REVIEW

Annals of Internal Medicine

Outpatient Treatment of Confirmed COVID-19: A Living, Rapid Review for the American College of Physicians

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Background: Clinicians and patients want to know the benefits and harms of outpatient treatment options for SARS-CoV-2 infection.

Purpose: To assess the benefits and harms of 12 different COVID-19 treatments in the outpatient setting.

Data Sources: Epistemonikos COVID-19 L·OVE Platform, searched on 4 April 2022.

Study Selection: Two reviewers independently screened abstracts and full texts against a priori–defined criteria. Randomized controlled trials (RCTs) that compared COVID-19 treatments in adult outpatients with confirmed SARS-CoV-2 infection were included.

Data Extraction: One reviewer extracted data and assessed risk of bias and certainty of evidence (COE). A second reviewer verified data abstraction and assessments.

Data Synthesis: The 26 included studies collected data before the emergence of the Omicron variant. Nirmatrelvir–ritonavir and casirivimab–imdevimab probably reduced hospitalizations (1% vs. 6% [1 RCT] and 1% vs. 4% [1 RCT], respectively; moderate COE). Nirmatrelvir–ritonavir probably reduced all-cause mortality (0% vs. 1% [1 RCT]; moderate COE), and regdanvimab probably improved recovery (87% vs. 72% [1 RCT]; moderate COE). Casirivimab–imdevimab reduced time to recovery by a median difference of 4 days (10 vs. 14 median days [1 RCT]; high COE). Molnupiravir may reduce all-cause mortality, sotrovimab and remdesivir may reduce hospitalization, and remdesivir may improve recovery (low COE). Lopinavir–ritonavir and azithromycin may have increased harms, and hydroxychloroquine may result in lower recovery rates (low COE). Other treatments had insufficient evidence or no statistical difference in efficacy and safety versus placebo.

Limitation: Many outcomes had few events and small samples.

Conclusion: Some antiviral medications and monoclonal antibodies may improve outcomes for outpatients with mild to moderate COVID-19. However, the generalizability of the findings to the currently dominant Omicron variant is limited.

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In the United States, COVID-19 has resulted in more than 1 million deaths (1) and led to a decrease in life expectancy of 1.87 years (2). Various pharmacologic therapies, including antiviral drugs, corticosteroids, and other repurposed medications, have emerged as treatment options for outpatients with COVID-19.

Several reviews have systematically assessed the efficacy and safety of these therapies (3–10). However, given the pace of the pandemic and the emerging evidence, without regular updates these reviews quickly become outdated. In addition, most included both inpatient and outpatient management and focused only on 1 specific COVID-19 treatment. The aim of this living, rapid review was to systematically collate and assess the evidence regarding the benefits and harms of COVID-19 treatments of interest to support the American College of Physicians (ACP) Scientific Medical Policy Committee (SMPC) in developing practice points on the use of COVID-19 treatments in adult outpatients.

See also:

Editorial comment 137
Related article 115
Summary for Patients I-24

Web-Only
Supplement
Annals Video Summary

METHODS

We conducted this living, rapid review in accordance with the Cochrane Rapid Reviews Methods Group guidance (11). We registered our protocol in PROSPERO (CRD42022323440) and made no changes to it. Throughout this review, we adhered to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (12).

Our methods differed from those of a systematic review in the following ways: We searched only 1 electronic database (the Epistemonikos COVID-19 L·OVE Platform [13]), and single reviewers extracted data and rated risk of bias and certainty of evidence (COE); a second, senior investigator verified data abstraction and assessments.

We plan to conduct monthly surveillance searches over a period of 1 year for new randomized controlled trials (RCTs). The study eligibility criteria might be revised if the treatments of interest change. The methodological approach will remain the same. The SMPC is planning to maintain this topic as living, rapid practice points with

literature surveillance and periodic updating of the living, rapid review and SMPC practice points. Details of the practice points' living process, including signals for updating and retirement, can be found in ACP's methods articles (14).

Research Questions and Eligibility Criteria

We addressed the following key questions (KQs):

KQ: What are the benefits and harms of COVID-19 treatments in symptomatic and asymptomatic adult patients with a confirmed SARS-CoV-2 infection in the outpatient setting?

KQa: Do the benefits and harms vary by patient characteristics (age, gender, or comorbid conditions), type of SARS-CoV-2 variant, immunity status (prior SARS-CoV-2 infection, vaccination status, or time since infection or vaccination), symptom duration, or disease severity?

We considered RCTs that included adult outpatients with a confirmed diagnosis of SARS-CoV-2 infection and were published in English. Treatments of interest included antiviral drugs, neutralizing monoclonal antibodies, antibiotic or antiparasitic drugs, convalescent plasma, corticosteroids, and fluvoxamine. Comparators were placebo to determine treatment efficacy or standard of care if no placebo-controlled trials were available, which was not the case for any of the treatments of interest.

The ACP SMPC selected all-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospitalization due to COVID-19, and incidences of serious or any adverse events as critical outcomes for decision making. Supplement Table 1 (available at Annals.org) presents the a priori–specified inclusion and exclusion criteria.

Data Sources and Searches

An experienced information specialist (I.K.) searched Epistemonikos COVID-19 L·OVE, a free-access repository and classification platform for COVID-19 evidence (13), up to 4 April 2022 (Supplement Table 2, available at Annals.org). In addition, we searched the COVID-NMA initiative website, a living evidence database of COVID-19 trials (15). On 17 August 2022, a surveillance search was conducted to identify studies to be included in periodic updating of the living, rapid review and SMPC practice points.

Study Selection

Two trained reviewers (from among I.S., A.D., D.L., I.M., E.P., K.T., and G.G.) independently screened titles, abstracts, and relevant full-text articles against predefined eligibility criteria using DistillerSR (Evidence Partners). Conflicts were resolved by discussion or by consulting a third reviewer. All results were tracked in an EndNote 20 database (Clarivate).

Data Extraction and Quality Assessment

One reviewer (I.S., A.D., D.L., I.M., E.P., or K.T.) abstracted characteristics of the study populations, settings, interventions, comparators, methods, and results from each included study. A second reviewer (I.S., A.D., D.L., I.M., E.P., or K.T.) checked all data abstractions for completeness and accuracy.

A single investigator assessed the risk of bias of the included RCTs using the Cochrane Risk of Bias Tool 2.0 (16). We validated the ratings against the risk-of-bias assessments provided by COVID-NMA, which had applied the same tool (15). If the ratings differed, we involved a second investigator to resolve the discrepancy. For trials that were not included in the COVID-NMA database, we dually assessed the risk of bias. Supplement Figure 1 (available at Annals.org) presents the risk-of-bias assessments.

Data Synthesis and Analysis

If we found 2 or more similar studies for a comparison of interest, we conducted meta-analyses. We chose the Bayesian random-effects model because it allows us to update the analyses without concern for *P* value inflation (17, 18). We conducted all analyses with R, version 4.1.3 (19), using the bayesmeta (20) and metafor (21) packages. We chose noninformative priors for both the treatment effect (mean, 0; SD, 4) and the heterogeneity (half-normal with a scale of 0.5). The results were calculated as risk ratios (RRs) and presented as forest plots.

