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[Intervention Review]

Nirmatrelvir combined with ritonavir for preventing and treating COVID-19

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ABSTRACT

Background

Oral nirmatrelvir/ritonavir (Paxlovid) aims to avoid severe COVID-19 in asymptomatic people or those with mild symptoms, thereby decreasing hospitalization and death. It remains to be evaluated for which indications and patient populations the drug is suitable.

Objectives

To assess the efficacy and safety of nirmatrelvir/ritonavir plus standard of care (SoC) compared to SoC with or without placebo, or any other intervention for treating COVID-19 or preventing SARS-CoV-2 infection.

To explore equity aspects in subgroup analyses.

To keep up to date with the evolving evidence base using a living systematic review (LSR) approach and make new relevant studies available to readers in-between publication of review updates.

Search methods

We searched the Cochrane COVID-19 Study Register, Scopus, and World Health Organization COVID-19 Research Database, identifying completed and ongoing studies without language restrictions and incorporating studies up to 15 May 2023.

This is a LSR. We conduct update searches every two months and make them publicly available on the open science framework (OSF) platform.

Selection criteria

We included randomized controlled trials (RCTs) comparing nirmatrelvir/ritonavir plus SoC to SoC with or without placebo, or any other intervention for treatment of people with confirmed COVID-19 diagnosis, irrespective of disease severity or treatment setting, and for prevention of SARS-CoV-2 infection.

We screened all studies for research integrity. Studies were ineligible if they had been retracted, or if they were not prospectively registered including appropriate ethics approval.

Data collection and analysis

We followed standard Cochrane methodology and used the Cochrane RoB 2 tool. We rated the certainty of evidence using the GRADE approach for the following outcomes: 1. to treat outpatients with mild COVID-19; 2. to treat inpatients with moderate to severe COVID-19: mortality, clinical worsening or improvement, quality of life, (serious) adverse events, and viral clearance; 3. to prevent SARS-CoV-2 infection in postexposure prophylaxis (PEP); and 4. pre-exposure prophylaxis (PrEP) scenarios: SARS-CoV-2 infection, development of COVID-19 symptoms, mortality, admission to hospital, quality of life, and (serious) adverse events.

We explored inequity by subgroup analysis for elderly people, socially-disadvantaged people with comorbidities, populations from low-income countries and low- to middle-income countries, and people from different ethnic and racial backgrounds.

Main results

As of 15 May 2023, we included two RCTs with 2510 participants with mild and mild to moderate symptomatic COVID-19 in outpatient and inpatient settings comparing nirmatrelvir/ritonavir plus SoC to SoC with or without placebo. All trial participants were without previous confirmed SARS-CoV-2 infection and at high risk for progression to severe disease. Randomization coincided with the Delta wave for outpatients and Omicron wave for inpatients. Outpatient trial participants and 73% of inpatients were unvaccinated. Symptom onset in outpatients was no more than five days before randomisation and prior or concomitant therapies including medications highly dependent on CYP3A4 were not allowed.

We excluded two studies due to concerns with research integrity. We identified 13 ongoing studies. Three studies are currently awaiting classification.

Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings

Nirmatrelvir/ritonavir plus SoC compared to SoC plus placebo may reduce all-cause mortality at 28 days (risk ratio (RR) 0.04, 95% confidence interval (CI) 0.00 to 0.68; 1 study, 2224 participants; low-certainty evidence) and admission to hospital or death within 28 days (RR 0.13, 95% CI 0.07 to 0.27; 1 study, 2224 participants; low-certainty evidence).

Nirmatrelvir/ritonavir plus SoC may reduce serious adverse events during the study period compared to SoC plus placebo (RR 0.24, 95% CI 0.15 to 0.41; 1 study, 2224 participants; low-certainty evidence). Nirmatrelvir/ritonavir plus SoC probably has little or no effect on treatment-emergent adverse events (RR 0.95, 95% CI 0.82 to 1.10; 1 study, 2224 participants; moderate-certainty evidence), and probably increases treatment-related adverse events such as dysgeusia and diarrhoea during the study period compared to SoC plus placebo (RR 2.06, 95% CI 1.44 to 2.95; 1 study, 2224 participants; moderate-certainty evidence). Nirmatrelvir/ritonavir plus SoC probably decreases discontinuation of study drug due to adverse events compared to SoC plus placebo (RR 0.49, 95% CI 0.30 to 0.80; 1 study, 2224 participants; moderate-certainty evidence).

No studies reported improvement of clinical status, quality of life, or viral clearance.

Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings

We are uncertain whether nirmatrelvir/ritonavir plus SoC compared to SoC reduces all-cause mortality at 28 days (RR 0.63, 95% CI 0.21 to 1.86; 1 study, 264 participants; very low-certainty evidence), or increases viral clearance at seven days (RR 1.06, 95% CI 0.71 to 1.58; 1 study, 264 participants; very low-certainty evidence) and 14 days (RR 1.05, 95% CI 0.92 to 1.20; 1 study, 264 participants; very low-certainty evidence).

No studies reported improvement or worsening of clinical status and quality of life. We did not include data for safety outcomes due to insufficient and inconsistent information.

Subgroup analyses for equity

For outpatients, the outcome 'admission to hospital or death' was investigated for equity regarding age (less than 65 years versus 65 years or greater) and ethnicity. There were no subgroup differences for age or ethnicity.

For inpatients, the outcome 'all-cause mortality' was investigated for equity regarding age (65 years or less versus greater than 65 years). There was no difference between subgroups of age.

No further equity-related subgroups were reported, and no subgroups were reported for other outcomes.

Nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection (PrEP and PEP)

No studies available.

Authors' conclusions

Low-certainty evidence suggests nirmatrelvir/ritonavir reduces the risk of all-cause mortality and hospital admission or death in high-risk, unvaccinated COVID-19 outpatients infected with the Delta variant of SARS-CoV-2. There is low- to moderate-certainty evidence of the safety of nirmatrelvir/ritonavir.

Very low-certainty evidence exists regarding the effects of nirmatrelvir/ritonavir on all-cause mortality and viral clearance in mildly to moderately affected, mostly unvaccinated COVID-19 inpatients infected with the Omicron variant of SARS-CoV-2. Insufficient and inconsistent information prevents the assessment of safety outcomes.

No reliable differences in effect size and direction were found regarding equity aspects.

There is no available evidence supporting the use of nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection.

We are continually updating our search and making search results available on the OSF platform.

PLAIN LANGUAGE SUMMARY

Is the combination of nirmatrelvir plus ritonavir effective for treating or preventing COVID-19?

Key messages

Nirmatrelvir/ritonavir (Paxlovid) is evaluated for the treatment of coronavirus disease 2019 (COVID-19).

Nirmatrelvir/ritonavir may lead to fewer deaths and improve patient condition, as assessed by need for hospitalization or death within 28 days for unvaccinated outpatients at increased risk for disease progression receiving treatment within five days of symptom onset.

We are very uncertain about the effectiveness of nirmatrelvir/ritonavir in inpatients.

We excluded two studies due to concerns with research integrity. We found 13 ongoing studies.

What is nirmatrelvir/ritonavir?

The combination of nirmatrelvir with ritonavir is a new medicine developed to treat infection with the SARS-CoV-2 virus and aims to avoid severe COVID-19 in people without symptoms, or those with mild symptoms. Ritonavir increases the effectiveness of nirmatrelvir but it can interact with many other medicines, which can increase side effects.

What did we want to find out?

We wanted to know if nirmatrelvir/ritonavir reduces death, illness, and length of infection in people with COVID-19, or if it is useful in prevention of the disease. We included studies comparing the medicine with placebo (dummy treatment), no treatment, usual care, or any other treatments for COVID-19. We addressed equity and wanted to know whether there are certain groups of people for which nirmatrelvir/ritonavir works best or is less effective. We looked at elderly people, socially disadvantaged people with other illnesses (comorbidities), people from low-income and low- to middle-income countries, and people from different ethnic and racial backgrounds.

We evaluated the effects of nirmatrelvir/ritonavir in people with COVID-19 regarding:

– people dying;

– whether COVID-19 symptoms got better or worse;

– quality of life;

– unwanted effects of the medicine;

– virus elimination.

For prevention, we sought the effect on preventing COVID-19 and SARS-CoV-2 infection.

What did we do?

We searched for randomized controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) that investigated nirmatrelvir/ritonavir to prevent or treat COVID-19. People receiving nirmatrelvir/ritonavir as treatment had to have laboratory-confirmed COVID-19 and be treated in hospital or as outpatients. People receiving nirmatrelvir/ritonavir to prevent an infection had to have a high risk of contracting the disease or had to have had a high-risk contact with a person with confirmed COVID-19.

We summarized the results of the studies and rated our confidence in the evidence, based on common criteria as to how reliable the evidence was.

We examined differences with respect to age, level of comorbidity, country according to the World Bank country classification by income level, and ethnicity.

What did we find?

We found two studies with 2510 participants that investigated nirmatrelvir/ritonavir compared to placebo or standard of care for the treatment of COVID-19 in people without previous confirmed SARS-CoV-2 infection and at increased risk for progression to severe disease due to a comorbidity or risk factor such as current smoking. Included outpatients were enrolled during the Delta wave, unvaccinated, and had a symptom onset of up to five days before starting treatment. Included inpatients were enrolled during the Omicron wave, mostly unvaccinated, and mildly to moderately affected.

We found 13 ongoing studies that have not yet been completed, and three studies are currently awaiting classification.

Main results

Treating outpatients with COVID-19

For the specific population of unvaccinated, high-risk patients, nirmatrelvir/ritonavir may:

– lead to fewer deaths;

– improve patients' condition assessed by need for admission to hospital or death within 28 days;

– reduce serious unwanted events.

For the specific population of unvaccinated, high-risk patients, nirmatrelvir/ritonavir probably:

– has little effect on any unwanted events;

– increases any treatment-related unwanted events (mostly taste disturbance and diarrhoea);

– decreases discontinuation of study medicine due to unwanted events.

Equity aspects

Most study participants were younger than 65 years and of white ethnicity. There was no difference in effectiveness between younger and older participants and participants from different ethnic groups. No subgroups were reported for different levels of comorbidity and World Bank country classification by income level.

Treating inpatients with COVID-19

We are uncertain whether, for the specific population of mildly to moderately affected, high-risk patients, nirmatrelvir/ritonavir:

– leads to fewer deaths; and

– increases virus elimination

Equity aspects

Most study participants were older than 65 years. There was no difference in effectiveness between younger and older participants. No subgroups were reported for different levels of comorbidity, ethnicity, and World Bank country classification by income level.

No subgroups were reported for other outcomes.

What are the limitations of the evidence?

Our confidence in the evidence is low to moderate for outpatients and very low for inpatients. The studies did not report everything we were interested in, such as quality of life and symptom resolution, and had a highly specific population of people at high risk of progression to severe COVID-19.

How up to date is this evidence?

The evidence is up to date to 15 May 2023.

According to this review's living approach, we will update our search every two months. We are making search results and new relevant studies publicly available.

SUMMARY OF FINDINGS

Summary of findings 1. Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings

Patient or population: unvaccinated, non-hospitalized people with mild symptomatic COVID-19 (WHO scale 2 to 3) at high risk for progression to severe disease

Setting: outpatient

Intervention: nirmatrelvir/ritonavir (plus standard of care)

Comparison: placebo (plus standard of care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with placebo	Risk with nirmatrelvir/ritonavir				
All-cause mortality at day 28	**11** per 1000	**0** per 1000	**RR 0.04** (0.00 to 0.68)	2224 (1 RCT)	⊕⊕⊖⊖ **Low**[a]	Nirmatrelvir/ritonavir may reduce all-cause mortality[1]
	Difference: **11 fewer per 1000** (11 fewer to 4 fewer)					
Worsening of clinical status within 28 days						
Admission to hospital or death	**61** per 1000	**8** per 1000	**RR 0.13** (0.07 to 0.27)	2224 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	Nirmatrelvir/ritonavir may reduce (COVID-19-related) hospitalization or death[2]
	Difference: **53 fewer per 1000** (57 fewer to 45 fewer)					
Admission to ICU or death	—	—	—	—	—	No studies reported admission to ICU or death
Improvement of clinical status						
All initial symptoms resolved at 28 days, and up to the longest follow-up	—	—	—	—	—	No studies reported all initial symptoms resolved
Time to symptom resolution	—	—	—	—	—	No studies reported time to symptom resolution

Quality of life up to 28 days and longest follow-up available	—	—	—	—	—	No studies reported quality of life
SAEs during the study period	**66** per 1000 Difference: **50 fewer per 1000** (56 fewer to 39 fewer)	**16 per 1000**	**RR 0.24** (0.15 to 0.41)	2224 (1 RCT)	⊕⊕⊖⊖ **Low**[c]	Nirmatrelvir/ritonavir may reduce SAEs[1]
Adverse events during the study period						
Any grade TEAE	**239** per 1000 Difference: **12 fewer per 1000** (43 fewer to 24 more)	**227** per 1000	**RR 0.95** (0.82 to 1.10)	2224 (1 RCT)	⊕⊕⊕⊖ **Moderate**[d]	Nirmatrelvir/ritonavir probably has little or no effect on any TEAE[1]
Any grade TRAE	**38** per 1000 Difference: **40 more per 1000** (17 more to 74 more)	**78** per 1000	**RR 2.06** (1.44 to 2.95)	2224 (1 RCT)	⊕⊕⊕⊖ **Moderate**[d]	Nirmatrelvir/ritonavir probably increases any TRAE (mostly attributed to dysgeusia and diarrhoea)[1]
Discontinuation of study drug due to adverse events	**42** per 1000 Difference: **21 fewer per 1000** (29 fewer to 8 fewer)	**21** per 1000	**RR 0.49** (0.30 to 0.80)	2224 (1 RCT)	⊕⊕⊕⊖ **Moderate**[d]	Nirmatrelvir/ritonavir probably decreases discontinuation of study drug due to adverse events[1]
Viral clearance at 14 days	—	—	—	—	—	No studies reported viral clearance

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SAE:** serious adverse event; **TEAE:** treatment-emergent adverse event; **TRAE:** treatment-related adverse event; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations on certainty in the evidence (GRADE)

[a]Downgraded one level for serious risk of bias (inappropriate analysis) and one level for serious imprecision (few events).

[b]Downgraded one level for serious risk of bias (inappropriate analysis) and one level for serious indirectness (COVID-19-related hospitalization).

[c]Downgraded one level for serious risk of bias (inappropriate analysis) and one level for serious imprecision (due to few SAEs other than hospitalization or death).

[d]Downgraded one level for serious risk of bias (inappropriate analysis).

Explanations on 'equity considerations'

Most study participants were younger than 65 years, of white ethnicity, and from upper middle- or high-income countries. No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated a high-risk population.

[1]No subgroup analyses were reported for age, ethnicity, and World Bank country classification by income level. We are uncertain whether results are applicable to all prespecified subgroups.

[2]Subgroup analyses were reported for age and ethnicity only. There was no difference between subgroups of age. The effects favoured a treatment with nirmatrelvir/ritonavir for the white ethnic group. Estimated effects of the other ethnic groups included the line of no effect (RR = 1). Numbers of participants in the other ethnic groups were low. No subgroups were reported for World Bank country classification by income level.

Summary of findings 2. Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings

Patient or population: hospitalized people with mild to moderate symptomatic COVID-19 (WHO scale 2 to 4) with severe comorbidities

Setting: inpatient

Intervention: nirmatrelvir/ritonavir (plus standard of care)

Comparison: standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with standard of care	Risk with nirmatrelvir/ritonavir				
All-cause mortality at day 28	**61** per 1000	**38** per 1000 Difference: **23 fewer per 1000** (48 fewer to 52 more)	**RR 0.63** (0.21 to 1.86)	264 (1 RCT)	⊕⊖⊖⊖ **Very low**[a]	We are uncertain whether nirmatrelvir/ritonavir reduces all-cause mortality[1]
Worsening of clinical status within 28 days						

Participants with new need for invasive mechanical ventilation or death	—	—	—	—	—	No studies reported worsening of clinical status
Improvement of clinical status within 28 days						
Participants discharged alive. Participants should be discharged without clinical deterioration or death	—	—	—	—	—	No studies reported improvement of clinical status
Quality of life up to 28 days and longest follow-up available	—	—	—	—	—	No studies reported quality of life
SAEs during the study period	—	—	—	—	—	Not assessed due to insufficient and inconsistent information
Adverse events during the study period						
Any grade TEAE	—	—	—	—	—	Not assessed due to insufficient and inconsistent information
Any grade TRAE	—	—	—	—	—	Not assessed due to insufficient and inconsistent information
Discontinuation of study drug due to adverse events	—	—	—	—	—	Not assessed due to insufficient and inconsistent information
Viral clearance						
Viral clearance at 7 days	**258** per 1000	**273** per 1000 Difference:**15 more per 1000** (75 fewer to 150 more)	**RR 1.06** (0.71 to 1.58)	264 (1 RCT)	⊕⊖⊖⊖ **Very low**[a]	We are uncertain whether nirmatrelvir/ritonavir increases viral clearance at 7 days[2]
Viral clearance at 14 days	**742** per 1000	**779** per 1000 Difference **37 more per 1000** (59 fewer to 148 more)	**RR 1.05** (0.92 to 1.20)	264 (1 RCT)	⊕⊖⊖⊖ **Very low**[a]	We are uncertain whether nirmatrelvir/ritonavir increases viral clearance at 7 days[2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the __relative effect__ of the intervention (and its 95% confidence interval).

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SAE:** serious adverse event; **TEAE:** treatment-emergent adverse event; **TRAE:** treatment-related adverse event; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations on certainty in the evidence (GRADE)

[a]Downgraded two levels for imprecision (minimally contextualized approach), and one level for indirectness (atypical hospital population: WHO 2 to 4).

Explanations on 'equity considerations'

Most study participants were older than 65 years. The study was conducted in China, which in general classifies as upper middle-income country; however, no further information was given about World Bank country classification by income level and race/ethnicity of study participants. No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated a high-risk population.

[1]Subgroup analyses were reported for age only. There was no difference between subgroups of age. Estimated effects included the line of no effect (RR = 1).

[2]No subgroup analyses were reported for age, comorbidity, ethnicity, and World Bank country classification by income level. We are uncertain whether results are applicable to all prespecified subgroups.

BACKGROUND

Description of the condition

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a public health emergency of international concern by the World Health Organization (WHO) between January 2020 and May 2023 (WHO 2020a). The COVID-19 pandemic led to severe global health system disruption, and economic and social upheaval. As of 18 June 2023, over 768 million confirmed cases and over 6.9 million deaths globally have been reported to the WHO; however, due to global reductions in testing and reporting, this is considered an underestimate of the true numbers (WHO 2023a). The risk of new virus variants that may lead to a surge in new cases remains an ongoing threat. The variant XBB.1.5 (an Omicron subvariant) is currently the most reported lineage worldwide (WHO 2023a). The WHO is currently tracking two variants of interest (XBB.1.5, XBB.1.16), and monitoring a further six variants and their descendant lineages.

SARS-CoV-2 is a positive-sense, double-stranded ribonucleic acid (RNA) virus that belongs to the *Coronaviridae* family (Kumar 2020).

SARS-CoV-2 uses its spike glycoprotein-S to bind to an angiotensin-converting enzyme 2 (ACE2) receptor on a host cell surface to initiate the infection process. ACE2 receptors are expressed in lung, heart, kidney, intestine, and endothelium in the human body. The main expression site that is central to the pathophysiology of COVID-19 is the respiratory epithelium of the nasopharynx. SARS-CoV-2 genes can then enter the human cell to begin viral replication and shedding. The process of viral replication is mediated by, and depends on, viral proteolytic enzymes (proteases), including main protease (M^{pro}, also known as 3C-like protease, $3CL^{pro}$) (Amin 2021; Anand 2003). Viral variants mainly present mutational changes in the spike glycoprotein (Harvey 2021). The spike glycoprotein is recognized by the immune system, and is the main target of vaccines against SARS-CoV-2 (Salvatori 2020; Walls 2020). In contrast, the M^{pro} active binding site is highly conserved between different virus variants and less affected by mutations.

Most individuals with COVID-19 are either asymptomatic or develop mild symptoms not requiring hospitalization (approximately 80% to 90%), depending on the time of the investigation, the cohort investigated, and the virus variant (Chen 2010; Funk 2021; Wu 2020). A smaller proportion is affected by severe (approximately 11% to 20%) or critical (approximately 1% to 5%) disease with hospitalization and intensive care unit (ICU) admittance due to respiratory failure, septic shock, or multiple organ dysfunction syndrome (Funk 2021; Wu 2020). Risk for severe disease, hospitalization, and mortality is higher for individuals aged 65 years or older, males, smokers, and individuals with certain underlying medical conditions (such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), moderate-to-severe asthma, immunocompromised state, obesity, sickle cell disease, or type 2 diabetes mellitus) (Booth 2021; Huang 2020; Karagiannidis 2020; Petrilli 2020; Williamson 2020). Most common symptoms and signs of acute infection include fever, cough, fatigue, and shortness of breath (Grant 2020). Infection with SARS-CoV-2 may also lead to long-term health conditions including persistent fatigue, cognitive dysfunction, and postexertional malaise (Huang 2021).

The gold standard for confirming a SARS-CoV-2 infection is the reverse transcription polymerase chain reaction (RT-PCR)-based detection of viral RNA from a nasopharyngeal swab test, anterior nares swab test (nasal swab), sputum, or tracheal secretion, with a sensitivity ranging from 70% to 98%, depending on pretest probability (Watson 2020). Offering lower sensitivity but greater practicality and accessibility, antigen tests can play a role in diagnosis or diagnostic triage, especially in point-of-care diagnostics of COVID-19 (Dinnes 2022; WHO 2020b). Antibody tests could be a useful diagnostic tool for those in whom molecular- or antigen-based tests have failed to detect the SARS-CoV-2 virus (Fox 2022).

Viral transmission is typically inferred from population-level information. Inherent properties of virus variants of concern, and individual differences in infectiousness among individuals or groups, and differences in local herd immunity make it difficult to contain its spread in the community (WHO 2021a). Currently, the most effective strategy to combat the pandemic is vaccination. COVID-19 vaccines are effective, reduce the risk of getting SARS-CoV-2, reduce the risk of severe COVID-19, and decrease hospitalization rates (CDC 2021; Graña 2022; Juthani 2021). However, vaccination can fail to produce a sufficiently robust immune response, and the response it does elicit can wane over time and be less effective against new variants (Lin 2022). Furthermore, some people cannot receive a COVID-19 vaccine for medical reasons, such as anaphylaxis, or may not develop sufficient immunogenicity following vaccination (NHS 2021). Others are hesitant to get vaccinated due to concerns about vaccine side effects and safety (Altulahi 2021; Wang 2021). The major obstacle in overcoming this pandemic, however, is vaccine inequity in different regions of the world (WHO 2021b). Additionally, emerging new virus variants can increase the risk of infection in all countries, including the vaccinated population if vaccines become less effective due to viral immune escape mutations as could be seen with Omicron variants (Ren 2022). Therefore, research on pre-exposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) of SARS-CoV-2 infection and treatment of COVID-19 is still of high relevance and is being carried out under great pressure worldwide.

Description of the intervention

Pfizer's drug combination nirmatrelvir/ritonavir (Paxlovid) aims to avoid severe COVID-19 in asymptomatic people or those with mild symptoms, thereby decreasing hospitalization and death. Nirmatrelvir/ritonavir is a combination of the SARS-CoV-2 protease inhibitor nirmatrelvir, and ritonavir, a CYP3A4 inhibitor used in the treatment of HIV to enhance HIV protease inhibitors. Nirmatrelvir blocks the activity of the SARS-CoV-2-$3CL^{pro}$ protease, an enzyme needed for viral replication. In humans, nirmatrelvir is metabolized by the P450 cytochrome enzyme CYP3A4. In order to remain active in the body for longer periods of time, nirmatrelvir is co-administered with low-dose ritonavir, to slow down the breakdown of nirmatrelvir (Pfizer 2021). Nirmatrelvir/ritonavir is to be administered orally within five days of symptom onset and taken twice daily for five days. Given the inactivation of CYP3A4 by ritonavir, a common enzyme in drug metabolism, ritonavir interferes with the metabolism of many drugs, can alter their plasma concentrations, and increase drug-related adverse effects. The applicability of nirmatrelvir/ritonavir may thus be limited in some populations at high risk of severe COVID-19, such as those with comorbidities requiring medications metabolized using the

CYP3A4 enzyme. As 3CL^{pro}, the substrate-binding site is highly conserved among all coronaviruses and shares no homology with human proteases, a SARS-CoV-2-3CL^{pro} antagonist will be highly specific to SARS-CoV-2 and less affected by virus mutations (Dai 2020) compared to antivirals binding to other sites, more prone to mutation.

There are several therapeutic options for people with COVID-19. Choice of therapy depends on severity of illness; drug availability; route of administration; time of onset of symptoms to starting treatment; co-administered medication; and patient-specific factors such as age, pregnancy, or current lactation. In people who are at the highest risk of hospitalization or progression to severe illness, including consideration in women who are pregnant or lactating, the WHO Living Guideline for Therapeutics and COVID-19 includes a strong recommendation for use of nirmatrelvir/ritonavir, in addition to symptomatic management (WHO 2023b). Alternative therapeutics for people in this group include remdesivir, which requires intravenous administration, and in some countries, the oral antiviral molnupiravir. Molnupiravir has a conditional recommendation for use by the WHO in people with non-severe COVID-19 at highest risk of hospitalization, excluding pregnant or breastfeeding women, and children. It is noted at the current time that the European Medicines Agency (EMA) has recommended the refusal of the marketing authorization of molnupiravir; however, this drug is available outside the EU.

Nirmatrelvir/ritonavir is not recommended by the WHO for people with severe COVID-19; recommended therapeutics in these patients include corticosteroids, interleukin-6 receptor blockers (tocilizumab, sarilumab), remdesivir (an antiviral), and the janus kinase inhibitor baricitinib in addition to cardiorespiratory support measures as indicated (WHO 2023b).

