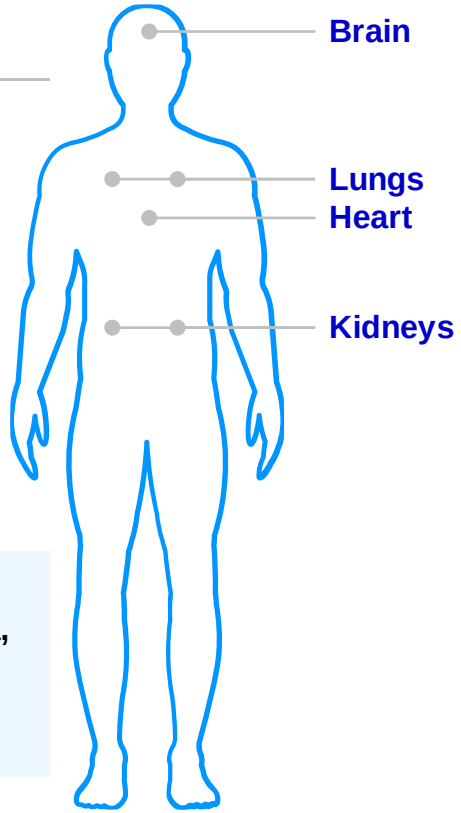


*Retrospective cohort study based on 273,618 COVID-19 survivors.

1. Centers for Disease Control and Prevention. Post-COVID conditions. Updated September 16, 2021. Accessed March 3, 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#print 2.National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. Version 1.13. Updated January 2, 2022. Accessed March 3, 2022. https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742 3. Davis HE, et al. *EClinicalMedicine*. 2021;38:101019. 4. Taquet M, et al. *PLoS Med*. 2021;18(9):e1003773.

Post-infection Risks Can Become a Chronic Concern

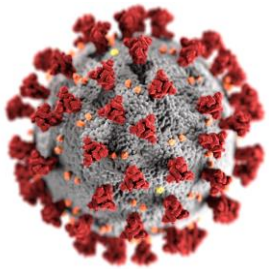
COVID-19 can precede the development of an autoimmune response, resulting in inflammation that affects multiple organs[1]



Persistent neurologic symptoms, hyperlipidemia, hypertension, and myocardial inflammation have been reported in post-COVID-19 patients[2,3]

Severe COVID-19 may **reactivate other latent viruses** due to weakened immunity. Examples include[4]

- EBV
- HHV-6/HHV-7
- HSV-1
- VZV



Latent pathogen reactivation has been associated with the development of many chronic conditions, including MS, RA, type 1 diabetes, lupus, and celiac disease[4]

EBV = Epstein-Barr virus; HHV-6/HHV-7 = human herpes viruses 6 and 7; HSV-1 = herpes simplex virus; MS = multiple sclerosis, RA = rheumatoid arthritis; VZV = varicella zoster virus.

1. Centers for Disease Control and Prevention. Post-COVID conditions. Updated September 16, 2021. Accessed March 3, 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#print 2. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated April 8, 2022. Accessed April 22, 2022. https://www.covid19treatmentguidelines.nih.gov 3. FAIR Health. A detailed study of patients with long-haul COVID. June 15, 2021. Accessed March 3, 2022. https://s3.amazonaws.com/media2.fairhealth.org/whitepaper/asset/A%20Detailed%20Study%20of%20Patients%20with%20Long-Haul%20COVID--An%20Analysis%20of%20Private%20Healthcare%20Claims--A%20FAIR%20Health%20White%20Paper.pdf 4. Proal A, VanElzakker MB. *Front Microbiol*. 2021;12:698169.

Severe COVID-19 Affects Ability of Symptomatic Patients to Return to Work

In a study of patients ~6 months post-hospitalization for a primary diagnosis of COVID-19*

All were associated most strongly with WHO Class 7-9 illness	
71%	**did not feel fully recovered**
20%	**had a new disability†**
18%	**of those who had been working were no longer working**
19%	**experienced a health-related change in occupation**

WHO Clinical Progression Scale

Class 7-9	Invasive mechanical ventilation or extracorporeal membrane oxygenation
Class 6	Continuous positive airway pressure ventilation, bilevel positive airway pressure, or high-flow nasal oxygen
Class 5	Continuous supplemental oxygen only
Class 3-4	No continuous supplemental oxygen needed

WHO = World Health Organization.

*Follow-up study of adults aged ≥18 discharged from hospitals in the UK with a clinical diagnosis of COVID-19 (N=1077). Median assessment was undertaken at 5.9 months postdischarge and included a detailed recording of symptoms and physiological and biochemical testing.

†As defined by the Washington Group Short Set of Functioning (WG-SS), a patient-reported outcome questionnaire measuring vision, hearing, walking, remembering, self-care, and communication. A participant is considered to have a new disability if response to any domain changed from "no difficulty" or "some difficulty" to "a lot of difficulty" or "cannot do it at all."

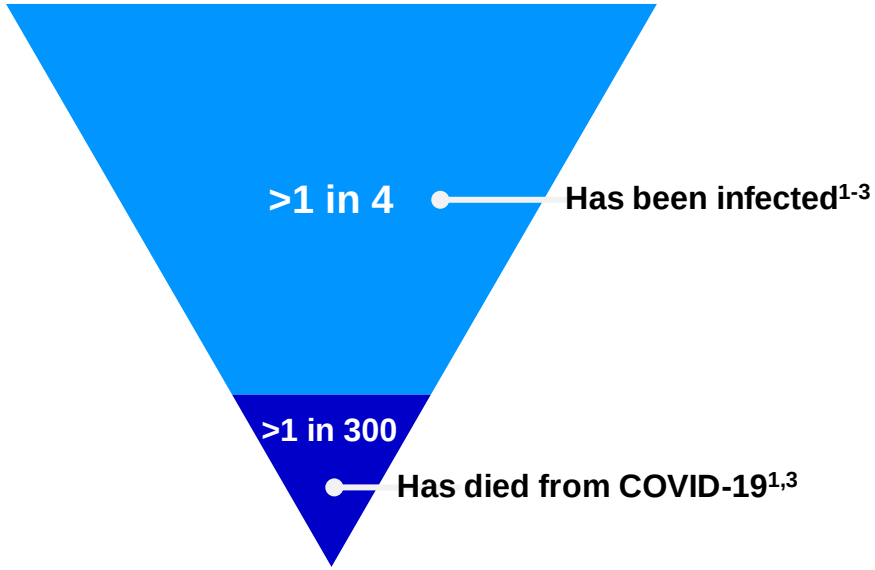
Evans RA, et al. *Lancet Respir Med.* 2021;9(11):1275-1287. Erratum in: *Lancet Respir Med*. 2021 Dec 1:S2213-2600(21)00540-3. doi:10.1016/S2213-2600(21)00383-0.

Epidemiology and Risks of COVID-19 in the US

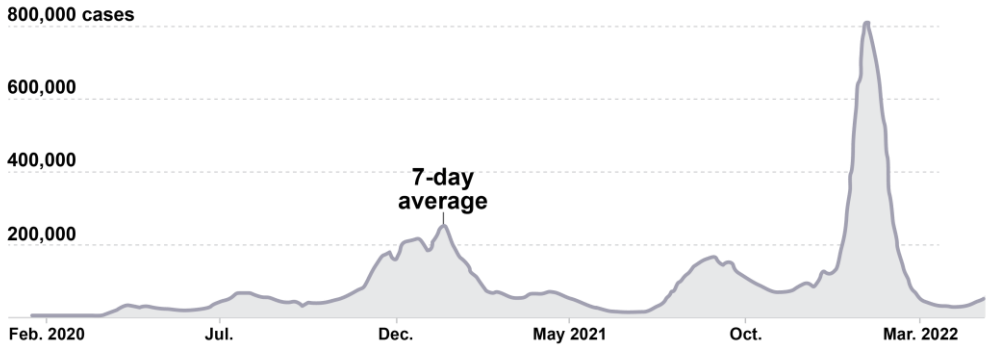
As of April 27, 2022

More than 1 in 300 Americans Aged 12+ Has Died From COVID-19

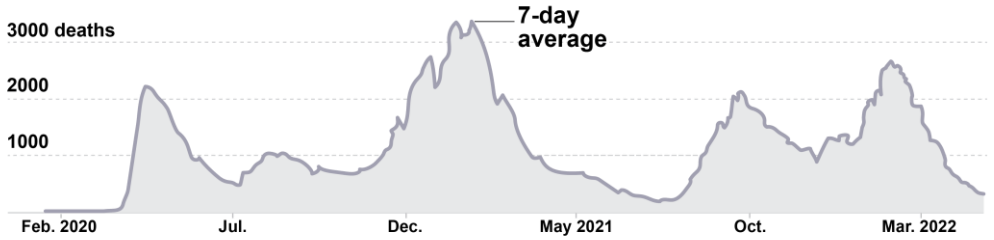
Of those aged 12+ with confirmed COVID-19*



New reported daily cases (all ages)[4]



New reported daily deaths (all ages)[4]



*Based on Centers for Disease Control and Prevention (CDC) data and extrapolated to Census Bureau population estimates. Of people in the US aged 12+, approximately 1 in 3.92 (including those who have been reinfected) have been diagnosed, and approximately 1 in 286 have died.

1. CDC. COVID Data Tracker. Demographic trends of COVID-19 cases and deaths in the US reported to CDC. April 27, 2022. Accessed April 28, 2022. https://covid.cdc.gov/covid-data-tracker/ - demographics 2. Leon TM, et al. *MMWR Morb Mortal Weekly Rep.* 2022;71(4):125-131. 3. US Census Bureau. Population on a date. Accessed April 28, 2022. https://www.census.gov/popclock/print.php?component=pop_on_date&image=https://www.census.gov/images/census-logo-whiteBG.png&date=20220427 4. *The New York Times*. Coronavirus in the U.S.: latest map and case count. April 28, 2022. Accessed April 28, 2022. https://www.nytimes.com/interactive/2021/us/covid-cases.html

Who's at Risk of Severe Disease?

Age and underlying medical conditions are the strongest risks for severe COVID-19 outcomes[1]

>97x mortality rate in adults with COVID-19 aged ≥65 vs those aged 18-29[1]

Underlying medical conditions associated with higher risk for severe COVID-19 include[1]

- Cancer
- Cerebrovascular disease
- Chronic kidney disease
- Chronic lung diseases*
- Chronic liver diseases†
- Diabetes mellitus, types 1 and 2
- Heart conditions (heart failure, coronary artery disease, cardiomyopathies)
- Human immunodeficiency virus
- Mental health disorders‡
- Obesity (body mass index ≥30 kg/m^2)
- Pregnancy and recent pregnancy
- Smoking, current and former
- Tuberculosis

3 in 5 US adults have a chronic disease.[2] Many of these conditions put them at high risk of becoming seriously ill from COVID-19[1,2]

*Interstitial lung disease, pulmonary embolism, pulmonary hypertension, chronic obstructive pulmonary disease, bronchiectasis.

