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Repurposed drug studies on the primary prevention of SARS-CoV-2 infection during the pandemic: systematic review and meta-analysis

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ABSTRACT

Objective Current evidence on the effectiveness of SARS-CoV-2 prophylaxis is inconclusive. We aimed to systematically evaluate published studies on repurposed drugs for the prevention of laboratory-confirmed SARS-CoV-2 infection and/or COVID-19 among healthy adults.

Design Systematic review.

Eligibility Quantitative experimental and observational intervention studies that evaluated the effectiveness of repurposed drugs for the primary prevention of SARS-CoV-2 infection and/or COVID-19 disease.

Data source PubMed and Embase (1 January 2020–28 September 2022).

Risk of bias Cochrane Risk of Bias 2.0 and Risk of Bias in Non-Randomised Studies of Interventions tools were applied to assess the quality of studies.

Data analysis Meta-analyses for each eligible drug were performed if ≥2 similar study designs were available.

Results In all, 65 (25 trials, 40 observational) and 29 publications were eligible for review and meta-analyses, respectively. Most studies pertained to hydroxychloroquine (32), ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) (11), statin (8), and ivermectin (8). In trials, hydroxychloroquine prophylaxis reduced laboratory-confirmed SARS-CoV-2 infection (risk ratio: 0.82 (95% CI 0.74 to 0.90), I^2=48%), a result largely driven by one clinical trial (weight: 60.5%). Such beneficial effects were not observed in observational studies, nor for prognostic clinical outcomes. Ivermectin did not significantly reduce the risk of SARS-CoV-2 infection (RR: 0.35 (95% CI 0.10 to 1.26), I^2=96%) and findings for clinical outcomes were inconsistent. Neither ACEi or ARB were beneficial in reducing SARS-CoV-2 infection. Most of the evidence from clinical trials was of moderate quality and of lower quality in observational studies.

Conclusions Results from our analysis are insufficient to support an evidence-based repurposed drug policy for SARS-CoV-2 prophylaxis because of inconsistency. In the view of scarce supportive evidence on repurposing drugs for COVID-19, alternative strategies such as immunisation of vulnerable people are warranted to prevent the future waves of infection.

PROSPERO registration number CRD42021292797.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous comprehensive systematic reviews were outdated, lacked a meta-analysis that compiles information from observational studies and did not quantitatively describe the large heterogeneity in the existing data.

WHAT THIS STUDY ADDS

⇒ This review provides an up-to-date comprehensive review of registered repurposed drugs for the potential prevention of SARS-CoV-2 infection and/or COVID-19 disease and summarised effect measures systematically and quantitatively, including both clinical trial and real-world study designs. We also performed a subgroup analysis to investigate whether effects were modified if used as pre-exposure or postexposure prophylaxis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Even though this review found some potential in preventing SARS-CoV-2 infection for some repurposed drugs, current evidence is inconsistent and of too low quality to base healthcare policy for SARS-CoV-2 prophylaxis on. More rigorous pharmacoepidemiological intervention studies and meticulous safety assessment are needed during a pandemic.

INTRODUCTION

As of 5 July 2023, SARS-CoV-2 has infected more than 767 million people worldwide.[1] Despite the WHO declaring on 4 May 2023, that COVID-19 no longer constitutes a public health emergency of international concern,[2] there is still a probability of recurring SARS-CoV-2 infections, especially during the winter time. Therefore, it is urgent to find effective prophylactic agents to prepare for the upcoming wave of infection because of waning natural immunity and vaccine-induced immunity. Managing severe acute respiratory distress syndrome can be complex

due to the challenges involved with non-invasive respiratory support[3–5] and inflammation. Therefore, it is preferable to adopt a proactive approach in dealing with the disease progression or even prevention. Although antibody tixagevimab-cilgavimab as pre-exposure prophylaxis (PrEP) has been granted for emergency use authorisation in the USA[6] and the UK,[7] safety issues and effectiveness against prevalent Omicron variants still concern. With the benefits of proven safety and affordable cost, repurposed drugs registered for other indications may serve as PrEP or postexposure prophylaxis (PEP) not only to protect populations at high risk of acquiring SARS-CoV-2 infection such as healthcare workers (HCWs),[8] household close contacts or geriatric populations with multiple comorbidities,[9] but also to mitigate the burden to healthcare system and economy.

Since the outbreak of the COVID-19 pandemic, clinical trials and observational intervention studies on a wide variety of repurposed drugs have been published at an unprecedented rate. However, current evidence is scattered and inconclusive due to heterogeneous study designs and settings. A well-designed systematic review and meta-analysis is warranted to summarise and scrutinise published findings and provide up-to-date evidence regarding the effectiveness of prophylactic agents in preventing SARS-CoV-2 infection and COVID-19 disease. Such a review may map the landscape of existing and future prophylactic candidates.

This review complements current guidelines[10 11] on preventive drugs and three earlier comprehensive reviews, which were based on articles published in 2020 and early 2021. Further substantial evidence on mostly studied drugs such as hydroxychloroquine (HCQ) and ivermectin and additional information on other repurposed drugs are warranted for guidelines update. Smit *et al*[12] and Andrade *et al*[13] conducted a systematic review of repurposed drugs used as prophylaxis for COVID-19. These findings did not describe the large heterogeneity in the existing data quantitatively using meta-analysis. Bartoszko *et al*[14] focused their review on randomised controlled trials (RCTs) only, without compiling real-world evidence from observational studies. Importantly, findings need to be differentiated between two different prophylaxis modes PrEP and PEP, because the timing and dosage of prescribing prophylactic agents may influence the preventive effect.[15]

This systematic review aimed to evaluate the effectiveness of repurposed drugs for the primary prevention of laboratory-confirmed SARS-CoV-2 infection and/or COVID-19 diseases in adults. For the drugs that have been studied as both PrEP and PEP, we further carried out a subgroup analysis to investigate the differential preventive effectiveness of these drugs when used as PrEP or PEP.

MATERIAL AND METHODS

This systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. An a priori study protocol is publicly available on the PROSPERO website (registration number CRD42021292797).

Search strategy and eligibility criteria

We performed a systematic search in PubMed and Embase with restriction to English language and period of publication 1 January 2020 to 22 November 2021 for quantitative experimental and observational intervention studies that evaluated the effectiveness of repurposed drugs for the primary prevention of SARS-CoV-2 infection and/or COVID-19 disease. We performed a second-round retrieval from PubMed and Embase as well to collect additional new articles which were published from 22 November 2021 to 28 September 2022. We compiled the search strategy combining free text and medical subject headings in the following four domains: disease ("SARS-CoV-2" or "coronavirus" or "COVID"), prophylaxis ("pre-exposure prophylaxis" or "post-exposure prophylaxis"), potential repurposed drugs ("hydroxychloroquine", "ivermectin", "arbidol", etc), and study design (online supplemental table S1). We included both experimental (randomised or non-randomised controlled trials, quasi trials or cross-over studies) and observational studies (cohort, test-negative case-control study, case-control study or cross-over studies) in this review.

Two reviewers (GZ and SV) undertook two-step selection independently. GZ did the complete screening for all articles, while SV screened 50% of articles that were chosen at random. In the first step, we screened title and abstract of each publication for inclusion. As a second step, we undertook full-text screening to determine inclusion. The third reviewer (EH) decided on the disagreements between the two reviewers (GZ and SV). The detailed inclusion and exclusion criteria on population, interventions, outcomes, study design, etc that we used to select articles are listed in online supplemental table S1.

Data extraction

The following variables were extracted for each included article, if available: study design (including inclusion and exclusion criteria), geographics, participants' characteristics, mean or median age, the proportion of males, ethnicity, type of prophylaxis (PrEP or PEP), median days of starting prophylaxis after exposure (if postexposure), number of participants, study drug, and comparator (including dosage and frequency), primary and secondary outcome measures, and follow-up period. The drug intervention was considered as PEP if the drugs were prescribed to close contacts of explicitly identified confirmed COVID-19 cases (index case), otherwise prophylaxis was categorised as PrEP. We extracted the corresponding outcome measures of all repurposed drugs investigated in the included articles, except the medications used as potential confounding variables. Preferably, we extracted participants' characteristics and outcome measures for study participants with negative

transcription-PCR (RT-PCR) status at baseline rather than all participants if information on this subgroup was available.

Outcomes

The study outcomes for the drugs of interest included: (1) laboratory-confirmed infection by RT-PCR assay for SARS-CoV-2 or serological test (confirmed cases)[16], (2) clinical-confirmed infection defined by symptoms compatible with COVID-19 (probable cases)[16], (3) COVID-19 diagnosis by all criteria (confirmed and probable cases), prognostic clinical outcomes including, (4) hospitalisation, (5) intensive care unit (ICU) admission, and (6) all-cause death.

Quality assessment and risk of bias

Two independent reviewers (GZ and SV) assessed the risk of bias for RCTs and non-randomised studies by using the Cochrane Risk of Bias 2.0 (RoB 2.0)[17] and Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tools,[18] respectively. The third reviewer (EH) decided on the disagreements between the two reviewers (GZ and SV).

RoB 2.0 covers five domains of bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The overall assessment of RoB 2.0 is subdivided into three categories: low risk of bias, some concerns, and high risk of bias. ROBINS-I covers seven domains of bias due to confounding, selection of participants into the study, classification of intervention, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. The overall assessment of ROBINS-I is subdivided into four categories: low risk of bias, moderate risk of bias, serious risk of bias, and critical risk of bias.

Data synthesis and statistical analysis

We performed meta-analyses for each eligible drug in this review if two or more studies were present with similar study design. We conducted the meta-analyses separately for different study designs and outcome measures (clinical trials, cohort studies or case-control studies). The effect of the drugs on dichotomous outcomes (SARS-CoV-2 infection, COVID-19 diagnosis or hospitalisation) in clinical trials were summarised using risk ratios (RRs) and 95% CIs, while those of case-control studies were summarised using ORs and 95% CIs, and cohort studies could estimate ORs with 95% CIs. As observational studies are susceptible to confounding bias, our meta-analyses only included effect estimates that were estimated with adjustment for confounders by multivariable regression or propensity-score matching, although not all confounders may be known or measured. Statistical heterogeneity was determined using I^2 statistics. If the heterogeneity was low to moderate (I^2<50%), meta-analysis was performed using a fixed-effect model (Mantel-Haenszel method), otherwise a random-effect model was applied when heterogeneity was high (I^2>50%). Within each comparison, we also conducted subgroup analyses comparing the difference of preventive effect between PrEP and PEP, if applicable. Besides, we performed a sensitivity analysis excluding effect measures from all high risk of bias studies. A funnel plot was generated to visualise publication bias.

All data analyses were performed using Review Manager (Version.5.4.1). The results of quality assessment were visualised using Robvis. The statistical significance threshold in this review was p<0.05. No adjustment for multiple testing has been performed.

RESULTS

The initial search identified 1833 and 1587 articles from PubMed and Embase, respectively. After removing duplicate entries manually, the titles and abstracts of 2676 articles were screened for inclusion using predefined inclusion and exclusion criteria. Subsequently, we assessed the full text of 121 articles for eligibility, and 43 articles were included. After second-round retrieval, we included a total of 65 articles in the review, among which 29 articles were eligible for meta-analysis (figure 1).