The WHO also has a conditional recommendation against the use of nirmatrelvir/ritonavir in people with non-severe illness at the lowest risk of hospitalization (WHO 2023b).

The WHO currently does not recommend any therapeutic to prevent COVID-19 in close contacts of infected patients or in other high-risk groups (WHO 2023c).

How the intervention might work

Viral non-structural proteins are important for replication and transcription of SARS-CoV-2. The SARS-CoV-2-3CL^{pro} plays a key role in the production of 16 non-structural proteins of SARS-CoV-2. Inhibition of 3CL^{pro} by nirmatrelvir blocks the release of these non-structural proteins, thereby suppressing further maturation and replication of SARS-CoV-2 (Zhang 2021). Boosting with ritonavir, a CYP3A4 inhibitor, is required to increase nirmatrelvir to a concentration that is effective against SARS-CoV-2 (Pfizer 2021). There is reason to presume that viral load, infectivity, and disease severity are positively correlated (Fajnzylber 2020; Kawasuji 2020; Liu 2020). Decreasing the viral load by blocking viral replication could thereby prevent disease progression and limit the infectivity of COVID-19 patients.

Nirmatrelvir (PF-07321332), the protease inhibitor agent in nirmatrelvir/ritonavir, was developed by modification of an earlier clinical candidate PF-00835231, originally developed as a potent inhibitor of recombinant SARS-CoV-1-3CL^{pro} during the SARS-CoV-1 pandemic in 2002/2003. SARS-CoV-1-3CL^{pro} and SARS-CoV-2-3CL^{pro} share 96% sequence homology (Zhang 2020). However, PF-00835231 needs to be administered intravenously, limiting its application mainly to hospital settings. Stepwise modification led to the new substance nirmatrelvir, with increased oral bioavailability. To date, nirmatrelvir has shown potent inhibition of 3CL^{pro} from all coronavirus types known to infect humans, as well as favourable selectivity profiles against mammalian proteases (Owen 2021).

Lufotrelvir, the phosphate prodrug of PF-00835231, with a similar mechanism of action to nirmatrelvir but with intravenous administration, is currently studied for safety and efficacy in the treatment of hospitalized people with COVID-19, including trials in conjunction with remdesivir, as in vitro data showed synergistic effects (de Vries 2020; NCT04501978; NCT04535167).

Why it is important to do this review

Current treatment for hospitalized people with COVID-19 includes supportive care with oxygen in moderate cases, systemic corticosteroids, remdesivir, baricitinib, interleukin-6 blockers, and non-invasive ventilation or invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) in severe or critical cases (Agarwal 2020). Overall, data from randomized controlled trials (RCTs) with exception to the aforementioned treatments do not demonstrate a clear, major clinical benefit with most drugs evaluated so far. Therapeutic options for treatment of COVID-19 in the outpatient setting or for prevention of a SARS-CoV-2 infection in close contacts of infected people or in people at risk are still limited. In light of the ongoing potential for evolving virus variants, scarcity of effective treatments, and global vaccination coverage issues, the role of effective oral therapies for people at high risk of severe disease is of utmost interest for reducing morbidity and mortality secondary to COVID-19.

The COVID-19 pandemic has brought social and racial injustice and health inequity in the spotlight of public health. The impact of COVID-19 disproportionally affects elderly, poor, racial and ethnic minorities, as well as a broad range of vulnerable populations, putting them at increased risk of illness and death (Killerby 2020). Reasons include, but are not limited to, inequitable viral spread in areas of dense population, and limited mitigation capacity due to a higher prevalence of chronic conditions or poor access to high-quality medical care (Shadmi 2020). Studies of the average effects of interventions, which control for confounding across individual and population-level characteristics, hide their impact on health equity (Welch 2012). Therefore, special consideration of health equity in studies and meta-analyses is needed, which can be obtained by reporting and analysis of population characteristics per outcome on the study-level.

Prevention of COVID-19 in people at high risk for developing severe disease requiring hospital-level treatment is critical, especially from a global perspective considering limited hospital capacity in low-income countries (LICs) and low- to middle-income countries (LMICs). Antiviral drugs such as nirmatrelvir/ritonavir might therefore be of vital importance in the global fight against SARS-CoV-2. However, it is yet to be determined whether the fact that nirmatrelvir/ritonavir has to be administered within five days of symptom onset may decrease its applicability due to inadequate healthcare infrastructures and lack of access to public health and medical care in LMICs, in older people, and in racial and ethnic minority populations.

To allow equity of access across countries, Pfizer has signed a voluntary licence agreement for nirmatrelvir/ritonavir with the Medicines Patent Pool (MPP), a United Nations-backed public health organization working to increase access to life-saving medicines for LMICs (MPP 2021a; Pfizer 2021). With the MPP having a licence on ritonavir for many years, the agreement will enable MPP to facilitate additional production and distribution of both ritonavir and nirmatrelvir by granting sublicenses to qualified generic medicine manufacturers (MPP 2021b). Pfizer further aims to offer a tiered pricing approach based on the income level of a country, with high-income countries (HICs) and upper-middle income countries (UMICs) paying more than LICs, which will pay a not-for-profit price (Pfizer 2021).

To date, several trials for nirmatrelvir/ritonavir on clinical outcomes for people with COVID-19 at high and standard risk are ongoing or terminated, but results have not been posted. A trial for PEP by Pfizer has been completed but not yet been published (Pfizer 2021). This review is designed as a living systematic review (LSR) with continuous monitoring of new and ongoing studies. We aim to keep the evidence base on clinical studies investigating nirmatrelvir/ritonavir for COVID-19 up to date.

This Cochrane Review will provide a complete evidence profile, based on current Cochrane standards, for nirmatrelvir/ritonavir with regard to efficacy and safety for PrEP and PEP and treatment of COVID-19 in out- and inpatient settings.

OBJECTIVES

To assess the efficacy and safety of nirmatrelvir/ritonavir plus standard of care (SoC) compared to SoC with or without placebo, or any other intervention for treating COVID-19 or preventing SARS-CoV-2 infection.

To explore equity aspects in subgroup analyses.

To keep up to date with the evolving evidence base using a living systematic review (LSR) approach and make new relevant studies available to readers in-between publication of review updates.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were eligible if they were RCTs.

We searched for full-text journal articles published in PubMed-indexed and non-indexed journals, preprint articles, results published in trials registers, clinical study reports (CSRs), and abstract publications. We applied no restrictions on the language of published articles.

We screened all identified studies for research integrity using a tool developed by our group to deal with problematic studies (see Selection of studies).

Types of participants

Treating COVID-19

Studies were eligible if they included participants with confirmed SARS-CoV-2 infection (RT-PCR or antigen testing), regardless of age, gender, ethnicity, serology status, vaccination status, previous SARS-CoV-2 infection, and risk factors for developing severe COVID-19. If studies included participants with a confirmed or suspected COVID-19 diagnosis, we used only the data for the population with confirmed COVID-19 diagnosis.

COVID-19 severity was classified according to the WHO clinical progression scale (Marshall 2020) into mild (WHO 1 to 3), moderate (WHO 4 to 5), and severe (WHO 6 to 9).

In cases where data were not reported separately for people with confirmed or suspected COVID-19 diagnosis, we excluded the study.

Preventing SARS-CoV-2 infection

We synthesized evidence for both PEP and PrEP scenarios. For PEP, we included studies investigating participants who were not infected with SARS-CoV-2 at enrollment (negative RT-PCR), but were at high risk of developing the infection following exposure to infected people or infectious viral particles. For PrEP, we included studies investigating participants who were not infected with SARS-CoV-2 at enrollment (negative RT-PCR) and were not yet exposed to infected people or infectious viral particles, but were at increased risk of contracting the disease (e.g. healthcare workers).

Participants in both settings were eligible regardless of age, gender, ethnicity, serology status, vaccination status, previous SARS-CoV-2 infection, and risk factors for developing severe COVID-19. Eligible trials must have reported the history of previous SARS-CoV-2 infection or serological evidence and the vaccination status of included participants. A history of SARS-CoV-2 infection or vaccination was not an exclusion criterion.

Types of interventions

All doses and regimens of nirmatrelvir/ritonavir were eligible for this systematic review. Nirmatrelvir/ritonavir is authorized and approved by the US Food and Drug Administration (FDA) at a dose of 300 mg (as two 150 mg tablets) of nirmatrelvir with one 100 mg tablet of ritonavir, given twice-daily for five days (EUA for Paxlovid).

We compared nirmatrelvir/ritonavir plus SoC to SoC with or without placebo, or to any other intervention for treating COVID-19 and for preventing SARS-CoV-2 infection including traditional Chinese medicine (TCM). We planned to investigate different active comparators in separate comparisons. Co-interventions (SoC) must have been comparable between the study arms.

Types of outcome measures

We evaluated core outcomes in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for people with COVID-19 (COMET 2020; Marshall 2020), and additional outcomes that have been prioritized by consumer representatives and the German guideline panel for treatment of people with COVID-19 (German AWMF Guideline 2021).

We used different outcome sets for the use of nirmatrelvir/ritonavir for treating people with COVID-19 in the out- and inpatient setting, and for preventing SARS-CoV-2 infection. If studies were eligible for inclusion regarding study design, population, intervention, and comparator, but no outcomes of interest were reported, they were not included for meta-analysis. However, we summarized reported outcomes for all included studies in the Characteristics of included studies table. We did not exclude studies if they did not report outcomes of interest.

Primary outcomes

Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings

- All-cause mortality at day 28, day 60, time-to-event, and up to the longest follow-up.
- Worsening of clinical status within 28 days.
  - Admission to hospital or death.
  - Admission to ICU or death.
- Improvement of clinical status.
  - All initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up.
  - Time to symptom resolution.
- Quality of life, including fatigue and neurological status, assessed with standardized scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days, and longest follow-up available.
- Serious adverse events (SAEs) during the study period, defined as number of participants with any event.
- Adverse events (AEs) during the study period, defined as number of participants with any event.
  - Any grade treatment-emergent adverse events (TEAEs; AEs temporally related to the study treatment).
  - Any grade treatment-related adverse events (TRAE; AEs assessed as causally related to the study treatment by the study investigator).
  - Discontinuation of study drug due to AEs.
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, and 3, 7, and 14 days.

Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings

We used a similar outcome set for treating people with COVID-19 in out- and inpatient settings, but with different definitions of the outcomes of 'Worsening of clinical status' and 'Improvement of clinical status'. For inpatient settings, we used the following definitions.

- Worsening of clinical status within 28 days.
  - Participants with new need for invasive mechanical ventilation or death.
  - Participants with need for ICU admission or death.
- Improvement of clinical status within 28 days.
  - Participants discharged alive. Participants should have been discharged without clinical deterioration or death.

Nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection (pre- and postexposure)

We used the same outcome set for PrEP and PEP scenarios, but with different time frames for the outcome assessment. For PEP studies, the relevant period is 14 to 28 days and for PrEP studies, a longer period of up to six months is relevant.

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days (PEP) and six months (PrEP).
- Development of clinical COVID-19 symptoms up to 28 days (PEP) and six months (PrEP); for example, assessed in accordance with individual items of the WHO scale (Marshall 2020), or any other standardized scale. If the study did not use the standardized WHO scale to assess the status of the participants, we would have categorized their status according to the WHO scale with the information provided by the study.
  - Uninfected (WHO scale 0).
  - Ambulatory mild disease (WHO scale 1 to 3).
  - Hospitalized with moderate disease (WHO scale 4 to 5).
  - Hospitalized with severe disease (WHO scale 7 to 9).
  - Mortality (WHO scale 10).
- All-cause mortality up to the longest follow-up.
- Admission to hospital or death within 28 days (PEP) and six months (PrEP).
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 28 days (PEP) and six months (PrEP), and at longest follow-up available.
- SAEs during the study period, defined as number of participants with any event.
- AEs during the study period, defined as number of participants with any event.
  - Any grade TEAE (AEs temporally related to the study treatment).
  - Any grade TRAE (AEs assessed as causally related to the study treatment by the study investigator).
  - Discontinuation of study drug due to AEs.

Timing of outcome measurement

We collected information on outcomes from all time points reported in the publications and study reports. If only a few studies contributed data to an outcome, we planned to pool different time points, provided the studies produced valid data and pooling was clinically reasonable. The current review version included two studies.

For time-to-event analysis (e.g. for time to death), we planned to use the longest follow-up time measured from randomization.

We reported time points of outcome measurement in the footnotes of the forest plots. We included SAEs and AEs occurring during the study period, including AEs during active treatment and long-term AEs. If sufficient data had been available, we planned to group the measurement time points of eligible outcomes into those measured directly after treatment (up to seven days), medium-term outcomes (up to 14 days), and longer-term outcomes (28 days or more).

Secondary outcomes

This review specifies no secondary outcomes. All outcomes were treated as a primary outcome set which informed the summary of findings tables.

Search methods for identification of studies

Electronic searches

Our Information Specialist (MIM) conducted systematic searches in the following sources from the inception of each database to 15 May 2023 and placed no restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates;
  - MEDLINE (PubMed), weekly updates;

- Embase, weekly updates;
- ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
- WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates;
- medRxiv (www.medrxiv.org), weekly updates.

- Scopus (Elsevier).
- WHO COVID-19 Research Database (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).

For detailed search strategies, see Appendix 1. As this review is a LSR, we conducted monthly update searches until December 2022 and changed to conduct search updates every two months thereafter (due to lack of publication of relevant studies) which are being made publicly available on OSF (osf.io/7g49c/; Reis 2022a). See section 'Methods for future updates' on specific LSR methodology.

We do not conduct separate searches of the databases required by the MECIR standards (Higgins 2021), since these databases are being regularly searched for the production of the CCSR.

Searching other resources

We searched for other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews, and meta-analyses.

Data collection and analysis

Selection of studies

Inclusion criteria

We performed study selection in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022). Three review authors (SR, RK, and SW) independently screened titles and abstracts of identified records. We retrieved full-text articles and independently assessed eligibility of the remaining records against the predefined eligibility criteria. We resolved discrepancies through discussion between the review authors. We included studies irrespective of whether measured outcome data were reported in a 'usable' way. We collated multiple reports of the same study, so that the study, rather than the report, was the unit of interest in the review.

Research integrity screening

Early in the COVID-19 pandemic several studies were identified as unsuitable for public use due to research ethics and integrity concerns and were retracted, withdrawn, or noted with concern (Bramstedt 2020). Cochrane has published a policy on managing problematic studies and guidance to facilitate research integrity checks in the reviews it publishes, but these checks have not routinely formed part of evidence synthesis processes to date (Cochrane policy – managing problematic studies). Current standard tools for systematic reviews do not systematically consider issues of research integrity. However, there are useful tools available such as the 'REAPPRAISED' checklist for evaluation of publication integrity (Grey 2020), or the data extraction sheet from the Cochrane Pregnancy and Childbirth Group that addresses scientific integrity and trustworthiness (Data extraction template 2021). We modified these existing tools and developed a specific tool for studies in this pandemic that we used for updating the Cochrane Review on ivermectin (Popp 2022; Weibel 2022). This tool, along with detailed methodological instructions and critical and important signalling questions to key aspects (domains), is described in Appendix 2, and elsewhere (Weibel 2022). Briefly, all trials fulfilling the PIC (patient, intervention, and comparator) eligibility criteria were assessed for issues with research integrity, such as retraction notices, prospective trial registration, ethics approval, plausible study authorship, sufficient reporting of methods regarding relevant eligibility criteria (e.g. randomization), and plausibility of study results. Studies were only eligible for the review if they met critical aspects assuring research integrity. Studies were excluded if they were retracted or if they were not prospectively registered in a national or international studies' registry according to the WHO guidelines for clinical trial registration (WHO 2018). All potentially eligible studies with disparities in the reporting of the methods and results were held in 'awaiting classification' until the study authors clarified certain questions upon request. The process was documented and decisions were transparently reported.

We documented the study selection process in a PRISMA flow diagram with the total number of studies included, excluded, awaiting classification, and ongoing. We listed the reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (SR and SW) independently extracted data using a standardized data extraction form, including details of the study, participants, intervention, comparator, and outcomes. If necessary, we attempted to obtain missing data by contacting the authors of relevant articles. At each step of data extraction, we resolved any discrepancies through discussion between the review authors. In case of discrepancies between different documents of one study (e.g. preprint, journal publication, clinical study reports, registered trial protocol), we planned to contact the authors for clarification.

We extracted the following information, if reported.

- General information: author, trial name, title, source, country, language, type of publication/report, and publication date.
- Study characteristics: setting and dates, inclusion/exclusion criteria, number of study arms, comparability of groups, length of follow-up, and funding.
- Participant characteristics: number of participants randomized/received intervention/analyzed, COVID-19 diagnostics, severity of disease, age, gender, race, ethnicity, comorbidities (e.g. diabetes, immunosuppression, obesity), concurrent medication, time since symptom onset, vaccination status (e.g. type of vaccine, number of doses), serology status, and history of SARS-CoV-2 infection.
- Intervention: dose, frequency, time from symptom onset to treatment initiation, and duration and route of administration.
- Control intervention: type of control, dose and frequency, and duration and route of administration.
- Outcomes: as specified under Types of outcome measures.

To address health equity, we considered the following population characteristics and report them per outcome at the study-level in additional tables.

- Elderly people (older than 65 years). People of advanced age are at increased risk for severe disease. The intervention

(nirmatrelvir/ritonavir) could potentially have greater impact on elderly people.

- People at social disadvantage due to the number of comorbid health conditions. The intervention (nirmatrelvir/ritonavir) is aimed at people with at least one risk factor for severe disease. Risk factors include individuals with a comorbid health condition, or multimorbidity, the presence of which is associated with social disadvantage (multimorbidity is associated with a reduction in quality of life, increased disability, and premature mortality). The intervention could potentially have greater impact on people with comorbid health conditions, promoting health equity.
- People from LICs, LMICs, UMICs, and HICs as defined by the World Bank 2022 (studies were categorized based on the date of first participant enrollment). Differences exist in access to care and the quality of care across LICs, LMICs, UMICs, and HICs. People from LICs and LMICs may not have access to the intervention within five days of onset of symptoms of COVID-19. Use of diagnostic tools in LICs and LMICs is also limited. In this context, nirmatrelvir/ritonavir could then be seen to have a potentially greater effectiveness for people from UMICs and HICs.
- People from different ethnic and racial backgrounds, including minorities. Differences exist in access to care and the quality of care across different ethnic and racial minority groups who may not have access to the intervention within five days of onset of symptoms of a SARS-CoV-2 infection. Nirmatrelvir/ritonavir could therefore be seen as having a lower impact in these population groups.

Assessment of risk of bias in included studies

We assessed the risk of bias in the included studies using RoB 2 (Higgins 2022a; Sterne 2019). The effect of interest is the effect of assignment at baseline, regardless of whether the interventions were received as intended (the 'intention-to-treat effect'). We assessed the risk of bias for all results (outcomes) reported in the included study that we specified as outcomes for the review and that contributed to the review's summary of findings tables.

Two review authors (SR, SW) independently assessed the risk of bias of all results. We resolved any disagreements through discussion with a third review author.

The RoB 2 tool considers the following domains:

- bias arising from the randomization process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We assessed the RoB 2 domains using the recommended signalling questions and the following response options:

- yes;
- probably yes;
- probably no;
- no; or
- no information.

RoB 2 algorithms map responses to signalling questions. We used the proposed algorithm after verification to reach a risk of bias judgement, and assigned one of three levels to each domain:

- low risk of bias;
- some concerns; or
- high risk of bias.

Similarly, we reached an overall risk of bias judgement for a specific outcome by considering all domains resulting in one of the three judgement options described above. Overall low risk of bias of the trial result was assumed when all domains were at low risk; some concerns of bias was assumed when the trial results were judged to raise some concerns in at least one domain for this result, but not at high risk of bias for any domain; overall high risk of bias of the trial result was assumed when the trials were at high risk of bias in at least one domain for this result or when it was judged to have some concerns for multiple domains in a way that substantially lowered confidence in the result (Higgins 2022a).

We used the RoB 2 Excel tool (version beta_v7) to implement RoB 2 (available at www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). We stored the full RoB 2 data (e.g. completed Excel tool) in an online repository.

Measures of treatment effect

For dichotomous outcomes, we recorded the number of events and the number of analyzed participants in the intervention and control groups. For any AEs, we counted the number of events as number of participants with (at least) one event. We used the risk ratio (RR) with 95% confidence interval (CI) as the effect measure.

For continuous outcomes, we planned to record the mean, the standard deviation (SD), and the number of analyzed participants in the intervention and control groups. If the SD was not reported, we planned to use standard errors (SEs), CIs, or P values to calculate the SD with the formulas described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b). If studies in future review updates have reported data as median with interquartile range (IQR), we will assume that the median is similar to the mean when the distribution of the outcome is similar to the normal distribution (e.g. symmetric IQR). In these cases, the width of the IQR is approximately 1.35 SDs (Higgins 2022b). We planned to use the mean difference (MD) with 95% CI as the effect measure. For continuous outcomes measured on different scales (e.g. quality of life), we planned to perform analyses using the standardized mean difference (SMD). For interpreting SMDs, we would have re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact. The current review version did not contain a continuous outcome.

If available in future review updates, we will extract and report hazard ratios (HRs) for time-to-event outcomes (e.g. time to death). If HRs are not available, we make every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar 1998 and Tierney 2007. If sufficient studies provide HRs, we plan to use HRs rather than RRs or MDs in a meta-analysis, as they provide more information. The current review version did not contain a time-to-event outcome.

We considered effect estimates of dichotomous outcomes with the range of the 95% CIs not crossing 1 (the line of null effect) and

continuous outcomes with the range of the 95% CIs not crossing 0 as statistically significant effect estimates. A statistically significant effect does not necessarily mean that the estimated effect is clinically relevant. Clinical experts assessed the clinical relevance of the effects based on anticipated absolute effects separately, and we reported this transparently.

Unit of analysis issues

The unit of analysis for this review was the randomized participant.

In studies with multiple intervention groups, we planned to combine groups if reasonable (e.g. study arms with different doses of nirmatrelvir/ritonavir). If it was not reasonable to pool the groups, we planned to split the 'shared' comparator group to avoid double-counting of participants. No study groups were pooled for the current review as neither of the included studies investigated multiple intervention groups.

Dealing with missing data

There are many potential sources of missing data in a systematic review or meta-analysis, which can affect the level of studies, outcomes, summary data, individuals, or study-level characteristics (Deeks 2022). Incomplete data can introduce bias into the meta-analysis, if they are not missing at random. We addressed all sources of missing data. Missing studies may be the result of reporting bias, and we addressed this as described in the Assessment of reporting biases section. Missing outcomes and summary data may be the result of selective reporting bias; missing individuals may be the result of attrition from the study or lack of intention-to-treat analysis. We addressed these sources of missing data using the RoB 2 tool (Assessment of risk of bias in included studies). If data were incompletely reported, we contacted the study authors to request additional information.

Assessment of heterogeneity

We planned to use the descriptive statistics reported in the Characteristics of included studies table to assess whether the studies within each pairwise comparison were homogeneous enough, with respect to study and intervention details and population baseline characteristics, that the assumption of homogeneity might be plausible. In case of excessive clinical heterogeneity, we planned not to pool the findings of included studies.

We planned to measure statistical heterogeneity using the Chi^2 test and the I^2 statistic (Deeks 2022), and the 95% prediction interval (PI) for random-effects meta-analysis (IntHout 2016). The PI helps in the clinical interpretation of heterogeneity by estimating what true treatment effects can be expected in future settings (IntHout 2016). Calculation of a 95% PI is restricted to meta-analyses with four or more studies (200 participants or more), since the interval is imprecise when a summary estimate is based on only a few small studies. The current review did not contain meta-analyses with a sufficient number of studies to investigate heterogeneity. We plan to use the open-source statistical software R package meta to calculate 95% PIs in review updates (Meta 2022). In future updates, we will declare statistical heterogeneity if the P value is less than 0.1 for the Chi^2 statistic, or the I^2 statistic is equal to or greater than 40% (40% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; and 75% to 100%: considerable heterogeneity; Deeks 2022), or the range of the 95% PI reveals a different clinical interpretation of the effect estimate compared to the 95% CI.

Assessment of reporting biases

We tried to identify all research that met our predefined eligibility criteria. Missing studies can introduce bias to the analysis. We searched for completed non-published trials in trial registers, and contacted authors to seek assurance that results will be made available. We classified these studies as 'awaiting classification' until the results were reported. We also planned to report the number of completed non-published trials. The current review did not identify completed non-published trials.

If there were 10 or more relevant studies pooled in a meta-analysis, we planned to investigate risk of reporting bias (publication bias) in pairwise meta-analyses using contour-enhanced funnel plots. If funnel plot asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses (e.g. Rücker's arcsine test for dichotomous data and Egger's linear regression test for continuous data) to further investigate funnel plot asymmetry. A P value of less than 0.1 is considered as the level of statistical significance. We planned to analyze reporting bias using the open-source statistical software R package meta (Meta 2022). The current review did not contain meta-analyses with a sufficient number of studies to investigate reporting bias.

Data synthesis

We compared nirmatrelvir/ritonavir plus SoC with SoC with or without placebo, or to any active comparator with efficacy. Co-interventions (SoC) must have been comparable between the study arms.

We created the following comparisons.

- nirmatrelvir/ritonavir plus SoC versus SoC (with or without placebo); and
- nirmatrelvir/ritonavir versus active pharmacological intervention (separate comparisons for different active interventions; no studies available for the current review version).

We planned to analyze trials with different objectives of nirmatrelvir/ritonavir use separately, as follows.

- Treatment of COVID-19 in an outpatient setting: participants with confirmed SARS-CoV-2 infection.
- Treatment of COVID-19 in an inpatient setting: participants with confirmed SARS-CoV-2 infection.
- Prevention of SARS-CoV-2 infection (PEP): RT-PCR-negative participants at baseline with a high risk of developing the infection following exposure to infected people or infectious viral particles (no studies available for the current review version).
- Prevention of SARS-CoV-2 infection (PrEP): RT-PCR-negative participants at baseline not yet exposed to infected people or infectious viral particles but at increased risk of contracting the disease (e.g. healthcare workers) (no studies available for the current review version).

