**Supplementary Material** for the 2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Treatment and Management of COVID-19: Antiviral Treatment for Mild to Moderate COVID-19 in Adults

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## METHODS

### Panel formation and conflicts of interest

The chair and vice chair of the guideline panel were selected by the leadership of IDSA. Twenty-six additional panelists comprised the full panel. The panel included clinicians with expertise in infectious diseases, pediatric infectious diseases, critical care medicine, pulmonology, maternal fetal medicine, and pharmacology, as well as biostatistics. Guideline methodologists oversaw all methodological aspects of the guideline development, including the identification and summarization of scientific evidence for each clinical question. IDSA staff oversaw all administrative and logistic issues related to the guideline panel.

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guidelines Subcommittee (SPGS) Chair, and if necessary, the Conflict of Interests Ethics Committee. This assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of the guideline for the disclosures reported to IDSA.

### Practice recommendations

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [IOM 2011]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [IDSA CPG Handbook].

### Review and approval process

Feedback was obtained from two external individual peer expert reviewers as well as the endorsing organizations. The IDSA Standards and Practice Guidelines Subcommittee (SPGS) and Board of Directors reviewed and approved the guideline prior to publication.

### Process for updating

IDSA guidelines are regularly reviewed for currency. The need for updates to the guideline is determined by a scan of current literature and the likelihood that any new data would impact the recommendations. Any changes to the guideline will be submitted for review and approval to the appropriate Committees and Board of IDSA.

### Clinical questions

Each clinical question was formatted according to the PICO style: Patient/Population (P), Intervention/Indicator (I), Comparator/Control (C), Outcome (O). For each PICO question, outcomes of interest were identified a priori and rated for their relative importance for decision-making.

**Literature search**
A literature search was conducted in Ovid Medline, Embase, and Cochrane Library in September 2024. Searches were limited to studies published in English.

Search strategy:
((("molnupiravir"[Supplementary Concept] OR "nirmatrelvir and ritonavir drug combination"[Supplementary Concept] OR "nirmatrelvir"[Supplementary Concept] OR "remdesivir"[Supplementary Concept] OR Lagevrio[tiab] OR molnupiravir[tiab] OR nirmatrelvir[tiab] OR "nirmatrelvir and ritonavir drug combination"[tiab] OR Paxlovid[tiab] OR remdesivir[tiab] OR Veklury[tiab]) AND (("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[Subheading] OR "trial"[tiab] OR "groups"[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])) AND (("2023/01/01"[dp] : "3000/12/31"[dp]) OR ("2023/01/01"[crdt] : "3000/12/31"[crdt]))) NOT ("address"[Publication Type] OR "autobiography"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "Book Illustrations"[Publication Type] OR "Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "Expression of Concern"[Publication Type] OR "interactive tutorial"[Publication Type] OR "interview"[Publication Type] OR "lecture"[Publication Type] OR "legal case"[Publication Type] OR "legislation"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "patient education handout"[Publication Type] OR "periodical index"[Publication Type] OR "personal narrative"[Publication Type] OR "portrait"[Publication Type] OR "hascommenton"[All Fields] OR "Cartoons as Topic"[Mesh] OR "case history"[tiab] OR "case histories"[tiab] OR "case report"[tiab] OR "case reports"[tiab]"case studies"[tiab]OR "case study"[tiab]))

**Study selection**
Inclusion and exclusion criteria were pre-defined. The eligibility criteria below were used.
Inclusion criteria:

- *Patient population*- Patients with mild or moderate COVID-19
- *Intervention*- Nirmatrelvir/ritonavir, molnupiravir, or remdesivir
- *Comparator*- No nirmatrelvir/ritonavir, no molnupiravir, or no remdesivir, respectively
- *Outcomes*- Mortality, hospitalization, symptom resolution, serious adverse events
- *Study design***-** RCTs

Exclusion criteria:

- *Patient population*- Patients without severe or critical COVID-19
- *Intervention*- N/A
- *Comparator*- N/A
- *Study design***-** Review articles, case reports

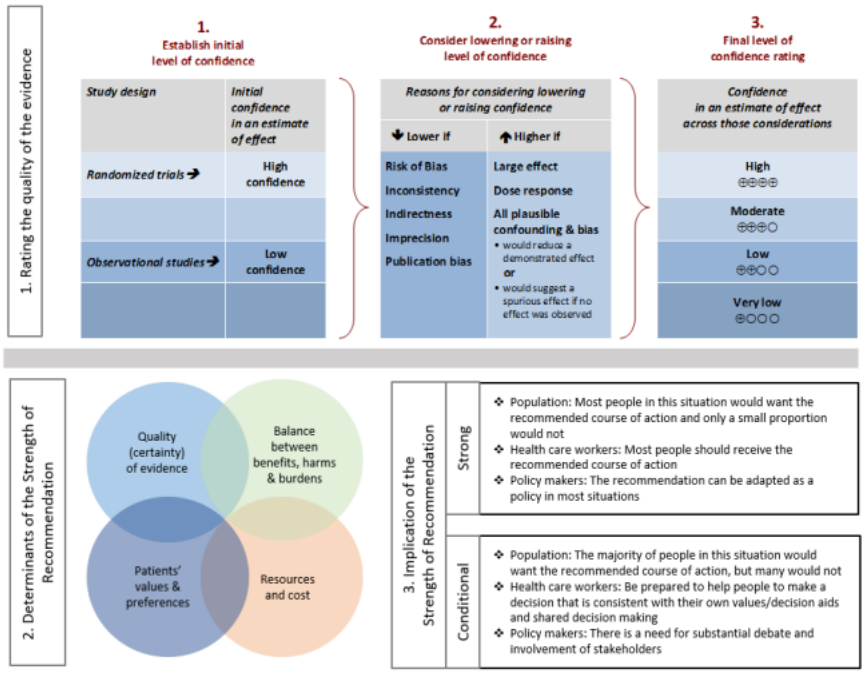
**Data extraction and analysis**
Guideline methodologists, with panelist assistance, extracted the data for each pre-determined patient-important outcome. If a relevant publication was missing raw data for an outcome prioritized by the panel, an attempt was made to contact the author(s) for the missing data.

**Evidence to decision**
Guideline methodologists prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. Risk of bias was assessed by using the Cochrane Risk of Bias tool for RCTs [Higgins 2011]. The certainty of evidence was determined first for each critical and important

outcome and then for each recommendation using the GRADE approach for rating the confidence in the evidence [Guyatt 2008, GRADE Handbook/Schunemann]. Evidence profiles were developed using the GRADEpro Guideline Development Tool [Guyatt 2008] and reviewed by panel members.
The Evidence to Decision framework [GRADEpro] was used to translate the evidence summaries into a practice recommendation. All recommendations are labeled as either "strong" or "conditional" according to the GRADE approach [IDSA CPG Handbook]. The words "we recommend" indicate strong recommendations and "we suggest" indicate conditional recommendations. Supplementary Figure 1 provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparator treatment or tests are not formally stated, the comparison of interest is implicitly referred to as "not using the intervention" (either not using a specific treatment or a diagnostic test).
All members of the panel participated in the preparation of the draft guideline and approved the recommendation.