†Cirrhosis, nonalcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis.

‡Mood disorders, including depression, and schizophrenia spectrum disorders.

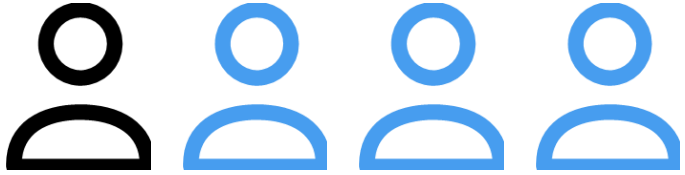
1. Centers for Disease Control and Prevention (CDC). Underlying medical conditions associated with higher risk for severe COVID-19: Information for healthcare professionals. Updated June 15, 2022. Accessed August 3, 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html 2. CDC. Chronic diseases in America. May 6, 2022. Accessed August 2, 2022. https://www.cdc.gov/chronicdisease/resources/infographic/chronic-diseases.htm

High-risk Conditions Are Associated With Higher-intensity Care

Patients with high-risk conditions* are

2x as likely to be hospitalized

3x more likely to be admitted to the intensive care unit



Average age of patients who are†

Treated in an outpatient setting:	**39**
Hospitalized:	**54**
Admitted to the ICU:	**54**

*vs COVID-19 patients without chronic kidney disease, chronic obstructive pulmonary disease, heart disease, diabetes, or obesity.

†Analysis of claims by the BlueCross BlueShield Association based on a geographically diverse sample of 4.5 million insured members.

BlueCross BlueShield Association. Infographic: COVID-19 patients with high-risk conditions 3x more likely to need the ICU. February 9, 2021. Accessed March 3, 2022. https://www.bcbs.com/coronavirus-updates/stories/infographic-covid-19-patients-high-risk-conditions-3x-more-likely-need-the-icu

COVID-19–Related Healthcare Resource Use

As of April 27, 2022

~1 in 91 Americans Aged 12+ Has Been Hospitalized for COVID-19[1-3]

~1 in 83

Number of Americans **aged ≥18** admitted for inpatient care[1-3*]

~1 in 50

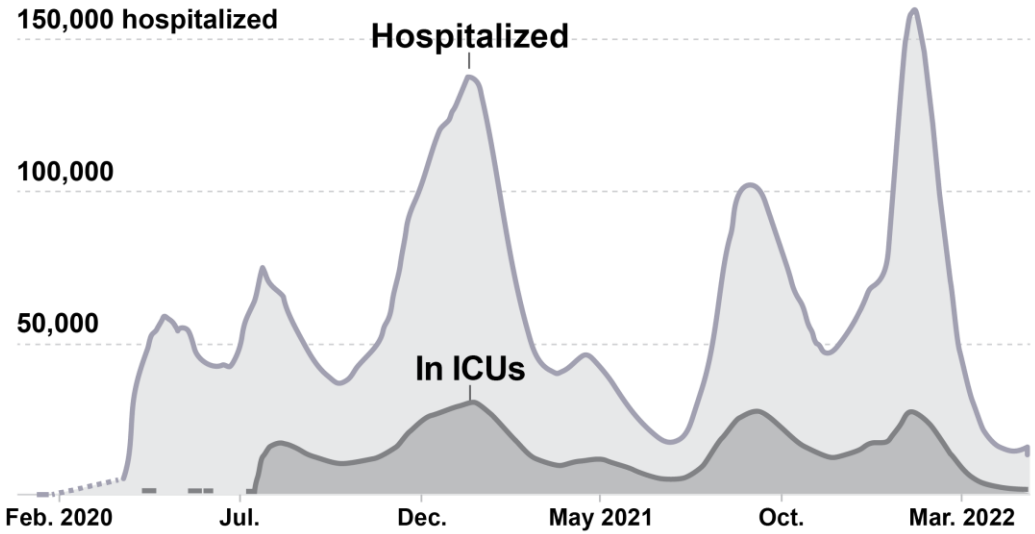
Number of adults **aged ≥50** admitted for inpatient care[1-3*]

7.3 days

Average **length of stay** (adults aged ≥30)[4†]

As of April 27, 2022

New reported daily hospitalizations (all ages)[5]



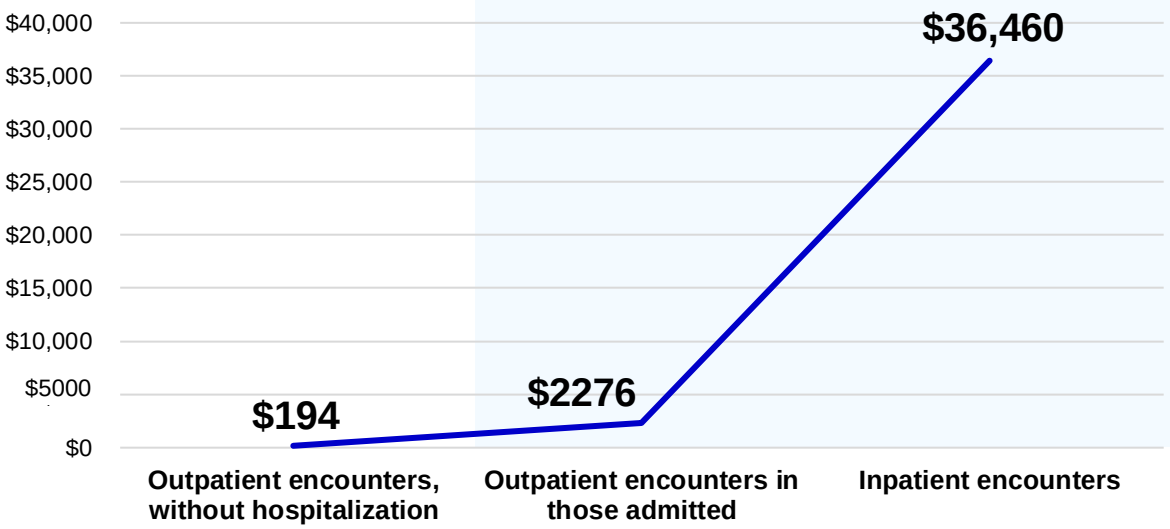
*Based on Centers for Disease Control and Prevention (CDC) data and extrapolated to 2022 Census Bureau estimates.

†National Hospital Care Survey, conducted by the National Center for Health Statistics, collected data on 68,901 inpatient confirmed COVID-19 discharges from UB-04 administrative claims from March 18, 2020 through November 30, 2021 from 40 hospitals. Length of stay shown is as of October 20, 2021. Data are considered preliminary and are not nationally representative.[4]

1. CDC. COVID-NET. Laboratory-confirmed COVID-19–associated hospitalizations. Through April 23, 2022. Accessed April 28, 2022. https://gis.cdc.gov/grasp/covidnet/covid19_3.html 2. CDC. COVID Data Tracker. Demographic trends of COVID-19 cases and deaths in the US reported to CDC. April 27, 2022. Accessed April 28, 2022. https://covid.cdc.gov/covid-data-tracker/#demographics 3. US Census Bureau. Population on a date. Accessed April 28, 2022. https://www.census.gov/popclock/print.php?component=pop_on_date&image=https://www.census.gov/images/census-logo-whiteBG.png&date=20220427 4. CDC. In-hospital mortality among hospital confirmed COVID-19 encounters by week from selected hospitals. March 22, 2022. Accessed April 28, 2022. https://www.cdc.gov/nchs/covid19/nhcs/hospital-mortality-by-week.htm 5. *The New York Times*. Coronavirus in the U.S.: latest map and case count. April 28, 2022. Accessed April 28, 2022. https://www.nytimes.com/interactive/2021/us/covid-cases.html

Costs Increase 200-fold When COVID-19 Progresses to Hospitalization

Median allowed amounts paid*



High-risk patients can be identified

Comorbidities in patients requiring admission

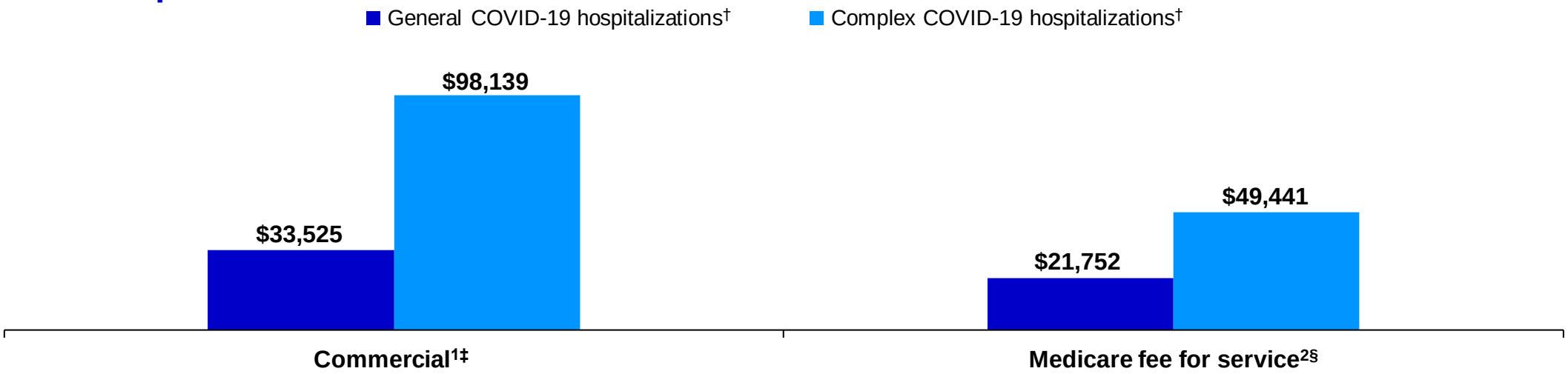
78% had hypertension	**66%** had gastrointestinal conditions	**60%** had cardiovascular disease	**~46%** had diabetes or were obese

*Retrospective analysis of Optum Clinformatics Data Mart (CDM) database to evaluate costs and treatment patterns of unvaccinated adults aged ≥18 with a confirmed primary or secondary outpatient diagnosis of COVID-19. Subjects were included if they had an outpatient-encounter claim (index date) between May 1, 2020, and December 10, 2020 (the day prior to the first administration of a COVID-19 vaccine), 12 months of continuous enrollment before the index date, and ≥60 days of continuous healthcare enrollment after the index date. Patients were excluded if they had a COVID-19 diagnosis ≤30 days before the index date, were admitted to a hospital for COVID-19 within 48 hours of an outpatient diagnosis in the outpatient setting (indicative of severe disease at diagnosis), or were admitted to a skilled nursing facility, hospice, or inpatient rehabilitation facility within ≥60 days of the index date. Costs shown are nonzero standard costs, which represent allowed amounts higher than $0 paid to providers, and include prescription drugs, outpatient encounters, and (for those admitted) inpatient encounters. Emergency department visits were calculated separately and are not shown on this slide.[1]

Scott A, et al. *J Med Econ*. 2022;25(1):287-298.