We determined the appropriateness of a meta-analysis by assessing the clinical and methodological heterogeneity following established guidance (22). Although we used an intention-to-treat-analysis for data we pooled in a meta-analysis, we relied on the data as reported in the individual studies for the narrative summary. When possible, we conducted sensitivity analysis to explore potential sources of heterogeneity. Although we had planned to perform subgroup analyses, we were unable to identify enough studies to do so.

Certainty of Evidence

We graded the COE on the basis of the guidance established by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (23). A single investigator assessed the COE for each key outcome, and a second senior investigator checked this for plausibility and consistency.

Role of the Funding Source

This living, rapid review was funded by ACP, which assisted in the development of the KQs and study inclusion criteria and selection of the outcomes of interest. The ACP was not involved in data collection, analysis, or manuscript preparation.

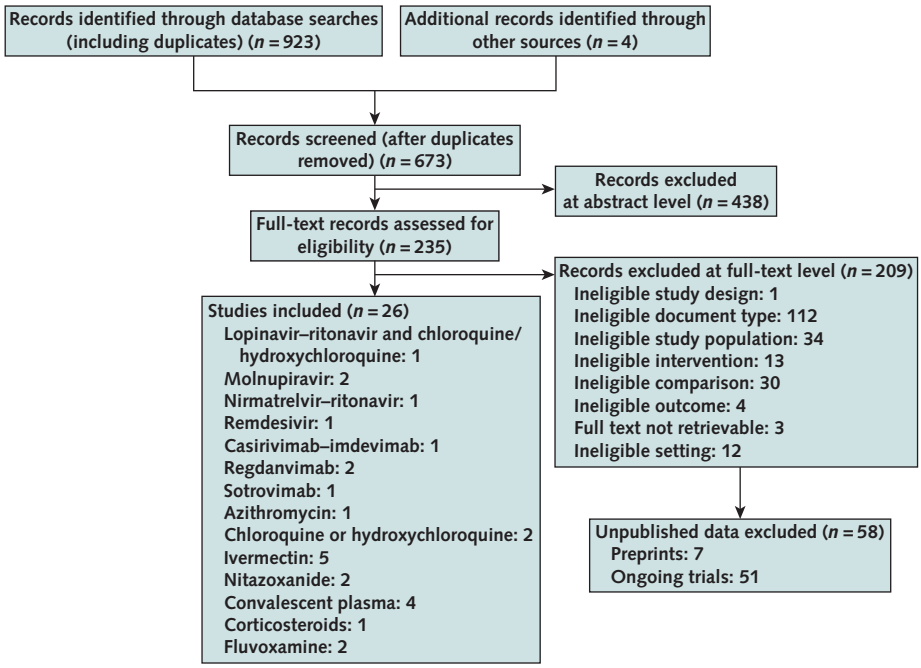
RESULTS

The searches yielded 679 references, from which we included 26 RCTs (24–49). Figure 1 shows the study selection process. Supplement Tables 3 to 5 (available at Annals.org) list eligible preprints, ongoing studies, and other excluded studies with the reasons for exclusion.

Study and Participant Characteristics

The number of participants in the included studies ranged from 18 to 5607. The median ages of participants varied from 26 to 77 years, and the proportion of females varied between 1% and 72%. Trials were conducted in the United States (31, 36, 40, 41, 43, 46), Canada (27,

Figure 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart.



45), Argentina (24, 47), Brazil (30, 32, 39, 49), Colombia (26), Spain (29, 37), Italy (48), the Middle East (28), or multiple countries (25, 33–35, 38, 42, 44). Out of 26 trials, 16 were funded with industry involvement (24, 25, 27, 31, 33–35, 37, 38, 41–46, 48). Among studies reporting vaccination status as an eligibility criterion, 11 studies (44%) (25, 28, 31, 33–37, 39, 44, 45) excluded vaccinated participants, and 4 studies (12%) included them (42, 43, 46, 49). Five studies excluded participants who had previously been diagnosed with COVID-19 (35, 37, 42, 43, 46); 1 study included them only if they had not been hospitalized or treated (44). All studies were conducted before the Omicron variant became the dominant strain.

Participants were symptomatic across studies except in 1 study that included both symptomatic and asymptomatic participants (41). Ten studies (24, 26, 30, 32, 34, 37, 39, 40, 42, 43) provided data on disease severity; in 6 of them, participants had only mild symptoms (24, 26, 30, 32, 39, 40, 42). In all studies, the SARS-CoV-2 infection status was confirmed by a diagnostic test, usually a reverse transcriptase polymerase chain reaction test; 7 studies (26, 34, 37, 38, 41, 46, 49) also accepted antigen tests. **Supplement Table 6** (available at Annals.org) presents the characteristics and results of the included studies; **Supplement Table 7** (available at Annals.org) lists the definitions of "recovery" that were used in the included studies.

We rated 9 studies as having low risk of bias (31, 33, 34, 37–39, 45–47), 16 as having some bias concerns (24–30, 32, 35, 36, 40–44, 49), and 1 as having high risk of bias (48). The risk-of-bias ratings of 8 studies differed from those in the COVID-NMA database (15) and required the involvement of a second reviewer. We dually assessed the risk of bias of 2 studies (42, 49) that were not available in the COVID-NMA database. Risk of bias included possible reporting bias, unclear blinding, lack of information on randomization and allocation concealment, or lack of an intention-to-treat analysis (**Supplement Figure** 1).

Efficacy and Risk for Harms of COVID-19 Treatments

Overall, only nirmatrelvir–ritonavir, remdesivir, casirivimab–imdevimab, and sotrovimab reduced hospitalizations due to COVID-19 compared with placebo (**Figure 2**). Lopinavir–ritonavir and azithromycin led to higher incidence of adverse events than placebo (**Figure 3**). Molnupiravir and nirmatrelvir–ritonavir reduced all-cause mortality (**Supplement Figure 2**, available at Annals.org). Nirmatrelvir–ritonavir, remdesivir, casirivimab–imdevimab, and sotrovimab reduced the incidence of serious adverse events (**Supplement Figure 3**, available at Annals.org).

The **Table** summarizes results and COE ratings for each treatment versus placebo. **Supplement Figures 4** to **19** (available at Annals.org) display meta-analyses, and **Supplement Table 8** (available at Annals.org) presents summary-of-findings tables.

