South African National Essential Medicine List
Evidence Review
Component: COVID-19

MEDICINE REVIEW

1. Executive Summary

Date: 30 March 2023
Medicine (INN): Nirmatrelvir plus Ritonavir
Medicine (ATC): J05AE30
Indication (ICD10 code): U07. 1
Patient population: COVID-19 virus infection
Prevalence of condition: 760 360 956 confirmed cases globally[1] (https://www.who.int/emergencies/diseases/novel-coronavirus-2019?adgroupsurvey={adgroupsurvey}&gclid=CjwKCAjwq-WgBhBMEiwAzKSH6AKs7eEiiFrusdB0HttZA2AcophGaFWUqkZuqpnrzs62kFwxH4V9YxoCpasQAvD_BwE). 4,055,656 positive cases identified in South Africa to date (21 March 2023)[2] (https://sacoronavirus.co.za/)
Level of Care: Primary Health Care & Hospital Level of care (adults and paediatric)
Prescriber Level: Medical Practitioner
Motivator/reviewer name(s): National Essential Medicines List Committee
PTC affiliation: n/a

Key findings

- *We conducted a review of clinical studies that assessed the effect of nirmatrelvir-ritonavir in patients with COVID-19 (no restriction to age, sex, disease severity, setting or vaccination status).*
- *We identified two systematic reviews that compared nirmatrelvir-ritonavir with placebo or standard of care. One systematic review included one randomised controlled trial (RCT) in high-risk unvaccinated patients only. The other included two RCTs in unvaccinated patients and 10 observational studies in a variety of patient populations. This review summarises the two systematic reviews. A further six observational studies (not included in either systematic review) were identified but are awaiting appraisal.*
- *Nirmatrelvir-ritonavir may reduce mortality compared to standard of care in high-risk unvaccinated patients (RR 0.04; 95% CI 0.00 to 0.68; n=2246, 1 RCT, low certainty evidence) with an absolute risk reduction (ARR) of 1.07% (95% CI 0.47 to 1.67%). The risk reduction was not statistically significant in a study that included both standard-risk unvaccinated patients and high-risk unvaccinated patients (RR 0.33; 95% CI 0.01 to 8.08; n=1075, 1 RCT). Mortality risk was also reduced in observational studies that included patients of various disease severities and vaccination statuses (RR 0.24; 95% CI 0.15 to 0.39; n=238 625; 7 retrospective cohorts). (Certainty of evidence not assessed.)*
- *Nirmatrelvir-ritonavir may reduce progression to hospitalisation compared to standard of care in high-risk unvaccinated patients (RR 0.12; 95% CI 0.06 to 0.25; n=2246, 1 RCT, high certainty evidence) with an ARR of 5.15% (95% CI 3.69 to 6.61%). The risk reduction was not statistically significant in standard risk unvaccinated patients and high-risk unvaccinated patients (RR 0.50;*

95% CI 0.17 to 1.46; n=1075, 1 RCT). Risk of hospitalisation was also reduced in observational studies that included patients of various disease severities and vaccination statuses (RR 0.46; 95% CI 0.32–0.66; n=363 945; 7 retrospective cohorts). (Certainty of evidence not assessed.)

- *Nirmatrelvir-ritonavir may result in little to no difference in serious adverse events compared to standard of care (RR 0.81; 95% CI: 0.34–1.94; n= 3686, 2 RCTs; moderate certainty evidence).*

NATIONAL ESSENTIAL MEDICINE LIST COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative. **(strong)**	We suggest not to use the option. **(conditional)**	We suggest using either the option or the alternative. **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The Committee suggests that nirmatrelvir-ritonavir not be used for the treatment of COVID-19.

Rationale: Although RCTs and systematic reviews of observational trials of patients at high-risk of progression to severe COVID-19 (both vaccinated and unvaccinated) indicate that nirmatrelvir - ritonavir may reduce mortality and hospitalisation, strong evidence of efficacy in immunised and previously infected populations is not yet available. In addition, information regarding local cost and availability is lacking. Generic products will only be accessible in the public sector, once registered.

Level of Evidence: Low to moderate certainty evidence

Review indicator: New high-quality evidence of a clinically relevant benefit (Systematic reviews of randomised controlled trials or observational studies). Declared price of product and availability of either branded or generic versions.

2. Name of author(s)/motivator(s)

Gary Reubenson, Jeremy Nel, Renee de Waal, Tamara Kredo, Milli Reddy, Natasha Gloeck.

Acknowledgement:
Andy Gray (UKZN) provided input on the background to the review, regulatory input, and considerations for the EtD, Mashudu Mthethwa (South African Medical Research Council) conducted the literature search and Joy Oliver (Cochrane South Africa, South African Medical Research Council) reviewed the literature search.

3. Author affiliation and conflict of interest details

GR (Department of Paediatrics & Child Health, University of the Witwatersrand); JN (Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand); RW (Centre for Infectious Disease Epidemiology and Research, University of Cape Town) and MR (Right to Care) have no interests pertaining to nirmatrelvir-ritonavir. TK (Health Systems Research Unit, South African Medical Research Council (SAMRC); Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; NG (Cochrane South Africa and Health Systems Research Unit, South African Medical Research Council); TK is co-director of the South African GRADE Network and TK and NG are partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-

104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.

4. Introduction/ Background

In December 2021, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for a co-packaged product containing nirmatrelvir and ritonavir tablets for the treatment of mild-to-moderate coronavirus disease (COVID-19). The EUA allowed use of nirmatrelvir-ritonavir in patients 12 years of age and older, weighing ≥40 kilograms, with laboratory-confirmed SARS-CoV-2 infection, at high risk for progression to severe disease, specifically hospitalisation or death.[3] On 16March 2023, the FDA's Antimicrobial Drugs Advisory Committee considered the clinical evidence of safety and efficacy for nirmatrelvir-ritonavir and recommended full registration.[4] The European Medicines Agency (EMA) currently recommends nirmatrelvir-ritonavir for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.[5]

Nirmatrelvir works by inhibiting M^{pro}, a viral enzyme critical to SARS-CoV-2 replication. Ritonavir increases the concentration of nirmatrelvir by slowing its metabolism through the cytochrome P450 pathway.[6]

In March 2022, the National Essential Medicines List (NEML) Ministerial Advisory Committee (MAC) on COVID-19 Therapeutics reviewed the evidence for the use of nirmatrelvir-ritonavir. At the time the committee made a conditional recommendation against the use of nirmatrelvir-ritonavir for the treatment of COVID-19. The rationale for the decision was although at the time there was evidence from a single randomised controlled trial that nirmatrelvir-ritonavir reduced the risk of hospitalisation and death in adults with mild to moderate COVID-19 who are at high-risk for progression to severe COVID-19, and is well tolerated, its use required rapid access to definitive diagnosis and initiation within 5 days of the onset of symptoms. Furthermore, nirmatrelvir-ritonavir was contraindicated in pregnancy, requiring women of childbearing potential to take effective contraception. Ritonavir, which increases the concentration of nirmatrelvir by slowing its metabolism through the cytochrome P450 pathway, could result in potential drug-drug interactions. Additionally, at the time, the efficacy and safety of nirmatrelvir-ritonavir had not been studied in patients previously vaccinated against COVID-19 and products containing nirmatrelvir and ritonavir (as co-packaged, separate oral solid dosage forms) were not yet registered in South Africa.

