J Antimicrob Chemother 2023; **78**: 1586–1598
https://doi.org/10.1093/jac/dkad132 Advance Access publication 12 May 2023

Journal of Antimicrobial Chemotherapy

Efficacy and safety of molnupiravir for the treatment of SARS-CoV-2 infection: a systematic review and meta-analysis

Jakob J. Malin [1,2]*, Stephanie Weibel[3], Henning Gruell [4], Nina Kreuzberger [5], Miriam Stegemann[6] and Nicole Skoetz[5]

[1]Department I of Internal Medicine, Division of Infectious Diseases, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; [2]Centre for Molecular Medicine Cologne (CMMC), Faculty of Medicine, University of Cologne, Cologne, Germany; [3]Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Wuerzburg, Germany; [4]Institute of Virology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; [5]Evidence-Based Medicine, Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; [6]Department of Infectious Diseases, Respiratory Medicine and Critical Care, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität of Berlin, Berlin, Germany

*Corresponding author. E-mail: jakob.malin@uk-koeln.de
@JJMalin

Received 19 January 2023; accepted 19 April 2023

Background: The role of molnupiravir for coronavirus disease 2019 (COVID-19) treatment is unclear.

Methods: We conducted a systematic review until 1 November 2022 searching for randomized controlled trials (RCTs) involving COVID-19 patients comparing molnupiravir [±standard of care (SoC)] versus SoC and/or placebo. Data were pooled in random-effects meta-analyses. Certainty of evidence was assessed according to the Grading of Recommendations, Assessment, Development and Evaluations approach.

Results: Nine RCTs were identified, eight investigated outpatients (29 254 participants) and one inpatients (304 participants). Compared with placebo/SoC, molnupiravir does not reduce mortality [risk ratio (RR) 0.27, 95% CI 0.07–1.02, high-certainty evidence] and probably does not reduce the risk for 'hospitalization or death' (RR 0.81, 95% CI 0.55–1.20, moderate-certainty evidence) by Day 28 in COVID-19 outpatients. We are uncertain whether molnupiravir increases symptom resolution by Day 14 (RR 1.20, 95% CI 1.02–1.41, very-low-certainty evidence) but it may make no difference by Day 28 (RR 1.05, 95% CI 0.92–1.19, low-certainty evidence). In inpatients, molnupiravir may increase mortality by Day 28 compared with placebo (RR 3.78, 95% CI 0.50–28.82, low-certainty evidence). There is little to no difference in serious adverse and adverse events during the study period in COVID-19 inpatients/outpatients treated with molnupiravir compared with placebo/SoC (moderate- to high-certainty evidence).

Conclusions: In a predominantly immunized population of COVID-19 outpatients, molnupiravir has no effect on mortality, probably none on 'hospitalization or death' and effects on symptom resolution are uncertain. Molnupiravir was safe during the study period in outpatients although a potential increase in inpatient mortality requires careful monitoring in ongoing clinical research. Our analysis does not support routine use of molnupiravir for COVID-19 treatment in immunocompetent individuals.

Introduction

During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, approved antivirals and various drug candidates with broad antiviral activity have been repurposed in efforts to improve the clinical course of coronavirus disease 2019 (COVID-19). The nucleoside analogue prodrug remdesivir was the first repurposed antiviral with a proven clinical effect in hospitalized patients.[1] The antiviral effect of nucleoside analogues is based on their ability to abrogate viral replication. Like other antivirals, nucleoside analogues are considered most effective when used early after infection during high-level viral replication based on their mode of action. Accordingly, early treatment with remdesivir of outpatients with risk factors seemed more beneficial than inpatient treatment.[1–3] However, remdesivir can only be administered IV. Consequently, there is

a high need for effective orally available antiviral drugs in order to support early COVID-19 therapy in the outpatient setting. To date, there are two oral treatment options available in many countries: nirmatrelvir (a protease inhibitor co-administered with ritonavir) and molnupiravir.

Molnupiravir [MK-4482; Emory Institute for Drug Development (EIDD)-2801] was granted emergency use authorization for early treatment of COVID-19 in the USA, UK and other countries in December 2021. It is a prodrug of the ribonucleoside analogue β-D-N^4-hydroxycytidine (NHC, EIDD-1931), which was initially identified during a screening campaign for antiviral molecules against influenza A virus and respiratory syncytial virus.[4,5] NHC has a broad antiviral spectrum *in vitro* that includes SARS-CoV-2 and other human coronaviruses.[6,7] EIDD-2801, a synthesized prodrug of NHC with increased oral bioavailability, demonstrated activity against SARS-CoV-2 in animal models, supporting its evaluation in clinical trials on COVID-19.[5,8]

Results from the MOVE-OUT Phase 3 trial published in December 2021 showed a significant reduction in 'hospitalization or death' in unvaccinated outpatients with COVID-19 who were treated with molnupiravir [absolute risk reduction (ARR) 2.9%].[9] However, these results did not meet the high expectations raised by an interim analysis suggesting a much greater effect (ARR 6.8%).[10,11] More recently, the results of the Oxford PANORAMIC trial indicated no reduction in the low rates for hospitalization or death among vaccinated outpatients with risk factors treated with molnupiravir.[12] Moreover, safety concerns have been raised based on its cytotoxic and mutagenic potential[13,14] and teratogenic effects in an animal reproduction study.[11] We set out to provide a systematic review and meta-analysis of the most recent evidence evaluating the efficacy and safety of molnupiravir in order to support guideline development and clinical decision making.

Methods

The protocol for this systematic review was registered on the International prospective register of systematic reviews (PROSPERO, identifier CRD42022306644) and made publicly available on 25 January 2022.

Eligibility criteria

Types of studies

Eligibility was restricted to randomized controlled trials (RCTs). We considered studies reported as full text only, either published as preprint or in a journal.

Types of participants

Included studies involved patients irrespective of age and sex with suspected or laboratory-confirmed SARS-CoV-2 infection. This includes symptomatic infection, mild disease (outpatient), moderate or severe disease (inpatient).

Types of interventions

We considered studies comparing molnupiravir (any dose regimen) in combination with standard of care (SoC) or alone versus SoC and/or placebo.

Types of outcome measures

We included studies irrespective of reported outcomes. We analysed the following outcomes:

1) Ambulatory managed individuals with asymptomatic or mild COVID-19 (outpatients):
- All-cause mortality at Day 28, Day 60, time-to-event and up to longest follow-up;
- Admission to hospital or death within 28 days;
- Resolution of COVID-19 symptoms:
  - All initial symptoms resolved (asymptomatic) at Day 14, Day 28 and up to longest follow-up;
  - Duration 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.

