Outpatient regimens to reduce COVID-19 hospitalizations: a systematic review and meta-analysis of randomized controlled trials.

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Abstract

During pandemics, out-of-hospital treatments reduce the health system burden. Controversies persist regarding the best treatment options for COVID-19 outpatients at risk for hospitalization. We assembled data from 47 randomized controlled trials investigating 51 distinct interventions in more than 60,000 outpatients until October 2022 with the endpoint of hospitalization. These trials, largely performed in unvaccinated cohorts during pre-Omicron waves, mostly targeted populations with at least one risk factor for COVID-19 hospitalization. Grouping by class, the COVID-19 convalescent plasma (CCP) (OR=0.69 [95% CI=0.53 to 0.9]), anti-Spike monoclonal antibodies (OR=0.32 [95% CI=0.24-0.42]) and small molecule antivirals (OR=0.57 [95% CI=0.3-1.09]) each had comparable efficacy for hospital relative risk reduction dependent on intervention dose and timing. Repurposed drugs had lower efficacy. The recent Omicron sublineages (XBB and BQ.1.1) *in vitro* resistance to monoclonal antibodies suggests a pressing need to reevaluate CCP recommendations for COVID-19 outpatients at risk for hospitalization, especially in constrained medical resource settings.

Introduction

By late October 2022 the world had recorded over 630 million cases and more than 6.6 million deaths from COVID-19. Hospitalization rates are about 6% in the US, where from August 2020 to October 2022, nearly 5 million individuals were hospitalized for COVID-19. A pronounced spike in hospitalizations for COVID-19 in the US took place in the first two months of 2022 with the introduction of the Omicron variant of concern (VOC). Vaccination boosts have substantially reduced the risk of hospitalization and death, but outpatients at risk still require early treatment to avoid disease progression to hospitalization.

The risk of hospitalization can be reduced by antivirals of different classes (COVID-19 convalescent plasma (CCP), anti-Spike monoclonal antibodies (mAbs) or small molecules) or supportive care drugs (which are largely repurposed). Randomized controlled trials (RCTs) in outpatients have tested therapeutic agents against placebo or standard of care, but no RCT has been conducted comparing the main classes of outpatient treatments. CCP was first administered to hospitalized patients across the world in March 2020, a few weeks after the pandemic began[1], but was initially FDA restricted to inpatient use in the US.

The first outpatient treatments for COVID-19 authorized by the FDA were anti-Spike mAbs (bamlanivimab, bamlanivimab plus etesevimab[2, 3] or casirivimab plus imdevimab[4]) approvals that preceded the introduction of mRNA vaccines[5, 6]. While many small molecules were repurposed as antivirals during the early stages of the pandemic, oral antivirals developed against SARS-CoV-2 for outpatients were not authorized and available until December 2021, when nirmatrelvir/ritonavir[7] and molnupiravir[8] were approved. The following month, intravenous remdesivir was also approved for outpatient use[9]. On December 2021, nearly two years after the first use of CCP, the FDA approved CCP outpatient use, but only for immunosuppressed patients[10, 11].

To date no head-to-head RCT has ever compared antiviral treatment options for COVID-19 outpatients (with the few exceptions of Eli Lilly comparing bebtelovimab to bebtelovimab+bamlanivimab+etesevimab[12] or metformin, ivermectin and fluvoxamine in COVID-OUT[13]), making treatment choices difficult. We assembled RCTs of different therapies all sharing hospitalization as an endpoint. A literature search of MEDLINE (through PubMed), medRxiv and bioRxiv databases was carried out inclusive of RCTs published from March 2020 to October 2022 summarized in the PRISMA chart (Figure 1). This systematic review and meta-analysis of RCTs of outpatient therapy for COVID-19, compared outcomes, taking into account risk factors for progression, dosage of the intervention, time between onset of symptoms and treatment administration, and predominant variants of concern at the time of the interventions.

Results

We reviewed in detail 47 distinct outpatient RCTs (51 different interventions), conducted from March 2020 to October 2022, across waves sustained by different SARS-CoV-2 variants of concern (VOC) and different vaccination periods. We focused on four different therapeutic categories – CCP, anti-Spike mAbs, small molecule antivirals and repurposed drugs.

Five large-scale outpatient RCTs investigating CCP have been published. A successful RCT from Argentina[14] was followed by another RCT (C3PO-SIREN) halted at 511 participants after the data safety monitoring board (DSMB) determined “futility” before completion[15]. The third RCT in Spain (CONV-ERT) involved methylene blue-treated CCP[16], raising concern about interference with Fc-dependent antibody function[17], and the fourth was a large RCT in the USA (CSSC-004)

[11]. A fifth RCT was run in The Netherlands (Cov-Early), originally published as combined analysis with the Spanish RCT[18] and later as individual data[19].

Eight anti-Spike mAb RCTs (bamlanivimab[2], bamlanivimab/ etesevimab[3], casirivimab/ imdevimab phase 1/2[20] and phase 3[21], sotrovimab[22], regdanvimab[23], bebtelovimab[12] and tixagevimab–cilgavimab[24]) led to FDA emergency use authorizations (EUA), with regdanvimab[23] approved in Europe only and bebtelovimab approved in US only.

Of 11 outpatient RCTs of small molecule antivirals - oral molnupiravir[8, 25, 26], oral nirmatrelvir/ritonavir[7] and intravenous remdesivir[27] led to EUAs. Other antivirals studied by RCTs included peginterferon lambda[28, 29, 30], sofosbuvir/daclatasvir[31], favipiravir[32] and lopinavir/ritonavir[33].

Additionally, 15 repurposed drugs tested in 23 outpatient RCTs were included in our analysis for context: metformin[13], fluvoxamine[13, 34, 35], ivermectin[13, 36, 37, 38], hydroxychloroquine[33, 39, 40, 41, 42], nitazoxanide[43], colchicine[44], niclosamide[45], four antithrombotics-aspirin, apixaban[46], sulodexide[47], enoxaparin[48, 49], inhaled ciclesonide[50], the herbal mixture Saliravira[51], azithromycin[52, 53], and resveratrol[54].

GRADE

The 5 CCP RCTs had a high GRADE (Supplementary Table 1). Most information is from results at low risk of bias or with some concerns, but unlikely to lower confidence in the estimate of effect. The GRADE for anti-Spike mAbs RCTs was moderate (downgraded for risk of bias (ROB)). The RCTs for small molecule antivirals had a GRADE level low for inconsistency (I^2=81) and ROB. The RCTs for repurposed antiviral drugs had a moderate GRADE score for ROB. All four trial classes showed reduced rates of hospitalization for each group. The ROB independently was evaluated by NMA-COVID-19 for most all of the RCTs (Supplementary Figure 1).

Trial populations

The 47 RCTs (51 interventions) ranged in duration between 1 and 16 months, averaging 9, 4, 5 and 7 months for the CCP, anti-Spike mAbs, small molecule antivirals and repurposed drugs, respectively (Figure 2, Table 1, Supplementary Table 2). 24 studies were completed in the pre-Alpha VOC period, with 14 encompassing either the Delta or Omicron wave only. All cause (n=30) or COVID-19 related (n=21) admissions by day 28-30 was the hospital endpoint for most RCTs (9 RCTs measuring at day 14-23, 1 at day 45 and 2 at day 90), excepting the single Argentinean CCP RCT, which used severe respiratory distress as a proxy for hospitalization[14] (Table 1). Of more than 60,000 participants enrolled, 55% were in RCTs of small molecule antivirals, 28% in RCTs of repurposed antiviral drugs, 12.5% in RCTs of anti-Spike mAbs and 4.5% in CCP RCTs. Nearly half of all recruited outpatients were from the single molnupiravir-PANORAMIC RCT, which recruited 25,000 participants[25].

Age and ethnicity

The median age of participants was about 50 years. The CCP group had a nonweighted trial average of median age equal to 58 years, while the anti-Spike mAbs, small molecule antivirals and repurposed drug groups younger average of median age was equal to 45 to 48 years. Most RCTs

had more women than men, and 84% of all RCT 60,043 participants had Caucasian ethnicity (Table 1, Supplementary Table 2).

Risk factors for COVID19 progression

The individual RCTs differed in the percentage of participants with risk factors for progression to severe COVID-19. Of the 37 RCTs reporting aggregated hospitalization risk factors, ten had 100% of participants with at least one hospitalization risk factor, while 5 had less than 50%. The Bebtelovimab placebo-controlled RCT explicitly focused exclusively on low-risk individuals [12]. Individual risk factors like diabetes mellitus occurred in 10 to 20% of participants within most RCTs. Obesity with BMI over 29 averaged near 40% of RCT participants in the 4 therapy groups after excluding the large single 25,000 molnupiravir-PANORAMIC RCT with 15% of participants over 30 BMI (Table 1) [25].

Seropositivity and timing from symptom onset

Of 18 RCTs reporting seropositivity rates at baseline, 11 had < 25% screening seropositivity (Table 1, Figure 2). The molnupiravir-PANORAMIC RCT was an outlier, with 98% seropositives[25]. All but one[44] of the RCTs enrolled within 8 days (median) of symptom onset. In RCTs of anti-Spike mAbs and small molecule antivirals, median time from illness onset to intervention was 3.5 to 4 days (Figure 3, Table 1, Supplementary Table 2). CCP and repurposed antiviral drug RCTs enrolled within 4.5 to 5.1 days from symptom onset.

Geography and time period

The CCP RCTs were conducted in the USA[11, 15], Argentina[14], Netherlands[18] and Spain[16] (Supplementary Table 2). The anti-Spike mAb RCTs all had a USA component, but were largely centered in the Americas except for the sotrovimab RCT, which took place in Spain[22]. Many of the repurposed drugs and nirmatrelvir/ritonavir RCTs recruited worldwide[7].

Four of the five CCP RCTs (COV-Early[18], CONV-ERT[16], Argentina[14] and C3PO[15]), and all eight anti-Spike mAb RCTs took place in the setting of the D614G variant and the Alpha VOC (Figure 2). By contrast, most of the molnupiravir, nirmatrelvir/ritonavir[7] and interferon lambda RCTs were conducted in the setting of the Delta VOC. The ivermectin[36] and fluvoxamine[34] RCTs ended as the Delta VOC wave began in August 2021. The remdesivir RCT spanned D614G, Alpha and Beta VOC but missed Delta[27]. The CSSC-004 RCT of CCP was the longest RCT reviewed, spanning periods characterized by D614G to Delta VOC infections[11].

Efficacy endpoints

Efficacy at preventing hospitalization

Because inclusion criteria varied across the RCTs, the power to detect a difference in hospitalization rates varied across studies. Three CCP RCTs had higher control arm hospitalization rates (11% - 31%) than all other antiviral RCTs, indicating that they studied sicker populations.[11] (Table 2 and Figure 4). The six mAb RCTs had hospitalization rates in the controls of 4.6-8.9%, the same range as CSSC-004[11] (6.3%). Control hospitalization rates in the molnupiravir-MOVE-OUT[7], nirmatrelvir/ritonavir[7] and remdesivir[27] RCTs, all agents that obtained FDA EUAs, ranged from 5.3% to 9.7%. Low hospitalization rates were found in RCTs that had many vaccinees (metformin-COVID-OUT – 3.2%[13]) or in which most participants were seropositive (molnupiravir-PANORAMIC – 0.8%). Low control arm hospitalization rates were also found in

two mAb RCTs – the bebtelovimab trial (1.6%)[12] and REGN-CoV phase 1/2 (<2%), with the bebtelovimab RCT focusing on low-risk patients [12]

Examining RCTs by agent class, statistically significant relative risk reductions in hospitalization were found in two of 5 CCP RCTs, 5 of 8 anti-Spike mAb RCTs, 4 of 11 small molecule antiviral RCTs, but just 2 of 23 repurposed drug RCTs (Table 2). Considering effect size, CCP efficacy in preventing hospitalization or progression was about 50% in both the Argentinean[14] and in CSSC-004 RCTs[11] and 36% and 31% in COV-Early[18] and C3PO[15]. Except for the bebtelovimab RCT (2 hospitalizations in each arm[12]), anti-Spike mAb RCTs reduced the risk of hospitalization by 69-80% (average 75%). Two of the three small molecule antiviral drugs (remdesivir[27] and nirmatrelvir/ritonavir[7]) showed very high levels of relative risk reduction - 86% and 88% respectively - but molnupiravir reduced risk of hospitalization by only 30%[7] (no reduction in the PANORAMIC RCT[25]), and the combination of lopinavir/ritonavir was associated with a non-significant increase in risk of hospitalization[33].

Among RCTs of repurposed drugs, all except metformin (57%) and sulodexide (40%), showed small and non-significant relative risk reductions of hospitalization - 11% for ivermectin[36], 20% for colchicine[44], 21% for fluvoxamine[34] and 24% for hydroxychloroquine[33]. The RCT of nitazoxanide[43] found one hospitalization among 184 treated participants compared to five hospitalizations among 195 controls, far too few events to achieve significance.

In the pooled meta-analysis by class group, the CCP RCTs had a fixed effect OR of 0.69 (95% CI=0.53 to 0.9) with moderate heterogeneity (I^2=43%), the anti-Spike mAbs had a fixed effect OR of 0.32 (95% CI=0.24-0.42) with low heterogeneity (I^2=0%), the small molecule antivirals had a random effect OR of 0.57 (95% CI=0.3-1.09) with high heterogeneity (I^2=80%) and the repurposed drugs had a fixed effect OR of 0.77 (95% CI- 0.68-0.88) with low heterogeneity (I^2=4%) (Figure 5, Supplementary Table 3). The meta-analysis of all interventions had a random effect OR of 0.62 (95% CI=0.51-0.74) with high heterogeneity (I^2=58%) (Supplementary Figure 2).

Overall, RCTs proved the value of early treatment. Ten RCTs by design began outpatient treatment within the 5-days window and an eleventh reported point estimate numbers. Relative risk reduction in hospitalization was 73% (OR=0.2, 95%CI-.06-0.71) in recipients of higher dose or higher antibody titer CCP in Argentina transfused within 3 days, [14] and was 80% (OR=0.18, 95%CI-.07-0.49) in participants treated within 5 days of symptoms in CSSC-004 [11] (Figure 6), which is comparable to nirmatrelvir[7] (OR=0.12, 95%CI-.06-0.24) and sotrovimab (OR=0.19, 95%CI-.08-0.46) therapy within 5 days of symptom onset (Supplementary Table 3).

The final certainty of the available evidence with GRADE assessment (Supplementary Table 1) showed high level of certainty within CCP trials, moderate certainty with mAbs, and low certainty with small molecule antivirals and repurposed drugs. The heterogeneity amongst all of the outpatient trials with hospitalization as an endpoint measured by the I^2 statistic is 58%, with p-value < 0.01. The main reason for downgrading individual studies was imprecision, related to small number of participants and the wide confidence intervals around the effect, followed by ROB (Supplementary Figure 1). In the cumulative analysis, small molecule antivirals were downgraded to low certainty of evidence because of ROB (some/high ROB in 4 RCTs) and inconsistency (due

to high heterogeneity), while repurposed drugs were downgraded to low certainty due to ROB (some/high ROB in 5 of the 11 comparisons) and indirectness (due to large difference in mechanism of action of the included drugs). Anti-Spike mAbs were downgraded to moderate certainty due to ROB (in 4 of the 8 included RCTs, ROB for the outcome hospitalization was judged of some concern). Of note, we could not find concerns in any of the GRADE factors for CCP RCTs and therefore they were graded as high level of certainty. Funnel plot analysis shows a low risk of publication bias except for the anti-Spike mAbs, for which either the efficacy of high dose antibodies or non-reporting bias are plausible explanations (Supplementary Figure 3).