Antiviral Drugs

Lopinavir–Ritonavir. One RCT (n = 471; some risk of bias) assessed 800 mg of lopinavir and 200 mg of ritonavir at the first 2 intakes, followed by 400 mg of lopinavir and 100 mg of ritonavir for the next 9 days, compared with placebo (30). Lopinavir–ritonavir may have no effect on hospitalization due to COVID-19 (5.6% vs. 4.8%; hazard ratio, 1.16 [95% confidence interval {CI}, 0.53 to 2.56]; low COE) but may increase the incidence of adverse events

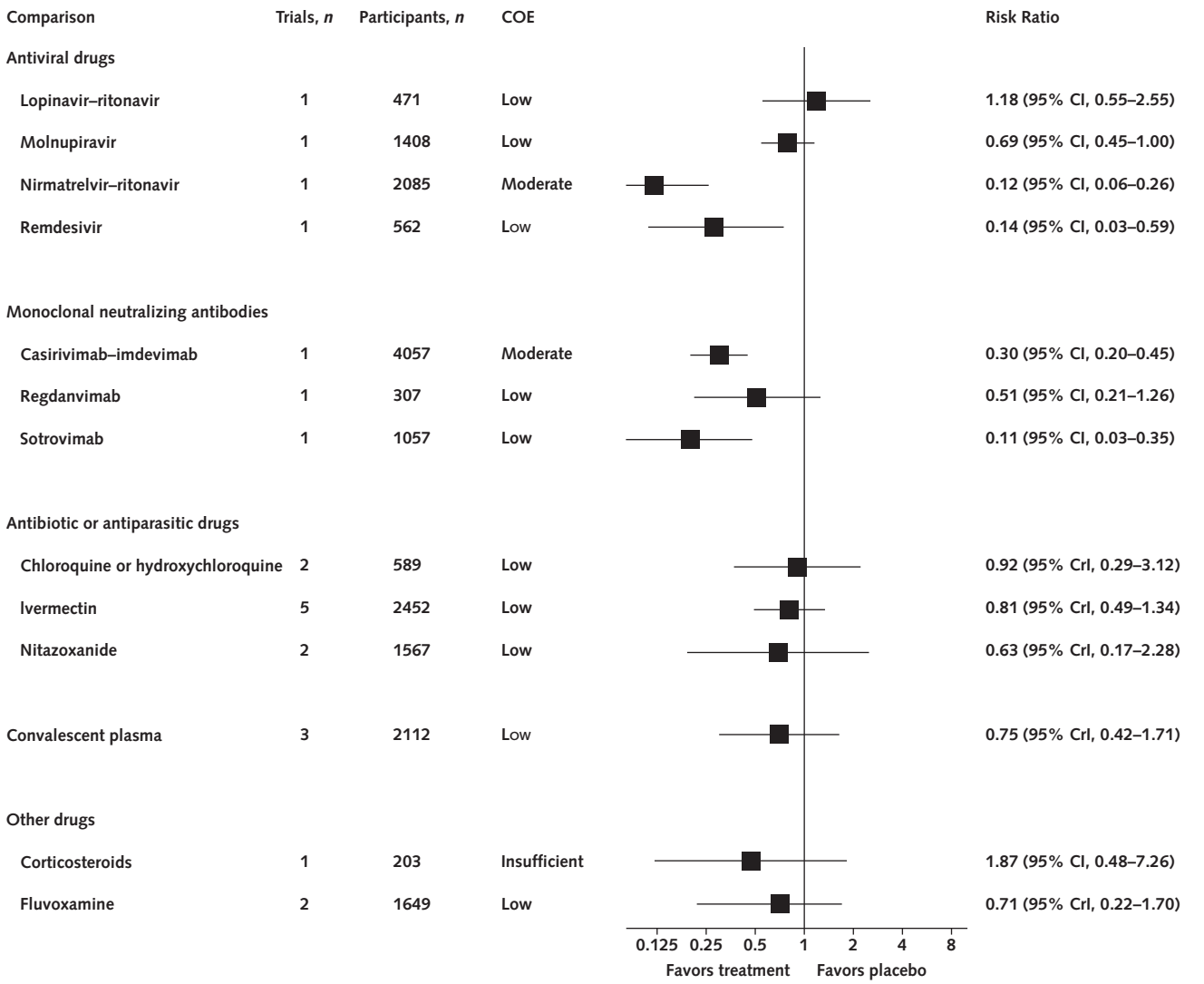
(39.7% vs. 20.9%; RR, 1.90 [CI, 1.40 to 2.57]; low COE). Although larger, the difference in serious adverse events between lopinavir–ritonavir and placebo was not statistically significant (8.6% vs. 5.5%; RR, 1.58 [CI, 0.79 to 3.16]; low COE). The evidence for all-cause mortality was insufficient to draw conclusions.

Molnupiravir. Two RCTs (n = 1637; low risk of bias) assessed molnupiravir, 800 mg (31, 33) or 200 to 800 mg (31), compared with placebo.

The MOVe-OUT study (33) reported a reduction in all-cause mortality (which corresponded to COVID-19–related mortality as all deaths were due to COVID-19) (<0.1% vs. 1.3%; RR, 0.11 [CI, 0.01 to 0.86]; low COE) with molnupiravir and no effect on hospitalization due to COVID-19 (6.3% vs. 9.2%; RR, 0.69 [CI, 0.45 to 1.00]; low COE). Molnupiravir at doses of 200, 400, or 800 mg probably results in similar recovery (48.4% vs. 48.3%; odds ratio, 1.04 [CI, 0.84 to 1.29]; 1 RCT; moderate COE) (31, 33) and time to recovery (median, 5.5 to 9.0 vs. 8.5 days; 1 RCT; low COE) compared with placebo (31, 33). The proportion of participants affected by serious or any adverse events in the 2 studies did not differ statistically between groups (serious adverse events: 6.1% vs. 8.7%; RR, 0.77 [95% credible interval {CrI}, 0.32 to 2.03]; low COE [**Supplement Figure 4**]; any adverse events: 30.1% vs. 32.0%; RR, 0.96 [CrI, 0.55 to 1.73]; moderate COE [**Supplement Figure 5**]).