2) Hospitalized individuals with moderate to severe COVID-19 (inpatients):
- All-cause mortality at Day 28, Day 60, time-to-event, and at hospital discharge;
- Clinical status at Day 28, Day 60, and up to longest follow-up, including:
  - Worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death;
  - Improvement of clinical status: participants discharged alive;
- Quality of life.

3) Safety of molnupiravir:
- Serious adverse events during the study period, defined as number of participants with any event;
- Adverse events (any grade) during the study period, defined as the number of participants with at least one adverse event independent of event and evaluated association with study drug;
- Long-term adverse events.

A deviation of ±1 day in the reported outcome was acceptable if no assessment on Days 14, 28 or 60 was available.

Information sources and search strategy

We searched the Cochrane COVID-19 Study Register (comprising MEDLINE, Embase, clinicaltrials.gov, WHO International Clinical Trials Registry Platform, medRxiv and the Cochrane Central Register of Controlled Trials), Web of Science (Science Citation Index and Emerging Sources Citation Index) and the WHO COVID-19 Global literature on coronavirus disease until 1 November 2022. We updated information regarding PANORAMIC, which was already included as preprint but whose full-text was published after the search date. There were no restrictions regarding language or reporting status. The full search strategy can be found in Appendix S1 (available as Supplementary data at *JAC* Online).

Data collection and analysis

Selection of studies

Two review authors (N.K. and N.S.) independently screened the titles and abstracts to identify potentially relevant RCTs. We then obtained full-text articles of all potentially relevant citations. Any disagreements regarding RCT selection were resolved by consulting a third review author (J.J.M.). The entire study selection process was reported according to PRISMA guidelines.[15]

Data collection

Two review authors independently performed data extraction in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*. Multiple reports of the same study were collated so that the study, rather than the report, was the unit of analysis. We extracted

data on study characteristics, outcome measures, financial support and sponsoring, and disclosure of conflicts of interest.

Assessment of risk of bias in included studies

Two review authors (N.K. and N.S.) independently assessed the risks of bias in studies fulfilling the review inclusion criteria using Cochrane's 'Risk of bias 2.0' tool.[16] Disagreements were resolved by discussion or by involving a third author where necessary. For each domain, we classified the study as having a low, some concerns or high risk of bias.

Data synthesis

Meta-analyses were based on the recommendations from the Cochrane Handbook.[17] We synthesized data using the package 'meta' version 5.2-0 in R.[18] For outpatient and inpatient studies, separate analyses were performed. Measures of effect were risk ratios (RRs), HRs or mean differences. For binary outcomes, the number of affected participants and the number of participants per group were recorded. Analyses were performed using the Mantel–Haenszel method under a random-effects model to report pooled RRs with 95% CIs. No meta-analyses on continuous outcomes were performed.

Analysis of subgroups or subsets

We performed post hoc subgroup analyses of vaccination status (one or more doses versus no vaccination) because vaccination status is considered a potential effect modifier. We used the test for subgroup differences and considered $P<0.05$ as statistically significant. We could not perform subgroup analyses on age (≥65 years or below) and dose due to lack of data.

Sensitivity analysis

In sensitivity analyses, we compared fixed-effects versus random-effects models and excluded studies at high or some concerns regarding risk of bias.

Certainty of evidence

The certainty of the evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach.[19] GRADE has four levels of certainty: very low, low, moderate and high. We downgraded our certainty of evidence one or two levels for risk of bias, imprecision, inconsistency, indirectness and probability of publication bias. Sensitivity analyses were used to inform GRADE. For interpretation of findings, we combined size and certainty of an effect. To communicate findings, we used informative statements as described by Santesso *et al.*[20] The credibility of subgroup effects was evaluated using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) for meta-analyses.[21]

Results

Search

The search strategy identified a total of 519 records (e.g. full-text journal publications, study registry entries, study protocols, secondary study publications). After removal of 116 duplicate studies, 403 titles and abstracts were screened by two authors (N.S. and N.K.) and assessed for relevance. Based on title and abstract, 306 abstracts were excluded. Full-text screening of 97 records revealed 56 records for exclusion of which 38 records belonged to 24 studies registered in study registries (currently ongoing or not yet recruiting); one study was a non-RCT, one study a platform trial, seven records of two studies were conducted in healthy individuals, three were press releases of included studies, and six were records of abstracts/press releases of ongoing or unpublished studies. Nine studies with 41 records, also comprising multiple study registry entries, were included in this review. Results of seven trials were published in peer-reviewed journals,[9,22–27] and the results of two trials are available as preprints.[12,28] The flow diagram with reasons for exclusion of records is summarized in Figure 1.

Study characteristics

In total, 29 558 participants in nine RCTs were eligible (for individual study details, see Table 1).[9,12,22–28] The Phase 3 PANORAMIC trial was the largest trial, contributing 25 783 outpatients (87% of all available study data) from the UK recruited between December 2021 and April 2022. Six trials were multicentre trials conducted in the UK,[27] USA,[23] India[28] or internationally.[9,25,26] Two trials were conducted at single centres in China[24] and the UK, respectively.[22] Seven out of eight studies on outpatients included patients with mild COVID-19 defined according to the study protocols (WHO scale 2–3). Another small Phase 3 single-centre study from China contributed 116 patients with mild (96%) to moderate (4%) disease who were hospitalized only for the trial conduct and therefore categorized as outpatients in this meta-analysis.[24] At least one risk factor for severe COVID-19 was present in 61%,[23] 75%,[25] 83%[12] and 100%[9] of the included outpatients. Risk factors were defined by the respective study protocols,[9,12,23,25] whereas age ≥60 years was considered as an independent risk factor for all included trials. PANORAMIC characterized participants as 'at risk' or 'extremely vulnerable' according to former priority criteria defined by the UK National Health Service.[12] MOVe-IN[26] with 304 participants is the only trial that included hospitalized, non-critically-ill COVID-19 patients (WHO scale 4–5).[26]

All studies included participants with laboratory-confirmed COVID-19 by a nucleic acid amplification test (preferred method)

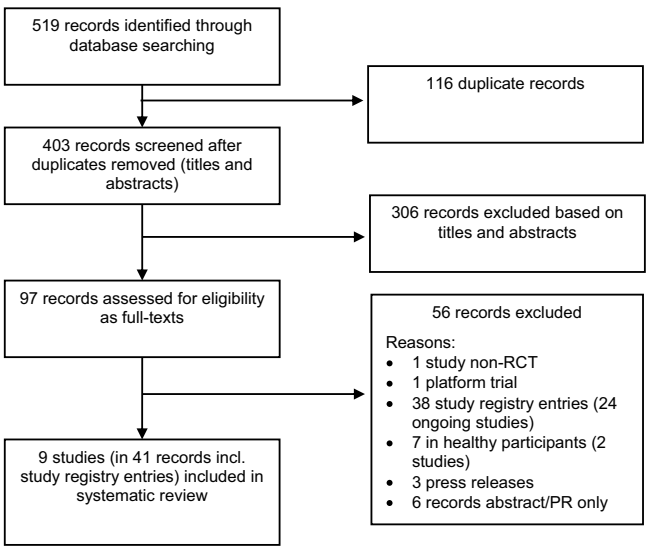

Figure 1. Flow diagram for identification of eligible clinical trials. PR, press release.

