COVID-19 Drug Treatment Guidelines National Clinical Evidence Taskforce

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Immunisation Coalition, 6th Feb 2023

NATIONAL COVID-19 CLINICAL EVIDENCE TASKFORCE

Talk outline

NATIONAL COVID-19 CLINICAL EVIDENCE TASKFORCE

- Overview of Taskforce – how guidelines are developed
- Limitations and challenges
- Overview of current treatment recommendations
  - Recent updates
  - Molnupiravir
- Additional tools – clinical flow charts, risk assessment tool

The Taskforce is a multi-disciplinary collaboration of 34 peak professional bodies across Australia, whose members provide clinical care to people with COVID-19

Role of the Taskforce during the COVID-19 pandemic:

To undertake continuous evidence surveillance to identify and rapidly synthesise emerging research

To provide national, continually updated, evidence-based guidelines for the clinical care of people with COVID-19

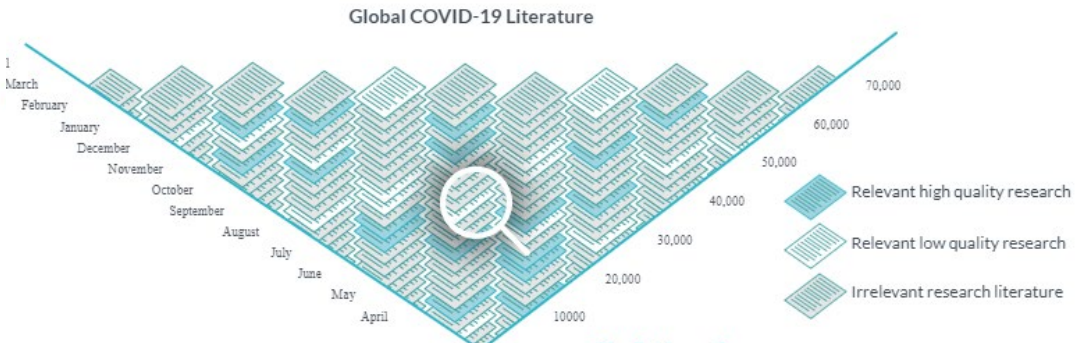
Offer a unified, national clinical voice providing guidance to Australian clinicians

Member Groups:

- Cochrane Australia (Secretariat)
- Allied Health Professions Australia (AHPA)
- Australian Association of Gerontology (AAG)
- Australian and New Zealand College of Anaesthetists (ANZCA)
- Australian and New Zealand Intensive Care Society (ANZICS)
- Australian and New Zealand Society for Geriatric Medicine (ANZSGM)
- Australian College of Critical Care Nurses (ACCCN)
- Australian College of Midwives (ACM)
- Australian College of Nursing (ACN)
- Australian College of Neonatal Nurses (ACNN)
- Australian College of Rural and Remote Medicine (ACRRM)
- Australian Primary Health Care Nurses Association (APNA)
- Australian Resuscitation Council (ARC)
- Australian Sleep Association (ASA [Sleep])
- Australian Society of Anaesthetists (ASA [Anaesthesia])
- Australasian Association of Academic Primary Care (AAAPC)
- Australasian College for Emergency Medicine (ACEM)
- Australasian College for Infection Prevention and Control (ACIPC)
- Australasian College of Paramedicine (ACP)
- Australasian Society for Infectious Diseases (ASID)
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
- College of Emergency Nursing Australasia (CENA)
- CRANAplus
- National Aboriginal Community Controlled Health Organisation (NACCHO)
- Palliative Care Australia
- Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ)
- Royal Australasian College of Physicians (RACP)
- Royal Australasian College of Surgeons (RACS)
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- Royal Australian and New Zealand College of Psychiatrists (RANZCP)
- Royal Australian College of General Practitioners (RACGP)
- Society of Hospital Pharmacists of Australia (SHPA)
- Thoracic Society of Australia and New Zealand (TSANZ)
- Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ)

COVID-19 Clinical Evidence Taskforce

NATIONAL COVID-19 CLINICAL EVIDENCE TASKFORCE



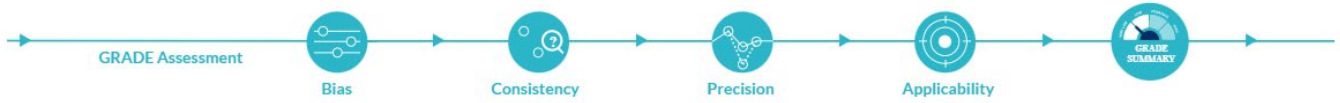
The Evidence Team

The engine room of the Taskforce.
The team of methodologists and evidence officers works with the panels to define questions for systematic review, undertake literature searches and use GRADE methods to critically appraise and present relevant findings.

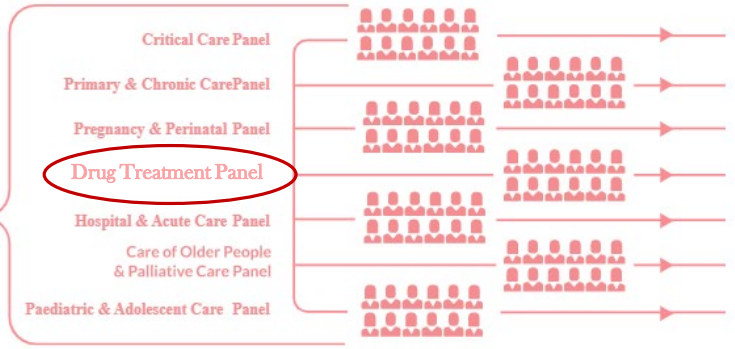
Searching

Globally, around 1000 studies are published every week that explore treatments for COVID-19. The role of the Evidence Team is to sift through these publications to identify the most reliable studies that will guide treatment recommendations.

Here are our search methods



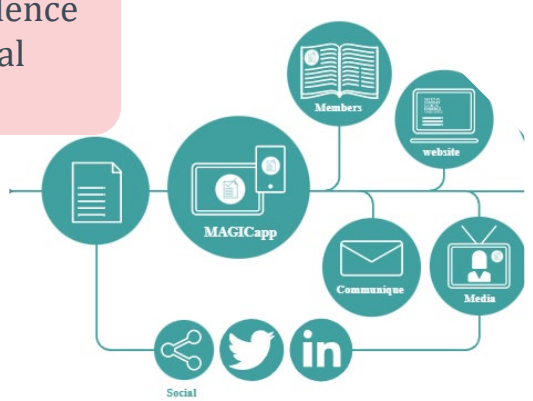
Evidence Team Prepares a Summary of the Evidence



Treatment Recommendation

Approval by Guideline Leadership Group and Steering Committee

Recommendation and evidence summary published, clinical flowcharts update



>24,000 studies screened

>200 recommendations

18 clinical flow charts

>660,000 users

>200 countries

Recommendations

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Recommended	Strong recommendation, high certainty of evidence that there is a benefit from the intervention
Conditional recommendation	Moderate certainty of evidence that there is benefit from the intervention
Only in research settings	Low certainty of evidence, insufficient evidence to determine if an intervention is effective or not
Not recommended	High certainty of evidence that there is no benefit from the intervention
Conditional recommendation against	Moderate certainty of evidence that there is no benefit from the intervention
Consensus recommendation	Can be given for or against, based on opinion of the panel, insufficient evidence to give a conditional recommendation

Assessing the Evidence

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- GRADE: Grading of Recommendations, Assessment, Development and Evaluations
- Provides a transparent and systematic approach for evaluating and presenting evidence
- For each intervention, all clinically relevant outcomes are separately evaluated, and certainty of evidence assigned for each outcome
- Where relevant, evidence considered separately for different patient groups
- Only RCTs considered, and data from new RCTs combined with data from previous RCTs
- For RCTs, certainty of evidence begins as high, downgraded for risk of bias, imprecision, inconsistency
- Recommendations based primarily on strength of the evidence for benefit vs harms
- Factors not incorporated into recommendations: cost, availability/accessibility

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CLINICAL CARE GUIDELINES

Disease-modifying treatments »

