EVIDENCE SUMMARY

RESEARCH QUESTION: Among COVID-19 patients, should paxlovid or nirmatrelvir+ritonavir be used for treatment?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of nirmatrelvir+ritonavir within 5 days of symptom onset among unvaccinated symptomatic adult patients with high risk* for progression to severe disease. *Risk factors include any of the following: ≥60 years of age; BMI >25kg/m^2; cigarette smoking; immunosuppressive disease (including HIV infection with CD4 cell count <200mm^3 and viral load <400 copies/mL) or prolonged iatrogenic immunosuppression; chronic lung, cardiovascular, kidney, or sickle cell disease; hypertension; diabetes; cancer; neurodevelopmental disorders or other medically complex conditions; or medical-related technological dependence	Moderate	Strong
We suggest the use of nirmatrelvir+ritonavir among unvaccinated, symptomatic pediatric patients 12 years of age and older weighing at least 40kg with high risk for progression to severe disease.	Low	Weak

Consensus Issues

Since ritonavir is a strong cytochrome P450 (CYP) 3A4 inhibitor, it poses the risk of having drug to drug interaction, increasing the blood concentration of certain drugs. It is important to consider other medication/s being taken by the patient before giving the drug. Here is a link of some of the drugs contraindicated with nirmatrelvir+ritonavir: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/.

Another issue raised during the panel meeting is the research gap that should be addressed. For one, the studies only included unvaccinated patients, so this must also be taken into consideration, such that the recommendation is made only among unvaccinated patients. Another is that one of the issues raised with the drug is COVID-19 reinfection, yet the study included did not include as an outcome those who developed re-infection. These research gaps must also be taken into consideration prior to the use of the drug.

For the use of the drug among children, one panelist abstained from voting for or against use of paxlovid in children citing that direct evidence on benefit and harm in this population was still lacking.

KEY FINDINGS

- There is one multinational randomized control trial (n=2,246) with moderate certainty of evidence included in this review.

- Nirmatrelvir+ritonavir decreases the risk of all-cause mortality and COVID-19 related hospitalization.
- Nirmatrelvir+ritonavir also decreased the risk of any serious adverse events.
- There was no significant difference in the risk of adverse events; however, there is an increased risk in adverse events considered related to the drug among those given nirmatrelvir+ritonavir.
- Common adverse events reported include dysgeusia, diarrhea, headache, nausea, and vomiting. No available studies are available for children and adolescents.

INTRODUCTION

Nirmatrelvir+ritonavir (Paxlovid) is the first orally bioavailable drug against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and contains two co-administered antiviral medications: nirmatrelvir and ritonavir [1]. Nirmatrelvir is a potent and selective inhibitor of the viral protease Mpro or 3CL pro, that prevents cleavage of proteins crucial for SARS-CoV-2 genome replication. It has limited potential for off-target activity since there are no identified human analogues. Nirmatrelvir is rapidly metabolized by CYP3A thereby lowering its systemic availability [2]. Ritonavir has no known activity against SARS-CoV-2, but it acts as a pharmacokinetic enhancer for nirmatrelvir by slowing down its metabolism through inhibition of the hepatic enzyme CYP3A [3].

REVIEW METHODS

A systematic search was done last September 19, 2022 from Pubmed, Cochrane Library and Google scholar using the text, MeSH terms and advance search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 and Paxlovid, Nirmatrelvir, Nirmatrelvir-Ritonavir. Ongoing studies were also searched in *clinicaltrials.gov*, EU Clinical Trials Register, Cochrane COVID-19 study register, and other trial registries. The COVID-NMA Initiative was also searched. Pre-prints search was also done in medrxiv, biorxiv and chinarxiv. Any other relevant cited references were manually searched. (Appendix 1) All randomized controlled trials (RCT) on paxlovid, nirmatrelvir and nirmatrelvir-ritonavir compared to placebo or standard of care on COVID-19 patients, regardless of severity were included.