We performed meta-analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). We used forest plots to visualize meta-analyses.

If clinical and methodological characteristics of individual studies were sufficiently homogeneous, we planned to pool the data in meta-analyses. When meta-analyses were feasible, we planned to use the random-effects model as we assume that the intervention effects were related but might not be the same in included studies. For dichotomous outcomes, we performed meta-analyses using the Mantel-Haenszel method using a random-effects model to calculate the summary (combined) intervention effect estimate as a weighted mean of the intervention effects estimated in the individual studies. For continuous outcomes, we planned to use the inverse-variance method.

We planned to present descriptive statistics only if we deemed meta-analysis inappropriate for a certain outcome because of heterogeneity, or because of serious study limitations leading to considerably high risk of bias (e.g. competing risk of death not taken into account in outcome measurement).

We used RevMan Web for meta-analysis and to calculate the effect estimate of the included studies (RevMan Web 2020).

Subgroup analysis and investigation of heterogeneity

We reported details of the intervention and population at baseline for the included studies in the footnotes of the forest plot.

The current review version included one study for inpatients and one study for outpatients, therefore investigation of heterogeneity between studies was not applicable. For future updates, we plan to investigate heterogeneity by visual inspection of the forest plot.

If statistical heterogeneity is present, we plan to investigate heterogeneity by subgroup analysis to calculate RR or MD in conjunction with the corresponding CIs for each subgroup, if sufficient studies are available.

The following characteristics will be used for subgroup analyses to explore statistical heterogeneity, if reported.

- Nirmatrelvir/ritonavir used as treatment (in- and outpatients):
  - studies including participants with different severities of condition at baseline (symptomatic versus asymptomatic);
  - studies including participants with a history of SARS-CoV-2 infection/vaccination versus participants with no history of infection/vaccination;
  - studies with different recruitment periods examining different dominant virus variants circulating at the time of the study (e.g. Alpha versus Beta versus Gamma versus Delta versus Omicron, etc.);
  - studies that started nirmatrelvir/ritonavir treatment early (five days or fewer) versus late (more than five days after symptom onset);
  - studies investigating different doses of nirmatrelvir/ritonavir (low versus recommended versus high). If necessary in future review updates, we will consider and categorize dosing schemes into recommended (nirmatrelvir 300 mg/ritonavir 100 mg, twice-daily for five days), low (less than recommended dose), and high doses (greater than recommended dose). We planned to analyze different doses in subgroup analysis, if sufficient studies are available. The one study considering treatment in the current review did not investigate different doses.
- Nirmatrelvir/ritonavir used for prevention:
  - studies including participants with a history of SARS-CoV-2 infection/vaccination versus participants with no history of infection/vaccination;
  - studies investigating different modes of exposure (e.g. working place, nursing home) and burden of exposure (e.g. living in a high-risk area, high-risk medical contact) in prevention studies;
  - studies with different recruitment periods examining different dominant virus variants circulating at the time of the study (e.g. Alpha versus Beta versus Gamma versus Delta versus Omicron, etc.);
  - studies investigating different doses of nirmatrelvir/ritonavir (low versus recommended versus high).

We investigated health equity considering elderly people, socially disadvantaged people with comorbidities, populations from LICs/LMICs, and people from different ethnic and racial backgrounds using subgroup analysis independent of statistical heterogeneity. We planned to perform the following subgroup analyses for treatment and prevention settings:

- studies including different populations regarding age of the population (children versus adults versus older adults (greater than 65 years));
- studies including participants with different levels of comorbidity (high-risk versus low-risk population);
- studies including participants from HICs, middle-income country, or LIC settings and populations according to the World Bank classification (World Bank 2022) (LICs/LMICs versus UMICs/HICs);
- studies including different racial and ethnic groups (Asian, Black, White, Hispanic, and minority ethnic groups);

Sensitivity analysis

We planned to conduct sensitivity analyses to test the robustness of the meta-analyses excluding:

- studies with overall high risk of bias;
- non-peer reviewed studies (including preprint articles);
- studies reporting data as median instead of mean for continuous outcomes;
- studies using no treatment in the comparator arm for participant-reported outcomes such as symptom resolution.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in summary of findings tables, including a rating of the certainty of evidence based on the GRADE approach. We followed current GRADE guidance as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022).

Two review authors (SR, SW) assessed the certainty of evidence, considering risk of bias, inconsistency, imprecision, indirectness, and publication bias. We used the overall RoB 2 assessment and RoB sensitivity analysis to inform the risk of bias judgement underlying the assessment of the certainty of evidence.

We planned to create separate summary of findings tables for the use of nirmatrelvir/ritonavir with different intentions (e.g.

treatment of people with COVID-19 in out- and inpatient settings, prevention of SARS-CoV-2 infection as PEP, and prevention as PrEP), and for different comparisons with regard to the intervention and comparator. The summary of findings tables included the following outcomes.

Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings.

- All-cause mortality; at longest follow-up and greater than 60 days most favourable; if not reported all-cause mortality day 60, followed by day 28, or time-to-event estimate, are reported in the summary of findings table.
- Admission to hospital or death within 28 days.
- Improvement of clinical status.
  - All initial symptoms resolved (asymptomatic) at day 14.
  - Time to symptom resolution.
- Quality of life at longest follow-up available.
- SAEs during the study period.
- AEs during the study period.
  - Any grade TEAE.
  - Any grade TRAE.
- Viral clearance at seven days.

Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings.

- All-cause mortality at longest follow-up and greater than 60 days most favourable; if not reported all-cause mortality day 60, followed by day 28, or time-to-event estimate, are reported in the summary of findings table.
- Worsening of clinical status within 28 days.
  - Participants with new need for invasive mechanical ventilation or death.
- Improvement of clinical status within 28 days.
  - Participants discharged alive. Participants should be discharged without clinical deterioration or death.
- Quality of life at longest follow-up available.
- SAEs during the study period.
- AEs during the study period.
  - Any grade TEAE.
  - Any grade TRAE.
- Viral clearance at seven days.

Nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection (PEP).

- SARS-CoV-2 infection at 14 days.
- Development of clinical COVID-19 symptoms up to 28 days.
- All-cause mortality up to the longest follow-up.
- Admission to hospital or death within 28 days.
- Quality of life at longest follow-up available.
- SAEs during the study period.
- AEs during the study period.
  - Any grade TEAE.
  - Any grade TRAE.

Nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection (PrEP).

- SARS-CoV-2 infection at six months.
- Development of clinical COVID-19 symptoms up to six months.
- All-cause mortality up to the longest follow-up.
- Admission to hospital or death within six months.
- Quality of life at longest follow-up available.
- SAEs during the study period.
- AEs during the study period.
  - Any grade TEAE.
  - Any grade TRAE.

The GRADE assessment result in one of four levels of certainty and these express our confidence in the estimate of effect (Balshem 2011).

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We addressed equity for all outcomes presented in summary of findings tables. Interpretation of evidence occurred for the specific populations which are defined as important recipients of the intervention (see Data extraction and management).

- Elderly people.
- People at social disadvantage due to the number of comorbid health conditions.
- People from LICs/LMICs.
- People from different ethnic and racial backgrounds, including minorities.

Interpretation considers the questions, whether findings are likely to be applicable in those populations, even if they did not make up a large proportion of the participant populations in included studies. We reported inequities in the footnotes of the summary of findings tables.

We used the MAGICapp to create summary of findings tables (MAGICapp), and incorporate the results into RevMan Web manually (RevMan Web 2020).

Methods for future updates – living systematic review considerations

Our Information Specialist (MIM) provides us with new search records each month, which two review authors screen, extract, evaluate, and integrate following the guidance for Cochrane LSRs. We maintain an Excel spreadsheet every second month, which lists the search results and new studies potentially to be included in this review. It is publicly available on the open science framework (OSF) platform (osf.io/7g49c/; Reis 2022a). Details on this 'living method' are available in Metzendorf 2022.

We manually check platform trials for new treatment arms investigating nirmatrelvir/ritonavir.

We wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We consider one or more of the following components to inform this decision.

- The findings of one or more prioritized outcomes.
- The credibility (e.g. GRADE rating) of one or more prioritized outcomes.
- New settings, populations, interventions, comparisons (not TCM), or outcomes studied.

In the case of emerging policy relevance due to global controversies regarding the intervention, we consider republishing an updated review even though our conclusions remain unchanged. We review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (e.g. when additional comparisons, interventions, subgroups, outcomes, or new review methods become available).

RESULTS

Description of studies

Results of the search

The literature search up to 15 May 2023 resulted in 739 records identified in 12 search updates. After deduplication in Endnote (EndNote 2013), 593 records remained. During title and abstract screening, we judged 497 records as irrelevant as they did not meet the prespecified inclusion criteria. We proceeded to full-text screening with 96 records. We considered published full-texts in journals or on preprint servers or, if these were unavailable, trials' register entries. A total of 31 records met our eligibility criteria regarding patient population, intervention, and comparator of which 14 records belonged to 13 ongoing studies and three studies with eight records are currently awaiting classification. We excluded 61 records (53 studies) with reasons after full-text assessment. Two studies with results were excluded due to concerns regarding research integrity.

We included nine records (two studies) with results in this review.

Finally, we included one study for outpatients and one study for inpatients in our qualitative synthesis. One study was in the original review (EPIC-HR 2021), and one study from this update (Liu 2023). Due to the limited number of available studies, meta-analysis was not possible. The search process is shown in Figure 1.

Figure 1. PRISMA flow diagram.

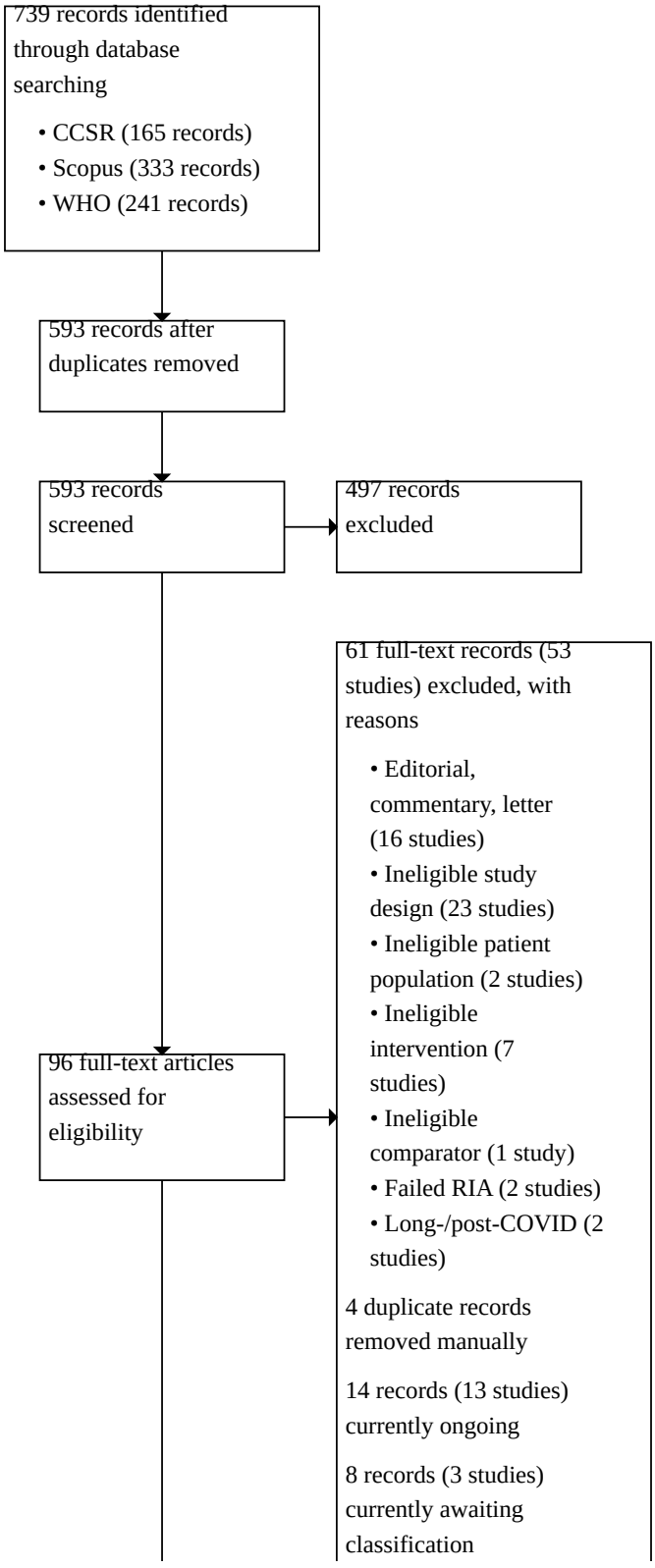
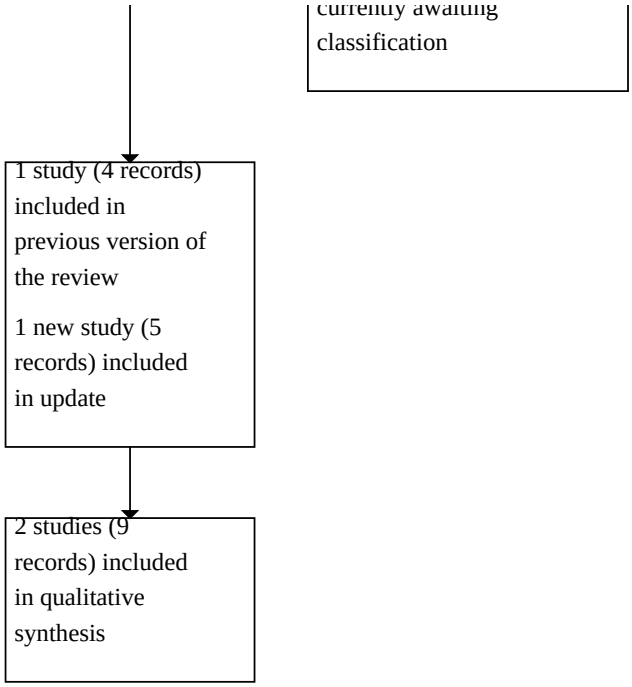


Figure 1. (Continued)



This is a LSR and we conduct update searches every two months which are being made publicly available on the OSF platform (osf.io/7g49c/; Reis 2022a).

Eligibility screening for research integrity

We evaluated four studies for issues with research integrity.

- Two studies with results identified by the search in April 2022 (EPIC-HR 2021) and March 2023 (Liu 2023) passed research integrity assessment. There were no retraction notice or concerns expressed elsewhere, and the trials were prospectively registered with adequate ethics approval. The method of randomization was sufficiently reported, and study results were plausible.
- We excluded two trials with results identified by the search in December 2022 (Balykova 2022) and March 2023 (Cao 2023). Balykova 2022 was a retrospective trial registration and there was no response from study authors regarding ethics approval. We excluded Cao 2023 as recruitment of participants (4 April 2022) started before ethics approval was obtained (23 April 2022).

The research integrity assessment is described in Appendix 2 and decisions regarding this review's study pool are transparently reported and publicly available (Supplementary File_Nirmatrelvir_Research Integrity).

Included studies

Details of both included studies are reported in the Characteristics of included studies table.

Design and publication status

We included two multicentre RCTs with 2510 randomized adults comparing nirmatrelvir/ritonavir with control (EPIC-HR 2021; Liu 2023). Both trials were available as peer-reviewed journal articles and comprised two trial arms. One trial had an open-label design using SoC as comparator (Liu 2023), the other trial was double-blinded and placebo-controlled (EPIC-HR 2021). One trial was conducted in China (Liu 2023), and the other at 343 sites worldwide (EPIC-HR 2021). EPIC-HR 2021 was funded by Pfizer, while Liu 2023 was funded by departmental resources and a Chinese government grant.

Setting

EPIC-HR 2021 investigated outpatients in 343 sites worldwide. Of those, 27 sites (7.9%) were placed in LICs and LMICs. The other 319 sites (92.1%) were set in UMICs or HICs. There was no information regarding the actual number of included participants per site/country. Participants were recruited during the Delta wave between July and December 2021. Liu 2023 investigated inpatients at five sites in the UMIC in China. Participants were recruited during the Omicron wave between April and May 2022.

Participants

The included studies investigated nirmatrelvir/ritonavir for treatment of non-hospitalized people with COVID-19 (EPIC-HR 2021) and hospitalized people with COVID-19 (Liu 2023). No study investigating nirmatrelvir/ritonavir for treating hospitalized people with COVID-19 and preventing SARS-CoV-2 infection has been included in this review.

Outpatient setting

One trial compared nirmatrelvir/ritonavir to placebo in an outpatient setting (EPIC-HR 2021).

For the outpatient setting, we classified participants as 2 to 3 on the WHO clinical progression scale (Marshall 2020). All participants had a confirmed SARS-CoV-2 infection with symptom onset of five days or less before randomization. Randomization coincided with the Delta wave. Mean time between symptom onset and start of treatment was 2.96 days with 66.3% of participants starting treatment within three days. As per the study exclusion criteria, all participants were unvaccinated against SARS-CoV-2. Further exclusion criteria were previous confirmed SARS-CoV-2 infection, hospitalization for COVID-19, or therapy with convalescent COVID-19 plasma.

Median age was 46 years (IQR 18 to 88) and 51.1% of participants were men. The trial excluded pregnant or breastfeeding women. Age was reported for the modified intention-to-treat (mITT1) population (2085 participants) according to groups aged 65 years or greater and less than 65 years, with 87.1% of participants younger than 65 years. Regarding race and ethnicity, most participants identified as White (71.5%), 14% as Asian, and 4.9% as Black.

Participants were eligible for inclusion into the trial if they were at high risk for progression to severe disease due to at least one coexisting condition or had other characteristics associated with an increased risk of developing severe illness from COVID-19 (EPIC-HR 2021). In the full analysis set (FAS), 61.0% of participants had two or more coexisting conditions or characteristics associated with an increased risk of developing severe COVID-19 (EPIC-HR 2021). The most common prespecified characteristics and comorbidities associated with an increased risk of developing severe disease were a body mass index (BMI) over 25 kg/m^2 in 1807 participants (80.5%), current smoking in 876 participants (39.0%), and hypertension in 739 participants (32.9%). Frequency of comorbidities were separately reported for the mITT1 population only (subgroup analyses); 79.7% had none or one comorbidity and 20.3% of the 2085 participants in the mITT1 population had two or more comorbidities, most commonly a BMI over 25 kg/m^2 (80.0%), hypertension (33.0%), and diabetes (12.1%). The study did not report the number of participants without any comorbidity. Few participants had other baseline comorbidities (e.g. chronic lung disease, cardiovascular disorder, chronic kidney disease, HIV infection, sickle cell disease, neurodevelopmental disorder, and cancer).

Inpatient setting

One trial compared nirmatrelvir/ritonavir to placebo in an inpatient setting (Liu 2023).

Liu 2023 classified participants according to the Guidelines on the Diagnosis and Treatment of COVID-19 (Ninth Trial Edition) which approximately translates to 2 to 4 on the WHO clinical progression scale (Marshall 2020; Xu 2022). All participants had confirmed SARS-CoV-2 infection with symptom onset of five days or less before randomization or a Ct value less than 25 by RT-PCR. Randomization occurred during the Omicron wave in China. Median time between symptom onset and hospital admission was three days, with a range of two to six days in the intervention group, and one to five days in the control group. About 73.48% of participants were unvaccinated, 25% of participants had received two or more doses of vaccination against SARS-CoV-2, the rest had received one dose (Liu 2023). Further exclusion criteria were previously confirmed SARS-CoV-2 infection, active liver disease, dialysis, HIV infection, and the expected use of amabacizumab/romlusevimab, intravenous COVID-19 human immunoglobulin, and convalescent plasma and tocilizumab during the treatment period.

Participants were older than those in EPIC-HR 2021, with a mean age of 70.4 (SD 13.12) years. About 53.8% of participants were men. Pregnant or breastfeeding women were excluded from the trial. Age was reported according to groups: greater than 65 years and 65 years or less with 31.8% of participants aged 65 years or less. The study did not report race or ethnicity. Liu 2023 investigated participants at risk of severe COVID-19. Participants were eligible for inclusion if they were hospitalized with mild to moderate COVID-19 and either severe comorbidities, or a Sequential Organ Failure Assessment (SOFA)/Charlson score of 2 or greater. About 61.7% of participants had two or more coexisting conditions. The most common prespecified comorbidity being cardiovascular disease in 141 participants (53.4%). The number of participants with multiple comorbidities was higher in Liu 2023 with 61.7% of participants having two or more comorbidities as compared to 20.3% of the EPIC-HR 2021 mITT. Median Charlson score was 3 with a range of 2 to 4 across both study arms and median SOFA score was 1 with a range of 0 to 2 across both study arms (Liu 2023).

Interventions and comparators

Both included studies administered nirmatrelvir/ritonavir orally at 300 mg/100 mg twice daily for five days and compared with either placebo plus SoC (EPIC-HR 2021), or SoC alone (Liu 2023). SoC in the EPIC-HR 2021 trial varied throughout study centres. The studies prohibited any medications or substances known to be strong inducers of CYP3A4 within 28 days prior to dosing of study intervention. Medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious or life-threatening (or both) events were not permitted during the study period. Treatment with COVID-19 monoclonal antibodies as part of SoC was allowed in US study centres only. SoC in Liu 2023 included antiviral and anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and nutrient support. While EPIC-HR 2021 allowed the concomitant use of monoclonal antibodies, Liu 2023 excluded people with expected use of amabacizumab/romlusevimab, intravenous COVID-19 human immunoglobulin, and convalescent plasma and tocilizumab during the treatment period.

No studies investigated other comparators.

Outcome measures

The included studies contributed outcomes to different prespecified outcome sets, one for outpatients (EPIC-HR 2021) and one for inpatients (Liu 2023).

Primary outcomes of the included studies were 'COVID-19-related hospitalization or death from any cause through day 28', which we used for the analysis of (any) 'admission to hospital or death within 28 days' (EPIC-HR 2021) and '28-days all-cause mortality' (Liu 2023). Subgroup analyses according to age for both these outcomes were available but with slightly different cut-offs: less than 65 years versus 65 years or over (EPIC-HR 2021) and 65 years or less versus greater than 65 years of age (Liu 2023). EPIC-HR

2021 further included subgroup analyses for White, Asian, Black/African American and a mixed ethnic group termed "other" (mITT1 population; see EPIC-HR 2021), while Liu 2023 reported subgroup analyses for the primary outcome in relation to vaccination status, COVID-19 severity, and the number of comorbidities.

For the outpatient setting, further outcomes eligible for this review included all-cause mortality at 28 days, any grade TRAEs, any grade TEAEs, SAEs, and discontinuation of study drug (EPIC-HR 2021). All safety outcomes were assessed within 34 days (EPIC-HR 2021).

For the inpatient setting, further outcomes eligible for this review included viral clearance at seven and 14 days. Regarding the safety of nirmatrelvir/ritonavir, the study reported on any grade TRAEs, TEAEs, SAEs, and discontinuation of study drug (Liu 2023). However, due to insufficient and inconsistent information on the time of the outcome assessment, the handling of missing outcome data, and the outcome assessment itself, we have excluded all safety outcomes from the quantitative analysis in this review. Upon enquiry, the study authors provided no further information regarding the outcomes.

The studies reported no subgroups for any outcome other than the primary outcome of the studies (EPIC-HR 2021; Liu 2023). The included studies did not report on worsening or improvement of clinical status, symptom resolution, time to symptom resolution, or quality of life at any of our prespecified time points.

Equity-related aspects

There were no study data for the following equity-related element of World Bank country classification by income level and level of comorbidity. For inpatients, there were no data for the equity-related element race/ethnicity (Liu 2023). Both studies reported data regarding age (EPIC-HR 2021; Liu 2023). EPIC-HR 2021 further reported on race/ethnicity.

Excluded studies

Details of excluded studies are reported in the Characteristics of excluded studies table.

We excluded 53 studies that did not match our inclusion criteria. Two studies analysed an ineligible study population of healthy participants without exposure to SARS-CoV-2 (NCT05690646; Singh 2022), seven studies focused on an intervention other than nirmatrelvir/ritonavir (AGILE 2020; Jittamala 2022; NCT04518410; NCT04864548; NCT05305547; PER-084-20; Razia 2023), one study investigated an ineligible comparator of nirmatrelvir/ritonavir plus remdesivir versus nirmatrelvir/ritonavir alone and of five days versus 10 days of nirmatrelvir plus ritonavir in immunocompromised participants (NCT05587894), two studies focused on participants with long-COVID or after COVID (NCT05576662; NCT05668091), 23 studies had an ineligible study design (Aggarwal 2022; ChiCTR2200059743; ChiCTR2200060700; ChiCTR2200063778; EPIC-PEDS 2022; ISRCTN12428408; ITMCTR2200005942; ITMCTR2200005943; ITMCTR2200005944; Kim 2022; Li 2022; NCT04756531; NCT05487040; NCT05813600; Park 2022; Ross 2022; Shao 2022; Spiliopoulou 2023; Wan 2023; Weng 2023; Xie 2023; Yan 2022; Yan 2023), two studies failed the research integrity assessment (Balykova 2022; Cao 2023), and 16 studies were classified as a commentary, letter, etc. (Australian Prescriber 2022; Beinfeld 2022; Biehle 2022; Caceres 2022; Doyno 2022; Ebell 2022; Elliott 2022; Enikeeva 2022; Gottlieb 2022; Pupo Correia 2022; Robinson 2021; Robinson 2022; Rosenberg 2022; Trøseid 2022; Vassilopoulos 2022; Wang 2022).

Studies awaiting classification

Details are available in the Characteristics of studies awaiting classification table.

Three studies are currently awaiting classification (EPIC-HOS; EPIC-PEP 2021; EPIC-SR 2021). One is investigating nirmatrelvir/ritonavir as PEP (EPIC-PEP 2021), while the other two are investigating nirmatrelvir/ritonavir as treatment for people with weakened immune systems or at increased risk for poor outcomes who are hospitalized due to severe COVID-19 (EPIC-HOS) and for people at standard risk (EPIC-SR 2021). All three studies were initiated and funded by Pfizer. One study has been completed without publication of results (EPIC-PEP 2021), while the other two have been terminated either due to challenges related to the operational feasibility of the study, taking into account the current epidemiology and declining hospitalization rates for severe COVID-19 (EPIC-HOS), or due to a very low rate of hospitalization or death observed in the standard-risk patient population (EPIC-SR 2021). Results have not been posted for any of the studies.