Recommended drug treatments

- Systemic corticosteroids
- Inhaled corticosteroids
- Antivirals:
  - Remdesivir
  - Nirmatrelvir/ritonavir (Paxlovid)
- Monoclonal Antibodies:
  - Sotrovimab
  - Tixagevimab/civgavimab (Evusheld)
  - Casirivimab + imdevimab (Ronapreve)
  - Regdanvimab
- Other immunomodulators
  - Tocilizumab
  - Baricitinib
  - Sarilumab
  - Abatacept
  - Infliximab

Drug treatments NOT recommended

- Aspirin
- Azithromycin
- Colchicine
- Convalescent plasma (for patients on oxygen)
- Favipiravir
- Hydroxycholoroquine
- Interferon β-1a
- Ivermectin
- Lopinavir-ritonavir
- *Molnupiravir (Conditional recommendation against)*

Drug treatments not recommended outside of clinical trials

Treatment Category	Treatment
Antiandrogens	Dutasteride
Antineoplastics	Angiotensin 2 receptor agonist (C21) Camostat mesilate Opaganib
Antiparasitic, antifungals and other anti-infective agents	Chloroquine Doxycycline Nitazoxanide
Antihypertensives	Telmisartan
Antithrombotic, antiplatelets and related therapies	Sulodexide
Antivirals	Baloxavir marboxil Darunavir-cobicistat Enisamium Ensovibep Sofosbuvir-daclatasvir Triazavirin Umifenovir
Human and blood derived products	Human unbilical cord mesenchymal stem cells Intravenous immunoglobulin
Immunomodulating drugs	Anakinra CD24Fc Lenzilumab Ruxolitinib Tofacitinib Interferon beta-1a (inhaled) Interferon beta-1b Interferon gamma Interferon kappa plus TFF2 Peginterferon lambda
Other antibody related therapies	Bamlanivimab Bebtelovimab
Other therapies	Almitrine Aprepitant Bromhexine hydrochloride Fluvoxamine Metformin Recombinant human GCSF Sabizabulin
Vitamins, supplements and cofactors	Combined metabolic activators (CMA) N-acetylcysteine Vitamin C Vitamin D analogues Zinc

Corticosteroids vs Standard Care

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5789 participants in 9 studies	316 per 1000	265 per 1000 Difference: **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Moderate** Due to some inconsistency	Corticosteroids probably decrease death at day 28 in adults who require oxygen. Intervention
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.80 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies	234 per 1000	187 per 1000 Difference: **47 fewer per 1000** (CI 95% 110 fewer — 44 more)	**Moderate** Due to serious inconsistency	Corticosteroids probably have little impact on serious adverse events in adults who require oxygen. No imp. diff.
Invasive mechanical ventilation or death [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3883 participants in 1 study	320 per 1000	282 per 1000 Difference: **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Moderate** Due to only one study	Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen. Intervention
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.10 (CI 95% 1.06 — 1.15) Based on data from 4952 participants in 2 studies	582 per 1000	640 per 1000 Difference: **58 more per 1000** (CI 95% 35 more — 87 more)	**Moderate** Due to serious inconsistency	Corticosteroids probably increases discharge from hospital in adults who require oxygen. Intervention
All-cause mortality [adults not requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1.00 — 1.61) Based on data from 1535 participants in 1 study	140 per 1000	178 per 1000 Difference: **38 more per 1000** (CI 95% 0 — 85 more)	**Moderate** Due to only one study	Corticosteroids probably increase death in adults who do not require oxygen. Comparator

6.1.3.1 Corticosteroids (systemic) for adults

Recommended

Use intravenous or oral dexamethasone for up to 10 days (or acceptable alternative regimen) in **adults with COVID-19 who require oxygen** (including mechanically ventilated patients).

The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- *hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days*
- *prednisolone: oral (50 mg), daily for up to 10 days*
- *methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain*

It is unclear whether older people living with frailty or cognitive impairment, or those requiring palliative care were included in the studies on which this recommendation is based. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

It is unclear whether high-dose corticosteroids (12–24 mg dexamethasone per day or equivalent for 10 days) provides any additional benefit compared with low-dose corticosteroids (6 mg dexamethasone per day or equivalent for 10 days) for the treatment of COVID-19 in hospitalised adults who require oxygen. Until further evidence is available, and considering the potential side effects associated with the use of high-dose corticosteroids, the Taskforce recommends 6 mg dexamethasone (or equivalent) per day for 10 days in line with the RECOVERY trial [38].

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation against

Do not routinely use dexamethasone (or other systemic corticosteroid) to treat COVID-19 in **adults who do not require oxygen**.

Corticosteroids may still be considered for other evidence-based indications in people who have COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance *[27]* of seven randomised trials of patients with critical COVID-19 *[31][32][33][34][36][37][497]*, one study of patients with moderate, severe or critical COVID-19 *[38]*, and one study of patients with severe COVID-19 *[39]*. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress *[28]* and sepsis *[29]*—provided indirect evidence for serious adverse events.

We have found three new studies comparing corticosteroids with standard care (Corral-Gudino et al. (GLUCOCOVID) Wien Klin Wochenschr doi: 10.1007/s00508-020-01805-8, Tang et al. Respiration doi: 10.1159/000512063 and Jamaati et al. Eur J Pharmacol doi: 10.1016/j.ejphar.2021.173947). These studies are currently under review and, although not expected to change the recommendation, an updated recommendation will be included in a future version of the guideline.

Study characteristics
Three studies compared dexamethasone with standard care *[34][36][38]*, three compared hydrocortisone with standard care *[31][33][497]* and three compared methylprednisolone with standard care *[32][37][39]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications possibly shows no difference in the incidence of gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was probably associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
In patients with severe or critical illness, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect) and invasive mechanical ventilation or death, and discharge from hospital (due to serious imprecision).

In patients with moderate illness, certainty is low for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to very serious imprecision (reliance on a single study and wide confidence intervals).

Challenges/limitations

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Evidence based guidelines – limited by quality/relevance of RCTs

- Study populations don't match current situation
  - Mostly delta variant
  - Vaccinated patients not always included
  - Small numbers of immunocompromised patients
- How to deal with *in vitro* data?

Consensus recommendations – allows Taskforce to provide recommendations which may not necessarily be based on evidence

Increasingly lengthy remarks added to recommendations…

6.1.5.1 Nirmatrelvir plus ritonavir (Paxlovid) for adults

Conditional recommendation

Consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in unvaccinated adults* with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which nirmatrelvir plus ritonavir is conditionally recommended for use (see Additional information), decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in individuals who have received any COVID-19 vaccine. See consensus recommendation for guidance on use of nirmatrelvir plus ritonavir in vaccinated adults or in immunocompromised patients regardless of vaccination status.*

Additional information

In adults with confirmed COVID-19 who do not require oxygen, nirmatrelvir plus ritonavir (Paxlovid) probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on a single phase 2/3 trial comparing nirmatrelvir plus ritonavir with placebo in 2246 unvaccinated adults with PCR-confirmed COVID-19 and mild illness (EPIC-HR) [417]. Within this trial participants were treated with oral nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days.

The benefit of nirmatrelvir plus ritonavir is likely to be greatest in those with the greatest risk of severe disease. Based on the population included within the trial, evidence demonstrates a reduction in hospitalisation when used in individuals with one or more of the following risk factors for disease progression:

- *Age ≥ 60 years*
- *Diabetes (requiring medication)*
- *BMI ≥ 25 kg/m2*
- *Cardiovascular disease*
- *Hypertension*
- *Chronic lung disease*

There were insufficient numbers of participants with the following risk factors to determine the extent to which nirmatrelvir plus ritonavir impacts hospitalisation or death, however as these conditions frequently result in poorer outcomes for patients following SARS-CoV-2 infection, they will likely benefit from treatment:

- *Chronic kidney disease (but where the eGFR ≥ 30 mL/min)**
- *Immunosuppressed (e.g. bone marrow or organ transplantation, primary immune deficiencies, prolonged use of immune-weakening medications)*
- *Medical related technological dependence (e.g. CPAP not related to COVID-19)*
- *HIV positive (CD4+ count < 200 cells/mm^3)*
- *Neurodevelopmental disorders (e.g. cerebral palsy, Down syndrome)*
- *Cancer (other than localised skin cancer)*
- *Sickle cell disease*

** Individuals with an eGFR < 30 mL/min were excluded from the trial. In individuals with CKD and an eGFR of 30–60 mL/min, the dose of nirmatrelvir should be halved; i.e. nirmatrelvir/ritonavir 150/100 mg twice daily for 5 days (FDA EUA).*

Pregnant and breastfeeding women and children and adolescents were not included in the trial.

Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial.

The study was conducted before the Omicron variant was prevalent. As a result, there are no data regarding the effectiveness of nirmatrelvir plus ritonavir specific to the Omicron variant.

The Taskforce notes the interim results of the EPIC-SR study from Pfizer. This trial is evaluating nirmatrelvir plus ritonavir (Paxlovid) in unvaccinated adults at low risk of hospitalisation or death, or vaccinated adults with one or more risk factors for progressing to severe illness. An analysis at 80% of enrolled patients found that 0.7% (3/428) of those who received Paxlovid were hospitalised compared with 2.4% (10/426) of patients who received placebo. No deaths were reported. These data will be reviewed when the results become available.

Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and are immunocompromised; or are at particularly high risk of severe disease on the basis of advanced age and multiple risk factors.

Additional information

Decisions about the appropriateness of nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

Available research does not currently provide enough evidence to determine the benefits of nirmatrelvir plus ritonavir (Paxlovid) in specific subgroups of adults. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which adults are most likely to benefit from nirmatrelvir plus ritonavir.

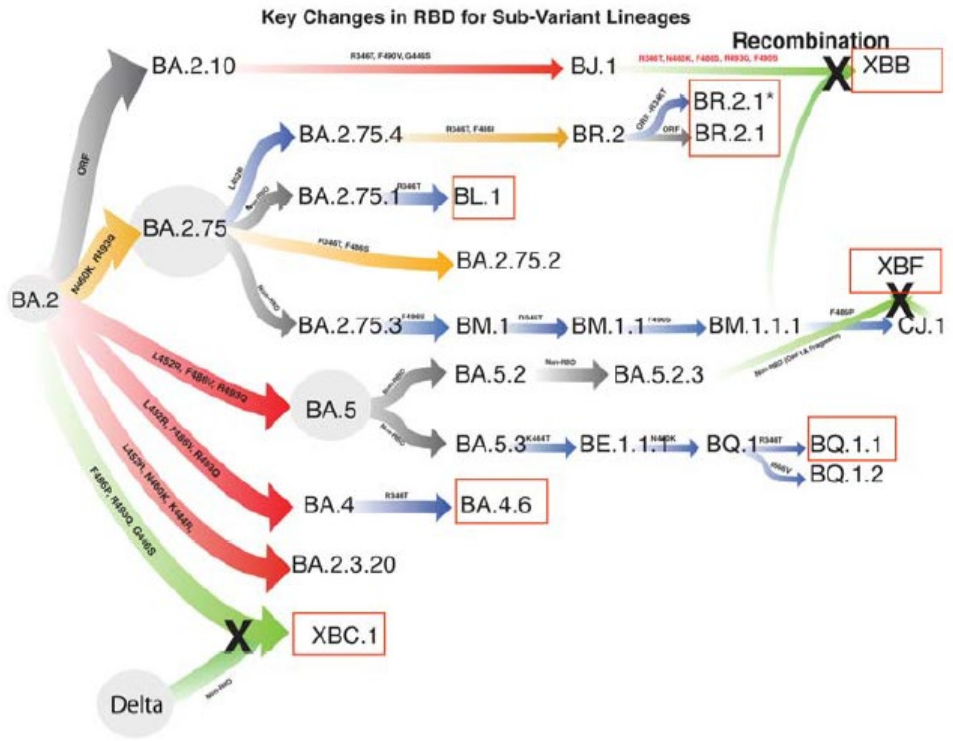
There is no evidence evaluating the effectiveness of nirmatrelvir plus ritonavir in individuals who have received any COVID-19 vaccine. Given this, and the lower risk of deterioration in these people, it is less likely that nirmatrelvir plus ritonavir will be of benefit in individuals who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, unless the patient is immunocompromised.

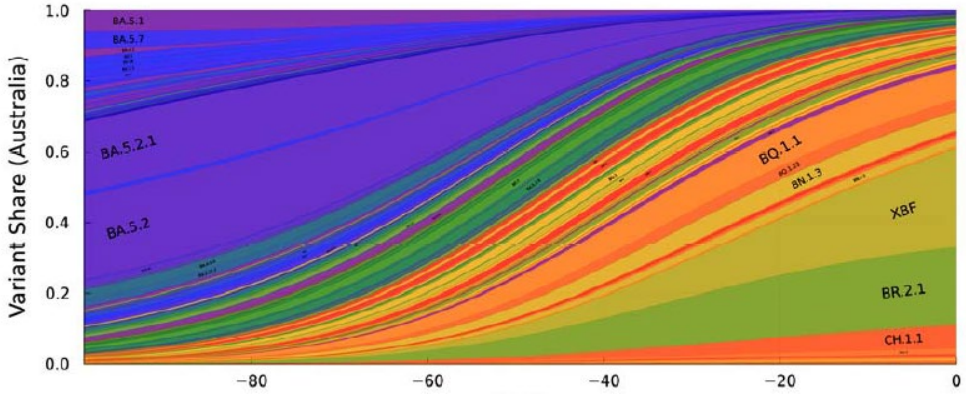
There is limited evidence on the effectiveness of nirmatrelvir plus ritonavir in immunocompromised patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that nirmatrelvir plus ritonavir will be beneficial for immunocompromised patients.

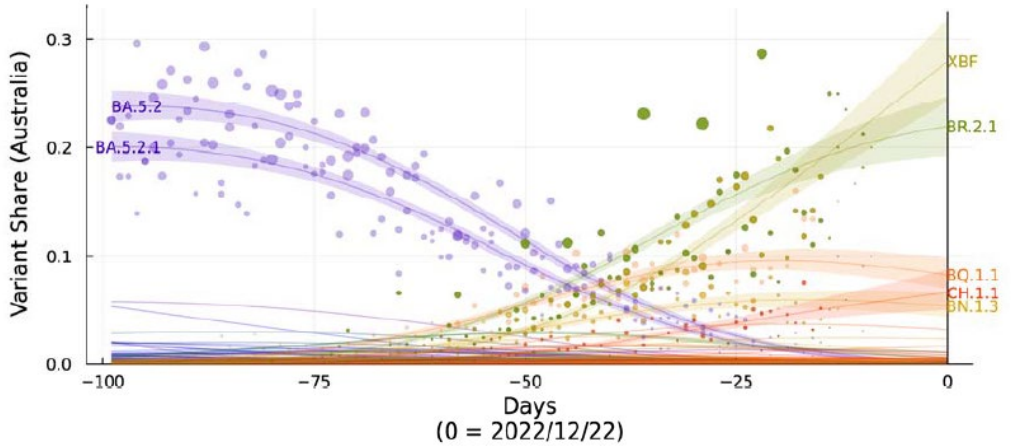
Emerging variants and *in vitro* data

Emergence and antibody evasion of BQ, BA.2.75 and SARS-CoV-2 recombinant sublineages in the face of maturing antibody breadth at the population level

Akerman et al. medRxiv Jan 17, 2023







mAbs	Developer/Product	IC50 ng/mL Ancestral (A.2.2)	XBB.1	BQ.1.1	BR.2.1 (R346T)	BR.2.1	BA.2.75.2	XBC.1	XBF
Sotrovimab	GSK/Xevudy	328.2	889.6	nn	880.7	3561.5	1756.8	1419.0	nn
Cilgavimab + Tixagevimab (1:1)	AstraZeneca/EVUSHELD	6.6	nn	nn	nn	nn	nn	614.2	nn
Cilgavimab (AZD1061)		18.4	nn	nn	nn	nn	nn	365.8	nn
Tixagevimab (AZD8895)		4.5	nn	nn	nn	nn	nn	nn	nn

nn, non-neutralising at 10,000ng/ml

Search SARS-CoV-2 resistance database

Stanford University
CORONAVIRUS ANTIVIRAL & RESISTANCE DATABASE
A Stanford HIVDB team website. Last updated on 2/2/2023, 8:21:59 AM.