In April 2022, the WHO recommended treatment (strong recommendation) with nirmatrelvir-ritonavir for patients with non-severe COVID-19 at highest risk of hospitalisation. Nirmatrelvir-ritonavir should be administered as soon as possible after the onset of symptoms, ideally within 5 days. The WHO indicates that "clinicians should not consider nirmatrelvir-ritonavir in patients with possible dangerous drug interactions and that fully informed shared decision-making should determine whether nirmatrelvir-ritonavir should be used in pregnant or breast-feeding women, given possible benefit and residual uncertainty regarding potential undesirable effects".[7]

On 24 January 2023 the South African Health Products Regulatory Authority (SAHPRA) registered nirmatrelvir-ritonavir (Trade Name: Paxlovid), manufactured by Pfizer, to treat COVID-19.[8] According to the professional information (PI) "nirmatrelvir-ritonavir is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19".[9] The package insert (PI) indicates that there are no data on the use of nirmatrelvir-ritonavir in pregnant women and that it is not recommended during pregnancy and in women of childbearing potential not using effective contraception. It is further noted that the use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Similarly Australian[10] and US[11] labelling recognises the risk of COVID-19 in pregnancy but is also clear about the lack of evidence of safety in pregnancy for nirmatrelvir-ritonavir.

Given that the originator product is now registered with SAHPRA, that WHO has issued a strong recommendation for its use in patients with non-severe COVID-19 at highest risk of hospitalisation, and that new randomised controlled trial (RCT) and observational data on use in vaccinated patients are available, the NEMLC requested an update on the March 2022 nirmatrelvir-ritonavir evidence review.

PICO question

Patient/Population: Patients with confirmed SARS-CoV-2 infection. No restriction to age or co-morbidity.
Sub-populations of interest: pregnant women, breast feeding woman, early initiation of treatment (within 5 days of symptom onset), late initiation of treatment (after 5 days of symptom onset), COVID-19 vaccinated and unvaccinated, children and elderly (over 65 years).

Intervention: Nirmatrelvir-ritonavir, either alone or in combination with other medicines.

Comparator: Standard of care or placebo.

Outcomes: Mortality; progression to hospitalisation; duration of hospitalisation; progression to requiring oxygen; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement; adverse reactions and adverse events.

Study design: We searched for systematic reviews of RCTs, systematic reviews of observational trials, RCTs and prospective observational studies (non-randomised studies (NRS)) published since February 2022 (the date of publication of the RCT reviewed in the first nirmatrelvir-ritonavir review).

5. Methods:

We developed a protocol prior to the initiation of the review.

i. **Data sources:** Cochrane COVID-19 Study Register; PubMed.

ii. **Search strategy:** A search strategy was developed for PubMed and adapted for the Cochrane COVID-19 Study Register (Appendix 1). The search was inclusive of all populations and there were no restrictions on language. We reached out to the WHO for any new studies but did not receive any response. We also searched the COVID-19 living data website (https://covid-nma.com/). We included systematic reviews of randomised controlled trials; systematic reviews of observational studies, RCTs and individual prospective observational studies. The search was conducted from the date of the trial included in the original review (February 2022) to 15 March 2023. A PRISMA diagram is provided in Appendix 2

iii. **Screening, data extraction and analysis, evidence synthesis:** Records were uploaded into the reference management software, Covidence. Titles and abstracts were screened independently and in duplicate (NG, MR, RdW). A third reviewer (JN) helped to resolve disagreements. Two reviewers (NG, MR) screened the full text of included studies, while a third reviewer (TK) served as a tie breaker in the event of conflicts. Data were extracted by one reviewer (MR) and checked by a second reviewer (NG). We planned to appraise observational studies in duplicate (NG & MR) using the ROBINS-I tool. We appraised systematic reviews using the AMSTAR II tool. Data were abstracted into a characteristic of included studies table (Table 1). Where available, we

reported on the GRADE (level of certainty) of the evidence. GRADE[12] is a system used to assess the overall confidence of the evidence considering various factors that may decrease confidence in the trial findings, including risk of bias, inconsistency, imprecision, publication bias and indirectness.

iv. **Excluded studies:** Reasons for excluding full texts were agreed in duplicate (NG & MR) with a third reviewer (TK) finalising any disputes (Appendix 3).

6. Results

i. Search results: We searched PubMed and the Cochrane COVID-19 Register on 15 March 2023. We identified 542 records which were imported for screening, with 14 duplicates removed. We screened 528 abstracts, of which 462 were irrelevant. Sixty-six full-text studies were assessed for eligibility; 49 studies were excluded. There were 15 included studies: five systematic reviews, two RCTs, six observational studies and two ongoing studies (see Appendix 4). Further, two studies were classified as "awaiting classification" due to unavailable full texts.

The systematic reviews included the already published randomised controlled trials and some of the observational studies. For this rapid review update, we appraised and summarised the systematic reviews, but did not appraise and summarise individual observational studies that were not included in either of the reviews. A list of observational studies identified for inclusion but not yet fully appraised is provided in Appendix 5. Appendix 5 excludes the prospective observational studies included in the systematic review (SR) (Cheema 2023[13]) summarised in this review.

ii. Description of included systematic reviews: Table 1 reports the characteristics of the included systematic reviews. We identified five systematic reviews for inclusion. However, three of these (Amani 2023, Budi 2022 and Pitre 2022) were not included due to poor methodological quality (Amani 2023), a review of the same data as the Cochrane review (Budi 2022) and being a network meta-analysis (Pitre 2022). The two systematic reviews that were included were:

- Cheema 2023[13]. Nirmatrelvir-ritonavir for the treatment of COVID-19.
- Reis 2022[14]. Nirmatrelvir combined with ritonavir for preventing and treating COVID-19.