Efficacy at reducing mortality

While several RCTs showed fewer deaths in the treatment arm, no outpatient study was powered to compare differences in mortality. Cumulatively, the two effective CCP RCTs (Argentine[14] and CSSC-004[11]) recorded 7 deaths in controls and 2 in the treatment arm, but C3PO reported 4 more deaths in the CCP arm[15]. Cumulatively, the anti-Spike mAbs RCTs had 21 deaths among controls and 4 in the intervention arm (Supplementary Table 4). The 3 emergency-authorized small molecule antiviral RCTs experienced 22 deaths in the control groups and 1 in the intervention groups while the total for all small molecule antiviral RCTs was 28 in the controls and 7 in the interventions. The repurposed drugs RCTs recorded 72 deaths in the control groups and 53 in the intervention groups. Because of the low rate of deaths during trials the absolute risk reductions amongst the 4 antiviral classes are all below 1% corresponding to relative risk reductions of 20%, 84%, 75% and 28% with OR of 0.80 (95% CI-.31-2.02), 0.16(95% CI-.06-.48), 0.25(95% CI-.11-.57), and 0.72(95% CI-.5-1.02), for CCP, anti-Spike mAbs, small molecule antivirals or repurposed drugs, respectively (Supplementary Table 4).

Efficacy at symptom resolution

The two effective CCP RCTs (Argentine[14] and CSSC-004[11]) did not compare time to symptom resolution, while the COV-Early[18] and ConV-ert[16] RCTs reported no difference in the median time of symptom resolution in the two groups[16] (Table 2). The anti-Spike mAbs noted faster resolution by 1, 2, 3 or 4 days for bamlanivimab/etesevimab[3], bebtelovimab[12], regdanvimab[23], and casirivimab/imdevimab[21], respectively. The smaller bamlanivimab-only RCT did not show a difference[2]. Of the three emergency-authorized small molecule antivirals that noted reductions in hospitalizations, molnupiravir was associated with no difference in time of symptom resolution in MOVe-OUT[7] but improvements in both PANORAMIC[25] and Aurobindo[27] RCTs. The 3-day outpatient remdesivir RCT showed that symptoms were alleviated by day 14 nearly twice as often in the treatment arm[27]. The nirmatrelvir/ritonavir RCT did not report on this parameter[7]. Six out of 9 RCTs in the antiviral group did not show faster symptom resolution with intervention. The three RCTs largely performed in Brazil for fluvoxamine, ivermectin[36] and hydroxychloroquine[33] noted no differences in symptom resolution. Metformin did not evidence faster symptom resolution despite reducing hospitalizations. 3 of the 18 RCTs reporting symptom resolution in the repurposed drug group noted faster symptom resolution.

Costs and resiliency against variants of concern

Anti-Spike mAbs and intravenous remdesivir schedules cost about 1000 to 2000 Euros per patient, respectively, while the oral drugs are much less than 1000 Euros per patient (Table 3). By comparison, the cost of CCP approximates 200 Euros per patient, and the cost for repurposed drugs is even lower. Considering the absolute risk reduction in hospitalization, the number needed to

treat to prevent a single hospitalization is often very high, as are the associated costs. With the recently patented antivirals, costs for outpatient treatment often exceeds the cost of a COVID-19 hospitalization[53].

mAb and mAb cocktails successively lost efficacy against Delta and Omicron, with cilgavimab (the only Omicron-active ingredient in Evusheld™) and bebtelovimab also failing against BQ.1.1 sublineages (Figure 7). This had led the FDA to withdraw EUAs, while EMA has not restricted usage at all. Small molecule antivirals retain *in vitro* efficacy against Omicron, but concerns remain: molnupiravir showed low efficacy *in vivo*[8] and is mutagenic for mammals *in vitro*[55], while nirmatrelvir/ritonavir has drug/drug interaction contraindications (CYP3 metabolites especially tacrolimus, anti-cholesterol, anti-migraine or many anti-depressants) and has been associated with early virological and clinical rebounds in immunocompetent patients[56]. CCP from unvaccinated donors does not inhibit Omicron, but CCP from donors having any sequence of vaccination and COVID-19 or having had boosted mRNA vaccine doses universally has high Omicron-neutralizing activity.

Discussion

Outpatient RCTs are more difficult to perform by non-industrial institutions compared to drug manufacturers during an infectious disease pandemic, since switching between already constrained inpatient academic /nonindustrial personnel and outpatient spaces is challenging. By contrast, the pharmaceutical industry has well established internal resources and economical support for running outpatient trials. The relative ease of conducting inpatient RCTs may have led most initial CCP, small molecule antiviral and repurposed trials –conducted principally by academic institutions - to be based in hospitals, often in patients treated too late for antiviral treatment to be expected to work given that antiviral therapy must be given early in disease. Consistent with this, the outpatient RCT data extant confirms that most antiviral/antimicrobial therapies are more effective when given before hospital admission. The paucity of head-to-head RCTs amongst outpatient COVID-19 therapy makes clinical comparisons difficult when the RCTs were run during different times, targeting different variants and in populations with different vaccination status. Cooperation to run head-to-head intervention RCTs between different pharmaceutical companies is always more difficult. Consequently, these limitations need to be considered in our head-to-head meta-analysis assembled COVID-19 outpatient placebo controlled RCTs.

SARS-CoV-2 antibodies, whether elicited by vaccines, or provided as polyclonal (CCP) or anti-Spike mAbs, have all been demonstrated to substantially prevent progression of COVID-19 to hospitalization, as have several small molecule antivirals. Either vaccination of immunocompetent subjects and therapeutic administration of anti-Spike mAbs, generate high serum levels of neutralizing antibodies (albeit of different subclasses and at different times): dose concerns still exist for monoclonals (e.g., tixagevimab-cilgavimab[57]), and the risk of treatment-emergent immune escape under selective pressure[58] has been marginally investigated. RCTs showed minimal effects of most agents on time to symptom resolution, but a more amplified effect of 50 to 80% reduction in rates of hospitalization was seen in the three major classes of outpatient treatment – CCP, anti-spike mAbs and small molecule antivirals.

Despite the heterogeneity of these 47 RCTs trials, which varied in participant age, medical risk factors, vaccination history and serological status, the assembly of these effective, yet molecularly

disparate interventions, outpatient RCTs shows the consistent importance of early outpatient treatment for patients at risk of progression [59]. Treatment within 5 days of illness onset was more effective than later treatment, as would be expected for an antiviral mechanism of action. Importantly, for CCP, increasing the dose in the Argentina RCT[14] and shortening the intervention interval to within five days of illness onset produced a relative risk reduction for hospitalization close to 80%, which is comparable to (or superior) to the findings of RCTs with anti-Spike mAbs and small molecule antivirals. Overall, a reduction in mortality is suggested with these outpatient therapies, but the individual RCTs are underpowered to investigate death as an outcome.

In recent months, the clinical armamentarium was reduced to small molecule antivirals-oral molnupiravir or nirmatrelvir/ritonavir as well as three day intravenous remdesivir and CCP, since single and double ("cocktail") anti-Spike MAbs have lost effectiveness against new VOCs. Both vaccine and disease elicited antibodies are polyclonal, meaning that they include various isotypes that provide functional diversity and target numerous epitopes making variant escape much more difficult with CCP. Hence, polyclonal antibody preparations are much more resilient to the relentless evolution of variants. This is in marked contrast to mAbs, which target single epitopes of SARS-CoV-2. The exquisite anti-Spike mAb (and receptor binding domain) specificity renders them susceptible to becoming ineffective with single amino acid changes. Adding boosters to the vaccine regimen and also producing vaccine-boosted CCP provide high amounts of neutralizing antibodies which can be effective against practically any existing VOC, including Omicron[60] (so-called "heterologous immunity" , likely due to the well-known phenomenon of "epitope spreading"). The vaccine-boosted CCP also has more than ten times the amount of total SARS-CoV-2 specific antibody as well as neutralizing activity compared to the pre-omicron CCP used in the effective outpatient CCP RCTs.

In addition to efficacy, other points to consider in an outpatient pandemic are tolerability, scalability and affordability. Repurposed drugs are generally well tolerated, widely available and relatively inexpensive, but have limited efficacy. On the contrary small molecule antivirals are often plagued by contraindications and side effects, which makes frail patient to rely on passive immunotherapies. Both small molecule antivirals and anti-Spike mAbs take time to develop and are unaffordable to low-and-middle income countries (LMIC). CCP is instead a tolerable, scalable, and affordable treatment.

As shown in Table 3, the market cost of anti-Spike mAbs is generally about 10 times higher than that for manufacturing CCP (at the same level of engagement), making CCP the only COVID-19 antiviral therapy affordably available in LMICs.

In light of our meta-analysis, we therefore urge the WHO to revise its guidelines in order to include CCP as an option for outpatients.

Methods

The protocol has been registered in PROSPERO, the prospective register of systematic reviews and meta-analysis of the University of York (protocol registration number CRD42022369181)

Literature search

We assembled outpatient COVID-19 RCTs with hospitalization as the primary outcome, by searching MEDLINE (through PubMed), medRxiv and bioRxiv databases for the period of March 1, 2020 to October 1, 2022, with English language as the only restriction. The Medical Subject Heading (MeSH) and search query used were: "("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019") AND ("treatment" OR "therapy") AND ("outpatient" OR "hospitalization")". In PubMed, the filter "Randomized Controlled Trial" was applied. We also screened the reference list of reviewed articles for additional studies not captured in our initial literature search. Interventions were classified as antiviral or supportive (repurposed) in nature. We also excluded case reports, case series, retrospective propensity matched studies, non-randomized clinical trials, review articles, meta-analyses, low number of participants with no hospitalizations, homeopathy and zinc vitamin C study with low number of participants and original research articles reporting only aggregate data. Articles underwent a blind evaluation for inclusion by two assessors (D.S. and D.F.) and disagreements were resolved by a third senior assessor (A.C.). Figure 1 shows a PRISMA flowchart of the literature reviewing process. The following parameters were extracted from studies: baseline SARS-CoV-2 serology status time from onset of symptoms to treatment, study dates, recruiting countries, gender, age (including the fraction of participants over age 50, 60 and 65), ethnicity, risk factors for COVID-19 progression (systemic arterial hypertension, diabetes mellitus, and obesity), sample size, dosage type of control, hospitalizations and deaths in each arm, and time to symptom resolution. Study dates were used to infer predominant VOCs.

Assessment of risk of bias and GRADE assessment

A risk of bias assessment of each selected RCT was performed by COVID-19- Network Meta-Analysis (NMA)[61, 62]. Within-trial risk of bias is assessed, using the Cochrane ROB tool for RCTs[63]. The Cochrane 'Risk of bias' tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other issues relating to bias. We explored clinical heterogeneity (e.g., risk factors for progression, time between onset of symptoms and treatment administration, and predominant variants of concern at the time of the interventions) and asses statistical heterogeneity using τ^2, Cochran's Q and estimated this using the I^2 statistic, which examines the percentage of total variation across studies that is due to heterogeneity rather than to chance.

We used the principles of the GRADE (The Grading of Recommendations Assessment, Development and Evaluation) system to assess the quality of the body of evidence associated with specific outcomes, and constructed a 'Summary of findings' table using the software Review Manager (RevMan), Version 5.4 The Cochrane Collaboration, 2020 (available at https://training.cochrane.org/online-learning/core-software/revman/revman-5-download). The certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias[63]. Publication bias was assessed by visual inspection of funnel plots.

Statistical methods

Descriptive analysis included time-to-treatment, geography (country) of the study, age, sex, race (white and black), ethnicity, seropositive, hospital type and medical high-risk conditions (e.g., diabetes, hypertension, and obesity or BMI > 30).

Absolute risk reduction (ARR, i.e., the arithmetic difference in hospitalization between the 2 groups) and relative risk reduction (RRR, i.e., percent reduction in risk) were used to represent the efficacy of treatment. The number needed to treat (NNT) to prevent a single hospitalization was calculated as 1/AAR.

Odds ratios (OR, the odds of hospitalization for the treatment group over the odds of hospitalization for the control group) and 95% confidence intervals (95% CI) were used to show the direction of effect and its significance in comparing treatment group and control groups. Weight, heterogeneity, between-study variance, and significance level were displayed in forest plots. Funnel plots were used to estimate the risk of publication bias.

The forest plot and the enrolment figure were used for visualization and comparison of the odds ratio among studies. The enrolment progress (duration and calendar months) of each study was shown as a Gantt plot. PRISMA flowchart was used to summarize the number of studies. The significance level was 0.05. The figures were created in Prism software, R (version 4.2.1, R Foundation) and its statistical package "meta" (version 6.0-0). All the data manipulation and the analyses were performed in Excel, Prism, MedCalc, R and REVMAN.5.

Declaration of interests

DS, DFH, AC were investigators in the CSSC-004 study; D.F. and M.F. were investigators in the TSUNAMI RCT of CCP. DJS reports AliquantumRx Founder and Board member with stock options (macrolide for malaria), Hemex Health malaria diagnostics consulting and royalties for malaria diagnostic test control standards to Alere- all outside of submitted work. AC reports being part of the scientific advisory board of SabTherapeutics and has received personal fees from Ortho Diagnostics, outside of the submitted work. All other authors report no relevant disclosures.

Contributors

DS wrote the first draft and extracted data verified by DF, and MF. DF curated Table 3 and 7 and revised the text. MC, JO, MF and DS performed statistical analyses. MC and DS performed GRADE assessment. AC, NP, MF and DH critically revised the manuscript. DS and DF directly accessed and verified the underlying data reported here. All authors read and agree with manuscript.

Data availability statement

Datasets used for this systematic review are publicly available in PubMed, medRxiv and bioRxiv.

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Table 1

Demographic and clinical characteristics of recruits in the RCTs analyzed in this review.