Ongoing studies

Details of ongoing studies are reported in the Characteristics of ongoing studies table.

We classified 13 studies as ongoing. All studies investigate nirmatrelvir/ritonavir for treatment of COVID-19 (2022-001362-35; ChiCTR2200059390; ChiCTR2200059726; ChiCTR2200059739; ChiCTR2200060010; NCT05041907; NCT05321394; NCT05386433; NCT05567952; NCT05614349; NCT05642910; PANORAMIC 2021; RECOVERY 2020). No study investigating nirmatrelvir/ritonavir as PEP or PrEP is currently ongoing. Of the 13 studies investigating nirmatrelvir/ritonavir for treatment of COVID-19, two studies are focusing on an inpatient setting (NCT05642910; RECOVERY 2020), while four others are investigating nirmatrelvir/ritonavir in outpatient settings (2022-001362-35; NCT05321394; NCT05614349; PANORAMIC 2021). Seven studies did not include information about the study setting in the trial registration (ChiCTR2200059390; ChiCTR2200059726; ChiCTR2200059739; ChiCTR2200060010; NCT05041907; NCT05386433; NCT05567952).

Four studies are investigating nirmatrelvir/ritonavir plus SoC versus SoC for treatment of COVID-19 (NCT05614349; NCT05386433; PANORAMIC 2021; RECOVERY 2020), one uses an additional placebo in the comparator group (2022-001362-35), and one compares nirmatrelvir/ritonavir to placebo plus ritonavir (NCT05567952). Seven studies are comparing nirmatrelvir/ritonavir with active comparators (ChiCTR2200060010; ChiCTR2200059390; ChiCTR2200059726; ChiCTR2200059739; NCT05041907; NCT05321394; NCT05642910). Four are platform trials with estimated enrollment numbers between 1500 and 50,000 participants (NCT05041907; NCT05614349; PANORAMIC 2021; RECOVERY 2020). For all other trials, estimated enrollment numbers range from 40 participants to about 1000 participants (2022-001362-35; ChiCTR2200059390; ChiCTR2200059726; ChiCTR2200059739; ChiCTR2200060010; NCT05321394; NCT05386433; NCT05567952; NCT05642910).

One ongoing trial is conducted in the UK (PANORAMIC 2021), one in Italy (NCT05321394), six in China (ChiCTR2200060010;

ChiCTR2200059390; ChiCTR2200059726; ChiCTR2200059739; NCT05386433; NCT05642910), and one in Canada (NCT05614349). Four trials are conducted in two to nine different countries including LICs, LMICs, UMICs, and HICs (2022-001362-35; NCT05041907; NCT05567952; RECOVERY 2020).

Two ongoing trials are funded by pharmaceutical companies (2022-001362-35; NCT05567952).

Eight studies are currently recruiting (ChiCTR2200059726; ChiCTR2200059390; NCT05041907; NCT05321394; NCT05567952; NCT05614349; NCT05642910; RECOVERY 2020), three are not yet recruiting (ChiCTR2200059739; ChiCTR2200060010; NCT05386433), and two give no further information about the current status of the trial (2022-001362-35; PANORAMIC 2021). Three trials were expected to be completed in 2022 (ChiCTR2200059390; NCT05321394; NCT05386433), four are estimated to be completed in 2023 (NCT05614349; NCT05567952; NCT05642910; PANORAMIC 2021), one in 2024 (NCT05041907), and one in 2032 (RECOVERY 2020). Four trials did not include information about the estimated completion date in the trial registration (2022-001362-35; ChiCTR2200059739; ChiCTR2200059726; ChiCTR2200060010).

Risk of bias in included studies

We assessed methodological quality and risk of bias using the RoB 2 tool recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). The two included trials contributed 17 study results to nine outcomes (EPIC-HR 2021; Liu 2023). Six outcomes for an outpatient population and three outcomes for an inpatient population. Regarding the outpatient population, six study results (whole study population) contributed to all six outcomes and six additional study results (two subgroups for age and four for ethnicity) contributed to one of the six outcomes (EPIC-HR 2021). To account for different analysis sets used for subgroup analyses in the trial, the outcome 'hospitalization or death' has been assessed for the whole population as well as the individual subgroups using RoB 2. Regarding the inpatient population, three study results (whole study population) contributed to all three outcomes and two additional study results (subgroups for age) contributed to one of the three outcomes. The RoB 2 judgements for all study results per outcome and for all domains are available in an interactive risk of bias table (Supplementary File_Nirmatrelvir_Risk of Bias) and are briefly summarized below. The completed RoB 2 tool with responses to all assessed signalling questions is available online at: Supplementary File_Nirmatrelvir_Risk of Bias.

Overall risk of bias by study

From 17 outcomes, we rated five (29.41%) at low risk of bias and noted some concerns in 12 (70.59%) study results. Regarding the respective studies, we included the following:

- EPIC-HR 2021: 12 study results with some concerns for the overall risk of bias;
- Liu 2023: five study results with low risk of bias.

Overall risk of bias by outcome

Nirmatrelvir/ritonavir versus placebo in outpatient settings

We have some concern regarding risk of bias for all outcomes included in the Summary of findings 1. For the outcomes 'all-cause mortality at 28 days', 'worsening of clinical status: admission to hospital or death at 28 days', 'SAEs during the study period', and 'any grade TEAEs during the study period', the included study was at overall some concern of bias due to use of an inappropriate per-protocol analysis (EPIC-HR 2021; Risk of bias table for Analysis 1.1; Risk of bias table for Analysis 1.2; Risk of bias table for Analysis 1.5; Risk of bias table for Analysis 1.6). For the outcome 'admission to hospital or death at 28 days', we applied the respective risk of bias assessments to the subgroup analyses, as well (EPIC-HR 2021; Risk of bias table for Analysis 1.3; Risk of bias table for Analysis 1.4). For the outcomes 'TRAEs during the study period' and 'discontinuation of study medication due to adverse events' the study has been assessed as overall some concern of bias due to use of an inappropriate per-protocol analysis and lack of prospective outcome registration (EPIC-HR 2021; Risk of bias table for Analysis 1.7; Risk of bias table for Analysis 1.8).

Nirmatrelvir/ritonavir versus standard of care in inpatient settings

We have no concern of bias regarding the outcomes included in the Summary of findings 2. For the outcomes 'all-cause mortality at 28 days', 'viral clearance at seven days', and 'viral clearance at 14 days', the included study was assessed at no concerns for bias (Liu 2023; Risk of bias table for Analysis 2.1; Risk of bias table for Analysis 2.3; Risk of bias table for Analysis 2.4). We also applied the respective risk of bias assessments to the subgroup analysis for age (Liu 2023; Risk of bias table for Analysis 2.2).

Effects of interventions

See: **Summary of findings 1** Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings; **Summary of findings 2** Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings

One study investigating nirmatrelvir/ritonavir for treatment of non-hospitalized people with COVID-19 (EPIC-HR 2021), and one study investigating nirmatrelvir/ritonavir for treatment of hospitalized people with COVID-19 (Liu 2023) were included in the qualitative synthesis of this review.

Subgroup analyses between studies to explore heterogeneity and sensitivity analysis to test robustness of the results could not be performed due to an insufficient number of studies.

We looked at subgroups to address health equity. Both included studies reported subgroups for their primary outcome only. EPIC-HR 2021 reported subgroups for age and ethnicity for the outcome 'admission to hospital or death at 28 days'. Liu 2023 reported subgroups for age for the outcome 'all-cause mortality at 28 days'. The studies reported no further results for relevant subgroups (EPIC-HR 2021; Liu 2023).

The main findings are summarized in Summary of findings 1 and Summary of findings 2.

Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings

See Summary of findings 1.

All-cause mortality at day 28

One study reported data on all-cause mortality at day 28 (EPIC-HR 2021). At 28 days, none of the participants in the nirmatrelvir/ritonavir group and 12 participants in the comparator group had died. Nirmatrelvir/ritonavir plus SoC may reduce all-cause mortality at 28 days compared to SoC plus placebo (RR 0.04, 95% CI 0.00 to 0.68; 1 study, 2224 participants; low-certainty evidence; Analysis 1.1). We downgraded the certainty of evidence one level for serious risk of bias due to inappropriate analysis and one level for serious imprecision due to few events.

Subgroup analysis

We could not perform subgroup analyses for age, ethnicity, comorbidity, and World Bank country classification by income level due to missing data (Table 1).

Worsening of clinical status within 28 days

Admission to hospital or death

One study reported data on worsening of clinical status assessed as admission to hospital or death within 28 days (EPIC-HR 2021). The study defined the outcome was defined as "COVID-19 related hospital admission or death". At 28 days, nine participants in the nirmatrelvir/ritonavir group and 68 participants in the comparator group had been admitted to hospital or were dead. Nirmatrelvir/ritonavir plus SoC may reduce admission to hospital or death within 28 days compared to SoC plus placebo (RR 0.13, 95% CI 0.07 to 0.27; 1 study, 2224 participants; low-certainty evidence; Analysis 1.2). We downgraded the certainty of evidence one level for serious risk of bias due to inappropriate analysis and one level for serious indirectness as the study only assessed COVID-19-related hospitalizations.

Subgroup analysis

Subgroup analyses were available regarding age and ethnicity for the mITT1 population (Table 1). We could not perform subgroup analyses for World Bank country classification by income level due to missing data. No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated people with COVID-19 at high risk for disease progression that was either due to coexisting conditions (e.g. current smoking) or comorbidities.

Participants under 65 years versus 65 years and older

Of 1817 adults younger than 65 years of age, seven in the nirmatrelvir/ritonavir group and 46 in the comparator group were admitted to hospital or died (RR 0.15, 95% CI 0.07 to 0.34; Analysis 1.3). Of 268 participants aged 65 years or older, one in the nirmatrelvir/ritonavir group and 20 in the comparator group were admitted to hospital or died (RR 0.05, 95% CI 0.01 to 0.38; Analysis 1.3). The test for subgroup differences indicated no difference between both groups (P = 0.33) and no heterogeneity (I^2 = 0%). In both groups, the RR favoured treatment with nirmatrelvir/ritonavir, but the number of the included participants 65 years or older was low.

Participants from different ethnic groups

Of 1486 participants identifying as White, eight in the nirmatrelvir/ritonavir group and 52 in the comparator group were admitted to hospital or died (RR 0.16, 95% CI 0.07 to 0.33; Analysis 1.4). Of 94 participants identifying as Black or African American, none in the nirmatrelvir/ritonavir group and one in the comparator group were admitted to hospital or died (RR 0.29, 95% CI 0.01 to 7.04; Analysis 1.4). Of 296 participants identifying as Asian, none in the nirmatrelvir/ritonavir and seven in the comparator group were admitted to hospital or died (RR 0.07, 95% CI 0.00 to 1.19; Analysis 1.4). Of 209 participants categorized as "other" ethnicity, none in the nirmatrelvir/ritonavir and six in the comparator group were admitted to hospital or died (RR 0.08, 95% CI 0.00 to 1.34; Analysis 1.4). The test for subgroup differences indicated no difference between all pairwise groups (P = 0.88) and no heterogeneity (I^2 = 0%). The estimated effect favoured treatment with nirmatrelvir/ritonavir for the White ethnic group, and all estimated effects of the other ethnic groups included the line of no effect (RR = 1). The numbers of participants in the other ethnic groups were low.

Admission to intensive care unit or death

No study reported data for worsening of clinical status assessed as admission to ICU or death within 28 days.

Improvement of clinical status

All initial symptoms resolved at 28 days and up to the longest follow-up

No study reported data for improvement of clinical status assessed as all initial symptoms resolved at 28 days and up to the longest follow-up.

Time to symptom resolution

No study reported data for improvement of clinical status assessed as time to symptom resolution.

Quality of life up to 28 days and longest follow-up available

No study reported data for quality of life at any time point.

Serious adverse events during the study period

One study reported data on SAEs during the study period (EPIC-HR 2021). Eighteen participants in the nirmatrelvir/ritonavir group and 74 participants in the comparator group experienced SAEs during the 34-day observation period. Nirmatrelvir/ritonavir plus SoC may reduce SAEs during the study period compared to SoC plus placebo (RR 0.24, 95% CI 0.15 to 0.41; 1 study, 2224 participants; low-certainty evidence; Analysis 1.5). We downgraded the certainty of evidence one level for serious risk of bias due to inappropriate analysis and one level for serious imprecision as there were few SAEs other than hospitalization or death.

Subgroup analysis

We could not perform subgroup analyses for age, ethnicity, comorbidity, and World Bank country classification by income level due to missing data (Table 1).

Adverse events during the study period

Any grade treatment-emergent adverse events

One study reported data on any grade TEAEs during the study period (EPIC-HR 2021). In total, 251 participants in the nirmatrelvir/ritonavir group and 266 participants in the placebo comparator group experienced TEAEs during the 34-day observation period (Analysis 1.6). Nirmatrelvir/ritonavir plus SoC probably has little or no effect on TEAEs during the study period compared to SoC plus

placebo (RR 0.95, 95% CI 0.82 to 1.10; 1 study, 2224 participants; moderate-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias due to inappropriate analysis.

Subgroup analysis

We could not perform subgroup analyses for age, ethnicity, comorbidity, and World Bank country classification by income level due to missing data (Table 1).

Any grade treatment-related adverse events

One study reported data on any grade TRAEs during the study period (EPIC-HR 2021). In total, 86 participants in the nirmatrelvir/ritonavir group and 42 participants in the comparator group experienced TRAEs during the 34-day observation period. Nirmatrelvir/ritonavir plus SoC probably increases TRAEs during the study period compared to SoC plus placebo (RR 2.06, 95% CI 1.44 to 2.95; 1 study, 2224 participants; moderate-certainty evidence; Analysis 1.7). TRAEs were mostly attributed to dysgeusia and diarrhoea. We downgraded the certainty of evidence one level for serious risk of bias due to inappropriate analysis.

Subgroup analysis

We could not perform subgroup analyses for age, ethnicity, comorbidity, and World Bank country classification by income level due to missing data (Table 1).

Discontinuation of study drug due to adverse events

One study reported data on discontinuation of study drug due to AEs (EPIC-HR 2021). In total, 23 participants in the nirmatrelvir/ritonavir group and 47 participants in the comparator group discontinued the study drug due to AEs. Nirmatrelvir/ritonavir plus SoC probably decreases discontinuation of study drug due to AEs compared to SoC plus placebo (RR 0.49, 95% CI 0.30 to 0.80; 1 study, 2224 participants; moderate-certainty evidence; Analysis 1.8). TRAEs were mostly attributed to dysgeusia and diarrhoea. We downgraded the certainty of evidence one level for serious risk of bias due to inappropriate analysis.

Subgroup analysis

We could not perform subgroup analyses for age, ethnicity, comorbidity, and World Bank country classification by income level due to missing data (Table 1).

Viral clearance at 14 days

No study reported data on viral clearance at 14 days.

Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings

All-cause mortality at day 28

One study reported data on all-cause mortality at day 28 (Liu 2023). At 28 days, five participants in the nirmatrelvir/ritonavir group and eight participants in the comparator group had died. We are uncertain whether nirmatrelvir/ritonavir plus SoC reduces all-cause mortality at 28 days compared to SoC alone (RR 0.63, 95% CI 0.21 to 1.86; 1 study, 264 participants; very low-certainty evidence; Analysis 2.1). We downgraded the certainty of evidence two levels for imprecision and one level for indirectness.

Subgroup analysis

We performed subgroup analyses for age. We did not perform subgroup analyses for ethnicity and World Bank country classification by income level due to missing data. No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated people with COVID-19 at high risk for disease progression defined as participants with severe comorbidities or a SOFA/Charlson score of 2 or greater (Table 2).

Participants 65 years and under versus over 65 years

Of 84 adults aged 65 years and under, one in the nirmatrelvir/ritonavir group and two in the comparator group had died at day 28 (RR 0.61, 95% CI 0.06 to 6.42; Analysis 2.2). Of 180 participants older than 65 years, four in the nirmatrelvir/ritonavir group and six in the comparator group had died at day 28 (RR 0.61, 95% CI 0.18 to 2.09; Analysis 2.2). The test for subgroup differences indicated no difference between both groups (P = 1.0) and no heterogeneity (I^2 = 0%). Estimated effects for both groups included the line of no effect (RR = 1). The number of included participants 65 years or younger was low.

Worsening of clinical status within 28 days

Participants with new need for invasive mechanical ventilation or death

No study reported data for worsening of clinical status assessed as new need for invasive mechanical ventilation or death.

Participants with need for intensive care unit admission or death

No study reported data for worsening of clinical status assessed as admission to ICU or death within 28 days.

Improvement of clinical status within 28 days

Participants discharged alive

No study reported data for participants discharged alive

Participants discharged without clinical deterioration or death

No study reported data for participants discharged without clinical deterioration or death.

Quality of life up to 28 days and longest follow-up available

No study reported data for quality of life at any time point.

Serious adverse events during the study period

We did not include data for the outcome SAEs during the study period in the quantitative analysis due to insufficient and inconsistent information on the time of the outcome assessment, the handling of missing outcome data, and the outcome assessment itself.

Adverse events during the study period

Any grade treatment-emergent adverse events

We did not include data for the outcome any grade TEAEs during the study period in the quantitative analysis due to insufficient and inconsistent information on the time of the outcome assessment, the handling of missing outcome data, and the outcome assessment itself.

Any grade treatment-related adverse events

We did not include data for the outcome any grade TRAEs during the study period in the quantitative analysis due to insufficient and inconsistent information on the time of the outcome assessment, the handling of missing outcome data, and the outcome assessment itself.

Discontinuation of study drug due to adverse events

We did not include data for the outcome discontinuation of study drug due to AEs in the quantitative analysis due to insufficient and inconsistent information on the time of the outcome assessment, the handling of missing outcome data, and the outcome assessment itself.

Viral clearance at seven days

One study reported data on viral clearance at seven days (Liu 2023). Thirty-six participants in the nirmatrelvir/ritonavir group and 34 participants in the comparator group reached viral clearance during the seven-day observation period. We are uncertain whether nirmatrelvir/ritonavir plus SoC increases viral clearance at seven days compared to SoC (RR 1.06, 95% CI 0.71 to 1.58; 1 study, 264 participants; very low-certainty evidence; Analysis 2.3). We downgraded the certainty of evidence two levels for imprecision and one level for indirectness.

Subgroup analysis

We could not perform subgroup analyses for age, ethnicity, comorbidity, and World Bank country classification by income level due to missing data. No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated people with COVID-19 at high risk for disease progression that was either due to severe comorbidities or a SOFA/Charlson score of 2 or greater (Table 2).

Viral clearance at 14 days

One study reported data on viral clearance at 14 days (Liu 2023). One hundred and three participants in the nirmatrelvir/ritonavir group and 98 participants in the comparator group reached viral clearance during the 14-day observation period. We are uncertain whether nirmatrelvir/ritonavir plus SoC increases viral clearance at 14 days compared to SoC (RR 1.05, 95% CI 0.92 to 1.20; 1 study, 264 participants; very low-certainty evidence; Analysis 2.4). We downgraded the certainty of evidence two levels for imprecision and one level for indirectness.

Subgroup analysis

We could not perform subgroup analyses for age, ethnicity, comorbidity, and World Bank country classification by income level due to missing data. No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated people with COVID-19 at high risk for disease progression which is either due to severe comorbidities or a SOFA/Charlson score of 2 or greater. (Table 2).

Nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection (pre- and postexposure)

No study with published results investigating nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection has been included in this review.

DISCUSSION

Summary of main results

This Cochrane Review aimed to assess the efficacy and safety of nirmatrelvir/ritonavir for treating and preventing COVID-19.

Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings

For people with a confirmed diagnosis of COVID-19, we identified one RCT with 2246 randomized participants with mild symptomatic COVID-19 (WHO 2 to 3) conducted during the Delta wave in the outpatient setting comparing nirmatrelvir/ritonavir plus SoC to SoC plus placebo. Trial participants were unvaccinated, without previous confirmed SARS-CoV-2 infection, had a symptom onset of five days or less before randomization, and were at high risk for progression to severe disease.

The study was assessed without concerns for research integrity.

The main findings of this review are summarized in Summary of findings 1.

- Nirmatrelvir/ritonavir may reduce all-cause mortality at 28 days and clinical worsening assessed as admission to hospital or death within 28 days (low-certainty evidence).
- Nirmatrelvir/ritonavir may reduce SAEs during the study period (low-certainty evidence); there were few SAEs other than hospitalization or death.
- Nirmatrelvir/ritonavir probably has little or no effect on any TEAEs during the study period (moderate-certainty evidence)
- Nirmatrelvir/ritonavir probably increases any TRAEs during the study period (moderate-certainty evidence); TRAEs were mostly attributed to dysgeusia and diarrhoea.
- Nirmatrelvir/ritonavir probably decreases discontinuation of study drug due to AEs (moderate-certainty evidence).

We identified no study results reporting on improvement of clinical status, quality of life, and viral clearance. We identified four ongoing trials investigating nirmatrelvir/ritonavir for treatment of people with mild COVID-19 in outpatient settings.

Equity

No subgroups were reported for World Bank country classification by income level.

No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated people with COVID-19 at high risk for disease progression that was either due to coexisting conditions (e.g. current smoking) or comorbidities. Reported only for the mITT1 patient population, 79.7% of participants had none or one comorbidity and 20.3% of the participants had two or more comorbidities, most commonly a BMI over 25 kg/m^2 (80.0%), hypertension (33.0%), and diabetes (12.1%). The study did not report the number of participants without any comorbidity. Few participants had other baseline comorbidities (e.g. chronic lung disease, cardiovascular disorder, chronic kidney disease, HIV infection, sickle cell disease, neurodevelopmental disorder, and cancer). For the FAS, the study reported only the combination of coexisting conditions or characteristics associated with an increased risk of developing severe COVID-19, with 61.0% of participants having two or

more such characteristics or comorbidities. The most common prespecified characteristic associated with an increased risk of developing severe disease was current smoking in 876 participants (39.0%).

Despite the study being conducted in 343 sites worldwide, only 27 sites were in LICs and LMICs, and the remaining 316 sites (92.1%) were in UMICs or HICs. There were no separate data available for participants from LICs, LMICs, UMICs, or HICs.

Regarding equity, we highlight that most participants in the included study were younger than 65 years and 71.3% identified as White.

For the outcome 'admission to hospital or death', we investigated the following subgroups for equity: age (less than 65 years versus 65 years and greater) and ethnicity (Asian versus Black versus White versus other). For age, the effects favoured treatment with nirmatrelvir/ritonavir in both groups, but the number of included participants in the subgroup of 65 years or older was low. For ethnicity, the effects favoured treatment with nirmatrelvir/ritonavir for the White ethnic group. Estimated effects of the other ethnic groups included the line of no effect (RR = 1). The test for subgroup differences indicated no difference between all pairwise groups as numbers of participants in the other ethnic groups were low.

For all other outcomes included in this review, no subgroups were reported. As most participants were younger than 65 years and of White ethnicity, we are uncertain whether results are applicable to the other prespecified subgroups.

Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings

For people with a confirmed diagnosis of COVID-19, we identified one RCT with 264 participants with mild to moderate symptomatic COVID-19 (WHO 2 to 4) conducted during the Omicron wave in the inpatient setting comparing nirmatrelvir/ritonavir plus SoC to SoC alone. Trial participants were hospitalized with mild to moderate COVID-19 and either severe comorbidities, or SOFA/Charlson score of 2 or greater. Duration from symptom onset to hospital admission was less than five days or Ct value less than 25 by RT-PCR.

The study was assessed without concerns for research integrity.

The main findings of this review are summarized in Summary of findings 2.

- We are uncertain whether nirmatrelvir/ritonavir plus SoC reduces all-cause mortality at 28 days compared to SoC (very low-certainty evidence).
- We are uncertain whether nirmatrelvir/ritonavir plus SoC increases viral clearance at seven days compared to SoC (very low-certainty evidence).
- We are uncertain whether nirmatrelvir/ritonavir plus SoC increases viral clearance at 14 days compared to SoC (very low certainty evidence).

We did not include any safety-related outcomes in the quantitative analysis due to insufficient and inconsistent information on the time of the outcome assessment, the handling of missing outcome data, and the outcome assessment itself. We identified no study results reporting on improvement or worsening of clinical status and quality of life. We identified two ongoing trials investigating nirmatrelvir/ritonavir for treatment of COVID-19 in inpatient settings.

Equity

The study was conducted in China which classifies as UMIC. Unfortunately, no subgroups were reported for World Bank country classification by income level or different racial and ethnic groups.

No subgroup analysis was possible for comorbidity (high-risk versus low-risk population) as the included study only investigated people with COVID-19 at high risk for disease progression that was either due to comorbidities or a SOFA/Charlson score of 2 or greater.

Regarding equity, we highlight that most study participants in the included study were aged over 65 years. For the outcome 'all-cause mortality at 28 days', there was no difference between participants aged 65 years or less and participants greater than 65 years as well as for participants with two or fewer comorbidities versus two or greater comorbidities. All estimated effects included the line of no effect (RR = 1).

Nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection (pre- or postexposure)

We did not identify any completed trials investigating nirmatrelvir/ritonavir for prevention of COVID-19 but one ongoing trial investigating nirmatrelvir/ritonavir as PEP after exposure to SARS-CoV-2.

Overall completeness and applicability of evidence

Originating from only one RCT with 2246 participants, the certainty of evidence for the efficacy of nirmatrelvir/ritonavir for treating COVID-19 in outpatient settings was low and for safety aspects low to moderate.

For hospitalized participants, data from one RCT with 264 participants was available. Certainty of evidence for the efficacy of nirmatrelvir/ritonavir for treating COVID-19 in outpatient settings was very low. Safety aspects of nirmatrelvir/ritonavir could not be assessed for this setting.