RESULTS

Characteristics of included studies

Only one (1) multinational phase 2-3 double-blind RCT was found.[4] Other studies are either observational studies or trials that are still ongoing recruitment. The summary on the characteristics of included study can be found in Appendix 2.

Study participants include unvaccinated, non-hospitalized symptomatic adults (with symptom onset no more than 5 days before randomization, and at least one sign or symptom of COVID-19 on the day of randomization). All study participants had laboratory-confirmed COVID-19 and were at high risk for progression to severe disease. Risk factors include any of the following: ≥60 years of age; BMI >25kg/m^2; cigarette smoking; immunosuppressive disease (including HIV infection with CD4 cell count <200mm^3 and viral load <400 copies/mL) or prolonged iatrogenic immunosuppression; chronic lung, cardiovascular, kidney, or sickle cell disease; hypertension; diabetes; cancer; neurodevelopmental disorders or other medically complex conditions; or medical-related technological dependence. Paxlovid was given as 300mg Nirmatrelvir plus 100mg ritonavir every 12 hours for 5 days. No RCTs involving children were found.

Overall Certainty of Evidence

The overall certainty of evidence is moderate due to serious risk of bias. The serious risk of bias is due to attrition bias. Although the number of dropouts were comparable in both groups, sensitivity analysis using the worst-case/best-case scenario leads to reversal of results. The risk of bias summary is shown in Appendix 3. The GRADE evidence summary is shown in Appendix 4.

Effectiveness Outcomes

The use of nirmatrelvir+ritonavir significantly reduced the risk of all-cause mortality by day 28 compared to placebo (RR 0.04, 95% CI 0.00-0.68). There was also significant reduction in hospitalization for COVID-19 among those treated with nirmatrelvir+ritonavir (RR 0.12, 95% CI 0.06-0.26). When considered as a composite outcome (death or COVID-19 related hospitalization), nirmatrelvir+ritonavir demonstrated significant benefit (RR 0.12, 95% CI 0.06-0.25).

Subgroup analysis according to timing of nirmatrelvir+ritonavir administration showed significant benefit in reducing death or COVID-19 related hospitalization among those given nirmatrelvir+ritonavir within 3 days of symptom onset (RR 0.11, 95% CI 0.04-0.28) and those given nirmatrelvir+ritonavir 3 to 5 days after onset of symptoms (RR 0.15, 95% CI 0.04-0.48). Subgroup analysis by age showed that nirmatrelvir+ritonavir had significant benefit in reducing death or COVID-19 related hospitalization among those <65 years old (RR 0.15, 95% CI 0.07-0.34) and those 65 years and above (RR 0.05, 95% CI 0.01-0.38). Subgroup analysis by SARS-COV-2 serologic status similarly showed that nirmatrelvir+ritonavir had significant benefit in reducing death or COVID-19 related hospitalization among seronegative patients (RR 0.13, 95% CI 0.06-0.27) and seropositive patients (RR 0.12, 95% CI 0.02-0.97)

Safety Outcomes

There was no significant difference in the risk of any adverse events among those given nirmatrelvir+ritonavir and placebo (RR 0.95, 95% CI 0.82-1.10). The use of nirmatrelvir+ritonavir significantly reduced the risk of adverse events leading to discontinuation of drug or placebo (RR 0.49, 95% CI 0.30-0.80). However, there was a significant increase in adverse events considered related to the drug/placebo among those given nirmatrelvir+ritonavir (RR=2.06, 95% CI 1.44-2.95). Common adverse events reported include dysgeusia, diarrhea, headache, nausea, vomiting, increase in fibrin D dimer, and hypertension.