Reset filters • View summary data • Suggest new study • report error

Last updated at 2/2/2023, 5:52:45 AM

covdb.stanford.edu

References
Any

Convalescent plasma
Any

Vaccinee plasma
Any

Monoclonal antibodies
Cilgavimab + Tixagevimab

Variants
Omicron/BR.2.1

Mutations
Any

RBM Class II/RBM Class I monoclonal antibodies

Cilgavimab (CIL) + Tixagevimab (TIX)

Cilgavimab and Tixagevimab (aka AZD7447) is a comination of two ACE2-competing monoclonal antibodies that bind RBD in the up and down configuration. Tixagevimab and Cilgavimab bind to nonoverlapping RBD epitopes. This combination is granted an emergence use authorization (EUA) by the FDA on December 8, 2021.

Cilgavimab and Tixagevimab are both developed by AstraZeneca.

MAb: Cilgavimab
Synonyms: COV2-2130, AZD1061
Availability: EUA
MAb Target: RBD
MAb Class: RBM Class II
Epitopes: 345, 346, 439, 440, 441, 443, 444, 445, 446, 447, 448, 449, 450, 452, 484, 490, 492, 493, 494, 499

MAb: Tixagevimab
Synonyms: COV2-2196, AZD8895
Availability: EUA
MAb Target: RBD
MAb Class: RBM Class I
Epitopes: 455, 456, 458, 475, 476, 477, 478, 479, 484, 485, 486, 487, 488, 489, 493

Omicron/BR.2.1 variant

Susceptibility data

CIL/TIX (n=3)
Omicron/BR.2.1 (n=3)

Monoclonal antibody - Variant / mutation combination: 1 publication, 3 results
Individual sample data are available: 1 publication, 3 results

MAb Susceptibility Data

Table dimensions: Reference Assay Antibodies Control Variant (Deselect all · Reset)

3 results; 3 experimental conditions (rows); 1 publication.

Copy to clipboard

Reference	Assay	Section	Antibodies	Control	Variant	# Results	IC50 (ng/ml)	Fold Reduction	Data Availability
Akerman, A (2022)	Virus isolate	Figure 4	Cilgavimab	Wild Type (A.2.2) IC50: 18 ng/ml	Omicron/BR.2.1	1	>100,000	>1000	✓
Akerman, A (2022)	Virus isolate	Figure 4	Tixagevimab	Wild Type (A.2.2) IC50: 4.5 ng/ml	Omicron/BR.2.1	1	>100,000	>1000	✓
Akerman, A (2022)	Virus isolate	Figure 4	Cilgavimab + Tixagevimab	Wild Type (A.2.2) IC50: 6.6 ng/ml	Omicron/BR.2.1	1	>100,000	>1000	✓

More challenges/limitations…

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- Relative effectiveness of recommended agents
    - Generally no head to head studies comparing recommended agents, eg. remdesivir vs Paxlovid, tocilizumab vs baricitinib (dex vs bari a recent exception)
- Use of agents in combination
    - Few, if any, studies evaluating safety of agents in combination
- Treatments in highly immunosuppressed

Lancet Respir Med 2022;
10: 888–99

Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial

Cameron R Wolfe, Kay M Tomashek, Thomas F Patterson, Carlos A Gomez, Vincent C Marconi, Mamta K Jain, Otto O Yang, Catharine I Paules, Guillermo M Ruiz Palacios, Robert Grossberg, Michelle S Harkins, Richard A Mularski, Nathaniel Erdmann, Uriel Sandkovsky, Eyad Almasri, Justino Regalado Pineda, Alexandra W Dretler, Diego Lopez de Castilla, Angela R Branche, Pauline K Park, Aneesh K Mehta, William R Short, Susan L F McLellan, Susan Kline, Nicole M Iovine, Hana M El Sahly, Sarah B Doernberg, Myoung-don Oh, Nikhil Huprikar, Elizabeth Hohmann, Colleen F Kelley, Mark Holodniy, Eu Suk Kim, Daniel A Sweeney, Robert W Finberg, Kevin A Grimes, Ryan C Maves, Emily R Ko, John J Engemann, Barbara S Taylor, Philip O Ponce, LuAnn Larson, Dante Paolo Melendez, Allan M Seibert, Nadine G Rouphael, Joslyn Strebe, Jesse L Clark, Kathleen G Julian, Alfredo Ponce de Leon, Anabela Cardoso, Stephanie de Bono, Robert L Atmar, Anuradha Ganesan, Jennifer L Ferreira, Michelle Green, Mat Makowski, Tyler Bonnett, Tatiana Beresnev, Varduhi Ghazaryan, Walla Dempsey, Seema U Nayak, Lori E Dodd, John H Beigel, Andre C Kalil, for the ACTT-4 Study Group*

- 1010 patients requiring O_2 (but not mechanically ventilated) randomised to remdesivir + bari + placebo or remdesivir + dexamethasone + placebo
- Dec 2020 – April 2021 (delta variant)
- No difference in 28-day mortality (12.4% in dex group vs 13.0% in baricitinib group)
- Adverse events: 37% in dex group vs 30%, p=0.014
- Treatment related AEs: 10% in dex group vs 4% in baricitinib group, p=0.00041
- Grade 3 or 4 AEs: 36% in dex group vs 28% in baricitinib group, p=0.012

Taskforce recommendations for Immunomodulators:

- Recommendations for: dexamethasone, tocilizumab, baricinitib, infliximab, abatercept
- Current evidence suggests that dexamethasone is safe in combination with other immunomodulators
- Limited data about safety of other combinations (although RECOVERY demonstrated benefit of dexamethasone + tocilizumab + baricitinib)
- Due to concerns about increased risk of side effects with multiple immunomodulators, the Taskforce recommends dexamethasone + one other immunomodulator
- In view of the ACTT-4 study by Wolfe et al., baricitinib may be considered as a stand-alone treatment in patients considered to be at high risk of side effects from dexamethasone

Immunomodulators for severe COVID-19

	Baricitinib	**Tocilizumab**	**Abatacept**	**Infliximab**
Drug Class	JAK Inhibitor	IL-6 receptor antagonist	Fusion protein (binds to CD80 and CD86 and attenuates T cell responses)	TNF-alpha inhibitor
Prescribed use	Rheumatoid arthritis	Rheumatoid arthritis	Psoriatic arthritis	Ulcerative colitis
Dose and route of administration	4 mg oral daily 14 – 28 days	8 mg/kg iv single dose	10 mg/kg iv single dose	5 mg/kg iv single dose
No. of studies (patients)	4 (n=10,815)	11 (n=7,200)	1 (n=1,019)	1 (n=1,033)
All-cause mortality absolute risk reduction (95% CI)	21 fewer per 1000 (32 fewer – 9 fewer)	39 fewer per 1000 (60 fewer – 21 fewer)	41 fewer per 1000 (71 fewer – 2 more)	45 fewer per 1000 (72 fewer – 5 more)
Relative Risk (95% CI)	0.84 (0.76 – 0.93)	0.79 (0.70 – 0.90)	0.73 (0.53 – 1.01)	0.50 (0.50 – 0.96)
Certainty of evidence	High	High	Moderate	Moderate
Use in renal impairment	Dose adjustment required, avoid if eGFR <30	No dose adjustment required	No dose adjustment required	No dose adjustment required
Pregnancy Category	**D**	C	C	C
Other comments			No evidence for mechanically ventilated patients	