Both included studies investigated participants with mild and mild to moderate symptomatic COVID-19, corresponding to WHO clinical progression scale 2 to 3 and 2 to 4, respectively. In the outpatient setting, only unvaccinated participants with high risk for disease progression due to coexisting conditions or characteristics were included in the trial, limiting external validity of the results as results may not be transferable to a broader population of vaccinated participants or those with standard risk for disease progression. As of 23 June 2023, there have been more than 760 million confirmed SARS-CoV-2 cases reported to the WHO and more than 13 billion vaccine doses have been administered (WHO 2021a). The influence of the vaccination status as well as previous SARS-CoV-2 infections could not be assessed for outpatients in this review.

While the study on inpatients included about 73% unvaccinated as well as 25% vaccinated (at least two doses) participants, it also investigated participants with a high risk for severe COVID-19 either due to severe comorbidities or a SOFA/Charlson score 2 or greater and without previous SARS-CoV-2 infection. Characteristics of the included participants suggest that the study population does not necessarily resemble typical COVID-19 inpatients and

a considerable proportion of participants would probably be managed ambulatory in many places. Whether this was due to political decisions and treatment guidelines was unclear. Again, this might limit external validity of the results as they may not be transferable to a broader population of moderately to severely affected participants with standard risk for disease progression and previous SARS-CoV-2 infection.

With ritonavir being a CYP3A4 inhibitor, nirmatrelvir/ritonavir bears the potential for significant drug–drug interactions with many medications commonly used, especially in people with comorbidities. The exclusion criteria of EPIC-HR 2021 prohibited prior or concomitant therapies including medications highly dependent on CYP3A4 for clearance. Pfizer published an extensive list of potentially significant drug interactions, including contraindicated drugs such as HMG-CoA reductase inhibitors and antiarrhythmics (Pfizer 2022). If known problematic concomitant medications cannot be discontinued or reduced, Pfizer advises against the use of nirmatrelvir/ritonavir, thereby further limiting the transferability of results to a broader high-risk population.

Surprisingly, only 6% of participants in EPIC-HR 2021 received or were expected to receive COVID-19 monoclonal antibody treatment, despite the sixth version of the WHO living guideline published 24 September 2021 suggesting "treatment with casirivimab and imdevimab for those at highest risk of hospital admission" (WHO 2021c). Since the emergence of the Omicron BA.1 variant, however, casirivimab and imdevimab have lost their efficacy (Takashita 2022). Concomitant treatment with monoclonal antibodies (ambacizumab/romlusevimab and tocilizumab) were prohibited in Liu 2023, as was treatment with COVID-19 immunoglobulins and convalescent plasma, again limiting external validity of the results.

All outpatient participants included in this review were enrolled until December 2021, which coincided with the Delta wave before the start of the Omicron wave; therefore, the findings for outpatients of this review might not be directly applicable to the treatment situation of outpatients which are infected with later (sub-)variants of SARS-CoV-2. The recruitment period for the included inpatient study co-occurred with the Omicron wave.

According to Pfizer, nirmatrelvir/ritonavir is to be administered within five days of symptom onset. In the included inpatient study, median time between symptom onset and start of treatment was three days (Liu 2023). In the included outpatient study, mean time between symptom onset and start of treatment was 2.96 days with 66.3% of participants starting treatment within three days, which might have increased the effectiveness of treatment (EPIC-HR 2021). At the same time, this limits applicability outside idealized study conditions where time between symptom onset, confirmation of SARS-CoV-2 infection, and treatment start may well exceed three days due to limited healthcare access or testing capacities in LICs and LMICs but also disadvantaged groups other than ethnic and racial minorities, for example, refugees, people with mental or physical disabilities, and women in HICs.

In both included studies, reported data were incomplete and inconsistent. For EPIC-HR 2021, outcome data on the overall population of 2246 randomized participants were missing and the FAS was not reported. Instead, multiple versions of mITT analyses (mITT, mITT1, and mITT2; Table S2; EPIC-HR 2021) are presented. The primary analysis of the original study protocol from 18 June 2021 was defined as the mITT1 population including participants who were treated five days or less after COVID-19 symptom onset. The mITT analysis set that is the main analysis set of the publication was added in amendment 2 (2 August 2021) to include only those participants who were treated within three days after COVID-19 symptom onset. Any clear explanation why the authors did not report the FAS but provide the mITT as main analyses is missing in the publication. We would have expected the FAS to be presented as the primary analysis set and the mITTs as additional sensitivity analyses. The presented mITT analyses focus on smaller populations. In the abstract, the interim and final analysis of the mITT population with 1379/2246 randomized participants was presented, with 13 deaths reported. However, according to the results section and Figure 2, only nine participants died in this mITT population, which is inconsistent and confusing. Finally, there is no detailed information on the clinical characteristics of included participants for the FAS, particularly with regard to the comorbidities as risk factors for disease progression. The distribution of comorbidities can only be extrapolated for the mITT population using the subgroup analyses presented in Figure S2c. The information for all participants (FAS) is absent.

For Liu 2023 the assessment of safety outcomes is poorly reported and not prespecified in the registered protocol. The exact assessment period, mode of outcome assessment, and handling of missing outcome data remain unclear. It is to be assumed that missing outcome data have been imputed; however, no information is given about the extent thereof.

To date, there are no completed studies that investigate nirmatrelvir/ritonavir for the prevention of COVID-19. We found 13 ongoing studies of which seven planned to be completed in either 2022 or 2023. No study investigating nirmatrelvir/ritonavir as PrEP or PEP is currently ongoing.

Certainty of the evidence

The certainty of evidence for prioritized outcomes presented in the summary of findings tables ranged from low to moderate for outpatients (Summary of findings 1), and was very low for inpatients (Summary of findings 2).

For outpatients, we downgraded the certainty of evidence for all outcomes included in our summary of findings table due to risk of bias arising from use of an inappropriate per-protocol analysis only including participants randomly assigned to study intervention who received one or greater more doses of study intervention and had one or more postbaseline visits by day 28. Additionally, the outcomes 'treatment-related adverse events during the study period; and 'discontinuation of study medication due to adverse events' were not prospectively registered. All-cause mortality at 28 days and SAEs during the study period were further downgraded for serious imprecision due to low number of events. The outcome 'admission to hospital or death within 28 days' was additionally downgraded for serious indirectness as the study only assessed COVID-19-related hospitalizations.

For inpatients, we downgraded the certainty of evidence for all outcomes included in our summary of findings table for indirectness due to an atypical hospital population of mildly to moderately affected patients and twice for imprecision using the minimally contextualized approach.

We did not consider downgrading for publication bias because the intervention is new and most of the studies are still ongoing.

We identified no study results reporting on improvement of clinical status, quality of life, and viral clearance.

Potential biases in the review process

We are confident that we identified all relevant studies using a broad search and will monitor ongoing studies after the publication of this review. This review is a LSR, and we maintain an Excel list of new studies potentially to be included in the next review update. This list is publicly available (osf.io/7g49c/; Reis 2022a).

We have changed the definition of our active comparator. In the protocol, we planned to compare nirmatrelvir/ritonavir with active comparisons with confirmed efficacy only. We decided to extend our definition of an eligible active comparator to any active comparator, including new interventions that will be investigated in future trials that may use nirmatrelvir/ritonavir as a comparator. We also included TCMs as an active comparator in this update since we identified several ongoing trials. TCMs are widely used in China and other countries to treat COVID-19 and living guidelines integrating Chinese and western medicine for COVID-19 are already available (Ge 2021).

None of the members of the review author team has any affiliation with any stakeholder group who favours or disapproves of nirmatrelvir/ritonavir or the comparators used in relevant studies.

Agreements and disagreements with other studies or reviews

One meta-analysis, published as letter to the editor and including 12 studies (one published RCT, one unpublished RCT, and 10 observational studies) found that nirmatrelvir/ritonavir is likely effective in reducing mortality and probably decreases the risk of hospitalization. However, both outcomes had high levels of heterogeneity across studies. Moreover, due to lack of RCTs, most of the evidence came from observational studies and hence, is susceptible to confounding bias (Cheema 2023).

Another systematic review with meta-analysis published in April 2023 compared nirmatrelvir/ritonavir to other antiviral drugs for the treatment of people with COVID-19. The meta-analysis results showed that nirmatrelvir/ritonavir decreased the risk of long-term mortality, hospitalization, and disease progression while showing little difference in safety compared to other antivirals (Tian 2023).

The WHO living guideline strongly recommends treatment with nirmatrelvir/ritonavir for people with non-severe COVID-19 at highest risk of hospitalization (including pregnant and breastfeeding women) and advises against treatment in people with non-severe COVID-19 at low risk of hospitalization (Lamontagne 2020). The evidence summary was last updated on 13 January 2023 and informed by two trials (EPIC-HR 2021; EPIC-SR 2021), of which the second one is to date only published as a press release with results from an interim analysis. Press releases are not eligible for the current review.

AUTHORS' CONCLUSIONS

Implications for practice

With ritonavir being a CYP3A4 inhibitor, nirmatrelvir/ritonavir bears the potential for significant drug–drug interactions with many medications commonly used, especially in people with comorbidities. If there are known or anticipated drug interactions with concomitant medications that cannot be discontinued or reduced, the manufacturer, Pfizer, advises against the use of nirmatrelvir/ritonavir, thereby limiting the transferability of results to a broader high-risk population.

Outpatients

Based on the current low-certainty evidence (one trial), in outpatients nirmatrelvir/ritonavir may reduce all-cause mortality and hospital admission or death within 28 days. Subgroup analyses regarding equity for admission to hospital or death suggested that there are no differences in efficacy regarding participants' age, but we only have data in a mostly White ethnic population and cannot, therefore, assess benefit in other ethnicities.

There is low- to moderate-certainty evidence that nirmatrelvir/ritonavir is safe in people without prior or concomitant therapies, including medications highly dependent on CYP3A4 for clearance and CYP3A4 inducers.

This review only included one trial for the outpatient setting investigating people who were unvaccinated without previous infection who were at high risk of disease progression due to coexisting conditions or other characteristics associated with an increased risk of developing severe illness from COVID-19. There is currently no evidence for the use of nirmatrelvir/ritonavir in a broader population of vaccinated people, those with previous SARS-CoV-2 infection, or those without increased risk for progression to severe disease. Therefore, external validity of the results is limited. All participants were enrolled until December 2021, which coincided with the Delta wave before the start of the Omicron wave; therefore, the findings of this review might not be directly applicable to the treatment situation of people who are infected with later (sub-)variants of SARS-CoV-2.

Inpatients

Based on the current low-certainty evidence (one trial), we are uncertain whether nirmatrelvir/ritonavir reduces all-cause mortality at 28 days or increases viral clearance at seven or 14 days. Subgroup analyses regarding equity for all-cause mortality suggested that there are no differences in efficacy regarding patients' age.

The safety of nirmatrelvir/ritonavir could not be assessed for the inpatient setting, due to insufficient and inconsistent information on the time of the outcome assessment, the handling of missing outcome data, and the outcome assessment itself. Upon enquiry, the authors provided no further information regarding the outcomes.

The study only included mildly to moderately affected participants, which might not resemble the typical hospitalized people with COVID-19. It only included participants without previous infection and most were unvaccinated who were at high risk of disease progression due to severe comorbidities or a SOFA/Charlson score

of 2 or greater. There is currently no evidence for the use of nirmatrelvir/ritonavir in more severely affected people as well as a broader population of participants with previous SARS-CoV-2 infection, or those without increased risk for progression to severe disease. Therefore, external validity of the results was limited. All participants were enrolled during the Omicron wave.

Currently, there is no evidence to explore the benefits and harms of nirmatrelvir/ritonavir as treatment as pre-exposure or postexposure prophylaxis.

Implications for research

There is a need for evidence for the use of nirmatrelvir/ritonavir as a treatment for in- and outpatients with previous SARS-CoV-2 infection or vaccination and those without increased risk for progression to severe disease. There is also a need for studies investigating the use of nirmatrelvir/ritonavir to prevent SARS-CoV-2 infection. For these scenarios and populations, we need high-quality randomized controlled trials (RCTs).

To address equity, we need further trials investigating:

- populations from low-income countries and low- to middle-income countries;
- people from different ethnic and racial backgrounds, including minorities.

We identified 13 ongoing studies investigating nirmatrelvir/ritonavir for treatment of COVID-19, which may change the findings of the review or the certainty of evidence, and broaden the applicability of results.

In accordance with the living approach of this review, we are continually updating our search and evaluating new potentially relevant trials for inclusion (osf.io/7g49c/; Reis 2022a).

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Emma Sydenham (Co-ordinating Editor, Cochrane Injuries) advised on trial regulatory compliance.

Editorial and peer reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editors: Dr Joseph Pryce and Professor George Rutherford (CIDG)
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Dr Deirdre Walshe (CIDG)
- Copy Editor (copy editing and production):
  - protocol stage: Luisa M Fernandez Mauleffinch, Cochrane Copy Edit Support
  - review stage: Heather Maxwell, Cochrane Copy Edit Support
  - review update stage: Anne Lawson, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision):
  - protocol stage: Dr Paul Hine, Liverpool, UK (clinical/content peer review); Dr Marty Chaplin, CIDG Statistical Editor (statistical peer review); Dr Vittoria Lutje, CIDG Information Specialist (search peer review); Maria Rosaria Cozzolino, RN MSN, Emergency Department, Barking, Havering and Redbridge University Hospitals Trust, UK (consumer peer review). One additional peer reviewer provided clinical content peer review, but chose not to be publicly acknowledged.
  - review stage: Dr Harshdeep Harshad Acharya, MD, Internal Medicine Resident Physician, Saint Peter's University Hospital, New Jersey, USA (clinical/content peer review); Dr Nour Essale, MD, Master of International Public Health, UK (clinical/content peer review); Dr Audrin Lenin, Department of Medicine, Christian Medical College, Vellore, India (clinical/content peer review); Dr Kerry Dwan, Cochrane Methods Support Unit (statistical peer review); Dr Vittoria Lutje, CIDG Information Specialist (search peer review); Jenny Negus, PPI Advocate and Cochrane Consumer Reviewer (consumer peer review).
  - review update stage: Dr Marty Chaplin, CIDG Statistical Editor (statistical peer review); Dr Vittoria Lutje, CIDG Information Specialist (search peer review).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

EPIC-HR 2021

Study characteristics	
Methods	Trial design: double-blind RCT with 2 parallel arms
	Type of publication: journal
	Setting: outpatient
	Recruitment dates: 16 July to 9 December 2021
	Country: worldwide
	Language: English
	Number of centres: 343 sites
	Study purpose (treatment, prevention): treatment
	Trial registration number: NCT04960202
	Date of registration: 13 July 2021

EPIC-HR 2021 *(Continued)*

Participants	Number of participants (randomized/analyzed): 2246/2224 Study populations: • full analysis set: all participants randomly assigned to study intervention (intervention/comparator 1120/1126) • safety analysis set: all participants randomly assigned to study intervention who received ≥ 1 dose of study intervention (intervention/comparator 1109/1115) • mITT: all participants randomly assigned to study intervention who received ≥ 1 dose of study intervention and had ≥ 1 postbaseline visit, did not receive or were not expected to receive COVID-19 monoclonal antibody treatment and were treated ≤ 3 days following symptom onset (intervention/comparator 697/682) • mITT1: all participants randomly assigned to study intervention who received ≥ 1 dose of study intervention and had ≥ 1 postbaseline visit and did not receive or were not expected to receive COVID-19 monoclonal antibody treatment (intervention/comparator 1039/1046) • mITT2: all participants randomly assigned to study intervention who received ≥ 1 dose of study intervention and had ≥ 1 postbaseline visit (intervention/comparator 1109/1115) Age median: 46 (IQR 18 to 88) years Males, n: 1148 (51.1%) Race/ethnicity: 1607 (71.5%) White, 315 (14%) Asian, 110 (4.9%) Black Severity of condition according to study definition: non-hospitalized, symptomatic Severity of condition according to WHO scale: 2 to 3 Comorbidities: 20.3% ≥ 2 comorbidities (mITT1) • Overweight: 80.5% with BMI > 25 kg/m^2 • Diabetes mellitus: 252 (12.1%) (mITT1) • Respiratory disease: 92 (4.4%) (mITT1) • Hypertension: 689 (33%) (mITT1) • Immunosuppression: 12 (1%) (mITT1) Vaccination status: unvaccinated (exclusion criterion) Virus detection performed at baseline (test-positive at baseline): RT-PCR, molecular or antigen tests (100%) Inclusion criteria: non-hospitalized, symptomatic adults with COVID-19, at high risk for progression to severe disease, confirmed SARS-CoV-2 infection, symptom onset ≤ 5 days before randomization with ≥ 1 sign or symptom of COVID-19 on the day of randomization and ≥ 1 characteristic or coexisting condition associated with high risk of progression to severe COVID-19 Exclusion criteria: previous confirmed SARS-CoV-2 infection or hospitalization for COVID-19, anticipated need for hospitalization within 48 hours after randomization, prior receipt of convalescent COVID-19 plasma or SARS-CoV-2 vaccine, prohibited prior or concomitant therapies included medications highly dependent on CYP3A4 for clearance, concurrent active systemic infection, pregnancy, breastfeeding
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg, twice daily for 5 days • route of administration: oral Details of control: • type and dose: placebo • route of administration: oral

EPIC-HR 2021 *(Continued)*

	Concomitant therapy: monoclonal antibodies allowed, otherwise no further information Duration of follow-up: 34 days Treatment cross-overs: none
Outcomes	Primary study outcome (as defined by the study) • Proportion of participants with COVID-19-related hospitalization or death from any cause at 28 days Relevant review outcomes reported • Proportion of participants with COVID-19-related hospitalization or death from any cause at 28 days • Incidence of TRAEs of nirmatrelvir/ritonavir relative to placebo at 34 days • Incidence of TEAEs of nirmatrelvir/ritonavir relative to placebo at 34 days • Incidence of adverse events leading to discontinuation of nirmatrelvir/ritonavir or placebo at 34 days • Incidence of SAEs of nirmatrelvir/ritonavir relative to placebo at 34 days • Proportion of participants who died (all cause) at 28 days Additional study outcomes reported • Viral titres measured by RT-PCR in nasal swabs at day 14
Notes	Date of publication: 16 February 2022 Sponsor/funding: Pfizer Information on ethics votum: trial sites in the countries Hungary, Spain, Czech Republic, and Bulgaria provided information on ethics approval in their trial registry entries and obtained the necessary permissions.

Liu 2023

Study characteristics	
Methods	Trial design: open-label RCT with 2 parallel arms Type of publication: journal publication Setting: inpatient Recruitment dates: 10 April to 19 May 2022 Country: China Language: English Number of centres: 5 Study purpose (treatment, prevention): treatment Trial registration number: ChiCTR2200058477 Date of registration: 9 April 2022
Participants	Number of participants (randomized/analyzed): 264/264 Study populations:

Liu 2023 *(Continued)*

	• ITT: all participants randomly assigned to study intervention who took ≥ 1 dose of study intervention, with ≥ 1 postbaseline visit and who did not receive/expect to receive COVID-19 treatment (intervention/comparator 132/132) • PP: participants in the ITT set who completed the protocol for treatment that they were originally allocated to (intervention/comparator 130/129) Age mean: 70.35 (SD 13.12) years Males, n (%): 142 (53.8%) Race/ethnicity: NA Severity of condition according to study definition: hospitalized with mild-to-moderate COVID-19 Severity of condition according to WHO scale: presumably 2 to 4 Comorbidities: • Overweight: NA • Diabetes mellitus: 97 (36.7%) • Respiratory disease: 53 (20.1%) • Cardiovascular disease: 141 (53.4%) • Immunosuppression: 1 (0.4%) Vaccination status: 26.52% vaccinated Virus detection performed at baseline (test-positive at baseline): RT-PCR, molecular or antigen tests (100%) Inclusion criteria: hospitalized with mild-to-moderate COVID-19 and either severe comorbidities, or SOFA/Charlson score ≥ 2; duration from symptom onset to hospital admission < 5 days or Ct value < 25 by RT-PCR Exclusion criteria: previous confirmed SARS-CoV-2 infection, history of liver disease, dialysis, HIV infection, concomitant therapy with ambacizumab/romlusevimab, COVID-19 immunoglobulin, convalescent plasma, or tocilizumab during treatment period
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg, twice daily for 5 days • route of administration: oral Details of control: • type and dose: SoC • route of administration: oral Concomitant therapy: corticosteroids (8 participants total, equal in both groups), excluding: ambacizumab/romlusevimab, COVID-19 immunoglobulin, convalescent plasma, tocilizumab during treatment period Duration of follow-up: 28 days Treatment cross-overs: none
Outcomes	Primary study outcome (as defined by the study) • 28-days all-cause mortality Relevant review outcomes reported • Nucleic acid negative rate within 7 days • Nucleic acid negative conversion rate within 14 days

Liu 2023 *(Continued)*

	Additional study outcomes reported • Inpatient mortality • Conversion rate of severe COVID-19 within 14 days • Acute exacerbation rate of chronic underlying diseases within 14 days • Nucleic acid negative time • Total in-hospital days • Duration of stay in ICU • Percentage requiring organ function support within 28 days
Notes	Date of publication: 5 February 2023 Sponsor/funding: National Natural Science Foundation of China Information on ethics votum: Shanghai Jiao Tong University School of Medicine, Ruijin Hospital Ethics Committee, and Ethic Committee at each participating site

BMI: body mass index; Ct: cycle threshold; ICU: intensive care unit; IQR: interquartile range; ITT: intention to treat; mITT: modified intention to treat; n: number; NA: not available; PP: per protocol; RCT: randomized controlled trial; RT-PCR: reverse transcription polymerase chain reaction; SAE: serious adverse event; SD: standard deviation; SoC: standard of care; SOFA: Sequential Organ Failure Assessment; TEAE: treatment-emergent adverse events; TRAE: treatment-related adverse events; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aggarwal 2022	Ineligible study design
AGILE 2020	Ineligible intervention
Australian Prescriber 2022	Editorial, commentary, letter, etc.
Balykova 2022	Failed RIA
Beinfeld 2022	Editorial, commentary, letter, etc.
Biehle 2022	Editorial, commentary, letter, etc.
Caceres 2022	Editorial, commentary, letter, etc.
Cao 2023	Failed RIA
ChiCTR2200059743	Ineligible study design
ChiCTR2200060700	Ineligible study design
ChiCTR2200063778	Ineligible study design
Doyno 2022	Editorial, commentary, letter, etc.
Ebell 2022	Editorial, commentary, letter, etc.
Elliott 2022	Editorial, commentary, letter, etc.
Enikeeva 2022	Editorial, commentary, letter, etc.