Inpatient Costs of COVID-19 Care Vary by Treatment Intensity

Mean amounts paid*



Cost of admission more than doubles when treatment requires ventilators or ICU stay

*Cost estimates differ by study, owing to methodological differences and study populations.

†In the commercial-population study, cost components of complex and general COVID-19 hospitalizations include lab tests, treatments and specialty drugs, radiology, room and board, and follow-up outpatient visits. Complex hospitalizations also include durable medical equipment (such as ventilators), blood and blood components, and ICU room and board. In the Medicare study, "complex" hospitalization refers to those in which a patient needed ventilator support.[1-2]

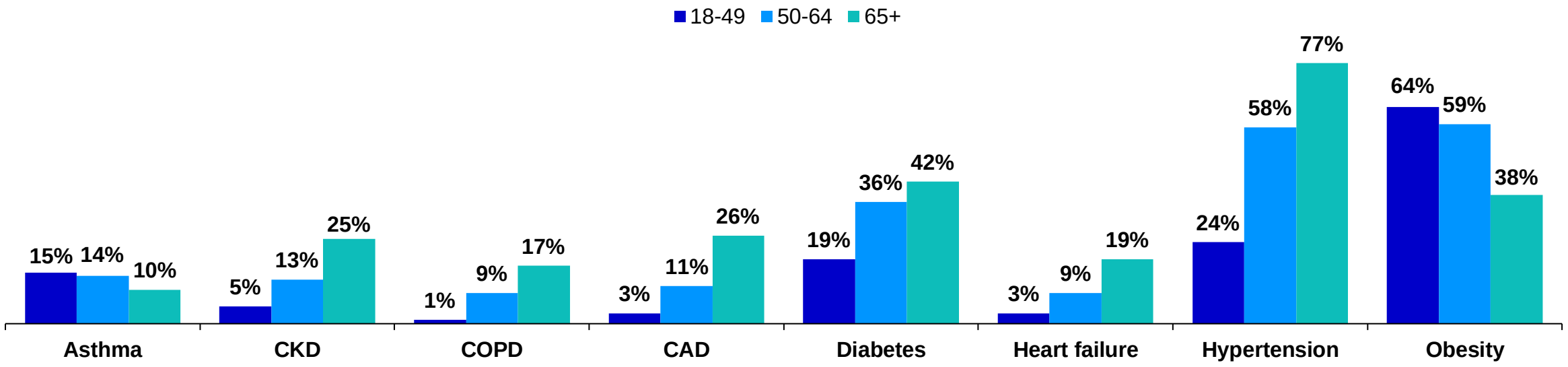
‡ Analysis of claims in FAIR Health's database of private healthcare claims data, which includes more than 35 billion claim records. Data are for encounters during September 2021.[1]

§ Retrospective analysis of fee-for-service claims representing 38 million beneficiaries with healthcare encounters from April 2020 through December 2020.[2]

1. FAIR Health. National average charge for a complex hospital stay for COVID-19 Is $317,810, FAIR Health finds. September 21, 2021. Accessed March 3, 2022. https://www.fairhealth.org/press-release/national-average-charge-for-a-complex-hospital-stay-for-covid-19-is-317-810-fair-health-finds 2. Tsai Y, et al. *Ann Int Med*. 2021;174(8):1101-1109.

Most Common Comorbidities Associated With COVID-19 Hospitalization

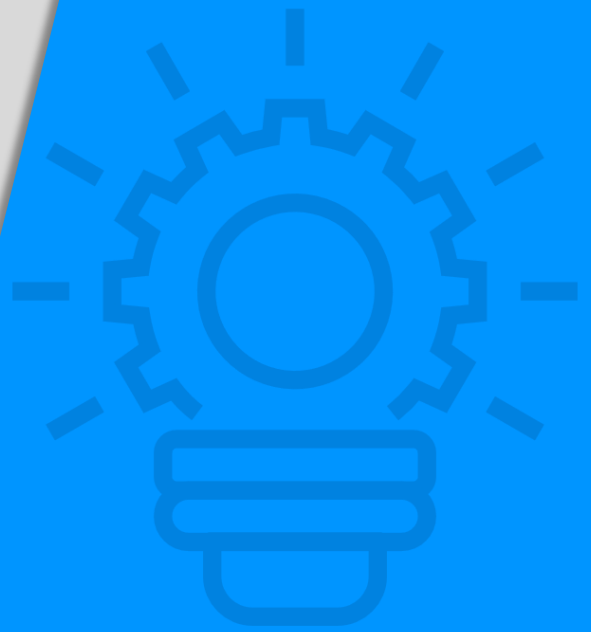
Prevalence of underlying medical conditions in hospitalized adults (March 2020 through December 2021)*



*The denominator for each underlying condition is the total number of patients with nonmissing data for that condition.
CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

Centers for Disease Control and Prevention. Disparities in COVID-19-associated hospitalizations. April 11, 2022. Accessed April 28, 2022. https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/racial-ethnic-disparities/disparities-hospitalization.html

Summary



Summary: The Burden of COVID-19

Severity, symptoms, and long-term implications

- Most COVID-19 patients will experience mild-to-moderate illness, but some will become seriously ill and require treatment[1]
- "Long COVID" symptoms, viral reactivation, and the potential for disability are concerns months after infection[2-4]

Epidemiology and risks of COVID-19 in the US

- Advanced age and the presence of certain underlying medical conditions are the greatest risks for progression to serious disease[5]
- 3 in 5 US adults have chronic conditions, many of which put them at increased risk for progression to severe COVID-19 disease[5,6]

COVID-19–related healthcare resource use

- >1 in 91 Americans aged 12+ years has been hospitalized for COVID-19[7-9*]
- COVID-19–related hospitalization costs fall largely on the unvaccinated population[10]

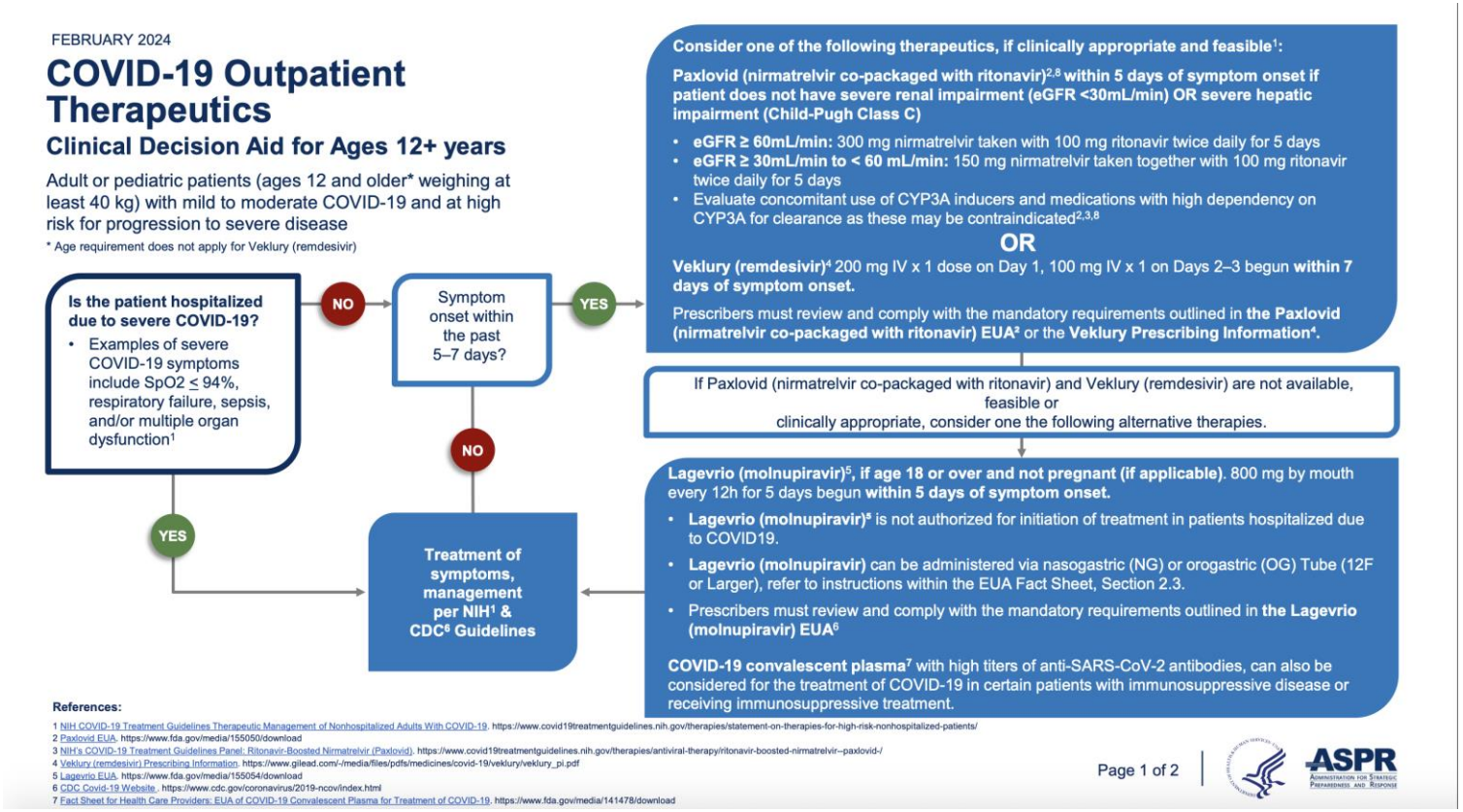
*As of April 27, 2022.