*Sarilumab not included as not available in Australia

Treatment options (antivirals) for mild COVID-19

	Nirmatrelvir/ritonavir (Paxlovid)	Remdesivir	Molnupiravir
Drug Class	Antiviral	Antiviral	Antiviral
Dose and route of administration	300 mg/100 mg orally BD for 5 days	200 mg iv D1, then 100 mg iv D2 and D3	800 mg orally BD for 5 days
Study (number of participants)	EPIC-HR (n=2246)	PINETREE (n=562)	MOVe-OUT (n=1433) and PANORAMIC (n=25,783)
Absolute risk reduction, hospitalization or death	55 fewer per 1000 (95% CI 59 – 47 fewer)	46 fewer per 1000 (95% CI 57 – 16 fewer)	1 more per 1000 (95% CI 2 fewer – 3 more)
Relative Risk	0.12 (95% CI 0.06 – 0.25)	0.28 (95% CI 0.11 – 0.75)	0.40 (95% CI 0.08– 2.06)
Certainty of evidence	Moderate	Moderate	High – no impact on mortality or hospitalisation
Use in renal impairment	**Dose adjustment required. Not recommended if eGFR <30**	Ok	Ok
Pregnancy Category	**B3**	B2	**D**
Other considerations	**Multiple drug interactions**		

MOVE-OUT

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

- Double-blind, randomised placebo controlled
- 1433 non-hospitalised unvaccinated adults

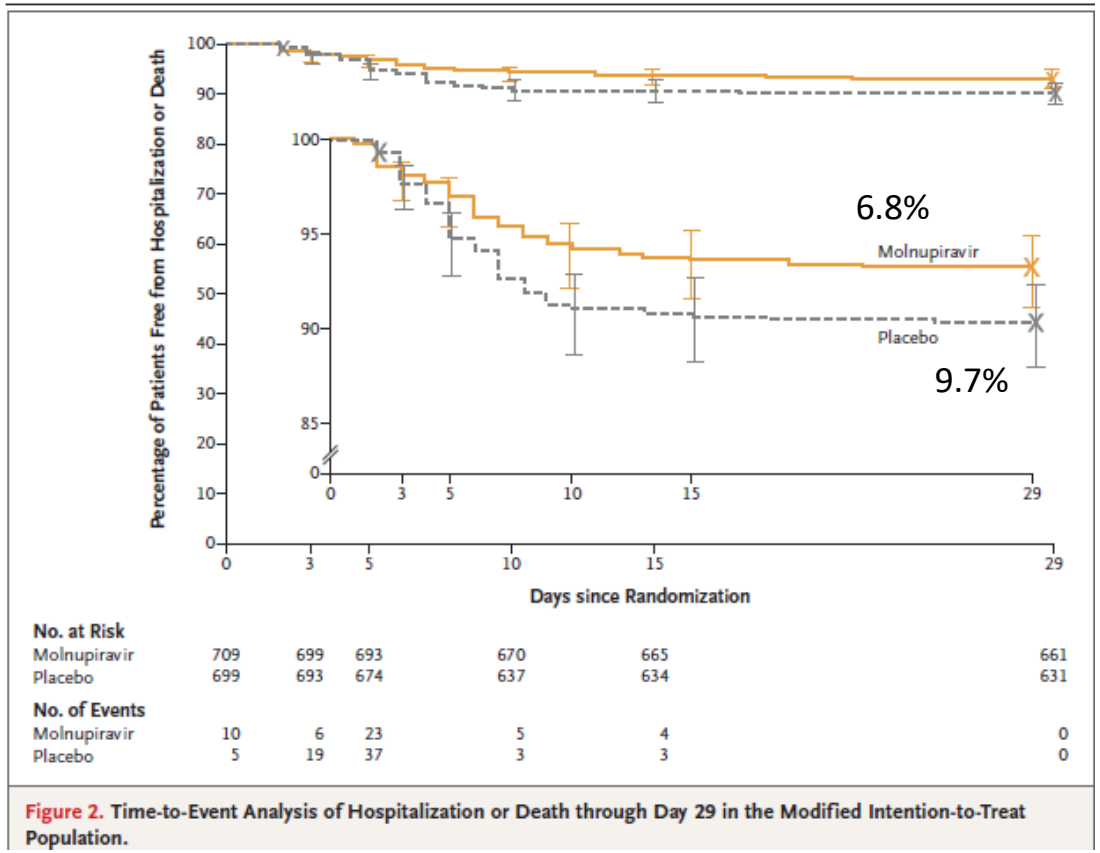


Figure 2. Time-to-Event Analysis of Hospitalization or Death through Day 29 in the Modified Intention-to-Treat Population.

Hospitalisation of death: 48/709 (6.8%) molnupiravir vs 68/699 (9.7%) placebo
RR 0.70 (95% CI 0.49 – 0.99)

Subgroup analyses based on study period and variant

	Molnupiravir	Placebo	RR (95% CI); Absolute effect estimate (range)
Interim	28/385 (7.3%)	53/377 (14.1%)	0.52 (0.33, 0.80); 68 fewer (94 – 28 fewer)
Final	48/709 (6.8%)	68/699 (9.7%)	0.70 (0.49, 0.99); 29 fewer (49 fewer – 1 fewer)*
Final - interim	20/324 (6.2%)	15/322 (4.7%)	1.33 (0.69, 2.54); 16 more (15 fewer – 72 more)*
Delta	18/237 (7.6%)	22/221 (10%)	0.76 (0.42, 1.38); 24 fewer (58 fewer – 38 more)
Gamma	0/37 (0%)	9/47 (19.2%)	0.07 (0.00, 1.11); 178 fewer (191 fewer – 21 more)
Mu	6/75 (8%)	13/82 (15.9%)	0.50 (0.20, 1.26); 80 fewer (127 fewer – 41 more)
Other	5/47 (10.6%)	7/38 (18.4%)	0.58 (0.20, 1.68); 77 fewer (147 fewer – 125 more)
Remainder (NR)	19/313 (6.1%)	16/311 (5.1%)	1.18 (0.62, 2.25); 9 more (19 fewer – 64 more)

Consensus recommendation

Consider use of molnupiravir within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and have one or more risk factors for disease progression, only where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Butler et al. Lancet 2023; 401:281

Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

- 26,411 patients enrolled in community, > 50 yr, or >18 yrs with comorbidities, within 5 days of symptom onset, confirmed COVID-19
- randomized to molnupiravir or usual care alone
- Primary outcome: all-cause hospitalization or death at 28 days
- Patients enrolled between Dec 2021 – April 2022 (Omicron variant)

- Patients at very high risk (ie, immunosuppressed or “extremely clinical vulnerable”) eligible to receive monoclonal Abs (sotrovimab) or antivirals through specialist COVID-19 clinics
- Participants followed up via online daily diary, non-responders telephoned on days 7, 14, 28
- Participants asked to record: symptoms rated on ordinal scale, overall well-being (1 – 10), hospitalisation of contact with health services, medications for COVID-19, household contacts with COVID-19

Baseline characteristics

	Molnupiravir plus usual care (n=12774)	Usual care (n=12 934)
Age, years	56·7 (12·5)	56·5 (12·7)
Days from symptom onset to randomisation	2 (1–3)	2 (1–3)
NHS priority category		
Age ≥80 years	256 (2%)	271 (2%)
Age 75–79 years	537 (4%)	574 (4%)
Age 70–74 years or 18–69 years and clinically extremely vulnerable	1116 (9%)	1111 (9%)
Age 65–69 years, not clinically extremely vulnerable	1493 (12%)	1464 (11%)
Age 18–64 years and in an at-risk group	6514 (51%)	6576 (51%)
Age 60–64 years, not clinically extremely vulnerable or in an at-risk group	745 (6%)	766 (6%)
Age 55–59 years, not clinically extremely vulnerable or in an at-risk group	994 (8%)	1060 (8%)
Age 50–54 years, not clinically extremely vulnerable or in an at-risk group	1119 (9%)	1112 (9%)
Predicted risk quintile‡		
1	2483 (19%)	2553 (20%)
2	2672 (21%)	2632 (20%)
3	2511 (20%)	2656 (21%)
4	2774 (22%)	2760 (21%)
5	2334 (18%)	2333 (18%)
COVID-19 vaccine doses		
At least one	12 632 (99%)	12 803 (99%)
One	86 (1%)	87 (1%)
Two	518 (4%)	454 (4%)
Three	11795 (92%)	12 022 (93%)