Study	Reason for exclusion
EPIC-PEDS 2022	Ineligible study design
Gottlieb 2022	Editorial, commentary, letter, etc.
ISRCTN12428408	Ineligible study design
ITMCTR2200005942	Ineligible study design
ITMCTR2200005943	Ineligible study design
ITMCTR2200005944	Ineligible study design
Jittamala 2022	Ineligible intervention
Kim 2022	Ineligible study design
Li 2022	Ineligible study design
NCT04518410	Ineligible intervention
NCT04756531	Ineligible study design
NCT04864548	Ineligible intervention
NCT05305547	Ineligible intervention: study drug S-217622
NCT05487040	Ineligible study design
NCT05576662	Long COVID/post-COVID
NCT05587894	Ineligible comparator
NCT05668091	Long COVID/post-COVID
NCT05690646	Ineligible patient population
NCT05813600	Ineligible study design
Park 2022	Ineligible study design
PER-084-20	Ineligible intervention
Pupo Correia 2022	Editorial, commentary, letter, etc.
Razia 2023	Ineligible study design
Robinson 2021	Editorial, commentary, letter, etc.
Robinson 2022	Editorial, commentary, letter, etc.
Rosenberg 2022	Editorial, commentary, letter, etc.
Ross 2022	Ineligible study design
Shao 2022	Ineligible study design

Study	Reason for exclusion
Singh 2022	Ineligible patient population: healthy adults
Spiliopoulou 2023	Ineligible study design
Trøseid 2022	Editorial, commentary, letter, etc.
Vassilopoulos 2022	Editorial, commentary, letter, etc.
Wan 2023	Ineligible study design
Wang 2022	Editorial, commentary, letter, etc.
Weng 2023	Ineligible study design
Xie 2023	Ineligible study design
Yan 2022	Ineligible study design
Yan 2023	Ineligible study design

RIA: research integrity assessment

Characteristics of studies awaiting classification *[ordered by study ID]*

EPIC-HOS

Methods	Trial design: quadruple-blind RCT with 2 parallel arms Type of publication: trial registry entry Setting: inpatients Recruitment dates: withdrawn (termination due to challenges related to the operational feasibility of the study, taking into account the current epidemiology and declining hospitalization rates for severe COVID-19) Country: USA, Bulgaria Language: English Number of centres: multicentre Study purpose (treatment, prevention): treatment Trial registration number: NCT05545319 Date of registration: 16 September 2022

Participants	Inclusion criteria
	
	• 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-19 ≤ 10 days prior to the day of randomization for non-immunocompromised participants (Category B)
	• Confirmed SARS-CoV-2 infection as determined by RT-PCR or acceptable test method performed by a healthcare provider in any specimen collected within 48 hours prior to randomization
	• Hospitalized for inpatient care for the treatment of clinical manifestations of severe COVID-19

EPIC-HOS *(Continued)*

	• Requirement for oxygen supplementation (via nasal cannula, mask, non-invasive ventilation, or high flow oxygen) to maintain $SpO_2 \geq 94\%$ at time of screening and randomization
	
	Exclusion criteria
	
	• Critical illness, defined by ≥ 1 of the following
	  ○ Requirement for mechanical ventilation or ECMO at randomization, or likely to require intermittent mandatory ventilation or ECMO within 12 hours of randomization
	  ○ Multi-organ dysfunction/failure
	  ○ Haemodynamically unstable, e.g. septic shock, cardiac failure or requiring vasopressors
	  ○ Participant not expected to survive 24 hours from time of randomization
	  ○ History of severe chronic liver disease
	  ○ Receiving dialysis of any type or severe renal impairment
	  ○ Use of nirmatrelvir/ritonavir as an outpatient to treat the current COVID-19-related illness ≤ 7 days of randomization

Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control: • placebo/ritonavir
Outcomes	Primary study outcome • Change from baseline in SARS-CoV-2 RNA level in NP swabs through day 5 Relevant review outcomes planned • Change from baseline in SARS-CoV-2 RNA level in NP swabs through day 5 • Incidence of TEAEs through day 45 • Incidence of AEs or SAEs leading to discontinuations through day 45 Additional study outcomes • Time to sustained clinical recovery through day 30 • Proportion of participants with death from any cause or initiation of invasive mechanical ventilation or ECMO through day 30 • Proportion of participants with SARS-CoV-2 RNA < LLOQ (defined as < 2.0 $\log^{10}$ copies/mL) in NP swabs through day 15 • Proportion of participants with sustained NP swab SARS-CoV-2 RNA < LLOQ (defined as < 2.0 $\log^{10}$ copies/mL) through day 45
Notes	Study withdrawn (termination due to challenges related to the operational feasibility of the study, taking into account the current epidemiology and declining hospitalization rates for severe COVID-19)

EPIC-PEP 2021

Methods	Trial design: double-blind RCT with 3 parallel arms Type of record: trial register entry Sample size: 2880 Setting: outpatient

EPIC-PEP 2021 *(Continued)*

	Country: UK Language: English Number of centres: 358 Study purpose (treatment, prevention): prevention Trial registration number: NCT05047601 Date of registration: 17 September 2021
Participants	Inclusion criteria • Participants who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts with exposure within 96 hours to an individual who is symptomatic and recently tested positive for SARS CoV-2. • Fertile participants must agree to use a highly effective method of contraception Exclusion criteria • History of SARS-CoV-2 infection in the past 6 months • Experiencing measured fever (documented temperature > 38 °C) or other signs or symptoms consistent with COVID-19 • Known medical history of active liver disease • Chronic kidney disease or have known moderate to severe renal impairment. • Known HIV infection with viral load > 400 copies/mL within the last 6 months or taking prohibited medications for HIV treatment • Suspected or confirmed concurrent active systemic infection • Active cancer requiring treatment with prohibited medication • Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4 • Has received approved, authorized, or investigational anti-SARS-CoV-2 mAb, convalescent plasma, other drugs for treatment of COVID-19, or other anti-SARS-CoV-2 biological products within 6 months of screening • Has received any SARS-CoV-2 vaccine within 6 months prior to screening or is expected to receive a SARS-CoV-2 vaccine or other approved, authorized, or investigational postexposure prophylaxis treatments to day 38 • Participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 • Known or prior participation in this trial or another trial involving PF-07321332 • Females who are pregnant or breastfeeding

Interventions	Details of intervention
	
	• Experimental 1:
	  ◦ type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days followed by placebo twice daily for days 6 to 10
	  ◦ route of administration: oral
	• Experimental 2:
	  ◦ type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 10 days
	  ◦ route of administration: oral
	
	Details of control
	
	• Placebo twice daily for 10 days

Outcomes	Primary study outcome

EPIC-PEP 2021 *(Continued)*

	• Proportion of participants who have a negative RT-PCR result at baseline who develop a symptomatic, RT-PCR or rapid antigen test confirmed SARS-CoV-2 infection to day 14 Relevant review outcomes planned • Proportion of participants who have a negative RT-PCR result at baseline who develop a symptomatic, RT-PCR or rapid antigen test confirmed SARS-CoV-2 infection on days 1 to 14 • Percentage of participants who experience AEs to day 38 • Proportion of participants with symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection to day 14 • Proportion of participants with COVID-19-related hospitalization or death from any cause • Proportion of participants with symptomatic or asymptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection • All-cause mortality in participants who have a negative RT-PCR result at baseline to day 38 Additional study outcomes • Time to SARS-CoV-2 infection • Duration of COVID-19-related signs and symptoms in participants who have a negative RT-PCR result at baseline to day 28 • Severity of COVID-19-related signs and symptoms in participants who have a negative RT-PCR result at baseline to day 28 • Minimal concentration of nirmatrelvir on day 1 postdose and day 5 predose • Viral titres measured via RT-PCR in nasal swabs in participants who have a negative or positive RT-PCR result at baseline to day 14 • Number of days of hospital and intensive care unit stay in participants with COVID-19-related hospitalization who have a negative RT-PCR result at baseline to day 28 • Number of COVID-19-related medical visits in participants who have a negative RT-PCR result at baseline to day 28
Notes	Recruitment status: completed Prospective completion date: 18 April 2022 Date last update posted: 6 May 2023 Sponsor/funding: Pfizer

EPIC-SR 2021

Methods	Trial design: double-blind RCT with 2 parallel arms Type of publication: trial registry entry Setting: outpatients Recruitment dates: NR Country: worldwide Language: English Number of centres: 372 study locations Study purpose (treatment, prevention): treatment Trial registration number: NCT05011513 Date of registration: 18 August 2021

EPIC-SR 2021 *(Continued)*

Participants	Inclusion criteria • Confirmed SARS-CoV-2 infection 5 days prior to randomization • Initial onset of COVID-19 signs/symptoms within 5 days of randomization • Fertile participants must agree to use a highly effective method of contraception Exclusion criteria • Has ≥ 1 underlying medical condition associated with an increased risk of developing severe illness from COVID-19 • History of or need for hospitalization for the medical treatment of COVID-19 • Prior diagnosis of SARS-CoV-2 infection (reinfection) • Known medical history of liver disease • Receiving dialysis or have known renal impairment • Known HIV infection with viral load > 400 copies/mL or taking prohibited medications for HIV treatment • Suspected or confirmed concurrent active systemic infection other than COVID-19 • Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4 • Has received or is expected to receive monoclonal antibody treatment or convalescent COVID-19 plasma • Has received any SARS-CoV-2 vaccine within 12 months of screening • Participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 • Known prior participation in this trial or other trial involving nirmatrelvir • Oxygen saturation < 92% on room air • Females who are pregnant or breastfeeding
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control: • placebo Concomitant therapy: NA
Outcomes	Primary study outcome • Time to sustained alleviation of all targeted COVID-19 signs/symptoms to day 28 Relevant review outcomes planned • Percentage of participants who experience AEs by day 34 • Percentage of participants who experience an AE or SAE that leads to study discontinuation by day 34 • Proportion of participants with COVID-19-related hospitalization or death from any cause by day 28 • Proportion of participants who died (all causes) by week 24 Additional study outcomes • Proportion of participants with severe signs/symptoms attributed to COVID-19 by day 28 • Time to sustained resolution of all targeted COVID-19 signs/symptoms by day 28 • Duration of each targeted COVID-19 sign/symptom by day 28

EPIC-SR 2021 *(Continued)*

	• Proportion of participants progressing to a worsening status in ≥ 1 COVID-19 signs/symptoms by day 28 • Proportion of participants with a resting peripheral oxygen saturation ≥ 95% on days 1 and 5 • Number of COVID-19-related medical visits by day 28 • Number of days in hospital and intensive care unit in participants with COVID-19-related hospitalization by day 28 • Minimal concentration of nirmatrelvir by day 5 • Viral titres measured (RT-PCR) in nasal swabs through day 14 • Time to sustained alleviation of all targeted COVID-19 signs/symptoms by day 28
Notes	Recruitment status: terminated (enrollment ceased due to a very low rate of hospitalization or death observed in the standard-risk patient population) Prospective completion date: 30 November 2022 Date last update posted: 12 December 2022 Sponsor/funding: Pfizer

AE: adverse event; ECMO: extracorporeal membrane oxygenation; LLOQ: lower limit of quantitation; NP: nasopharyngeal; RCT: randomized controlled trial; RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction; SAE: serious adverse event; SpO_2: oxygen saturation; TEAE: treatment-emergent adverse event

Characteristics of ongoing studies *[ordered by study ID]*

2022-001362-35

Study name	A study to learn about the study medicines called nirmatrelvir/ritonavir in people at least 12 years of age with COVID-19 who are immunocompromised
Methods	Trial design: RCT with 2 parallel arms Type of publication: trial registry entry Number of study participants: 150 Setting: outpatients Country: Australia, Brazil, Bulgaria, Canada, Hungary, Mexico, Slovakia, Spain, the USA Language: English Number of centres: NA Study purpose (treatment, prevention): treatment Trial registration number: 2022-001362-35 Date of registration: 1 August 2022 (Bulgaria)
Participants	Inclusion criteria • Participants aged ≥ 12 years and weighing ≥ 40 kg at screening • Confirmed SARS-CoV-2 infection as determined by RT-PCR or other acceptable test method in any specimen collected within 5 days prior to randomization • ≥ 1 signs/symptoms attributable to COVID-19 present on the day of randomization • Immunocompromised Exclusion criteria

2022-001362-35 *(Continued)*	• Current need for hospitalization or anticipated need for hospitalization within 24 hours after randomization in the clinical opinion of the site investigator • Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class C, or acute liver failure • History of hypersensitivity or other contraindication to any of the components of the study interventions, as determined by the investigator • Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention • Any comorbidity requiring hospitalization or surgery (or both) within 7 days prior to study entry, or that is considered life-threatening within 30 days prior to study entry, as determined by the investigator • Receiving dialysis or have known age-specific eGFR or eCrCl < 30 mL/minute/1.73 m^2 at screening as measured by a serum creatinine point of care device • Oxygen saturation < 92% on room air obtained at rest within 24 hours prior to randomization • Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgement, make the participant inappropriate for the study. • Current use of any prohibited concomitant medication(s). • Current or previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Authorized or products with conditional approval are not considered investigational. • Prior participation in this trial. • Females who are pregnant at < 14 weeks' gestation. Pregnancy ≥ 14 weeks is not exclusionary. • Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control: • placebo
Outcomes	Primary study outcome • Viral RNA levels in NP swabs Relevant review outcomes planned • Viral RNA levels in NP swabs • Viral clearance. • Safety and tolerability • Hospitalization and all-cause mortality • Duration and severity of signs and symptoms Additional study outcomes • Rate of sustained virological clearance • COVID-19-related healthcare resource utilization
Starting date	NA
Contact information	Pfizer

2022-001362-35 *(Continued)*	Tel: +18007181021 Email: ClinicalTrials.gov_Inquiries@pfizer.com
Notes	Recruitment status: ongoing Estimated study completion date: 1 December 2023 Date last update posted: 22 May 2023 Sponsor/funding: Pfizer

ChiCTR2200059390

Study name	A randomized controlled study on the efficacy and safety of Huashi Baidu granule and paxlovid in the treatment of novel coronavirus pneumonia (COVID-19) with high risk factors
Methods	Trial design: open-label RCT with 3 parallel arms Type of record: trial register entry Sample size: 300 Setting: NR Country: China Language: Chinese, English Number of centres: 1 Study purpose (treatment, prevention): treatment Trial registration number: ChiMCTR2200005942 Date of registration: 28 April 2022

Participants	Inclusion criteria
	• Aged ≥ 18 years, regardless of gender
	• Meet the diagnostic criteria of COVID-19
	• All participants were required to meet ≥ 1 of the following high-risk factors for progression to severe COVID-19, including death
	  ○ Aged ≥ 60 years
	  ○ Cardiovascular disease (including congenital heart disease) or hypertension
	  ○ Chronic lung diseases (e.g. COPD, asthma (moderate to severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
	  ○ Diabetes
	  ○ Immunosuppressive diseases or receiving immunosuppressive treatment (such as the decline of immune function caused by long-term use of corticosteroids or other immunosuppressive drugs)
	  ○ Obese or overweight (BMI > 25 kg/m^2)
	  ○ Active cancer
	  ○ Chronic kidney disease
	  ○ Current smokers
	  ○ Neurodevelopmental diseases (e.g. cerebral palsy, Down's syndrome) or other diseases that lead to medical complexity (e.g. genetic or metabolic syndrome and severe congenital abnormalities)

ChiCTR2200059390 *(Continued)*

- Need relevant medical support (not related to COVID-19) (such as organotomy, gastrostomy, or positive pressure ventilation)
- Other medical conditions or factors judged by researchers may also put individual patients at high risk of developing severe COVID-19. The benefits and risks of individual participants should be weighed

- Voluntarily participate in the experiment and sign the written informed consent.

Exclusion criteria

- According to the judgement of the researcher, the subject may progress to severe/critical illness COVID-19 before randomization
- $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 \leq 300$ in indoor air at sea level, or respiratory rate ≥ 30/minute
- Mechanical ventilation is needed or expected to be urgently needed
- Subject has eye diseases (such as inflammation, vascular malformation, retinal haemorrhage or detachment, optic neuropathy or fundus disease)
- During the screening period, there are 1 of the following situations:
  - ALT or AST > 1.5 × ULN
  - eGFR < 30 mL/minute
- Known allergy to any ingredient used in the intervention drug dosage form
- Any medical treatment that the investigator believes will impair the subject's safety
- Has received SARS-CoV-2 monoclonal antibody treatment or preventive or antiviral treatment
- Has received convalescent COVID-19 plasma treatment
- Used the drugs prohibited in the combination Manual of Mahavir tablets/ritonavir tablets
- Participated in clinical studies involving study drug intervention in the past 30 days
- If the half-life of drug intervention is long, it should go through 5 half-life or 30 days (whichever is longer)
- Any other type of medical research that the subjects are considered to be incompatible with the research in science or medicine at the same time
- Pregnant or breastfeeding or planned pregnancy during the study period
- Wife or partner of males planned to become pregnant during the study period

Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir (300 mg/100 mg), twice daily for 5 days • route of administration: oral Details of control group 1: • type and dose: Huashi Baidu granule, 1 pack, 3 times a day, for 7 days • route of administration: NR Details of control group 2: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg, twice daily for 5 days + Huashi Baidu granule, 1 pack, 3 times a day, for 7 days • route of administration: NR
Outcomes	Primary study outcome • Average time of nucleic acid conversion to negative: time from participant taking the novel coronavirus nucleic acid test report positive for the first time to 2 times of conversion to negative at an interval > 24 hours Relevant review outcomes planned • Nucleic acid negative rate within 7 days of treatment • Clinical symptom efficacy: disappearance rate and improvement rate of clinical symptoms before and after treatment. The rate of turning to severe within 28 days

ChiCTR2200059390 *(Continued)*

	Additional study outcomes • Average length of stay from admission to discharge
Starting date	May 2022
Contact information	Fang Min Tel: +86 021-20256052 Email: fm6505928@sohu.com Address: 528 Zhangheng Road, Pudong New Area, Shanghai
Notes	Recruitment status: recruiting (planned 1 May 2022 to 30 June 2022) Planned completion date: 231 December 2022 Date last update posted: 19 March 2023 Sponsor/funding: Shuguang Hospital Affiliated to Shanghai University of traditional Chinese Medicine

ChiCTR2200059726

Study name	Clinical study of YinQiaoSan combined with SiNiSan in the treatment of sub-designated hospital Omicron COVID-19 infection
Methods	Trial design: RCT with 4 parallel arms Type of record: trial register entry Sample size: 132 Setting: NR Country: China Language: English, Chinese Number of centres: 1 Study purpose (treatment, prevention): treatment Trial registration number: ChiCTR2200059726 Date of registration: 10 May 2022
Participants	Inclusion criteria • Those who meet the diagnostic criteria for people with novel coronavirus infection and the criteria for the diagnosis and treatment of TCM exogenous fever emergencies and wind-heat exogenous diseases • Aged 18 to 85 years • Acute onset, the course of disease within 5 days • The total number of white blood cells > 3.5×10^9/L and ≤ 10.0×10^9/L, the absolute value of neutrophils ≤ 7.0×10^9/L • Informed consent, voluntary subject, complying with good clinical practice regulations • Type of new crown is in accordance with the standard of *Diagnosis and Treatment of Novel Coronavirus Pneumonia* (Trial Ninth Edition)

ChiCTR2200059726 *(Continued)*

	Exclusion criteria • Fever caused by other respiratory, digestive, urinary, and blood system diseases • Pregnant and lactating women • Patients with serious primary cardiovascular diseases, liver diseases, kidney diseases, haematological diseases and lung diseases, or serious diseases affecting their survival are in an unstable period and need active treatment, such as tumours or AIDS • Patients who need haemodialysis or radiotherapy and chemotherapy • Allergic diseases (such as allergic rhinitis, allergic asthma, etc.), or allergies to test drugs, including allergic history to the ingredients of this product, paracetamol, or pharmaceutical excipients • During this course, antiviral drugs have been given before randomization • Unable or unwilling to co-operate with clinical trials due to other diseases • Suspect or have a history of alcohol or drug abuse • Have participated in other clinical trials or are participating in clinical trials of other drugs in the past 3 months
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control group 1: • type and dose: YinQiaoSan, 1 dose daily, divided into 2 doses in the morning and evening • route of administration: NR Details of control group 2: • type and dose: YinQiaoSan and SiNiSan, 1 dose daily, divided into 2 doses in the morning and evening • route of administration: NR Details of control group 3: • type and dose: needle burial at acupuncture points (Dazhui, Hegu, Quchi, Waiguan), daily only • route of administration: NR
Outcomes	Primary study outcome • Body temperature • COVID-19 nucleic acid testing Additional study outcomes: none
Starting date	5 May 2022
Contact information	Ouyang Yang Tel: +86 13321951632 Email: ssdouyang@163.com Address: 185 Pu'an Road, Huangpu District, Shanghai, China
Notes	Recruitment status: recruiting Prospective completion date: NR Date last update posted: 1 March 2023

ChiCTR2200059726 *(Continued)*	Sponsor/funding: Shuguang Hospital Affiliated of Shanghai University of Traditional Chinese Medicine

ChiCTR2200059739

Study name	A single center, prospective, randomized controlled study of paxlovid compared to Lianhua Qingwen in shortening the negative time of novel coronavirus positive patients
Methods	Trial design: RCT with 2 parallel arms Type of record: trial register entry Sample size: 220 Setting: NR Country: China Language: English Number of centres: 1 Study purpose (treatment, prevention): treatment Trial registration number: ChiCTR2200059739 Date of registration: 10 May 2022
Participants	Inclusion criteria • Sign the informed consent in writing before the start of any research-specific operation or treatment • Aged 18 to 90 years old, gender is not limited • Infected with the novel coronavirus and confirmed by RT-PCR • Nucleic acid has not turned negative 8 days after the initial treatment • ECOG activity status score of 0 or 1 • Sufficient baseline organ function and haematological function as determined by screening examination • Must agree and be able to comply with the research visit plan and other requirements stipulated in the protocol, including telephone follow-up Exclusion criteria • Pregnant or lactating women with ECOG score ≥ 2 • There are untreated tumour CNS metastases. If ≥ 4 weeks after the end of the treatment of CNS metastasis, the subjects who have no new metastasis or progression of metastasis are allowed to enter this study. The CNS imaging examination during the screening period is not mandatory, and only those with clinical indications need to do it • Those who have undergone major surgery within 28 days before randomization in this study • Has uncontrolled active bleeding or bleeding tendency • Clinically significant gastrointestinal abnormalities, which may affect the absorption of the study drug or even increase the risk of bleeding or perforation, any previous history of gastrointestinal perforation • With other malignant tumours requiring treatment in the past 3 years • Poorly controlled hypertension, defined as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg Antihypertensive drugs allowed and rescreened • ≥ 1 of the following medical history within 6 months before randomization: symptomatic peripheral vascular disease; coronary artery bypass surgery; myocardial infarction or unstable angi-

ChiCTR2200059739 *(Continued)*

	na; cardiac angioplasty or stent implantation; cerebrovascular accident, including transient ischaemic attack
	• New York Heart Association class III or IV congestive heart failure
	• Uncontrolled concurrent diseases, and these factors will affect the subject's compliance with the relevant requirements of this study;
	• There are the following incompatibilities:
	  ○ alpha-1 receptor blocker: alfuzosin
	  ○ analgesics: pethidine, piroxicam, propoxyphene
	  ○ anti-anginal drugs: ranolazine
	  ○ anticancer drugs: neratinib, venetoclax
	  ○ antiarrhythmic drugs: amiodarone, bepridil, quinidine, propafenone, flecainide
	  ○ antibiotics: fusidic acid
	  ○ antifungal drug: voriconazole
	  ○ antihistamines: astemizole, terfenadine
	  ○ antigout drug: colchicine
	  ○ antimycobacterial drug: rifabutin
	  ○ antipsychotics/psycholeptics: lurasidone, clozapine;
	  ○ ergot derivatives: ergotamine, ergonovine
	  ○ gastrointestinal motility drug: cisapride
	  ○ blood lipid regulator β-hydroxy β-methylglutaryl-CoA reductase inhibitors: lovastatin, simvastatin
	  ○ phosphodiesterase-5 inhibitors: avanafil, sildenafil, vardenafil
	  ○ sedative/hypnotics: diazepam, diazepam, and oral midazolam

Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days followed by placebo twice daily for days 6 to 10 • route of administration: oral Details of control: • type and dose: Lianhua Qingwen granule 6 g/bag. 3 times a day, 2 bag each time or Lianhua Qingwen Capsule 0.35 g, 4 capsules each time, 3 times a day • route of administration: oral
Outcomes	Primary study outcome • Nucleic acid negative conversion time and negative conversion rate Additional study outcomes: none
Starting date	8 May 2022
Contact information	Wei Zhai Tel: +86 18701771959 Email: jackyzw2007@163.com Address: 160 Pujian Road, Pudong New Area, Shanghai, China
Notes	Recruitment status: pending Prospective completion date: NR Date last update posted: 20 March 2023

ChiCTR2200059739 *(Continued)*

	Sponsor/funding: Renji Hospital, Shanghai Jiaotong University School of Medicine

ChiCTR2200060010

Study name	Open-label, head-to-head, randomized, controlled clinical study of Molnupiravir capsules and Paxlovid tablets in patients with mild and general type of COVID-19 in high-risk populations
Methods	Trial design: open-label RCT with 2 parallel arms Type of record: trial register entry Sample size: 100 Setting: NR Country: China Language: Chinese, English Number of centres: 1 Study purpose (treatment, prevention): treatment Trial registration number: ChiCTR2200060010 Date of registration: 14 May 2022

Participants	Inclusion criteria
	• Adults (aged ≥ 18 years) with mild or common novel coronavirus pneumonia who have tested positive for SARS-CoV-2 virus
	• Within 5 days after the onset of symptoms or positive initial screening
	• Ct value < 30 when enrolled
	• Have any of the following risk factors:
	  ◦ aged ≥ 60 years
	  ◦ active cancers (excluding small cancers not associated with immunosuppression or significant morbidity/mortality (such as basal cell carcinoma))
	  ◦ chronic kidney disease (excluding people receiving dialysis or eGFR reduction < 30 mL/minute/1.73 m^2)
	  ◦ chronic pulmonary obstruction
	  ◦ obesity (BMI > 30 kg/m^2)
	  ◦ severe heart disease, such as heart failure, coronary heart disease, or cardiomyopathy
	  ◦ diabetes mellitus
	  ◦ immunodeficiency or immunosuppression (long-term hormone therapy, organ transplantation, ongoing chemotherapy, immune modulation therapy)
	  ◦ uncontrolled asthma, COPD, bronchitis, chronic kidney disease, chronic respiratory disease, anaemia, etc.
	• Informed consent signed by the patient or the entrusted agent
	• No pregnancy plan and voluntarily take effective contraceptive measures within 4 months after randomization
	• Oral medication may be used or received
	Exclusion criteria
	• Severe vomiting and difficulty in taking drugs orally or resulting in difficulty in taking drugs after oral administration
	• Had taken traditional Chinese medicine or proprietary Chinese medicine or other antiviral drugs within 3 days before enrollment

ChiCTR2200060010 *(Continued)*

	• They should not stop taking traditional Chinese medicine or proprietary Chinese medicine or other antiviral drugs after enrollment • Allergic to monapivir or its pharmaceutical components • Allergic to paravide or its pharmaceutical components • Suspected or confirmed active systemic infections other than COVID-19 • Patients in which there is no clinical expectation of survival and only hospice care is provided, or cases in deep coma that do not respond to supportive care within 3 hours of admission • Pregnant or lactating females • Mental disorders • Severe liver function injury • Contraindications of monapivir or Parovide or who cannot discontinue contraindicated contraindications • The researchers judged that it was not suitable to participate in this study
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir, dose NR • route of administration: NR Details of control: • molnupiravir • dose regimen NR
Outcomes	Primary study outcome (as defined by the study) • Days of virus nucleic acid turning from positive to negative Relevant review outcomes reported • Rate of progression (defined as progression to critical/critical or all-cause death) by day 28 Additional study outcomes reported • Severe cases • Duration of fever • ICU duration • Time of discharge • Clinical outcome 28 days after initial administration • Time for improvement in lung imaging
Starting date	20 April 2022
Contact information	Study leader: Jin Ronghua Study leader's telephone: +86 13811611118 Study leader's E-mail: ronghuajin@ccmu.edu.cn Study leader's address: 8 Jingshun Road East, Chaoyang District, Beijing
Notes	Recruitment status: not yet recruiting Prospective completion date: NR Date last update posted: 4 March 2023 Sponsor/funding: Beijing Ditan Hospital Capital Medical University

NCT05041907

Study name	Finding treatments for COVID-19: a trial of antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV)
Methods	Trial design: platform trial Type of publication: trial registry entry Number of participants: 1500 Setting: NR Country: Brazil, Lao People's Democratic Republic, Thailand Language: English Number of centres: multicentre Study purpose (treatment, prevention): treatment Trial registration number: NCT05041907 Date of registration: 31 October 2022
Participants	Inclusion criteria • Patient understands the procedures and requirements and is willing and able to give informed consent for full participation in the study • Previously healthy adults, male or female, aged 18 to 50 years at time of consent with early symptomatic COVID-19 • SARS-CoV-2-positive by lateral flow antigen test OR a positive PCR test for SARS-CoV-2 within the last 24 hours with a Ct value < 25 (all viral targets) • Symptoms of COVID-19 (including fever, or history of fever) for < 4 days (96 hours) • Oxygen saturation ≥ 96% measured by pulse oximetry at time of screening • Able to walk unaided and unimpeded in activities of daily living • Agrees and is able to adhere to all study procedures, including availability and contact information for follow-up visits • Healthy women on the oral contraceptive pill are eligible to join the study Exclusion criteria • Taking any concomitant medications or drugs • Presence of any chronic illness/condition requiring long-term treatment, or other significant co-morbidity (e.g. diabetes, obesity) • Laboratory abnormalities discovered at screening • For females: pregnancy, actively trying to become pregnant, or lactation • Contraindication to taking, or known hypersensitivity reaction to, any of the proposed therapeutics • Currently participating in another COVID-19 therapeutic or vaccine trial • Evidence of pneumonia (although imaging is NOT required)
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control: • SoC