Table 1. Study characteristics of included randomized controlled trials

Study Reference	Study design	Recruitment period	Setting and patient status	Randomized patients	Intervention	Comparator	Reported outcomes evaluated
MOVe-IN[26] NCT04575584	RCT, double-blind, Phase 2/3, 65 centres/15 countries	19 October 2020 to 12 January 2021	Hospitalized adults with laboratory-confirmed COVID-19 with sign/symptom onset 10 or fewer days before randomization, unvaccinated, non-critically COVID-19, not severely immunocompromised, 74% with at least one risk factor	304 (1:1:1:1)	Molnupiravir (200, 400, 800 mg twice daily, 5 days) + SoC	Placebo + SoC	All-cause mortality Day 28, death, longest follow-up, any adverse events, serious adverse events
AGILE Phase 1[22] NCT04746183	RCT, open-label, Phase 1, single centre/UK	17 July 2020 to 30 October 2020	Adult outpatients with PCR-confirmed COVID-19 within 5 days of symptom onset, unvaccinated, mild to moderate COVID-19, no comorbidities	18 (2:1)	Molnupiravir (300, 600, 800 mg twice daily, 5 days) plus SoC	SoC	Symptom resolution by Days 15 and 29 (defined as WHO clinical progression scale score 0 or 1), any adverse events, serious adverse events
AGILE Phase 2[27] NCT04746183	RCT, double-blind, Phase 2, 5 centres/UK	18 November 2020 to 16 March 2022	Adult outpatients with PCR-confirmed COVID-19 within 5 days of symptom onset, mild to moderate COVID-19, no comorbidities, vaccinated (50% with at least one vaccine dose)	180 (1:1)	Molnupiravir (800 mg twice daily, 5 days) plus SoC	Placebo + SoC	All-cause mortality Day 28, hospitalization (no definition) Day 28, symptom resolution by Days 15 and 29 (defined as WHO clinical progression scale score 0 or 1), any adverse events, serious adverse events
Fischer *et al.*[23] NCT04405570	RCT, double-blind, Phase 2a, 10 centres/USA	19 June 2020 to 21 January 2021	Adult outpatients with laboratory-confirmed COVID-19 within 7 days of symptom onset, unvaccinated, at least one COVID-19 symptom, 61% with at least one risk factor for severe disease	202 (3:1)	Molnupiravir (200, 400, 800 mg twice daily, 5 days)	Placebo	Symptom resolution reported as median time to resolution (assessed by patient diaries), any adverse events, serious adverse events
MOVe-OUT Phase 2[25] NCT04575597	RCT, double-blind, Phase 2, 82 centres/14 countries	Initiated October 2020	Adult outpatients with laboratory-confirmed COVID-19 with symptom onset up to (and including) 7 days before randomization, unvaccinated, mild or moderate COVID-19 (WHO 2 to 3)[a], 75% with at least one risk factor for severe disease, enrolment was limited to no more than 50% of participants with moderate COVID-19	302 (1:1:1:1)	Molnupiravir (200, 400, 800 mg twice daily, 5 days), SoC allowed	Placebo + SoC	Hospitalization (defined as ≥24 h of acute in-hospital care) OR death Day 28, all-cause mortality Day 28, symptom resolution by Day 15 (defined as WHO clinical progression scale score 0 or 1), any adverse events, serious adverse events
MOVe-OUT Phase 3[9] NCT04575597	RCT, double-blind, Phase 3, 107	6 May 2021 to 2 October 2021	Adult outpatients with laboratory-confirmed COVID-19 within 5 days of symptom onset, unvaccinated, mild or moderate	1433 (1:1); planned interim analysis at 50% of 1550	Molnupiravir (800 mg twice daily, 5 days), SoC allowed	Placebo + SoC	Hospitalization for any cause (defined as ≥24 h of acute in-hospital care) OR death through Day 28, all-cause

Continued

Table 1. *Continued*

Study Reference	Study design	Recruitment period	Setting and patient status	Randomized patients	Intervention	Comparator	Reported outcomes evaluated
	centres/20 countries		COVID-19 (WHO 2 to 3)[a], with at least one risk factor for severe disease	participants had been followed through Day 29			mortality Day 28, any adverse events, serious adverse events; symptom resolution was reported as categorized using WHO clinical progression scale scores
Tippabhotla *et al.*[28] CTRI/2021/07/034588 (Preprint)	RCT, open-label, Phase 3, 16 centres/India	1 July 2021 to 24 August 2021	Outpatients aged ≥18 and ≤60 years with laboratory-confirmed (RT-PCR positive) SARS-CoV-2 infection, unvaccinated and with mild to moderate COVID-19, uncomplicated upper respiratory tract symptoms	1220 (1:1)	Molnupiravir (800 mg twice daily, 5 days) plus SoC	SoC	All-cause hospitalization (defined as hospital admission for >24 h with respiratory rate ≥24/min and SpO_2 ≤93% in room air, requiring oxygen supplementation) Day 28, mortality Day 28, resolution of COVID-19 symptoms by Day 14 (defined as a decrease of at least 2 points on the WHO 11-point scale since baseline; maximum score of 3 for all participants), any adverse events, serious adverse events
PANORAMIC[12] ISRCTN30448031	RCT, open-label, Phase 3, multicentre/UK	8 December 2021 to 27 April 2022	Outpatients aged ≥50, or ≥18 years with comorbidities, and unwell ≤5 days with confirmed COVID-19 (by PCR or rapid antigen test) in the community, vaccinated (99% with at least one vaccine dose, 93% three doses), 78% either ≥65 years old or dedicated to 'at risk' or 'extremely vulnerable' groups according to former NHS priority criteria	25 783 (1:1)	Molnupiravir (800 mg twice daily, 5 days) plus SoC	SoC	All-cause hospitalization (defined as at least one overnight stay in hospital or 'Hospital at Home') OR death Day 28, all-cause mortality Day 28, resolution of COVID-19 symptoms by Days 14 and 28 (self-reported recovery on the question 'Do you feel recovered today?'), serious adverse events
Zou *et al.*[24] ChiCTR2200056817	RCT, open-label, Phase 3, single-centre/China	3 March 2022 to 21 March 2022	Patients hospitalized for study conduct ≥18 years and ≤80 years with confirmed SARS-CoV-2 omicron infection, mild (96%)/moderate (4%) COVID-19 symptoms, and onset of symptoms for ≤5 days prior to treatment, vaccinated (92% with at least two doses, 61% three doses)	116 (2:1)	Molnupiravir (800 mg twice daily, 5 days) plus SoC	SoC	Any adverse events, serious adverse events