1. World Health Organization. Coronavirus disease (COVID-19). Accessed March 3, 2022. https://www.who.int/health-topics/coronavirus#tab=tab_1 2. Centers for Disease Control and Prevention (CDC). Post-COVID conditions. Updated September 16, 2021. Accessed March 3, 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#print 3. Proal A, VanElzakker MB. *Front Microbiol*. 2021;12:698169. 4. Evans RA, et al. *Lancet Respir Med*. 2021;9(11):1275-1287. Erratum in: *Lancet Respir Med*. 2021 Dec 1:S2213-2600(21)00540-3. doi:10.1016/S2213-2600(21)00383-0. 5. CDC. Underlying medical conditions associated with higher risk for severe COVID-19: Information for healthcare professionals. Updated June 15, 2022. Accessed August 3, 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html 6. CDC. Chronic diseases in America. May 6, 2022. Accessed August 2, 2022. https://www.cdc.gov/chronicdisease/resources/infographic/chronic-diseases.htm 7. CDC COVID-NET. Laboratory-confirmed COVID-19-associated hospitalizations. Through April 23, 2022. Accessed April 28, 2022. https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html 8. CDC. COVID Data Tracker. Demographic trends of COVID-19 cases and deaths in the US reported to CDC. April 27, 2022. Accessed April 28, 2022. https://covid.cdc.gov/covid-data-tracker/#demographics 9. US Census Bureau. Population on a date. Accessed April 27, 2022. https://www.census.gov/popclock/print.php?component=pop_on_date&image=https://www.census.gov/images/census-logowhiteBG.png&date=20220427 10. Amin K, Cox C. Unvaccinated COVID-19 hospitalizations cost billions of dollars. Peterson-KFF Health System Tracker. December 22, 2021. Accessed March 3, 2022. https://www.healthsystemtracker.org/brief/unvaccinated-covid-patients-cost-the-u-s-health-system-billions-of-dollars/

Oral Therapy for COVID19

In patients who are high risk patients for progression to severe disease

CDC COVID19 Management guidelines



FEBRUARY 2024

COVID-19 Outpatient Therapeutics

Clinical Decision Aid for Ages 12+ years

Adult or pediatric patients (ages 12 and older* weighing at least 40 kg) with mild to moderate COVID-19 and at high risk for progression to severe disease

* Age requirement does not apply for Veklury (remdesivir)

Is the patient hospitalized due to severe COVID-19?

- Examples of severe COVID-19 symptoms include SpO2 ≤ 94%, respiratory failure, sepsis, and/or multiple organ dysfunction[1]

NO

Symptom onset within the past 5–7 days?

YES

NO

YES

Treatment of symptoms, management per NIH[1] & CDC[6] Guidelines

Consider one of the following therapeutics, if clinically appropriate and feasible[1]:

Paxlovid (nirmatrelvir co-packaged with ritonavir)[2,8] within 5 days of symptom onset if patient does not have severe renal impairment (eGFR <30mL/min) OR severe hepatic impairment (Child-Pugh Class C)

- **eGFR ≥ 60mL/min:** 300 mg nirmatrelvir taken with 100 mg ritonavir twice daily for 5 days
- **eGFR ≥ 30mL/min to < 60 mL/min:** 150 mg nirmatrelvir taken together with 100 mg ritonavir twice daily for 5 days
- Evaluate concomitant use of CYP3A inducers and medications with high dependency on CYP3A for clearance as these may be contraindicated[2,3,8]

OR

Veklury (remdesivir)[4] 200 mg IV x 1 dose on Day 1, 100 mg IV x 1 on Days 2–3 begun **within 7 days of symptom onset.**

Prescribers must review and comply with the mandatory requirements outlined in **the Paxlovid (nirmatrelvir co-packaged with ritonavir) EUA[3]** or the **Veklury Prescribing Information[4].**

If Paxlovid (nirmatrelvir co-packaged with ritonavir) and Veklury (remdesivir) are not available, feasible or clinically appropriate, consider one the following alternative therapies.

Lagevrio (molnupiravir)[5], if age 18 or over and not pregnant (if applicable). 800 mg by mouth every 12h for 5 days begun **within 5 days of symptom onset.**

- **Lagevrio (molnupiravir)[5]** is not authorized for initiation of treatment in patients hospitalized due to COVID19.
- **Lagevrio (molnupiravir)** can be administered via nasogastric (NG) or orogastric (OG) Tube (12F or Larger), refer to instructions within the EUA Fact Sheet, Section 2.3.
- Prescribers must review and comply with the mandatory requirements outlined in **the Lagevrio (molnupiravir) EUA[6]**

COVID-19 convalescent plasma[7] with high titers of anti-SARS-CoV-2 antibodies, can also be considered for the treatment of COVID-19 in certain patients with immunosuppressive disease or receiving immunosuppressive treatment.

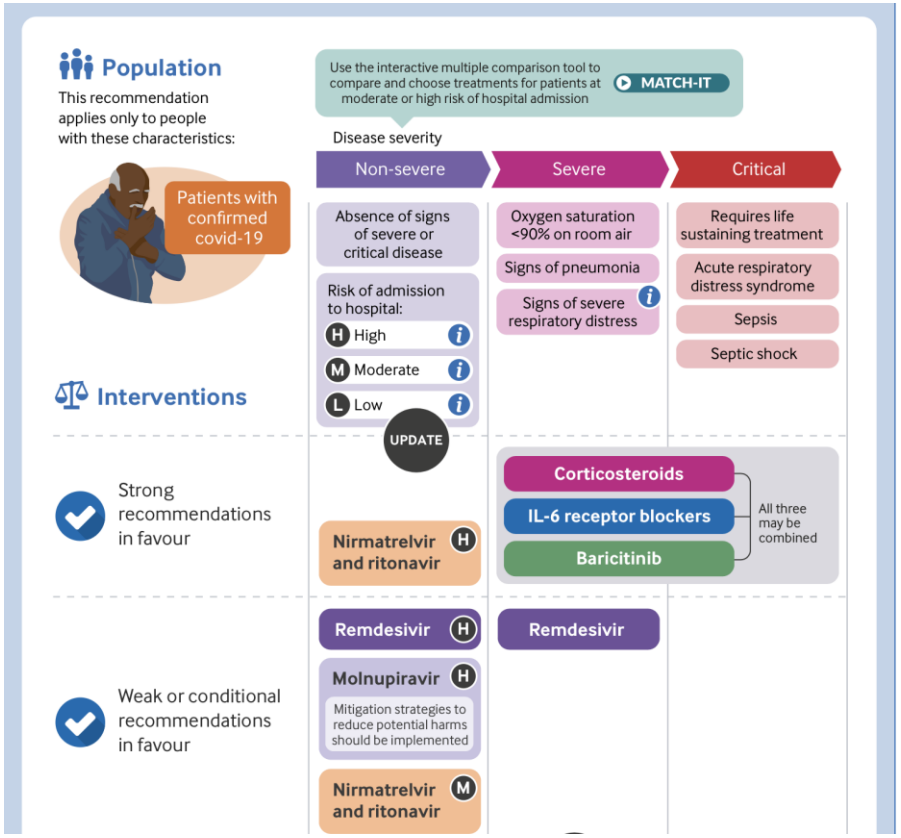
References:

1 NIH COVID-19 Treatment Guidelines Therapeutic Management of Nonhospitalized Adults With COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/
2 Paxlovid EUA. https://www.fda.gov/media/155050/download
3 NIH's COVID-19 Treatment Guidelines Panel: Ritonavir-Boosted Nirmatrelvir (Paxlovid). https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/
4 Veklury (remdesivir) Prescribing Information. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
5 Lagevrio EUA. https://www.fda.gov/media/155054/download
6 CDC Covid-19 Website. https://www.cdc.gov/coronavirus/2019-ncov/index.html
7 Fact Sheet for Health Care Providers: EUA of COVID-19 Convalescent Plasma for Treatment of COVID-19. https://www.fda.gov/media/141478/download

Page 1 of 2

ASPR Administration for Strategic Preparedness and Response

WHO endorsed / BMJ COVID management Guidelines



DHA COVID19 Management guidelines

6. **RECOMMENDATION TWO:** MANAGEMENT OF COVID-19 IN ADULT PATIENTS WITH MILD TO MODERATE SYMTOPMS BUT NOT HOSPITALIZED

6.1. Consider the following in the order of medications described below in order of priority, subject to availability, for patients who are at high risk for progressing to severe COVID-19 and/or hospitalization. Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 test and within 10 days of symptom onset.

6.1.1. Paxlovid – (nirmatrelvir 300mg plus ritonavir 100mg orally twice daily for 5 days) within 5 days of symptom onset.

Or

6.1.2. Molnupiravir 800mg orally twice daily for 5 days within 5 days of symptom onset.

Or

6.1.3. Sotrovimab 500mg administered as single intravenous infusion.

Or

6.1.4. Remdesivir 200mg IV on Day 1, followed by 100mg IV on days 2 and 3.

6.3. **High-risk individuals** (with mild to moderate disease who are at-risk of progression to severe disease and/or hospitalization) as specified who meet at least one of the following criteria:

6.3.1. Age ≥ 65 years

6.3.2. Obesity (BMI ≥25 kg/m2)

6.3.3. Diabetes mellitus

6.3.4. Cardiovascular disease (including congenital heart disease) or hypertension

6.3.5. Chronic lung disease (e.g. chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)

6.3.6. An immunocompromising condition or immunosuppressive treatment

6.3.7. Chronic kidney disease

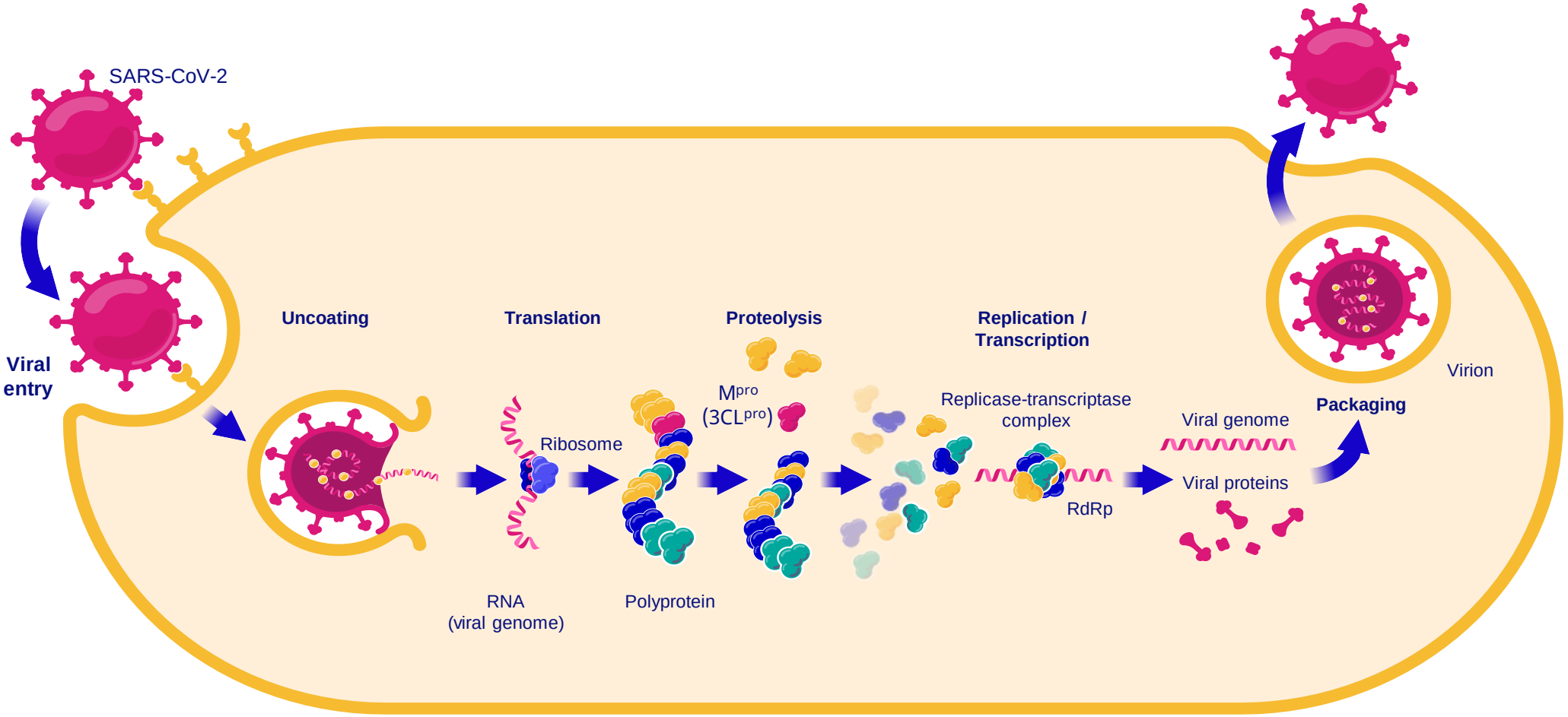
6.3.8. Pregnancy

6.3.9. Sickle cell disease.

What is PAXLOVID (nirmatrelvir/ritonavir)?

Pfizer

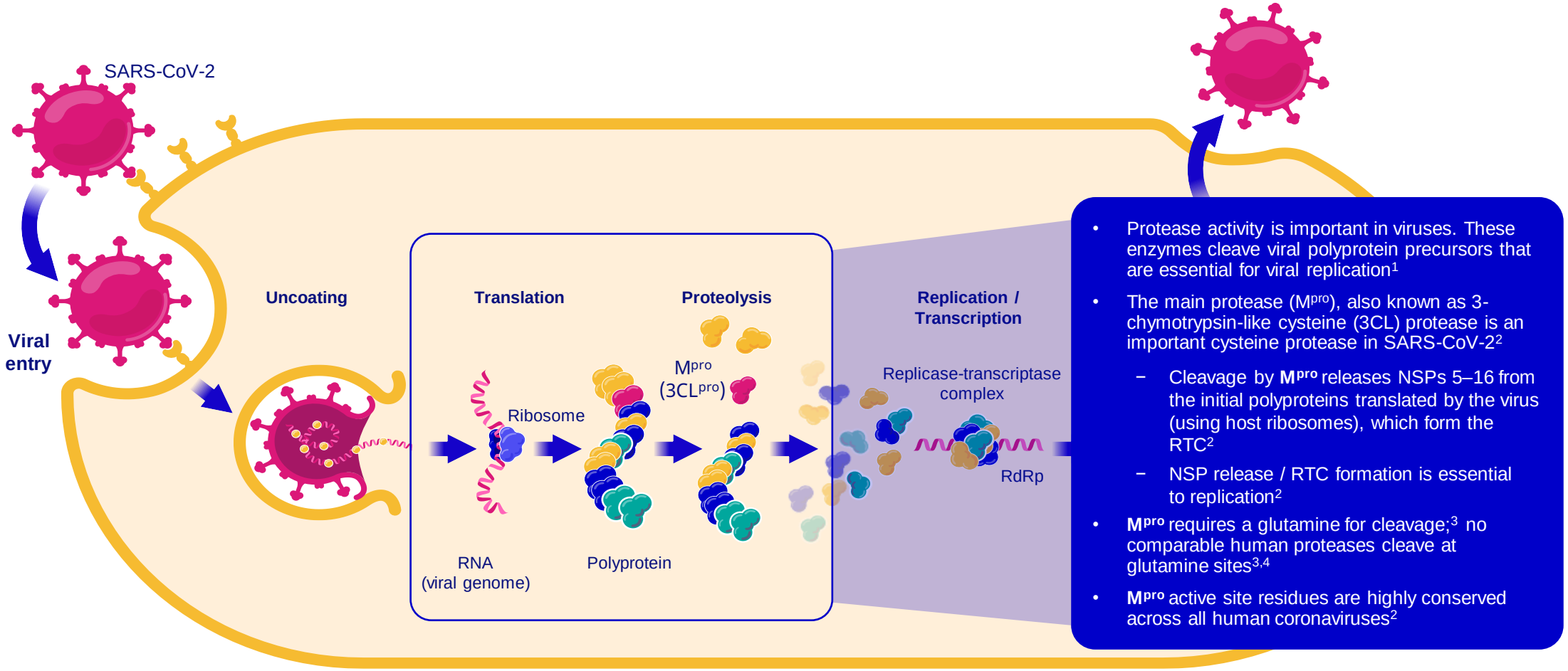
The SARS-CoV-2 virus utilises a host cell to replicate[1–2]



3CL^{pro}, 3-chymotrypsin-like protease; M^{pro}, main protease; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid.

1. Pluskota-Karwatka D, et al. *J Pharm Anal* 2021;11(4):383-97; 2. V'Kovski P, et al. *Nat Rev Microbiol* 2021;19(3):155-70.

M^{pro} is essential to the SARS-CoV-2 lifecycle[1–4]



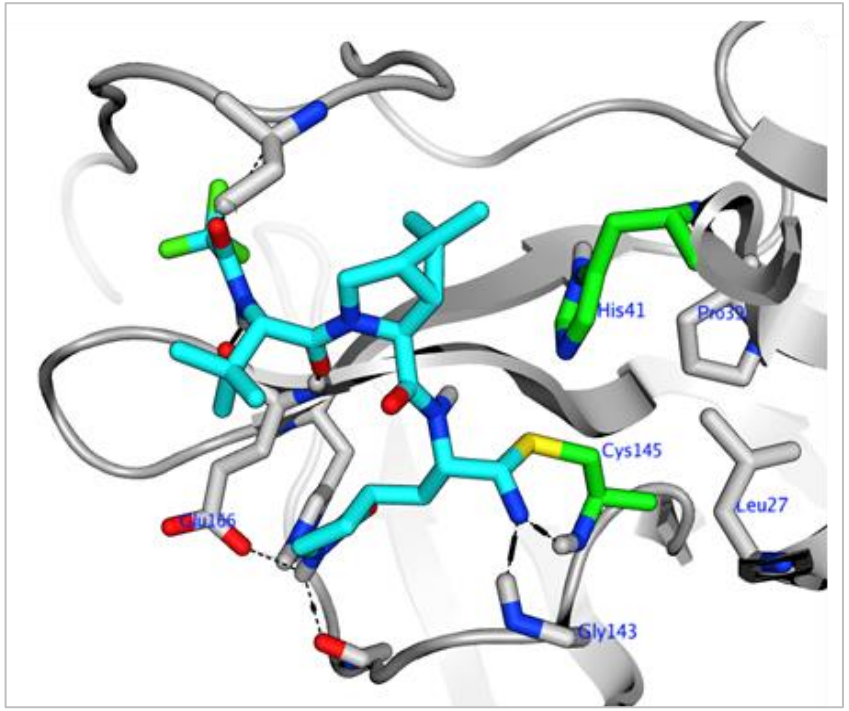
- Protease activity is important in viruses. These enzymes cleave viral polyprotein precursors that are essential for viral replication[1]
- The main protease (M^{pro}), also known as 3-chymotrypsin-like cysteine (3CL) protease is an important cysteine protease in SARS-CoV-2[2]
  - Cleavage by **M^{pro}** releases NSPs 5–16 from the initial polyproteins translated by the virus (using host ribosomes), which form the RTC[2]
  - NSP release / RTC formation is essential to replication[2]
- **M^{pro}** requires a glutamine for cleavage;[3] no comparable human proteases cleave at glutamine sites[3,4]
- **M^{pro}** active site residues are highly conserved across all human coronaviruses[2]

$3CL^{pro}$, coronavirus 3-chymotrypsin-like-protease; M^{pro}, main protease; NSP, nonstructural protein; RdRp, RNA dependent RNA polymerase; RNA, ribonucleic acid; RTC, replication and transcription complex.

1. Steinkühler C. Viral Proteases. In: Offermanns S, Rosenthal W (eds). *Encyclopedia of Molecular Pharmacology*. 2008, Springer, Berlin, Heidelberg. Available at: https://doi.org/10.1007/978-3-540-38918-7_146. Accessed: November 2023; 2. V'kovski P, et al. *Nat Rev Microbiol* 2021;19:155–70; 3. Owen DR, et al. *Science* 2021;374(6575):1586–93; 4. Mengist HM, et al. *Front Chem*. 2021 Mar 12;9:622898.

Nirmatrelvir, also known as nirmatrelvir, has been designed to inhibit M^{pro}

- **M^{pro} is one of the most attractive drug targets among coronaviruses**
  - Essential for viral replication[1]
  - Substrate-recognition pocket is highly conserved[2]
  - The 3CL recognition sequence (Leu-Gln↓Ser-Ala-Gly) is **not associated with any known human proteases**[2]



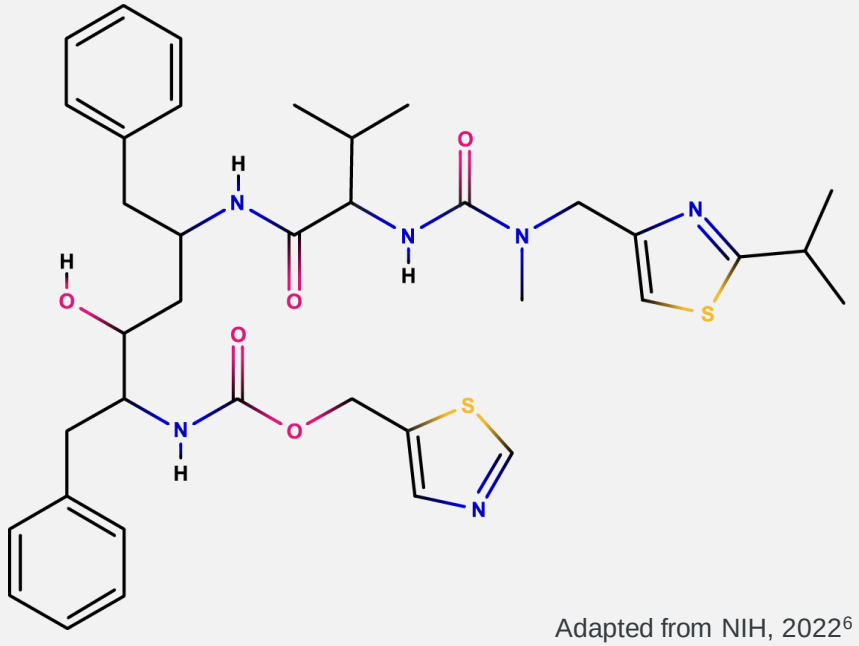
- **Nirmatrelvir binds to the active site of M^{pro}** and forms a reversible covalent bond with the catalytic cysteine residue, Cys145[3,4]
- Inhibition of M^{pro} renders the protein incapable of processing polyprotein precursors, which leads to the **prevention of viral replication**[3]

3CL, 3-chymotrypsin-like; Ala, alanine; Cys, cysteine; Gln, glutamine; Gly, glycine; Leu, leucine; M^{pro}, main protease; Ser, serine.