The use of nirmatrelvir+ritonavir showed significant benefit in reducing any serious adverse events (RR 0.24, 95% CI 0.15-0.41). In terms of serious adverse events considered related to the drug/placebo, the evidence is inconclusive (RR 3.02, 95% CI 0.12-73.96). There was only one reported serious adverse event considered related to the drug, and this occurred in the nirmatrelvir+ritonavir group.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of recommendations from other groups

Regulatory Agency	Recommendation	Strength of Recommendation / Certainty of Evidence
World Health Organization (WHO) v12.1[13] (as of September 16, 2022)	We recommend treatment with nirmatrelvir-ritonavir for patients with non-severe COVID-19 at highest risk of hospitalization. It should be administered as soon as possible after onset of symptoms, ideally within 5 days. **High risk includes unvaccinated, older people, immunodeficiency, chronic disease*	Strong recommendation
	We suggest not to use treatment with nirmatrelvir-ritonavir for patients with non-severe COVID-19 at low risk of hospitalization	Conditional recommendation against
	Clinicians should not consider nirmatrelvir-ritonavir in pregnant women, children or those with possible drug interaction.	Conditional recommendation against

US National Institutes of Health (NIH)[14] (as of May 13, 2022)	The COVID-19 Treatment Guidelines Panel (the Panel) recommends using nirmatrelvir 300mg with ritonavir 100mg (Paxlovid) orally (PO) twice daily for 5 days in non-hospitalized adults and pediatric patients aged ≥12 years and weighing ≥40 kg with mild to moderate COVID-19 who are at high risk of disease progression; treatment should be initiated as soon as possible and within 5 days of symptom onset.	Strong recommendation
Infectious Diseases Society of America Guidelines[15] (as of May 10, 2022; with section review done last 29 December 2021 and evidence profile updated last February 3, 2022)	In ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests nirmatrelvir/ritonavir initiated within five days of symptom onset rather than no nirmatrelvir/ritonavir.	Conditional recommendation, Low certainty of evidence
Australian Guideline for COVID-19 Version 64[16] (as of September 16, 2022)	Consider using nirmatrelvir plus ritonavir (Paxlovid) 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 (age ≥60 years; diabetes requiring medication; BMI ≥25 kg/m^2; cardiovascular disease, hypertension, chronic lung disease).	Conditional 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.	Consensus recommendation
	Consider using, in exceptional circumstances, nirmatrelvir plus ritonavir for the treatment of COVID-19 within 5 days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40kg who do not require oxygen and who are at high risk of deterioration.	Consensus recommendation
	Consider using nirmatrelvir plus ritonavir in eligible children and adolescents who have not received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, or those who are immunocompromised regardless of vaccination / previous infection status. Do not routinely use nirmatrelvir plus ritonavir in children and adolescents who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months unless immunocompromised.	Consensus recommendation
	Decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age,	Consensus recommendation

	presence of multiple risk factors, and whether they have received a COVID-19 vaccine dose or had a SARS-CoV-2 infection in the past 6 months.	

RESEARCH GAPS

As of September 25, 2022, there are nine ongoing clinical trials for Paxlovid and Nirmatrelvir for COVID-19 patients registered on *clinicaltrials.gov,* Chinese Clinical Trials Registry and Cochrane COVID-19 Study Register. Four (4) of these trials are ongoing recruitment.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

Nirmatrelvir+Ritonavir (Paxlovid) has been granted emergency use authorization by the Philippine FDA [5]. Recommended dosage is two 150mg tablets of nirmatrelvir and one 100mg tablet of ritonavir twice a day for 5 days. The full treatment course is estimated to cost $529[6] or ₱31,061.80 [7]. A cost-effectiveness study show that Paxlovid would cost $21,000/QALY gained or $18,000/life year gained [8]. Currently it is available locally as generic nirmatrelvir+Ritonavir for ₱2,742.87 or Paxovir for ₱18,750 for the entire 5-day course (Pharmacy department of East Avenue Medical Center and St. Luke's Medical Center, Quezon City, Personal communication, October-November 2022).