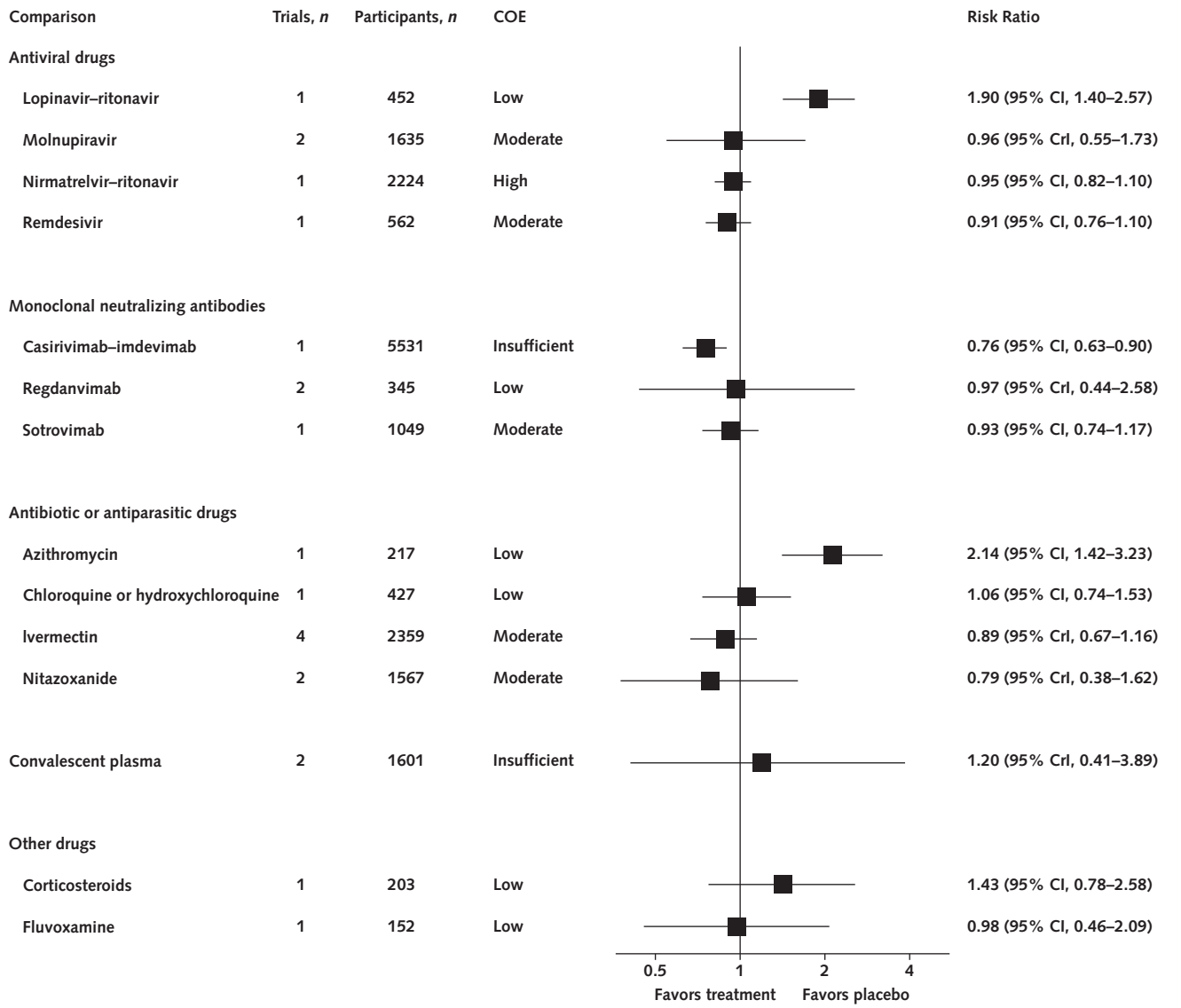
Nirmatrelvir–Ritonavir. One RCT (n = 2246; some risk of bias) assessed nirmatrelvir–ritonavir (300 and 100 mg) every 12 hours for 5 days compared with placebo (35).

Figure 2. Summary plot of hospitalization due to COVID-19.



The risk ratios were self-calculated. CI = confidence interval; COE = certainty of evidence; CrI = credible interval.

Figure 3. Summary plot of incidence of adverse events.



The risk ratios were self-calculated. CI = confidence interval; COE = certainty of evidence; CrI = credible interval.

Nirmatrelvir–ritonavir probably reduced all-cause mortality (0% vs. 1.1%; RR, 0.04 [CI, 0.002 to 0.68]; moderate COE) and hospitalization due to COVID-19 for patients with 5 or fewer days of symptoms (0.7% vs. 6.2%; RR, 0.12 [CI, 0.06 to 0.26]; moderate COE). The incidence of any adverse events did not statistically differ compared with placebo (22.6% vs. 23.9%; RR, 0.95 [CI, 0.82 to 1.10]; high COE).

Remdesivir. One RCT (n = 584; some risk of bias) assessed remdesivir, 200 mg on day 1 and 100 mg on days 2 and 3, compared with placebo (44).

Remdesivir may improve recovery between days 1 and 14 (36.1% vs. 20.0%; rate ratio, 1.92 [CI, 1.26 to 2.94]; low COE) and reduce hospitalization due to COVID-19 (0.7% vs. 5.3%; RR, 0.14 [CI, 0.03 to 0.59]; low COE). There was no statistical difference in incidence of any adverse events (42.3% vs. 46.3%; RR, 0.91 [CI, 0.76 to 1.10]; moderate COE). Evidence was insufficient to draw conclusions about other outcomes.

Monoclonal Neutralizing Antibodies

We identified studies for 3 out of 5 monoclonal neutralizing antibodies approved by the U.S. Food and Drug Administration or the European Medicines Agency at the date of our search (4 April 2022).

Casirivimab–Imdevimab. One RCT (n = 4057; some risk of bias) assessed casirivimab–imdevimab, 1200 to 8000 mg, compared with placebo (25). Casirivimab–imdevimab reduced time to recovery (10 vs. 14 median days; high COE) and probably decreased hospitalizations due to COVID-19 (1.3% vs. 4.4%; RR, 0.30 [CI, 0.20 to 0.45]; moderate COE). Evidence was insufficient to draw conclusions about other outcomes.