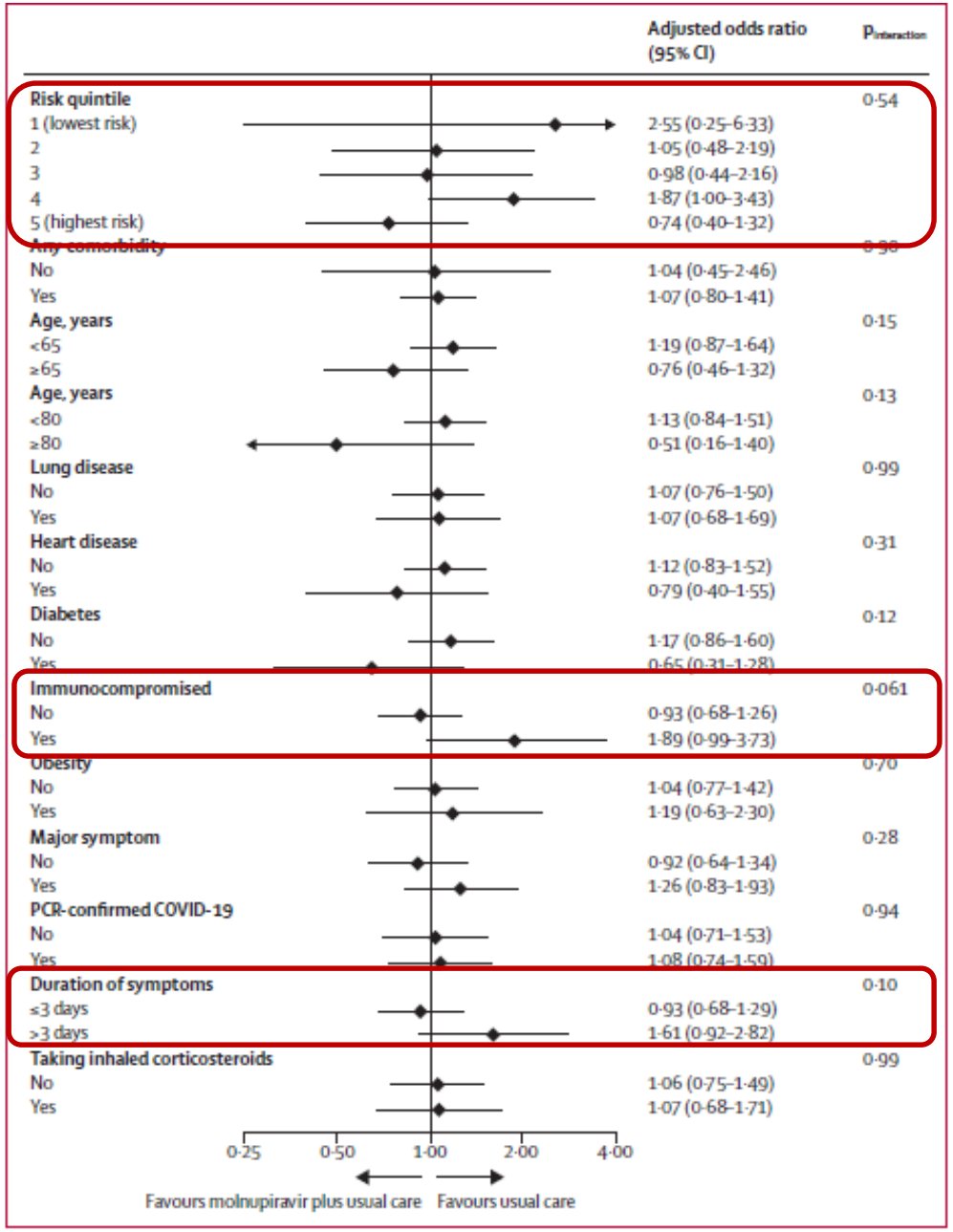
n=3865

n=10,201

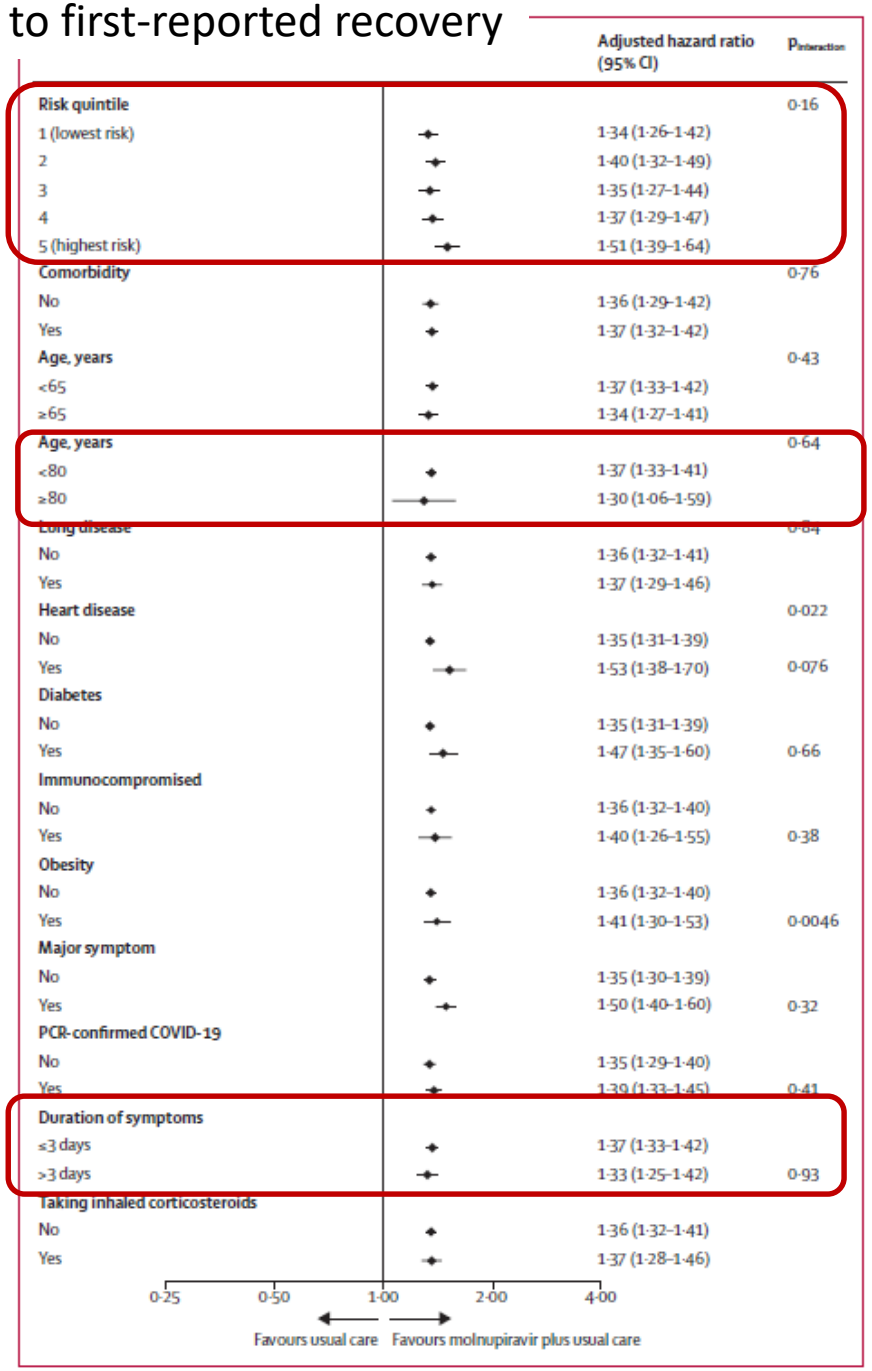
Outcomes

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% BCI)	Estimated benefit (95% BCI)	Probability of superiority
Primary outcomes					
Hospitalisations	103	96	..	..	..
Deaths	3	5	..	..	..
Hospitalisation or death	105/12 529 (1%)	98/12 525 (1%)	1·06 (0·81–1·41)*	..	0·33*
Secondary outcomes					
First reported recovery	9728/12 403 (78%)	8374/12 140 (69%)	..	..	..
Days to first reported recovery	9 (5–23)	15 (7–not reached)	1·36 (1·32–1·40)†	4·2 (3·8–4·6)†	>0·99†
Early sustained recovery	3628/11 395 (32%)	2446/10 823 (23%)	1·62 (1·53–1·72)‡	..	>0·99‡
Sustained recovery	8547/12 403 (69%)	7302/12 140 (60%)	..	..	..
Days to sustained recovery	21 (10–not reached)	24 (14–not reached)	1·24 (1·21–1·28)†	3·5 (3·0–3·9)†	>0·99†
Alleviation of all symptoms	8992/9664 (93%)	8351/9395 (89%)	..	..	..
Days to alleviations of all symptoms	4 (2–7)	4 (2–9)	1·18 (1·15–1·22)†	0·66 (0·54–0·78)†	>0·99†
Sustained alleviation of all symptoms	8164/9664 (84%)	7510/9395 (80%)	..	..	..
Days to sustained alleviation of all symptoms	9 (3–22)	12 (4–25)	1·15 (1·11–1·19)†	2·01 (1·58–2·45)†	>0·99†
Initial reduction of symptom severity	10 850/12 375 (88%)	9819/12 123 (81%)	..	..	..
Days to initial reduction of symptom severity	7 (4–14)	9 (5–19)	1·28 (1·24–1·31)†	1·8 (1·60–2·00)†	>0·99†
Participant rating of wellness§					
Day 7	7·3 (1·7)	6·8 (1·8)	0·5 (0·5–0·6)¶	..	<0·0001¶
Day 14	7·9 (1·7)	7·6 (1·7)	0·3 (0·2–0·3)¶	..	<0·0001¶