Summary of included articles

The full details of all 65 included articles were listed in online supplemental table S2. The majority of articles were observational studies (N=40, 61.5%), with 22 cohort studies, 16 case-control studies, and 2 retrospective observational studies. Among the 25 clinical trials (22 RCTs and three non-randomised clinical trials), 18 studies fulfilled the conditions for meta-analysis. As for the prophylaxis type, most of the studies (N=56, 86.2%) focused on repurposing drugs for PrEP.Regarding the potential prophylactic drug interventions, the most frequently studied drugs were HCQ (32 of 65, 49.2%), ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) (11 of 65, 16.9%), statin (8 of 65, 12.3%), and ivermectin (8 of 65, 12.3%). Less often studied drugs were: antivirals (arbidol, lopinavir/ritonavir, tenofovir disoproxil fumarate/emtricitabine (FTC), sofosbuvir/daclatasvir), antidiabetics (metformin, insulin, thiazolidinedione, etc), antihypertensives (beta-blocker, diuretics, calcium channel blocker (CCB)), anticoagulants, antiplatelets (aspirin, warfarin), proton-pump inhibitor, non-steroidal anti-inflammatory drug, antipsychotics, thymosin, and monoclonal antibody (bamlanivimab) (online supplemental table S3). Out of 65 studies, 24 (36.9%) were performed in Asian countries (India, China, South Korea, Singapore, Israel, Iran, Pakistan, and Thailand), 22 (33.8%) in European countries (Italy, Spain, France, Sweden, Switzerland, Denmark, Portugal, Russia, and England), 15 (23.1%) in American countries (the USA, Canada, Mexico, Argentina, and the Dominican

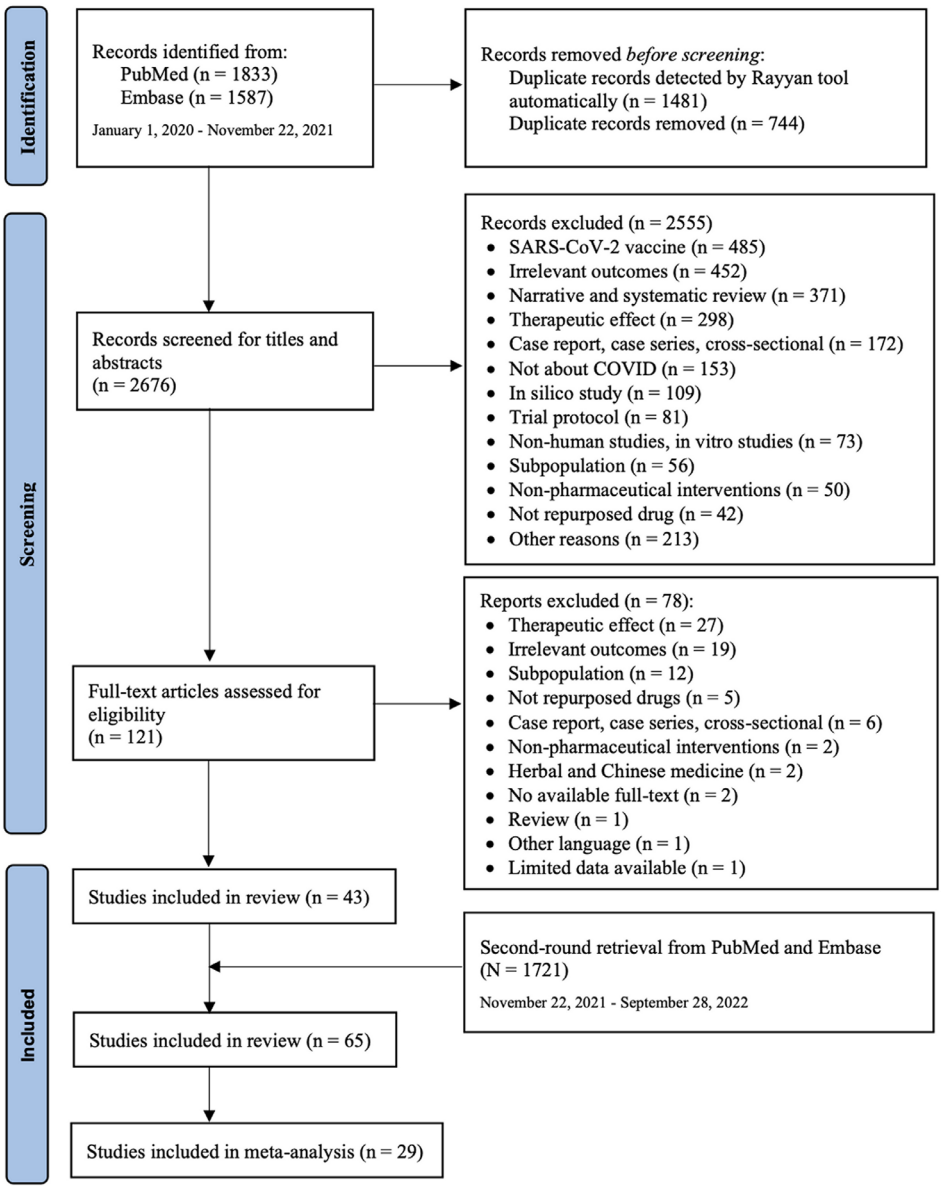

Figure 1 PRISMA flow diagram of article selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Republic), 2 (3.1%) in African countries (Tunisia and South Africa), 1 in Turkey, and 1 in Egypt. Among the 25 clinical trials, 9 (36.0%) were performed in American countries (the USA, Canada, Argentina, and Mexico), 7 (28.0%) in Asian countries (Singapore, Iran, India, Thailand, and Pakistan), 6 (24.0%) in European countries (Spain, Switzerland, and Russia), 2 (8.0%) in African countries (South Africa and Tunisia), and 1 in Egypt.

Quality assessment of included articles

Online supplemental figures S1 and S2 illustrate the risk of bias from RCTs evaluated by RoB 2.0. Out of 22 articles, 5 (22.7%) were scored as low risk, 13 (59.1%) as some concerns, 4 (18.2%) as high risk. Bias mostly arose from the randomisation process, blinding process, and selection of reported results. We used ROBINS-I to assess the quality of non-randomised studies (online supplemental figures S3 and S4). Around half of the 43 studies were of moderate risk (N=18), while the remaining studies were of low risk (N=12), serious risk (N=12), and critical risk (N=1). Possible selection bias and misclassification, which represented bias due to selection of participants and bias in classification of interventions, respectively, were common. Prestudy protocol and statistical plan were not always accessible for both RCTs and observational studies.

Effects of repurposed drug interventions per class

Online supplemental table S3 is a summary of all the effect measures extracted from 65 included articles.

Hydroxychloroquine

Of the 32 studies on HCQ (15 trials and 17 observational studies), only 9 articles demonstrated a statistically

significant beneficial effect of HCQ prophylaxis on preventing SARS-CoV-2 infection, while none of the 32 studies showed a significant association between HCQ prophylaxis and risk of hospitalisation, ICU admission, or death (online supplemental table S3).

In a meta-analysis of laboratory-confirmed SARS-CoV-2 infection (confirmed cases), the overall RR of HCQ-users having infection was 0.82 (95% CI 0.74 to 0.90) (I^2=48%, fixed-effect model) when compared with non-users in clinical trials. When separating into PrEP or PEP subgroup, the RR was 0.77 (95% CI 0.69 to 0.86) (I^2=47%) and 0.96 (95% CI 0.77 to 1.19) (I^2=14%), respectively (figure 2A). Meta-analysis of case-control studies indicated that the overall OR of having laboratory-confirmed infection was 0.68 (95% CI 0.45 to 1.04) (I^2=93%, random-effect model) (figure 2B), while the overall OR

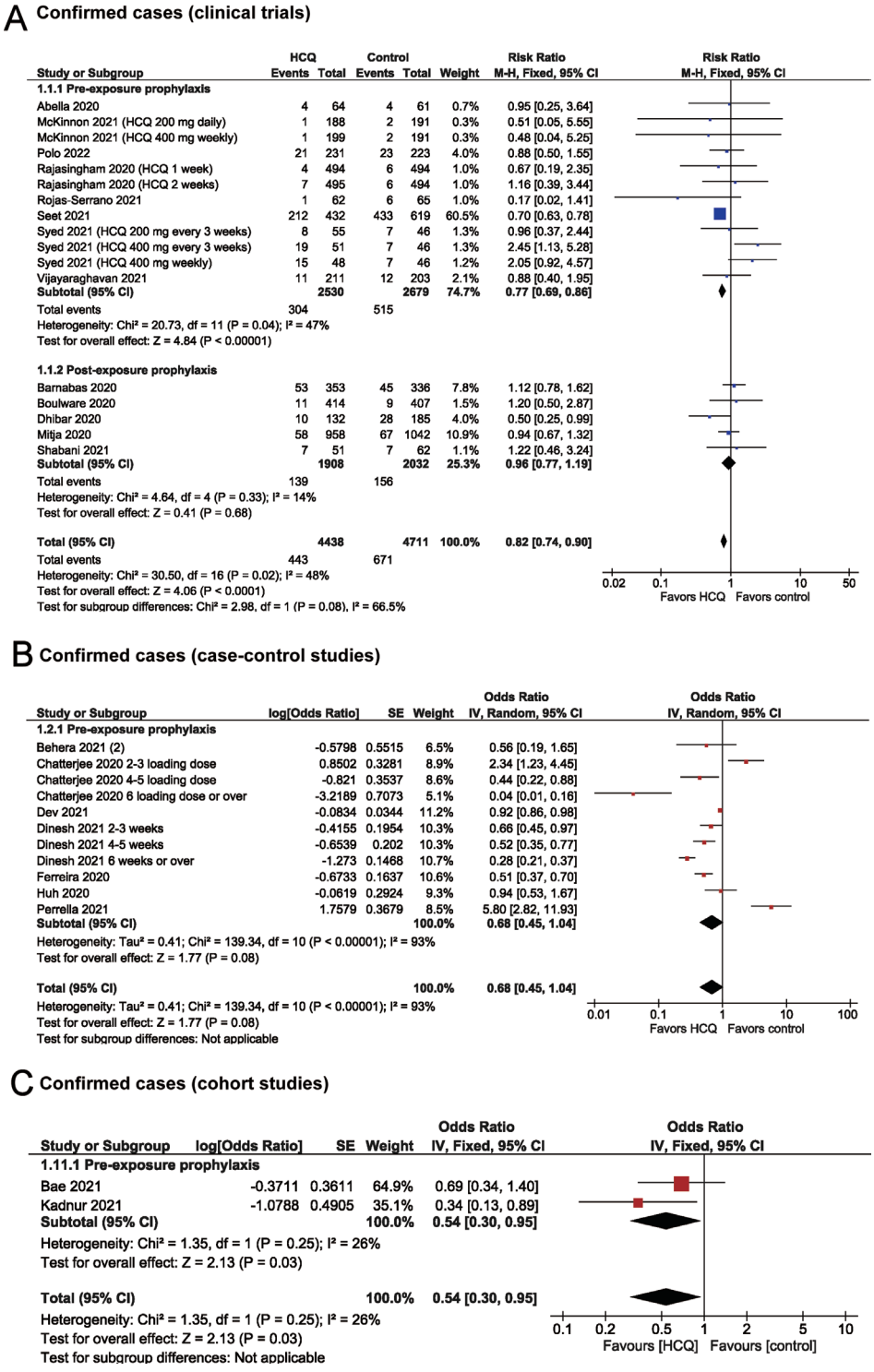

Figure 2 Meta-analysis of the effect of HCQ prophylaxis on laboratory-confirmed SARS-CoV-2 infection in (A) clinical trials; (B) case-control studies; (C) cohort studies. HCQ, hydroxychloroquine; IV, inverse variance; M-H, Mantel-Haenszel.

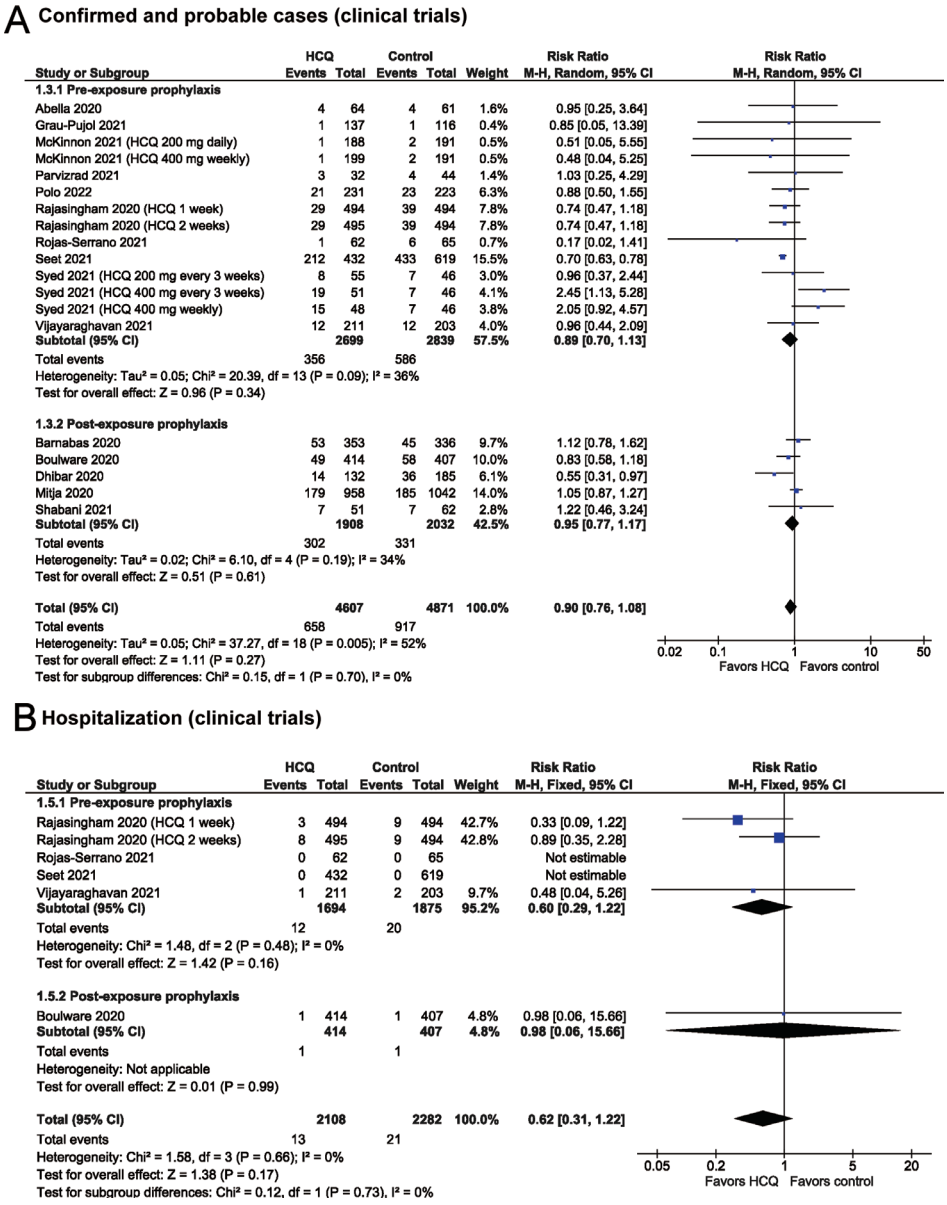

Figure 3 Meta-analysis of the effect of HCQ prophylaxis on (A) laboratory-confirmed or clinical-confirmed infection; or (B) hospitalisation in clinical trials. HCQ, hydroxychloroquine; M-H, Mantel-Haenszel.

of cohort studies was 0.54 (95% CI 0.30 to 0.95) (I^2=26%, fixed-effect model) (figure 2C). Most of the evidence from HCQ clinical trials was of moderate quality, while lower quality was observed from observational studies. Publication bias was less likely to occur in the evidence of HCQ studies on laboratory-confirmed infection (online supplemental figure S5).