## TABLES AND FIGURES

**Supplementary Figure 1.** Approach and implications to rating the quality of evidence and strength of recommendations using GRADE methodology (unrestricted use of figure granted by the U.S. GRADE Network)



**Supplementary Table 1.** Characteristics of included studies

| Author Year | Country/ Hospital | Study design | N (intervention / comparator); % female | Age mean (SD)/Median (IQR) | Severity of disease | Intervention (study arms) | Comparator | Co-interventions | Outcomes reported | Funding source |
|---|---|---|---|---|---|---|---|---|---|---|
| Hammond 2024 (Epic-SR) | USA, UK, Mexico, Turkey, Argentina, Brazil, Thailand, Bulgaria, Ukraine, Romania, Malaysia, Slovakia, Poland, Hungary, Czech Republic, South Africa, Japan, South Korea, Spain, Puerto Rico, Poland, Colombia/NA | RCT | 1296 (Nirmatrelvir-ritonavir: 658/Placebo: 638);<br><br>54% female | 42 (18-87) | Outpatient adults with RT-PCR or rapid antigen confirmed SARS-CoV-2 infection and associated signs and symptoms of COVID-19 occurring ≤5 days before randomization | Nirmatrelvir (300 mg) and ritonavir (100 mg) every 12 hours for 5 days | Placebo with inactive filler every 12 hours for 5 days | N/A | Time to sustained alleviation of all COVID-19 symptoms through day 28, COVID-19 related hospitalization or death from any cause through day 28, Number of medical visits and number of days in hospital/ICU through day 28, Day 5 viral load, Day 10 or 14 viral load rebound, Symptom rebound, Side-effect profile | Pfizer |
| Hammond 2022 (Epic-HR) | USA, South Africa, Turkey, Argentina, Mexico, Bulgaria, Russia, Ukraine, Thailand, Colombia, Czech Republic, Malaysia, Japan, | RCT | 2246 (Nirmatrelvir-ritonavir 1120/ Placebo 1126);<br><br>53.2% female | 45 (18-86) | Asymptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe disease | Nirmatrelvir (300 mg) and ritonavir (100 mg) every 12 hours for 5 days + placebo after completion | Matching placebo capsules for 5 days | N/A | COVID-19 related hospitalizations through day 28, Viral load from baseline through day 14, Incidence of adverse effects | Pfizer |

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| | Poland, Hungary/NA | | | | | | | | | |
| Liu 2023 | China: 5 COVID-19-designated hospitals | Parallel RCT | 264 (132/132);<br><br>46.2% female | Mean (SD):<br><br>Paxlovid + standard care: 71.50 (11.61)<br><br>Standard treatment: 69.20 (14.43) | Hospitalized patients 18-90 years with severe comorbidities, confirmed SARS CoV-2 infection by real-time PCR within the previous 48 h, duration from symptoms onset to hospital admission <5 days or SARS-CoV-2 nucleic acid Ct value ≤25 by RT-PCR<br><br>Severe defined as severe comorbidities, SOFA or Charlson score ≥2. Severe comorbidities defined as immunosuppressive disease or immunosuppressive status, chronic obstructive pulmonary disease, hypertension complicated with target organ injury, acute and chronic cardiac insufficiency, chronic renal insufficiency, etc. | Received Paxlovid at a dose of 300 mg nirmatrelvir (two tablets) + 100 mg ritonavir (one tablet), orally administered every 12 h for 5 days | Standard care including antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and nutrient support, etc. | Standard care including antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and nutrient support, etc. | 28-day all-cause mortality,<br>Risk of death assessed in subgroup participants based on duration since symptoms onset to hospital admission,<br>Efficacy included in-hospital mortality,<br>Proportion of progress to severe COVID-19 within 14 days,<br>Proportion of acute exacerbation from the chronic disease within 14 days,<br>SARS–CoV-2 RNA clearance within 7 days and 14 days,<br>Duration of SARS–CoV-2 RNA clearance, length of hospital and ICU stay,<br>Organ support days to 28 days,<br>Adverse events occurring during and after treatment period | National Natural Science Foundation of China |

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| Horby 2024 RECOVERY | 75 hospitals in UK | RCT | 923 (445/478);<br><br>40.7% female | Age: Mean (SD)<br><br>Nirmatrelvir/r 75.8 (13.1)<br><br>Usual care: 69.3 (14.1)<br><br>Molnupiravir: 71.2 (14.3)<br><br>Usual care: 71.6 (14.0) | Adults admitted to the hospital with confirmed SARS-CoV-2 infection | Nirmatrelvir/r 300 mg/100 mg twice daily for 5 days<br><br>Molnupiravir 800 mg orally twice daily for 5 days | Usual care | None | All-cause mortality at 28 days,<br>Time to discharge from hospital,<br>Progression to invasive mechanical ventilation or death within 28 days | UK Research and Innovation (Medical Research Council)<br><br>National Institute of Health and Care Research<br><br>Wellcome Trust |
| Beigel 2020 | USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore/ 60 trial sites and 13 subsites | RCT | 1062<br><br>(541/521);<br><br>35.6% female | Mean: 58.9 (15) | Met 1 of the following suggestive of lower respiratory tract infection at time of enrollment: radiographic infiltrates by imaging study, $SpO_2$ ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation | Remdesivir 200 mg loading dose once day 1, 100 mg maintenance dose once daily days 2-10 | (1) Placebo 200 mg once day 1, 100 mg once daily days 2-10 | Supportive care according to the standard of care for the trial site hospital; if a hospital had a written policy or guideline for use of other treatments for COVID-19, patients could receive those treatments | Mortality at day 14,<br>Number of recoveries,<br>Time to recovery (days),<br>Hazard ratio of mortality,<br>Hospital discharge,<br>Adverse events | National Institute of Allergy and Infectious Diseases<br><br>National Institutes of Health, Bethesda, MD<br><br>Governments of Japan, Mexico, Denmark, and Singapore<br><br>Seoul National University Hospital<br><br>United Kingdom |