Study	mITT	median age (range)	total female n(%)	White n(%)	Black n(%)	Hispanic n(%)	1 or more medical high risk conditons for COVID-19 progession	diabetes n(%)	hypertension n(%)	obesity or BMI > 30 n(%)	median duration symptoms	Seropositive at baseline n(%)	Hospital type	Endpoint days for hosp
CCP (5 RCTs) totals or averages	**2634**	**58**	**1409 (53)**	**2213 (84)**	**266 (10)**	**862 (33)**	**2074 (79)**	**326 (15)**	**606 (33)**	**854 (38)**	**4.5**	**73 (9)**		
anti-Spike mAbs (8 RCTs) totals or averages	**7421**	**47**	**3944 (53)**	**6214 (84)**	**455 (6)**	**3113 (42)**	**6562 (88)**	**1067 (14)**	**1249 (17)**	**3197 (43)**	**3.5**	**1087 (15)**		
Small molecule antivirals (11 RCTs) totals or averages	**33148**	**45.4**	**18116 (55)**	**28726 (87)**	**399 (1)**	**2458 (7)**	**22400 (68)**	**3150 (10)**	**6954 (21)**	**6271 (19)**	**4**	**25710 (77) {710/8148=9% w/o-Mol-Pan.)**		
Repurposed drugs (27 RCTs) totals or averages	**16840**	**48**	**9595 (57)**	**14752 (89)**	**815 (5)**	**4212 (32)**	**8669 (88)**	**2174 (13)**	**4318 (27)**	**6615 (46)**	**5.1**	**2303 (51)**		
CCP-CONV-ert[16]	376	56	173 (46)	0	0	376 (100)	278 (74)	49 (13)	not reported	96 (26)	4.4	43 (11)	All cause	28-30
CCP-COV-Early[19]	406	58	187 (46)	406 (100)	0	0	278 (68)	not reported	not reported	not reported	5 (iqr4-6)	30 (8)	All cause	28-30
CCP-C3PO[15]	511	54	274 (54)	237 (46)	103 (20)	156 (31)	511 (100)	142 (28)	216 (42)	302 (59)	4	not reported	All cause	15
CCP-Argentina[14]	160	77 (65-90+)	100 (62)	0	0	160 (100)	131 (82)	36 (23)	114 (71)	12 (8)	3	not reported	hypoxia resp rate def	28-30

CCP-CSSC-004[11]	1181	43 (18-85)	675 (57)	934 (79)	163 (14)	170 (14)	470 (40)	99 (8)	276 (23)	444 (38)	6	not reported	COVID-19 related	28-30
Bamlanivimab-BLAZE-1[2]	452	45 (18-86)	249 (55)	389 (86)	29 (6)	198 (44)	310 (69)		not reported	201 (44)	4	not reported	COVID-19 related + ED visit	28-30
Sotrovimab-COMET-ICE[23]	1057	53(17-96)	571 (54)	919 (87)	42 (4)	687 (65)	1055 (99.9)	233 (23)	not reported	665 (63)	3	not reported	All cause	28-30
Bamlanivimab/etesevimab-BLAZE-1[3]	1035	54 (12-77+)	538 (52)	896 (87)	83 (8)	304 (29)	983 (95)	285 (28)	not reported	median 34 bmi	4	not reported	COVID-19 related	28-30
Casirivimab/imdevimab-REGEN-COV Ph 3[21]	2696	50 (iqr 39-50)	1407 (52)	2297 (85)	143 (5)	935 (35)	2696 (100)	412 (15)	993 (37)	1559 (58)	3	620 (23)	COVID-19 related	28-30
Casirivimab/imdevimab-REGEN-COV Ph 1/2[20]	799	42 (iqr 31-52)	423 (53)	681 (85)	74 (9)	403 (50)	483 (61)			298 (37)	3	304 (38)	All cause	28-30
Bebtelovimab-BLAZE-4[12]	253	34	135 (53)	187 (74)	48 (19)	91 (36)	0 (0)	not reported	not reported		3	27 (11)	COVID-19 related	28-30
Regdanvimab-CT-P59[23]	307	51 (iqr40-60)	166 (51)	286 (87)	0	27 (8)	226 (69)	29 (9)	not reported	52 (16)	3	9 (3)	All cause	28-30
Tixagevimab–cilgavimab-TACKLE[24]	822	46 (sd 15.2)	455 (50)	559 (62)	36 (4)	468 (52)	809 (90)	108 (12)	256 (28)	388 (43)	5	127 (14)	COVID-19 related	28-30
Molnupiravir-MOVe-OUT[7]	1408	43 (18-90)	735 (51.3)	813 (56)	75 (5)	711 (49)	1424 (99.4)	228 (15.9)%	not reported	1056(73)	3	620 (23)	All cause	28-30
Molnupiravir-PANORAMIC[25]	25000	57 (18-99)	15101 (59)	24270 (94)	155 (0.6)		17759 (69)	2195 (9)%	5782 (22)	3912 (15)%	3	25333 (98) 2+ doses of vaccine	All cause	28-30
Molnupiravir-Aurobindo[27]	1220	36 (18-60)	468 (38)	1220 (100)	0	0	90 (7.3)				3	not reported	All cause	28-30
Nirmatrelvir/ritonavir-EPIC-HR[7]	2085	46 (18-88)	1098 (49)	1607 (72)	110 (4.9)	1010 (45)	2085 (100)	252 (11)	739 (33)	744 (36)	3	27 (11)	COVID-19 related	28-30

Remdesivir-PINETREE[27]	562	50 (12-77+)	269 (48)	452 (80)	42 (7.5)	235 (41)	562 (100)	346 (62)	268 (48)	310 (55)	5	9 (3)	COVID-19 related	28-30
Interferon Lambda-TOGETHER[30]	1936										not reported	not reported	COVID-19 related	28-30
Interferon Lambda-ILIAD[28]	60	46 (iqr32-54)	35 (60)	31	6		9			12	5	5/51 (10)	COVID-19 related	14
Interferon Lambda-COVID-Lambda[29]	120	36 (18-71)	50 (42)	33 (28)		74 (63)		12 (10)	14 (12)		5 (iqr3-6)	49 (41)	All cause	28-30
Sofosbuvir and daclatasvir-SOVODAK[31]	55	<50	29 (53)	55 (100)							not reported	not reported	All cause	28-30
Favipiravir-Avi-Mild-19[32]	231	37 (iqr32-44)	76 (33)	231 (100)	0	0		25 (11)	14 (6)	39 (17)	3	not reported	All cause	28-30
Lopinavir/ritonavir-TOGETHER[33]	471	53 (IQR 18-94)	255 (54)	14 (3)	11 (2)	428 (91)	471 (100)	92 (20)	137 (29)	198 (42)	6	not reported	COVID-19 related	90
Metformin-COVID-OUT[13]	1197	46 (iqr 37-55)	741 (56)	1091 (82)	90 (7)			26 (2)	353 (27) cvd	646 (49)	5	690 (52fv)	COVID-19 related	28-30
Fluvoxamine-TOGETHER[35]	1497	<50	862 (58)	1486 (99)	5 (1)	1486 (99)	1497 (100)	243 (16)	194 (13)	751 (50)	4	not reported	COVID-19 related	28-30
Fluvoxamine -STOP COVID[36]	152	46	109 (72)	106 (70)	38 (25)	5 (3)		17 (11)	30 (20)	75 (49)	4	not reported	COVID-19 related	15 (2 noncovid after day 15 to day 28
Fluvoxamine-COVID-OUT[13]	592	44 (iqr37-53)	358 (54)	539 (82)	51 (8)			7 (1)	172 (26) cvd	302 (46)	5	373 (56fv)	COVID-19 related	28-30
Ivermectin-TOGETHER[37]	1349	49	791 (58)	1310 (98)	12 (1)	1310 (98)	1349 (100)	180 (13)	114 (8)	675 (50)	4	not reported	COVID-19 related	28-30

Ivermectin-COVID-OUT[13]	730	46 (iqr37-56)	442 (55)	662 (82)	59 (7)			13 (2)	184 (23) cvd	383 (47)	5	449 (56fv)	COVID-19 related	28-30
Ivermectin Iran[38]	549	35 (5-87)	294 (48)	582 (100)	0	0	112 (20)	42 (7.3)	46 (7.8)	101 (21)	3	not reported	All cause	not stated
Ivermectin-ACTIV-6[39]	1591	47 (iqr39-56)	932 (59)	1286 (81)	113(7)	163 (10)		184	415	648	6	753 (fv47)	All cause	28-30
Hydroxychloroquine-TOGETHER[34]	441	53 (IQR 18-81)	243 (55)	422 (96)	7 (1)	422 (96)	441 (100)	89 (20)	210 (48)	177 (40)	6	not reported	COVID-19 related	90
Hydroxychloroquine-COVID-19 PEP[42]	423	40 (iqr 32-50)	238 (56)	235 (48)	15 (3)	28 (6)		15 (3)	46 (11)		2	not reported	All cause	14
Hydroxychloroquine-AH COVID-19[41]	148	47	66 (45)	51	12			29	41		7 (iqr5-8)	not reported	All cause	28-30
Hydroxychloroquine-BCN PEP-CoV-2[40]	293	42 (12 sd)	201 (69)				156 (53)	20 (7)			3 (iqr 2-4)	not reported	All cause	28-30
Hydroxychloroquine-BMG[43]	231	37 (18-78)	131 (57)	117 (51)	26 (11)	71 (31)	129 (56)	17 (7)	27 (12)	98 (42)	6	not reported	COVID-19 related	28-30
Nitazoxanide-Romark[43]	379	40 (12-83)	214 (57)	233 (61)	8 (2)	130 (34)	238 (63%)				2	38 (10)	COVID-19 related	28-30
Colchicine-COLCORONA[44]	4488	54 (iqr 47-61)	2421 (54)	4182 (93)	233 (5)	<10%	4488 (100)	894 (20)	1629 (36)	2052 (46)	5.3	not reported	COVID-19 related	28-30
Niclosamide[45]	67	36 mean	26 (39)	53 (79)	4 (6)	7 (10)			5 (8)	4 (7)	not reported	not reported	All cause	28-30
aspirin-ACTIV-4B[46]	280	54 (iqr 46-59)	191 (58)	250 (76)	36 (11)	93 (28)		53 (16)	109 (33)	164 (50)	10 (diagnosis)	not reported	All cause	45
2.5-mg apixaban-ACTIV-4B[46]	271	54 (iqr 46-59)	191 (58)	255 (78)	38 (12)	91 (28)		60 (18)	120 (37)	164 (50)	10 (diagnosis)	not reported	All cause	45
5-mg apixaban ACTIV-4B[46]	279	54 (iqr	198 (6	251 (77)	36 (11)	80 (24)		55 (17)	111 (34)	164 (50)	10 (diagnosis)	not reported	All cause	45

		46-59)												
Sulodexide[47]	243	55	128 (53)	243 (100)		243 (100)		50 (21)	83 (43)		3	not reported	All cause	21
Enoxaparin-ETHIC[49]	219	59 (iqr51-66)	96 (44)	129 (59)	5 (2)	12 (5)		50/152 (33)	114/152 (75)	109 (49)	5	not reported	All cause	21
Enoxaparin-OVID[50]	572	56 (iqr53-62)	217 (38)	446 (78)	3 (1)			38 (7)	115 (20)		3 (dx)	not reported	All cause	28-30
Inhaled ciclesonide-COVERAGE[50]	217	63 (50-86)	111 (51)	217 (100)	0	0	157 (72)	33(16)	89 (41)	52 (24)	4	not reported	All cause	28-30
Saliravira[51]	143	50 (24-80)	59 (41)	143 (100)					33 (23)		not reported	not reported	All cause	23
Azithromycin-Atomic2[52]	292	46	143 (49)	201 (68)	11 (4)		70 (24)	25 (9)	52 (18)		6	not reported	All cause	28-30
Azithromycin-ACTION[53]	197	43	130 (66)	169 (86)	9 (5)	59 (30)		24 (12)	26 (13)		6	not reported	All cause	21
Resveratrol[54]	100	55 (45-84)	62 (59)	93 (89)	4 (4)	2 (2)	32 (30)	10 (10)		50 (50)	5	not reported	All cause	21

Table 2

Hospital rates, risk reductions, NNT, numbers and symptom resolution

Study	Control hospitalizations %	hospitalizations % in intervention arm	ARR percent (95% CI)	RRR percent (95% CI)	NNT to prevent 1 hospitalization	Hospitalization (n) in control arm	total pts in control arm (n)	Hospitalization (n) in intervention arm	Total pts (n) in intervention arm	Symptom resolution: median duration- Intervention to control in days
CCP (5 RCT) % or totals	**12.0**	**8.8**	**3.2 (0.9, 5.6)**	**26.8 (8.1, 41.7)**	**31**	**158**	**1315**	**116**	**1319**	
anti-Spike mAbs (8 RCT) % or totals	**5.5**	**1.8**	**3.7 (2.8, 4.6)**	**67.2 (57.1, 74.9)**	**27**	**190**	**3443**	**72**	**3978**	
Small molecule antiviral (11 RCTs) total or average	**1.9**	**1.3**	**0.7 (0.4, 0.9)**	**34.5 (22.2, 44.9)**	**149**	**322**	**16606**	**210**	**16542**	
Small molecule antiviral (10 RCTs -w/o Mol-Pan.) total or average	**5.5**	**2.7**	**2.8 (2.0, 3.7)**	**51.5 (39.2, 61.3)**	**35**	**226**	**4122**	**107**	**4026**	
Repurposed drugs (20 RCTs) total or average	**6.5**	**5.1**	**1.4 (0.7, 2.1)**	**21.9 (11.7, 30.9)**	**70**	**541**	**8316**	**433**	**8524**	
All (47 RCTs) total or average	**4.1**	**2.7**	**1.3 (1.1, 1.6)**	**32.9 (26.8, 38.5)**	**74**	**1211**	**29680**	**831**	**30363**	
CCP-CONV-ert[16]	11.2	11.7	-0.5 (-7.0, 5.9)	-4.8 (-83.9, 40.3)	-188	21	188	22	188	NO difference 12 d vs 12 d
CCP-COV-Early[19]	9.3	5.9	3.4 (-1.8, 8.5)	36.2 (-27.9, 68.2)	29	19	204	12	202	NO difference 13 d vs 12 d
CCP-C3PO[15]	22.0	20.2	1.8 (-5.3, 8.9)	8.2 (-28.3, 34.4)	55	56	254	52	257	NO difference

CCP-Argentina[14]	31.3	16.3	15.0 (2.0, 28.0)	48.0 (5.8, 71.3)	7	25	80	13	80	Not reported
CCP-CSSC-004[11]	6.3	2.9	3.4 (1.0, 5.8)	54.3 (19.7, 74.0)	29	37	589	17	592	Not reported
CCP-Argentina (high titer)[14]	8.3	31.3	22.9 (9.3, 36.5)	73.3 (17.4, 91.4)	4	25	80	3	36	Not reported
CCP-CSSC-004 (<= 5 days) [11]	1.9	9.7	7.7 (3.7, 11.7)	79.9 (48.4, 92.2)	13	25	259	5	257	Not reported
Bamlanivimab-BLAZE-1[2]	6.3	1.6	4.7 (0.5, 8.9)	74.3 (24.7, 91.2)	21	9	143	5	309	NO difference 11 d to 11 d
Sotrovimab-COMET-ICE[23]	5.7	1.1	4.5 (2.4, 6.7)	80.0 (52.3, 91.6)	22	30	529	6	528	Not reported
Bamlanivimab/etesevimab-BLAZE-1[3]	7.0	2.1	4.8 (2.3, 7.4)	69.5 (40.8, 84.3)	21	36	517	11	518	YES- 8d vs 9d p=0.007
Casirivimab/imdevimab-REGEN-COV Ph 3[21]	4.6	1.3	3.3 (2.0, 4.6)	71.3 (51.7, 82.9)	30	62	1341	18	1355	YES- 10 d vs 14 p=0.0001
Casirivimab/imdevimab-REGEN-COV Ph 1/2[20]	1.9	0.6	1.3 (-0.4, 3.1)	70.1 (-24.4, 92.8)	76	5	266	3	533	Not reported
Bebtelovimab-BLAZE-4[12]	1.6	1.6	-0.4 (-3.1, 3.0)	-2.4 (-615.7, 85.4)	-2667	2	128	2	125	YES- 6d to 8d p=0.003
Regdanvimab-CT-P59[23]	8.7	4.4	4.2 (-1.9, 10.3)	48.8 (-25.2, 79.0)	23	9	104	9	203	YES 6 d vs 9 d p=0.01
Tixagevimab–cilgavimab-TACKLE[24]	8.9	4.4	4.5 (1.1, 7.9)	50.4 (14.3, 71.3)	22	37	415	18	407	Not reported
Molnupiravir-MOVe-OUT[7]	9.7	6.8	3.0 (0.1, 5.8)	30.4 (0.8, 51.2)	34	68	699	48	709	NO difference
Molnupiravir-PANORAMIC[25]	0.8	0.8	-0.1 (-0.3, 0.2)	-7.0 (-41.2, 18.9)	-1853	96	12484	103	12516	YES 9 d vs 15 d
Molnupiravir-Aurobindo[27]	0.0	0.0	NC	NC	0	0	610	0	610	Yes 10 d vs 14 d p<0.001