Regarding laboratory-confirmed infection or illness compatible with COVID-19 (confirmed and probable cases), HCQ prophylaxis did not significantly reduce the risk of infection in clinical trials (RR: 0.90 (95% CI 0.76 to 1.08), I^2=52%, random-effect model) (figure 3A). There was no significant association between HCQ prophylaxis and hospitalisation rate either (RR: 0.62 (95% CI 0.31 to 1.22), I^2=0%, fixed-effect model) (figure 3B).

In the sensitivity analysis excluding effect measures from all high risk of bias studies, the pooled risk of laboratory-confirmed infection in clinical trials did not change substantially (RR: 0.77 (95% CI 0.69 to 0.85), I^2=44%, fixed-effect model) (online supplemental figure S6A), while the estimate was more towards to null effect with a wider 95% CI in case-control studies after excluding low-quality evidence (OR: 0.75 (95% CI 0.32 to 1.72), I^2=91%, random-effect model) (online supplemental figure S6B). The pooled estimate of confirmed and probable infection became statistically significant in sensitivity analysis (RR: 0.76 (95% CI, 0.69 to 0.84), I^2=31%, fixed-effect model) because more study weight was given to the Seet *et al* trial (online supplemental figure S6C).

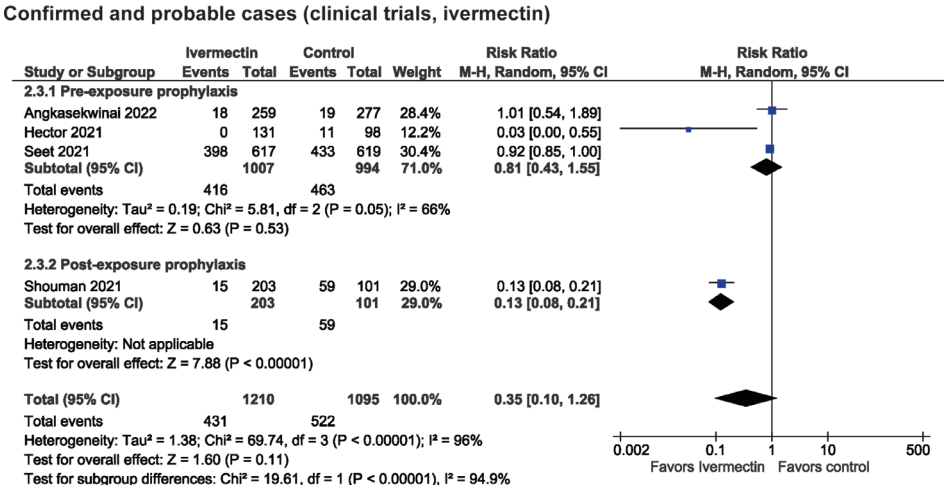

Figure 4 Meta-analysis of the effect of ivermectin prophylaxis on laboratory-confirmed or clinical-confirmed SARS-CoV-2 infection in clinical trials. M-H, Mantel-Haenszel.

Ivermectin

Among eight articles on ivermectin, five studies (three clinical trials and two observational studies) showed that the use of ivermectin significantly reduced the risk f SARS-CoV-2 infection. However, in the meta-analysis of the four clinical trials, the result was not statistically significant (RR: 0.35 (95% CI 0.10 to 1.26), I^2=96%, random-effect model) (figure 4). When separating into PrEP or PEP subgroup, the RR was 0.81 (95% CI 0.43 to 1.55) (I^2=66%) and 0.13 (95% CI 0.08 to 0.21) (I^2 not applicable), respectively. No significant association between ivermectin prophylaxis and prognostic clinical outcomes was observed either.

ACEi or ARB

All of the 11 studies on ACEi or ARB were observational studies, among which three reported significant reduction of laboratory-confirmed SARS-CoV-2 infection risk with the pre-exposure ACEi/ARB use, while one study by Huh *et al*[19] did not favour the use of ACEi to prevent SARS-CoV-2 infection (aOR: 1.50 (95% CI 1.00 to 2.24)). Meta-analyses of ACEi indicated that the overall OR of having SARS-CoV-2 infection was 0.74 (95% CI 0.47 to 1.16) (I^2=88%, random-effect model) in cohort studies (figure 5A) and 1.15 (95% CI 0.75 to 1.76) (I^2=77%, random-effect model) in case-control studies (figure 5B), while those of ARB were 0.78 (95% CI 0.46 to 1.33) (I^2=86%, random-effect model) in cohort studies (figure 5C) and 0.98 (95% CI 0.90 to 1.06) (I^2=0%, fixed-effect model) in case-control studies (figure 5D), respectively. No significant association between ACEi or ARB prophylaxis and prognostic clinical outcomes was observed by the 11 articles, either.

Statin

All of the eight studies on statin were observational studies. Studies by Oh *et al*[20] (aOR: 0.65 (95% CI 0.60 to 0.71)) and Fung *et al*[21] (aHR: 0.97 (95% CI 0.96 to 0.98)) identified that statin therapy significantly reduced the risk of laboratory-confirmed infection. The potential of statins in decreasing hospitalisation and death from COVID-19 was also reported by Fung *et al*,[21] Bergqvist *et al*[22], and Bouillon *et al*.[23]

Other infrequently studied repurposed drugs

With moderate quality of evidence, disulfiram,[24] carvedilol,[25] beta-blocker,[26] bamlanivimab,[27] warfarin[21], and doxycycline with or without zinc[28] were associated with significantly lower risk of SARS-CoV-2 infection, while the effects of insulin,[29] oral anticoagulant[29], and famotidine[21] on SARS-CoV-2 infection were not favourable. Regarding prognostic outcomes, warfarin showed significant reduction in hospitalisation and death from COVID-19,[21] while CCB[26] and aspirin[30] increased the risk of serious illness and hospitalisation, respectively (see details in online supplemental table S3).

DISCUSSION

In this systematic review involving 65 studies, we found that despite some studies suggesting potential positive effects of drugs such as HCQ, ivermectin, ACEi, ARB, statin, carvedilol, beta-blocker, warfarin, doxycycline, and bamlanivimab etc, the results across these studies were inconsistent. Furthermore, the quality of the studies varied greatly and the available data was inadequate to draw a definitive conclusion.

HCQ was originally indicated for malaria, rheumatic arthritis, systemic lupus erythematosus and other autoimmune diseases with a low cost and favourable safety profile. Since HCQ has proven to be able to prevent SARS-CoV-2 infection in vitro,[31 32] a number of clinical trials and observational studies embarked on evaluating HCQ as prophylaxis to contain SARS-CoV-2 in the human body. Most of these studies reported non-significant associations between HCQ prophylaxis and reduced SARS-CoV-2 infection rate,[15 19 21 33–50] while only a few reported

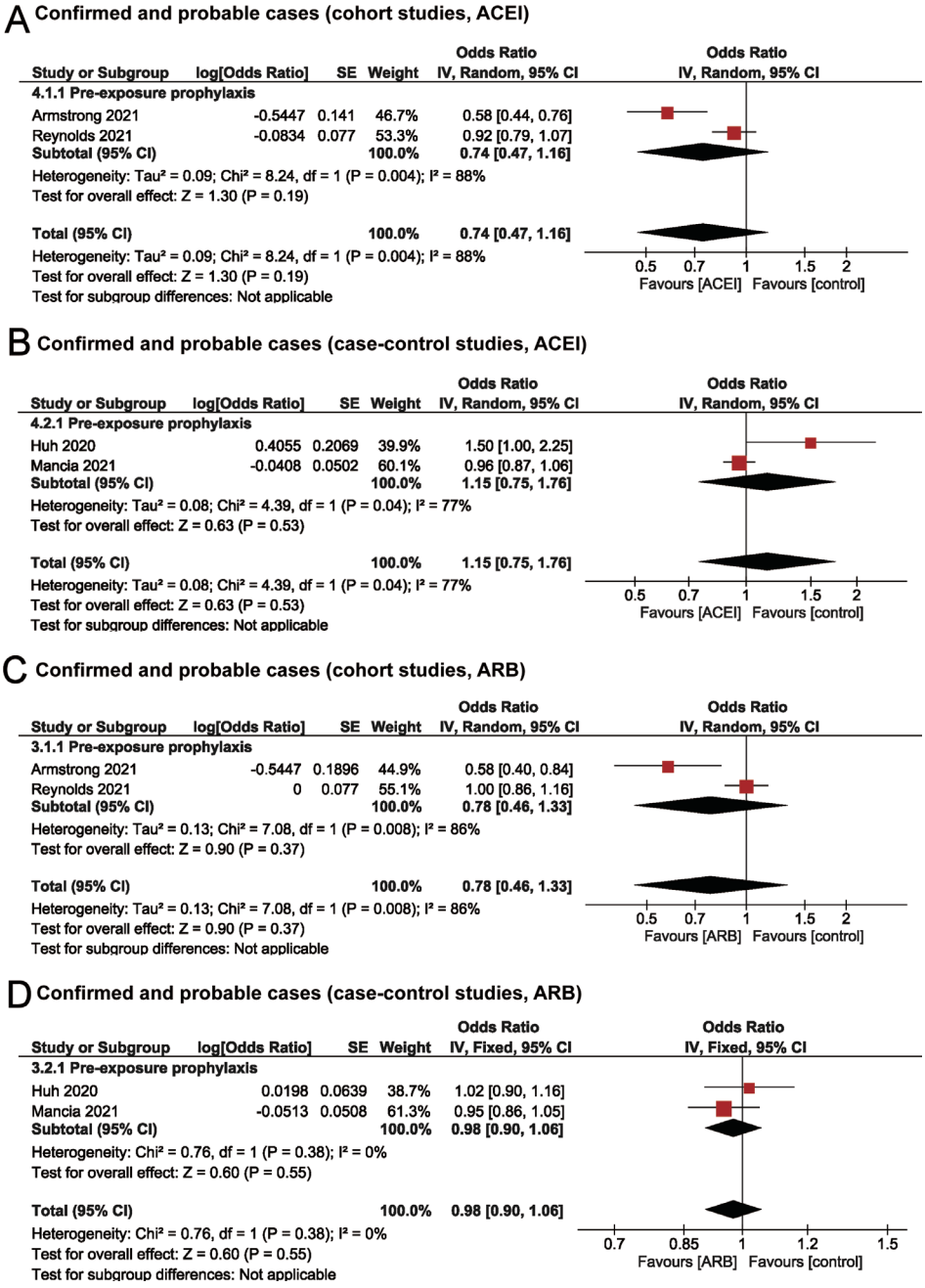

Figure 5 Meta-analysis of the effect of prophylaxis on laboratory-confirmed or clinical-confirmed SARS-CoV-2 infection: (A) ACEI, cohort studies; (B) ACEI, case-control studies; (C) ARB, cohort studies; (D) ARB, case-control studies. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; IV, inverse variance.

HCQ prophylaxis could significantly decrease SARS-CoV-2 infection rate.[51–59] Our findings of significant association between PrEP use of HCQ and reduced risk of SARS-CoV-2 infection in clinical trials are consistent with another meta-analysis of cohort studies among high-risk HCWs performed by Stricker and Fesler.[60] However, the other six meta-analyses of RCTs did not support the prophylactic use of HCQ in preventing SARS-CoV-2 due to non-significant associations and increased adverse events,[14 61–65] which is in line with the WHO recommendations against using HCQ as prophylaxis for COVID-19 updated in 2021.[10 66] We believe this is due to the fact that these meta-analyses did not include a recent trial by the Seet *et al*[51] published in 2021, while our favourable result was substantially driven by this trial (weight: 60.5%). Besides, it is conceivable that the inconsistency across studies arose from considerable variation in dosage and frequency of HCQ prophylaxis, participant selection criteria, follow-up, criteria in defining confirmed SARS-CoV-2 infection and time window of PCR test (varying from 7 to 42 days).