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

The US FDA revised the emergency use authorization (UEA) for Nirmatrelvir + Ritonavir (Paxlovid), to now authorize state-licensed pharmacists to prescribe Paxlovid to eligible patients with certain limitations. Paxlovid is authorized for the treatment of mild to moderate COVID 19 in adults and pediatric patients (12 years of age and older weighing at least 40kg) with positive results of direct SARS-CoV-2, who are at high risk for progression to severe COVID-19. Patients in the authorized population who report to their provider a positive home test from rapid antigen test or positive PCR test are eligible for Paxlovid under the UEA [9].

A special warning and precaution for drug interactions are considered since medicinal products that are either highly dependent on CYP3A for clearance or are CYP3A inducers may cause clinically significant adverse reactions or loss of therapeutic effect of these drugs and/or Paxlovid when used concomitantly [10].

Another concern for Paxlovid was the recurrence of COVID-19 after treatment or the COVID-19 rebound. A meta-analysis of three observational studies (two of which are pre-prints) showed Paxlovid had inconclusive effect on incidence of COVID-19 rebound (RR 0.99, 95% CI 0.28-3.57, I^2=59%) with moderate heterogeneity [11]. The Centers for Disease Control and Prevention released a health advisory that with the limited information on COVID-19 rebound and Paxlovid, Paxlovid is still recommended for early stage treatment of mild to moderate COVID-19 among persons at high risk for progression to severe disease [12].

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=8/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					• Yes, COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large (3)	Moderate (4)	Small	Uncertain (1)			• The use of nirmatrelvir+ritonavir **significantly reduced the risk of all-cause mortality by day 28 compared to placebo** (RR 0.04, 95% CI 0.00-0.68). • There was also **significant reduction in hospitalization for COVID-19** among those treated with nirmatrelvir+ritonavir (RR 0.12, 95% CI 0.06-0.26). • When considered as a **composite outcome (death or COVID-19 related hospitalization), Nirmatrelvir+ritonavir demonstrated significant benefit** (RR 0.12, 95% CI 0.06-0.25).
Harm	Large	Moderate (2)	Small (4)	Trivial	Varies (1)	Uncertain (1)	• There was **no significant difference in the risk of any adverse events** among those given nirmatrelvir+ritonavir and placebo (RR 0.95, 95% CI 0.82-1.10). • Common adverse events reported include dysgeusia, diarrhea, headache, nausea, vomiting, increase in fibrin D dimer, and hypertension. • The use of nirmatrelvir+ritonavir showed **significant benefit in reducing any serious adverse events** (RR 0.24, 95% CI 0.15-0.41). • In terms of serious adverse events considered related to the drug/placebo, the evidence is inconclusive (RR 3.02, 95% CI 0.12-73.96).

Certainty of Evidence	High	Moderate (7)	Low (1)	Very low			• The overall certainty of evidence is **moderate** due to serious risk of bias. The serious risk of bias is due to attrition bias.
Balance of effects	Favors intervention (3)	Probably favors intervention (5)	Does not favor intervention	Probably favors no intervention	Favors no intervention	Varies	• Nirmatrelvir+ritonavir decreases the risk of all-cause mortality and COVID-19 related. Nirmatrelvir+ritonavir also decreased the risk of any serious adverse events.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (4)	Probably no important uncertainty or variability (2)	No important uncertainty or variability			• Special warning and precaution for drug interaction (CYP3A) Precaution for COVID rebound
Resources Required	Uncertain	Large cost (7)	Moderate Cost (1)	Negligible cost or savings	Moderate savings	Large savings	• The local price of Paxlovid is at **₱2,742.87 to ₱18,750 for the 5 day course** • Nirmatrelvir + Ritonavir (Paxlovid) has been granted emergency use authorization by the Philippine FDA.[5] Recommended dosage is two 150mg tablets of nirmatrelvir and one 100mg tablet of ritonavir twice a day for 5 days. The full treatment course is estimated to cost **$529[6] or ₱31,061.8**
Certainty of evidence of required resources	No included studies	Very low (1)	Low (2)	Moderate (5)	High		• The suggested retail price is from an article published in a medical journal (BMJ).
Cost effectiveness	No included studies (5)	Favors using the comparison (1)	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the invention (1)	Favors the intervention (1)	• Cost-effectiveness study at $529 or ₱31,061.80: **$21,000 or ₱1,192,590.00/QALY gained** or **$18,000 or ₱1,022,220.00/life year gained**
Equity	Uncertain (2)	Varies (1)	Probably reduced (3)	Probably no impact	Probably increased (1)	Increased (1)	