Nirmatrelvir/ritonavir-EPIC-HR[7]	6.3	0.8	5.5 (4.0, 7.1)	87.8 (74.7, 94.1)	18	66	1046	8	1039	Not reported
Remdesivir-PINETREE[27]	5.3	0.7	4.6 (1.8, 7.4)	86.5 (41.4, 96.9)	22	15	283	2	279	YES- Alleviation of symptoms by day 14 (rate ratio, 1.92; 95% CI, 1.26 to 2.94)
Interferon Lambda-TOGETHER[30]	5.6	2.7	2.9 (1.1, 4.6)	51.2 (22.5, 69.2)	35	57	1020	25	916	Not reported
Interferon Lambda-ILIAD[28]	3.3	3.3	0 (-9.1, 9.1)	0 (-1426, 93.4)		1	30	1	30	No difference
Interferon Lambda-COVID-Lambda[29]	3.3	3.3	0 (-6.4, 6.4)	0 (-586.9, 85.4)		2	60	2	60	NO difference 20 d vs 20 d
Sofosbuvir and daclatasvir-SOVODAK[31]	14.3	3.7	10.6 (-4.2, 25.4)	74.1 (-117, 96.9)	9	4	28	1	27	NO difference in 7 d symptoms
Favipavir-Avi-Mild-19[32]	1.7	5.4	-3.7 (-8.4, 1.1)	-219 (-1447, 34.3)	-27	2	119	6	112	NO difference 7d vs 7d
Lopinavir/ritonavir-TOGETHER[33]	4.8	5.7	-0.9 (-4.9, 3.1)	-18.4 (-155.4, 45.1)	-112	11	227	14	244	NO difference by Cox proportional HR
Metformin-COVID-OUT[13]	3.2	1.3	1.8 (0.1, 3.5)	57.5 (3.8, 81.3)	55	19	601	8	596	NO difference
Fluvoxamine-TOGETHER[35]	12.8	10.1	2.7 (-0.5, 5.9)	21.1 (-4.8, 40.6)	37	97	756	75	741	NO difference- 40% resolved by day 14
Fluvoxamine-STOP COVID[36]	8.3	0.0	8.3 (1.9, 14.7)	1 (1, 1)	12	6	72	0	80	YES (100% vs 91.7% resolved on day 7) p=0.009
Fluvoxamine-COVID-OUT[13]	1.7	2.0	-0.3 (-2.5, 1.9)	-17.6 (-281, 63.7)	-333	5	293	6	299	No difference (14 symptoms on 4 pt scale over 14 days)
Ivermectin-TOGETHER[37]	15.9	14.1	1.8 (-2.1, 5.6)	11.1 (-14.7, 31.1)	57	107	675	95	674	NO difference- 40% resolved by day 14
Ivermectin-COVID-OUT[13]	1.4	1.1	0.3 (-1.3, 1.9)	23.9 (-181, 79.4)	299	5	356	4	374	No difference (14 symptoms on 4 pt scale over 14 days

Ivermectin Iran[38]	5.0	7.1	-2.1 (-6.1, 1.9)	-42.3 (-178, 27.2)	-47	14	281	19	268	NO difference
Ivermectin-ACTIV-6[39]	1.2	1.2	-0.1 (-1.1, 1.0)	-5.3 (-158, 57.0)	-1634	9	774	10	817	No difference (12d vs 13 d)
Hydroxychloroquine-TOGETHER[34]	4.8	3.7	1.1 (-2.7, 4.9)	22.9 (-88.1, 68.4)	90	11	227	8	214	NO difference by Cox proportional HR
Hydroxychloroquine-COVID-19 PEP[42]	4.7	2.4	2.4 (-1.1, 5.9)	50.2 (-43.1, 82.7)	42	10	211	5	212	NO Difference in symptom severity score over 14 days
Hydroxychloroquine -AH COVID-19[41]	0.0	3.6	-3.6 (-7.1, -0.1)	NA	-28	0	37	4	111	NO difference 14 d vs 12 d
Hydroxychloroquine-BCN PEP-CoV-2[40]	7.0	5.9	1.1 (-4.5, 6.7)	16.0 (-103, 65.2)	89	11	157	8	136	NO difference 10 d vs 12 d
Hydroxychloroquine-BMG[43]	4.8	3.4	1.4 (-4.0, 6.9)	29.9 (-154, 80.6)	69	4	83	5	148	NO difference 11 d vs 12 d
Nitazoxanide-Romark[43]	2.6	0.5	2.0 (-0.4, 4.5)	78.8 (-79.7, 97.5)	49	5	195	1	184	Yes mild illness (13 d vs 18 d , p=0.01), NO difference for moderate illness
Colchicine-COLCORONA[44]	5.8	4.7	1.2 (-0.1, 2.5)	20.0 (-2.8, 37.7)	86	131	2253	104	2235	Not reported
Niclosamide[45]	2.9	0.0	2.9 (-2.7, 8.6)	1 (1, 1)	34	1	34	0	33	NO difference 12 d vs 15 d
Aspirin-ACTIV-4B[46]	0.7	0.7	0.04 (-1.9, 2.0)	5.6 (-1395, 94)	2448	1	136	1	144	Not reported
2.5-mg apixaban-ACTIV-4B[46]	0.7	0.7	-0.01 (-2.0, 2.0)	-0.7 (-1494, 93.6)	-18360	1	136	1	135	Not reported
5-mg apixaban ACTIV-4B[46]	0.7	1.4	-0.7 (-3.1, 1.7)	-90.2 (-1974, 82.6)	-151	1	136	2	143	Not reported
Sulodexide[47]	29.4	17.7	11.7 (1.1, 22.3)	39.7 (3.5, 62.3)	9	35	119	22	124	Not reported
Enoxaparin-ETHIC[49]	10.5	11.4	-0.9 (-9.2, 7.4)	-8.6 (-131, 49.0)	-111	12	114	12	105	Not reported

Enoxaparin-OVID[50]	3.4	3.4	-0.1 (-3.3, 3.2)	-1.7 (-166, 61.2)	-1740	8	238	8	234	Not reported
Inhaled ciclesonide-COVERAGE[50]	11.2	12.7	-1.5 (-10.1, 7.1)	-13.5 (-134, 45.0)	-66	12	107	14	110	NO difference 13 d vs 12 d
Saliravira[51]	28.6	0.0	28.6 (16.7, 40.4)	1 (1, 1)	4	16	56	0	87	YES 9d vs 14 d p<0.05
Azithromycin-Atomic2[52]	11.6	10.3	1.2 (-5.9, 8.4)	10.5 (-72.3, 53.6)	82	17	147	15	145	Not reported
Azithromycin-ACTION[53]	0.0	4.0	-4.0 (-7.4, -0.6)	NA	-25	0	72	5	125	No difference resolution day 14
Resveratrol[54]	6.0	2.0	4.0 (-3.6, 11.6)	66.7 (-210, 96.4)	25	3	50	1	50	Not reported

Table 3

Summary of historical efficacy of different therapeutics against SARS-CoV-2 VOCs. White = drug not available at that time; green = effective; orange = partially effective; red= not effective. Restriction reported refer to initial restrictions by FDA. NNT : number needed to treat.

	approximate cost per patient	average NNT (sourced from Table 2)	cost to prevent a single hospitalization (€)	efficacy against VOC Alpha	efficacy against VOC Delta	efficacy against VOC BA.1	efficacy against VOC BA.2	efficacy against BA.4/5	efficacy against BQ.1.1
bamlanivimab+etesesevimab	2000	21	42,000		restricted 04/2021				
casirivimab+imdevimab	2000	30	60,000			restricted 01/2022			
sotrovimab	1000	22	22,000				restricted 03/2022		
tixagevimab+cilgavimab	1000	22	22,000						restricted 10/22
regdanvimab	300	23	6,900						
bebtelovimab	2000	Not calculated (low-risk pts)	Not calculated (low-risk pts)						
nirmatrelvir	635 (5 days)	18	11,435						
molnupiravir	635 (5 days))	34	21,590						
remdesivir	1600 (3 days)	22 (MOVE-Out)	35,200						
CCP	200 (600-ml)	31	6,200						
Vax-CCP									

Figure 1

PRISMA flowchart for randomized controlled trials (RCT) selection in this systematic review.

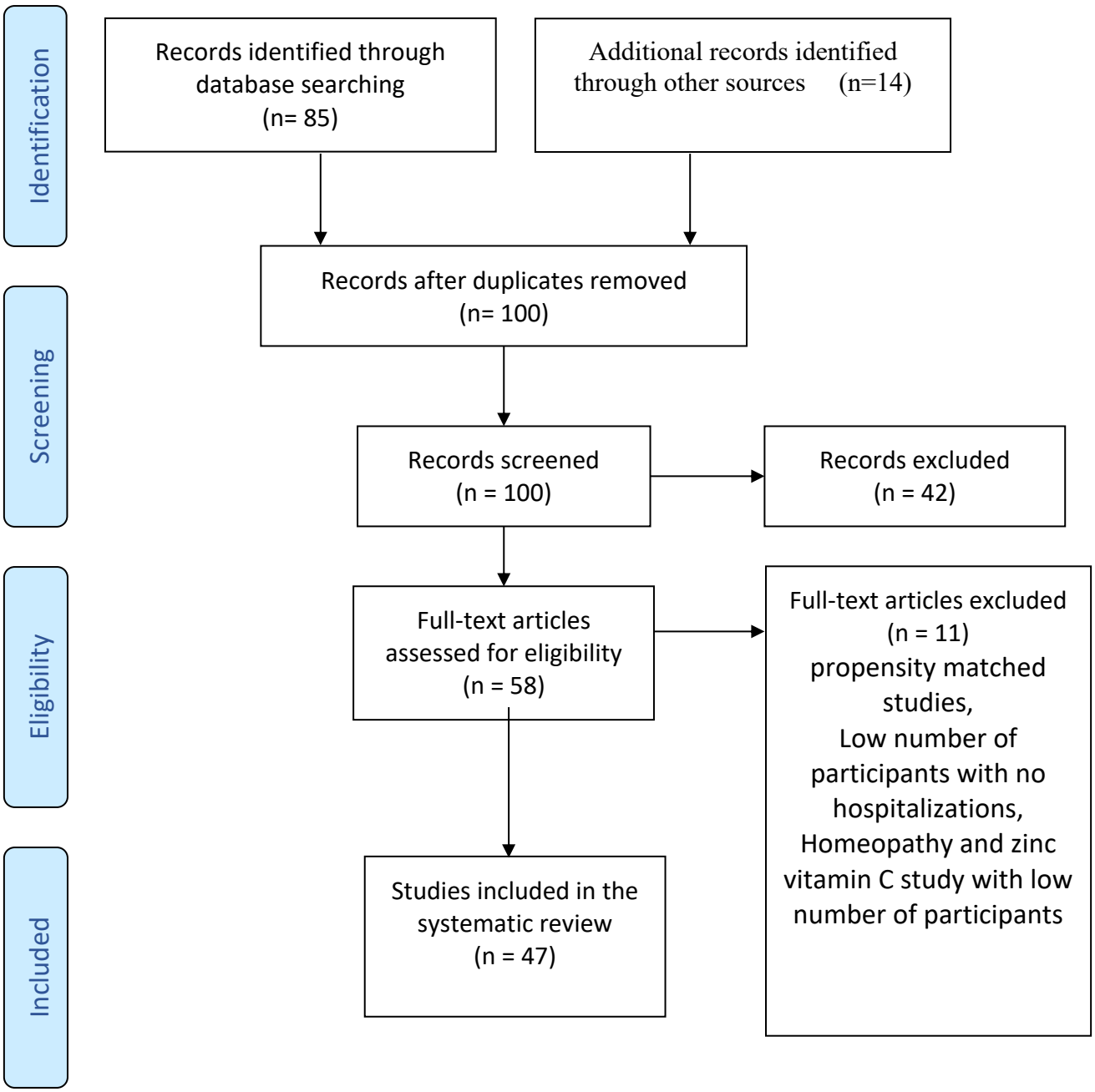


Figure 2

Duration and calendar months of the RCT in context of dominant variant(s) of concern and seropositivity rates. Study start and end for enrollments are charted with approximate time periods for variants of concern.

Study	mont	MAR-20	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN-21	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN-21	FEB	MAR	Baseline Antibody Positive %
CCP-CONV-ert	9									1	2	3	4	5	6	7	8	9									11%
CCP-COV-early	10								1	2	3	4	5	6	7	8	9	10									8%
CCP-C3PO	7						1	2	3	4	5	6	7														NR
CCP-Argentina	5				1	2	3	4	5																		NR
CCP-CSSC-004	16				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16							NR
Bamlanivimab-BLAZE-1	3							1	2	3																	NR
Sotrovimab-COMET-ICE	6							1	2	3	4	5	6														NR
Bamlanivimab/etesevimab-	3							1	2	3																	NR
Casirivimab/imdevimab-REGEN-	4								1	2	3	4															23%
Casirivimab/imdevimab-REGEN-	3					1	2	3																			38%
Bebtelovimab-BLAZE-4	3															1	2	3									11%
Regdanvimab-CT-P59	2								1	2																	3%
Tixagevimab–cilgavimab-TACKLE	6												1	2	3	4	5	6									14%
Molnupiravir-MOVe-OUT	6															1	2	3	4	5	6						23%
Molnupiravir-PANORAMIC	5										1	2	3	4	5												98%
Molnupiravir-Aurobindo	2																	1	2								NR
Nirmatrelvir/ritonavir-EPIC-HR	6																	1	2	3	4	5	6				11%
Remdesivir-PINETREE	8							1	2	3	4	5	6	7	8												3%
Interferon Lambda-TOGETHER	9																	1	2	3	4	5	6	7	8	9	NR
Interferon Lambda- ILIAD	4			1	2	3	4																				10%
Interferon Lambda-COVID-Lambda	2			1	2																						41%
Sofosbuvir & daclatasvir-SOVC	1		1																								NR
Favipiravir-Avi-Mild-19	12						1	2	3	4	5	6	7	8	9	10	11	12									NR
Lopinavir/ritonavir-TOGETHER	4				1	2	3	4																			NR
Metformin-COVID-OUT	13											1	2	3	4	5	6	7	8	9	10	11	12	13			52% FV
Fluvoxamine-TOGETHER	8											1	2	3	4	5	6	7	8								NR
Fluvoxamine -STOP COVID	4		1	2	3	4																					NR
Fluvoxamine-COVID-OUT	13											1	2	3	4	5	6	7	8	9	10	11	12	13			56% FV
Ivermectin-TOGETHER	5														1	2	3	4	5								NR
Ivermectin-COVID-OUT	13											1	2	3	4	5	6	7	8	9	10	11	12	13			56% FV
Ivermectin Iran	7												1	2	3	4	5	6	7								NR
Ivermectin-ACTIV-6	7																	1	2	3	4	5	6	7			47%
Hydroxychloroquine-TOGETHER	4				1	2	3	4																			NR
Hydroxychloroquine-COVID-19 PEP	2	1	2																								NR
Hydroxychloroquine -AH COVID-19	1			1																							NR
Hydroxychloroquine-BCN PEP-CoV-2	2		1	2																							NR
Hydroxychloroquine-BMG	3		1	2	3																						NR
Nitazoxanide-Romark	5						1	2	3	4	5																10%
Colchicine-COLCORONA	9	1	2	3	4	5	6	7	8	9																	NR
Niclosamide	7								1	2	3	4	5	6	7												NR
Aspirin-ACTIV-4B	10							1	2	3	4	5	6	7	8	9	10										NR
2.5-mg apixaban-ACTIV-4B	10							1	2	3	4	5	6	7	8	9	10										NR
5-mg apixaban ACTIV-4B	10							1	2	3	4	5	6	7	8	9	10										NR
Sulodexide	2				1	2																					NR
Enoxaparin-ETHIC	12									1	2	3	4	5	6	7	8	9	10	11	12						NR
Enoxaparin-OVID	17						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17				NR
Inhaled ciclesonide-COVERAGE	7											1	2	3	4	5	6	7									NR
Saliravira	3										1	2	3														NR
Azithromycin-Atomic2	8				1	2	3	4	5	6	7	8															NR
Azithromycin-ACTION	9				1	2	3	4	5	6	7	8	9														NR
Resveratrol	3							1	2	3																	NR
614G		614G	614G	614G	614G	614G	614G	614G	614G	614G	614G	614G	614G	614G	614G												
Alpha												α	α	α	α	α	α										
Beta													β	β	β	β											
Delta																		δ	δ	δ	δ	δ	δ	δ			
Omicron																							ο	ο	ο	ο	

Figure 3

Comparison of mean interval from symptom onset to enrollment/intervention as well as per protocol interval inclusion limit for all participants.