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| | | | | | | | | | | Medical Research Council |
| Spinner 2020 | United States, Europe, and Asia/ 105 hospitals | RCT | 584<br><br>(193/191/200);<br><br>% female not reported | N/A | Moderate COVID-19 pneumonia (any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air) | Remdesivir (5-Day Group) 200 mg once daily day 1, 100 mg once daily days 2-5 via IV | (1) Remdesivir (10-Day Group): 200 mg once daily day 1, 100 mg once daily days 2-10 via IV<br><br>(2) SoC | Steroids, HCQ, Lopinavir-ritonavir, TCZ, AZ | Day 11 clinical status on 7-point scale, No. (%) (Includes Mortality at Day 11), Clinical improvement (at day 5, 7, 11, 14, 28), Recovery (at day 5, 7, 11, 14, 28), Adverse events | Gilead Sciences |
| WHO Solidarity Trial Consortium (Pan) 2021 | 30 countries | RCT | 11266 (total)<br><br>(Remdesivir 2743/2708);<br><br>38.0% female | N/A | Age ≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, no anticipated transfer within 72 hours, and, in the physician's view, no contraindication to any study drug | Remdesivir 200 mg once daily day 0, 100 mg once daily days 1-9 | (1) SoC | Corticosteroids, convalescent plasma, anti-IL-6 drug, non-trial interferon, non-trial antiviral | Mortality at day 28, Ventilation in those not already being ventilated at the time of randomization | Participating countries covered almost all local costs and WHO covered all other study costs, receiving no extra funding |
| Gottlieb 2021 | 64 sites in US, Spain, Denmark, and UK | RCT | 562 (279/283); 47.9% female | 50 (15) | SARS CoV-2 PCR positive within 4 days prior to screening with ≥1 symptom and symptom onset ≤7 days | Remdesivir 200 mg x 1 day, then 100 mg daily for 2 days | Placebo | None | Mortality, All cause hospitalization, COVID-19 related hospitalization , COVID-19 related medically attended visits, Change in nasopharyngeal viral load, Serious adverse events | Gilead |

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| Sise 2024 | 55 sites in Brazil, Portugal, Spain, UK, and US | RCT | 243 (160/80);<br><br>42.8% female | 69 (14) | Age ≥12 years, ≥40kg, hospitalized with COVID-19, oxygen saturation ≤94%, and either severely reduced kidney function or kidney failure | Intravenous remdesivir 200 mg on day 1, 100 mg daily up to day 5 | Saline placebo | Corticosteroids, monoclonal antibodies | All-cause death or invasive mechanical ventilation through day 29,<br>All-cause death through day 29,<br>Clinical status assessed by an 8-point ordinal scale at days 15 and 29,<br>Adverse events,<br>Serious adverse events,<br>Plasma concentrations of remdesivir | Gilead Sciences |
| Jayk Bernal 2021 | 107 sites in 20 countries | RCT | 1433 (716/717);<br><br>51.3% female | 43.0 (Range: 18-90) | Ambulatory adults with mild or moderate COVID-19 (≥1 symptom), a positive SARS-CoV-2 test within 5 days, and ≥1 risk factor for the development of severe disease | Molnupiravir 800 mg twice daily for 5 days | Placebo | Standard of care including antipyretics, anti-inflammatory agents, glucocorticoids | Mortality,<br>Hospitalization,<br>Rate of hospitalization,<br>Clinical improvement,<br>Serious adverse events | Merck |
| Khoo 2023 | UK | RCT | 180 (90/90);<br><br>57.0% female | Median: 43 | Adult outpatients (50/50 vaccinated) with PCR-confirmed SARS-CoV-2 infection within five days of symptom onset | Molnupiravir at 800 mg twice daily for 10 doses over 5 days | Matching placebo twice daily for 10 doses over 5 days | Standard of care (symptomatic relief including antipyretics) | Time from randomization to negative PCR with an exploratory virological endpoint of change in viral titer;<br>Change in viral titer at day 5;<br>Clinical progression: WHO Clinical Progression Scale for COVID- 19, NEWS2 score (UK Royal College of Physicians | Ridgeback Biotherapeutics, UK National Institute for Health and Care Research, Medical Research Council and The Wellcome Trust |

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| | | | | | | | | | measuring acute illness, the FLU-PRO; Patient-reported: presence/severity of influenza-like symptoms across 6 domains of nose, throat, eyes, chest/respiratory, gastrointestinal and body/system at day 15 and 29; Overall survival (time-to-event); Safety, tolerability | |
| Sinha 2022 | 23 hospitals in India | RCT | 1218 (608/610);<br><br>31.6% female | Age: Mean (SD)<br><br>Molnupiravir: 35.2 (10.8)<br><br>Standard of care: 34.8 (10.8) | Adults with mild COVID-19 symptoms confirmed positive within 48 hours of enrollment and within 5 days of first symptom onset | Molnupiravir 800 mg administered orally every 12 hours for 5 days | Standard of care including hydration, antipyretics, antitussive multivitamins, ivermectin, or hydroxychloroquine | None | Rate of hospitalization up to day 14 and 28; Proportion with clinical improvement; Rate of SARS-CoV-2 RT-PCR negativity; Change in SARS-CoV-2 viral load at end of treatment, day 10 and 14; Time to clinical improvement through day 14; Severity of treatment-emergent adverse events; Proportion who discontinued study drug use due to adverse events | Hetero Molnupiravir Investigator group |
| Zou 2022 | China/Third People's Hospital of Shenzhen | RCT | 108 (77/31);<br><br>44.4% female | Median (range) molnupiravir: 39 (20, 63) | Adults with mild/moderate COVID-19 who tested positive for SARS-CoV-2 Omicron variant | Molnupiravir (800 mg twice per day) plus basic | Basic treatment for 5 days | Basic treatment, which consisted of vitamin C, lianhuaqingw | Time of viral RNA; Percentage of patients who were negative for SARS-CoV-2 infectious | National Key Research and Development Project, Shenzhen |

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| | | | | Median (range) Control: 42 (22, 61) | and had initial onset of symptoms for ≤5 days prior to treatment | treatment for 5 days | | en granule, and nasal irrigation | virus on days 5, 7, and 10;<br>Duration of fever, time to symptom alleviation and laboratory test results (AST, ALT, CK, CK-MB, LDH, IL-6, CRP, Bun, Cr);<br>Serious adverse events | Science and Technology Research and Development Project and in part from the National Science and Technology Major Projects |
| Butler 2023 | UK | RCT | 25783 (12821/12962);<br><br>58.6% female | Mean (range): 56.6 (18 to 99) | Adults with comorbidities and ongoing symptoms from COVID-19 that started within the previous 5 days and a positive PCR or rapid antigen SARS-CoV-2 test within the past 7 days | Molnupiravir 800 mg twice daily for 5 days | Usual care | Usual care | All-cause, non-elective hospital admission and/or death within 28 days of randomization,<br>Time to self-reported recovery,<br>Time to early sustained recovery (recovered by day 14 and remained recovered until day 28)<br>Time to sustained recovery (date participant first reported recovery and subsequently remained well until 28 days),<br>0-10 rating of how well participants felt,<br>Time to initial alleviation of symptoms (date first reported as minor/none),<br>Time to sustained alleviation of symptoms (date first | NIHR |