1. Yang H, et al. *PLoS Biol* 2005:3(10):e324; 2. Razali R, et al. *Microorganisms* 2021;9(12):2481; 3. Owen DR, et al. *Science* 2021;374(6575):1586–93; 4. Ahmad B, et al. *Int J Mol Sci* 2021;22(17):9124.

Adding ritonavir as a PK enhancer for Nirmatrelvir

- Ritonavir is an oral antiretroviral originally developed to treat HIV-1 infection[1]
  - Strong CYP3A inhibitor
  - Well known safety profile[1]
- A low dose is often used in combination with other protease inhibitors as a PK enhancer[2,3]
- **Co-administration of ritonavir enhances the bioavailability of Nirmatrelvir** by slowing its metabolism by CYP3A[4]
- A dose of 300mg; 100 mg Nirmatrelvir /ritonavir BID is anticipated to achieve exposures of Nirmatrelvir several-fold over the *in vitro* EC_{90}[5]



Adapted from NIH, 2022[6]

PAXLOVID is Nirmatrelvir tablets co-packaged with ritonavir tablets[7]

BID, twice daily; CYP, cytochrome P450; EC_{90}, 90% effective concentration; HIV, human immunodeficiency virus; PK, pharmacokinetic.

1. NORVIR Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209512lbl.pdf. Accessed: November 2023; 2. Cooper, CL et al. *Clin Infect Dis* 2003;36(12):1585–92; 3. Hill A et al. *AIDS* 2009;23:2237–45; 4. Owen DR, et al. *Science* 2021;374(6575):1586–93; 5. Singh, RSP, et al. medRxiv 2022. doi: 10.1101/2022.02.08.22270649; 6. National Institutes of Health. Compound summary: Ritonavir. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Ritonavir. Accessed: November 2023; 7. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for PAXLOVID™. Available from: www.fda.gov/media/155050/download. Accessed: November 2023.

Summary

- The enzyme M^{pro} is vital to the coronavirus lifecycle, making it an attractive drug target[1,2]
- Nirmatrelvir has demonstrated inhibition of M^{pro} of SARS-CoV-2, as well as related coronaviruses[1]
- Nirmatrelvir has shown *in vitro* efficacy against SARS-CoV-2 VOCs, including Omicron[3-6]
- Co-administration of ritonavir enhances the bioavailability of Nirmatrelvir by slowing its metabolism by CYP3A4[1]
- PAXLOVID is Nirmatrelvir tablets co-packaged with ritonavir tablets[7]

CYP, cytochrome P450; M^{pro}, main protease; VOC, variant of concern.

1. Owen DR, et al. *Science* 2021;374(6575):1586–93; 2. Yang H, et al. *PLoS Biol* 2005:3(10):e324; 3. Rai DK, et al. Pre-print: bioRxiv 2022. doi: 10.1101/2022.01.17.476644; 4. Greasley SE, et al. Pre-print: bioRxiv 2022. doi: 10.1101/2022.01.17.476556; 5. Rosales R, et al. Pre-print: bioRxiv 2022. doi: 10.1101/2022.01.17.476685; 6. Vangeel L, et al. Pre-print: bioRxiv 2022. doi: 10.1101/2021.12.27.474275; 7. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for PAXLOVID™. Available from: www.fda.gov/media/155050/download. Accessed: November 2023.

Demonstrating the effectiveness of PAXLOVID: The EPIC Phase 2 / 3 clinical trial programme

Evaluation of Protease Inhibition for COVID-19

Pfizer

Evaluation of Protease Inhibition for COVID-19 (EPIC): A global Phase 2 / 3 clinical trial programme for PAXLOVID

Trial	Phase	Population	Duration	Intervention(s)	Primary endpoint(s)
EPIC-HR[1]	2 / 3	High-risk unvaccinated outpatients (N=2,246)[5]	24 weeks	• PAXLOVID q12h for 5 days • Placebo q12h for 5 days	Proportion of participants with COVID-19-related hospitalisation or death from any cause through Day 28
EPIC-SR[2]	2 / 3	Standard-risk and vaccinated high-risk outpatients (N=1,150 estimated)	24 weeks	• PAXLOVID q12h for 5 days • Placebo q12h for 5 days	Time to sustained alleviation of all targeted COVID-19 signs / symptoms through Day 28
EPIC-PEP[3]	2 / 3	Household contacts (N=2,880 estimated)	Up to 6 weeks	• PAXLOVID q12h for 5 days followed by placebo q12h for 5 days • PAXLOVID q12h for 10 days • Placebo q12h for 10 days	Proportion of participants with a negative RT-PCR at baseline who develop a symptomatic, RT-PCR-confirmed SARS-CoV-2 infection (Days 1–14)
EPIC-Peds[4,5]	2 / 3	Paediatric outpatients (N=140 estimated)	Up to 5 weeks	• Weight ≥40 kg (≥6 to <18 years): PAXLOVID (PF-07321332; ritonavir 300 mg; 100 mg) q12h for 5 days* • Weight ≥20 to <40 kg: PAXLOVID (PF-07321332; ritonavir 150 mg; 100 mg) q12h for 5 days*	*PK*: PK parameters including C_{max} and $AUC_{0\text{-}tau}$ (and if the data permit t1/2, C_{trough}) of PF-07321332 and ritonavir† *Safety*: Incidence of TEAEs, SAEs, AEs leading to discontinuations, and vital sign measurements

* There may be planned amendments to the protocol to include doses for additional cohorts and information regarding the changes in formulations[4]; † In adolescents (≥12 years to <18 years of age), robust PK sampling will be performed. A sparser approach will be incorporated for younger participants as PK samples are more difficult to obtain[4].

AE, adverse event; $AUC_{0\text{-}tau}$, area under the curve to the end of the dosing period; C_{max}, maximum plasma concentration; C_{trough}, minimum concentration; EPIC, Evaluation of Protease Inhibition for COVID-19; HR, high risk; PEP, post-exposure prophylaxis; PK, pharmacokinetic; q12h, every 12 hours; RT-PCR, reverse-transcription polymerase chain reaction; SAE, serious adverse event; SR, standard risk; TEAE, treatment-emergent adverse event.

1. ClinicalTrials.gov. NCT04960202. Available from: https://clinicaltrials.gov/ct2/show/NCT04960202. Accessed: November 2023; 2. ClinicalTrials.gov. NCT05011513. Available from: https://clinicaltrials.gov/ct2/show/NCT05011513. Accessed: November 2023; 3. ClinicalTrials.gov. NCT05047601. Available from: https://www.clinicaltrials.gov/ct2/show/NCT05047601. Accessed: November 2023; 4. Pfizer. Data on File_C4671026 Final Protocol, 21 Jan 2022; 5. ClinicalTrials.gov. NCT05261139. Available at: https://clinicaltrials.gov/ct2/show/NCT05261139. Accessed: November 2023.

EPIC-HR

Evaluation of Protease Inhibition for COVID-19 in High-Risk participants

Pfizer

EPIC-HR

Study design

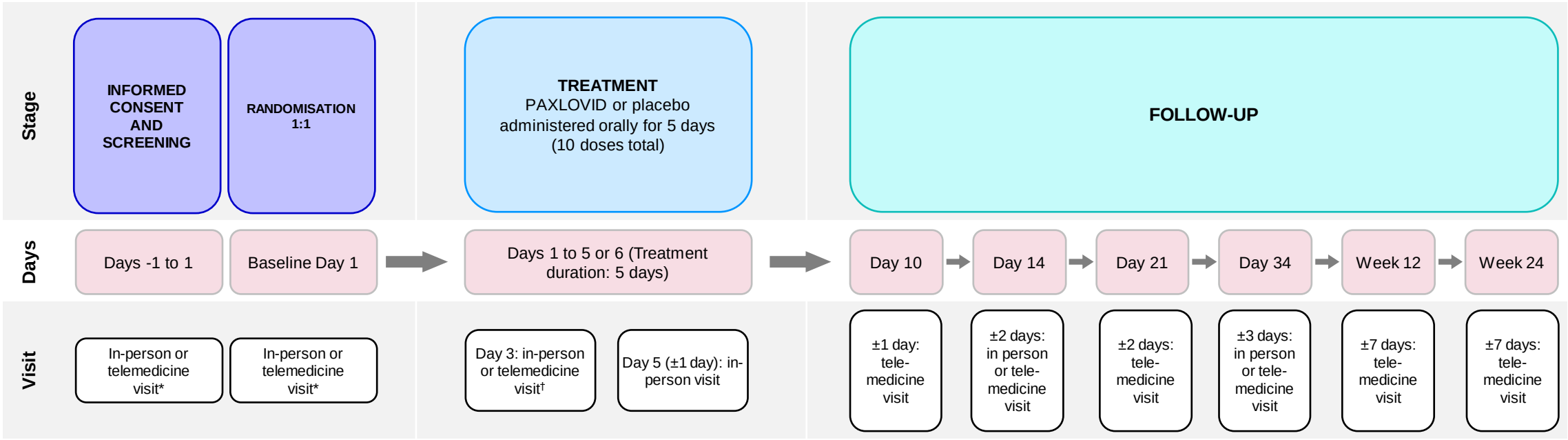
Objective of EPIC-HR

- Phase 2 / 3, randomised, double-blind, placebo-controlled trial
- Designed to evaluate the **efficacy, viral load and safety** associated with **PAXLOVID**
- In non-hospitalised, symptomatic adults with COVID-19 who were at **high risk** for progression to severe disease

Hammond J, et al. N Engl J Med. 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