Acceptability	Uncertain (1)	Varies (1)	No (1)	Probably no	Probably yes (5)	Yes	
Feasibility	Uncertain (1)	Varies (3)	No	Probably no (1)	Probably yes (3)	Yes	
Recommendation	For (7)	Against (1)					
Strength	Weak (4)	Strong (4)					

Appendix 2: Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Paxlovid OR Nirmatrelvir OR Nirmatrelvir-Ritonavir)	9/19/2022 5:40pm	268	1
CENTRAL	Paxlovid OR Nirmatrelvir OR Nirmatrelvir-Ritonavir	9/19/2022 6:44PM	10	1
COVID-NMA Initiative	Nirmatrelvir/Ritonavir	9/19/2022 6:52PM	1	1
Google Scholar	Paxlovid OR Nirmatrelvir OR Nirmatrelvir-Ritonavir AND COVID AND randomized trial	9/19/2022 6:54PM	1,880	1
ClinicalTrials.gov	Paxlovid OR Nirmatrelvir/ritonavir	9/25/2022 8:14AM	18	0 (7)
Chinese Clinical Trial Registry	Paxlovid OR Nirmatrelvir	9/25/2022 9:07AM	9	0 (3)
EU Clinical Trials Register	Paxlovid OR Nirmatrelvir	9/25/2022 9:35AM	1	0
Republic of Korea – Clinical Research Information Service	Paxlovid OR Nirmatrelvir	9/25/2022 9:37AM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Paxlovid OR Nirmatrelvir	9/25/2022 9:39AM	0	0
CenterWatch	Paxlovid OR Nirmatrelvir	9/25/2022 9:41AM	10	0 (3)
Cochrane COVID-19 Study Register	Paxlovid OR Nirmatrelvir	9/25/2022 9:18AM	38	0 (6)
chinaxiv.org	Paxlovid OR Nirmatrelvir	9/25/2022 9:55AM	0	0
Medrxiv.org	Paxlovid OR Nirmatrelvir	9/25/2022 9:37AM	68	0
Biorxiv.org	Paxlovid OR Nirmatrelvir	9/25/2022 10:05AM	86	0

Appendix 3: Characteristics of Included Studies

Title/Author	Study Design	Country	Population	Intervention Group(s)	Control	Outcomes
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19 EPIC-HR Hammond, 2022	Double blind randomized control trial	Multiple sites: United States (41%), Europe (30%), South America (12.3%) and India (9%). Asia (5%) and Africa (0.6%) United States Bulgaria, South Africa, Brazil, India, Mexico, Ukraine, Turkey, Japan and Spain, Russia, Argentina and Colombia, Poland and South Korea, Hungary, Taiwan, Malaysia and Czech Republic, and Thailand and Puerto Rico	Unvaccinated, non-hospitalized symptomatic adults with confirmed COVID-19 at high risk for progression to severe disease N = 2,246	300mg Nirmatrelvir plus 100mg ritonavir every 12 hours x 5 days	Placebo	• Percentage of patients with COVID-19 related hospitalization or death from any cause • Viral load • Adverse events • Serious adverse events