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| | | | | | | | | | reported as minor/none and subsequently remained minor/none until 28 days),<br>Time to initial reduction of severity of symptoms,<br>Contacts with health and social services,<br>Hospital assessment without admission,<br>Oxygen administration,<br>New household COVID-19 infections,<br>Safety outcome measures | |
| Caraco 2021 | 173 sites in 23 countries | RCT | 302 (228/74);<br><br>47.4% female | Mean (range): 49.2 (18-84) | Adults with mild, moderate, or laboratory-confirmed COVID-19 with onset of symptoms up to 7 days before randomization | Molnupiravir 200 mg twice daily for 5 days<br><br>Molnupiravir 400 mg twice daily for 5 days<br><br>Molnupiravir 800 mg twice daily for 5 days | Placebo twice daily for 5 days | None | Proportion of patients who were hospitalized/died,<br>Time to improvement of COVID-19 symptoms,<br>Time to progression of COVID-19 symptoms,<br>WHO Clinical Progression Scale Score,<br>Presence/severity of COVID-19 symptoms | Merck Sharp & Dohme Corp. |
| Fischer 2021 | 10 sites in US | RCT | 202;<br><br>51.5% female | Age: Median (range by treatment arm)<br><br>Molnupiravir 200 mg: 32 (19-65) | Unvaccinated adults with a positive test for SARS-CoV-2 infection within 96 hours and onset of symptoms within 7 days of | Molnupiravir 200 mg every 12 hours x 5 days<br><br>Molnupiravir 400 mg every | Placebo | None | Mortality,<br>Change in SARS-CoV-2 viral load from baseline,<br>Median time to COVID-19 symptom resolution,<br>Isolation of infectious virus, | Merck and Ridgeback Biotherapeutics |

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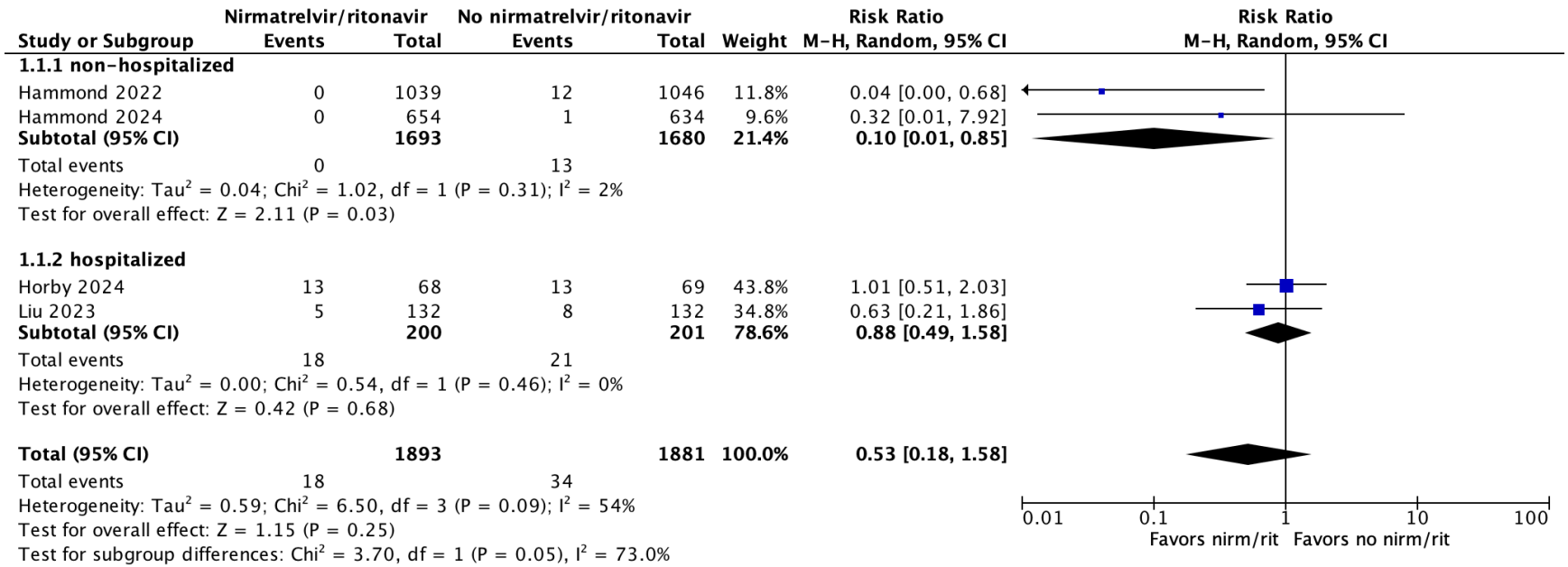
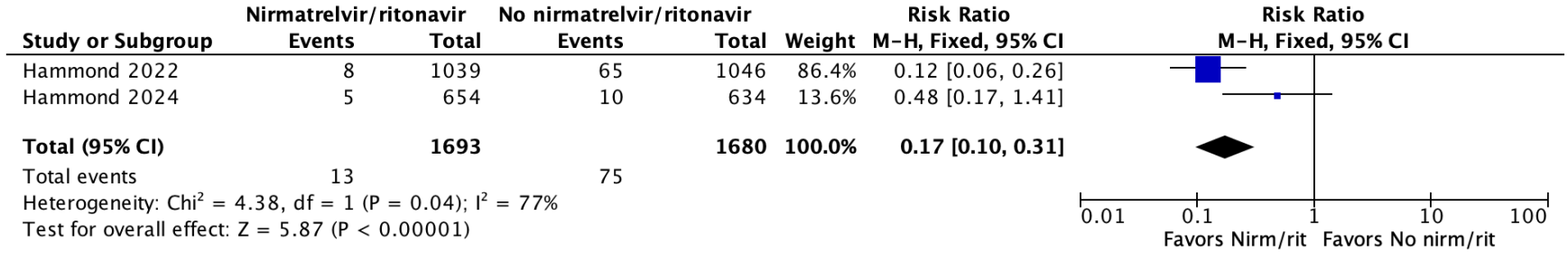
| | | | | Molnupiravir 400 mg: 42.5 (19-82)<br><br>Molnupiravir 800 mg: 42 (18-68)<br><br>Placebo: 39 (19-71) | treatment initiation | 12 hours x 5 days<br><br>Molnupiravir 800 mg every 12 hours day x 5 days | | | SAEs | |
| Arribas 2022 | 65 sites in 15 countries | RCT | 304 (226/78);<br><br>43.4% female | Age: Mean (SD)<br><br>Molnupiravir 200 mg: 56.9 (14.2)<br><br>Molnupiravir 400 mg: 57.0 (14.0)<br><br>Molnupiravir 800 mg: 56.8 (13.7)<br><br>Placebo: 57.1 (14.2) | Adults requiring in-hospital treatment for laboratory-confirmed COVID-19 with sign/symptom onset ≤10 days before randomization | Molnupiravir 200 mg twice daily orally for 5 days<br><br>Molnupiravir 400 mg twice daily orally for 5 days<br><br>Molnupiravir 800 mg twice daily orally for 5 days | Placebo | Remdesivir, glucocorticoids | Safety (adverse events),<br>Sustained recovery through day 29,<br>All-cause mortality through day 29,<br>WHO Clinical Progression Scale,<br>Pulmonary scale (7-point ordinal scale),<br>National Early Warning Score | Merck Sharp & Dohme Corp. |
| Guan 2023 | NR | RCT | 1408 (709/699);<br><br>51.3% female | Median (range): 43 (18-90) | Patients with ≥1 risk factor for progression to severe COVID-19, ≥1 COVID-19 symptom with onset ≤5 days prior to randomization | Molnupiravir 800 mg twice daily orally for 5 days | Placebo twice daily orally for 5 days | NR | 15-item symptom diary,<br>Time to sustained resolution/improvement of symptoms through day 29,<br>Time to progression,<br>Time to first symptom resolution/alleviation | Merck Sharp & Dohme LLC |