Ivermectin is approved by the food and drug administration for the long-term treatment of parasitic diseases. Ivermectin is deemed to be a promising effective

chemoprophylaxis against SARS-CoV-2 infection in several studies.[44 67–69] Even though three meta-analyses[70–72] demonstrated the effectiveness of prophylactic ivermectin, the evidence was of low certainty due to few included trials and high risk of bias. Our pooled estimate of ivermectin on SARS-CoV-2 infection with large heterogeneity between studies did not show this statistically significant association, which is in line with the advice from European Medicines Agency (EMA) in 2021 against the use of ivermectin for prevention of COVID-19 outside RCTs.[73] Nevertheless, this advice from the EMA only referred to limited number of articles on prophylaxis with low certainty of evidence and inconsistencies, which were common in ivermectin trials.[74] Therefore, a robust and definite meta-analysis is needed to further aggregate more evidence of ivermectin from well-designed RCTs and observational studies to draw conclusions whether ivermectin is effective in COVID-19 prevention.

There are no solid evidences on whether ACEi or ARB plays a protective or harmful role in SARS-CoV-2 infection because of the complexity of the effects of ACEi or ARB on renin-angiotensin system. Based on the meta-analyses of observational studies in our review, ACEi or ARB did not significantly reduce the risk of having SARS-CoV-2 infection, which is consistent with meta-analysis by Ma *et al*.[75]

Based on our findings, the PrEP use of HCQ showed greater effectiveness than the PEP use in clinical trials, meaning that early prescription and continuous use may be essential for HCQ prophylaxis. Besides, the pharmacokinetic profile of HCQ (large volume of distribution accounting for slow onset of action[76]) might attenuate the effectiveness of short-term PEP use. Future research on HCQ should pay more attention to PrEP mode and early treatment. The mechanisms of HCQ, ivermectin, ARB or ACEi inhibiting SARS-CoV-2 replication are all related to the viral entry phase such as receptor binding and membrane fusion.[77] Therefore, we hypothesise that the above treatments might be effective in preventing SARS-CoV-2 virus entry. Once the viruses have replicated and accumulated in the host cells, these drugs might do little in improving disease progression or deterioration. This hypothesis is corroborated by our findings as well, emphasising the importance of the timing of prescribing and achieving therapeutic concentration for HCQ, ivermectin, ARB and ACEi again.

Until now, vaccines are still the most promising approach to prevent SARS-CoV-2 infection in the general population especially vulnerable people, except for immunocompromised population. Considering the minimal beneficial effects on SARS-CoV-2 infection and prognosis from repurposed drugs so far, the future studies should consider carefully whether the repurposed drugs being studied are worthy to invest time and money on.

The clutter of the publications may interfere with decision-making during pandemic. In this review, we noticed that during the pandemic not all research was conducted in a prudent and rigorous way, even if clinical trials had issues with patient selection, small sample size, randomisation, and blinding. The implementation of COVID-19 clinical trials in a pandemic-impacted healthcare setting has been found to be quite challenging and tends to be more of a reactionary approach rather than a proactive one.[78] Furthermore, non-experimental studies are more vulnerable to selection bias (especially collider bias in the context of COVID-19 research[79]), misclassification bias, and confounding bias, which diminishes the internal validity of findings. Under the circumstance of pandemic-related decreased in-person healthcare encounters, drug stockpiling, and increased treatment discontinuations, observational studies using electronic medical records in the future should consider the above issues and attach more importance to mitigating the effect of bias and reinforcing validity using statistical methods such as stratification, standardisation, regression adjustment or inverse probability weights. Researchers should keep in mind that only a meticulous and well-designed study could generate trustworthy results that could support global implementation, otherwise efforts and money are wasted.

Our review has several strengths. This review provided an up-to-date (till 28 September 2022) comprehensive review of potential preventive registered drugs for SARS-CoV-2 infection and COVID-19 prognostic outcomes and summarised their effect measures quantitatively and systematically. Moreover, both clinical trials and real-world studies were selected and included in our review. We also performed a subgroup analysis to investigate whether the prophylaxis mode (PrEP or PEP) could influence the prophylactic effect. This review could provide additional information on the scope and magnitude of repurposed drugs to complement current guidelines, which were largely depending on studies published before 2022.

There are some potential limitations to our review. First, we only studied prophylaxis effectiveness data, without examining drug safety data. Therefore, advocacy of all drugs in this review in real practice should be made only after carefully examining possible drug adverse events and whether the benefits outweigh the risk. Second, variability among comparators indeed poses a challenge, as the studies included in our meta-analyses used varied comparators, such as placebo, standard of care or vitamin C. Addressing this heterogeneity completely can be difficult, especially when our goal is to include a broad range of studies to provide a comprehensive analysis of the existing data. To mitigate this issue to a degree, we have employed a random-effects model, which inherently accounts for some heterogeneity across studies. Third, due to limited data and heterogeneous effect measures, a substantial part of drugs and severe outcomes such as ICU admission and death were not eligible for meta-analyses. Fourth, some studies did not provide specific details on PrEP and PEP. Consequently, we classified studies as PrEP when they did not clearly define an index COVID-19 case, or if the subjects were active users at baseline without a clear indication of drug

use before or after exposure. As a result, our classification of PrEP is more comprehensive, which may compromise the precision of the pooled results pertaining to PrEP. Finally, our results may be overestimated due to possible publication bias, because we only abstracted published data and excluded preprint studies. From the funnel plots in our review, the included studies of HCQ were not very likely to have publication bias. However, the studies of other drugs are too few to detect any publication bias, therefore, its potential impact may be substantial. Even so, the peer-review process is indispensable to ensure the reliability and robustness of reported evidence, especially in the era of article race during the pandemic.

Conclusion

Our review provided an exhaustive summary of the effectiveness of all potential drugs repurposed for SARS-CoV-2 and COVID-19 prevention. Potential preventive effects against SARS-CoV-2 infection were observed in some studies of HCQ, ivermectin, ACEi or ARB, statin, carvedilol, beta-blocker, warfarin, doxycycline, and bamlanivimab etc in this review, nevertheless, current evidence is inadequate to make a solid advocacy policy for SARS-CoV-2 prophylaxis, especially in the absence of careful drug safety assessment. According to our meta-analysis results, even though a significant association was observed between HCQ prophylaxis and decreased SARS-CoV-2 infection, this finding is primarily driven by favourable results from one single clinical trial. Ivermectin, ACEi, and ARB did not significantly reduce the risk of having SARS-CoV-2 infection. In the view of scarce supportive evidence on repurposing drugs for COVID-19, the use of these repurposed drugs is not recommended as prophylaxis for COVID-19 in the clinical settings. Alternative strategies such as immunisation of vulnerable people are warranted to prevent the future waves of infection.

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Table S1 Inclusion and exclusion criteria for article selection

Characteristics	**Inclusion criteria**	**Exclusion criteria**
Population	Unselected adult subjects ≥ 18 years of age	• Lab-confirmed COVID-positive patients at the entry date • Studies with primary focus on specific populations (e.g. those with specific comorbidities such as cardiovascular or renal diseases)
Interventions	Pharmaceutical prophylactic drug interventions (pre- or/and post-exposure), which are originally indicated or approved for other diseases regardless of route of administration	• Non-pharmaceutical preventive approaches (e.g. social distancing, mask-wearing, medical devices) • SARS-CoV-2 vaccines • Not repurposed drugs (e.g. new drugs indicated for COVID-19, dietary supplements without certain indications, other vaccines) • Chinese traditional medicine, natural products, or herbal medicine
Outcomes	Lab-confirmed SARS-CoV-2 infection and/or symptom defined COVID-19 disease	• Safety profiles of interventions • Studies reporting on outcomes related to other prevention approaches or therapeutic agents • Secondary prevention for COVID-related complications in lab-confirmed COVID-positive patients • Other outcomes such as pharmacokinetic or pharmacodynamic, pharmacoeconomic outcomes
Study design	Articles with primary data of prophylactic candidates for SARS-CoV-2 infection or COVID-19 disease, including experimental and observational studies	• Studies focusing on other virus strains (e.g. SARS-CoV, Middle East respiratory syndrome (MERS)) • Non-human studies: in vitro studies, animal studies, genomic analysis • In silico studies: simulation, docking, modeling, virtual screening • Systematic review • Opinion or narrative review • Case reports, case series, cross-sectional studies • Trial protocols

Period	January 1, 2020 - November 22, 2021 November 22, 2021 -September 28, 2022 (second round retrieval)	Before January 1, 2020
Language	English only	Other languages
Type of publication	Journal	Letter to editor, preprints in medRxiv or bioRxiv, News, comment, or editorial
Accessibility	Studies with accessible full-text	Studies with no accessible full-text

Table S2 Characteristics of included articles

Study ID	Country	Study design	No of participants	Average age (years)	Male (%)	Patients characteristics	Type of prophylaxis	Study component and comparator	Outcome
Abella 2020 [15]	US	RCT (double-blind)	125	33.0	31.1	Healthcare workers worked ≥ 20 hours per week in hospital-based units, had no SARS-CoV-2 infection history and compatible symptoms of COVID-19	PrEP	HCQ (600 mg once daily for 8 weeks); placebo	Laboratory-confirmed SARS-CoV-2 infection, rate of serologic antibody positivity
Barnabas 2020 [16]	US	RCT (double-blind)	689	39.0	40.2	Close contacts (household: 82.3%, healthcare workers: 17.7%) aged 18-80 years and had exposure within the prior 96 hours	PEP	HCQ (400 mg once daily for 3 days followed by 200 mg once daily for additional 11 days); Vitamin C	Laboratory-confirmed SARS-CoV-2 infection, symptomatic COVID-19 disease
Boulware 2020 [11]	US and Canada	RCT (double-blind)	821	40.0	48.4	Close contacts (household or occupational) to a confirmed COVID-19 person at a distance of < 6 ft for > 10 minutes, aged ≥ 18 years	PEP	HCQ (800 mg once, then 600 mg 6-8 hours later, then 600 mg daily for 4 days); placebo	Laboratory-confirmed SARS-CoV-2 infection or illness compatible with COVID-19, laboratory-confirmed SARS-CoV-2 infection, symptoms compatible with COVID-19, hospitalization
Rajasingham 2020 [17]	US and Canada	RCT (double-blind)	1483	41.0	48.8	Healthcare workers aged ≥ 18 years with ongoing exposure to COVID-19 persons	PrEP	HCQ (400 mg twice separated by 6-8 hours, then 400 mg once weekly for 12 weeks), HCQ (400 mg twice separated by 6-8 hours, then 400 mg twice weekly for 12 weeks); placebo	Laboratory-confirmed SARS-CoV-2 infection or illness compatible with COVID-19, laboratory-confirmed SARS-CoV-2 infection, possible COVID-19, hospitalization
Mitja 2020 [18]	Spain	RCT (open-label)	2314	48.6	27.1	Close contacts aged ≥ 18 years to a PCR-confirmed COVID-19 patient (> 15 minutes within 2 meters, up to 7 days before enrollment), no COVID-like symptoms before enrollment	PEP	HCQ (800 mg once daily on day 1, followed by 400 mg once daily for 6 days); usual care	Laboratory-confirmed and symptomatic COVID-19, laboratory-confirmed SARS-CoV-2 infection or illness compatible with COVID-19, laboratory-confirmed SARS-CoV-2 infection, symptoms compatible with COVID-19
Cohen 2021 [19]	US	RCT (double-blind)	966	53.0	25.3	Residents and staff at nursing and assisted living facilities aged ≥ 18 years	PrEP	Bamlanivimab (4200 mg intravenous infusion); placebo	Laboratory-confirmed and symptomatic COVID-19, moderate or severe COVID-19, laboratory-confirmed SARS-CoV-2 infection, death due to COVID-19