NHS, UK National Health Service; RCT, randomized controlled trial; SoC, standard of care (usual care).
[a]Defined according to trial protocol.

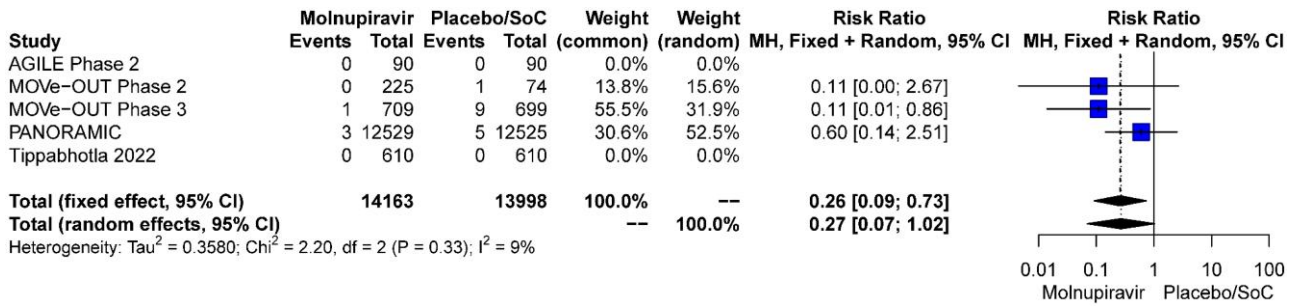

Figure 2. Association between molnupiravir and all-cause mortality by Day 28 in outpatients. MH, Mantel–Haenszel method. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

or authorized antigen test (Table 1). Six studies included only unvaccinated patients,[9,22,23,25,26,28] whereas three studies included patients having received at least one vaccine dose (50%[27] and 99%[12] of participants, respectively) or having received at least two vaccine doses (92%[24] of participants). In consequence, at least 88% of all outpatients included in the systematic review received at least one vaccine dose. Of 99% of patients with at least one dose included in PANORAMIC, 93% had received three vaccine doses (82% of the total outpatient population). Molnupiravir was investigated at different doses from 200 to 800 mg and compared with either placebo (five double-blinded trials[9,23,25–27]) or SoC (four open-label trials).[12,22,24,28] Based on exposure–response analyses from Phase 2 trials, the most recent and largest Phase 3 trials (PANORAMIC and MOVe-OUT Phase 3) investigated the 800 mg dose of molnupiravir only.

In the outpatient setting, the PANORAMIC trial with 88% of all participants included in this systematic review and another four studies contributing 6% investigated participants within 5 days of symptom onset.[9,12,22,24,27] In addition, two studies included COVID-19 participants within 7 days of symptom onset[23,25] and one study[28] included patients irrespective of symptom duration (54% randomized within 3 days of symptom onset). In the inpatient study, treatment was initiated within 10 days of symptom onset.[26]

Risk of bias in included studies

In total, the nine studies contributed results to five outcomes for outpatients and three outcomes for inpatients of this review that were assessed using the 'Risk of bias 2.0' tool (Table S1). For outpatients, the outcome all-cause mortality was rated as low risk of bias for all five studies that reported the outcome. The combined outcome 'hospitalization or death' at Day 28 was rated as low risk of bias in one study,[27] and of some concern in four out of five studies[9,12,25,28] due to a lack of criteria for hospitalizations in four studies and additional lack of reporting in one study.[28] From studies that reported adverse events and serious adverse events, for these outcomes, two were rated as high risk of bias due to possible differences in outcome measurement between groups[22] or attrition bias,[24] three were rated as having some concerns due to a general lack of blinding in the studies[28] and unavailability of protocol,[23] and three studies were considered as being at low risk of bias.[9,25,27] Symptom resolution on Days 14 and 28 was rated as low risk in one study[27] and as some concerns in four studies[12,22,23,28] due to a lack of protocol[23,28] and unblinded participants.[12,22,28] It was rated as high risk of bias in two studies due to potential selective reporting.[9,25] The one study that reported on inpatients[26] had a low overall risk of bias for all assessed outcomes.

Efficacy in outpatients with COVID-19

Early treatment with molnupiravir does not reduce all-cause mortality by Day 28 in COVID-19 outpatients (eight deaths fewer per 10 000; RR 0.27, 95% CI 0.07–1.02, 28 161 participants, five studies, high-certainty evidence; Figure 2 and Table 2). The risk of dying with placebo/SoC was very low (11 per 10 000) in the control group.

Molnupiravir probably does not reduce hospitalization or death by Day 28 (two events fewer per 1000; RR 0.81, 95% CI 0.55–1.20, 28 161 participants, five studies, moderate-certainty evidence; Figure 3 and Table 2) compared with placebo/SoC. We are uncertain whether molnupiravir increases symptom resolution by Day 14 (52 events more per 1000; RR 1.20, 95% CI 1.02–1.41, 23 773 participants, five studies, very low-certainty evidence due to serious risk of bias and very serious inconsistency; Figure 4 and Table 2) compared with placebo/SoC. Molnupiravir may make no difference on symptom resolution by Day 28 (RR 1.05, 95% CI 0.92–1.19, 24 874 participants, four studies, low-certainty evidence due to serious risk of bias and serious inconsistency; Figure 5 and Table 2). Sensitivity analysis using the fixed-effects model favours molnupiravir due to the larger weight of PANORAMIC (RR 1.14, 95% CI 1.12–1.16; Figure 5) at Day 28.