Table. Results and COE Ratings for Each Treatment Versus Placebo

Treatment	All-Cause Mortality	COVID-19–Specific Mortality	Recovery	Time to Recovery	Hospitalization Due to COVID-19	Serious Adverse Events	Adverse Events
Antiviral drugs							
Lopinavir–ritonavir vs. placebo (30)	Studies: 1 Participants: 471 Study duration: 90 d Treatment effect: 1% vs. 0.4%; RR, 1.86 (95% CI, 0.17 to 20.38)* Insufficient COE	No evidence	No evidence	No evidence	Studies: 1 Participants: 471 Study duration: 90 d Treatment effect: 6% vs. 5%; HR, 1.16 (95% CI, 0.53 to 2.56) Low COE for non-statistically different effect	Studies: 1 Participants: 452 Study duration: 90 d Treatment effect: 9% vs. 6%; RR, 1.58 (95% CI, 0.79 to 3.16)* Low COE for non-statistically different effect	Studies: 1 Participants: 452 Study duration: 90 d Treatment effect: 40% vs. 21%; RR, 1.90 (95% CI, 1.40 to 2.57)* Low COE for higher risk with lopinavir–ritonavir
Molnupiravir vs. placebo (31, 33)	Studies: 1 Participants: 1433 Study duration: 29 d Treatment effect: 0.1% vs. 1%; RR, 0.11 (95% CI, 0.01 to 0.86)* Low COE for lower risk with molnupiravir	Studies: 1 Participants: 1433 Study duration: 29 d Treatment effect: 0% vs. 1%; RR, 0.11 (95% CI, 0.01 to 0.86)* Low COE for lower risk with molnupiravir	Studies: 1 Participants: 1295 Study duration: 29 d Treatment effect: 48% vs. 48%; OR, 1.04 (95% CI, 0.84 to 1.29) Moderate COE for non-statistically different effect	Studies: 1 Participants: 202 Study duration: 28 d Treatment effect: molnupiravir, 5.5 to 9 d; placebo, 8.5 d Low COE for similar effect with molnupiravir	Studies: 1 Participants: 1408 Study duration: 29 d Treatment effect: 6% vs. 9%; RR, 0.69 (95% CI, 0.45 to 1.00)* Low COE for non-statistically different effect	Studies: 2 Participants: 1635 Study duration: 28 to 29 d Treatment effect: 6% vs. 9%; RR, 0.77 (95% CI, 0.32 to 2.03)* Low COE for non-statistically different effect	Studies: 2 Participants: 1635 Study duration: 28 to 29 d Treatment effect: 30% vs. 32%; RR, 0.96 (95% CrI, 0.55 to 1.73)* Moderate COE for non-statistically different effect
Nirmatrelvir–ritonavir vs. placebo (35)	Studies: 1 Participants: 2085 Study duration: 28 d Treatment effect: 0% vs. 1%; RR, 0.04 (95% CI, 0.002 to 0.68)* Moderate COE for lower risk with nirmatrelvir–ritonavir	No evidence	No evidence	No evidence	Studies: 1 Participants: 2085 Study duration: 28 d Treatment effect: 1% vs. 6%; RR, 0.12 (95% CI, 0.06 to 0.26)* Moderate COE for lower risk with nirmatrelvir–ritonavir	Studies: 1 Participants: 2224 Study duration: 34 d Treatment effect: 2% vs. 7%; RR, 0.25 (95% CI, 0.16 to 0.38)* Insufficient COE	Studies: 1 Participants: 2224 Study duration: 34 d Treatment effect: 23% vs. 24%; RR, 0.95 (95% CI, 0.82 to 1.10)* High COE for non-statistically different effect
Remdesivir vs. placebo (44)	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	Studies: 1 Participants: 334 Study duration: 14 d Treatment effect: 36% vs. 20%; rate ratio, 1.92 (95% CI, 1.26 to 2.94) Low COE for greater effect with remdesivir	No evidence	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 1% vs. 5%; HR, 0.13 (95% CI, 0.03 to 0.59) Low COE for lower risk with remdesivir	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 2% vs. 7%; RR, 0.27 (95% CI, 0.10 to 0.70) Insufficient COE	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 42% vs. 46%; RR, 0.91 (95% CI, 0.76 to 1.10) Moderate COE for non-statistically different effect
Monoclonal neutralizing antibodies							
Casirivimab–imdevimab vs. placebo (25)	Studies: 1 Participants: 4057 Study duration: 29 d Treatment effect: 0.1% vs. 0.2%; RR, 0.33 (95% CI, 0.06 to 1.97) Insufficient COE	No evidence	No evidence	Studies: 1 Participants: 3432 Study duration: 29 d Treatment effect: 10 vs. 14 d; P = 0.0001 High COE for greater effect with casirivimab–imdevimab	Studies: 1 Participants: 4057 Study duration: 29 d Treatment effect: 1% vs. 4%; RR, 0.30 (95% CI, 0.20 to 0.45) Moderate COE for lower risk with casirivimab–imdevimab	Studies: 1 Participants: 5531 Study duration: 45 d Treatment effect: 1% vs. 4%; RR, 0.34 (95% CI, 0.24 to 0.48) Insufficient COE	Studies: 1 Participants: 5531 Study duration: 45 d Treatment effect: 8% vs. 3%; RR, 0.76 (95% CI, 0.63 to 0.90) Insufficient COE
Regdanvimab vs. placebo (34, 42)	Studies: 1 Participants: 325 Study duration: 28 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	Studies: 1 Participants: 285 Study duration: 28 d Treatment effect: 87% vs. 72%; RR, 1.21 (95% CI, 1.05 to 1.38) Moderate COE for greater effect with regdanvimab	Studies: 2 Participants: 303 Study duration: 14 to 28 d Treatment effect: regdanvimab, 5.5 to 9 d; placebo, 8.0 to 8.5 d Low COE for non-statistically different effect	Studies: 1 Participants: 307 Study duration: 28 d Treatment effect: 4% vs. 9%; RR, 0.51 (95% CI, 0.21 to 1.26) Low COE for non-statistically different effect	Studies: 2 Participants: 345 Study duration: 14 to 28 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 2 Participants: 345 Study duration: 14 to 28 d Treatment effect: 29% vs. 31%; RR, 0.97 (95% CrI, 0.44 to 2.58) Low COE for non-statistically different effect