Seet 2021 [20]	Singapore	RCT (open-label)	3037	33.0	100.0	Dormitory residents aged 21-60 years	PrEP	HCQ (400 mg once, followed by 200 mg daily for 42 days), Ivermectin (single dose of 12 mg), Povidone-iodine throat spray (270 mg/day for 42 days); Vitamin C	Laboratory-confirmed SARS-CoV-2 infection, acute respiratory symptoms, symptomatic COVID-19 disease, pneumonia requiring hospitalization, death
Labhardt 2021 [21]	Switzerland Brazil	RCT (open-label)	318	39.7	50.6	Close contacts aged ≥ 16 years to a PCR-confirmed COVID-19 patient (> 15 minutes within 2 meters, or shared closed space for 12 hours), < 48 hours before onset of symptoms in index case and within 7 days of enrollment, < 72 hours after diagnosis of index case	PEP	LPV/r (2 tablets of LPV/r 200/50 mg twice daily for 5 days); usual care	Laboratory-confirmed and symptomatic COVID-19, laboratory-confirmed SARS-CoV-2 infection
Grau-Pujol 2021 [22]	Spain	RCT (double-blind)	269	39.9	26.8	Adult healthcare workers working at least 3 days a week in a trial hospital	PrEP	HCQ (400 mg once daily for 4 days, followed by 400 mg weekly for 6 months; placebo	Laboratory-confirmed SARS-CoV-2 infection or illness compatible with COVID-19 with seroconversion
Shoumann 2021 [23]	Egypt	RCT (open-label)	304	39.1	51.3	Asymptomatic household close contacts to PCR-confirmed COVID-19 people (aged ≥ 16 years)	PEP	Ivermectin (1 dose at day 1 and day 3, dose adjusted by body weight); usual care	COVID-19 (suggestive clinical history with positive contact history, and/or laboratory results, and/or suspicious HRCT findings), symptoms compatible with COVID-19
Garcia-Garcia 2022 [24]	Spain	RCT (double-blind)	314	40.0	18.8	Healthcare workers not having a previous COVID-19 diagnosis and having negative serologic test result before randomization	PrEP	Melatonin (2mg orally before bedtime for 12 weeks); placebo	Laboratory-confirmed SARS-CoV-2 infection
Parvizrad 2021 [25]	Iran	RCT (open-label)	76	34.8	23.7	Healthcare workers working in COVID-19 referral hospitals	PrEP	HCQ (400 mg/week for 8 weeks); usual care	COVID-19 occurrence
Syed 2021 [26]	Pakistan	RCT (single-blind)	200	30.6	54.5	Healthcare workers without COVID-19 symptoms	PrEP	HCQ (400 mg twice a day on day 1 followed by 400 mg weekly), HCQ (400 mg once every 3 weeks), HCQ (200 mg once every 3 weeks); placebo	Laboratory-confirmed SARS-CoV-2 infection
Rojas-Serrano 2021 [27]	Mexico	RCT (double-blind)	127	31.5	42.5	Healthcare workers aged ≥ 18 years, asymptomatic	PrEP	HCQ (200 mg daily for 60 days); placebo	Laboratory-confirmed and symptomatic COVID-19,

						with negative RT-PCR test at baseline			hospitalization for severe COVID-19
Sokhela 2022 [28]	South Africa	RCT (open-label)	828	24.0	51.8	Healthcare workers aged ≥ 18 years, no previous or current SARS-CoV-2 infection, no vaccination against SARS-CoV-2	PrEP	Nitazoxanide (500 mg twice daily for 1 week and 1000 mg twice daily thereafter), sofosbuvir/daclatasvir (400 mg/60 mg once daily for 24 weeks); no intervention	Laboratory-confirmed SARS-CoV-2 infection, laboratory-confirmed and symptomatic COVID-19
McKinnon 2021 [29]	US	RCT (double-blind)	578	44.9	41.9	Asymptomatic healthcare workers aged 18-75 years	PrEP	HCQ (400 mg weekly), HCQ (200 mg daily after a loading dose of 400 mg on day 1); placebo	Laboratory-confirmed SARS-CoV-2 infection, laboratory-confirmed and symptomatic COVID-19
Vijayaraghavan 2021 [30]	India	RCT (open-label)	416	32.1	52.6	Healthcare workers without a history of laboratory-confirmed COVID-19 infection	PrEP	HCQ plus PPE (400 mg twice on day 1, followed by 400 mg once weekly for 12 weeks); PPE	Laboratory-confirmed SARS-CoV-2 infection, hospitalization due to COVID-19, ICU admission, all-cause mortality, need for respiratory support
Polo 2022 [31]	Spain, Bolivia, Venezuela	RCT (double-blind)	907	38.0	37.5	Healthcare workers aged 18-70 years without previous and current SARS-CoV-2 infection	PrEP	HCQ (200 mg once daily for 12 weeks), TDF/FTC (245 mg/200 mg once daily for 12 weeks); placebo	Laboratory-confirmed and symptomatic COVID-19, laboratory-confirmed SARS-CoV-2 infection
Stambouli 2022 [32]	Tunisia	RCT (double-blind)	172	38.4	61.0	Healthcare workers aged 20-65 years who did not have COVID-19 symptoms and positive SARS-CoV-2 laboratory test results	PrEP	Doxycycline (100 mg daily) and zinc (15 mg daily) for 6 weeks, doxycycline only; placebo	Laboratory-confirmed SARS-CoV-2 infection
Mikhaylov 2022 [33]	Russia	RCT (open-label)	50	40.6	42.0	Healthcare workers aged ≥ 18 years without previous and current SARS-CoV-2 infection	PrEP	Bromhexine hydrochloride (8 mg 3 times daily); no intervention	Laboratory-confirmed SARS-CoV-2 infection, moderate COVID-19, severe COVID-19 with hospitalization
Angkasekwinai 2022 [34]	Thailand	RCT (double-blind)	536	37.6	42.2	Participants aged ≥ 18 years without previous and current SARS-CoV-2 infection	PrEP	Ivermectin (400-600 µg/kg/d) for 3 days; placebo	Laboratory-confirmed SARS-CoV-2 infection
Chahla 2021 [35]	Argentina	RCT (open-label)	234	38.5	42.7	Healthcare workers aged 18-60 years without presenting COVID-19 related symptoms	PrEP	Ivermectin (2 tablets of 6 mg every 7 days) plus iota-carrageenan (6 sprays daily for 4 weeks); no intervention	COVID-19 diagnosis
Blanc 2021 [36]	France	Test-negative case-control	179	84.1	31.8	Elderly patients who underwent nasopharyngeal swab testing for SARS-CoV-2	PrEP	PPI, ACEi, ARB, statin, NSAID, insulin, metformin,	Laboratory-confirmed SARS-CoV-2 infection

								paracetamol, antipsychotics, OAD	
Yang 2020 [37]	China	Case-control	164	37.0	38.4	In-service health professionals	PrEP	Arbidol (200 mg daily, taken within 2 weeks before first symptom)	Laboratory-confirmed SARS-CoV-2 infection, hospitalization
Liu 2020 [38]	China	Retrospective cohort	435	NA	6.2	Medical staffers	PrEP and PEP	Thymosin drugs; control	Laboratory-confirmed and symptomatic COVID-19
Shabani 2021 [39]	Iran	Quasi-experimental trial	113	42.1	48.7	Adult household close contacts to confirmed COVID-19 people at a distance of < 6 ft for > 10 minutes	PEP	HCQ (200 mg 3 times daily for 1 week); control	Laboratory-confirmed SARS-CoV-2 infection, symptoms compatible with COVID-19
Kamstrup 2021 [40]	Denmark	Retrospective cohort	60334	57.4	20.4	All people residing in Denmark	PrEP	HCQ; control	Laboratory-confirmed SARS-CoV-2 infection, hospitalization
Zhang 2020 [41]	China	Retrospective cohort	66	40.5	43.9	Household close contacts to PCR-confirmed COVID-19 people	PEP	Arbidol; control	Laboratory-confirmed and symptomatic COVID-19
			124	34.3	18.5	Healthcare workers who had close contact to PCR-confirmed COVID-19 people			
Gendelman 2020 [42]	Israel	Test-negative case-control	14520	37.3	52.6	All individuals tested for SARS-CoV-2, including people returning from abroad travels or close contacts to a confirmed or probable COVID-19 cases in the last 14 days	PrEP	HCQ, colchicine	Laboratory-confirmed SARS-CoV-2 infection
Bae 2021 [43]	South Korea	Retrospective cohort	3711	57.2	18.0	Adults who underwent RT-PCR for SARS-CoV-2	PrEP	HCQ (median prescribed daily dose: 200 mg); control	Laboratory-confirmed SARS-CoV-2 infection, death due to COVID-19
Ferreira 2020 [44]	Portugal	Test-negative case-control	360304	50.9	39.0	All individuals underwent RT-PCR for SARS-CoV-2	PrEP	HCQ (at least 2 grams of HCQ per month on average)	Laboratory-confirmed SARS-CoV-2 infection
Dhibar 2020 [45]	India	Clinical trial (open-label)	317	37.2	54.9	Asymptomatic adults who had undertaken international travel in the last 2 weeks or had direct contact with a confirmed COVID-19 case	PEP	HCQ (400 mg every 12 hours on day 1, followed by 400 mg once weekly for 3 weeks); usual care	Laboratory-confirmed SARS-CoV-2 infection or illness compatible with COVID-19, laboratory-confirmed SARS-CoV-2 infection, symptoms compatible with COVID-19, moderate-to-severe COVID-19
Zhou 2020 [46]	US	Test-negative case-control	26779	NA	40.9	Individuals tested for SARS-CoV-2	PrEP	Melatonin, carvedilol	Laboratory-confirmed SARS-CoV-2 infection
Ozturk 2021 [47]	Turkey	Retrospective	508	35.9	35.4	Healthcare personnel tested for SARS-CoV-2	PrEP	HCQ; control	COVID-19 (by PCR, and/or symptoms, and/or chest CT)

		observational study							
Svensson 2021 [48]	Sweden	Case-control	11946	62.0	74.9	Case: patients with severe COVID-19 admitted to the ICU requiring invasive mechanical ventilation Control: randomly selected from the Swedish Population Register	PrEP	ARB, ACEi, insulin, biguanides, glitazones, DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors, meglitinides, CCB, diuretics, statin, aspirin, other antiplatelets, warfarin, NOAC	ICU admission due to COVID-19, severe COVID-19 requiring mechanical ventilation
Huh 2020 [49]	South Korea	Test-negative case-control	44046	47.3	40.5	All adults who tested for COVID-19	PrEP	ARB, ACEi, metformin, thiazolidinedione, statin, NSAID, HCQ, azithromycin, mycophenolate, amiodarone, camostat, ciclesonide	Laboratory-confirmed SARS-CoV-2 infection, severe disease
Khider 2020 [50]	France	Prospective cohort	96	65.1	59.4	All consecutive patients aged > 18 years, fulfilling hospitalization criteria or direct in-patient referral, with an infectious syndrome suspect of COVID-19	PrEP	Statin, OAD, insulin, beta-blocker, CCB, ACEi or ARB, diuretics, central acting agent, anticoagulants; control	Laboratory-confirmed SARS-CoV-2 infection, circulating endothelial cells level
Fillmore 2021 [51]	US	Retrospective cohort	944127	64.0	88.4	Veterans with at least one SARS-CoV-2 test result	PrEP	Disulfiram; control	Laboratory-confirmed SARS-CoV-2 infection, ICU admission, mechanical ventilation, death
Chatterjee 2020 [52]	India	Test-negative case-control	751	34.1	54.2	Healthcare workers who tested for SARS-CoV-2	PrEP	HCQ	Laboratory-confirmed SARS-CoV-2 infection
Bergqvist 2021 [53]	Sweden	Retrospective cohort	963876	60.3	48.4	All individuals aged ≥ 45 years residing in Stockholm	PrEP	Statin; control	Death from COVID-19
Armstrong 2021 [54]	US	Retrospective cohort	9101	Mostly 30-50 years	54.7	Household close contacts	PrEP	ACEi/ARB, ACEi, ARB; control	Laboratory-confirmed SARS-CoV-2 infection
Dinesh 2021 [55]	India	Prospective cohort	2727	Mostly ≤ 45 years	53.3	Healthcare workers who were likely to be exposed to COVID-19 cases	PrEP	HCQ (400 mg twice on day 1, followed by 400 mg weekly); control	Laboratory-confirmed SARS-CoV-2 infection
Loader 2021 [56]	Sweden	Retrospective cohort	164655	64.0	49.9	All residents of Sweden in monotherapy with an antihypertensive drug	PrEP	ACEi, ARB; CCB or TZD	Hospitalization, death due to COVID-19
Vivanco-Hidalgo 2021 [57]	Spain	Prospective cohort	20238	57.0	15.8	All population in Catalonia	PrEP	CQ/HCQ; control	SARS-CoV-2 infection or COVID-19 diagnosis, hospitalization