The subgroup analysis on vaccination status showed no difference for molnupiravir on all-cause mortality by Day 28 between vaccinated and unvaccinated patients ($P=0.14$; Figure S1). Although tests for subgroup differences were significant for 'hospitalization or death' by Day 28 ($P=0.03$; Figure S2), symptom resolution by Day 14 ($P<0.01$; Figure S3), and symptom resolution by Day 28 ($P=0.02$; Figure S4), credibility of these subgroups was rated as low according to the ICEMAN criteria[21] particularly due to between-trial effects and the small number of trials ($n=1$) for the subgroup including vaccinated participants (Table S2). Quality of life was not reported in any study.

Safety in outpatients with COVID-19

Compared with placebo/SoC, molnupiravir has little or no difference on adverse events (RR 0.98, 95% CI 0.89–1.08, 3435 participants, seven studies, high-certainty evidence; Figure 6 and

Table 2. Meta-analysis of efficacy and safety outcomes of molnupiravir versus control in outpatients with COVID-19

Outcome	Study population	Risk ratio, MH, random (95% CI)	Absolute effect estimates (95% CI)		Heterogeneity	Overall risk of bias per outcome	Certainty of evidence
			Placebo/ SoC	Molnupiravir			
All-cause mortality by Day 28	28 161 participants, 5 studies[9,12,25,27,28]	0.27 (0.07–1.02)	11 per 10 000	3 per 10 000 Difference: 8 fewer per 10 000 (95% CI: 10 fewer to 0 fewer)	$Chi^2 = 2.20$, df = 2 ($P = 0.33$); $I^2 = 9\%$	Low	High-certainty evidence
Hospitalization or death by Day 28	28 161 participants, 5 studies[9,12,25,27,28]	0.81 (0.55–1.20)	12 per 1000	10 per 1000 Difference: 2 fewer per 1000 (95% CI: 5 fewer to 2 more)	$Chi^2 = 6.08$, df = 3 ($P = 0.11$); $I^2 = 51\%$	Unclear	Moderate-certainty evidence due to serious risk of bias[a]
Symptom resolution by Day 14	23 773 participants, 5 studies[12,22,25,27,28]	1.20 (1.02–1.41)	259 per 1000	311 per 1000 Difference: 52 more per 1000 (95% CI: 5 more to 106 more)	$Chi^2 = 49.78$, df = 4 ($P < 0.01$); $I^2 = 92\%$	Unclear	Very low-certainty evidence due to serious risk of bias[b] and very serious inconsistency[c]
Symptom resolution by Day 28	24 874 participants, 4 studies[12,22,25,27]	1.05 (0.92–1.19)	603 per 1000	633 per 1000 Difference: 30 more per 1000 (95% CI: 48 fewer to 115 more)	$Chi^2 = 6.61$, df = 3 ($P = 0.09$); $I^2 = 55\%$	Unclear	Low-certainty evidence due to serious risk[b] of bias and serious inconsistency[d]
Any adverse events during the study period	3435 participants, 7 studies[9,22–25,27,28]	0.98 (0.89–1.08)	274 per 1000	269 per 1000 Difference: 5 fewer per 1000 (95% CI: 30 fewer to 22 more)	$Chi^2 = 3.19$, df = 6 ($P = 0.79$); $I^2 = 0\%$	Low	High-certainty evidence
Serious adverse events during the study period	29 143 participants, 8 studies[9,12,22–25,27]	0.85 (0.59–1.22)	8 per 1000	7 per 1000 Difference: 1 fewer per 1000 (95% CI: 3 fewer to 2 more)	$Chi^2 = 4.90$, df = 4 ($P = 0.30$); $I^2 = 18\%$	Unclear	Moderate-certainty evidence due to serious risk of bias[e]

MH, Mantel–Haenszel method; SoC, standard of care.

[a]Downgraded one level for serious study limitations: some concern in four studies due to a lack of criteria for hospitalizations in four studies and additional lack of reporting in one study.

[b]Downgraded one level for serious study limitations: some concerns in four studies due to a lack of protocol and unblinded participants; high risk of bias in two studies due to potential selective reporting.

[c]Downgraded two levels due to very serious inconsistency: heterogeneity in outcome definitions, considerable statistical heterogeneity.

[d]Downgraded one level for serious inconsistency: heterogeneity in outcome definitions, moderate statistical heterogeneity.

[e]Downgraded one level for study limitations: high risk of bias in two studies due to possible differences in outcome measurement between groups or attrition bias; some concerns in three studies due to lack of blinding and unavailability of protocol.

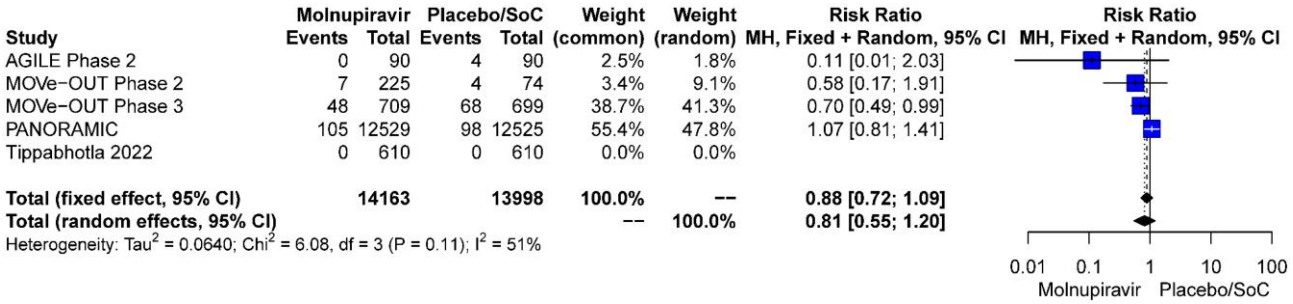

Figure 3. Association between molnupiravir and hospitalization or death by Day 28 in outpatients. MH, Mantel–Haenszel method. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

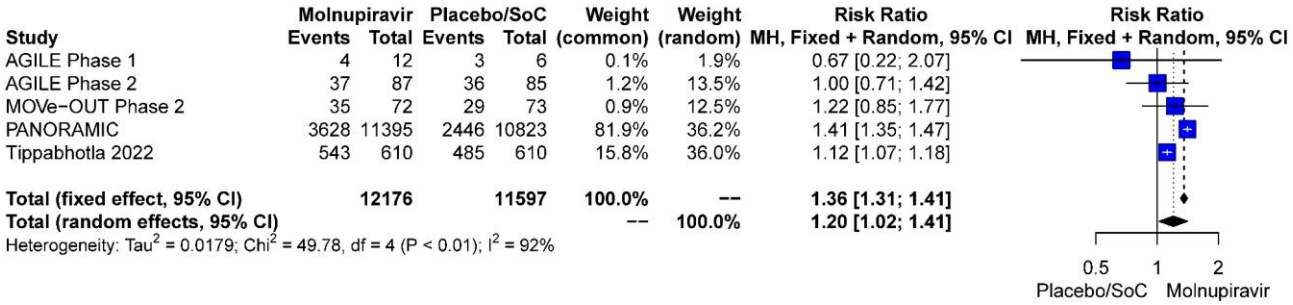

Figure 4. Association between molnupiravir and symptom resolution by Day 14 in outpatients. MH, Mantel–Haenszel method. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