Cheema 2023[13] reviewed evidence of the efficacy and safety of nirmatrelvir-ritonavir for the treatment of COVID-19. The setting was generally not specified, and both randomised controlled trials (RCTs) and non-randomised studies (NRS) were included. The two RCTs included were the EPIC-HR (in high-risk unvaccinated adults) and EPIC-SR (in standard risk unvaccinated adults and high risk vaccinated adults) studies. The latter is currently unpublished, but interim results are available via FDA briefing documents and other sources. The NRS included both retrospective and prospective cohort studies, and generally included both vaccinated and unvaccinated individuals. The majority of the NRS were performed in patients with risk factors for severe disease. Primary outcome measures were the risk of all-cause mortality and hospitalisation. Secondary outcomes included the proportion of patients not achieving virological clearance (positive viral PCR test) at the end of study follow-up, adverse events (AEs) and serious adverse events (SAEs). Outcome results are summarised in Table 1. Cheema 2023 had a critically low AMSTAR II rating due to no explanation of choice of study design for the review, no list of excluded studies with justifications, no reporting on source of funding of included studies, statistical inconsistencies, and inadequate explanation of heterogeneity. Authors for Cheema 2023[13] GRADEd NRS together with RCTs – due to this methodological inconsistency, the GRADE certainty of evidence reported for combined NRS and RCTs was not included in this report.

Reis 2022[14], a living Cochrane systematic review with monthly search updates, reviewed the efficacy and safety of nirmatrelvir-ritonavir plus standard of care to any other intervention for treating and preventing COVID-19. The setting was not specified, and only RCTs were included. Only one trial (Hammond 2022[15] (EPIC-HR 2021) was included. In terms of treating COVID-19, primary outcomes included 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; improvement of clinical status; quality of life assessed with standard scales at up to seven days, up to 28 days, and up to longest follow up; serious adverse events; adverse events; and viral clearance. There were no secondary outcomes. Reis 2022[14] had a moderate AMSTAR II rating.

iii. Description of excluded studies We excluded 46 full texts with reasons (Appendix 3). Three of the five SRs included initially during full text review were not reported in this review and were later excluded: Budi et al included only one RCT, Hammond 2022[15](EPIC-HR 2021), which was also summarised in the Cochrane review included in this update (Reis 2022[14]). Amani 2023 contained serious methodological flaws and was excluded during quality assessment. Pitre 2022[16] is a frequentist network meta-analysis and was not included.

7. Effectiveness of the intervention

i. Mortality

- Cheema 2023: Nirmatrelvir-ritonavir may reduce mortality compared standard of care.
    - RCTs: RR 0.10; 95% CI 0.01 to 0.84; I^2 = 0%; n= 3321; 2 trials; certainty of evidence for RCTS only was not reported.
        - EPIC-SR: RR 0.33; 95% CI 0.01 to 8.08; n=1075
        - Hammond 2022 (EPIC-HR): RR 0.04; 95% CI 0.00 to 0.68; n=2224
    - NRS: RR 0.24; 95% CI 0.15 to 0.39; I^2 = 54%; n=238 625; 7 retrospective cohorts; certainty of evidence for NRS only was not reported.
- Reis 2022: All-cause mortality at day 28. unvaccinated high-risk outpatients with asymptomatic or mild disease: nirmatrelvir-ritonavir may reduce all-cause mortality. RR 0.04; 95% CI 0.00 to 0.68; n=2224; 1 trial; low certainty evidence (downgraded for serious risk of bias and serious imprecision).
    - Participants <65 years vs over ≥65 years: Admitted to hospital or died.
        - 18 to 65 years: seven participants in the nirmatrelvir-ritonavir group compared to 46 participants in the comparator group were admitted to hospital or died (RR 0.15, 95% CI 0.07 to 0.34; I^2=n/a; n=1817, p<0.00001)
        - ≥65 years or older: one participant in the nirmatrelvir-ritonavir group compared to 20 participants in the comparator group were admitted to hospital or died (RR 0.05, 95% CI 0.01 to 0.38; I^2=n/a; n=268, p=0.004)
        - The test for subgroup differences showed no differences between groups (I^2=0%; p=0.33)
        - In both groups, the risk ratio favoured treatment with nirmatrelvir-ritonavir, but the number of the included participants 65 years or older was low.

ii. Progression to hospitalisation

- Cheema 2023: Nirmatrelvir-ritonavir may reduce progression to hospitalisation compared standard of care.
    - RCTs: RR 0.23; 95% CI 0.06 to 0.94; I^2 =79%; n= 3686; 2 trials; certainty of evidence for RCTS only was not reported.
        - EPIC-SR: RR 0.50; 95% CI 0.17 to 1.46; n=1075
        - Hammond 2022 (EPIC-HR): RR 0.12; 95% CI 0.06 to 0.25; n=2246

- NRS: RR 0.46; 95% CI 0.32–0.66, I^2 = 90%; n=363 945; 7 retrospective cohorts; certainty of evidence for NRS only was not reported.
- Subgroup analyses (RCTs): the analysis combined both NRS and RCTs in one forest plot. Reported in this review are the induvial results for the RCTs.
    - Age ≥ 65 years: Hammond 2022 (EPIC-HR): RR 0.05; 95% CI 0.01 to 0.38; 1 trial; n=not provided
    - Age < 65 years: Hammond 2022 (EPIC-HR): RR 0.15; 95% CI 0.07 to 0.34; 1 trial; n=not provided
    - Previous immunity to SARS-CoV-2: EPIC-SR: RR 0.43; 95% CI 0.11 to 1.64; 1 trial; n=not provided
    - No Previous immunity to SARS-CoV-2:
        - Hammond 2022 (EPIC-HR): RR 0.12; 95% CI 0.06 to 0.25; 1 trial; n=not provided
        - EPIC-SR: RR 0.65; 95% CI 0.11 to 3.84; 1 trial; n=not provided
- Of note, overall (RCTs and NRS) reduction in risk of hospitalisation was more pronounced in those without previous immunity to SARS-CoV-2 (RR 0.27; 95% CI 0.10-0.73, I^2 85%) than in those with previous immunity (RR 0.48; 95% CI 0.29-0.80, I^2 = 83%). In all but 1 study, previous immunity was defined as vaccination, whereas in the remaining 1 cohort study, previous immunity included both vaccinated individuals and those with past infection.