Morgenstern 2021 [58]	Dominican Republic	Retrospective cohort	542	35.2	21.0	Adult healthcare workers who adhered to the ivermectin prophylaxis program	PrEP	Ivermectin (weekly dose of 0.2 mg/kg); control	Laboratory-confirmed and symptomatic COVID-19, deterioration, death
Dubina 2021 [59]	Russia	Prospective cohort	367	27.0	37.3	Healthy healthcare workers who deliver care and services to COVID-19 patients	PrEP	Glutathione and inosine; control	Laboratory-confirmed SARS-CoV-2 infection
Perrella 2021 [60]	Italy	Case-control	Not retrievable	NA	NA	Case: tested positive for SARS-CoV-2 Control: randomly selected from the targeted population	PrEP	HCQ	Laboratory-confirmed SARS-CoV-2 infection
Khurana 2021 [61]	India	Test-negative case-control	181	35.2	64.1	Healthcare workers who tested for SARS-CoV-2	PrEP	HCQ (full course: 7 weeks); not taken or incomplete course	Laboratory-confirmed SARS-CoV-2 infection
Behera 2021 (1) [62]	India	Prospective cohort	3532	30.6	67.6	Healthcare workers	PrEP	Ivermectin (one dose of 300 µg/kg), ivermectin (two doses of 300 µg/kg taken 72 hours apart); control	Laboratory-confirmed SARS-CoV-2 infection
Dev 2021 [63]	India	Test-negative case-control	759	31.3	64.2	Healthcare workers who tested for SARS-CoV-2	PrEP	HCQ	Laboratory-confirmed SARS-CoV-2 infection
Kumar 2020 [64]	India	Retrospective observational study	50	28.7	44.0	Healthcare workers who were quarantined after exposure to confirmed or suspected COVID-19 cases or due to influenza-like symptoms	PrEP	HCQ; control	Laboratory-confirmed SARS-CoV-2 infection
Hippisley-Cox 2020 [65]	England	Prospective cohort	8275949	48.5	49.7	All patients aged 20-99 years	PrEP	ACEi, ARB; control	Laboratory-confirmed SARS-CoV-2 infection, ICU admission
Behera 2021 (2) [66]	India	Test-negative case-control	372	29.2	67.2	Healthcare workers who tested for SARS-CoV-2	PrEP	Ivermectin (300 µg/kg on day 1 and day 4, followed by 300 µg/kg once monthly), HCQ	Laboratory-confirmed SARS-CoV-2 infection
Oh 2021 [67]	South Korea	Retrospective cohort	34312	NA	36.2	Individuals aged ≥ 20 years	PrEP	Statin; non-continuous or non-users	Laboratory-confirmed SARS-CoV-2 infection, death in hospital
Esposti 2021 [68]	Italy	Retrospective cohort	126370	73.4	7.1	Health-assisted individuals of the local health units	PrEP	Amino-bisphosphonates; control	Hospitalization, ICU admission, all-cause death
Mancia 2020 [69]	Italy	Case-control	37031	68.0	63.1	Case: patients with SARS-CoV-2 infection Control: matched beneficiaries of the Regional Health Service	PrEP	ACEi, ARB, CCB, beta-blockers, OAD, insulin, OAC, NSAID	COVID-19 diagnosis

Reynolds 2020 [70]	US	Retrospective cohort	12594	49.0	41.5	All patients in the New York University Langone Health electronic health record with COVID-19 test results	PrEP	ACEi, ARB, beta-blockers, CCB, diuretics; non-user	Laboratory-confirmed SARS-CoV-2 infection, severe COVID-19 illness
Hector 2020 [71]	Argentina	Pilot clinical trial	229	NA	NA	Healthcare workers aged ≥ 18 years without previous and current SARS-CoV-2 infection	PrEP	Ivermectin plus iota-carrageenan; no intervention	Laboratory-confirmed SARS-CoV-2 infection
Botton 2022 [72]	France	Retrospective cohort	31072642	73.0	44.9	Patients aged ≥ 40 years without known cardiovascular diseases	PrEP	Low-dose aspirin (< 320 mg); non-user	Hospitalization for COVID-19, death for COVID-19
Fung 2021 [73]	US	Case-control	2240875	NA	NA	Case: patients aged ≥ 65 years with at least one record of COVID-19 diagnosis Control: matched non-COVID-19 people	PrEP	ACEi, ARB, statin, warfarin, famotidine, HCQ	COVID-19 diagnosis, COVID-19 hospitalization, death after a COVID-19 diagnosis
Bouillon 2022 [74]	France	Matched-cohort	4116498	68.7	46.6	Individuals aged ≥ 40 years receiving at least 1 health care reimbursement after February 15, 2019	PrEP	Statin; non-user	Hospitalization for COVID-19, in-hospital death from COVID-19
Rao 2021 [75]	India	Prospective cohort	1294	31.0	39.0	Healthcare workers < 55 years, working in 6-hour long daily shifts for 7 consecutive days	PrEP	HCQ; non-user	Laboratory-confirmed SARS-CoV-2 infection
Kadnur 2022 [76]	India	Prospective cohort	358	31.2	60.3	Healthcare workers	PrEP	HCQ; non-user	Laboratory-confirmed SARS-CoV-2 infection
Son 2021 [77]	South Korea	Case-control	11475	NA	36.7	Case: patients ≥ 20 years tested positive for SARS-CoV-2 with full demographic data Control: matched to case	PrEP	Aspirin; non-user	Laboratory-confirmed SARS-CoV-2 infection, composite of complications, death
De Abajo 2020 [78]	Spain	Case-population	12529	69.1	61.0	Case: patients aged ≥ 18 tested positive for SARS-CoV-2 who were admitted to hospital Control: matched to case	PrEP	ACEi, ARB; other antihypertensive drugs	Hospitalization with COVID-19

Abbreviations: RCT, randomized controlled trial; PrEP, pre-exposure prophylaxis; PEP, post-exposure prophylaxis; HCQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ACEi, angiotensin converting enzyme inhibitors; PPE, personal protective equipment; ARB, angiotensin receptor blocker; PPI, proton pump inhibitors; OAD, oral antidiabetic drugs; CCB, calcium channel blockers; TZD, thiazolidinediones; NSAID, non-steroidal anti-inflammatory drug; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitor; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SGLT-2 inhibitors, sodium-glucose co-transporter-2 inhibitors; NOAC, new oral anticoagulants; OAC, oral anticoagulants; RT-PCR, reverse transcription- polymerase chain reaction; HRCT, high-resolution computed tomography; CT, computed tomography; NA, not available

Table S3 Summary of effect measures from included articles

Study ID	Component	Comparator	Type of prophylaxis	Outcome	No. of events in exposed (case)	No. of events in unexposed (control)	Adjusted measure (95% CI)	Favorable or not
HCQ or CQ								
Abella 2020 [15]	HCQ	Placebo	PrEP	Laboratory-confirmed infection within 8 weeks	4 / 64 (6.25%)	4 / 61 (6.56%)	/	NS
Barnabas 2020 [16]	HCQ	Vitamin C	PEP	Laboratory-confirmed infection on Day 14	53 / 353 (15.01%)	45 / 336 (13.39%)	aHR: 1.10 (0.73-1.66)	NS
				Laboratory-confirmed infection on Day 28	58 / 353 (16.43%)	48 / 336 (14.29%)	aHR: 1.16 (0.77-1.73)	NS
				Symptomatic COVID-19 disease	43 / 353 (12.18%)	33 / 336 (9.82%)	aHR: 1.27 (0.79-2.03)	NS
Boulware 2020 [11]	HCQ	Placebo	PEP	Laboratory-confirmed infection or illness compatible with COVID-19 within 14 days	49 / 414 (11.84%)	58 / 407 (14.25%)	/	NS
				Laboratory-confirmed infection within 14 days	11 / 414 (2.66%)	9 / 407 (2.21%)	/	NS
				Symptomatic COVID-19 disease	48 / 414 (11.59%)	55/ 407 (13.51%)	/	NS
				Hospitalization	1 / 414 (0.24%)	1 / 407 (0.25%)	/	NS
Rajasingham 2020 [17]	HCQ (1 week)	Placebo	PrEP	Laboratory-confirmed infection or illness compatible with COVID-19 within 12 weeks	29 / 494 (5.87%)	39 / 494 (7.89%)	HR: 0.72 (0.44-1.16)	NS
	HCQ (2 week)	Placebo	PrEP	Laboratory-confirmed infection or illness compatible with COVID-19 within 12 weeks	29 / 495 (5.86%)	39 / 494 (7.89%)	HR: 0.74 (0.46-1.19)	NS
	HCQ (1 week)	Placebo	PrEP	Laboratory-confirmed infection within 12 weeks	4 / 494 (0.81%)	6 / 494 (1.21%)	HR: 0.65 (0.18-2.32)	NS
	HCQ (2 week)	Placebo	PrEP	Laboratory-confirmed infection within 12 weeks	7 / 495 (1.41%)	6 / 494 (1.21%)	HR: 1.18 (0.40-3.51)	NS
	HCQ (1 week)	Placebo	PrEP	Probable COVID-19 with symptoms	29 / 494 (5.87%)	38 / 494 (7.69%)	HR: 0.73 (0.45-1.19)	NS
	HCQ (2 week)	Placebo	PrEP	Probable COVID-19 with symptoms	28 / 495 (5.66%)	38 / 494 (7.69%)	HR: 0.74 (0.45-1.20)	NS
	HCQ (1 week)	Placebo	PrEP	Hospitalization	3 / 494 (0.61%)	9 / 494 (1.82%)	/	NS
	HCQ (2 week)	Placebo	PrEP	Hospitalization	8 / 495 (1.62%)	9 / 494 (1.82%)	/	NS
Mitja 2020 [18]	HCQ	Usual care	PEP	Laboratory-confirmed and symptomatic COVID-19 within 14 days	29 / 958 (3.03%)	45 / 1042 (4.32%)	RR: 0.68 (0.34-1.34)	NS
				Laboratory-confirmed infection or illness compatible with COVID-19 within 14 days	179 / 958 (18.68%)	185 / 1042 (17.75%)	RR: 1.03 (0.77-1.38)	NS
				Laboratory-confirmed infection within 14 days	58 / 958 (6.05%)	67 / 1042 (6.43%)	/	NS
				Symptoms compatible with COVID-19	144 / 958 (15.03%)	150 / 1042 (14.40%)	/	NS

Seet 2021 [20]	HCQ	Vitamin C	PrEP	Laboratory-confirmed infection within 42 days	212 / 432 (49.07%)	433 / 619 (69.95%)	RR: 0.70 (0.44-0.97)	**Yes**
				Acute respiratory symptoms	31 / 432 (7.18%)	69 / 619 (11.15%)	/	NS
				Symptomatic COVID-19	29 / 212 (13.68%)	64 / 433 (14.78%)	/	NS
				Pneumonia requiring hospitalization	0 / 432 (0.00%)	0 / 619 (0.00%)	/	NS
				Death	0 / 432 (0.00%)	0 / 619 (0.00%)	/	NS
Shabani 2021 [39]	HCQ	Control	PEP	Laboratory-confirmed infection on Day 7	7 / 51 (13.73%)	7 / 62 (11.29%)	HR: 1.50 (1.37-1.64)	NS
				COVID-19 symptoms on Day 7	2 / 51 (3.92%)	3 / 62 (4.84%)	/	NS
Kamstrup 2021 [40]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	188 / 5488 (3.43%)	2040 / 54846 (3.72%)	aHR: 0.90 (0.76-1.07)	NS
				Hospitalization within 14 days of SARS-CoV-2 positivity	/	/	OR: 1.44 (0.78-2.65)	NS
Gendelman 2020 [42]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	3 / 1317 (0.23%)	33 / 13203 (0.25%)	/	NS
Bae 2021 [43]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	16 / 743 (2.15%)	91 / 2968 (3.07%)	aOR: 0.69 (0.34-1.38)	NS
				Death due to COVID-19 among infected	0 / 16 (0.00%)	0 / 91 (0.00%)	/	NS
Ferreira 2020 [44]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	77 / 26815 (0.29%)	1215 / 333489 (0.36%)	aOR: 0.51 (0.37-0.70)	**Yes**
Dhibar 2020 [45]	HCQ	Non-user	PEP	Laboratory-confirmed infection or illness compatible with COVID-19	14 / 132 (10.61%)	36 / 185 (19.46%)	RR: 0.59 (0.33-1.05)	NS
				Laboratory-confirmed infection	10 / 132 (7.58%)	28 / 185 (15.14%)	RR: 0.50 (0.25-0.99)	**Yes**
				New-onset symptoms with COVID-19	6 / 132 (4.55%)	15 / 185 (8.11%)	/	NS
				Moderate to severe COVID-19	0 / 132 (0.00%)	0 / 185 (0.00%)	/	NS
Grau-Pujol 2021 [22]	HCQ	Placebo	PrEP	Laboratory-confirmed infection or illness compatible with COVID-19 with seroconversion	1 / 137 (0.73%)	1 / 116 (0.86%)	/	NS
Ozturk 2021 [47]	HCQ	Non-user	PrEP	COVID-19 diagnosis by PCR, and/or symptoms, and/or chest CT	15 / 152 (9.87%)	25 / 356 (7.02%)	/	NS
Huh 2020 [49]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	17 / 7341 (0.23%)	105 / 36705 (0.29%)	aOR: 0.94 (0.53-1.66)	NS
				Severe disease among infected	5 / 878 (0.57%)	3 / 1927 (0.16%)	aOR: 3.51 (0.76-16.22)	NS
Chatterjee 2020 [52]	HCQ (2-3 loading dose)	Non-user	PrEP	Laboratory-confirmed infection	70 / 378 (18.52%)	37 / 373 (9.92%)	aOR: 2.34 (1.23-4.83)	**No**
	HCQ (4-5 loading dose)	Non-user	PrEP	Laboratory-confirmed infection	42 / 378 (11.11%)	67 / 373 (17.96%)	aOR: 0.44 (0.22-0.88)	**Yes**
	HCQ (≥ 6 loading dose)	Non-user	PrEP	Laboratory-confirmed infection	12 / 378 (3.17%)	56 / 373 (15.01%)	aOR: 0.04 (0.01-0.16)	**Yes**
Dinesh 2021 [55]	HCQ (2-3 week)	Non-user	PrEP	Laboratory-confirmed infection	80 / 1119 (7.15%)	101 / 1608 (6.28%)	aOR: 0.66 (0.45-0.96)	**Yes**
	HCQ (4-5 week)	Non-user	PrEP	Laboratory-confirmed infection	88 / 1119 (7.86%)	97 / 1608 (6.03%)	aOR: 0.52 (0.35-0.76)	**Yes**
	HCQ (≥ 6 week)	Non-user	PrEP	Laboratory-confirmed infection	247 / 1119 (22.07%)	370 / 1608 (23.01%)	aOR: 0.28 (0.21-0.37)	**Yes**