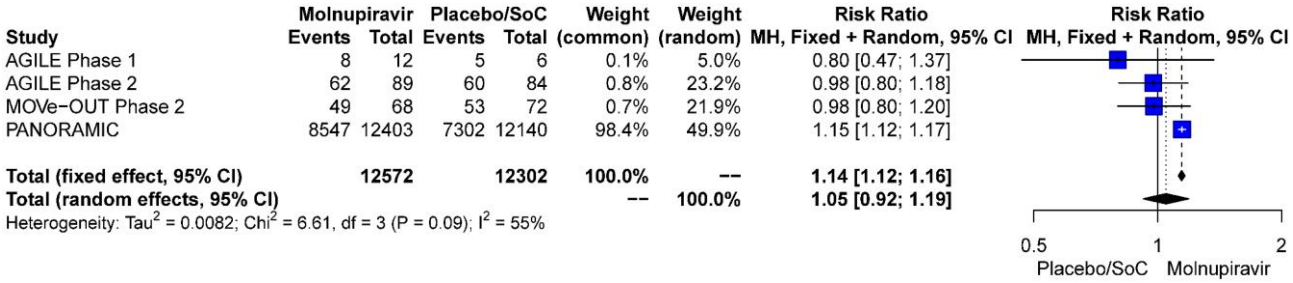

Figure 5. Association between molnupiravir and symptom resolution by Day 28 in outpatients. MH, Mantel–Haenszel method. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

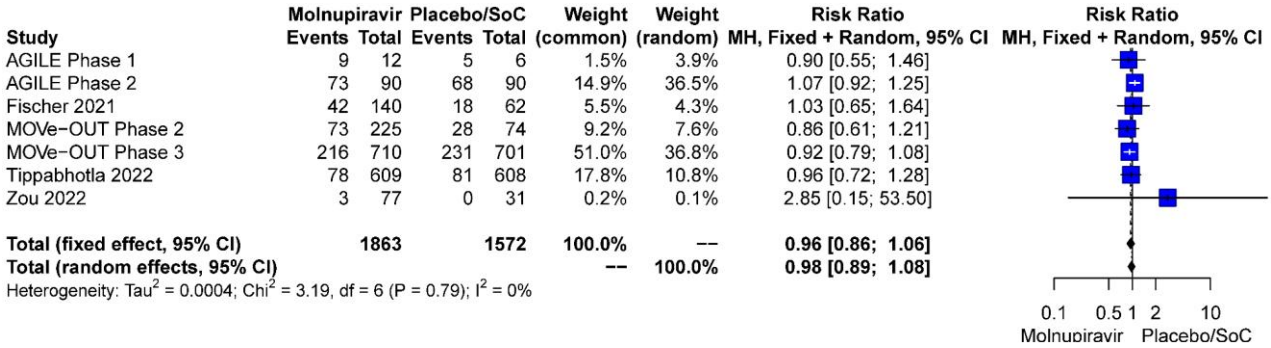

Figure 6. Association between molnupiravir and adverse events in outpatients. MH, Mantel–Haenszel method. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 3. Meta-analysis of efficacy and safety outcomes of molnupiravir versus control in inpatients with COVID-19

Outcome	Study population	Risk ratio, MH, random (95% CI)	Absolute effect estimates (95% CI)		Heterogeneity	Risk of bias	Certainty of evidence
			Placebo/SoC	Molnupiravir			
All-cause mortality by Day 28	293 participants, 1 study[26]	3.78 (0.50–28.82)	13 per 1000	49 per 1000	na	Low	Low-certainty evidence due to very serious imprecision[a]
			Difference: 36 more per 1000 (95% CI: 7 fewer to 362 more)				
Any adverse events during the study period	293 participants, 1 study[26]	0.90 (0.73–1.12)	613 per 1000	552 per 1000	na	Low	Moderate-certainty evidence due to serious imprecision[b]
			Difference: 61 fewer per 1000 (95% CI: 166 fewer to 74 more)				
Serious adverse events during the study period	293 participants, 1 study[26]	0.95 (0.52–1.73)	160 per 1000	152 per 1000	na	Low	Moderate-certainty evidence due to serious imprecision[b]
			Difference: 8 fewer per 1000 (95% CI: 77 fewer to 117 more)				

MH, Mantel–Haenszel method; na, not applicable; SoC, standard of care.
[a]Downgraded two levels for very serious imprecision: very small number of events, very large 95% CI; possibility for either benefit or harm.
[b]Downgraded one level for serious imprecision: small sample size, effect estimate includes both benefit and harm.

Table 2) and probably little or no effect on serious adverse events (RR 0.85, 95% CI 0.59–1.22, 29 143 participants, eight studies, moderate-certainty evidence; Figure 7 and Table 2) during the study period. Certainty of evidence for serious adverse events was downgraded for serious risk of bias due to open-label study design (Table S1). The largest trial (PANORAMIC) only reported on serious adverse events. The subgroup analysis on vaccination status showed no evidence for a difference for molnupiravir on adverse events ($P=0.48$; Figure S5) or serious adverse events ($P=0.08$; Figure S6) between vaccinated and unvaccinated patients. Long-term adverse events were not reported in any study.

Efficacy in inpatients with COVID-19

In hospitalized patients, molnupiravir may increase all-cause mortality by Day 28 compared with placebo/SoC (RR 3.78, 95% CI 0.50–28.82, 293 participants, one study, low-certainty evidence; Table 3). Certainty of evidence for all-cause mortality was downgraded for very serious imprecision due to low events and wide CIs (Table S1). Changes in clinical status and quality of life were not reported.

Safety in inpatients with COVID-19

Molnupiravir compared with placebo/SoC has probably little or no difference on overall adverse events (RR 0.90, 95% CI 0.73–1.12, 293 participants, one study, moderate-certainty evidence; Table 3) and overall serious adverse events (RR 0.95, 95% CI 0.52–1.73, 293 participants, one study, moderate-certainty evidence; Table 3) during the study period. Certainty of evidence for safety outcomes was downgraded for serious imprecision due to wide CIs or few events (Table S1). Long-term adverse events were not reported in any study.