Appendix 4: Risk of Bias Summary Table

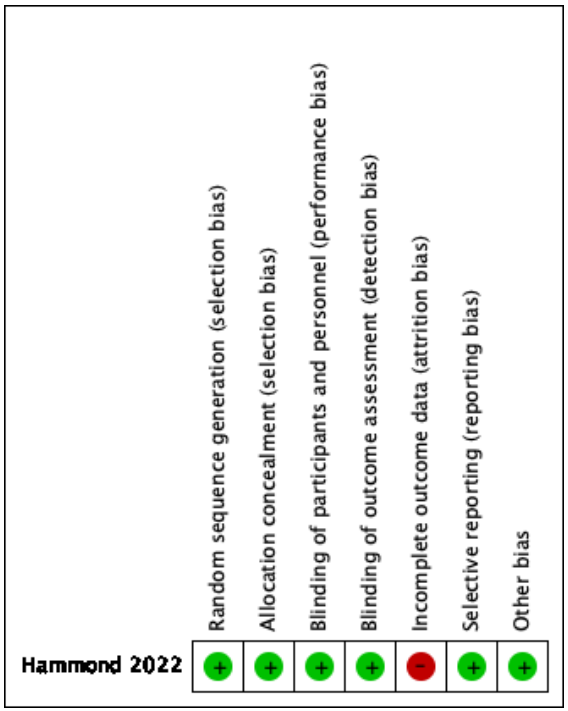

Figure 1. Risk of bias summary table

Appendix 5: GRADE Table

Author(s): Natasha Esteban-Ipac, MD, Carol Tan-Lim, MD
Question: Paxlovid compared to Placebo for COVID-19 in adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paxlovid	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality by day 28												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	0/1039 (0.0%)	12/1046 (1.1%)	**RR 0.04** (0.00 to 0.68)	**11 fewer per 1,000** (from 4 fewer to --)	⊕⊕⊕○ Moderate	CRITICAL
COVID-19 related hospitalization												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	8/1039 (0.8%)	65/1046 (6.2%)	**RR 0.12** (0.06 to 0.26)	**55 fewer per 1,000** (from 58 fewer to 46 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Mortality or COVID-19 related hospitalization (composite outcome)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	8/1039 (0.8%)	66/1046 (6.3%)	**RR 0.12** (0.06 to 0.25)	**56 fewer per 1,000** (from 59 fewer to 47 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Serious adverse events (any)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	18/1109 (1.6%)	74/1115 (6.6%)	**RR 0.24** (0.15 to 0.41)	**50 fewer per 1,000** (from 56 fewer to 39 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Adverse events (any)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	251/1109 (22.6%)	266/1115 (23.9%)	**RR 0.95** (0.82 to 1.10)	**12 fewer per 1,000** (from 43 fewer to 24 more)	⊕⊕⊕○ Moderate	IMPORTANT

a. High risk of attrition bias

Author(s): Natasha Esteban-Ipac, MD, Carol Tan-Lim, MD
Question: Paxlovid compared to Placebo for COVID-19 in children

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paxlovid	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality by day 28												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	0/1039 (0.0%)	12/1046 (1.1%)	**RR 0.04** (0.00 to 0.68)	**11 fewer per 1,000** (from 4 fewer to --)	⨁◯◯◯ Low	CRITICAL
COVID-19 related hospitalization												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	8/1039 (0.8%)	65/1046 (6.2%)	**RR 0.12** (0.06 to 0.26)	**55 fewer per 1,000** (from 58 fewer to 46 fewer)	⨁◯◯◯ Low	CRITICAL
Mortality or COVID-19 related hospitalization (composite outcome)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	8/1039 (0.8%)	66/1046 (6.3%)	**RR 0.12** (0.06 to 0.25)	**56 fewer per 1,000** (from 59 fewer to 47 fewer)	⨁◯◯◯ Low	CRITICAL
Serious adverse events (any)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	18/1109 (1.6%)	74/1115 (6.6%)	**RR 0.24** (0.15 to 0.41)	**50 fewer per 1,000** (from 56 fewer to 39 fewer)	⨁◯◯◯ Low	CRITICAL
Adverse events (any)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	251/1109 (22.6%)	266/1115 (23.9%)	**RR 0.95** (0.82 to 1.10)	**12 fewer per 1,000** (from 43 fewer to 24 more)	⨁◯◯◯ Low	IMPORTANT