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Treatment	All-Cause Mortality	COVID-19-Specific Mortality	Recovery	Time to Recovery	Hospitalization Due to COVID-19	Serious Adverse Events	Adverse Events
Sotrovimab vs. placebo (38)	Studies: 1 Participants: 1057 Study duration: 29 d Treatment effect: 0% vs. 0.4%; RR, 0.20 (95% CI, 0.01 to 4.12) Insufficient COE	No evidence	No evidence	No evidence	Studies: 1 Participants: 1057 Study duration: 29 d Treatment effect: 1% vs. 5%; RR, 0.11 (95% CI, 0.03 to 0.35) Low COE for lower risk with sotrovimab	Studies: 1 Participants: 1049 Study duration: 29 d Treatment effect: 2% vs. 6%; RR, 0.3 (95% CI, 0.18 to 0.68) Insufficient COE	Studies: 1 Participants: 1049 Study duration: 29 d Treatment effect: 22% vs. 23%; RR, 0.93 (95% CI, 0.74 to 1.17) Moderate COE for non-statistically different effect
Antibiotic or antiparasitic drugs							
Azithromycin vs. placebo (41)	Studies: 1 Participants: 197 Study duration: 21 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	Studies: 1 Participants: 201 Study duration: 14 d Treatment effect: 50% vs. 50%; RR, 1.02 (95% CI, 0.91 to 1.13) Low COE for non-statistically different effect	No evidence	No evidence	Studies: 1 Participants: 217 Study duration: 21 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 217 Study duration: 3 d Treatment effect: 57% vs. 26%; RR, 2.14 (95% CI, 1.42 to 3.23) Low COE for higher risk with azithromycin
Chloroquine or hydroxychloroquine vs. placebo (27, 28, 30)	Studies: 3 Participants: 893 Study duration: 21 to 90 d Treatment effect: 0% vs. 0.2%; RR, 0.5 (95% CrI, 0.06 to 3.98)* Insufficient COE	Studies: 2 Participants: 452 Study duration: 21 to 30 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 147 Study duration: 30 d Treatment effect: 61% vs. 78%; RR, 0.78 (95% CI, 0.62 to 0.97)* Low COE for lower effect with chloroquine/hydroxychloroquine	Studies: 1 Participants: 148 Study duration: 30 d Treatment effect: 14 vs. 12 d Low COE for non-statistically different effect	Studies: 2 Participants: 589 Study duration: 30 to 90 d Treatment effect: 4% vs. 4%; RR, 0.92 (95% CrI, 0.29 to 3.12)* Low COE for non-statistically different effect	Studies: 3 Participants: 893 Study duration: 21 to 90 d Treatment effect: 3% vs. 3%; RR, 1.06 (95% CrI, 0.38 to 3.11)* Low COE for non-statistically different effect	Studies: 1 Participants: 427 Study duration: 90 d Treatment effect: 22% vs. 21%; RR, 1.06 (95% CI, 0.74 to 1.53) Low COE for non-statistically different effect
Ivermectin vs. placebo (26, 29, 47–49)	Studies: 5 Participants: 2452 Study duration: 21 to 30 d Treatment effect: 2% vs. 2%; RR, 0.89 (95% CrI, 0.42 to 1.91) Low COE for non-statistically different effect	Studies: 3 Participants: 593 Study duration: 21 to 30 d Treatment effect: 0% vs. 0.4%; RR, 0.55 (95% CI, 0.07 to 4.37) Insufficient COE	Studies: 2 Participants: 569 Study duration: 21 to 30 d Treatment effect: 68% vs. 66%; RR, 1.04 (95% CrI, 0.61 to 1.72)* Moderate COE for non-statistically different effect	Studies: 3 Participants: 1836 Study duration: 21 to 30 d Treatment effect: ivermectin, 10 to 29 d; placebo, 12 to 14 d Insufficient COE	Studies: 5 Participants: 2452 Study duration: 21 to 30 d Treatment effect: 8% vs. 10%; RR, 0.81 (95% CI, 0.49 to 1.34) Low COE for non-statistically different effect	Studies: 5 Participants: 2452 Study duration: 21 to 30 d Treatment effect: 2% vs. 2%; RR, 1.06 (95% CI, 0.47 to 2.5) Insufficient COE	Studies: 4 Participants: 2359 Study duration: 21 to 30 d Treatment effect: 28% vs. 32%; RR, 0.89 (95% CrI, 0.67 to 1.16) Moderate COE for non-statistically different effect
Nitazoxanide vs. placebo (32, 43)	Studies: 2 Participants: 1567 Study duration: 14 to 28 d Treatment effect: 0.2% vs. 0%; RR, 2.08 (95% CI, 0.19 to 22.35) Insufficient COE	Studies: 1 Participants: 1092 Study duration: 28 d Treatment effect: 0.2% vs. 0%; RR, 2.68 (95% CI, 0.13 to 55.74) Insufficient COE	Studies: 1 Participants: 392 Study duration: mean, 5 d Treatment effect: 70% vs. 74%; RR, 0.94 (95% CI, 0.83 to 1.07) Moderate COE for non-statistically different effect	Studies: 1 Participants: 379 Treatment effect: median days, 13.3 (IQR, 6.3 to 21) vs. 12.4 (IQR, 7.2 to 21) Moderate COE for non-statistically different effect	Studies: 2 Participants: 1567 Study duration: 5 to 28 d Treatment effect: 1% vs. 1%; RR, 0.63 (95% CrI, 0.17 to 2.28) Low COE for non-statistically different effect	Studies: 2 Participants: 1567 Study duration: 5 to 28 d Treatment effect: 0.3% vs. 1%; RR, 0.33 (95% CrI, 0.07 to 1.56) Low COE for non-statistically different effect	Studies: 2 Participants: 1567 Study duration: 5 to 28 d Treatment effect: 14% vs. 19%; RR, 0.79 (95% CrI, 0.38 to 1.62) Moderate COE for non-statistically different effect
Convalescent plasma							
Convalescent plasma vs. placebo (24, 36, 37, 46)	Studies: 4 Participants: 2272 Study duration: 15 to 28 d	Studies: 2 Participants: 1385 Study duration: 15 to 28 d	No evidence	Studies: 1 Participants: 376 Study duration: 30 d Treatment effect: 12	Studies: 3 Participants: 2112 Study duration: 28 to 30 d	Studies: 4 Participants: 2272 Study duration: 15 to 28 d	Studies: 2 Participants: 1601 Study duration: 28 d

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Treatment	All-Cause Mortality	COVID-19-Specific Mortality	Recovery	Time to Recovery	Hospitalization Due to COVID-19	Serious Adverse Events	Adverse Events
	Treatment effect: 1% vs. 1%; RR, 0.68 (95% CrI, 0.20 to 2.34) Low COE for non–statistically different effect	Treatment effect: 0.3% vs. 1%; RR, 0.37 (95% CrI, 0.08 to 1.84) Insufficient COE		vs. 12 d; HR, 1.05 (95% CI, 0.85 to 1.30) Low COE for non–statistically different effect	Treatment effect: 8% vs. 11%; RR, 0.75 (95% CrI, 0.42 to 1.31) Low COE for non–statistically different effect	Treatment effect: 1% vs. 1%; RR, 1.09 (95% CrI, 0.38 to 3.78) Low COE for non–statistically different effect	Treatment effect: 7% vs. 8%; RR, 1.2 (95% CrI, 0.41 to 3.89) Insufficient COE
Other drugs							
Ciclesonide vs. placebo (45)	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 215 Study duration: 14 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 66% vs. 58%; RR, 1.13 (95% CI, 0.91 to 1.40) Low COE for non–statistically different effect	No evidence	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 6% vs. 3%; RR, 1.87 (95% CI, 0.48 to 7.26) Insufficient COE	Studies: 1 Participants: 209 Study duration: 14 d Treatment effect: 6% vs. 7%; RR, 1.36 (95% CI, 0.45 to 4.15) Low COE for non–statistically different effect	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 22% vs. 15%; RR, 1.43 (95% CI, 0.79 to 2.58) Low COE for non–statistically different effect
Fluvoxamine vs. placebo (39, 40)	Studies: 2 Participants: 1649 Study duration: 15 to 28 d Treatment effect: 2% vs. 3%; RR, 0.71 (95% CrI, 0.24 to 2.10) Low COE for non–statistically different effect	Studies: 1 Participants: 152 Study duration: 15 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	No evidence	Studies: 2 Participants: 1649 Study duration: 15 to 28 d Treatment effect: 9% vs. 12%; RR, 0.71 (95% CrI, 0.22 to 1.70) Low COE for non–statistically different effect	Studies: 1 Participants: 152 Study duration: 15 d Treatment effect: 1% vs. 7%; RR, 0.18 (95% CI, 0.02 to 1.50) Insufficient COE	Studies: 1 Participants: 152 Study duration: 15 d Treatment effect: 15% vs. 15%; RR, 0.98 (95% CI, 0.46 to 2.09) Low COE for non–statistically different effect

CI = confidence interval; COE = certainty of evidence; CrI = credible interval; HR = hazard ratio; OR = odds ratio; RR = risk ratio.
* The RR was self-calculated.

Regdanvimab. Two RCTs (*n* = 345; 1 with low risk of bias and 1 with some risk of bias) assessed regdanvimab, 20 to 80 mg/kg of body weight, compared with placebo (34, 42).