Discussion

Discussion of main results

Based on our systematic review of eight RCTs including 29 254 vaccinated and unvaccinated outpatients with mild to moderate COVID-19, early treatment with molnupiravir has no effect on mortality in the studied outpatient population. Our results do not support an increased benefit on mortality in unvaccinated outpatients because subgroup analysis did not find a significant difference in the outcome compared with vaccinated individuals (Figure S1). However, the number of participants and events in the unvaccinated subgroup was low, thereby limiting the interpretation of this finding. We found that early treatment with molnupiravir probably does not reduce the combined outcome 'hospitalization or death' by Day 28. In this aspect our meta-analysis, which includes recent results of the PANORAMIC trial, contrasts with earlier findings of the pivotal MOVe-OUT Phase 3 trial, which indicated a moderate but statistically significant reduction in the combined outcome (−3% ARR, 95% CI −5.9 to −0.1).[9] PANORAMIC and MOVe-OUT differed in their study populations (vaccinated versus unvaccinated) and were conducted in settings of differing dominant viral variants (omicron versus delta/mu), both of which may have contributed to lower morbidity and mortality observed in the PANORAMIC trial.[9,29] Subgroup analyses on hospitalization or death by Day 28 for studies including unvaccinated versus vaccinated participants indicated that molnupiravir may slightly decrease the combined outcome in an unvaccinated population ($P=0.03$ for group difference; Figure S2), supporting the hypothesis that differences in vaccination status may have contributed to differences in study results for this outcome. However, the credibility of these subgroup effects was rated as low (Table S2). We suggest to focus on the

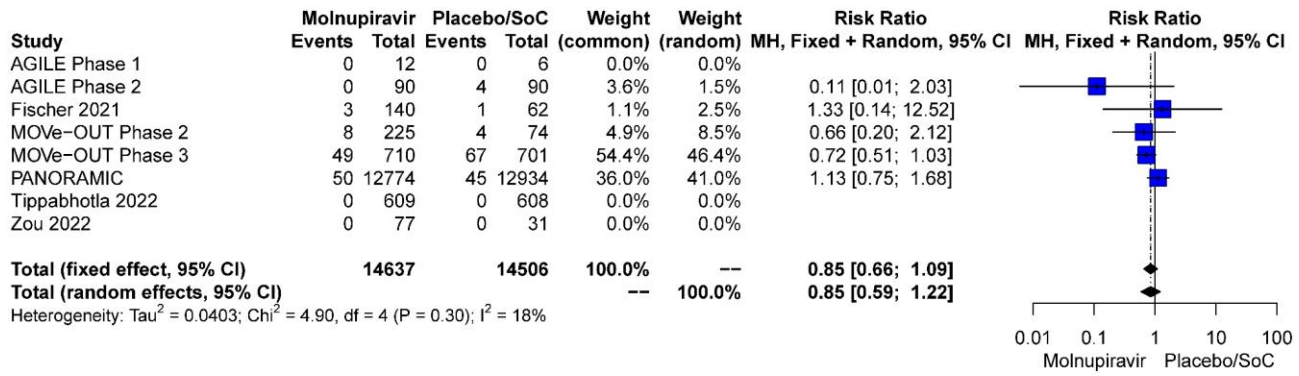

Figure 7. Association between molnupiravir and serious adverse events in outpatients. MH, Mantel–Haenszel method. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

overall effect estimate until data with higher credibility for subgroup effects are available. We are unsure whether molnupiravir increases symptom resolution by Day 14 in outpatients due to very low certainty of evidence. In fact, studies contributing the majority of patients to this outcome had an open-label design, which is disadvantageous for assessing a relatively subjective outcome. There was no effect on symptom resolution by Day 28, which probably reflects the overall mild natural course of COVID-19 in the majority of infected individuals. Subgroup analysis on symptom resolution by Day 14 and Day 28 showed significant group differences for studies including vaccinated versus unvaccinated patients ($P<0.01$ and $P=0.01$, respectively; Figure S3–4) pointing towards a more pronounced effect of molnupiravir in vaccinated individuals based on results of the PANORAMIC trial. However, the credibility of these subgroup effects was rated as low (Table S2). In the meta-analysis, molnupiravir had a favourable safety profile in outpatients with COVID-19 during the study period because it had little or no effect on the incidence of adverse events and serious adverse events in doses up to 800 mg twice daily compared with placebo.

For inpatients with COVID-19, we identified one RCT with 304 patients. Based on limited available data of the MOVe-IN trial, molnupiravir may increase mortality compared with placebo whereas it has little or no effect on other serious adverse and adverse events. It should be mentioned that the majority of patients (~57%) had a mild or moderate disease (no supplemental oxygen) although being hospitalized. In theory, differences in mortality might have been influenced by concomitant administration of remdesivir (22.6% versus 25.6%) or corticosteroids (65% versus 73.1%) in intervention versus placebo arms. Another influencing factor might be a slightly higher proportion of patients with two or more risk factors for progressive disease included in the molnupiravir arm (36.7% versus 30.8%).[26] Further RCTs are required to determine the role of molnupiravir for patients hospitalized for COVID-19, and such trials are ongoing.[30]

Agreements and disagreements with other studies or reviews

Lawrence *et al.* conducted a meta-analysis of four RCTs including COVID-19 outpatients: PANORAMIC, MOVe-OUT, Tippabhotla et al. and another Indian trial not included in our analysis of which preliminary data were published in the Conference on Retroviruses and Opportunistic Infections in February 2022.[31] The authors found no effect of molnupiravir on their key outcome, hospitalization (RR 0.71; 95% CI 0.42–1.22), which is in agreement with our findings.[32] The WHO living guideline group conducted a network meta-analysis that included unpublished data provided by trial authors. Based on six RCTs with 4796 outpatients, the guideline panel concluded in May 2022 that molnupiravir may have a small effect on mortality and probably reduces hospital admission.[33] Based on the inclusion of unpublished data we cannot evaluate the quality of additionally included data or subgroup analyses with respect to vaccination status and time frame of inclusion. However, MOVe-OUT Phase 3 and other RCTs that recruited unvaccinated patients most probably have contributed substantially to the measured effect whereas the largest outpatient trial (PANORAMIC) with 25 783 participants was not included. We assume that interpretation and recommendations regarding molnupiravir may be updated when more recent data from PANORAMIC are being included in the WHO network analysis.