**Supplementary Figure 2.** Forest plot for the outcome of mortality for nirmatrelvir/ritonavir



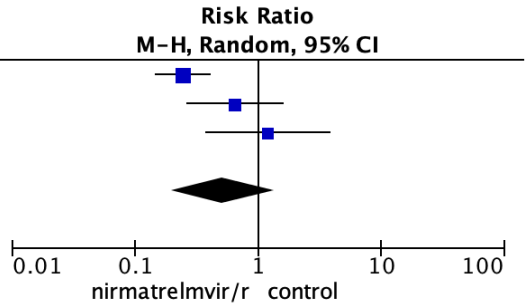

**Supplementary Figure 3.** Forest plot for the outcome of hospitalizations for nirmatrelvir/ritonavir



**Supplementary Figure 4.** Forest plot for the outcome of serious adverse events (SAEs) for nirmatrelvir/ritonavir

| Study or Subgroup | Nirmatrelvir/ritonavir Events | Total | No nirmatrelvir/ritonavir Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hammond 2022 | 18 | 1109 | 74 | 1115 | 40.1% | 0.24 [0.15, 0.41] |
| Hammond 2024 | 8 | 654 | 12 | 634 | 32.6% | 0.65 [0.27, 1.57] |
| Liu 2023 | 6 | 132 | 5 | 132 | 27.2% | 1.20 [0.38, 3.84] |
| **Total (95% CI)** | | **1895** | | **1881** | **100.0%** | **0.52 [0.20, 1.35]** |
| Total events | 32 | | 91 | | | |

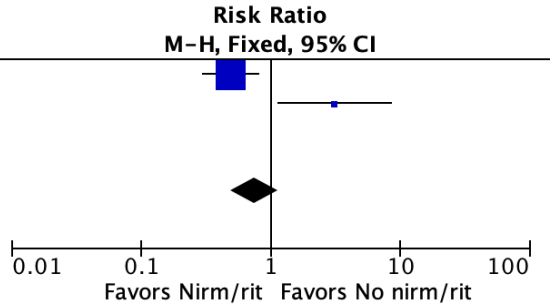
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 8.06$, df = 2 (P = 0.02); $I^2 = 75\%$
Test for overall effect: Z = 1.34 (P = 0.18)




**Supplementary Figure 5.** Forest plot for the outcome of adverse events leading to treatment discontinuation for nirmatrelvir/ritonavir

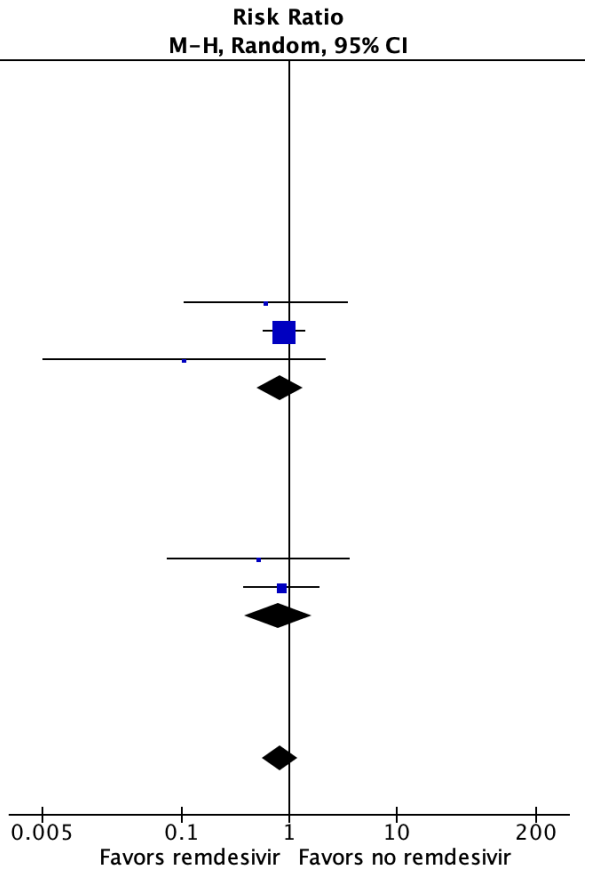
| Study or Subgroup | Nirmatrelvir/ritonavir Events | Total | No nirmatrelvir/ritonavir Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hammond 2022 | 23 | 1109 | 47 | 1115 | 90.2% | 0.49 [0.30, 0.80] |
| Hammond 2024 | 16 | 654 | 5 | 634 | 9.8% | 3.10 [1.14, 8.42] |
| Liu 2023 | 4 | 132 | 132 | 0 | | Not estimable |
| **Total (95% CI)** | | **1895** | | **1749** | **100.0%** | **0.75 [0.50, 1.13]** |
| Total events | 43 | | 184 | | | |

Heterogeneity: $Chi^2 = 10.58$, df = 1 (P = 0.001); $I^2 = 91\%$
Test for overall effect: Z = 1.39 (P = 0.16)



**Supplementary Figure 6.** Forest plot for the outcome of mortality for remdesivir

| Study or Subgroup | Remdesivir Events | Remdesivir Total | No remdesivir Events | No remdesivir Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **25.1.1 non-hospitalized** | | | | | | |
| Gottlieb 2021 | 0 | 279 | 0 | 283 | | Not estimable |
| **Subtotal (95% CI)** | | **279** | | **283** | | **Not estimable** |
| Total events | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **25.1.2 hospitalized (5-day Rx)** | | | | | | |
| Beigel 2020 | 2 | 55 | 3 | 50 | 4.4% | 0.61 [0.11, 3.48] |
| Sise 2024 | 41 | 166 | 23 | 83 | 69.6% | 0.89 [0.58, 1.38] |
| Spinner 2020 | 0 | 191 | 2 | 100 | 1.5% | 0.11 [0.01, 2.17] |
| **Subtotal (95% CI)** | | **412** | | **233** | **75.4%** | **0.82 [0.50, 1.34]** |
| Total events | 43 | | 28 | | | |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.06$, df = 2 (P = 0.36); $I^2 = 3\%$ | | | | | | |
| Test for overall effect: Z = 0.80 (P = 0.42) | | | | | | |
| **25.1.3 hospitalized (10-day Rx)** | | | | | | |
| Spinner 2020 | 2 | 193 | 2 | 100 | 3.5% | 0.52 [0.07, 3.62] |
| WHO Solidarity Trial Consortium 2021 | 11 | 661 | 13 | 664 | 21.0% | 0.85 [0.38, 1.88] |
| **Subtotal (95% CI)** | | **854** | | **764** | **24.6%** | **0.79 [0.38, 1.65]** |
| Total events | 13 | | 15 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 (P = 0.64); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.53) | | | | | | |
| **Total (95% CI)** | | **1545** | | **1280** | **100.0%** | **0.83 [0.57, 1.19]** |
| Total events | 56 | | 43 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.28$, df = 4 (P = 0.68); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.03 (P = 0.30) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.94), $I^2 = 0\%$ | | | | | | |