NCT05041907 *(Continued)*

Outcomes	Primary outcomes • Rate of viral clearance for newly available and repurposed drugs through day 7 • Rate of viral clearance for positive controls (e.g. monoclonal antibodies) through day 7 • Rate of viral clearance for small novel molecule drugs through day 7 Relevant review outcomes planned • Rate of viral clearance for newly available and repurposed drugs through day 7 • Rates of hospitalisation by treatment arm (hospitalisation for clinical reasons) through day 28 Additional study outcomes • Viral kinetic levels in early COVID-19 disease by day 7 • Number of antiviral treatment arms that are shown to be effective i.e. a positive signal (> 90% probability of > 12.5% acceleration in viral clearance) by day 7 • Rates of viral clearance by treatment arm, as compared against REGN-COV2 (monoclonal antibody cocktail) or other licenced and available therapeutics with evidence of accelerated viral clearance by day 7
Starting date	30 September 2021
Contact information	William Schilling, MD Tel: +662 203 6333 Email: william@tropmedres.ac Nicholas J White, Professor Tel: +662 203 6333 Email: nickw@tropmedres.ac
Notes	Recruitment status: recruiting Prospective completion date: August 2024 Date last update posted: 10 January 2023 Sponsor/funding: University of Oxford

NCT05321394

Study name	Adaptive, randomized, non-inferiority trial on the use of monoclonal antibodies or antivirals in outpatients with mild or moderate COVID-19
Methods	Trial design: open-label RCT with parallel assignment Type of record: trial register entry Sample size: 1095 Setting: outpatient Country: Italy Language: English Number of centres: 19

NCT05321394 *(Continued)*

	Study purpose (treatment, prevention): treatment Trial registration number: NCT05321394 Date of registration: 11 April 2022
Participants	Inclusion criteria • Age ≥ 50 years • Informed consent by the participant or legally authorized representative • Laboratory-confirmed SARS-CoV-2 infection, as determined by PCR or other commercial or public health assay in any specimen, ≤ 4 days prior to the study drug administration • Peripheral oxygen saturation ≥ 94% on room air and not requiring supplemental oxygen • Onset of symptom is ≤ 4 days prior to the study drug administration. Onset time of symptom is defined as the time when the patient experienced the presence of ≥ 1 of the following (but not limited to) SARS-CoV-2 infection-associated symptom: nasal obstruction or congestion, cough, fever > 37.3 °C, sore throat, body pain or muscle pain, headache, loss of taste or smell, nausea or vomiting, diarrhoea Exclusion criteria • Previously or currently hospitalized or requiring hospitalization • Respiratory distress with respiratory rate ≥ 25 breaths/minute • Heart rate ≥ 125 beats per minute • Peripheral oxygen saturation ≤ 93% on room air at sea level • Known allergies to any of the components used in the formulation of the interventions • Severe renal impairment (eGFR < 30 mL/minute) • Severe hepatic impairment (Child-Pugh Class C) • Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious or life-threatening (or both) reactions • Co-administration with potent CYP3A inducers • Haemodynamic instability requiring use of pressors within 24 hours of randomization • Suspected or confirmed serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that could potentially lead to hospitalization in within 30 days • Any comorbidity requiring surgery within 7 days or that is considered life-threatening within 90 days • History of a positive SARS-CoV-2 test prior to the 1 serving as eligibility for this study • Other investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing • Previous treatment with a SARS-CoV-2 specific monoclonal antibody • History of convalescent COVID-19 plasma treatment • Participation, within the last 30 days, in a clinical study involving an investigational intervention • Pregnancy or breastfeeding • Investigator site personnel directly affiliated with this study • Sexually-active women of childbearing potential or sexually active men who are unwilling to practice effective contraception prior to the initial dose/start of the first treatment, during the study, and for ≥ 6 months after the last dose • Inability to participate in the study follow-up

Interventions	Details of intervention
	
	• Experimental 1:
	  ◦ type and dose: tixagevimab/cilgavimab 300 mg/300 mg
	  ◦ route of administration: 2 separate consecutive intramuscular injections
	• Experimental 2:
	  ◦ type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days
	  ◦ route of administration: oral

NCT05321394 *(Continued)*

	Details of control
	• Active comparator:
	  ○ type and dose: sotrovimab 500 mg administered in 100 mL prefilled 0.9% sodium chloride injection infusion solution over 30 minutes
	  ○ route of administration: IV

Outcomes	Primary study outcome • COVID-19 progression; assessed as hospitalization or need of supplemental oxygen therapy at home or death within 14 days of randomization Relevant review outcomes planned • Death rate at 28 days of randomization • Death rate at 90 days of randomization Additional study outcomes • Number of visits to the emergency department without subsequent hospitalization within 28 days of randomization • Days of supplemental oxygen therapy within 90 days of randomization • Days of any hospitalization within 90 days of randomization • Rate of patients undergoing non-invasive ventilation within 28 days of randomization • Days of non-invasive ventilation within 90 days of randomization • Rate of patients undergoing mechanical ventilation within 28 of randomization • Days of mechanical ventilation within 90 days of randomization • Days of symptoms within 90 days of randomization
Starting date	7 March 2022
Contact information	Professor Evelina Tacconelli Email: evelina.tacconelli@univr.it
Notes	Recruitment status: recruiting Estimated study completion date: 30 December 2023 Date last update posted: 23 November 2022 Sponsor/funding: Azienda Ospedaliera Universitaria Integrata Verona

NCT05386433

Study name	Paxlovid in the treatment of COVID-19 patients with uremia
Methods	Trial design: open-label RCT Type of record: trial register entry Sample size: 40 Setting: NA Country: China Language: English

NCT05386433 *(Continued)*

	Number of centres: 1 Study purpose (treatment, prevention): treatment Trial registration number: NCT05386433 Date of registration: 23 May 2022
Participants	Inclusion criteria • Age ≥ 18 years • Positive nucleic acid test for COVID-19 before randomization • ≥ 1 symptom or sign of COVID-19 at the time of enrollment Exclusion criteria • History of active liver disease, including chronic or active hepatitis B or C, primary biliary cirrhosis, Child-Pugh B or C, or acute liver failure • HIV infection with viral load > 400 copies/mL • Suspected or confirmed active systemic infections that may have an impact on the study evaluation except for COVID-19 • Acute heart failure, respiratory failure, severe chronic kidney disease, and cardiovascular disease caused by uraemia-related complications • Allergic to any ingredients of nirmatrelvir/ritonavir
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control: • SoC
Outcomes	Primary study outcome • Time to negative conversion of SARS-CoV-2 nucleic acid • Proportion of ICU transfer or disease progression to severe or critical illness Relevant review outcomes planned: none Additional study outcomes: none
Starting date	June 2022
Contact information	Jieming QU, PhD, Ruijin Hospital
Notes	Recruitment status: not yet recruiting Prospective completion date: August 2022 Date last update posted: 23 May 2022 Sponsor/funding: Ruijin Hospital

NCT05567952

Study name	A study to learn about a repeat 5-day treatment with the study medicines (called nirmatrelvir/ritonavir) in people 12 years old or older with return of COVID-19 symptoms and SARS-CoV-2 positivity after finishing treatment with nirmatrelvir/ritonavir
Methods	Trial design: triple-blind RCT with 2 parallel arms Type of record: trial register entry Sample size: 411 Setting: outpatient Country: USA, Canada, Greece, Taiwan Language: English Number of centres: 69 Study purpose (treatment, prevention): treatment Trial registration number: NCT05567952 Date of registration: 3 October 2022
Participants	Inclusion criteria • Documentation of nirmatrelvir/ritonavir treatment with participant-reported 100% compliance. Symptom alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms after completing an initial 5-day course of nirmatrelvir/ritonavir • Onset of rebound in COVID-19 symptoms within 2 weeks (14 days) after the completion of the initial 5-day course of nirmatrelvir/ritonavir • Onset of rebound in signs/symptoms attributable to COVID-19 within 48 hours prior to randomization and ≥ 1 sign/symptom attributable to COVID-19 present on the day of randomization • SARS-CoV-2 infection as determined by rapid antigen testing within 24 hours prior to randomization • ≥ 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 Exclusion criteria • Current need for hospitalization, hospitalized for the COVID-19 infection or anticipated need for hospitalization within 24 hours after randomization • History of severe chronic liver disease • Receiving dialysis or have known age-specific eGFR or eCrCl < 30 mL/minute/1.73 m^2 at screening as measured by a serum creatinine point of care device • Oxygen saturation < 92% on room air obtained at rest within 24 hours prior to randomization • Immunocompromised • Current use of any prohibited concomitant medication(s) • Females who are pregnant and < 14 weeks' gestation
Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days followed by placebo twice daily for days 6 to 10 • route of administration: oral Details of control: • placebo twice daily for 10 days
Outcomes	Primary study outcome

NCT05567952 *(Continued)*

	• Change in viral SARS-CoV-2 RNA level as measured in NP swabs Relevant review outcomes planned • Change in viral SARS-CoV-2 RNA level as measured in NP swabs • Time to sustained alleviation of all targeted signs and symptoms defined as the first of 2 consecutive days when symptoms scored moderate/severe at baseline are scored mild/absent and symptoms scored mild/absent at baseline are scored absent by day 28 • Incidence of TEAEs by week 24 • Incidence of SAEs and AEs leading to discontinuation by week 24 Additional study outcomes: none
Starting date	19 October 2022
Contact information	Pfizer CT.gov Call Center Tel: 1-800-718-1021 Email: ClinicalTrials.gov_Inquiries@pfizer.com
Notes	Recruitment status: recruiting Prospective completion date: 28 November 2023 Date last update posted: 21 February 2023 Sponsor/funding: Pfizer

NCT05614349

Study name	Canadian Adaptive Platform Trial of Treatments for COVID-19 in Community Settings (CanTreat-COVID)
Methods	Trial design: platform trial Type of record: trial register entry Sample size: 12000 Setting: outpatient Country: Canada Language: English Number of centres: 1 Study purpose (treatment, prevention): treatment Trial registration number: NCT05614349 Date of registration: 14 November 2022
Participants	Inclusion criteria • Age ≥ 50 years or 18 to 49 years with ≥ 1 chronic high-risk medical conditions or immunosuppression (or both): chronic respiratory disease (including COPD, cystic fibrosis, and asthma requiring at least daily use of preventive or reliever medication (or both)); chronic heart or vascular disease; chronic kidney disease; chronic liver disease; chronic neurological disease (including dementia, stroke, epilepsy); severe and profound learning disability; Down's syndrome; diabetes (Type 1 or

NCT05614349 *(Continued)*

Type 2); immunosuppression: primary (e.g. inherited immune disorders resulting from genetic mutations) or secondary due to disease or treatment (e.g. sickle cell, HIV, cancer, chemotherapy); solid organ, bone marrow and stem cell transplant recipients; morbid obesity (BMI > 35 kg/m^2); severe mental illness; care home resident

- Confirmed SARS-CoV-2 by nucleic acid testing or rapid antigen testing with proof of a positive test provided via a picture of the result
- Able to be enrolled and begin the study drug within 5 days of onset of symptoms associated with SARS-CoV-2 infection

Exclusion criteria

- Admitted to hospital or emergency department for > 24 hours
- Previously randomized to CanTreatCOVID
- Currently participating in a clinical trial of a therapeutic agent for acute SARS-CoV-2 infection that is not/suspected not compatible with the study therapeutic drug
- Already taking a study drug or contraindication to a study drug
- Inability for participant or caregiver to provide informed consent

Nirmatrelvir /ritonavir exclusion criteria

- History of clinically significant hypersensitivity to the active substances in nirmatrelvir/ritonavir or to any of its excipients
- Patients with known rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption
- Patients with known current severe liver impairment (characterized by severe ascites, encephalopathy, jaundice, or prolonged international normalized ratio. People with liver disease without any of these features are eligible)
- Patients with known moderate or severe renal disease (defined as chronic kidney disease stage 3, 4, or 5 or current acute kidney injury or most recent eGFR in the past 6 months < 60 mL/minute)
- Currently taking nirmatrelvir /ritonavir
- Clinical requirement to continue taking a drug which is contraindicated or not recommended for administration with nirmatrelvir /ritonavir in the context of CanTreatCOVID or is taking a drug which in the opinion of the investigator would put the subject at unacceptable risk
- Has a known or suspected pregnancy
- Is breastfeeding
- Is of childbearing potential and is unwilling to use a highly effective contraceptive

Interventions	Details of intervention
	• Experimental 1:
	  ◦ type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days
	  ◦ route of administration: oral
	• Experimental 2:
	  ◦ other emerging interventions
	• Experimental 3:
	  ◦ other emerging interventions
	Details of control
	• SoC

Outcomes	Primary study outcome • All-cause hospitalization or death rate by day 28 • Time to recovery by day 14 Relevant review outcomes planned • All-cause hospitalization or death rate by day 28

NCT05614349 *(Continued)*

	• Time to recovery by day 14 • Quality of life at baseline, 21 days, 28 days, 90 days, and 36 weeks • Early discontinuation and severe adverse events by day 28 Additional study outcomes • Symptom severity by day 28 • Rate of postacute sequelae of SARS-CoV-2 at 90 days and 36 weeks • Treatment costs at 12 and 24 months
Starting date	16 January 2023
Contact information	Benita Hosseini, PhD Tel: +14163604000 Email: benita.hosseini@unityhealth.to Address: Unity Health Toronto, Toronto, Ontario, Canada, M5B 1W8
Notes	Recruitment status: recruiting Prospective completion date: January 2025 Date last update posted: 13 February 2023 Sponsor/funding: Unity Health Toronto

NCT05642910

Study name	The efficacy of azvudine and paxlovid in high-risk patients with COVID-19: a prospective randomized controlled trial
Methods	Trial design: RCT with 2 parallel arms Type of record: trial register entry Sample size: 540 Setting: inpatient Country: China Language: English Number of centres: 1 Study purpose (treatment, prevention): treatment Trial registration number: NCT05642910 Date of registration: 7 December 2022
Participants	Inclusion criteria • Aged 18 to 85 years (inclusive) • Meet the diagnostic criteria for COVID-19 • ≥ 1 high-risk factor for progression to severe COVID-19 • ≤ 5 days from the onset of clinical symptoms • Sign informed consent form.

NCT05642910 *(Continued)*

	Exclusion criteria • Severe or critically people with COVID-19 • Have received neutralizing antibodies or convalescent plasma therapy due to COVID-19 • Child-Pugh grade C or acute liver failure • Chronic renal failure (eGFR < 30 mL/minute) • Grade III or IV cardiac function, or known left ventricular ejection fraction < 30% • Known or suspected history of active or extrapulmonary tuberculosis • Allergic to the active ingredient of the drug • Pregnant and lactating women
Interventions	Details of intervention: • type and dose: azvudine daily for 7 days • route of administration: oral Details of control: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral
Outcomes	Primary study outcome • Proportion of participants RT-PCR-negative for SARS-CoV-2 at 7 days Relevant review outcomes planned • Proportion of participants RT-PCR-negative for SARS-CoV-2 at 7 days • Proportion of participants RT-PCR-negative for SARS-CoV-2 at 14 days Additional study outcomes • Time to conversion from a positive RT-PCR test to 2 continuously negative test
Starting date	18 October 2022
Contact information	Songqiao Liu, MD, PhD Tel: 086-13770723635 Email: liusongqiao@ymail.com Junjing Zhang, MD, PhD Tel: 086-04175281618 Email: zhang.jj@vip.163.com
Notes	Recruitment status: recruiting Prospective completion date: 30 April 2023 Date last update posted: 8 December 2022 Sponsor/funding: Southeast University, China

PANORAMIC 2021

Study name	A clinical trial investigating novel treatments for COVID-19 in the community (PANORAMIC trial)

PANORAMIC 2021 *(Continued)*

Methods	Trial design: double-blind RCT platform trial Type of record: trial register entry Sample size: 5319 Setting: outpatients Country: UK Language: English Number of centres: NR Study purpose (treatment, prevention): treatment Trial registration number: ISRCTN30448031 Date of registration: 28 October 2021

Participants	Inclusion criteria
	
	• Participant or their legal representative is able and willing to provide informed consent
	• Symptoms attributable to COVID-19 started within past 5 days and ongoing
	• Positive PCR SARS-CoV-2 test within the past 7 days
	• Aged ≥ 50 years or aged 18 to 49 years with any known underlying chronic health condition considered to make them clinically vulnerable:
	  ○ chronic respiratory disease (including COPD, cystic fibrosis, and asthma requiring at least daily use of preventive or reliever medication (or both))
	  ○ chronic heart or vascular disease
	  ○ chronic kidney disease
	  ○ chronic liver disease
	  ○ chronic neurological disease (including dementia, stroke, epilepsy)
	  ○ severe and profound learning disability
	  ○ Down's syndrome
	  ○ diabetes mellitus (Type or Type II)
	  ○ immunosuppression due to disease or treatment (e.g. sickle cell, HIV, cancer, chemotherapy)
	  ○ solid organ, bone marrow, and stem cell transplant recipients
	  ○ morbid obesity (BMI > 35 kg/m^2)
	  ○ severe mental illness
	  ○ care home resident
	  ○ judged by recruiting clinician or research nurse (registered medical practitioner or trained study nurse) to be clinically vulnerable
	
	Exclusion criteria
	
	• Currently admitted to hospital
	• Previous randomization in the PANORAMIC trial
	• Currently participating in a clinical trial of a therapeutic agent for acute COVID-19
	• Participation in an investigational COVID-19 vaccine trial within previous 28 days
	• Additional exclusions specific to each intervention arm, if any, as listed in the Intervention Specific Appendices of currently open trial arms

Interventions	Details of intervention: • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control:

PANORAMIC 2021 *(Continued)*

	• SoC Concomitant therapy: NA
Outcomes	Primary study outcome • Non-elective hospitalizations/deaths in higher risk, symptomatic patients with confirmed COVID-19 within 28 days of randomization measured using patient records Relevant review outcomes planned • Non-elective hospitalizations/deaths in higher risk, symptomatic patients with confirmed COVID-19 within 28 days of randomization measured using patient records • AEs as defined in the Intervention Specific Appendices up to 6 months Additional study outcomes • Time to recovery (defined as the first instance that a participant report feeling recovered from the illness) measured using daily online symptom scores. Telephone call or text on days 7, 14, and 28 if data are not obtained through the online diary. Also, at 3 and 6 months • Participant reported illness severity, reported by daily rating of how well participant feels, enabling identification of sustained recovery • Duration of severe symptoms and symptom recurrence measured using general practitioner's notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days. Medical notes review for up to 10 years • Contacts with the health services reported by patients or captured by reports of patients' medical records (or both) up to 12 months • New infections in household measured using daily diary for 28 days • Longer-term effects measured using patient contact at 3 and 6 months, electronic medical record search for up to 1 year • Cost-effectiveness measured using resource use and cost data and EQ-5D-5L at baseline and day 28
Starting date	Overall trial start date 1 September 2021
Contact information	Professor Christopher Butler Tel: +44 (0)1865 289670 Email: panoramic@phc.ox.ac.uk Address: Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Oxford, UK
Notes	Recruitment status: recruiting Prospective completion date: 31 March 2024 Date last update posted: 2 February 2023 Sponsor/funding: Department of Health and Social Care, National Institute for Health Research (NIHR) (UK)

RECOVERY 2020

Study name	Randomised evaluation of COVID-19 therapy (RECOVERY)
Methods	Trial design: platform trial

RECOVERY 2020 *(Continued)*

	Type of record: trial register entry Sample size: 50,000 Setting: inpatients Country: Ghana, India, Indonesia, Nepal, South Africa, Sri Lanka, UK, Vietnam Language: English Number of centres: 195 Study purpose (treatment, prevention): treatment Trial registration number: NCT04381936 Date of registration: 11 May 2020
Participants	Inclusion criteria • Hospitalized • Viral pneumonia syndrome • SARS-CoV-2 infection (clinically suspected or laboratory confirmed) • No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial Exclusion criteria • If the attending clinician believes that there is a specific contraindication to 1 of the active drug treatment arms or that the patient should definitely be receiving 1 of the active drug treatment arms then that arm will not be available for randomization for that patient • For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial.
Interventions	Details of intervention (Part L): • type and dose: nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days • route of administration: oral Details of control: • SoC Concomitant therapy: NA
Outcomes	Primary study outcomes • All-cause mortality within 28 days after randomization Relevant review outcomes planned: • All-cause mortality within 28 days after randomization Additional study outcomes • Duration of hospital stay within 28 days and up to 6 months after the main randomization • Composite endpoint of death or need for mechanical ventilation or ECMO within 28 days and up to 6 months after the main randomization • Need for (and duration of) ventilation within 28 days and up to 6 months after the main randomization • Need for renal replacement within 28 days and up to 6 months after the main randomization

RECOVERY 2020 *(Continued)*	• Number of patients who had thrombotic events within 28 days and up to 6 months after the main randomization
Starting date	Overall trial start date 19 March 2020
Contact information	Richard Haynes Tel: +44 (0)1865 743743 Email: recoverytrial@ndph.ox.ac.uk
Notes	Recruitment status: recruiting Prospective completion date: November 2023 Date last update posted: 9 January 2023 Sponsor/funding: • University of Oxford • UK Research and Innovation • National Institute for Health Research, UK • Wellcome • Bill and Melinda Gates Foundation • Department for International Development, UK • Health Data Research UK • Medical Research Council Population Health Research Unit • NIHR Clinical Trials Unit Support Funding • NIHR Health Protection Research Unit in Emerging and Zoonotic Infections

ALT: alanine aminotransferase; AST: aspartate transferase; BMI: body mass index; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; eCrCl: estimated creatinine clearance; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; EQ-5D-5L: EuroQol 5 Dimensions 5 Levels; ICU: intensive care unit; IV: intravenous; NA: not available; NP: nasopharyngeal; NR: not reported; RCT: randomized controlled trial; RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction SAE: serious adverse event; SoC: standard of care; ULN: upper limit of normal.