Vivanco-Hidalgo 2021 [57]	CQ/HCQ	Non-user	PrEP	SARS-CoV-2 infection or COVID-19 diagnosis	97 / 6746 (1.44%)	183 / 13492 (1.36%)	aHR: 1.08 (0.83-1.44)	NS
				Hospitalization due to COVID-19	40 / 6746 (0.59%)	50 / 13492 (0.37%)	aHR: 1.46 (0.91-2.34)	NS
Perrella 2021 [60]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	/	/	aOR: 5.80 (2.82-11.93)	**Yes**
Khurana 2021 [61]	HCQ (full course)	Non- or incomplete user	PrEP	Laboratory-confirmed infection	6 / 94 (6.38%)	16 / 87 (18.39%)	/	**Yes**
Dev 2021 [63]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	155 / 506 (30.63%)	105 / 253 (41.50%)	aOR: 0.92 (0.86-0.99)	**Yes**
Kumar 2020 [64]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	0 / 3 (0.00%)	7 / 47 (14.89%)	/	NS
Behera 2021 (2) [66]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	7 / 186 (3.76%)	12 / 186 (6.45%)	aOR: 0.56 (0.19-1.63)	NS
Parvizrad 2021 [25]	HCQ	Usual care	PrEP	COVID-19 occurrence	3 / 32 (9.38%)	4 / 44 (9.09%)	aRR: 0.96 (0.83-1.11)	NS
Syed 2021 [26]	HCQ (400 mg weekly)	Placebo	PrEP	Laboratory-confirmed infection	15 / 48 (31.25%)	7 / 46 (15.22%)	/	/ (4 groups comparison, NS)
	HCQ (400 mg every 3 weeks)	Placebo	PrEP	Laboratory-confirmed infection	19 / 51 (37.25%)	7 / 46 (15.22%)	/	/
	HCQ (200 mg every 3 weeks)	Placebo	PrEP	Laboratory-confirmed infection	8 / 55 (14.54%)	7 / 46 (15.22%)	/	/
Rojas-Serrano 2021 [27]	HCQ	Placebo	PrEP	Laboratory-confirmed and symptomatic COVID-19	1 / 62 (1.61%)	6 / 65 (9.23%)	aHR: 0.18 (0.21-1.59)	NS
				Hospitalization for COVID-19	0 / 1 (0.00%)	0 / 6 (0.00%)	/	NS
McKinnon 2021 [29]	HCQ (400 mg weekly)	Placebo	PrEP	Laboratory-confirmed infection	1 / 199 (0.50%)	2 / 191 (1.05%)	/	NS
				Laboratory-confirmed and symptomatic COVID-19	1 / 199 (0.50%)	1 / 191 (0.52%)	/	NS
	HCQ (200 mg daily)	Placebo	PrEP	Laboratory-confirmed infection	1 / 188 (0.53%)	2 / 191 (1.05%)	/	NS
				Laboratory-confirmed and symptomatic COVID-19	1 / 188 (0.53%)	1 / 191 (0.52%)	/	NS
Vijayaraghavan 2021 [30]	HCQ plus PPE	PPE	PrEP	Laboratory-confirmed infection	11 / 211 (5.21%)	12 / 203 (5.91%)	aOR: 0.85 (0.35-2.07)	NS
				Laboratory-confirmed infection or illness compatible with COVID-19	12 / 211 (5.69%)	12 / 203 (5.91%)	aOR: 0.94 (0.39-2.24)	NS
				Hospitalization due to COVID-19	1 / 211 (0.47%)	2 / 203 (0.98%)	/	NS
				ICU admission	1 / 211 (0.47%)	0 / 203 (0.00%)	/	NS
				All-cause mortality	0 / 211 (0.00%)	0 / 203 (0.00%)	/	NS
Polo 2022 [31]	HCQ	Placebo	PrEP	Laboratory-confirmed and symptomatic COVID-19	3 / 231 (1.30%)	5 / 223 (2.24%)	RR: 0.49 (0.00-2.29)	NS
				Laboratory-confirmed infection	21 / 231 (9.09%)	23 / 223 (10.31%)	RR: 0.73 (0.41-1.38)	NS
Fung 2021 [73]	HCQ	Non-user	PrEP	COVID-19 diagnosis	2879 / 374299 (0.77%)	11846 / 1866576 (0.63%)	aHR: 0.95 (0.91-1.00)	NS
				COVID-19 hospitalization	/	/	aHR: 1.06 (0.98-1.14)	NS

				Death after a COVID-19 diagnosis	/	/	aHR: 1.08 (0.95-1.24)	NS
Rao 2021 [75]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	16 / 273 (5.86%)	67 / 1021 (6.56%)	RR: 0.89 (0.53-1.52)	NS
Kadnur 2022 [76]	HCQ	Non-user	PrEP	Laboratory-confirmed infection	10 / 258 (3.88%)	15 / 100 (15.00%)	aOR: 0.34 (0.13-0.83)	**Yes**
Ivermectin								
Seet 2021 [20]	Ivermectin	Vitamin C	PrEP	Laboratory-confirmed infection within 42 days	398 / 617 (64.51%)	433 / 619 (69.95%)	RR: 0.93 (0.71-1.18)	NS
				Acute respiratory symptoms	35 / 617 (5.67%)	69 / 619 (11.15%)	/	**Yes**
				Symptomatic COVID-19	32 / 398 (8.04%)	64 / 433 (14.78%)	/	**Yes**
				Pneumonia requiring hospitalization	0 / 617 (0.00%)	0 / 619 (0.00%)	/	NS
				Death	0 / 617 (0.00%)	0 / 619 (0.00%)	/	NS
Shouman 2021 [23]	Ivermectin	Placebo	PEP	COVID-19 by Day 14 (suggestive clinical history with positive contact history, and/or laboratory results, and/or suspicious HRCT findings)	15 / 203 (7.39%)	59 / 101 (58.42%)	aOR: 11.44 (4.44-29.48)	**Yes**
Morgenstern 2021 [58]	Ivermectin	Non-user	PrEP	Laboratory-confirmed and symptomatic COVID-19 within 28 days	5 / 271 (1.85%)	18 / 271 (6.64%)	aHR: 0.26 (0.10-0.71)	**Yes**
				Deterioration	0 / 271 (0.00%)	2 / 271 (0.74%)	/	NS
				Death	0 / 271 (0.00%)	0 / 271 (0.00%)	/	NS
Behera 2021 (1) [62]	Ivermectin (single-dose)	Non-user	PrEP	Laboratory-confirmed infection	23 / 186 (12.37%)	133 / 1147 (11.60%)	aRR: 1.04 (0.69-1.58)	NS
	Ivermectin (double-dose)	Non-user	PrEP	Laboratory-confirmed infection	45 / 2199 (2.05%)	133 / 1147 (11.60%)	aRR: 0.17 (0.12-0.23)	**Yes**
Behera 2021 (2) [66]	Ivermectin (single-dose)	Non-user	PrEP	Laboratory-confirmed infection	/	/	aOR: 1.30 (0.44-3.85)	NS
	Ivermectin (≥ 2 doses)	Non-user	PrEP	Laboratory-confirmed infection	/	/	aOR: 0.27 (0.15-0.51)	**Yes**
Angkasekwinai 2022 [34]	Ivermectin	Placebo	PrEP	Laboratory-confirmed infection within 14 days	18 / 259 (6.95%)	19 / 277 (6.96%)	/	NS
Chahla 2021 [35]	Ivermectin plus iota-carrageenan	No intervention	PrEP	COVID diagnosis	4 / 117 (3.42%)	25 / 117 (21.37%)	/	**Yes**
Hector 2020 [71]	Ivermectin plus iota-carrageenan	No intervention	PrEP	Laboratory-confirmed infection within 14 days	0 / 131 (0.00%)	11 / 98 (11.22%)	/	/
ARB or ACEi								
Blanc 2021 [36]	ARB	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 1.32 (0.58-2.98)	NS
Svensson 2021 [48]	ARB	Non-user	PrEP	ICU admission due to COVID-19	218 / 1086 (20.07%)	1694 / 10860 (15.60%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 1.07 (0.88-1.30)	NS
Huh 2020 [49]	ARB	Non-user	PrEP	Laboratory-confirmed infection	835 / 7341 (11.37%)	4106 / 36705 (11.19%)	aOR: 1.02 (0.90-1.15)	NS
				Severe disease among infected	236 / 878 (26.88%)	384 / 1927 (19.93%)	aOR: 1.11 (0.87-1.42)	NS

Armstrong 2021 [54]	ARB	Non-user	PrEP	Laboratory-confirmed infection	/	/	aOR: 0.58 (0.40-0.84)	**Yes**
Loader 2021 [56]	ARB	CCB or TZD	PrEP	Hospitalization with COVID-19	135 / 68239 (0.20%)	107 / 48418 (0.22%)	aHR: 0.94 (0.70-1.27)	NS
				Death with COVID-19	19 / 68239 (0.03%)	26 / 48418 (0.05%)	aHR: 1.25 (0.63-2.49)	NS
Hippisley-Cox 2020 [65]	ARB	Non-user	PrEP	Laboratory-confirmed infection	1417 / 308881 (0.46%)	18069 / 7967068 (0.23%)	aHR: 0.63 (0.59-0.67)	**Yes**
				ICU admission due to COVID-19	154 / 308881 (0.05%)	1132 / 7967068 (0.01%)	aHR: 1.02 (0.83-1.25)	NS
Mancia 2020 [69]	ARB	Non-user	PrEP	COVID-19 diagnosis	1394 / 6272 (22.22%)	5910 / 30759 (19.21%)	aOR: 0.95 (0.86-1.05)	NS
Reynolds 2020 [70]	ARB	Non-user	PrEP	Laboratory-confirmed infection	778 / 1328 (58.58%)	5116 / 11266 (45.41%)	aOR: 1.00 (0.86-1.15)	NS
				Severe COVID-19 illness	193 / 778 (24.81%)	809 / 5116 (15.81%)	aOR: 0.96 (0.77-1.21)	NS
Fung 2021 [73]	ARB	Non-user	PrEP	COVID-19 diagnosis	83290 / 374299 (22.25%)	421264 / 1866576 (22.57%)	aHR: 0.92 (0.91-0.92)	**Yes**
				COVID-19 hospitalization	/	/	aHR: 0.92 (0.91-0.94)	**Yes**
				Death after a COVID-19 diagnosis	/	/	aHR: 0.85 (0.83-0.87)	**Yes**
De Abajo 2020 [78]	ARB	Other antihypertensive drugs	PrEP	Hospitalization with COVID-19	237 / 1139 (20.81%)	1552 / 11390 (13.62%)	aOR: 1.10 (0.88-1.37)	NS
Blanc 2021 [36]	ACEi	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 1.60 (0.79-3.30)	NS
Svensson 2021 [48]	ACEi	Non-user	PrEP	ICU admission due to COVID-19	168 / 1086 (15.47%)	1310 / 10860 (12.06%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.99 (0.81-1.22)	NS
Huh 2020 [49]	ACEi	Non-user	PrEP	Laboratory-confirmed infection	42 / 7341 (0.57%)	129 / 36705 (0.35%)	aOR: 1.50 (1.00-2.24)	**No**
				Severe disease among infected	12 / 878 (1.37%)	24 / 1927 (1.25%)	aOR: 0.70 (0.33-1.48)	NS
Armstrong 2021 [54]	ACEi	Non-user	PrEP	Laboratory-confirmed infection	/	/	aOR: 0.60 (0.44-0.82)	**Yes**
Loader 2021 [56]	ACEi	CCB or TZD	PrEP	Hospitalization with COVID-19	94 / 47998 (0.20%)	107 / 48418 (0.22%)	aHR: 0.89 (0.64-1.23)	NS
				Death with COVID-19	16 / 47998 (0.03%)	26 / 48418 (0.05%)	aHR: 0.97 (0.48-1.93)	NS
Hippisley-Cox 2020 [65]	ACEi	Non-user	PrEP	Laboratory-confirmed infection	2864 / 645577 (0.44%)	16622 / 7630372 (0.22%)	aHR: 0.71 (0.67-0.74)	**Yes**
				ICU admission due to COVID-19	266 / 645577 (0.04%)	1020 / 7630372 (0.01%)	aHR: 0.89 (0.75-1.06)	NS
Mancia 2020 [69]	ACEi	Non-user	PrEP	COVID-19 diagnosis	1502 / 6272 (23.95%)	6569 / 30759 (21.36%)	aOR: 0.96 (0.87-1.07)	NS
Reynolds 2020 [70]	ACEi	Non-user	PrEP	Laboratory-confirmed infection	627 / 1044 (60.06%)	5267 / 11550 (45.60%)	aOR: 0.92 (0.79-1.08)	NS