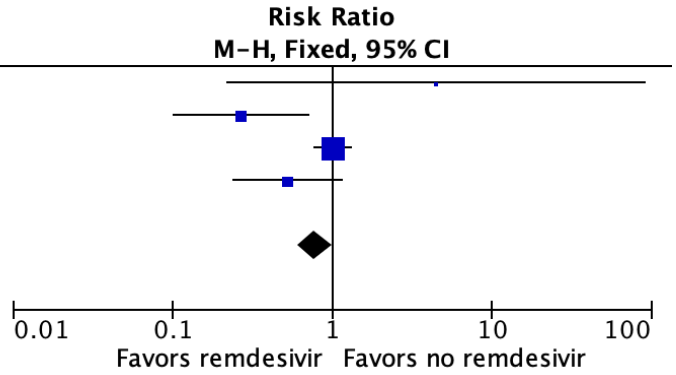


**Supplementary Figure 7.** Forest plot for the outcome of serious adverse events (SAEs) for remdesivir

| Study or Subgroup | Remdesivir Events | Remdesivir Total | No remdesivir Events | No remdesivir Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Beigel 2020 | 2 | 55 | 0 | 49 | 0.6% | 4.46 [0.22, 90.78] |
| Gottlieb 2021 | 5 | 279 | 19 | 283 | 20.8% | 0.27 [0.10, 0.70] |
| Sise 2024 | 82 | 163 | 40 | 80 | 59.2% | 1.01 [0.77, 1.31] |
| Spinner 2020 | 9 | 191 | 18 | 200 | 19.4% | 0.52 [0.24, 1.14] |
| **Total (95% CI)** | | **688** | | **612** | **100.0%** | **0.78 [0.61, 1.00]** |
| Total events | 98 | | 77 | | | |

Heterogeneity: $Chi^2 = 10.50$, df = 3 (P = 0.01); $I^2 = 71\%$

Test for overall effect: Z = 1.95 (P = 0.05)

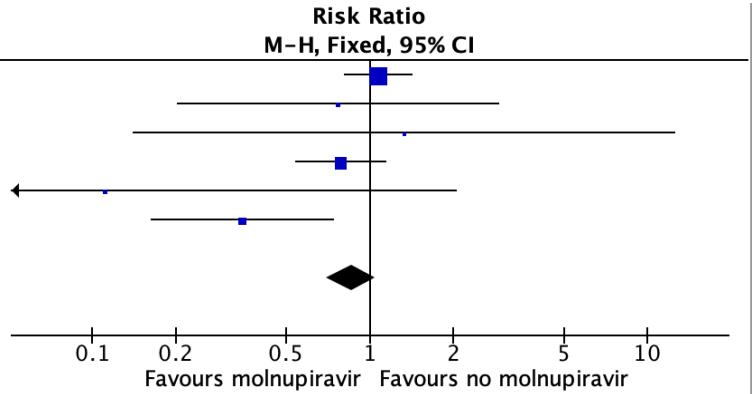


**Supplementary Figure 8.** Forest plot for the outcome of hospitalization for molnupiravir

| Study or Subgroup | Molnupiravir Events | Molnupiravir Total | No molnupiravir Events | No molnupiravir Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Butler 2022 | 103 | 12529 | 96 | 12525 | 50.1% | 1.07 [0.81, 1.41] |
| Caraco 2022 | 7 | 225 | 3 | 74 | 2.4% | 0.77 [0.20, 2.89] |
| Fischer 2022 | 3 | 140 | 1 | 62 | 0.7% | 1.33 [0.14, 12.52] |
| Jayk Bernal 2022 | 47 | 709 | 59 | 699 | 31.0% | 0.79 [0.54, 1.14] |
| Khoo 2023 | 0 | 90 | 4 | 90 | 2.3% | 0.11 [0.01, 2.03] |
| Sinha 2022 | 9 | 608 | 26 | 610 | 13.5% | 0.35 [0.16, 0.73] |
| **Total (95% CI)** | | **14301** | | **14060** | **100.0%** | **0.86 [0.70, 1.05]** |
| Total events | 169 | | 189 | | | |

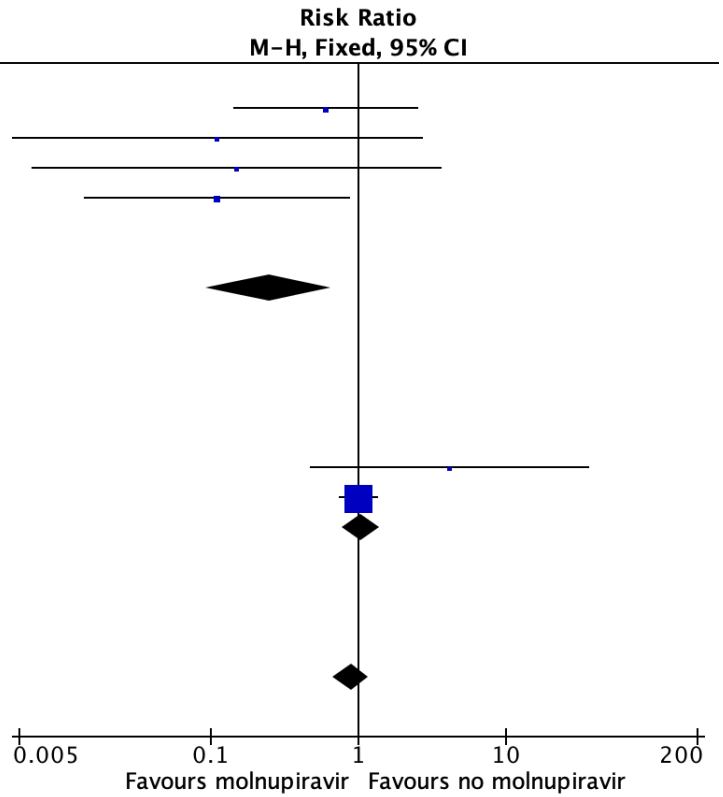
Heterogeneity: $Chi^2 = 10.38$, df = 5 (P = 0.07); $I^2 = 52\%$

Test for overall effect: Z = 1.47 (P = 0.14)