- Reis 2022: Worsening of clinical status assessed as admission to hospital or death within 28 days: Nirmatrelvir-ritonavir plus standard of care may reduce admission to hospital or death within 28 days vs standard of care plus placebo.
    - At day 28, nine participants in the nirmatrelvir-ritonavir vs. 68 in the comparator group had been admitted to hospital or had died (RR 0.13; 95% CI 0.07 to 0.27; 1 study, n=2224; low certainty evidence (downgraded by one level for serious risk of bias due to inappropriate analysis and one level for serious indirectness as the study only assessed COVID-19)).

iii. Duration of hospitalisation

- Cheema 2023: Not reported.
- Reis 2022: Not reported.

iv. Progression to requiring oxygen

- Cheema 2023: Not reported.
- Reis 2022: Not reported.

v. Progression to ICU admission

- Cheema 2023: Not reported.
- Reis 2022: Not reported.

vi. Progression to mechanical ventilation

- Cheema 2023: Not reported.
- Reis 2022: Not reported.

vii. Duration of ICU stay

- Cheema 2023: Not reported.
- Reis 2022: Not reported.

viii. Clinical improvement on an ordinal scale at chosen time points

- Cheema 2023: Not reported.
- Reis 2022: Not reported.

ix. Time to clinical improvement

- Cheema 2023: Not reported.
- Reis 2022: Not reported.

x. Adverse events

Any grade treatment-emergent adverse events during the study period

- Cheema 2023: reported this outcome but as the analysis combined both NRS and RCTs in one forest plot, the combined result is not reported. Individual study results are presented for two RCTs and one prospective observational study:
    - RCTs: RR 0.93; 95% CI 0.82 to 1.05; two trials; n= 3159; certainty of evidence for RCTS only was not reported.
        - EPIC-HR: RR 0.90; 95% CI 0.80 to 1.22
        - EPIC-SR: RR 2.38; 95% CI 1.74 to 3.26
    - NRS: 0.95; 95% CI 0.77 to 1.18; one study; n=482; certainty of evidence for NRS only was not reported.

- Reis 2022: Nirmatrelvir-ritonavir plus standard of care probably has little or no effect on treatment-emergent adverse events during the study period compared to standard of care plus placebo.
    - 251 patients in the nirmatrelvir-ritonavir group vs 266 in the placebo comparator group experienced treatment emergent adverse events during the 34 days observation period (RR 0.95; 95% CI 0.82 to 1.10; 1 study, n=2224; moderate certainty evidence (downgraded the certainty of evidence one level for serious risk of bias due to inappropriate analysis)).

xi. Serious adverse events (SAEs)

- Cheema 2023: Nirmatrelvir-ritonavir may result in little to no difference in serious adverse events compared to standard of care.
    - RCTs: RR 0.81; 95% CI: 0.34–1.94; I^2= n/a; n= 3686, 2 trials; moderate certainty evidence
- Reis 2022: Nirmatrelvir-ritonavir plus standard of care may reduce serious adverse events during the study period compared to standard of care plus placebo.
    - 18 patients in the nirmatrelvir-ritonavir vs. 74 in the comparator group experienced serious adverse events during the 34 days observation period (RR 0.24, 95% CI 0.15 to 0.41; 1 trial; n=2224; low-certainty evidence (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 serious adverse events other than hospitalisation or death)).

8. Conclusion

Two systematic reviews suggest that nirmatrelvir-ritonavir may reduce mortality and hospitalisation compared to placebo/standard of care. However, the magnitude of effect is likely to be heterogenous, depending on the population. Whereas the EPIC-HR trial, conducted in high-risk unvaccinated outpatients, demonstrated a clear reduction in mortality and hospitalisation, these benefits were not statistically significant in the EPIC-SR trial, conducted in lower risk individuals. Observational data included in the systematic review by Cheema et al. (which

included vaccinated and unvaccinated individuals, most of whom were at otherwise high-risk of severe disease) are supportive of a reduction in the risk of mortality and hospitalisation. The reduction in hospitalisation was attenuated but still present in patients with prior immunity (mostly via vaccination). There were no data examining the majority of our prespecified subgroups. Where subgroup analyses were available, these had to be interpreted with caution as they were a mix of RCT and observational data. A full review of prospective cohort studies may provide additional insight into the efficacy and safety of nirmatrelvir-ritonavir for patients with COVID-19, including the subgroups of interest listed in our PICO. At this time, although the innovator product is registered in South Africa, there is no declared single exit price. Affordability therefore remains unclear for South Africa, even if used only for “high-risk patients”. Additionally, what would constitute “high-risk” in the local setting remains unclear.

Table 1: Characteristics of included studies (Systematic Review)

Citation	Study design	Population (n)	Treatment	Inclusion Criteria	Main findings	Risk of bias

Cheema HA, Jafar U, Sohail A, Shahid A, Sahra S, Ehsan M, Athar F, Shah J, Sah R. Nirmatrelvir-ritonavir for the treatment of COVID-19 patients: A systematic review and meta-analysis. J Med Virol. 2023 Feb;95(2):e28471. doi: 10.1002/jmv.28471. PMID: 36606609.	SR & MA
	
	RCTs & Observational Studies
		2 RCTS (n=3686)
		
		&
		
		10 (n=367 584) Observational
			RCTs (n=2)- Nirmatrelvir–rtv - every 12 h for 5 days (10 doses total)
			
			Observational studies:
			-At least one dose of Nirmatrelvir–rtv during study period (n=1)
			- Nirmatrelvir–rtv (n=2)
			- Nirmatrelvir–rtv within 5 days of diagnosis (n=1)
			- Nirmatrelvir–rtv every 12 h for 5 consecutive days (10 doses in total) (n=1)
			- Nirmatrelvir–rtv, Molnupiravir (n=4)
			- Nirmatrelvir–rtv / Molnupiravir (n=1)
				RCTs and comparative observational studies which evaluated nirmatrelvir–ritonavir for the treatment of COVID-19 patients.	**Mortality:** Nirmatrelvir-ritonavir may reduce mortality vs standard of care
					
					- RCTs: RR 0.10; 95% CI 0.01 to 0.84; I2 = 0%; n= 3686; 2 trials; not GRADEd.
					  o EPIC-SR: RR 0.33; 95% CI 0.01 to 8.08; n=1075
					  o Hammond 2022 (EPIC-HR): RR 0.04; 95% CI 0.00 to 0.68; n=2246
					-
					- NRS: RR 0.24; 95% CI 0.15 to 0.39; I2 = 54%; n=238625; 7 retrospective cohorts; not GRADEd
					
					Progression to Hospitalisation: Nirmatrelvir-ritonavir may reduce progression to hospitalisation vs standard of care:
					- RCTS: RR 0.23; 95% CI 0.06 to 0.94; I2 =79%; n= 3686; 2 trials; not GRADEd.
					  o EPIC-SR: RR 0.50; 95% CI 0.17 to 1.46; n=1075
					  o Hammond 2022 (EPIC-HR): RR 0.12; 95% CI 0.06 to 0.25; n=2246
					
					- NRS: RR 0.46; 95% CI 0.32–0.66, I2 = 90%; n=363 945; 7 retrospective cohorts; not GRADEd
					
					- **Subgroup analyses (RCTs):** the analysis combined both NRS and RCTs in one forest plot. Reported in this review are the induvial results for the RCTs
					  o Age ≥ 65 years: Hammond 2022 (EPIC-HR): RR 0.05; 95% CI 0.01 to 0.38; 1 trial; n=not provided
					  o Age < 65 years: Hammond 2022 (EPIC-HR): RR 0.15; 95% CI 0.07 to 0.34; 1 trial; n=not provided
					  o Previous immunity to SARS-CoV-2: EPIC-SR: RR 0.43; 95% CI 0.11 to 1.64; 1 trial; n=not provided
					  o No Previous immunity to SARS-CoV-2:
					  o Hammond 2022 (EPIC-HR): RR 0.12; 95% CI 0.06 to 0.25; 1 trial; n=not provided
						AMSTAR II Rating: Critically low (Appendix 6)
						
						Due to:
						• no explanation of choice of study designs for the review,
						• no list of excluded studies with justifications,
						• no reporting on source of funding of included studies,
						• statistical inconsistencies, and inadequate explanation of heterogeneity.