Day 21	8·2 (1·6)	8·0 (1·7)	0·2 (0·1–0·2)¶	..	<0·0001¶
Day 28	8·4 (1·5)	8·3 (1·6)	0·2 (0·1–0·2)¶	..	<0·0001¶
New infections in household	3887/10 803 (36%)	3873/10 548 (37%)	0·97 (0·91–1·02)*	..	0·88*
Contact with health and social care services					
NHS 111	583/12 401 (5%)	776/12 134 (6%)	0·72 (0·64–0·80)*	..	>0·99*
General practitioner	2425/12 401 (20%)	2876/12 135 (24%)	0·77 (0·73–0·82)*	..	>0·99*
Ambulance service (not hospitalised)	342/12 396 (3%)	331/12 120 (3%)	1·01 (0·87–1·18)*	..	0·46*
Community nurse	265/12 401 (2%)	275/12 131 (2%)	0·94 (0·79–1·11)*	..	0·78*
Physiotherapist	141/12 401 (1%)	90/12 131 (1%)	1·55 (1·18–2·01)*	..	0·0006*
Counsellor	91/12 401 (1%)	106/12 131 (1%)	0·84 (0·63–1·10)*	..	0·90*
Social worker	27/12 401 (<1%)	32/12 131 (<1%)	0·84 (0·49–1·35)*	..	0·78*
Home carer	88/12 400 (1%)	95/12 129 (1%)	0·90 (0·66–1·20)*	..	0·78*
Occupational therapist	261/12 400 (2%)	240/12 131 (2%)	1·07 (0·90–1·26)*	..	0·26*
Hospital emergency department	702/12 401 (6%)	674/12 132 (6%)	1·02 (0·92–1·14)*	..	0·37*
Outpatient respiratory clinic	234/12 401 (2%)	252/12 130 (2%)	0·90 (0·75–1·07)*	..	0·88*
Hospital at home for COVID-19	350/12 401 (3%)	430/12 131 (4%)	0·79 (0·68–0·91)*	..	>0·99*
Other services	583/12 401 (5%)	646/12 130 (5%)	0·87 (0·77–0·98)*	..	0·99*

Hospitalisation or death



Time to first-reported recovery



Molnupiravir (Lagevrio)

Conditional recommendation against Updated

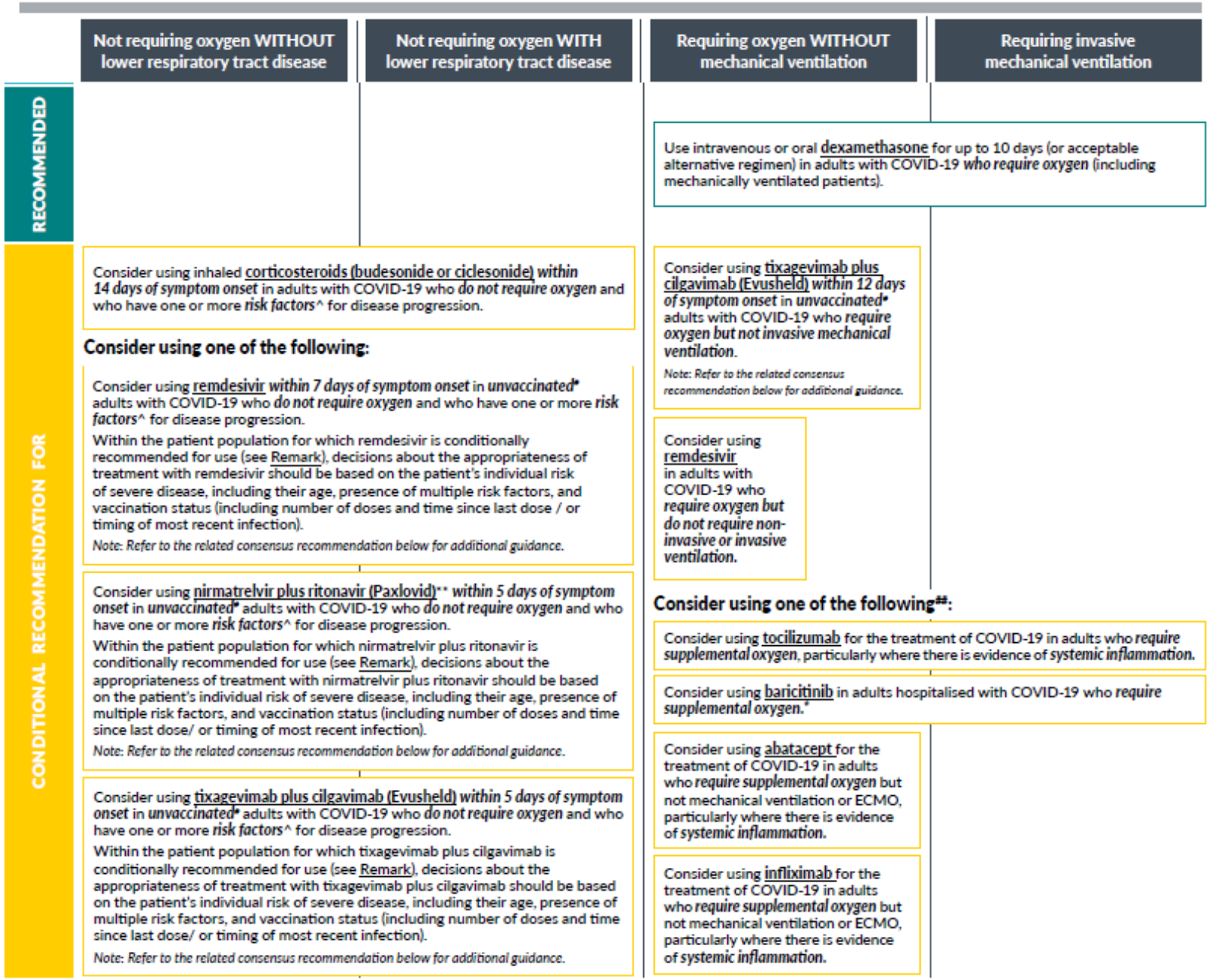
Do not routinely use molnupiravir for the treatment of COVID-19.