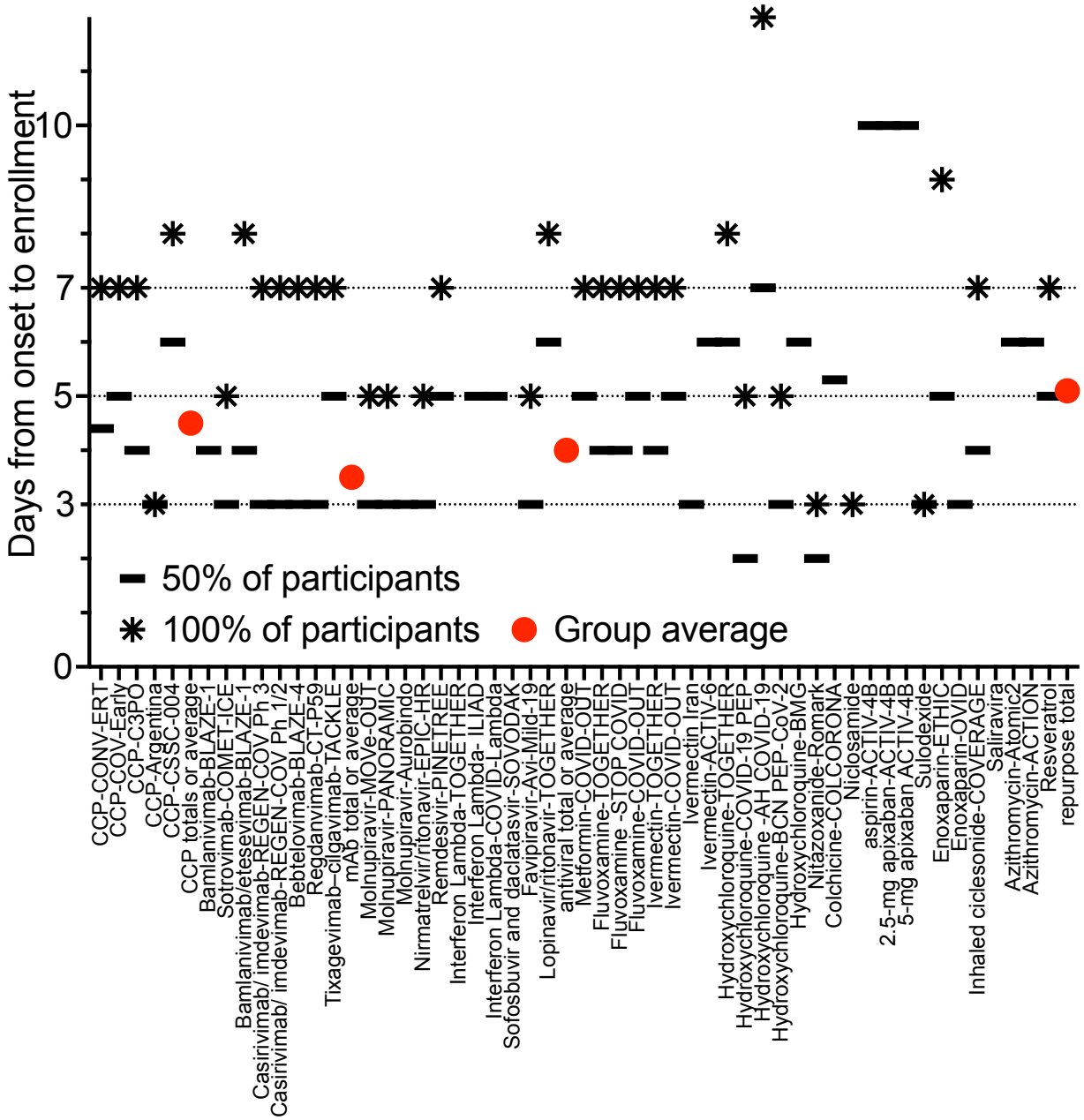


Figure 4

Percent hospitalizations in control groups sorted by therapy type and descending control hospitalization rates.

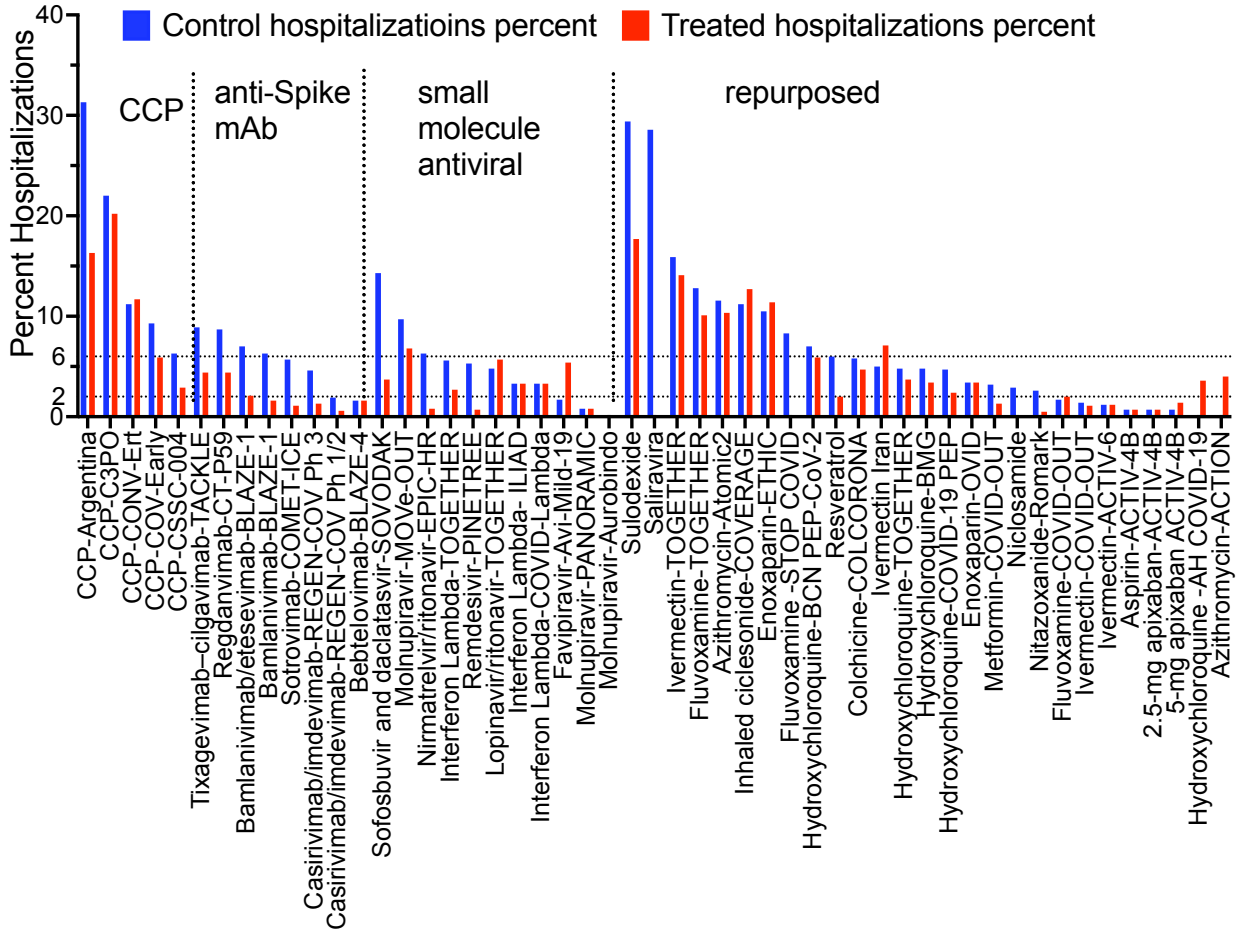
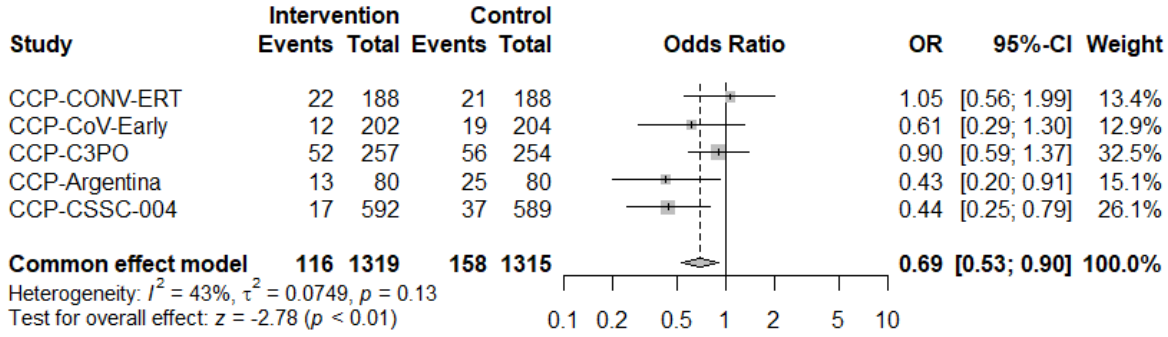


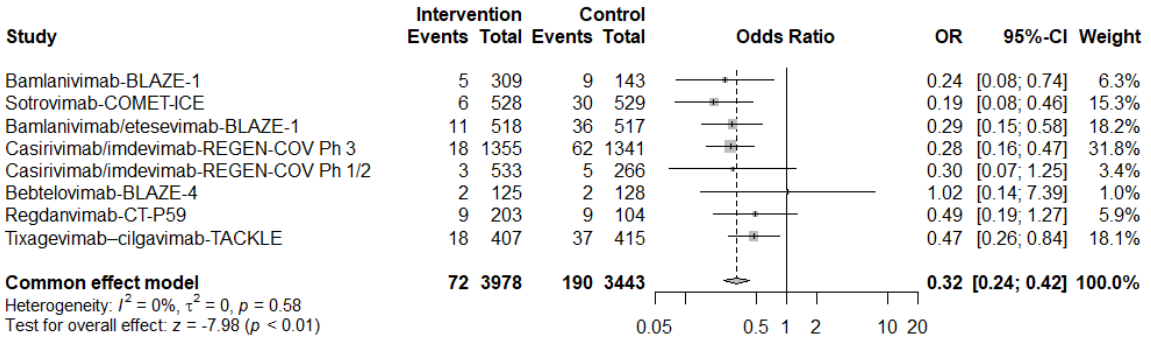
Figure 5

Odds ratio for hospitalizations with diverse therapeutic interventions, grouped according to mechanism of action (CCP, anti-Spike mAbs, small molecule antivirals and repurposed drugs).

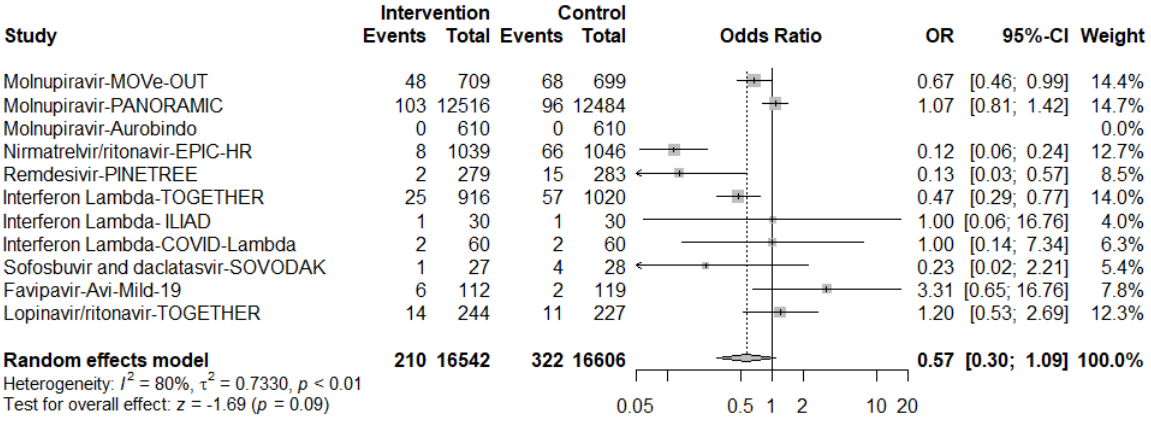
CCP- Fixed effect model



Anti-Spike mAbs- Fixed effect model



Small Molecule antivirals- Random effect model



Repurposed Drugs-Fixed effect model

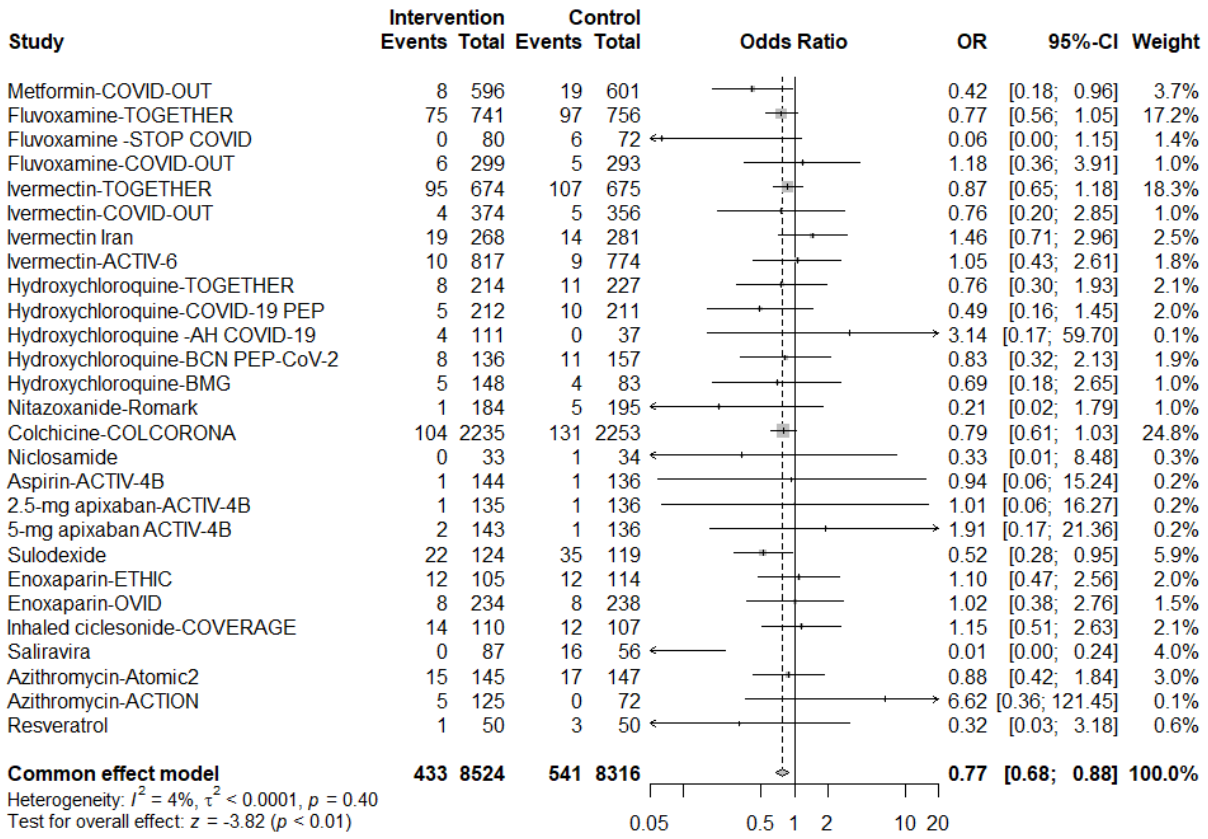


Figure 6

Odds ratio for hospitalization in RCT subgroups treated within 5 days since onset of symptoms