a. High risk of attrition bias
b. Study done in adults

Appendix 6: Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. The Effect of Paxlovid in the Treatment of COVID-19 Patients With Uremia (NCT05386433) Not yet recruiting	Age ≥18 years old maintenance hemodialysis patients infected with SARS-CoV-2. COVID-19 (nucleic acid test positive) was diagnosed before randomization. At least 1 symptom or sign of COVID-19 at the time of being enrolled into the study(symptoms and signs related to COVID-19 including cough, expectoration, dyspnea, fever, chills, fatigue, muscle soreness, diarrhea, headache, sore throat, stuffy nose, runny nose, etc.).	Experimental: Paxlovid Control: SOC (includes oxygen inhalation, antibiotics, traditional medicine, etc.)	Time to negative conversion of SARS-CoV-2 nucleic acid Proportion of ICU transfer or disease progression to severe or critical illness	Open label, randomized clinical trial
2. Randomised Evaluation of COVID-19 Therapy (RECOVERY trial) (NCT04381936) Recruiting	All (child, adult, older adult) hospitalized with viral pneumonia, SARS-CoV-2 infection clinically suspected or laboratory confirmed	Active comparator: Paxlovid Other active comparator: Corticosteroids, Hydroxychloroquine, Lopinavir-Ritonavir, Azithromycin, Convalescent Plasma, Tocilizumab, IV Ig, Synthetic Neutralizing Antibodies, Aspirin, Colchicine, Baricitinib, Anakinra, Dimethyl fumarate, Empagliflozin, Sotrovimab, Molnupiravir Control: SOC	Primary outcome: All-cause mortality Secondary outcome Duration of hospital stay Need for ventilation Need for renal replacement	Open label, factorial assignment randomized trial
3. A Multicenter, Single-blind, Randomized, Controlled Study to Evaluate the	18 years old and older with positive SARS-CoV-2 test result, one or more mild or moderate COVID-19 symptoms, one or more	Experimental: JT001 (VV116) Active comparator: Paxlovid	Primary outcome: Time to sustained clinical recovery Secondary outcomes	Randomized, triple blind clinical trial

Efficacy and Safety of JT001 (VV116) Compared With Paxlovid for the Early Treatment of COVID-19 in Participants With Mild to Moderate COVID-19 (NCT05341609/ChiCTR2200057856) Completed Recruitment	of the following requirements: ≤7 days from the first positive test for SARS-CoV-2 virus infection to the first dose; ≤5 days from the first onset of COVID-19 symptoms to the first dose; one or more than one of the following high risks for progression to severe COVID-19		Aes and SAEs Percentage of patients who experiences Aes and SAEs Percentage of clinical recovery patients Change of COVID-19 symptom scores Change of WHO clinical progression scale Percentage of participants who turned negative for SARS-CoV-2 Change of SARS-CoV2 Ct value Change of chest CT scan Percentage of participants who have progression of COVID-19 Percentage of participants whose "WHO clinical progression scale" reduced at least one level Time to sustained disappearance of clinical symptoms Percentage of participants with no clinical symptoms	
4. A Study to Learn About the Study Medicines (Called Nirmatrelvir/Ritonavir) in People 12 years old or older with COVID 19 who are immunocompromised. (An interventional efficacy and safety, phase 2 randomized, double blind, 3 arm study to investigate nirmatrelvir/ritonavir in nonhospitalized participants at least 12 years of age with symptomatic COVID	Child, adult, and older adult >12 years old with confirmed SARS-CoV2 infection with onset of symptoms within 5 days prior to screening; is immunocompromised	Triple arm (5 days, 10 days and 15 days) Nirmatrelvir Ritonavir Placebo	Virologic clearance Safety and tolerability Hospitalization and all-cause mortality Death Need for mechanical ventilator or ECMO Adverse events Serious adverse events	Randomize, parallel assignment, triple masking clinical trial