Other meta-analyses included up to five RCTs for efficacy outcomes, all of which are included in our analysis.[34–37] Wen *et al.*[37] included one RCT and two press releases of an interim analysis of MOVe-OUT Phase 3 and the above mentioned Phase 3 trial from India,[31] which was not included in the present meta-analysis because of incomplete publication of trial protocol and data. Moreover, some concerns on data validity have been raised based on study registry entries.[38,39] One meta-analysis focused on safety outcomes based on four RCTs all of which were included in the present analysis.

More recently, several observational studies on molnupiravir were published.[40–43] Zheng *et al.*[42] found that outpatients treated with molnupiravir ($n=2689$) had a higher risk of hospitalization or death within 28 days compared with patients treated with the monoclonal antibody sotrovimab ($n=3331$). There was no control group to assess the overall effect of molnupiravir. Arbel *et al.*[43] used a Cox proportional regression model adjusting for comorbidities and COVID-19 immunity to compare outcomes of 1069 outpatients treated with molnupiravir with untreated controls ($N=18\,799$). Among patients aged 65 and above they found that molnupiravir reduced the risk of hospitalization (HR 0.55;

95% CI 0.34–0.88) whereas this was not the case for younger individuals. Two studies investigated the use of molnupiravir in hospitalized patients. Wong *et al.*[40] compared 1856 patients without supplemental oxygen who were admitted within 5 days of symptom onset and treated with molnupiravir during the omicron BA.2 surge in Hong Kong with 1856 matched controls. The authors concluded there was a reduced risk of all-cause mortality among molnupiravir recipients (crude incidence rate 19.98 versus 38.07 events per 10 000 person-days, HR 0.48; 95% CI 0.4–0.59). Of note, the rate of fully vaccinated participants was only about 6% and 9% in molnupiravir and control groups, respectively. It remains unclear why 13% of the molnupiravir group and 20% of the control group received dexamethasone, which is not recommended in COVID-19 patients not requiring supplemental oxygen because increased mortality has been described.[44–48] Flisiak *et al.*[41] compared outcomes of 203 patients from a Polish national registry who were hospitalized during the omicron surge and treated with molnupiravir with 387 unmatched controls who did not receive any antiviral treatment. The authors observed a significant reduction in mortality during a 28 day follow-up (9.9% versus 16.3%). In this retrospective study, vaccination status was not available and more patients in the control arm received concomitant dexamethasone or baricitinib compared with the molnupiravir arm.

In conclusion, one observational study points towards a reduced risk of hospitalization among outpatients aged 65 or above who were treated with molnupiravir. Unfortunately, subgroup analysis for age was not feasible in our meta-analysis to further evaluate this factor. There is limited evidence for a mortality reduction in hospitalized patients from observational data, which may be influenced by differences in immunization and concomitant COVID-19 treatments. Nonetheless, results from observational studies may also indicate potential benefit of molnupiravir for hospitalized risk groups who are currently not covered by existing RCTs.

Limitations

There are inherent limitations to the external validity of the trials included in this meta-analysis that are related to the highly dynamic pandemic situation. First, changes in levels of population immunity, SARS-CoV-2 variant pathogenicity, and drug susceptibility may affect the relative benefit of antiviral drugs and the applicability of study results obtained in the past to the present. Of note, *in vitro* studies suggest sustained molnupiravir activity against all tested SARS-CoV-2 variants.[49–52]

A general limitation is that included RCTs did not focus on high-risk patients with severe immunosuppression, precluding any conclusions on effects in this vulnerable group. Another limitation is that subgroup analyses for vaccination status were not feasible at a patient level due to the lack of raw data. Our analysis was therefore limited to compare studies exclusively including unvaccinated participants with participants of the PANORAMIC trial (at least 99% of whom had received at least one vaccine dose). In addition, subgroup analyses on different status of immunization (number of vaccine doses, previous infections) or other specific risk factors were not feasible due to lack of data. Due to differences in reporting of included age groups, we were also unable to conduct subgroup analyses for different age categories. This is particularly limiting because age-specific effects of molnupiravir and another oral antiviral, nirmatrelvir, have been demonstrated in observational studies including vaccinated COVID-19 patients.[43,53,54]

The meta-analysis based on eight studies with 29 254 outpatients indicates a favourable safety profile. Here, one limitation is that PANORAMIC only reported on serious adverse events. In addition, none of the studies reported on long-term adverse events. Concerns on the safety of molnupiravir have arisen from preclinical experiments and its mode of action. In *in vitro* studies, prolonged exposure to high doses of molnupiravir was associated with mammalian host cell DNA mutagenesis.[13] Moreover, concentrations higher than those obtained by standard dosing resulted in teratogenic effects in an animal reproduction study.[11] Although our analysis does not indicate harms in outpatients receiving a standard course of treatment, mutagenic or teratogenic effects were not specifically assessed and their identification may require prolonged follow-up.[14]

Conclusions

Our meta-analysis indicates that early molnupiravir treatment in a community of predominantly immunized COVID-19 outpatients does not reduce mortality and probably does not reduce the risk for the combined endpoint ‘hospitalization or death’. The evidence is uncertain about beneficial effects on symptom resolution. Subgroup analyses did not identify a consistent benefit of molnupiravir in unvaccinated COVID-19 outpatients but were limited by low numbers of unvaccinated participants and events. For inpatient treatment, we found a potential increase in mortality, which requires careful monitoring in ongoing clinical trials. We therefore conclude that current data do not support routine use of molnupiravir in immunocompetent individuals with COVID-19. There are limited data on high-risk groups, including patients with severe immunosuppression, who may benefit from antiviral treatment. Controlled clinical trials comparing molnupiravir and other antivirals in high-risk groups could provide additional insights to guide treatment recommendations.

Funding

This research was carried out as part of our routine work.

Transparency declarations

J.J.M. has received funds for symposia or lectures organized by Gilead Sciences. He attended advisory board meetings of Gilead Sciences and Astra Zeneca. All other authors: none to declare.

Author contributions

N.S., J.J.M. and S.W. conceptualized the research question and study protocol. Risk of bias assessment for included RCTs was done by S.W., N.S. and N.K. Data extraction, statistical analysis and visualization was performed by S.W., N.K. and N.S. J.J.M., S.W., H.G., N.K., M.S. and N.S. were involved in critical discussion of the results from a clinical, virological and methodological point of view. J.J.M., S.W. and N.S. wrote the original manuscript. All authors were involved in critical revision for important intellectual content and approved the final version of the manuscript.

Supplementary data

Figures S1 to S6, Tables S1 and S2, and Appendix S1 are available as Supplementary data at *JAC* Online.

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