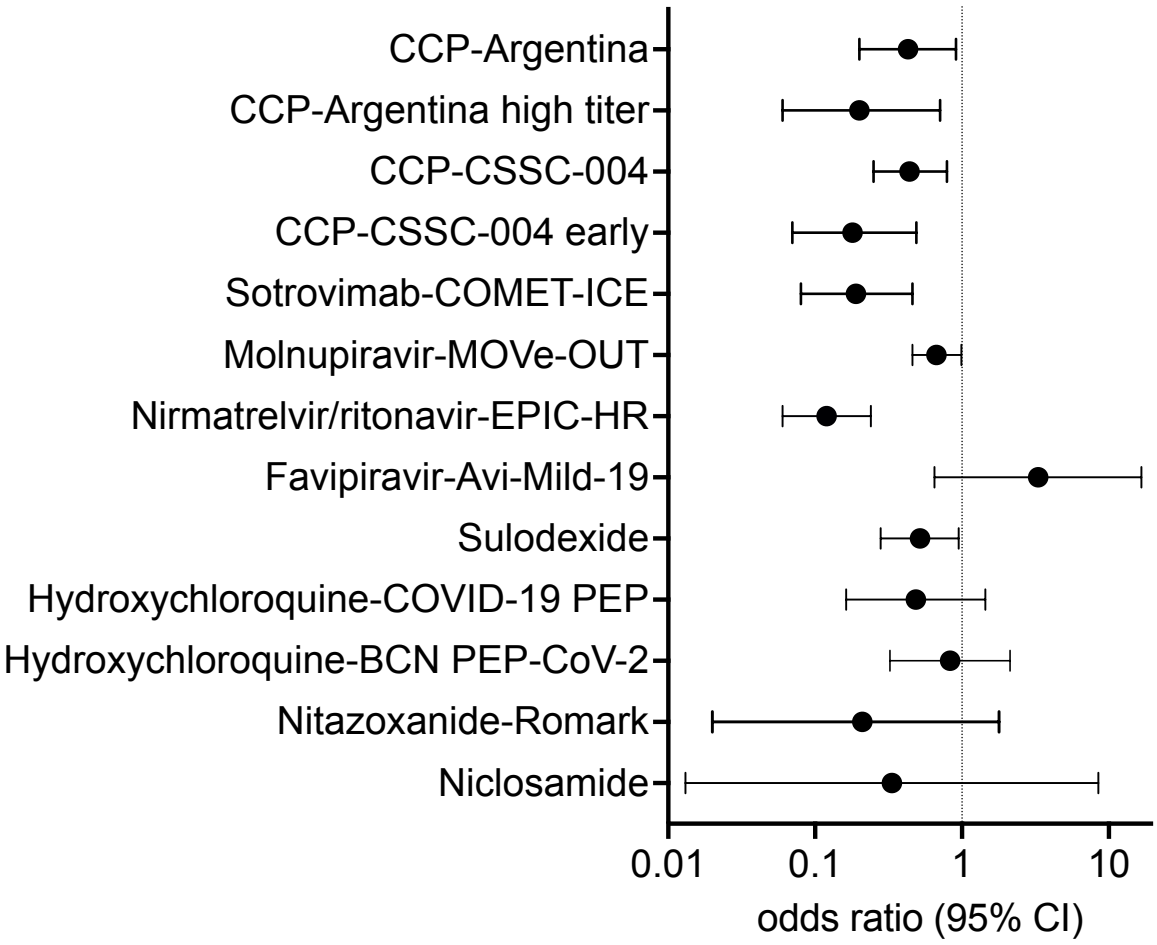
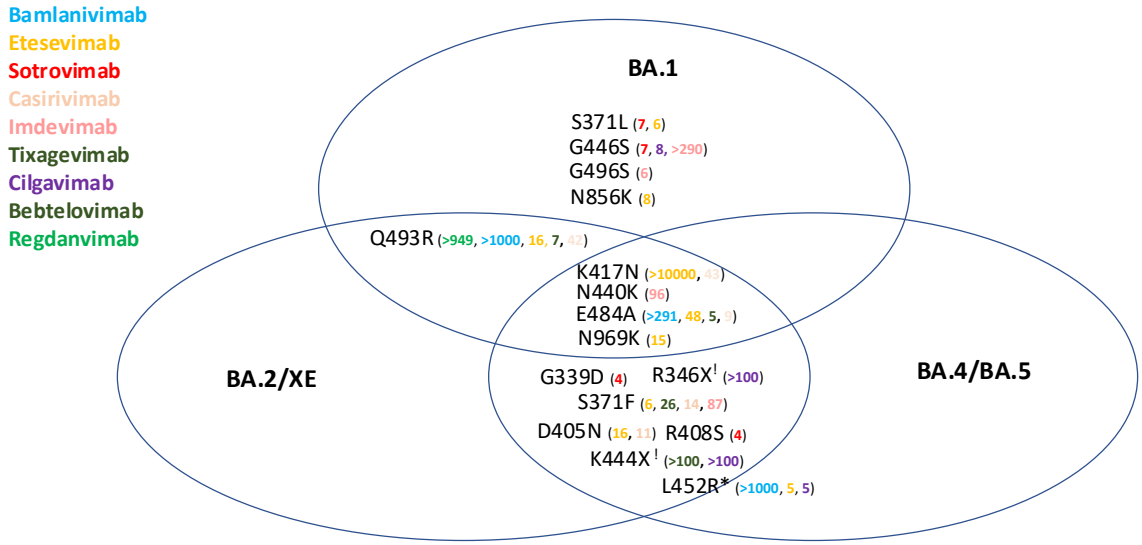


Figure 7

Venn diagram of anti-Spike mAb efficacy against Omicron sublineages. *In vitro* activity of currently approved anti-Spike mAbs against Omicron sublineages circulating as of October 2022. Specific Omicron Spike amino acid mutations causing baseline ≥ 4-fold-reduction in neutralization against mAbs are reported. Mutations for which the majority of studies are concordant are reported: the different fold-reductions for each mAb are identified across concordant studies as color coded numbers defining the mean median values of specific reduction in each study. Sourced from https://covdb.stanford.edu/page/susceptibility-data (accessed on November 7, 2022

* L452R occurs in all BA.4/BA.5 lineages, but only in several BA.2. sublineages.

! R346X and K444X occur in a growing number of BA.2 and BA.4/5 sublineages as a result of convergent evolution.



Supplementary Table 1
GRADE evaluation by RCT.
Patient or population: COVID-19 outpatients
Settings: Ambulatory patients with COVID-19
Intervention: COVID-19 convalescent plasma, anti-Spike mAbs, small molecule antivirals and repurposed drugs
Comparison: standard of care, placebo

Study	Assumed risk-controls Illustrative comparative risks* (95% CI)	Corresponding risk-Intervention Illustrative comparative risks* (95% CI)	Effect size: OR (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
CCP						
CCP-CONV-ert[16]	111 per 1000	116 per 1000 (from 61 to 219)	1.05 (0.55/1.98)	376 (1)	⊕⊕⊕⊖ moderate (downgraded for imprecision-95% CI includes line of no effect)	CCP does not reduce hospitalization compared to placebo
CCP-COV-Early[19]	93 per 1000	57.6 per 1000 (from 26.9 to 120.9)	0.62 (0.29/1.30)	406 (1)	⊕⊕⊕⊖ moderate (downgraded for imprecision-95% CI includes line of no effect)	It is unclear if CCP reduces hospitalization compared to placebo
CCP-C3PO[15]	220 per 1000	198 per 1000 (from 127 to 301)	0.9 (0.58/1.37)	511 (1)	⊕⊕⊕⊖ moderate (downgraded for imprecision-95% CI includes line of no effect)	It is unclear if CCP reduces hospitalization compared to placebo
CCP-Argentina[14]	312 per 1000	133 per 1000 (from 62 to 180)	0.43 (0.20/0.91)	160 (1)	⊕⊕⊕⊖ moderate (downgraded for imprecision due to low number of participants)	CCP reduces rate of hospitalization compared to placebo
CCP-CSSC-004[11]	62.8 per 1000	27.6 per 1000 (from 15.7 to 49.6)	0.44 (0.25/0.79)	1181 (1)	⊕⊕⊕⊕ high (there are no concerns in any of the	CCP reduces rate of hospitalization compared to placebo

					GRADE factors)	
CCP-mITT all cause hospitalization: cumulative results	120 per 1000	82 per 1000 (from 63 to 108)	0.69(0.53/0.90)	2634 participants (5 RCTs)	⊕⊕⊕⊕ high (there are no concerns in any of the GRADE factors)	CCP reduces significantly need of hospitalization compared to placebo. Most information is from results at low risk of bias or with some concerns, but unlikely to lower confidence in the estimate of effect.
Anti-Spike mAbs						
Bamlanivimab[2]	62.9 per 1000	15 per 1000 (from 5 to 46.5)	0.24 (0.08/0.74)	919 (1 RCT)	⊕⊕⊕⊖ moderate(downgraded for imprecision)	Bamlanivimab reduces need of hospitalization compared to placebo
Sotrovimab-COMET-ICE[23]	56.7 per 1000	10.7 per 1000 (from 4.5 to 26)	0.19 (0.08/0.46)	1061 (1 RCT)	⊕⊕⊕⊖ moderate (downgraded for ROB)	Sotrovimab reduces need of hospitalization compared to placebo
Bamlanivimab/etesevimab[3]	69.3 per 1000	20 per 1000 (from 10.3 to 40.1)	0.29 (0.15/0.58)	1035 (1 RCT)	⊕⊕⊖⊖ low(downgraded for imprecision and ROB)	Bamlanivimab/etesevimab in combination reduce need of hospitalization compared to placebo
Casirivimab/imdevimab[21]	41.6 per 1000	11.6 per 1000 (from 7.0 to 19.1)	0.28 (0.17/0.46)	3495 (2 RCT)	⊕⊕⊖⊖ low (downgraded for ROB and imprecision due to low number of events)	Casirivimab/imdevimab in combination reduce need of hospitalization compared to placebo
Bebtelovimab-BLAZE-4[12]	15.6 per 1000	15.9 per 1000 (from 2.1 to 115)	1.02 (0.14/7.39)	253 (1 RCT)	⊕⊕⊖⊖ low (downgraded twice for serious imprecision)	Bebtelovimab does not reduce need of hospitalization compared to placebo

Regdanvimab-CT-P59[23]	86.5 per 1000	42.3 per 1000 (from 16.4 to 109)	0.49 (0.19/1.27)	307 (1 RCT)	⊕⊕⊖⊖ low (downgraded for ROB and imprecision)	It is unclear if regdanvimab reduces hospitalization compared to placebo
Tixagevimab–cilgavimab-TACKLE[24]	89.1 per 1000	41.8 per 1000 (from 24 to 74.7)	0.47 (0.27/0.84)	822 (1)	⊕⊕⊕⊖ moderate (downgraded for imprecision)	Tixagevimab-cilgavimab reduces hospitalization compared to placebo in unvaccinated adults
mAbs: combined results	55.1 per 1000	17.6 per 1000 (from 13.2 to 23.1)	0.32(0.24/0.42)	7411 (8 trials)	⊕⊕⊕⊖ moderate (downgraded for ROB)	Anti-Spike mAbs reduce hospitalization compared to placebo
Small molecule antivirals						
Molnupiravir[8, 25, 26]	11.8 per 1000	10.8 per 1000 (from 8.6 to 13.4)	0.91 (0.73/1.14)	27628 (3 RCTs)	⊕⊕⊖⊖ low (downgraded for inconsistency and imprecision)	It is unclear if Molnupiravir reduces hospitalization compared to placebo
Nirmatrelvir/ritonavir[7]	63 per 1000	7.5 per 1000 (from 3.7 to 15.1)	0.12 (0.06/0.24)	2085 (1)	⊕⊕⊖⊖ low (downgraded for ROB and imprecision)*	Nirmatrelvir/ritonavir reduces hospitalization compared to placebo in unvaccinated adults
Remdesivir[27]	53 per 1000	6.8 per 1000 (from 1.5 to 50.2)	0.13 (0.03/0.57)	562 (1)	⊕⊕⊖⊖ low (downgraded for ROB and imprecision)	Remdesivir reduces hospitalization compared to placebo
Favipiravir[32]	16.8 per 1000	55.6 per 1000 (from 10.9 to 281)	3.31 (0.65/16.76)	231 (1)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	Favipiravir does not reduce need of hospitalization compared to placebo
Peg-interferon lambda [28, 29, 30]	54.5 per 1000	26.7 per 1000 (from 16.8 to 47.5)	0.49 (0.31/0.78)	2116 (3 RCTs)	⊕⊕⊕⊖ moderate (downgraded for ROB)	-Peginterferon lambda reduces hospitalization compared to placebo.

Sofosbuvir and daclatasvir-SOVODAK[31]	142.8 per 1000	32.8 per 1000 (from 2.8 to 315)	0.23 (0.02/2.21)	55 (1)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	It is unclear if sofosbuvir/daclatasvir reduces hospitalization compared to placebo
Lopinavir/ritonavir-TOGETHER[33]	48.4 per 1000	58 per 1000 (from 25.6 to 130.1)	1.20 (0.53/2.69)	471 (1)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	Lopinavir/ritonavir does not reduce need of hospitalization compared to placebo
Small molecule antivirals: combined results	19.3 per 1000	12.5 per 1000 (from 10.4 to 15)	0.65 (0.54/0.78)	33148 (11)	⊕⊕⊖ ⊖ low (downgraded for inconsistency (I^2=81) and ROB)	-Antivirals reduce rate of hospitalization compared to placebo
Repurposed						
Metformin-COVID-OUT[13]	31.6 per 1000	13.2 per 1000 (from 5.6 to 30.3)	0.42 (0.18/0.96)	1197 (1)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	Metformin reduces hospitalization compared to placebo.
Fluvoxamine[13, 34, 35]	96.3 per 1000	69.1 per 1000 (from 30.7 to 156.4)	0.72 (0.32/1.63)	2241 (3 RCTs)	⊕⊖⊖⊖ very-low (downgraded for imprecision, inconsistency and ROB)	It is unclear if fluvoxamine reduces hospitalization compared to placebo
Ivermectin[13, 36, 37, 38]	64.4 per 1000	60.5 per 1000 (from 47 to 78.5)	0.94(0.73/1.22)	4228 (4 RCTs)	⊕⊕⊕⊖ moderate (downgraded for imprecision)	-It is unclear if Ivermectin reduces rate of hospitalization compared to placebo
Hydroxychloroquine[33, 39, 40, 41, 42]	41.9 per 1000	31 per 1000 (from 18.8 to 51.5)	0.74 (0.45/1.23)	1536 (5 RCTs)	⊕⊕⊕⊖ moderate (downgraded for imprecision-95% CI includes line of no effect)	It is unclear if hydroxychloroquine reduces hospitalization compared to placebo
Nitazoxanide-Romark[43]	25.6 per 1000	5.3 per 1000 (from 0.5 to 45.8)	0.21 (0.02/1.79)	379 (1)	⊕⊖⊖⊖ very-low (downgraded for serious imprecision and ROB)	It is unclear if nitazoxanide reduces

						hospitalization compared to placebo
Colchicine-COLCORONA[44]	58.1 per 1000	45.8 per 1000 (from 35.4 to 59.8)	0.79 (0.61/1.03)	379 (1)	⊕⊕⊕⊖ moderate (downgraded for imprecision-95% CI includes line of no effect)	It is unclear if colchicine reduces hospitalization compared to placebo
Niclosamide[45]	29.4 per 1000	9.5 per 1000 (from 0.29 to 249)	0.33 (0.01/8.48)	67 (1)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	It is unclear if niclosamide reduces hospitalization compared to placebo
aspirin	7.3 per 1000	6.8 per 1000 (from 0.4 to 11)	0.94 (0.06/15.2)	280 (1)	⊕⊖⊖⊖ very-low (downgraded for serious imprecision and indirectness)	Aspirin does not reduce need of hospitalization compared to placebo
apibaxan	7.3 per 1000	7.3 per 1000 (from 1 to 52)	1.0 (0.14/7.18)	414 (2 arms)	⊕⊖⊖⊖ very-low (downgraded for serious imprecision and indirectness)	Apibaxan 2.5-5 mg does not reduce need of hospitalization compared to placebo
Sulodexide[47]	294 per 1000	223.4 per 1000 (from 82.3 to 279.3)	0.52 (0.28/0.95)	243 (1)	⊕⊕⊕⊖ moderate (downgraded for imprecision)	Sulodexide reduces hospitalization compared to placebo
Enoxaparin-LMW heparin[48, 49]	56.8 per 1000	60.2 per 1000 (from 31.8 to 115.3)	1.06 (0.56/2.03)	691 (2)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	LMW heparin does not reduce hospitalization compared to placebo
Inhaled ciclesonide[50]	112 per 1000	128.8 per 1000 (from 57.1 to 294.5)	1.15 (0.51/2.63)	217 (1)	⊕⊖⊖⊖ very-low (downgraded for serious imprecision and ROB)	Inhaled ciclesonide does not reduce need of hospitalization compared to placebo
Saliravira[51]	285 per 1000	133.9 per 1000 (from 82.6 to 220.2)	0.47 (0.29/0.77)	143 (1)	⊕⊖⊖⊖ very-low (downgraded for serious imprecision and serious ROB)	Saliravira reduces hospitalization compared to control