19 who are immunocompromised (NCT05438602) Recruiting				
5. An Interventional Efficacy and Safety, Phase 2, Double Blind, 2 arm study to investigate orally administered Nirmatrelvir/Ritonavir compared with placebo/ritonavir for the treatment of severe COVID-19 in hospitalized participants who are immunocompromised or at increased risk for severe COVID-19 outcomes (EPIC-HOS) (NCT05545319) Not yet recruiting	12 years and older meeting 1 of the 2 categories of COVID-19 risk: Category A: immunocompromised Category B: non-immunocompromised but with ≥2 risk factors; onset of signs/symptoms attributable to COVID-10 ≤10 days prior to the day of randomization for non-immunocompromised participants Confirmed SARS-COV infection Hospitalized for inpatient care Requirement for oxygen supplementation	Nirmatrelvir/ritonavir Placebo/ritonavir	Time to sustained clinical recovery Proportion of participants with death from any cause Incidence of treatment-related adverse events Incidence of adverse events or serious adverse events leading to discontinuation	Randomized, parallel assignment, quadruple masking clinical trial
6. Finding Treatments for COVID-19: A Phase 2 Multi-centre Adaptive Platform Trial to Assess Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV) (NCT05041907)	18 years old to 50 years old with positive SARS COV2 by lateral flow antigen or PCR test, symptoms of COVID-19 for less than 4 days, oxygen saturation ≥96%	Active comparator: Monoclonal antibodies Experimental: Favipiravir, Ivermectin, Remdesivir, Fluoxetine, Molnupiravir, Nirmatrelvir/ritonavir (Paxlovid), Nitazoxanide Negative control group: no treatment	Rate of viral clearance Rate of hospitalization by treatment arm	Randomized, parallel assignment, open label clinical trial

Recruiting				
7. Non-inferiority Trail on Treatments in Early COVID 19 (Adaptive, Randomized, Non-inferiority Trial on the Use of Monoclonal Antibodies or Antivirals in Outpatients with Mild or Moderate COVID-19) (NCT05321394) Recruiting	50 years old and above with laboratory confirmed SARS-COV2 infection, not requiring supplemental oxygen Onset of symptoms is no more than 4 days prior to the study drug administration	Active comparator: Sotrovimab Experimental: Tixagevimab Cilgavimab and Nirmatrelvir Ritonavir	Primary outcome: COVID-19 progression Secondary outcome Visits to Emergency room Duration of supplemental oxygen therapy Duration of hospitalization Non-invasive ventilation Duration of non-invasive ventilation Mechanical ventilation Duration of mechanical ventilation 28-day mortality 90-day mortality Duration of symptoms	Open label, randomized, parallel assignment clinical trial
8. Clinical efficacy and safety of Paxlovid in the treatment of severe adult patients with SARS-Cov-2 infection: a multicenter, randomized, controlled study (ChiCTR2200058477) Completed recruitment	>18 and < 90 years old, hospitalized with SARS-CoV2 mild or common COVID-19 confirmed by PCR; within 48 hours of admission, within 5 days of initial symptoms; severely ill people with one or more of the following: immunosuppressive disease or condition, chronic use of immunosuppressive drugs or conditions that cause medical complications	Standard COVID-19 treatment protocol set Paxlovid	28-day all-cause mortality In hospital mortality Conversion rate of severe COVID 19 within 14 days Acute exacerbation rate of chronic underlying diseases within 14 days Total in hospital days Stay in ICU days Percentage requiring organ function support within 28 days	Multicenter, randomized controlled study
9. Open-label, head-to-head, randomized, controlled clinical study of Molnupiravir capsules and	Adult patients (≥18 years old) with mild or common COVID-19 who tested positive for SARS-COV2 virus, within 5 days of onset of symptoms with risk factors	Molnupiravir Paxlovid	Days of virus nucleic acid turning negative Rate of progression Severe cases Duration of fever ICU duration Time of discharge	Randomized, controlled trial

Paxlovid tablets in patients with mild and general type of COVID-19 in high-risk populations (ChiCTR2200060010) Not yet recruiting			Clinical outcome Time for improvement in lung imaging	