Although 1 study (*n* = 250) found that regdanvimab probably improved recovery (86.6% vs. 71.7%; RR, 1.21 [CI, 1.05 to 1.38]; moderate COE) (34), together the studies did not find a statistically significant effect on time to recovery (5.5 to 9.0 vs. 8.0 to 8.5 median days; low COE). The results for hospitalization due to COVID-19 (4.4% vs. 8.7%; RR, 0.51 [CI, 0.21 to 1.26]; 1 RCT; low COE) (34) and incidence of adverse events (29.4% vs. 30.7%; RR, 0.97 [CrI, 0.44 to 2.58]; 2 RCTs; low COE) (**Supplement Figure** 6) also did not differ statistically between groups. Evidence was insufficient to draw conclusions about any of the other outcomes.

Sotrovimab. One RCT (*n* = 1057; low risk of bias) assessed sotrovimab, 500 mg, compared with placebo (38).

Sotrovimab may reduce hospitalization due to COVID-19 (0.6% vs. 5.3%; RR, 0.11 [CI, 0.03 to 0.35]; low COE) and resulted in no statistical difference in incidence of adverse events (21.8% vs. 23.4%; RR, 0.93 [CI, 0.74 to 1.17]; moderate COE). Evidence was insufficient to draw conclusions about other outcomes.

Antibiotic or Antiparasitic Drugs

Azithromycin. One RCT (*n* = 263; some risk of bias) assessed azithromycin in a single 1.2-g dose compared with placebo (41).

Azithromycin may have no effect on recovery at day 14 (50.4% vs. 50.0%; RR, 1.02 [CI, 0.91 to 1.13]; low COE) and may increase the incidence of adverse events (56.6% vs. 26.4%; RR, 2.14 [CI, 1.42 to 3.23]; low COE). Evidence was insufficient to draw conclusions about other outcomes.

Chloroquine or Hydroxychloroquine. Three RCTs (*n* = 893; some risk of bias) assessed hydroxychloroquine, 800 mg on day 1 followed by 400 mg/d for 5 days then 600 mg/d for 9 days, compared with placebo (27, 28, 30).

Hydroxychloroquine may reduce the likelihood of recovery (60.9% vs. 78.4%; RR, 0.78 [CI, 0.62 to 0.97]; 1 RCT; low COE), but the median time to recovery (14 vs. 12 days; low COE) did not differ statistically between the treatment groups after 30 days (27). Hydroxychloroquine may not reduce risk for hospitalization due to COVID-19 (3.7% vs. 4.2%; RR, 0.92 [CrI, 0.29 to 3.12]; 2 RCTS; low COE) (**Supplement Figure 7**). Hydroxychloroquine may not result in any statistical difference in serious adverse events (2.9% vs. 2.9%; RR, 1.06 [CrI, 0.38 to 3.11]; 3 RCTs; low COE) (**Supplement Figure 8**) or any adverse events (22.2% vs. 20.9%; RR, 1.06 [CI, 0.74 to 1.53]; 1 RCT; low COE) (30). Evidence was insufficient to draw conclusions about other outcomes.

Ivermectin. Five RCTs (*n* = 2452; 4 with some risk of bias and 1 with high risk of bias) compared ivermectin,

200 to 1200 mcg/kg in a single dose or for 2 to 5 days, with placebo (26, 29, 47–49).

Ivermectin may not have any statistically significant benefit on all-cause mortality (2.0% vs. 2.3%; RR, 0.89 [CrI, 0.42 to 1.91]; low COE) (**Supplement Figure 9**), recovery (68.2% vs. 65.6%; RR, 1.04 [CrI, 0.61 to 1.72]; moderate COE) (**Supplement Figure 10**), or hospitalization due to COVID-19 (8.1% vs. 9.9%; RR, 0.81 [CI, 0.49 to 1.34]; low COE) (**Supplement Figure 11**). A sensitivity analysis without the study that had high risk of bias found similar results for reduced hospitalization (8.1% vs. 10.2%; RR, 0.78 [CrI, 0.46 to 1.28]). There was no statistical difference in incidence of adverse events (27.7% vs. 31.8%; RR, 0.89 [CrI, 0.67 to 1.16]; moderate COE) (**Supplement Figure 12**). Evidence was insufficient to draw conclusions about other outcomes.

Nitazoxanide. Two RCTs (n = 1567; some risk of bias) assessed nitazoxanide, 1200 or 500 mg/d, compared with placebo (32, 43).

Nitazoxanide resulted in no statistical difference in recovery (69.3% vs. 73.7%; RR, 0.94 [CI, 0.83 to 1.07]; moderate COE) (32), median number of days to sustained clinical recovery (13.3 [IQR, 6.3 to 21] vs. 12.4 [IQR, 7.2 to 21]; P = 0.88; moderate COE) (43), or hospitalization due to COVID-19 (0.7% vs. 1.3%; RR, 0.63 [CrI, 0.17 to 2.28]; low COE) (**Supplement Figure 13**). There were also no statistical differences in the incidence of serious adverse events (0.3% vs. 1.1%; RR, 0.33 [CrI, 0.07 to 1.56]; low COE) (**Supplement Figure 14**) or any adverse events (14.2% vs. 19.3%; RR, 0.79 [CrI, 0.38 to 1.62]; moderate COE) (**Supplement Figure 15**). Evidence was insufficient to draw conclusions about other outcomes.

Convalescent Plasma

Four RCTs (n = 2272; 2 with low risk of bias and 2 with some risk of bias) assessed convalescent plasma, 250 to 300 mL in a single dose, compared with placebo (24, 36, 37, 46).

Convalescent plasma may have no statistical effect on all-cause mortality (0.6% vs. 0.9%; RR, 0.68 [CrI, 0.20 to 2.34]; 4 RCTs; low COE) (**Supplement Figure 16**), hospitalization due to COVID-19 (8.1% vs. 10.8%; RR, 0.75 [CrI, 0.42 to 1.31]; 3 RCTs; low COE) (**Supplement Figure 17**), incidence of serious adverse events (1.1% vs. 1.1%; RR, 1.09 [CrI, 0.38 to 3.78]; 4 RCTs; low COE) (**Supplement Figure 18**), or time to symptom resolution (12 vs. 12 median days; hazard ratio, 1.05 [CI, 0.85 to 1.30]; 1 RCT; low COE) (46). Evidence was insufficient to draw conclusions about other outcomes.

Other Drugs

Corticosteroids. One RCT (n = 215; low risk of bias) assessed ciclesonide, 1200 mcg inhaled twice daily or 200 mcg intranasally per day, compared with placebo (45).

Ciclesonide may result in no statistically significant difference for recovery (65.7% vs. 58.2%; RR, 1.13 [CI, 0.91 to 1.40]; low COE), incidence of serious adverse events (6.6% vs. 4.9%; RR, 1.36 [CI, 0.45 to 4.15]; low COE), or incidence of any adverse events (21.9% vs. 15.3%; RR, 1.43 [CI, 0.79 to 2.58]; low COE). Evidence was insufficient to draw conclusions about other outcomes.

Fluvoxamine. Two trials (n = 1649; 1 with low risk of bias and 1 with some risk of bias) assessed fluvoxamine, 100 mg/d, compared with placebo (39, 40).