Citation	Study design	Population (n)	Treatment	Inclusion Criteria	Main findings	Risk of bias
					○ EPIC-SR: RR 0.65; 95% CI 0.11 to 3.84; 1 trial; n=not provided **Duration of hospitalisation:** Not reported **Adverse Events:** - RCTs: RR 0.93; 95% CI 0.82 to 1.05; two trials; n= 3159 ○ EPIC-HR: RR 0.90; 95% CI 0.80 to 1.22 ○ EPIC-SRRCT: RR 2.38; 95% CI 1.74 to 3.26 ○ NRS: 0.95; 95% CI 0.77 to 1.18; one study; n=482 **Risk of SAEs:** Nirmatrelvir-ritonavir may result in little to no difference in serious adverse events vs standard of care. ○ RCTS: RR 0.81; 95% CI: 0.34–1.94; I2= n/a; n= 3686, 2 trials; moderate certainty evidence - NRS: Not reported	
Reis S, Metzendorf MI, Kuehn R, Popp M, Gagyor I, Kranke P, Meybohm P, Skoetz N, Weibel S. Nirmatrelvir combined with ritonavir for preventing and treating COVID-19. Cochrane Database Syst Rev. 2022 Sep 20;9(9):CD015395. doi: 10.1002/14651858.CD015395.pub2. PMID: 36126225;	SR	1 RCT – n=2246 outpatient settings with mild symptomatic COVID-19 comparing. Patients were unvaccinated and at high risk of severe COVID-19.	Nirmatrelvir-ritonavir plus standard of care VS Standard of care plus placebo.	RCTs comparing nirmatrelvir-ritonavir + standard of care (SOC) with 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, & for prevention of SARS-CoV-2 infection.	**Mortality:** **All-cause mortality at day 28 patients in outpatient setting with asymptomatic or mild disease:** nirmatrelvir-ritonavir may reduce all-cause mortality. - RR 0.04; 95% CI 0.00 to 0.68; n=2224; 1 trial; low certainty evidence <65 years vs over ≥65 years: Admitted to hospital or died - <u>18 to 65 years:</u> 7 in nirmatrelvir-ritonavir group vs 46 in comparator group admitted to hospital or died (RR 0.15, 95% CI 0.07 to 0.34; I^2 =n/a; n=1817, p<0.00001) - <u>≥65 years or older:</u> 1 in nirmatrelvir-ritonavir group vs 20 in comparator group admitted to hospital or died (RR 0.05, 95% CI 0.01 to 0.38; I^2 =n/a; n=268, p=0.004) - No differences between subgroups (I2=0%; p=0.33) - Risk ratio favoured nirmatrelvir-ritonavir, but low number of participants ≥65 years included. **Progression to hospitalisation:** Nirmatrelvir-ritonavir plus standard of care may reduce admission to hospital or death within 28 days vs standard of care plus placebo: - At day 28, 9 in nirmatrelvir-ritonavir vs 68 in the comparator group had been admitted to hospital or	AMSTAR II Rating: Moderate quality (Appendix 6)

Citation	Study design	Population (n)	Treatment	Inclusion Criteria	Main findings	Risk of bias
PMCID: PMC9487421					had died. RR 0.13; 95% CI 0.07 to 0.27; 1 study, n=2224; low certainty evidence **Adverse events:** 251 in nirmatrelvir-ritonavir group vs 266 in the placebo group experienced treatment emergent adverse events during the 34-day observation period. o RR 0.95; 95% CI 0.82 to 1.10; 1 study, n=2224; moderate certainty evidence **Serious Adverse Events (SAEs):** 18 in nirmatrelvir-ritonavir vs 74 in the comparator group experienced serious adverse events during the 34 days observation period. - RR 0.24, 95% CI 0.15 to 0.41; 1 trial; n=2224; low-certainty evidence	

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Two Systematic Reviews summarised in Table 1: Characteristics of included studies – critically low to moderate quality of evidence (AMSTAR II)

EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?**
	Large ☐ Moderate ☐ Small ☒ None ☐
	Moderate: very vulnerable population (non-immunised)
		See details in Table 1 – Characteristics of Included Studies (Systematic Reviews)
		Mortality: Nirmatrelvir-ritonavir may reduce mortality vs standard of care
		- RCTs: RR 0.10; 95% CI 0.01 to 0.84; I2 = 0%; n= 3686; 2 trials; not GRADEd.
		  ○ EPIC-SR: RR 0.33; 95% CI 0.01 to 8.08; n=1075
		  ○ Hammond 2022 (EPIC-HR): RR 0.04; 95% CI 0.00 to 0.68; n=2246; ARR 1.07%; 96% CI 0.47 to 1.67%; low certainty evidence
		- NRS: RR 0.24; 95% CI 0.15 to 0.39; I2 = 54%; n=238625; 7 retrospective cohorts; not GRADEd
		
		Progression to Hospitalisation: Nirmatrelvir-ritonavir may reduce progression to hospitalisation vs standard of care:
		- RCTS: RR 0.23; 95% CI 0.06 to 0.94; I2 =79%; n= 3686; 2 trials; not GRADEd.
		  ○ EPIC-SR: RR 0.50; 95% CI 0.17 to 1.46; n=1075
		  Hammond 2022 (EPIC-HR): RR 0.12; 95% CI 0.06 to 0.25; n=2246; ARR 5.15%; 95% 3.69 to 6.61%;
		- NRS: RR 0.46; 95% CI 0.32–0.66, I2 = 90%; n=363 945; 7 retrospective cohorts; not GRADEd
		