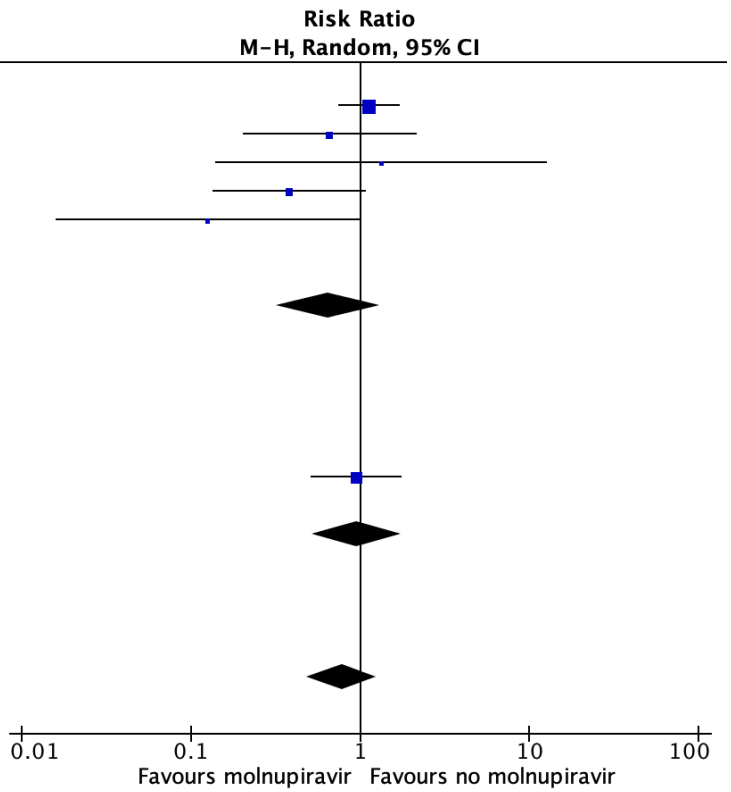
**Supplementary Figure 9.** Forest plot for the outcome of mortality for molnupiravir

| Study or Subgroup | Molnupiravir Events | Molnupiravir Total | No molnupiravir Events | No molnupiravir Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **24.1.1 Non-hospitalized** | | | | | | |
| Butler 2022 | 3 | 12529 | 5 | 12525 | 5.2% | 0.60 [0.14, 2.51] |
| Caraco 2022 | 0 | 225 | 1 | 74 | 2.4% | 0.11 [0.00, 2.69] |
| Fischer 2022 | 0 | 140 | 1 | 62 | 2.2% | 0.15 [0.01, 3.61] |
| Jayk Bernal 2022 | 1 | 709 | 9 | 699 | 9.5% | 0.11 [0.01, 0.86] |
| Khoo 2023 | 0 | 90 | 0 | 90 | | Not estimable |
| Sinha 2022 | 0 | 608 | 0 | 610 | | Not estimable |
| **Subtotal (95% CI)** | | **14301** | | **14060** | **19.2%** | **0.25 [0.09, 0.66]** |
| Total events | 4 | | 16 | | | |
| Heterogeneity: $Chi^2 = 2.41$, df = 3 (P = 0.49); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 2.78 (P = 0.005) | | | | | | |
| **24.1.2 hospitalized** | | | | | | |
| Arribas 2021 | 4 | 72 | 1 | 75 | 1.0% | 4.17 [0.48, 36.39] |
| Horby 2024 | 74 | 445 | 79 | 478 | 79.7% | 1.01 [0.75, 1.34] |
| **Subtotal (95% CI)** | | **517** | | **553** | **80.8%** | **1.05 [0.79, 1.39]** |
| Total events | 78 | | 80 | | | |
| Heterogeneity: $Chi^2 = 1.63$, df = 1 (P = 0.20); $I^2 = 39\%$ | | | | | | |
| Test for overall effect: Z = 0.31 (P = 0.76) | | | | | | |
| **Total (95% CI)** | | **14818** | | **14613** | **100.0%** | **0.89 [0.68, 1.17]** |
| Total events | 82 | | 96 | | | |
| Heterogeneity: $Chi^2 = 9.72$, df = 5 (P = 0.08); $I^2 = 49\%$ | | | | | | |
| Test for overall effect: Z = 0.83 (P = 0.41) | | | | | | |
| Test for subgroup differences: $Chi^2 = 7.59$, df = 1 (P = 0.006), $I^2 = 86.8\%$ | | | | | | |