- Rationale:
  - High certainty of evidence that molnupiravir does not reduce hospitalisations or deaths
  - Molnupiravir may improve recovery, but low certainty of evidence due to serious risk of bias

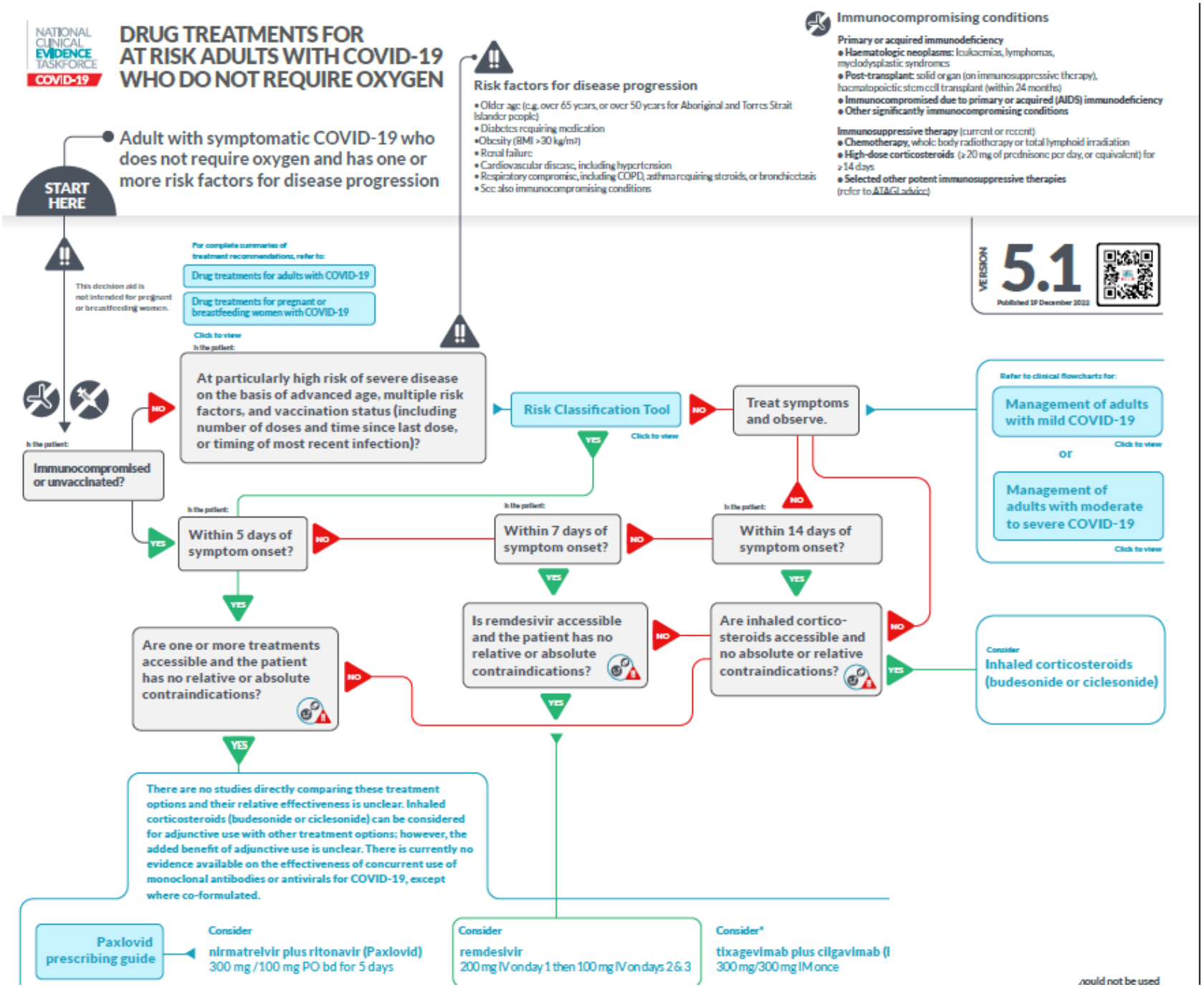
CLINICAL FLOWCHARTS

Flowcharts incorporating living guideline recommendations and guidance issued or endorsed by Taskforce members

DRUG TREATMENTS FOR ADULTS WITH COVID-19



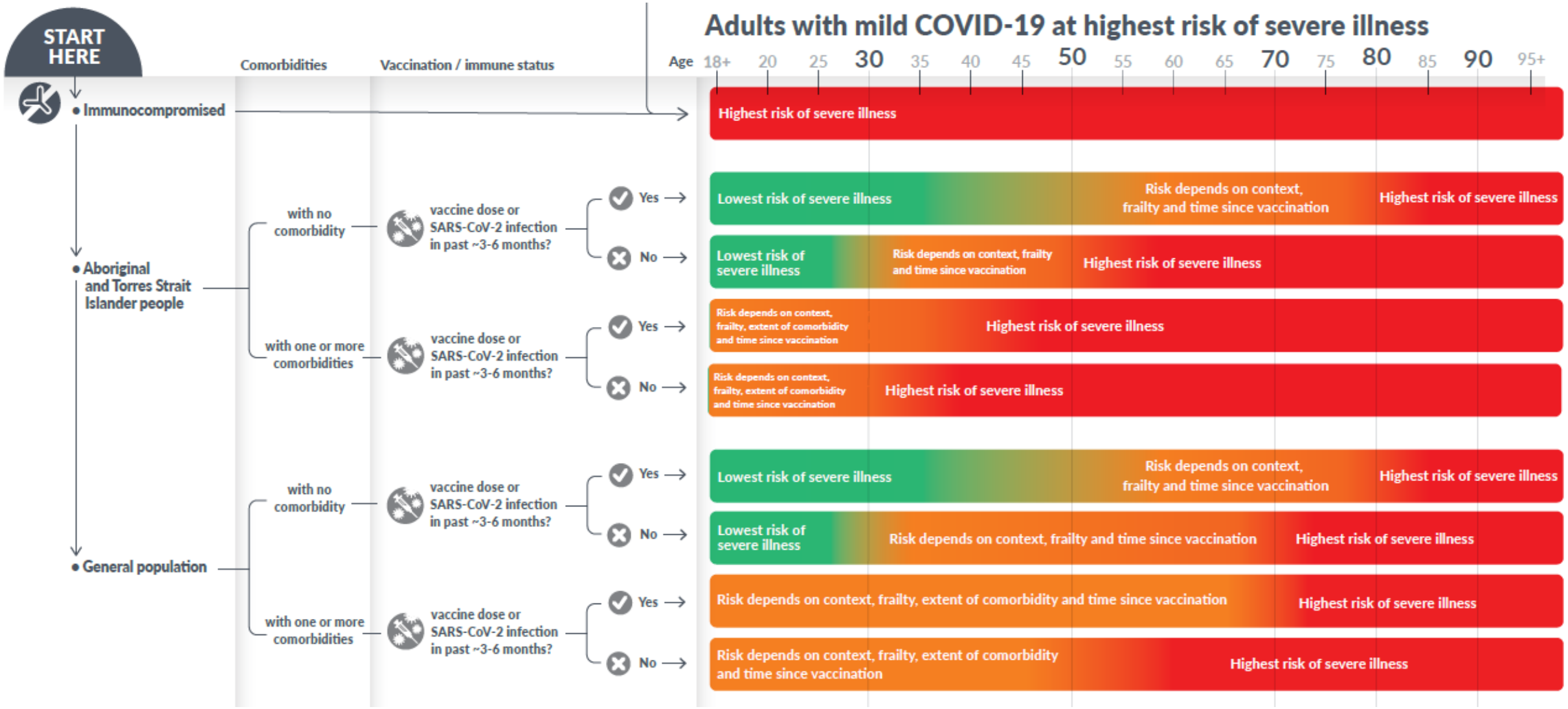
Decision Tool for adults with mild COVID-19



Notes:

- Molnupiravir should not be used routinely for the treatment of COVID-19. Click here for further information.
- Sotrovimab or Ronapreve (casirivimab plus imdevimab) can be used in the target population but have been omitted due to reduced effectiveness against the circulating Omicron variant.
- The Taskforce is aware of concerns about the potential for decreased effectiveness of Evusheld (tixagevimab plus cilgavimab) against the BA.4 and BA.5 Omicron sub-variants, based on in vitro data. Recommendations will be updated when definitive evidence becomes available.

Risk classification tool for adults with mild COVID-19



Acknowledgements

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