		Subgroup analyses (RCTs): the analysis combined both NRS and RCTs in one forest plot. Reported in this review are the induvial results for the RCTs:
		  ○ Age ≥ 65 years: Hammond 2022 (EPIC-HR): RR 0.05; 95% CI 0.01 to 0.38; 1 trial; n=not provided
		  ○ Age < 65 years: Hammond 2022 (EPIC-HR): RR 0.15; 95% CI 0.07 to 0.34; 1 trial; n=not provided
		  ○ Previous immunity to SARS-CoV-2: EPIC-SR: RR 0.43; 95% CI 0.11 to 1.64; 1 trial; n=not provided
		  ○ No Previous immunity to SARS-CoV-2:
		  ○ Hammond 2022 (EPIC-HR): RR 0.12; 95% CI 0.06 to 0.25; 1 trial; n=not provided
		  ○ EPIC-SR: RR 0.65; 95% CI 0.11 to 3.84; 1 trial; n=not provided

QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect	Two Systematic Reviews summarised in Table 1: Characteristics of included studies – critically low to moderate quality of evidence (AMSTAR II)

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	Low quality: some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] None [x]	**See details in Table 1 – Characteristics of Included Studies (Systematic Reviews)** **Adverse Events (Cheema 2023):** RCTs: RR 0.93; 95% CI 0.82 to 1.05; two trials; n= 3159 o EPIC-HR: RR 0.90; 95% CI 0.80 to 1.22 o EPIC-SRRCT: RR 2.38; 95% CI 1.74 to 3.26 o NRS: 0.95; 95% CI 0.77 to 1.18; one study; n=482 **Adverse Events (Reis 2022):** o RR 0.95; 95% CI 0.82 to 1.10; 1 study, n=2224; moderate certainty evidence **Serious Adverse Events (SAEs) (Cheema 2023):** Nirmatrelvir-ritonavir may result in little to no difference in serious adverse events vs standard of care. o RCTS: RR 0.81; 95% CI: 0.34–1.94; I2= n/a; n= 3686, 2 trials; moderate certainty evidence NRS: Not reported. **Serious Adverse Events (SAEs) (Reis 2022):** 18 in nirmatrelvir-ritonavir vs 74 in the comparator group experienced serious adverse events during the 34 days observation period. - RR 0.24, 95% CI 0.15 to 0.41; 1 trial; n=2224; low-certainty evidence
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [x] Favours control [ ] Intervention = Control *or* Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [x] List the members of the group. List specific exclusion from the group:	There are at present no registered alternative antivirals for early treatment of COVID-19 in South Africa. Molnupiravir and remdesivir have been accessed via Section 21, but neither are recommended for use by the NELMC.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	**Availability:** Originator product is registered by SAHPRA. However, no generic applications have been submitted to SAHPRA yet. In addition, the Medicines Patent Pool (MPP) voluntary licence (VL) requires sublicensed companies to obtain WHO prequalification (PQ) or registration with a stringent regulatory

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		authority (SRA) before commercialisation in any market. This has implications for SAHPRA, which will not be able to rely on Section 21 to enable access to generic nirmatrelvir-ritonavir. SAHPRA is not recognised as an SRA, which is equivalent to maturity level (ML) 4. SAHPRA has ML3 status only for vaccine approval at this point. It has ML4 status for vaccine batch release.
RESOURCE USE	**How large are the resource requirements?** More intensive: X Less intensive: Uncertain:	**Price of medicines/ treatment course** Nirmatrelvir-RTV | None | Not disclosed **Other resources:** US$282 per course (https://healthpolicy-watch.news/overcoming-intellectual-property-barriers-covid-china/)
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: Major: Uncertain: X **Is the option acceptable to key stakeholders?** Yes: No: Uncertain: X	
EQUITY	**Would there be an impact on health inequity?** Yes: No: Uncertain: x	

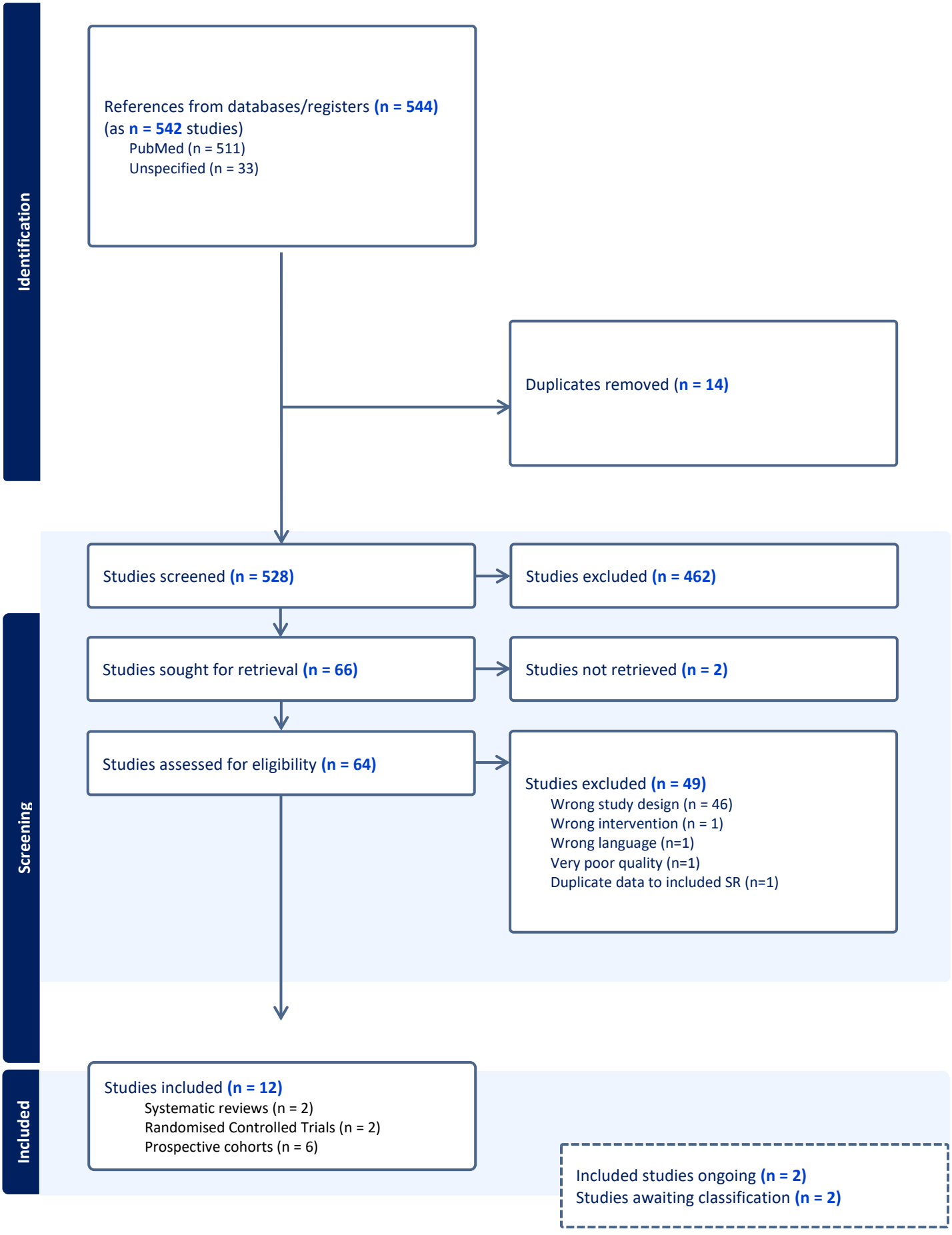
Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	14 March 2022	GR, JN, RdW, TK, NB, NG, MR, TL	Nirmatrelvir+RTV not be used for the treatment of COVID-19. Single RCT shows reduction in hospitalisation and death in adults with mild to moderate COVID-19, at high-risk for progression to severe COVID-19. However, rapid access and initiation within 5 days of onset of symptoms by patients with confirmed COVID-19. Use of nirmatrelvir+RTV is contraindicated in pregnancy, so women of childbearing potential need to take effective contraception. There is a potential of many drug-drug interactions. Not been studied in patients previously vaccinated against COVID-19. Products have yet to be registered in South Africa. Review will be updated when there is more information on availability and pricing of generic products.
2.0	14 March 2022	GR, JN, RdW, TK, NB, NG, MR, TL	Editorial amendment.
3.0	14 March 2022	GR, JN, RdW, TK, NB, NG, MR, TL	Error amended from, “The absolute risk reduction (ARR) of 1.07% (95% CI 0.47 to 0.67%)” to “The absolute risk reduction (ARR) of 1.07% (95% CI 0.47 to 1.67%)”.
4.0	30 March 2023	GR, JN, RdW, TK, MR, NG	Nirmatrelvir-ritonavir not be used for the treatment of COVID-19. Although, RCTs and SRs of observational trials of patients at high-risk of progression to severe COVID-19 (both vaccinated and unvaccinated) indicate that nirmatrelvir-ritonavir may reduce mortality and hospitalisation; information regarding local cost and availability and strong efficacy data in immunised and previously infected populations are not yet available.