Fluvoxamine may have no statistically significant effect on all-cause mortality (2.1% vs. 3.0%; RR, 0.71 [CrI, 0.24 to 2.10]; 2 RCTs; low COE) (**Supplement Figure 19**), hospitalization due to COVID-19 (9.1% vs. 12.2%; RR, 0.71 [CrI, 0.22 to 1.70]; 2 RCTs; low COE) (**Supplement Figure 20**), or any adverse events (15.0% vs. 15.3%; RR, 0.98 [CI, 0.46 to 2.09]; 1 RCT; low COE). Evidence was insufficient to draw conclusions about other outcomes.

Subgroup Analysis

One fluvoxamine trial (39) found no statistically significant interaction for the effect of age, sex, time from symptom onset, and comorbidities for hospitalization or extended emergency department visit due to COVID-19.

Several other trials reported comparisons of the study groups in population subsets but without testing for interaction. Most confirmed the overall result (30, 32, 35, 41, 43, 46). Two studies reported an increased or decreased risk for hospitalization due to COVID-19 or recovery for certain subgroups despite the overall effect showing no difference between the groups (33, 34) (**Supplement Table 9**, available at Annals.org).

Surveillance

The first surveillance search yielded 6 eligible RCTs (50–55). The studies compared molnupiravir (51), ivermectin (50–52, 54), fluvoxamine (55), and the monoclonal neutralizing antibodies tixagevimab–cilgavimab (53) with placebo (**Supplement Table 10**, available at Annals.org). The study on tixagevimab–cilgavimab (53) reported a reduction in COVID-19–related deaths or progression to severe disease (4% vs. 10%; RR, 0.43 [CI, 0.25 to 0.75]) and an increase in any adverse events (29% vs. 36%; RR, 0.81 [CI, 0.67 to 0.98]). It was conducted before the emergence of the Omicron variant. The remaining 5 studies reported no beneficial or harmful effects for outcomes of interest (50–52, 54, 55).

DISCUSSION

This living, rapid review on 12 COVID-19 outpatient treatments, which included 26 RCTs conducted before dominance of the current Omicron variant, found that nirmatrelvir–ritonavir and the monoclonal antibodies casirivimab–imdevimab and regdanvimab had the strongest evidence for benefit in outpatients with COVID-19, with reduced hospitalizations, reduced all-cause mortality, or both. Molnupiravir and remdesivir may also reduce all-cause mortality and remdesivir may improve recovery, but evidence is less certain. However, these findings must be interpreted with caution because all studies were conducted before the dominance of the current Omicron variant. Specifically, a preprint article of the unblinded PANORAMIC (Platform Adaptive trial of NOvel antiviRals for eArly treatMent of covid-19 In the Community) trial

(*n* = 25 783), which was conducted in the United Kingdom during dominance of the Omicron variant, reports no difference for hospitalization, mortality, or serious adverse events but improved early sustained recovery and time to first reported recovery between molnupiravir plus usual care and usual care (56). However, as a preprint article that has not yet been subject to peer review, this study did not meet the inclusion criteria for our surveillance.

Several in vitro studies have found that the monoclonal antibodies that were found to be effective in our review (casirivimab–imdevimab, regdanvimab, and sotrovimab) are ineffective against the Omicron subvariant BA.5 (57–59). Because Omicron and its subvariants have become the dominant strains in the United States during 2022 (60), the U.S. Food and Drug Administration has revoked authorization for casirivimab–imdevimab (in January 2022) and sotrovimab (in May 2022) (61, 62). Regdanvimab was never approved in the United States. The antivirals remdesivir, molnupiravir, and nirmatrelvir–ritonavir have been shown to retain susceptibility to Omicron subvariants, including BA.5, similar to that for the ancestral strain (63). Despite retaining neutralizing activities, the absolute effect of antivirals to prevent hospitalization and death might be lower due to the reduced overall severity of the Omicron variant compared with previous variants (64). Current evidence does not support the efficacy of convalescent plasma and several drugs that were repurposed for use in outpatients with COVID-19, such as ivermectin, lopinavir–ritonavir, azithromycin, chloroquine or hydroxychloroquine, nitazoxanide, inhaled or intranasal corticosteroids, and fluvoxamine. Lopinavir–ritonavir and azithromycin may even have harmful effects, and hydroxychloroquine may lead to lower recovery rates.

We did not identify any results related to COVID-19 rebound, a phenomenon in which patients develop symptoms of COVID-19 after taking the drug (65). However, because rebound has also been observed in untreated persons with COVID-19 (66), clinical trials are needed to understand the effects of antivirals on rebound.

Our results are largely consistent with findings from other reviews, which were conducted in mixed populations of inpatients and outpatients and used standard of care as a comparison in addition to placebo. In line with our review, Cochrane reviews found beneficial effects for monoclonal antibodies (3) and nirmatrelvir–ritonavir (10) and no beneficial effects for chloroquine or hydroxychloroquine (5), convalescent plasma (9), ivermectin (6), or azithromycin (4). Other reviews showed that remdesivir increased recovery and reduced time to recovery and serious adverse events but also increased adverse events in hospitalized patients (67), and that fluvoxamine led to fewer hospitalizations in outpatients (68) when, unlike in this review, unpublished data were included.

This living, rapid review considered many aspects not evaluated in previous reviews. One of its strengths is its comprehensive assessment of the benefits and harms of 12 COVID-19 treatments of interest. Another strength of this study is its focus on placebo-controlled trials, which is the most rigorous study design for evaluating treatment efficacy because it ensures assay sensitivity (the ability to distinguish between effective and ineffective treatments) (69).

This review also has limitations. Although we restricted the literature search to only 1 database, evaluations of the Epistemonikos COVID-19 L·OVE Platform database have shown that it provides a comprehensive compilation of COVID-19 treatments, containing nearly all cited studies (70). To prevent missing relevant studies, we double-checked our list of included studies with that of the COVID-NMA database (15).

Another limitation of our review is the lack of sufficient data for some outcomes. Included studies provided very low rates of hospitalization and mortality and low power in a population with mild to moderate disease severity. Insufficient data also precluded the exploration of heterogeneity across studies (71). The reported subgroup analyses were predominantly limited to exploratory or post hoc analyses and relied on small sample sizes. Although these analyses are useful for generating new hypotheses, recommendations for clinical practice should rely on prespecified subgroup analyses (72).

Finally, the greatest limitation is that included studies were conducted before the Omicron variant became dominant and lacked information on vaccination or prior infection status, which reduces the generalizability of the findings.

In conclusion, some antivirals and some monoclonal antibodies may improve recovery and reduce the risk for hospitalization in outpatients with mild to moderate COVID-19 from previous variants of SARS-CoV-2. However, the benefits of these therapies, particularly monoclonal antibodies, may be limited against the currently dominant Omicron variants.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Sommer (e-mail, isolde.sommer@donau-uni.ac.at). *Statistical code and data set:* Available from Mr. Emprechtinger (e-mail, robert.emprechtinger@donau-uni.ac.at).

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Author contributions are available at Annals.org.

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