Azithromycin[52, 53]	77.6 per 1000	85.3 per 1000 (from 43.4 to 169.1)	1.10 (0.56/2.18)	489 (2)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	azithromycin does not reduce hospitalization compared to placebo
Resveratrol[54]	60 per 1000	19.2 per 1000 (from 1.8 to 190.8)	0.32 (0.03/3.18)	100 (1)	⊕⊕⊖⊖ low (downgraded for serious imprecision)	It is unclear if resveratrol reduces hospitalization compared to placebo
Repurposed drugs combined results	64.9 per 1000	50 per 1000 (from 44.1 to 57.1)	0.77 (0.68/0.88)	16840 (27 arms, 15 comparisons)	⊕⊕⊕⊖ moderate (downgraded for ROB)	Repurposed treatments reduce rate of hospitalization compared to placebo

*The basis for the assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect (the Risk Difference, also called ARR, absolute risk reduction)of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnote: OR, Odds Ratio; CIs, confidence intervals; ROB, risk of bias. GRADE, Grading of Recommendations, Assessment, Development and Evaluations

Supplementary Table 2
Additional baseline data from RCTs

Study	Enrollment Period	Study months	Geography	Enrolled	age over 65 n(%)	age over 60 n(%)	age over 50 n(%)	symptoms <= 8 days n(%)	symptoms <=7 days n(%)	symptoms <= 5 days n(%)	symptoms <= 3 days n(%)
CCP-CONV-ert[16]	Nov 10 2020 -July 28 2021	9	Spain	376			376 (100)		376 (100)		
CCP-COV-Early[19]			Netherlands	406			351 (86)		406 (100)		
CCP-C3PO[15]	Aug 2020-Feb 2021	7	USA	511			511 (100)		511 (100)		246 (48)
CCP-Argentina[14]	Jun 4 2020 – Oct 25 2020	5	Argentina	160	160 (100)						160 (100)
CCP-CSSC-004[11]	June 3 2020-Oct 2021	16	USA	1225	80 (7)		410 (35)	1181 (100)		517 (44)	
Bamlanivimab-BLAZE-1[2]	June 2020-Aug 2020	3	USA	467	53 (12)					226 (50)mean	
Sotrovimab-COMET-ICE[23]	Aug 27 2020-March 2021	6	United States, Canada, Brazil, and Spain	1057	211(20)					1057 (100)	624 (59)
Bamlanivimab/etesevimab-BLAZE-1[3]	Sept 2020-Dec 2020	3	USA	1035	323 (31)			979 (95)			
Casirivimab/ imdevimab-REGEN-COV Ph 3[21]	Sept 24 2020-Jan 17 2021	4	USA Mexico	2696	358 (13)				2696 (100)		1489 (66)
Casirivimab/ imdevimab-REGEN-COV Ph 1/2[20]	June 16, 2020 - Sept 23, 2020	3	USA	799					799 (100)	599 (75)	400 (50)
Bebtelovimab-BLAZE-4[12]	May 2021-July 2021	3	USA	253	1 (<1)				253 (100)		

Regdanvimab-CT-P59[23]	Oct 2020-Dec 2020	2	South Korea, Romania, Spain, USA	327		85 (26)			327 (100)		
Tixagevimab–cilgavimab-TACKLE[24]	Jan 28, 2021- July 22, 2021,	6	USA, Latin America, Europe, and Japan.	1014	116 (13)				910 (100)		
Molnupiravir-MOVe-OUT[7]	May 2021-Oct 2021	6	worldwide	1433		246 (17)				1408 (100)	674 (48)
Molnupiravir-PANORAMIC[25]	Dec 8-2021 - April 27, 2022	5	UK	25783	6838 (27)					22510 (87)	
Molnupiravir-Aurobindo[27]	July 1, 2021 - Aug 24, 2021	2	India	1220							661 (54)
Nirmatrelvir/ritonavir-EPIC-HR[7]	July 1 2021 - Dec 2021	6	worldwide	2246	287(12.8)					2246 (100)	1489 (66.3)
Remdesivir-PINETREE[27]	Sept 2020-Apr 2021	8	USA, Spain, Denmark UK	562		170 (30)			562 (100)		
Interferon Lambda-TOGETHER[30]	July 6 2021-March 2022	15	Brazil	1936							
Interferon Lambda-ILIAD[28]	May 18, 2020-Sep 4 2020	4	Canada	60					60 (100)		
Interferon Lambda-COVID-Lambda[29]	Apil 25 2020-July 7 2020	2	USA	120							
Sofosbuvir and daclatasvir-SOVODAK[31]	April 8 2020-May 19 2020	1	Iran	55							

Favipiravir-Avi-Mild-19[32]	July 23, 2020- Aug 4 2021	12	Saudi Arabia	245			30 (13)			231 (100)	
Lopinavir/ritonavir-TOGETHER[33]	June 2 2020-Oct 9 2020	4	Brazil	471			275	471 (100)		74 (16)	
Metformin-COVID-OUT[13]	Dec 30 2020 - Jan 28 2022	13	USA	1323					1197 (100)		
Fluvoxamine-TOGETHER[35]	Jan 2021 - Aug 2021	8	Brazil	1497			655 (44)		1497 (100)		638 (43)
Fluvoxamine -STOP COVID[36]	April 10 2020 - Aug 5 2020	4	USA	152					152 (100)	114 (75)	
Fluvoxamine-COVID-OUT[13]	Dec 30 2020 - Jan 28 2022	13	USA	661					733 (100)		
Ivermectin-TOGETHER[37]	March 23 - Aug 2 2021	5	Brazil	1358					1358 (100)		597 (44)
Ivermectin-COVID-OUT[13]	Dec 30 2020 - Jan 28 2022	13	USA	808					592 (100)		
Ivermectin Iran[38]	Feb 19 21 - Aug 30 21	7	iran	582							291 (50)
Ivermectin-ACTIV-6	June 23 2021 - Feb 4 2022	7	USA	1591			680 (43)	1193 (75)			
Hydroxychloroquine-TOGETHER[34]	June 2 2020-Oct 9 2020	4	Brazil	441			262 (59)	441 (100)		77 (17)	
Hydroxychloroquine-COVID-19 PEP[42]	March 22 2020 - May 20 2020	2	USA canada	491			99 (20)			423 (100)	

Hydroxychloroquine -AH COVID-19[41]	April 15 2020 -May 22 2020	1	Canada	148							
Hydroxychloroquine-BCN PEP-CoV-2[40]	March 17 2020-May 26 2020	2	Spain	293						293 (100)	
Hydroxychloroquine-BMG[43]	April 15 2020-July 27 2020	3	USA	231		23 (10)			143 (62)	85 (37)	
Nitazoxanide-Romark[43]	Aug 2020-Jan 2021	5	USA Peurto rico	379							379 (100)
Colchicine-COLCORONA[44]	March 2020-Dec 2020	9	Brazil, Canada, Greece, South Africa, Spain, and the USA	4488		1122 (25)		3590 (80)			
Niclosamide[45]	Oct 1 2020-April 20 2021	7	USA	73							67 (100)
aspirin-ACTIV-4B[46]	Sept 1 2020 - June 17 2021	10	USA	328		~82 (25)				82 (25)	
2.5-mg apixaban-ACTIV-4B[46]	Sept 1 2020 - June 17 2021	10	USA	329		~82 (25)				82 (25)	
5-mg apixaban ACTIV-4B[46]	Sept 1 2020 - June 17 2021	10	USA	328		~82 (25)				82 (25)	
Sulodexide[47]	June 5 2020 - August 5 2020	2	Mexico	243							243 (100)

Enoxaparin-ETHIC[49]	Oct 27 2020 - Nov 8 2021	12	Belgium, Brazil, India, South Africa, Spain, and the UK).	219			164 (75)			121 (50)	
Enoxaparin-OVID[50]	Aug 5 2020-Jan 14 2022	17	Switzerland and Germany	572			572 (100)			429 (dx 75)	
Inhaled ciclesonide-COVERAGE[50]	Dec 29 2020-July 22 2021	7	France	217		151 (70)	217 (100)		217 (100)		
Saliravira[51]	Dec 21 2020 - March 1 2021	3	Iran	143							
Azithromycin-Atomic2[52]	June 3, 2020- Jan 29, 2021,	8	UK	292							
Azithromycin-ACTION[53]	May 22 2020 - March 16 2021	9	USA	197		18 (9)			197 (100)		
Resveratrol[54]	September 13, 2020 - December 11, 2020,	3	USA	100	16 (16)					50 (50)	

Supplementary Table 3
Hospitalized Odds Ratio statistics

Study	Hospitalization Odds ratio	Hospitalization 95 CI low	Hospitalization 95 CI high	Hospitalization significance (p)	Hospitalization z statistic
Total CCP	**0.71**	**0.55**	**0.91**	**0.0035**	**2.697265**
Total mAb	**0.32**	**0.24**	**0.42**	**P<0.001**	**8.213656**
Total antivirals	**0.65**	**0.55**	**0.77**	**P<0.001**	**4.814847**
Total repurposed	**0.76**	**0.66**	**0.88**	**P<0.001**	**3.953106**
Total	**0.65**	**0.59**	**0.71**	**P<0.001**	**9.021468**
CCP-CONV-ERT[16]	1.05	0.56	1.99	0.4356	0.162033
CCP-CoV-Early[19]	0.61	0.29	1.30	0.1021	1.269694
CCP-C3PO[15]	0.90	0.59	1.37	0.3078	0.502004
CCP-Argentina[14]	0.43	0.20	0.91	0.0140	2.197789
CCP-CSSC-004[11]	0.44	0.25	0.79	0.0031	2.737543
CCP-Argentina (high titer)[14]	0.20	0.06	0.71	0.0132	2.478
CCP-CSSC-004 (<= 5 days) [11]	0.18	0.07	0.49	0.0007	3.38
Bamlanivimab-BLAZE-1[2]	0.24	0.08	0.74	0.0066	2.479993
Sotrovimab-COMET-ICE[23]	0.19	0.08	0.46	0.0001	3.663844
Bamlanivimab/etesevimab-BLAZE-1[3]	0.29	0.15	0.58	0.0002	3.534471
Casirivimab/ imdevimab-REGEN-COV Ph 3[21]	0.28	0.16	0.47	0.0000	4.734662
Casirivimab/ imdevimab-REGEN-COV Ph 1/2[20]	0.30	0.07	1.25	0.0484	1.660556
Bebtelovimab-BLAZE-4[12]	1.02	0.14	7.39	0.4905	0.023906
Regdanvimab-CT-P59[23]	0.49	0.19	1.27	0.0716	1.463817

Tixagevimab–cilgavimab-TACKLE[24]	0.47	0.26	0.84	0.0057	2.528551
Molnupiravir-MOVe-OUT[7]	0.67	0.46	0.99	0.0223	2.00829
Molnupiravir-PANORAMIC[25]	1.07	0.81	1.42	0.3156	0.479984
Molnupiravir-Aurobindo[27]	NA	NA	NA	NA	NA
Nirmatrelvir/ritonavir-EPIC-HR[7]	0.12	0.06	0.24	0.0000	5.731691
Remdesivir-PINETREE[27]	0.13	0.03	0.57	0.0034	2.703067
Interferon Lambda-TOGETHER[30]	0.47	0.29	0.77	0.0011	3.054966
Interferon Lambda-ILIAD[28]	1.00	0.06	16.76	0.5000	0
Interferon Lambda-COVID-Lambda[29]	1.00	0.14	7.34	0.5000	0
Sofosbuvir and daclatasvir-SOVODAK[31]	0.23	0.02	2.21	0.1018	1.271414
Favipiravir-Avi-Mild-19[32]	3.31	0.65	16.76	0.0739	1.44706
Lopinavir/ritonavir-TOGETHER[33]	1.20	0.53	2.69	0.3333	0.430926
Metformin-COVID-OUT[13]	0.42	0.18	0.96	0.0198	2.057
Fluvoxamine-TOGETHER[35]	0.77	0.56	1.05	0.0505	1.640023
Fluvoxamine -STOP COVID[36]	0.06	0.00	1.15	0.0310	1.866043
Fluvoxamine-COVID-OUT[13]	1.18	0.36	3.91	0.3935	0.270145
Ivermectin-TOGETHER[37]	0.87	0.65	1.18	0.1831	0.903781
Ivermectin-COVID-OUT[13]	0.76	0.20	2.85	0.3414	0.408715
Ivermectin Iran[38]	1.46	0.71	2.96	0.1507	1.033341
Ivermectin-ACTIV-6[39]	1.05	0.43	2.61	0.4553	0.112309
Hydroxychloroquine-TOGETHER[34]	0.76	0.30	1.93	0.2840	0.570928

Hydroxychloroquine-COVID-19 PEP[42]	0.49	0.16	1.45	0.0971	1.298164
Hydroxychloroquine -AH COVID-19[41]	3.14	0.17	59.70	0.2232	0.761332
Hydroxychloroquine-BCN PEP-CoV-2[40]	0.83	0.32	2.13	0.3486	0.389184
Hydroxychloroquine-BMG[43]	0.69	0.18	2.65	0.2945	0.54027
Nitazoxanide-Romark[43]	0.21	0.02	1.79	0.0766	1.428571
Colchicine-COLCORONA[44]	0.79	0.61	1.03	0.0407	1.742726
Niclosamide[45]	0.33	0.01	8.48	0.2529	0.665353
Aspirin-ACTIV-4B[46]	0.94	0.06	15.24	0.4838	0.040562
2.5-mg apixaban-ACTIV-4B[46]	1.01	0.06	16.27	0.4979	0.005238
5-mg apixaban ACTIV-4B[46]	1.91	0.17	21.36	0.2988	0.527902
Sulodexide[47]	0.52	0.28	0.95	0.0167	2.128119
Enoxaparin-ETHIC[49]	1.10	0.47	2.56	0.4155	0.213485
Enoxaparin-OVID[50]	1.02	0.38	2.76	0.4862	0.034489
Inhaled ciclesonide-COVERAGE[50]	1.15	0.51	2.63	0.3659	0.34277
Saliravira[51]	0.01	0.00	0.24	0.0016	2.9467
Azithromycin-Atomic2[52]	0.88	0.42	1.84	0.3694	0.333472
Azithromycin-ACTION[53]	6.62	0.36	121.45	0.1015	1.272994
Resveratrol[54]	0.32	0.03	3.18	0.1654	0.972432