Appendix 1: Search Strategy

15 March 2023

Search	Query	Results
#5	Search: #4 AND #3	75
#4	Search: #1 AND #2	550
#3	Search: (Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] or placebo [tiab] OR clinical trials as topic [mesh:noexp] OR randomly [tiab] OR trial [ti] OR groups [tiab]) NOT (animals [mesh] NOT humans [mesh])	3,091,214
#2	Search: Nirmatrelvir and ritonavir drug combination [supplementary concept] OR nirmatrelvir [tiab] OR Paxlovid*[tiab] OR nirmatrelvir [Supplementary Concept] OR PF-07321332 [tiab] OR PF07321332 [tiab]	594
#1	Search: Coronavirus[mh:noexp] OR coronavirus*[tiab] OR corona virus[tiab] OR COVID-19 [mesh] OR COVID-19 [tiab] OR COVID19 [tiab] OR COVID 2019 OR 2019-nCoV [tiab] OR SARS-Cov-2[mh] OR SARS-CoV-2 [tiab] OR SARS-CoV2[tiab] OR SARSCov2[tiab] OR Severe acute respiratory syndrome-related coronavirus[mesh] OR Severe Acute Respiratory Syndrome Coronavirus 2 [tiab] OR 2019-nCoV [tiab] OR 2019nCov [tiab] OR nCov2019 [tiab] OR nCOV-2019[tiab] OR hCOV*[tiab] OR n-cov [tiab] OR ncov*[tiab]	355,259

Appendix 2: PRISMA Flow Chart



Appendix 3: Table of excluded studies, with reasons

Author, date	Type of study	Reason for exclusion
1. Aggarwal 2023	Retrospective cohort	Wrong study design
2. Akinosoglou 2022	Narrative review	Wrong study design
3. Al-Obaidi 2023	Retrospective cohort	Wrong study design
4. Amani 2023	Systematic review	Very poor quality
5. Arbel 2022	Retrospective cohort	Wrong study design
6. Bajema 2022	Retrospective cohort	Wrong study design
7. Budi 2022	Systematic review	Duplicate study to included SR (Reis 2022)
8. Bruno 2022	Retrospective cohort	Wrong study design
9. Cai 2022	Letter to the editor	Wrong study design
10. De Bito 2022	Retrospective cohort	Wrong study design
11. Dryden-Peterson 2022	Retrospective cohort	Wrong study design
12. Ebell 2022	Clinical question response	Wrong study design
13. Evans 2023	Retrospective cohort	Wrong study design
14. Ganatra 2022	Retrospective cohort	Wrong study design
15. Gentile 2022	Retrospective cohort	Wrong study design
16. Gentry 2023	Retrospective cohort	Wrong study design
17. Hashash 2023	Retrospective cohort	Wrong study design
18. Hedvat 2022	Retrospective cohort	Wrong study design
19. Kane 2023	Retrospective cohort	Wrong study design
20. Lai 2022	Retrospective cohort	Wrong study design
21. Lanthier 2022	Randomised controlled trial	Wrong language
22. Lewnard 2023	Matched Observational Cohort Study (Retrospective)	Wrong study design
23. Liu 2023	Retrospective cohort	Wrong study design
24. Mazzitelli 2023	Retrospective cohort	Wrong study design
25. McDonald 2022	Fact page	Wrong study design
26. Najar-Debbiny 2023	Retrospective cohort	Wrong study design
27. Nield 2022	Letter to the editor	Wrong study design
28. Park 2022 A	Retrospective cohort	Wrong study design
29. Park 2022 B	Retrospective cohort	Wrong study design
30. Pitre 2022	Network meta-analysis	Wrong study design
31. Qi 2023	Retrospective cohort	Wrong study design

32. Qian 2022	Retrospective cohort	Wrong study design
33. Ranganath 2023	Retrospective cohort	Wrong study design
34. Schwartz 2023	Retrospective cohort	Wrong study design
35. Shah 2023	Retrospective cohort	Wrong study design
36. Sommer 2023	Narrative summary of SR	Wrong study design
37. Tadmor 2023	Retrospective cohort	Wrong study design
38. Tort 2022	Summary of a review	Wrong study design
39. Wai 2023	Retrospective cohort	Wrong study design
40. Wang 2023 A	Narrative review	Wrong study design
41. Wang 2023 B	Retrospective cohort	Wrong study design
42. Weiss 2022	Letter to the editor	Wrong study design
43. Wen 2022	Meta-analysis	Wrong intervention
44. Weng 2023	Retrospective cohort	Wrong study design
45. Wong 2022 A	Retrospective cohort	Wrong study design
46. Wong 2022 B	Retrospective cohort	Wrong study design
47. Wong 2022 C	Narrative commentary	Wrong study design
48. Yip 2023	Retrospective cohort	Wrong study design
49. Australian Prescriber 2022	Narrative summary	Wrong study design