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 All-cause mortality at day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
EPIC-HR 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.2 Worsening of clinical status at day 28: admission to hospital or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
EPIC-HR 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.3 Worsening of clinical status at day 28: admission to hospital or death (subgroup analysis based on age)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.3.1 Children						
Subgroup 1.3.2 Aged < 65 years						
EPIC-HR 2021	✓	~	✓	✓	✓	~
Subgroup 1.3.3 Age ≥ 65 years						
EPIC-HR 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.4 Worsening of clinical status at day 28: admission to hospital or death (subgroup analysis based on ethnicity)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 White						
EPIC-HR 2021	✓	~	✓	✓	✓	~
Subgroup 1.4.2 Black/African American						
EPIC-HR 2021	✓	~	✓	✓	✓	~
Subgroup 1.4.3 Asian						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
EPIC-HR 2021	✓	~	✓	✓	✓	~
Subgroup 1.4.4 Other						
EPIC-HR 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.5 Serious adverse events during the study period

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
EPIC-HR 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.6 Any grade treatment-emergent adverse events during the study period

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
EPIC-HR 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.7 Any grade treatment-related adverse events during the study period

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
EPIC-HR 2021	✓	~	✓	✓	~	~

Risk of bias for analysis 1.8 Discontinuation of study drug due to adverse events during the study period

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
EPIC-HR 2021	✓	~	✓	✓	~	~

Risk of bias for analysis 2.1 All-cause mortality at day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Liu 2023	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 All-cause mortality at day 28 (subgroup analysis based on age)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.2.1 Aged ≤ 65 years						
Liu 2023	✓	✓	✓	✓	✓	✓
Subgroup 2.2.2 Aged > 65 years						
Liu 2023	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.3 Viral clearance at day 7

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Liu 2023	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 Viral clearance at day 14

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Liu 2023	✓	✓	✓	✓	✓	✓

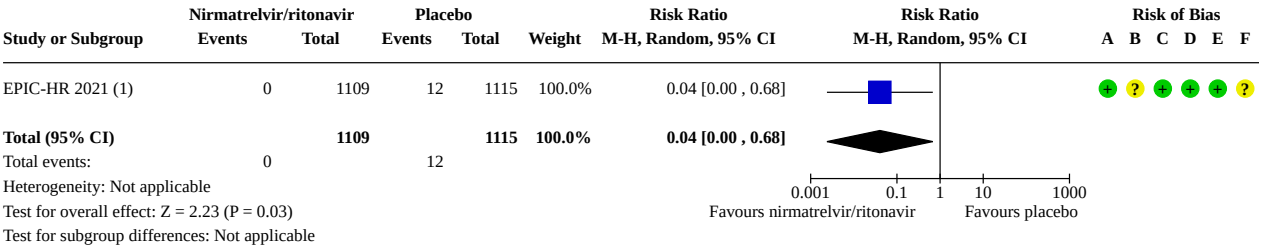
DATA AND ANALYSES

Comparison 1. Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at day 28	1	2224	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.00, 0.68]
1.2 Worsening of clinical status at day 28: admission to hospital or death	1	2224	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.07, 0.27]
1.3 Worsening of clinical status at day 28: admission to hospital or death (subgroup analysis based on age)	1	2085	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.06, 0.27]
1.3.1 Children	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3.2 Aged < 65 years	1	1817	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.07, 0.34]
1.3.3 Age ≥ 65 years	1	268	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.38]
1.4 Worsening of clinical status at day 28: admission to hospital or death (subgroup analysis based on ethnicity)	1	2085	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.07, 0.29]
1.4.1 White	1	1486	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.07, 0.33]
1.4.2 Black/African American	1	94	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 7.04]
1.4.3 Asian	1	296	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.19]
1.4.4 Other	1	209	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Serious adverse events during the study period	1	2224	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.15, 0.41]
1.6 Any grade treatment-emergent adverse events during the study period	1	2224	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.82, 1.10]
1.7 Any grade treatment-related adverse events during the study period	1	2224	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.44, 2.95]
1.8 Discontinuation of study drug due to adverse events during the study period	1	2224	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.30, 0.80]

Analysis 1.1. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 1: All-cause mortality at day 28



Footnotes

(1) Time point (28 days), participants (WHO 2 to 3, unvaccinated, high risk); intervention (nirmatrelvir/ritonavir); comparator (placebo)

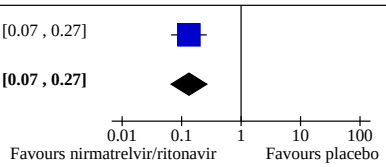
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 2: Worsening of clinical status at day 28: admission to hospital or death

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
EPIC-HR 2021 (1)	9	1109	68	1115	100.0%	0.13 [0.07 , 0.27]	+	?	+	+	+	?
Total (95% CI)		**1109**		**1115**	**100.0%**	**0.13 [0.07 , 0.27]**						
Total events:	9		68									

Heterogeneity: Not applicable
Test for overall effect: Z = 5.73 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

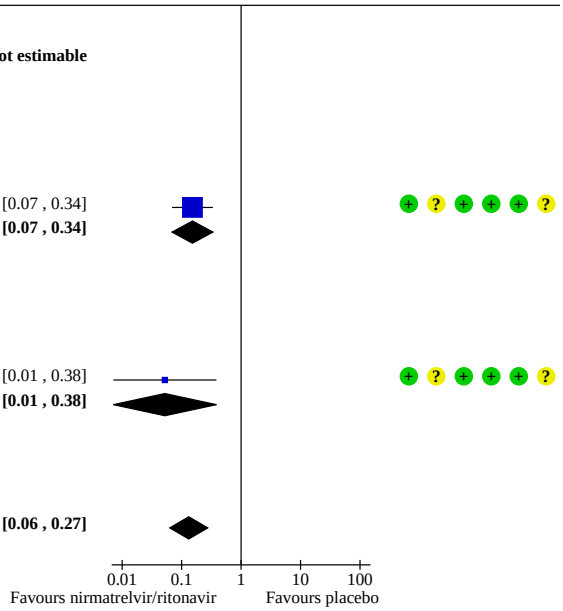
(1) COVID-19-related hospitalisation or death from any cause; time point (28 days), participants (WHO 2 to 3); intervention (nirmatrelvir/ritonavir); comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 3: Worsening of clinical status at day 28: admission to hospital or death (subgroup analysis based on age)

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Children						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.2 Aged < 65 years						
EPIC-HR 2021 (1)	7	908	46	909	86.4%	0.15 [0.07 , 0.34]
Subtotal (95% CI)		**908**		**909**	**86.4%**	**0.15 [0.07 , 0.34]**
Total events:	7		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.67 (P < 0.00001)						
1.3.3 Age ≥ 65 years						
EPIC-HR 2021 (1)	1	131	20	137	13.6%	0.05 [0.01 , 0.38]
Subtotal (95% CI)		**131**		**137**	**13.6%**	**0.05 [0.01 , 0.38]**
Total events:	1		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)		**1039**		**1046**	**100.0%**	**0.13 [0.06 , 0.27]**
Total events:	8		66			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 5.41 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%						



Footnotes

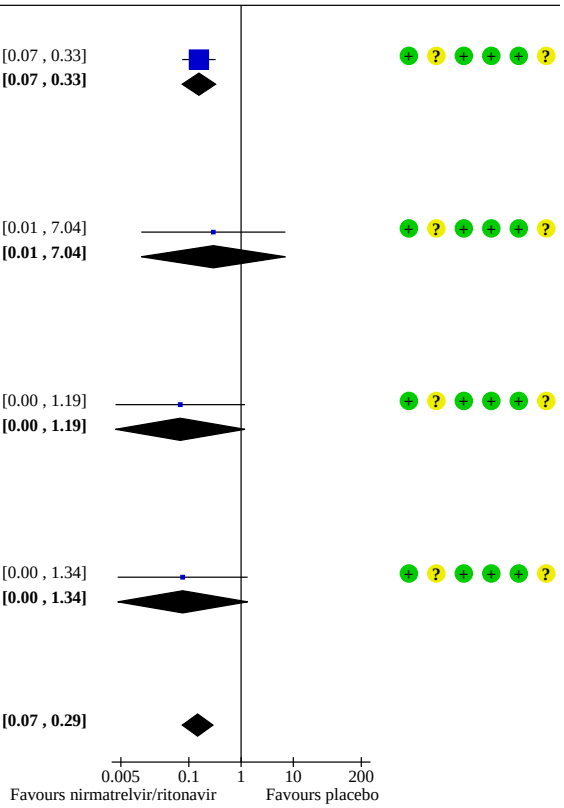
(1) COVID-19-related hospitalisation or death from any cause; time point (28 days), participants (WHO 2 to 3); nirmatrelvir/ritonavir vs placebo

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 4: Worsening of clinical status at day 28: admission to hospital or death (subgroup analysis based on ethnicity)

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 White						
EPIC-HR 2021 (1)	8	738	52	748	84.2%	0.16 [0.07 , 0.33]
Subtotal (95% CI)		**738**		**748**	**84.2%**	**0.16 [0.07 , 0.33]**
Total events:	8		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.94 (P < 0.00001)						
1.4.2 Black/African American						
EPIC-HR 2021 (1)	0	50	1	44	4.5%	0.29 [0.01 , 7.04]
Subtotal (95% CI)		**50**		**44**	**4.5%**	**0.29 [0.01 , 7.04]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
1.4.3 Asian						
EPIC-HR 2021 (1)	0	146	7	150	5.6%	0.07 [0.00 , 1.19]
Subtotal (95% CI)		**146**		**150**	**5.6%**	**0.07 [0.00 , 1.19]**
Total events:	0		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
1.4.4 Other						
EPIC-HR 2021 (1)	0	105	6	104	5.6%	0.08 [0.00 , 1.34]
Subtotal (95% CI)		**105**		**104**	**5.6%**	**0.08 [0.00 , 1.34]**
Total events:	0		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
Total (95% CI)		**1039**		**1046**	**100.0%**	**0.15 [0.07 , 0.29]**
Total events:	8		66			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 5.55 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.69, df = 3 (P = 0.88), I² = 0%						



Footnotes

(1) COVID-19-related hospitalisation or death from any cause; time point (28 days), participants (WHO 2 to 3); nirmatrelvir/ritonavir vs placebo

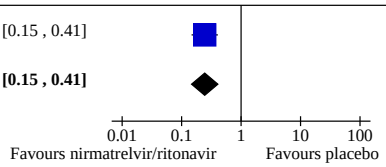
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 5: Serious adverse events during the study period

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
EPIC-HR 2021 (1)	18	1109	74	1115	100.0%	0.24 [0.15 , 0.41]
Total (95% CI)		**1109**		**1115**	**100.0%**	**0.24 [0.15 , 0.41]**
Total events:	18		74			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.43 (P < 0.00001)
Test for subgroup differences: Not applicable



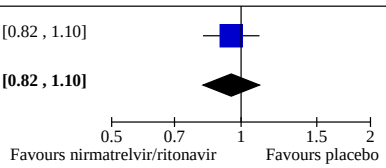
Footnotes
(1) Time point (34 days), participants (WHO 2 to 3); nirmatrelvir/ritonavir vs placebo

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 6: Any grade treatment-emergent adverse events during the study period

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
EPIC-HR 2021 (1)	251	1109	266	1115	100.0%	0.95 [0.82 , 1.10]
Total (95% CI)		**1109**		**1115**	**100.0%**	**0.95 [0.82 , 1.10]**
Total events:	251		266			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)
Test for subgroup differences: Not applicable



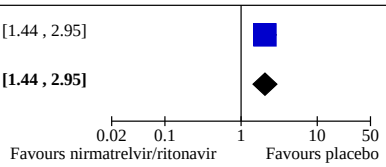
Footnotes
(1) Time point (34 days), participants (WHO 2 to 3); nirmatrelvir/ritonavir vs placebo

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 7: Any grade treatment-related adverse events during the study period

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
EPIC-HR 2021 (1)	86	1109	42	1115	100.0%	2.06 [1.44 , 2.95]	+ ? + + ? ?
Total (95% CI)		**1109**		**1115**	**100.0%**	**2.06 [1.44 , 2.95]**	
Total events:	86		42				

Heterogeneity: Not applicable
Test for overall effect: Z = 3.94 (P < 0.0001)
Test for subgroup differences: Not applicable



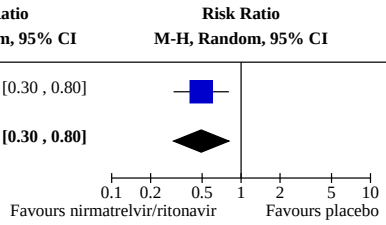
Footnotes
(1) Time point (34 days), participants (WHO 2 to 3); nirmatrelvir/ritonavir vs placebo

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Nirmatrelvir/ritonavir for treating people with asymptomatic or mild COVID-19 in outpatient settings, Outcome 8: Discontinuation of study drug due to adverse events during the study period

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
EPIC-HR 2021 (1)	23	1109	47	1115	100.0%	0.49 [0.30 , 0.80]	+ ? + + ? ?
Total (95% CI)		**1109**		**1115**	**100.0%**	**0.49 [0.30 , 0.80]**	
Total events:	23		47				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.83 (P = 0.005)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (34 days), participants (WHO 2 to 3); nirmatrelvir/ritonavir vs placebo

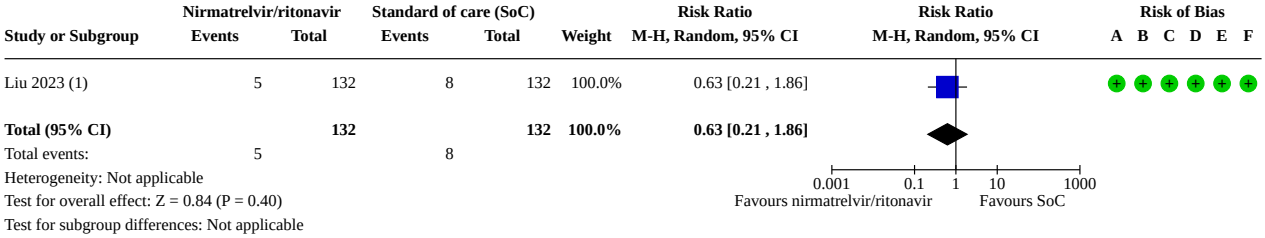
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality at day 28	1	264	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.21, 1.86]
2.2 All-cause mortality at day 28 (subgroup analysis based on age)	1	264	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.20, 1.81]
2.2.1 Aged ≤ 65 years	1	84	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.06, 6.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.2 Aged > 65 years	1	180	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.18, 2.09]
2.3 Viral clearance at day 7	1	264	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.58]
2.4 Viral clearance at day 14	1	264	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.92, 1.20]

Analysis 2.1. Comparison 2: Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings, Outcome 1: All-cause mortality at day 28



Footnotes

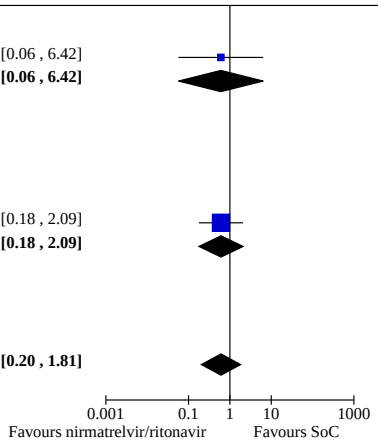
(1) Time point (28 days), participants (WHO 2 to 4, high risk, 25% vaccinated); nirmatrelvir/ritonavir vs SoC

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings, Outcome 2: All-cause mortality at day 28 (subgroup analysis based on age)

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Standard of care (SoC) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Aged ≤ 65 years						
Liu 2023 (1)	1	38	2	46	21.4%	0.61 [0.06 , 6.42]
Subtotal (95% CI)		**38**		**46**	**21.4%**	**0.61 [0.06 , 6.42]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						
2.2.2 Aged > 65 years						
Liu 2023 (1)	4	94	6	86	78.6%	0.61 [0.18 , 2.09]
Subtotal (95% CI)		**94**		**86**	**78.6%**	**0.61 [0.18 , 2.09]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**132**		**132**	**100.0%**	**0.61 [0.20 , 1.81]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



Footnotes

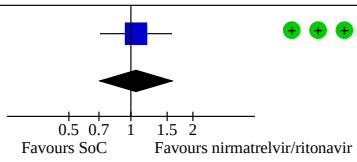
(1) Time point (28 days), participants (WHO 2 to 4, high risk, 25% vaccinated); nirmatrelvir/ritonavir vs SoC

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings, Outcome 3: Viral clearance at day 7

Study or Subgroup	Nirmatrelvir/ritonavir Events	Total	Standard of care (SoC) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Liu 2023 (1)	36	132	34	132	100.0%	1.06 [0.71 , 1.58]
Total (95% CI)		**132**		**132**	**100.0%**	**1.06 [0.71 , 1.58]**
Total events:	36		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Not applicable						



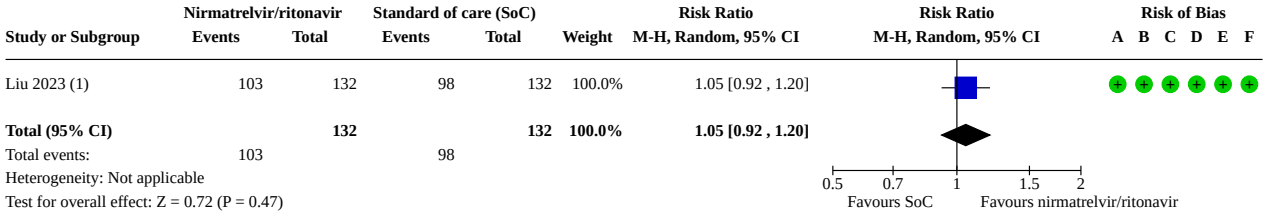
Footnotes

(1) Time point (7 days), participants (WHO 2 to 4, high risk, 25% vaccinated); nirmatrelvir/ritonavir vs SoC

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Nirmatrelvir/ritonavir for treating people with moderate to severe COVID-19 in inpatient settings, Outcome 4: Viral clearance at day 14



Footnotes

(1) Time point (14 days), participants (WHO 2 to 4, high risk, 25% vaccinated); nirmatrelvir/ritonavir vs SoC

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Equity assessment – outpatients

Outcome	Study	Age, n (%)	Comorbidities, n (%)	Race/ethnicity, n (%)	World Bank country classification by income level, n (%)
All-cause mortality at 28 days	EPIC-HR 2021	NR	NR	NR	NR
Worsening of clinical status: admission to hospital or death at 28 days	EPIC-HR 2021	Children: NR Adults < 65 years: 1817 (87%)[a] Adults ≥ 65 years: 268 (13%)[a]	NR	Asian: 296 (14%)[a] Black: 94 (4.5%)[a] Hispanics: NR White: 1486 (71.3%)[a] Minorities: NR Other: 209 (10%)[a]	NR
Serious adverse events during the study period	EPIC-HR 2021	NR	NR	NR	NR
Any grade treatment-emergent adverse events during the study period	EPIC-HR 2021	NR	NR	NR	NR
Any grade treatment-related adverse events during the study period	EPIC-HR 2021	NR	NR	NR	NR

Table 1. Equity assessment – outpatients *(Continued)*

Discontinuation of study drug due to adverse events during the study period	EPIC-HR 2021	NR	NR	NR	NR

[a]Modified intention to treat (mITT1), 2085 participants.
n: number of participants; NR: not reported.

Table 2. Equity assessment – inpatients

Outcome	Study	Age, n (%)	Comorbidities, n (%)	Race/ethnicity, n (%)	World Bank country classification by income level, n (%)
All-cause mortality at 28 days	Liu 2023	Children: NR Adult ≤ 65 years: 84 (32%) Adult > 65 years: 180 (68%)	< 2: 101 (38%) ≥ 2: 163 (62%)	NR	NR
Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at 7 days	Liu 2023	NR	NR	NR	NR
Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at 14 days	Liu 2023	NR	NR	NR	NR
Serious adverse events during the treatment period	Liu 2023	NR	NR	NR	NR
Any grade treatment-emergent adverse events during the treatment period	Liu 2023	NR	NR	NR	NR
Any grade treatment-related adverse events during the treatment period	Liu 2023	NR	NR	NR	NR
Discontinuation of study drug due to adverse events during the treatment period	Liu 2023	NR	NR	NR	NR

n: number of participants; NR: not reported; RT-PCR: reverse transcription polymerase chain reaction.

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register (CCSR)
Search string**:** "PF-07321332" OR "PF 07321332" OR "PF07321332" or paxlovid* or nirmatrelvir*

Study characteristics:
1) "Intervention assignment": “Randomised” OR
2) "Study design": "Parallel/Crossover" OR "Unclear" OR
3) "Study type": "Adaptive/Platform"

Scopus
TITLE-ABS-KEY (("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*) AND (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII"))

WHO COVID-19 Global literature on coronavirus disease
Title, abstract, subject: (("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*) AND (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII"))

Appendix 2. Critical and important criteria for the Research Integrity Assessment of RCTs investigating nirmatrelvir/ritonavir

Domain		Signalling questions to critical and important criteria	Assessment	Decision
1	**Retraction or expression of concern**	Is the study retracted?	Check for postpublication amendments in the systematic search for studies and on the Retraction Watch Database (retractiondatabase.org/RetractionSearch.aspx?)	If study is retracted, **exclude** the study
		Is there an expression of concerns published elsewhere?	Check for expressed concerns on the journal's homepage or preprint server	If expression of concerns are published, 1. send a request to the authors or the journal editors or wait until resolution of the concerns and 2. hold the study in **awaiting classification** until clarification
2	**Trial registration**	Does the study report a trial registry number?	Check in the publication or study report	If study is not prospectively registered, **exclude** the study
		Is the study prospectively registered?	Check in the trials register the date of protocol submission and first posted. Prospective registration is defined as registration of a trial before enrollment of the first participant as defined by the WHO. It must be determined whether the registers registered (date first posted) without delay at this point in the pandemic. In case of doubt, check for the date first submitted or the authors must be asked for the submission date.	
		Are there any inconsistencies in details such as dates and study methods reported in the publication and in the registration documents?	Compare study dates (enrollment, duration, completion) and methods (study type, allocation, blinding) between publication and protocol.	If date of registration is unclear or if prospectively registered, but with inconclusive information, 1. send a request to the

(Continued)

				authors and 2. hold the study in **awaiting classification** until clarification
3	**Ethics approval**	Is an ethics approval reported in the publication?	e.g. the study was authorized by the ethics committee XY located in XY.	If ethics approval or participants' consent is not adequate, **exclude** the study. If ethics approval or participants' consent is unclear or incomplete, 1. send a request to the authors and 2. hold the study in **awaiting classification** until clarification.
		Is an ethics approval number reported?	Check in the publication, study report and study protocol	
		Is the name and location of the ethics committee reported?	Check in the publication, study report and study protocol	
		Does a nationally recognized ethics committee as defined in the country's clinical trial regulations give the ethics committee approval?	Check the ethics committee on the World Health Organization list of national ethics committees (apps.who.int/ethics/national-committees/) and the specific regulations for the country on NIH Clinical Trials Regulation website (clinregs.niaid.nih.gov/country/mexico#_top).	
		Does the study require written informed consent from participants?	Check in the publication, study report and study protocol	
4	**Study authorship**	Are the authors' affiliations and countries the study is reported to have taken place in consistent?	Check in the publication, study report, and study protocol	If study authorship is unclear, 1. send a request to the authors and 2. hold the study in **awaiting classification** until clarification. If study authorship is still not plausible after contacting the authors,**exclude** the study.
		Are countries specified in different parts of the article or as compared to the trials registry consistent?	Check in the publication, study report, and study protocol	
		Is the number of authors plausible for the study design (e.g. a single author article reporting a randomized controlled trial is impossible)?	Check in the publication, study report, and study protocol	
5	**Methods reporting**	Is the study design (e.g. randomization) reported in sufficient detail?	It has to be clear that the study was truthfully randomized. The method used for the randomization must be described and the process must lead to a random allocation of the participants. The sole designation "randomized study" is not sufficient.	If study design is not reported in sufficient detail, 1. send a request to the authors and 2. hold the study in **awaiting classification** until clarification. If study turns out to be non-randomized following author contact, **exclude** the study.

(Continued)

		Are baseline details reported in sufficient detail to assess whether randomization worked properly?	Check whether patient's characteristics, e.g. risk factors for COVID-19 (age, gender, comorbidities) and co-interventions, are reported	
6	**Results**	Is the number of participants recruited within the time frame with the condition plausible?	Check in the publication. Justify the decision based on clinical experience. The decision should be verifiable.	If study results are not plausible, 1. send a request to the authors and 2. hold the study in **awaiting classification** until clarification. If, after contacting the author, it turns out that study results are not plausible or fabricated,**exclude** the study.
		Is there a realistic response rate or number of participants lost to follow-up? In cases with 0 losses to follow-up, is there a plausible explanation (e.g. small number of participants, short-term follow-up)?		
		Is the study free from results that could be implausible (e.g. massive risk reduction, unexpected outlier data, unusual frequency of an outcome)?		
		Does the number of participants (e.g. women) in each group coincide with the reported randomization method (e.g. block randomization)?	Check in the publication, study report and study protocol	
		Is there no noteworthy overlap in text/data with other published articles by the same or different authors without explanation?		
		Is there no excessive similarity or difference in the characteristics of the study participants between groups?		
		Are there no discrepancies between data reported in figures, tables, and text?		
		Are there no calculation errors (e.g. number of participants, percentages, proportions)?		

Potentially eligible randomized controlled trials (RCTs) identified during screening were assessed for research integrity hierarchically considering domain 1 to 6. Retraction, lack of prospective registration, lack of adequate ethical approval with informed written consent, implausible study authorship, lack of truthful randomization, implausible study results were triggers that led to exclusion of an RCT. Concerns in any domain put the study in 'awaiting classification' and led to further investigations. If no concerns appeared through all domains or could be clarified, e.g. in correspondence with study authors, the RCT met the criteria for inclusion in the review and was processed further. For the next review update, included RCTs and RCTs 'awaiting classification' must be reassessed for retraction notices.

WHAT'S NEW

Date	Event	Description
30 November 2023	New citation required and conclusions have changed	New evidence for the efficacy of nirmatrelvir/ritonavir in inpatients has been added. The review authors' confidence in the evidence is still very low in the inpatient setting and low to moderate in outpatient settings.
30 November 2023	New search has been performed	The date of search was updated to 15 May 2023.

HISTORY

Protocol first published: Issue 4, 2022
Review first published: Issue 9, 2022

CONTRIBUTIONS OF AUTHORS

SR: conception and design of the review; search and selection of studies for inclusion; collection of data; assessment of research integrity and risk of bias in included studies; analysis of data; assessment of the certainty of the evidence; interpretation of data, and writing of the review.

MIM: search strategy design, conduct of living search and writing of the review.

RK: conception and design of the review; search and selection of studies for inclusion; interpretation of data; writing the review.

MP: conception and design of the review; interpretation of data; proofreading of the review.

IG: conception and design of the review; interpretation of data; proofreading of the review.

PK: conception and design of the review; interpretation of data; proofreading of the review.

PM: conception and design of the review; interpretation of data; proofreading of the review.

NS: conception and design of the review; interpretation of data; proofreading of the review.

SW: conception and design of the review; co-ordination of the review; search and selection of studies for inclusion; collection of data; assessment of research integrity and risk of bias in included studies; analysis of data; assessment of the certainty of the evidence; interpretation of data, and writing of the review.

DECLARATIONS OF INTEREST

SR: none.

MIM: none.

RK: is a CIDG editorial team member, but was not involved in the editorial processing of this review. She has no known conflicts of interest to declare.

MP: none.

IG: none.

PK: none.

PM: none.

NS: none.

SW: none.

SOURCES OF SUPPORT

Internal sources

- Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Würzburg, Germany

Departmental funding

- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth, and Development Office (FCDO), UK

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Following the rational from Pfizer that nirmatrelvir/ritonavir is developed to manage outpatients with COVID-19, an outcome set for inpatients was not included in the protocol avoiding the impression that studies for this population are needed. However, we do not know whether nirmatrelvir/ritonavir might be a valuable antiviral option for people with COVID-19 at high risk who are hospitalized early after infection. Therefore, we have planned if we identify inpatient studies we include them and use the outcome set for hospitalized people with COVID-19 published elsewhere (Popp 2021). On 28 March 2022, the RECOVERY trial announced that Paxlovid (nirmatrelvir plus ritonavir) was to be investigated as a potential treatment for people hospitalized with COVID-19. We added the outcome set for hospitalized people with COVID-19 to the review.
- We have changed the definition of our active comparator. In the protocol, we planned to compare nirmatrelvir/ritonavir to active comparisons with proven efficacy only. We decided to extend our definition of an eligible active comparator to any active comparator, including new interventions that would be investigated in future trials that may use nirmatrelvir/ritonavir as comparator.

Differences between original review publication and first update

- We also included traditional Chinese medicine (TCM) as an active comparator since we identified several ongoing trials. TCM is widely used in China and other countries to treat COVID-19 and living guidelines integrating Chinese and western medicine for COVID-19 are already available (Ge 2021). However, new studies using TCM as a comparator are not considered as a trigger to update the living systematic review.

INDEX TERMS

Medical Subject Headings (MeSH)

*COVID-19 Drug Treatment; Cytochrome P-450 CYP3A; Cytochrome P-450 CYP3A Inducers; Ritonavir [therapeutic use]; SARS-CoV-2

MeSH check words

Aged; Humans