EPIC-HR was a 24-week study of PAXLOVID versus placebo

- Participants were randomised 1:1 to receive either **PAXLOVID or placebo** every 12 hours for 5 days
- Randomisation was stratified by geographic region and receipt or expected receipt of mAb treatment for COVID-19

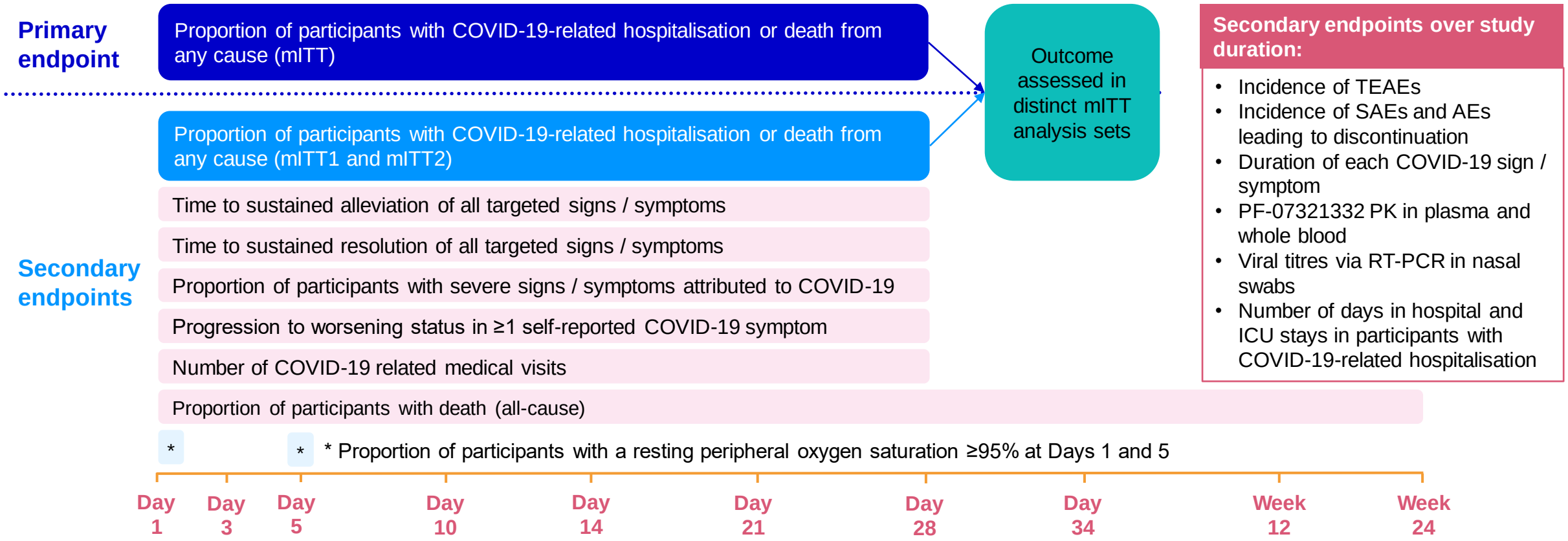


* The baseline and screening visits may be a combination of in-person and telemedicine visits; † The Day 3 visit was conducted in person for the first 68 participants (sentinel cohort) and thereafter only if a PK sample was collected or an ECG was required.

ECG, electrocardiogram; mAb, monoclonal antibody; PK, pharmacokinetic.

Hammond J, et al. N Engl J Med. 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

EPIC-HR assessed a composite primary endpoint of COVID-19-related hospitalisation or death from any cause

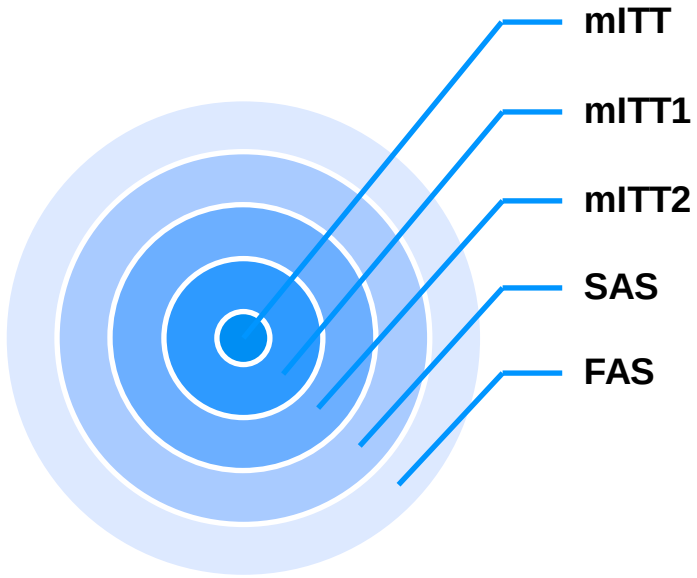


AE, adverse event; ICU, intensive care unit; mITT, modified intent-to-treat; PK, pharmacokinetics; RT-PCR, reverse-transcription polymerase chain reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Protocol for: Hammond J, et al. *N Engl J Med.* 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

Statistical analysis

- **Full analysis set (FAS):** All patients randomised to a study intervention
- **Safety analysis set (SAS):** All participants who received ≥1 dose of study intervention
- **Modified intent-to-treat (mITT):** All subjects who received ≥1 dose of study intervention, with ≥1 post-baseline visit through Day 28, and who were:



mITT2	mITT1	mITT
treated within **5 days*** of symptom onset†	treated within **5 days*** of symptom onset, and who at baseline **did not receive nor were expected to receive mAb** treatment for COVID-19	treated within **3 days*** of symptom onset, and who at baseline **did not receive nor were expected to receive mAb** treatment for COVID-19

*Inclusive; †Overall population.

FAS, final analysis set; mAb, monoclonal antibody; mITT, modified intent-to-treat; SAS, safety analysis set.

Hammond J, et al. *N Engl J Med.* 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

EPIC-HR

Participants

Study patients were enrolled at 343 centres globally

- Between 16 July and 9 December 2021, **2,246 patients** were enrolled from 343 centres worldwide

Region	% of patients randomised
United States	41
Europe	30
South America	12.3
India	9
Asia	5
Africa	0.6

Hammond J, et al. *N Engl J Med.* 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

Baseline characteristics and demographics: FAS

- Patient characteristics were similar in the two groups and were largely representative of the expected patient population

Characteristics	PAXLOVID (N=1,120)	Placebo (N=1,126)
Age, years		
Median (range)	45 (18, 86)	46.5 (18, 88)
Sex, n (%)		
Male	566 (50.5)	582 (51.7)
Female	554 (49.5)	544 (48.3)
Race, n (%)		
White	800 (71.4)	807 (71.7)
Black or African American	60 (5.4)	50 (4.4)
Asian	154 (13.8)	161 (14.3)
American Indian or Alaska Native	96 (8.6)	95 (8.4)
Multiracial	1 (<0.1)	2 (0.2)
Not reported	8 (0.7)	9 (0.8)
Unknown	1 (<0.1)	2 (0.2)

FAS, full analysis set.

Hammond J, et al. *N Engl J Med.* 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

EPIC-HR

Results

An interim analysis of the mITT population was conducted

- A pre-specified interim analysis of the primary endpoint* was performed by an external data monitoring committee once **~45%** of participants completed assessments through Day 28[1]
- At the recommendation of an independent data monitoring committee, and in consultation with the U.S. FDA, enrolment into EPIC-HR ceased on 5 November 2021 due to the **efficacy demonstrated in interim analysis results**[2]
- At the time of the decision to stop recruitment, enrolment was at 70% of the 3,000 planned, with 45% of patients located in the U.S.[2]

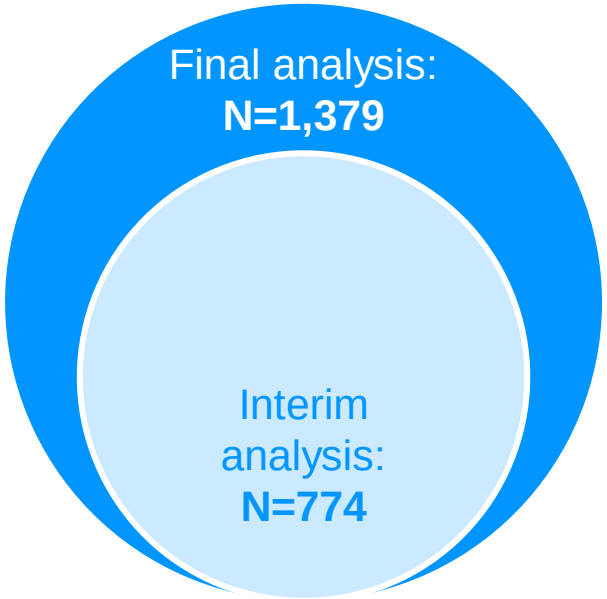
* Conducted for efficacy, futility, and sample size re-estimation.

FDA, Food and Drug Administration; mITT, modified intent-to-treat.

1. Hammond J, et al. N Engl J Med. 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print; 2. Pfizer. Pfizer's novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in interim analysis of Phase 2/3 EPIC-HR study. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate. Accessed: November 2023.

The primary endpoint was assessed in the mITT population at interim and final analysis timepoints

- **Primary endpoint*:** Proportion of participants with **COVID-19-related hospitalisation or death** from any cause through Day 28
- **mITT dataset:** All subjects who received ≥1 dose of study intervention, with ≥1 post-baseline visit through Day 28, treated within **3 days** of symptom onset, and who at baseline **did not receive nor were expected to receive mAb** treatment for COVID-19



*The cumulative proportion of patients hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan–Meier method. P-values are based on normal data approximation. Please refer to the safety section for reasons for death.
mAb, monoclonal antibody; mITT, modified intent-to-treat.
Hammond J, et al. *N Engl J Med.* 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

Primary efficacy of PAXLOVID in the mITT population was consistent between interim and final analyses

- **PAXLOVID resulted in significantly fewer COVID-19-related hospitalisation or death events by Day 28 versus placebo (P<0.001)***
  - The relative risk reduction (RRR) was **89.1%** and **88.9%** at the interim and final analysis timepoints, respectively
  - All events for PAXLOVID were COVID-19-related hospitalisations that did not result in death

	Interim analysis (N=774)		Final analysis (N=1,379)	
	PAXLOVID (N=389)	**Placebo (N=385)**	**PAXLOVID (N=697)**	**Placebo (N=682)**
Hospitalisations, n (%)	3 (0.77)	27 (7.01)	5 (0.72)	44 (6.45)
Deaths, n (%)	0	7 (1.82)	0	9 (1.32)
Absolute reduction versus placebo, % (95% CI)	6.32 (−9.04%, −3.59%)		5.81 (−7.78, −3.84)	
P-value*	<0.001		<0.001	
RRR versus placebo, %	**89.1**		**88.9**	

* P-values are based on normal data approximation.