Supplementary Table 4
Deaths during RCTs

Study	ARR%	RRR%	95% CI ARR	95% CI RRR	Odds ratio	95 CI low	95 CI high	z statistic	significance (p)
Total CCP	0.15	20	(-0.48, 0.78)	(-101, 68.4)	0.80	0.31	2.02	0.4785	0.3162
Total mAb	0.51	84	(0.23, 0.79)	(52.0, 94.3)	0.16	0.06	0.48	3.3107	0.0005
Total antivirals	0.13	75	(0.06, 0.20)	(42.6, 89.0)	0.25	0.11	0.57	3.2733	0.0005
Total repurposed	0.24	28	(-0.02, 0.50)	(-2.3, 49.6)	0.72	0.5	1.02	1.8362	0.0332
Total	0.20	46	(0.11, 0.30)	(28.4, 59.7)	0.54	0.4	0.72	4.2423	1E-05
Study	**Deaths control**	**Total control**	**Deaths intervent.**	**Total intervent.**	**Total both arms**	**% death control**	**% death intervent.**		
Total CCP	10	1315	8	1319	2634	0.76	0.61		
Total mAb	21	3443	4	3978	7421	0.61	0.10		
Total antivirals	28	16606	7	16542	33148	0.17	0.04		
Total repurposed	72	8316	53	8524	16840	0.87	0.62		
Total	131	29680	72	30363	60043	0.44	0.24		
CCP-CONV-ert[16]	2	188	0	188	376	1.06	0.00		
CCP-CoV-Early[19]	0	204	1	202	406	0.00	0.50		
CCP-C3PO[15]	1	254	5	257	511	0.39	1.95		
CCP-Argentina[14]	4	80	2	80	160	5.00	2.50		
CCP-CSSC-004[11]	3	589	0	592	1181	0.51	0.00		
Bamlanivimab-BLAZE-1[2]	0	143	0	309	452	0.00	0.00		
Sotrovimab-COMET-ICE[23]	2	529	0	528	1057	0.38	0.00		
Bamlanivimab/etesevimab-BLAZE-1[3]	10	517	0	518	1035	1.93	0.00		

Casirivimab/ imdevimab-REGEN-COV Ph 3[21]	3	1341	1	1355	2696	0.22	0.07		
Casirivimab/ imdevimab-REGEN-COV Ph 1/2[20]	0	266	0	533	799	0.00	0.00		
Bebtelovimab-BLAZE-4[12]	0	128	0	125	253	0.00	0.00		
Regdanvimab-CT-P59[23]	0	104	0	203	307	0.00	0.00		
Tixagevimab–cilgavimab-TACKLE[24]	6	415	3	407	822	1.45	0.74		
Molnupiravir-MOVe-OUT[7]	9	699	1	709	1408	1.29	0.14		
Molnupiravir-PANORAMIC[25]	5	12484	2	12516	25000	0.04	0.02		
Molnupiravir-Aurobindo[27]	0	610	0	610	1220	0.00	0.00		
Nirmatrelvir/ritonavir-EPIC-HR[7]	12	1046	0	1039	2085	1.15	0.00		
Remdesivir-PINETREE[27]	1	283	0	279	562	0.35	0.00		
Interferon Lambda-TOGETHER[30]	1	1020	4	916	1936	0.10	0.44		
Interferon Lambda- ILIAD[28]	0	30	0	30	60	0.00	0.00		
Interferon Lambda-COVID-Lambda[29]	0	60	0	60	120	0.00	0.00		
Sofosbuvir and daclatasvir-SOVODAK[31]	0	28	0	27	55	0.00	0.00		
Favipiravir-Avi-Mild-19[32]	0	119	0	112	231	0.00	0.00		
Lopinavir/ritonavir-TOGETHER[33]	0	227	0	244	471	0.00	0.00		
Metformin-COVID-OUT[13]	1	601	1	596	1197	0.17	0.17		
Fluvoxamine-TOGETHER[35]	25	756	17	741	1497	3.31	2.29		
Fluvoxamine -STOP COVID[36]	0	72	0	80	152	0.00	0.00		
Fluvoxamine-COVID-OUT[13]	0	293	0	299	592	0.00	0.00		
Ivermectin-TOGETHER[37]	24	675	21	674	1349	3.56	3.12		

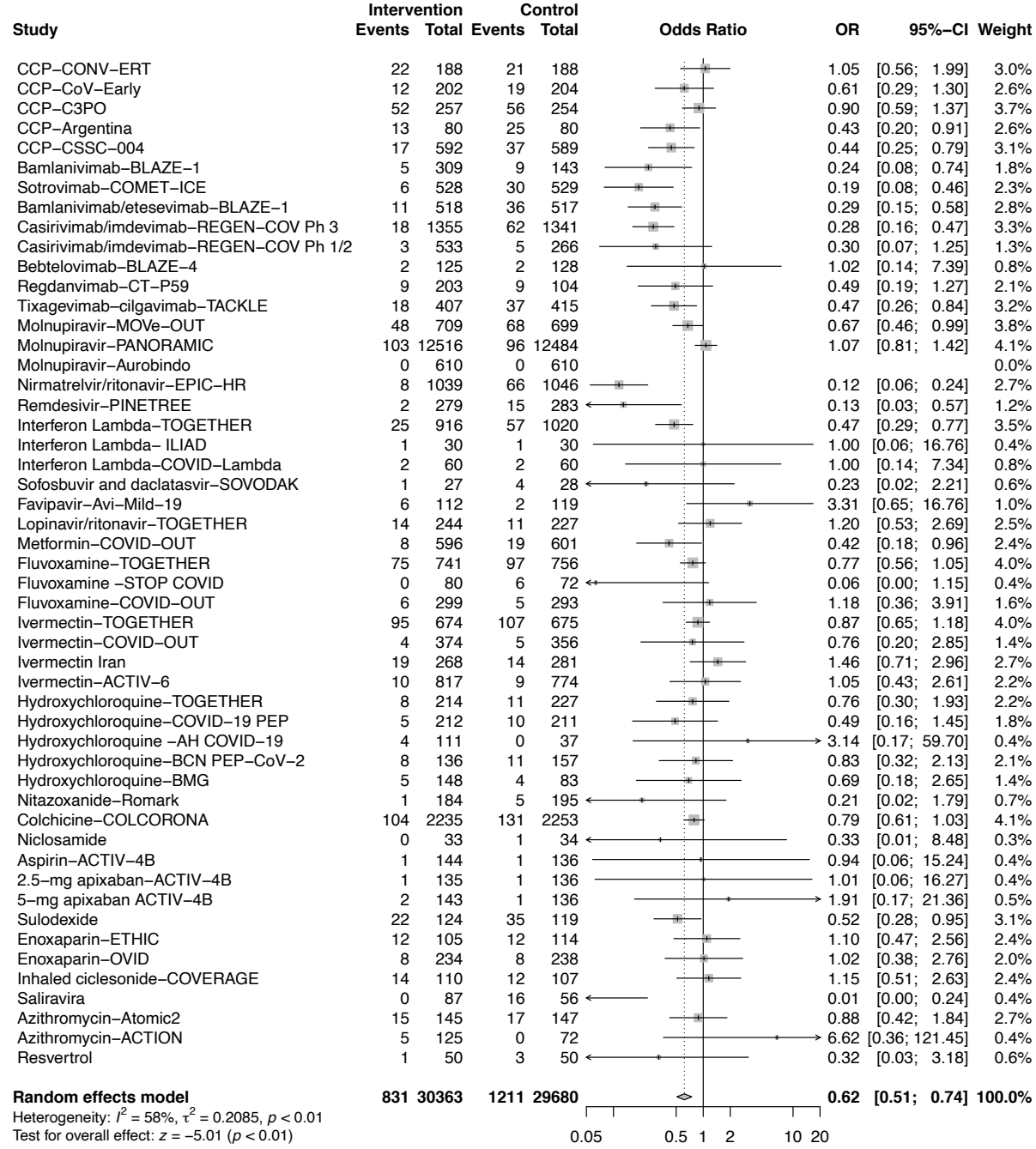
Ivermectin-COVID-OUT[13]	0	356	1	374	730	0.00	0.27		
Ivermectin Iran[38]	1	281	1	268	549	0.36	0.37		
Ivermectin-ACTIV-6[39]	0	774	1	817	1591	0.00	0.12		
Hydroxychloroquine-TOGETHER[34]	1	227	0	214	441	0.44	0.00		
Hydroxychloroquine-COVID-19 PEP[42]	1	211	1	212	423	0.47	0.47		
Hydroxychloroquine -AH COVID-19[41]	0	37	0	111	148	0.00	0.00		
Hydroxychloroquine-BCN PEP-CoV-2[40]	0	157	0	136	293	0.00	0.00		
Hydroxychloroquine-BMG[43]	0	83	0	148	231	0.00	0.00		
Nitazoxanide-Romark[43]	0	195	0	184	379	0.00	0.00		
Colchicine-COLCORONA[44]	9	2253	5	2235	4488	0.40	0.22		
Niclosamide[45]	0	34	0	33	67	0.00	0.00		
Aspirin-ACTIV-4B[46]	0	136	0	144	280	0.00	0.00		
2.5-mg apixaban-ACTIV-4B[46]	0	136	0	135	271	0.00	0.00		
5-mg apixaban ACTIV-4B[46]	0	136	0	143	279	0.00	0.00		
Sulodexide[47]	7	119	3	124	243	5.88	2.42		
Enoxaparin-ETHIC[49]	0	114	1	105	219	0.00	0.95		
Enoxaparin-OVID[50]	0	238	0	234	472	0.00	0.00		
Inhaled ciclesonide-COVERAGE[50]	2	107	0	110	217	1.87	0.00		
Saliravira[51]	0	56	0	87	143	0.00	0.00		
Azithromycin-Atomic2[52]	1	147	1	145	292	0.68	0.69		
Azithromycin-ACTION[53]	0	72	0	125	197	0.00	0.00		
Resveratrol[54]	0	50	0	50	100	0.00	0.00		

Supplementary Figure 1
Risk of bias by RCT

TYPE	Study	Radomization	Deviations from intervention	Missing outcome data	Mesaurement of the outcome	Selection of the reported results	Overall risk of bias	ROB Source
Ab-CCP	CCP-CONV-ert	Low	Low	Low	Low	Low	Low	https://covid-nma.com/
Ab-CCP	CCP-COV-early							pending in NMA-COVID
Ab-CCP	CCP-C3PO	Low	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
Ab-CCP	CCP-Argentina	Low	Low	Low	Low	Some concerns	Some concerns	https://covid-nma.com/
Ab-CCP	CCP-CSSC-004	Low	Low	Low	Low	Low	Low	https://covid-nma.com/
Ab-MONO	Bamlanivimab-BLAZE-1	Low	Low	Low	Low	Low	Low	https://covid-nma.com/
Ab-MONO	Sotrovimab-COMET-ICE	Low	Low	Some concerns	Low	Some concerns	Some concerns	https://covid-nma.com/
Ab-MONO	BLAZE-1	Low	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
Ab-MONO	Casirivimab/imdevimab-REGEN-COV Ph 3	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	https://covid-nma.com/
Ab-MONO	Casirivimab/imdevimab-REGEN-COV Ph 1/2	Low	Low	Low	Low	Low	Low	https://covid-nma.com/
Ab-MONO	Bebtelovimab-BLAZE-4	Low	Low	Low	Low	Low	Low	https://covid-nma.com/
Ab-MONO	Regdanvimab-CT-P59	Low	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
Ab-MONO	Tixagevimab–cilgavimab-TACKLE	Low	Some concerns	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-AV	Molnupiravir-MOVe-OUT	Low	Low	Low	Low	Low	Low	https://covid-nma.com/
DRUG-AV	Molnupiravir-PANORAMIC	Low	Some concerns	HIGH	Some concerns	Low	HIGH	https://covid-nma.com/
DRUG-AV	Molnupiravir-Aurobindo	Low	Low	Low	Some concerns	Some concerns	Some concerns	https://covid-nma.com/
DRUG-AV	Nirmatrelvir/ritonavir-EPIC-HR	Low	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-AV	Remdesivir-PINETREE	Some concerns	Low	Low	Low	Low	Some concerns	https://covid-nma.com/
DRUG-AV	Interferon Lambda-TOGETHER							data not published Eiger
DRUG-AV	Interferon Lambda- ILIAD	Low	Low	Low	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-AV	Interferon Lambda-COVID	Low	Low	Low	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-AV	SOVODAK	little evidence to sc	little evidence to sc	little evidence to sc	little evidence to score	little evidence to score	little evidence to	https://covid-nma.com/
DRUG-AV	Favipiravir-Avi-Mild-19	Low	Low	Low	Some concerns	Low	Some concerns	https://covid-nma.com/
DRUG-AV	Lopinavir/ritonavir-TOGETHER	Low	Low	Some concerns	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	Metformin-COVID-OUT	Low	Low	Unclear	Low	Low	Low	RevMan pending in NMA-COVID
DRUG-RP	Fluvoxamine-TOGETHER	Low	Some concerns	Low	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	Fluvoxamine -STOP COVID	Low	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	Fluvoxamine-COVID-OUT	Low	Low	Unclear	Low	Low	Low	RevMan pending in NMA-COVID
DRUG-RP	Ivermectin-TOGETHER	Low	Low	Unclear	Low	Low	Low	Revman and https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015017.pub3/references#riskOfBias2
DRUG-RP	Ivermectin-COVID-OUT	Low	Low	Unclear	Low	Low	Low	RevMan pending in NMA-COVID
DRUG-RP	Ivermectin Iran							pending in NMA-COVID
DRUG-RP	Ivermectin-ACTIV-6	Low	Low	Low	Low	Low	Unclear	RevMan pending in NMA-COVID
DRUG-RP	TOGETHER	Low	Low	Some concerns	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	19 PEP	Some concerns	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	COVID-19	Low	Low	Low	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	CoV-2	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	Hydroxychloroquine-BMG	Low	Low	Some concerns	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	Nitazoxanide-Romark	Low	Low	Some concerns	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	Colchicine-COLCORONA	Low	Low	Low	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	Niclosamide	Some concerns	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	Aspirin-ACTIV-4B	Low	Some concerns	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	2.5-mg apixaban-ACTIV-4B	Low	Some concerns	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	5-mg apixaban ACTIV-4B	Low	Some concerns	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	Sulodexide	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	Enoxaparin-ETHIC							pending in NMA-COVID
DRUG-RP	Enoxaparin-OVID							pending in NMA-COVID
DRUG-RP	Inhaled ciclesonide-COVERAGE	Low	Low	Low	Low	Low	Low	https://covid-nma.com/
DRUG-RPH	Saliravira							pending in NMA-COVID
DRUG-RP	Azithromycin-Atomic2	Low	Low	Low	Some concerns	Some concerns	Some concerns	https://covid-nma.com/
DRUG-RP	Azithromycin-ACTION	Low	Low	Some concerns	Low	Low	Some concerns	https://covid-nma.com/
DRUG-RP	Resveratrol							pending in NMA-COVID

Supplementary Figure 2

Odds ratio for hospitalizations from all therapeutic interventions, ordered according to mechanism of action (CCP, anti-Spike mAbs, small molecule antivirals and repurposed drugs



Supplementary Figure 3
Funnel plots by RCTs class A) CCP, B) anti-Spike mAbs C) small molecule antivirals and D) repurposed drugs. For anti-Spike mAbs RCTs, there is a suggestion of missing studies on the right side of the plot, where results would be unfavourable to the experimental intervention, for which either very high efficacy of high-dose anti-Spike mAbs or non-reporting bias is a plausible explanation.