Appendix 4: Table of ongoing trials

Citation	Study Design	Population (n)	Treatment
EUCTR2022-002447-22-SK. An interventional efficacy and safety, phase 2, double blind, two arm study to investigate orally administered nirmatrelvir/ritonavir compared with placebo/ritonavir for the treatment of severe COVID-19 in hospitalised participants who are immunocompromised or at increased risk for severe COVID-19 outcomes. 2023 Jan 30. [Accessed 2023 Mar 27]. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2022-002447-22-SK	Parallel/Crossover RCT	Hospitalized participants ≥12 years of age with severe COVID-19 who are immunocompromised or at increased risk for severe COVID 19 outcomes (target n=279)	Nirmatrelvir-ritonavir vs placebo/ritonavir
NCT05601167. Open Multicentre Study of the Safety and Efficacy Against COVID-19 of Nirmatrelvir/Ritonavir in the Adult Population. 2022. [Accessed 2023 Mar 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT05601167	Phase 3 RCT	Adult participants aged 18 to 80 years old with mild or moderate COVID-19 infection (target n = 264)	Nirmatrelvir-ritonavir vs standard of care

Appendix 5: Observational studies identified for potential inclusion

Citation	Study Design	Population (n)	Aim
Sun F, Lin Y, Wang X, Gao Y, Ye S. Paxlovid in patients who are immunocompromised and hospitalised with SARS-CoV-2 infection. Lancet Infect Dis. 2022 Sep;22(9):1279. doi: 10.1016/S1473-3099(22)00430-3. Epub 2022 Jul 14. PMID: 35843259; PMCID: PMC9282758.	Nirmatrelvir-ritonavir hospital registry study	Symptomatic patients hospitalised with SARSCoV-2 (n=114)	To study Nirmatrelvir-ritonavir in patients who are immunocompromised and hospitalised with SARS-CoV-2 infection
Guo X, Duan S, Liu Y, Yuan Y. Adverse drug events in the prevention and treatment of COVID-19: a data mining study on the FDA adverse event reporting system. Front. 2022;13:954359. Doi: https://doi.org/10.3389/fphar.2022.954359	Pharmacovigilance study	COVID-19 associated cases in US FDA FAERS (n= 66 879)	To investigate the adverse drug events of some drugs (i.e., "hot drugs" in this study) in COVID-19 prevention and treatment based on the data from the US Food and Drug Administration (FDA) adverse event reporting system (FAERS).
Lee E, Park S, Choi J, Kim M, Yang E, Ham SY, et al. Short-term effectiveness of oral nirmatrelvir/ritonavir against the SARS-CoV-2 Omicron variant and culture positive viral shedding. J Korean Med Sci. 2023 Feb 27; 38(8):e59. Doi: https://doi.org/10.3346/jkms.2023.38.e59	Prospective cohort	Participants with mild to moderate COVID-19 (n = 51)	To assess the clinical and virologic responses to oral nirmatrelvir-ritonavir in mild to moderate COVID-19 patients with risk factors for severe illness in a real-world setting.
Pandit JA, Radin JM, Chiang D, Spencer EG, Pawelek JB, Diwan M, et al. The COVID-19 Rebound Study: A Prospective Cohort Study to Evaluate Viral and Symptom Rebound Differences in Participants Treated with Nirmatrelvir Plus Ritonavir Versus Untreated Controls. Clin Infect Dis. 2023 Feb 22:ciad102. doi: 10.1093/cid/ciad102. Epub ahead of print. PMID: 36810665.	Prospective cohort	Participants with a positive rapid antigen test for SARS-CoV-2 prescribed nirmatrelvir-ritonavir through a telehealth visit regardless of whether they intended to take the medicine (n=170: n=127 nirmatrelvir-ritonavir vs n= 43 controls)	To prospectively compare the epidemiology of rebound in nirmatrelvir-ritonavir-treated and untreated participants with acute COVID-19 infection.
Tiseo G, Barbieri C, Galfo V, Occhineri S, Matucci T, Almerigogna F, et al. Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World	Prospective cohort	COVID-19 outpatients with at least one risk factor for disease progression. Overall,	To describe a real-world experience of outpatient management of COVID-19 subjects at high risk of progression.

Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience. Infect Dis Ther. 2023 Jan;12(1):257-271. doi: 10.1007/s40121-022-00729-2. Epub 2022 Nov 28. PMID: 36441485; PMCID: PMC9707131.		n=562 outpatients (n=252 nirmatrelvir-ritonavir)	
Yan G, Zhou J, Zhu H, Chen Y, Lu Y, et al. The feasibility, safety, and efficacy of Paxlovid treatment in SARS-CoV-2-infected children aged 6-14 years: a cohort study. Ann Transl Med. 2022 Jun;10(11):619. doi: 10.21037/atm-22-2791. PMID: 35813342; PMCID: PMC9263777.	Prospective cohort	n=5 nirmatrelvir-ritonavir paediatric COVID-19 cases (mildly and moderately ill)	To analyse the feasibility, safety, and efficacy of Paxlovid treatment in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected children aged 6–14 years

Appendix 6: AMSTAR II Appraisal Summary

	Cheema 2023: AMSTAR II		Reis 2023: AMSTAR II	
	Reviewer 1	**Reviewer 2**	**Reviewer 1**	**Reviewer 2**
1. Did the research question and inclusion criteria for the review include the components of PICO?	Y	Y	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y	PY	PY	Y
3. Did the review authors explain their selection of the study designs for inclusion in the review?	N	N	N	N
4. Did the review authors use a comprehensive literature search strategy?	PY	PY	PY	Y
5. Did the review authors perform study selection in duplicate?	Y	Y	Y	Y
6. Did the review authors perform data extraction in duplicate?	Y	Y	Y	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	N	N	Y	Y
8. Did the review authors describe the included studies in adequate detail?	PY	PY	Y	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (RCT)	Y	Y	Y	Y
(NRS)	-	PY	N/A	N/A
10. Did the review authors report on the sources of funding for the studies included in the review?	N	N	Y	Y
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (RCT)	Y	N	N/A	N/A
(NRS)	Y	Y	N/A	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y	Y	N/A	N/A
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y	Y	Y	Y

	Cheema 2023: AMSTAR II		Reis 2023: AMSTAR II	
	Reviewer 1	**Reviewer 2**	**Reviewer 1**	**Reviewer 2**
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y	N	Y	Y
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y	Y	N/A	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y	Y	PY	Y
OUTCOME	Low quality	Critically low quality	Moderate quality	Moderate quality

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