CI, confidence interval; mITT, modified intent-to-treat; RRR, relative risk reduction.

Hammond J, et al. N Engl J Med. 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

The incidence of AEs was similar for PAXLOVID and placebo

- The incidence of AEs that emerged during or after the treatment period was similar among recipients of PAXLOVID (22.6%) and placebo (23.9%)
- Most TEAEs in both treatment groups were mild to moderate (Grade 1–2) in severity
- A lower proportion of patients receiving PAXLOVID experienced SAEs compared with patients receiving placebo
- No patients in the PAXLOVID group experienced an AE resulting in death (Grade 5); there were 13 deaths among placebo recipients*

	PAXLOVID (N=1,109)	Placebo (N=1,115)
Events that emerged during treatment period through Day 34		
Number of AEs	476	525
Patients with AEs, n (%)		
Any AE	251 (22.6)	266 (23.9)
SAE	18 (1.6)	74 (6.6)
Maximum Grade 3 or 4 AE	45 (4.1)	93 (8.3)
Maximum Grade 5 AE (death)	0	13* (1.2)
Discontinued drug or placebo because of AE	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to AE	4 (0.4)	4 (0.4)

* All reported deaths were COVID-19-related: COVID-19 pneumonia, n=8; COVID-19, n=3; pneumonitis, n=1; and acute respiratory failure, n=1.

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Hammond J, et al. *N Engl J Med.* 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

Summary

- EPIC-HR is a Phase 2 / 3, randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy, viral load, and safety associated with PAXLOVID among non-hospitalised, symptomatic adults with COVID-19 who were at high risk for progression to severe disease

- Primary endpoint: proportion of participants with COVID-19-related hospitalisation or death from any cause through Day 28
  - In participants treated within 3 days of symptom onset, and who at baseline did not receive nor were expected to receive mAb treatment for COVID-19, PAXLOVID was associated with an absolute reduction of 5.81% (P<0.001) in the primary endpoint (relative risk reduction: 88.9%)
  - There were no deaths in the PAXLOVID arm, versus nine in the placebo arm
  - Results were consistent in patients treated within 5 days of symptom onset, and in those who at baseline did not receive nor were expected to receive mAb treatment for COVID-19

- There was an approximately 10-fold decrease in viral load for PAXLOVID versus placebo

- AEs were mostly mild or moderate, and frequency was similar among recipients of PAXLOVID and placebo

AE, adverse event; mAb, monoclonal antibody.

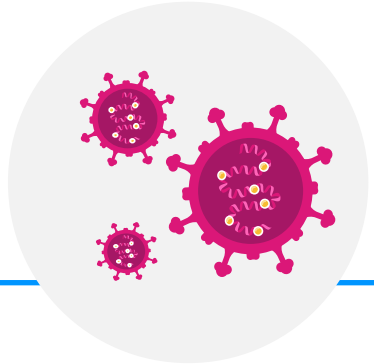
Hammond J, et al. N Engl J Med. 2022; doi: 10.1056/NEJMoa2118542. Epub ahead of print.

Authorised use of PAXLOVID (nirmatrelvir/ritonavir)

In the EU

Summary of Product Characteristics

Therapeutic indication



Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19

1. PAXLOVID Summary of Product Characteristics, UAE, Bahrain and Qatar revision date October, 2022

Posology[1]

- The recommended dosage is **300 mg Nirmatrelvir** (two 150 mg tablets) with **100 mg ritonavir** (one 100 mg tablet) all taken together orally every 12 hours for 5 days
- PAXLOVID should be administered **as soon as possible** after positive results of direct SARS-CoV-2 viral testing and **within 5 days of symptom onset**
- **Completion of the full 5-day treatment course is recommended** even if the patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with PAXLOVID

Missed dose

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

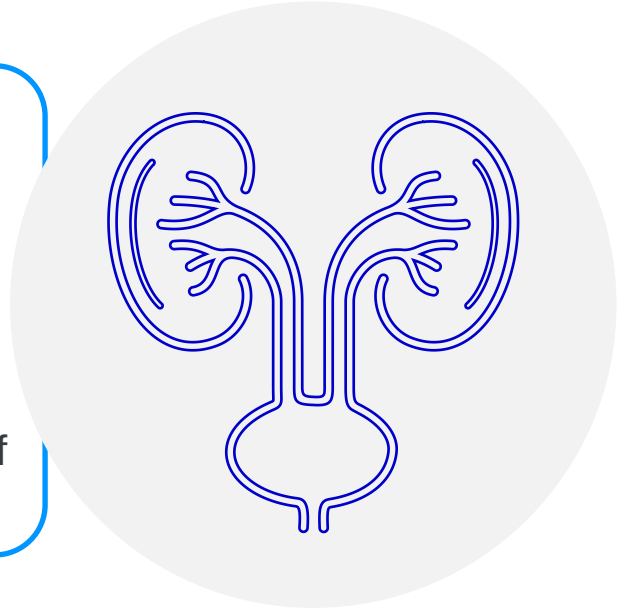
1. PAXLOVID Summary of Product Characteristics, UAE, Bahrain and Qatar revision date October, 2022

Special populations: Renal impairment[1]

- **No dosage adjustment** is needed in patients with **mild renal impairment**
- In patients with **moderate renal impairment,** the dose of **PAXLOVID should be reduced** to Nirmatrelvir /ritonavir 150 mg/100 (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements
- **PAXLOVID should not be used in patients with severe renal impairment** or with **renal failure** as the appropriate dose has not yet been determined

Special attention for patients with moderate renal impairment:

- The daily blister contains two separated parts each containing two tablets of Nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose
- Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of Nirmatrelvir should be taken with the tablet of ritonavir every 12 hours



eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease.

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Special populations: Hepatic impairment[1]

- **No dose adjustment** of PAXLOVID is needed for patients with either **mild** (Child-Pugh Class A) **or moderate** (Child-Pugh Class B) **hepatic impairment**
- **PAXLOVID should not be used in patients with severe hepatic impairment**

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Special populations: Paediatric population[1]

- The safety and efficacy of PAXLOVID in patients below 18 years of age have not been established
- No data are available

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Method of administration[1]

- For **oral** use
- Nirmatrelvir **must be co-administered** with ritonavir
  - Failure to correctly co-administer nirmatrelvir with ritonavir will result in plasma levels of this active substance that will be insufficient to achieve the desired therapeutic effect
- PAXLOVID can be taken **with or without food**
- The tablets should be **swallowed whole** and not chewed, broken or crushed.

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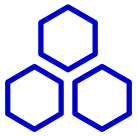
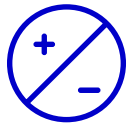
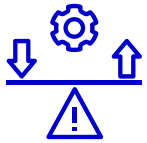
Interaction with other medicinal products and other forms of interaction[1]

- PAXLOVID is an inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when coadministered with Nirmatrelvir/ ritonavir. Thus, coadministration of Nirmatrelvir/ ritonavir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and / or life-threatening events is contraindicated.
- Ritonavir has a high affinity for several CYP isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Ritonavir also has a high affinity for P-gp and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.
- **Co-administration of other CYP3A4 substrates that may lead to potentially significant interaction should be considered only if the benefits outweigh the risks**
- Nirmatrelvir and ritonavir are CYP3A substrates; therefore, medicinal products that induce CYP3A may decrease Nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect
- As a conservative measure, the drug-drug interactions pertaining to ritonavir used in chronic HIV infection (600 mg BID when originally used as an antiretroviral agent and 100 mg BID as currently used as a pharmacokinetic enhancer with antiretroviral agents), should apply for PAXLOVID. Future investigations may enable to adjust the recommendations related to drug-drug interactions to the 5 days treatment duration of PAXLOVID.

BID, twice daily; CYP, cytochrome P450; HIV, human immunodeficiency virus; P-gp, P-glycoprotein.

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Contraindications[1]*

- **Antiarrhythmics:** amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine
- **Lipid-modifying agents:**
  - HMG Co-A reductase inhibitors: lovastatin, simvastatin
  - MTTP inhibitor: lomitapide
- **Sedative/hypnotics:** clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam

- **Alpha1-adrenoreceptor antagonist:** alfuzosin
- **Analgesics:** pethidine, piroxicam, propoxyphene
- **Antianginal:** ranolazine
- **Anticancer drugs:** neratinib, venetoclax
- **Antibiotics:** fusidic acid, rifampicin
- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **Anti-gout:** colchicine
- **Antihistamines:** astemizole, terfenadine
- **Antipsychotics/neuroleptics:** lurasidone, pimozide, clozapine, quetiapine
- **Ergot derivatives:** dihydroergotamine, ergonovine, ergotamine, methylergonovine
- **GI motility agents:** cisapride
- **Herbal products:** St. John's wort (Hypericum perforatum)
- **PDE5 inhibitor:** avanafil, sildenafil, vardenafil

* Medicinal products listed are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated with PAXLOVID.
GI, gastrointestinal; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; MTTP, Microsomal triglyceride transfer protein; PDE5, Phosphodiesterase type 5.

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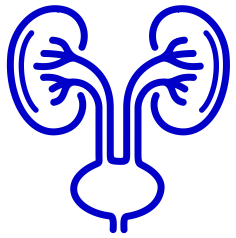
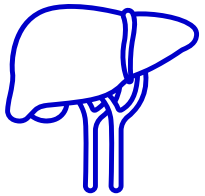
Special warnings and precautions for use (continued)[1]



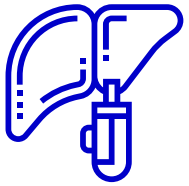
Severe renal impairment

- **Paxlovid is not recommended in patients with severe renal impairment or with renal failure** as the appropriate dose has not yet been determined.
- Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with severe renal impairment was 48% and 204% higher, respectively.



Severe hepatic impairment

- No PK and clinical data are available in patients with severe hepatic impairment
- Therefore, **PAXLOVID should not be used in patients with severe hepatic impairment**



Hepatotoxicity

- Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir
- Therefore, **caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases**, liver enzyme abnormalities, or hepatitis

AUC, Area under the curve;PK, pharmacokinetics.

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COVID19 Drug interactions made Easy

- Liverpool COVID19 drug interactions checker:
- https://www.covid19-druginteractions.org/checker

Final Thoughts

In Conclusion

- COVID19 seems here to stay for now
- Is still having a significant impact globally
- Primary care's role is vital in infection prevention and control – reducing severe disease
- Worth being familiar with guidelines for mild to moderate COVID19
- Consider testing in high risk patients and treating if positive
- Oral therapy is available for such patients

Thank you