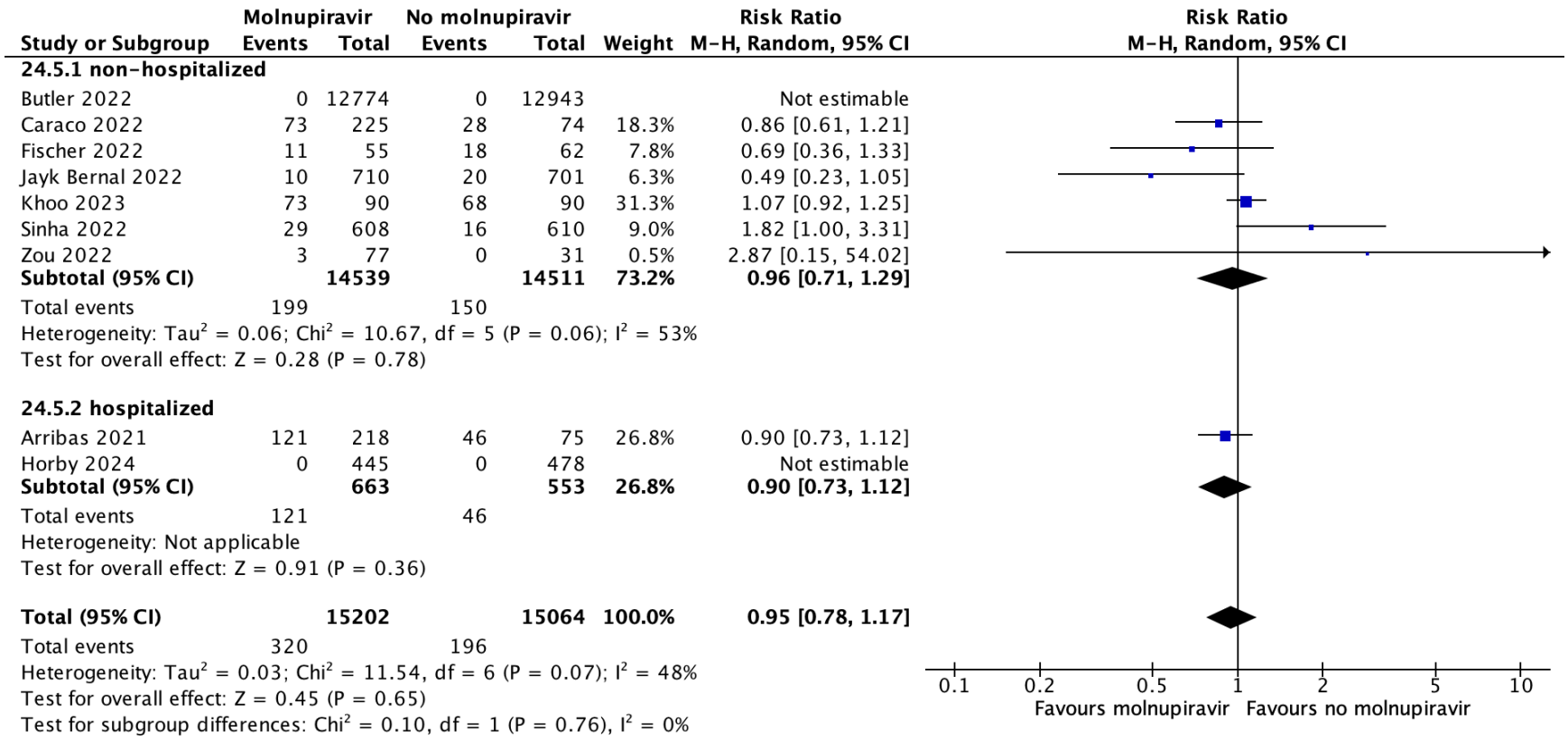


**Supplementary Figure 10.** Forest plot for the outcome of serious adverse events (SAEs) for molnupiravir

| Study or Subgroup | Molnupiravir Events | Molnupiravir Total | No molnupiravir Events | No molnupiravir Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **24.4.1 non-hospitalized** | | | | | | |
| Butler 2022 | 50 | 12774 | 45 | 12943 | 36.9% | 1.13 [0.75, 1.68] |
| Caraco 2022 | 8 | 225 | 4 | 74 | 12.2% | 0.66 [0.20, 2.12] |
| Fischer 2022 | 3 | 140 | 1 | 62 | 4.0% | 1.33 [0.14, 12.52] |
| Jayk Bernal 2022 | 5 | 710 | 13 | 701 | 14.8% | 0.38 [0.14, 1.06] |
| Khoo 2023 | 1 | 90 | 8 | 90 | 4.7% | 0.13 [0.02, 0.98] |
| Sinha 2022 | 0 | 608 | 0 | 610 | | Not estimable |
| Zou 2022 | 0 | 77 | 0 | 31 | | Not estimable |
| **Subtotal (95% CI)** | | **14624** | | **14511** | **72.6%** | **0.65 [0.32, 1.32]** |
| Total events | 67 | | 71 | | | |
| Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 7.92$, df = 4 (P = 0.09); $I^2 = 49\%$ | | | | | | |
| Test for overall effect: Z = 1.20 (P = 0.23) | | | | | | |
| **24.4.2 hospitalized** | | | | | | |
| Arribas 2021 | 33 | 218 | 12 | 75 | 27.4% | 0.95 [0.52, 1.73] |
| Horby 2024 | 0 | 445 | 0 | 478 | | Not estimable |
| **Subtotal (95% CI)** | | **663** | | **553** | **27.4%** | **0.95 [0.52, 1.73]** |
| Total events | 33 | | 12 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.18 (P = 0.86) | | | | | | |
| **Total (95% CI)** | | **15287** | | **15064** | **100.0%** | **0.78 [0.49, 1.24]** |
| Total events | 100 | | 83 | | | |
| Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 7.94$, df = 5 (P = 0.16); $I^2 = 37\%$ | | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.29) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.63$, df = 1 (P = 0.43), $I^2 = 0\%$ | | | | | | |



**Supplementary Figure 11**. Forest plot for the outcome of adverse events for molnupiravir



**Supplementary Table 2.** Risk of bias assessment for randomized controlled trials

| Study | Bias in randomization process | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in measurement of outcome | Bias in selection of the reported result |
|---|---|---|---|---|---|
| Liu 2023 | | | | | |
| Hammond 2022 | | | | | |
| Hammond 2024 | | | | | |
| Horby 2024 | | | | | |
| Beigel 2020 | | | | | |
| Gottlieb 2021 | | | | | |
| Sise 2024 | | | | | |
| Spinner 2020 | | | | | |
| Wang 2020 | | | | | |
| WHO Solidarity Trial Consortium (Pan) 2021 | | | | | |
| Butler 2023 | | | | | |
| Caraco 2022 | | | | | |
| Fischer 2021 | | | | | |
| Horby 2024 | | | | | |
| Jayk Bernal 2021 | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Khoo 2023 | | | | | |
| Sinha 2022 | | | | | |
| Zou 2022 | | | | | |
| Arribas 2022 | | | | | |
| Guan 2023 | | | | | |

| Low | High | Unclear |
|---|---|---|

**REFERENCES**


Arribas JR, Bhagani S, Lobo SM, et al. Randomized trial of molnupiravir or placebo in patients hospitalized with Covid-19. NEJM Evid **2022**; 1(2):EVIDoa2100044.

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med **2020**; 383(19):1813-26.

Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet **2023**; 401(10373):281-93.

Caraco Y, Crofoot GE, Moncada PA, et al. Phase 2/3 Trial of Molnupiravir for treatment of Covid-19 in nonhospitalized adults. NEJM Evid **2022**; 1(2):EVIDoa2100043.

Fischer WA, 2nd, Eron JJ, Jr., Holman W, et al. A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med **2021**; 14(628):eabl7430.

Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. N Engl J Med **2022**; 386(4):305-15.

Guan Y, Puenpatom A, Johnson MG, et al. Impact of molnupiravir treatment on patient-reported COVID-19 symptoms in the Phase 3 MOVe-OUT trial: a randomized, placebo-controlled trial. Clin Infect Dis **2023**; 77(11):1521-30.

Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendation. BMJ **2008**; 336:924-6.

Hammond J, Fountaine RJ, Yunis C, et al. Nirmatrelvir for vaccinated or unvaccinated adult outpatients with Covid-19. N Engl J Med **2024**; 390(13):1186-95.epic-hr

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med **2022**; 386(15):1397-408.

Higgins JPT, Altman DG, Gotsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ 2011; 343:d5928.

Infectious Diseases Society of America. IDSA Handbook on Clinical Practice Guideline Development. Available at: https://www.idsociety.org/practice-guideline/clinical-practice-guidelines-development-training-and-resources/. Accessed 04/21/2025.

IOM (Institute of Medicine). Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press, **2011**.

Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med **2021**; 386(6):509-20.

Khoo SH, FitzGerald R, Saunders G, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Infect Dis **2023**; 23(2):183-95.

Liu J, Pan X, Zhang S, et al. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac **2023**; 33: 100694.

RECOVERY Collaborative Group, Horby PW, Staplin N, Peto L, et al. Molnupiravir or nirmatrelvir-ritonavir versus usual care in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Infect Dis **2025**; S1473-3099(25)00093-3.

Sinha S, Kumarasamy N, Suram VK, et al. Efficacy and safety of molnupiravir in mild COVID-19 patients in India. Cureus **2022**; 14(11):e31508.

Sise ME, Santos JR, Goldman JD, et al. Efficacy and safety of remdesivir in people with impaired kidney function hospitalized for COVID-19 pneumonia: a randomized clinical trial. Clin Infect Dis **2024**; 79(5):1172-81.

Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA **2020**; 324(11):1048-57.

WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. N Engl J Med **2021**; 384(6),497-511.

Wang L, Berger NA, Davis PB, Kaelber DC, Volkow ND, Xu R. COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.06.21.22276724. [Preprint 22 June 2022].

Zou R, Peng L, Shu D, et al. Antiviral efficacy and safety of molnupiravir against Omicron variant infection: a randomized controlled clinical trial. Front Pharmacol **2022**; 13:939573.