				Severe COVID-19 illness	150 / 627 (23.92%)	852 / 5267 (16.18%)	aOR: 0.90 (0.71-1.13)	NS
Fung 2021 [73]	ACEi	Non-user	PrEP	COVID-19 diagnosis	97843 / 374299 (26.14%)	517078 / 1866576 (27.70%)	aHR: 0.91 (0.90-0.92)	**Yes**
				COVID-19 hospitalization	/	/	aHR: 0.98 (0.97-1.00)	**Yes**
				Death after a COVID-19 diagnosis	/	/	aHR: 0.88 (0.86-0.90)	**Yes**
De Abajo 2020 [78]	ACEi	Other antihypertensive drugs	PrEP	Hospitalization with COVID-19	240 / 1139 (21.07%)	2192 / 11390 (19.24%)	aOR: 0.80 (0.64-1.00)	NS
Khider 2020 [50]	ARB or ACEi	Non-user	PrEP	Laboratory-confirmed infection	21 / 66 (31.82%)	9 / 30 (30.00%)	/	NS
Armstrong 2021 [54]	ARB or ACEi	Non-user	PrEP	Laboratory-confirmed infection	280 / 1499 (18.68%)	1140 / 7602 (15.00%)	aOR: 0.60 (0.44-0.81)	**Yes**
Loader 2021 [56]	ARB or ACEi	CCB or TZD	PrEP	Hospitalization with COVID-19	228 / 115684 (0.20%)	107 / 48927 (0.22%)	aHR: 0.92 (0.70-1.22)	NS
				Death with COVID-19	35 / 115684 (0.03%)	29 / 48927 (0.06%)	aHR: 1.22 (0.68-2.19)	NS
Statin								
Blanc 2021 [36]	Statin	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 0.87 (0.39-1.92)	NS
Svensson 2021 [48]	Statin	Non-user	PrEP	ICU admission due to COVID-19	288 / 1086 (26.52%)	2242 / 10860 (20.64%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.84 (0.63-1.13)	NS
Huh 2020 [49]	Statin	Non-user	PrEP	Laboratory-confirmed infection	960 / 7341 (13.08%)	4762 / 36705 (12.97%)	aOR: 0.95 (0.86-1.05)	NS
				Severe disease among infected	267 / 878 (30.41%)	478 / 1927 (24.81%)	aOR: 0.89 (0.72-1.10)	NS
Khider 2020 [50]	Statin	Non-user	PrEP	Laboratory-confirmed infection	13 / 66 (19.70%)	3 / 30 (10.00%)	/	NS
Bergqvist 2021 [53]	Statin	Non-user	PrEP	Death due to COVID-19	765 / 169642 (0.45%)	1780 / 794234 (0.22%)	aHR: 0.88 (0.79-0.97)	**Yes**
Oh 2021 [67]	Statin	Non-user	PrEP	Laboratory-confirmed infection	938 / 17156 (5.47%)	1395 / 17156 (8.13%)	aOR: 0.65 (0.60-0.71)	**Yes**
				Death among infected	/	/	aOR: 0.74 (0.52-1.05)	NS
Fung 2021 [73]	Statin	Non-user	PrEP	COVID-19 diagnosis	187374 / 374299 (50.06%)	915226 / 1866576 (49.03%)	aHR: 0.97 (0.96-0.98)	**Yes**
				COVID-19 hospitalization	/	/	aHR: 0.95 (0.94-0.96)	**Yes**
				Death after a COVID-19 diagnosis	/	/	aHR: 0.81 (0.80-0.83)	**Yes**
Bouillon 2022 [74]	Statin	Non-user	PrEP	Hospitalization for COVID-19	4372 / 2058249 (0.21%)	5024 / 2058249 (0.24%)	aHR: 0.84 (0.81-0.88)	**Yes**
				In-hospital death from COVID-19	734 / 2058249 (0.04%)	914 / 2058249 (0.04%)	aHR: 0.77 (0.69-0.86)	**Yes**
Antivirals								
Labhardt 2021 [21]	LPV/r	Surveillance	PEP	Laboratory-confirmed and symptomatic COVID-19 within 21 days	8 / 175 (4.57%)	7 / 103 (6.80%)	aHR: 0.58 (0.16-2.07)	NS

				Laboratory-confirmed infection within 21 days	12 / 174 (6.90%)	7 / 103 (6.80%)	aHR: 1.02 (0.34-3.07)	NS
Yang 2020 [37]	Arbidol	Non-user	PrEP	Laboratory-confirmed infection	19 / 82 (23.17%)	48 / 82 (58.54%)	OR: 0.21 (0.11-0.42)	**Yes**
				Hospitalization among infected	5 / 34 (14.71%)	12 / 34 (35.29%)	/	NS
Zhang 2020 [41]	Arbidol	Non-user	PEP	COVID-19 determined by RT-PCR and the co-existence of viral pneumonia on chest CT (family close contact)	1 / 45 (2.22%)	12 / 21 (57.14%)	aHR: 0.03 (0.003-0.209)	**Yes**
				COVID-19 determined by RT-PCR and the co-existence of viral pneumonia on chest CT (healthcare workers)	1 / 55 (1.82%)	7 / 69 (10.14%)	aHR: 0.06 (0.005-0.662)	**Yes**
Polo 2022 [31]	TDF/FTC	Placebo	PrEP	Laboratory-confirmed and symptomatic COVID-19	3 / 233 (1.29%)	5 / 223 (2.24%)	RR: 0.34 (0.00-2.06)	NS
				Laboratory-confirmed infection	20 / 233 (8.58%)	23 / 223 (10.31%)	RR: 0.81 (0.44-1.49)	NS
Sokhela 2022 [28]	Sofosbuvir/daclatasvir	No intervention	PrEP	Laboratory-confirmed infection	87 / 217 (40.09%)	111 / 265 (41.89%)	RR: 1.51 (0.87-1.52)	NS
				Laboratory-confirmed and symptomatic COVID-19	18 / 217 (8.29%)	37 / 265 (13.96%)	RR: 0.71 (0.41-1.25)	NS
Antidiabetics								
Blanc 2021 [36]	Insulin	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 2.38 (0.97-6.46)	NS
Svensson 2021 [48]	Insulin	Non-user	PrEP	ICU admission due to COVID-19	80 / 1086 (7.37%)	391 / 10860 (3.60%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.85 (0.62-1.16)	NS
Khider 2020 [50]	Insulin	Non-user	PrEP	Laboratory-confirmed infection	5 / 66 (7.58%)	2 / 30 (6.67%)	/	NS
Mancia 2020 [69]	Insulin	Non-user	PrEP	COVID-19 diagnosis	338 / 6272 (5.39%)	863 / 30759 (2.80%)	aOR: 1.37 (1.19-1.58)	**No**
Blanc 2021 [36]	Metformin	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 2.34 (0.83-7.37)	NS
Huh 2020 [49]	Metformin	Non-user	PrEP	Laboratory-confirmed infection	329 / 7341 (4.48%)	1545 / 36705 (4.21%)	aOR: 0.96 (0.82-1.12)	NS
				Severe disease among infected	104 / 878 (11.85%)	168 / 1927 (8.72%)	aOR: 1.01 (0.75-1.37)	NS
Blanc 2021 [36]	OADs	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 1.74 (0.70-4.54)	NS
Khider 2020 [50]	OADs	Non-user	PrEP	Laboratory-confirmed infection	9 / 66 (13.64%)	2 / 30 (6.67%)	/	NS
Mancia 2020 [69]	OADs	Non-user	PrEP	COVID-19 diagnosis	861 / 6272 (13.73%)	3158 / 30759 (10.27%)	aOR: 1.07 (0.97-1.17)	NS
Svensson 2021 [48]	Biguanides	Non-user	PrEP	ICU admission due to COVID-19	200 / 1086 (18.42%)	855 / 10860 (7.87%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 1.40 (1.01-1.94)	**No**
	Sulfonylureas	Non-user	PrEP	ICU admission due to COVID-19	28 / 1086 (2.58%)	93 / 10860 (0.86%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 1.17 (0.72-1.91)	NS
	Glitazones	Non-user	PrEP	ICU admission due to COVID-19	6 / 1086 (0.55%)	10 / 10860 (0.09%)	/	NS

				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 2.86 (1.04-7.85)	**No**
	DPP-4 inhibitors	Non-user	PrEP	ICU admission due to COVID-19	44 / 1086 (4.05%)	210 / 10860 (1.93%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.91 (0.62-1.33)	NS
	GLP-1 RAs	Non-user	PrEP	ICU admission due to COVID-19	37 / 1086 (3.41%)	184 / 10860 (1.69%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 1.24 (0.82-1.87)	NS
	SGLT-2 inhibitors	Non-user	PrEP	ICU admission due to COVID-19	46 / 1086 (4.24%)	184 / 10860 (1.69%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 1.20 (0.82-1.74)	NS
	Meglitinides	Non-user	PrEP	ICU admission due to COVID-19	4 / 1086 (0.37%)	34 / 10860 (0.31%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.55 (0.19-1.61)	NS
Huh 2020 [49]	Thiazolidinedione	Non-user	PrEP	Laboratory-confirmed infection	51 / 7341 (0.69%)	234 / 36705 (0.64%)	aOR: 1.17 (0.83-1.65)	NS
				Severe disease among infected	17 / 878 (1.94%)	30 / 1927 (1.56%)	aOR: 0.96 (0.51-1.81)	NS
Antihypertensives								
Zhou 2020 [46]	Carvedilol	Non-user	PrEP	Laboratory-confirmed infection	/	/	aOR: 0.74 (0.56-0.97)	**Yes**
Svensson 2021 [48]	Beta-blocker	Non-user	PrEP	ICU admission due to COVID-19	222 / 1086 (20.44%)	1849 / 10860 (17.03%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.90 (0.73-1.11)	NS
Khider 2020 [50]	Beta-blocker	Non-user	PrEP	Laboratory-confirmed infection	8 / 66 (12.12%)	5 / 30 (16.67%)	/	NS
Mancia 2020 [69]	Beta-blocker	Non-user	PrEP	COVID-19 diagnosis	1826 / 6272 (29.11%)	7123 / 30759 (23.16%)	aOR: 0.99 (0.91-1.08)	NS
Reynolds 2020 [70]	Beta-blocker	Non-user	PrEP	Laboratory-confirmed infection	912 / 1686 (54.09%)	4982 / 10908 (45.67%)	aOR: 0.87 (0.77-0.99)	**Yes**
				Severe COVID-19 illness	230 / 912 (25.22%)	772 / 4982 (15.50%)	aOR: 0.92 (0.75-1.11)	NS
Svensson 2021 [48]	CCB	Non-user	PrEP	ICU admission due to COVID-19	239 / 1086 (22.01%)	1648 / 10860 (15.17%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 1.25 (1.03-1.52)	**No**
Khider 2020 [50]	CCB	Non-user	PrEP	Laboratory-confirmed infection	13 / 66 (19.70%)	7 / 30 (23.33%)	/	NS
Mancia 2020 [69]	CCB	Non-user	PrEP	COVID-19 diagnosis	1446 / 6272 (23.05%)	5926 / 30759 (19.26%)	aOR: 1.03 (0.95-1.12)	NS
Reynolds 2020 [70]	CCB	Non-user	PrEP	Laboratory-confirmed infection	992 / 1672 (59.33%)	4902 / 10922 (44.88%)	aOR: 1.01 (0.89-1.15)	NS
				Severe COVID-19 illness	263 / 992 (26.51%)	739 / 4902 (15.08%)	aOR: 1.24 (1.02-1.50)	**No**
Svensson 2021 [48]	Diuretics	Non-user	PrEP	ICU admission due to COVID-19	51 / 1086 (4.70%)	522 / 10860 (4.81%)	/	NS

				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.74 (0.53-1.03)	NS
Khider 2020 [50]	Diuretics	Non-user	PrEP	Laboratory-confirmed infection	6 / 66 (9.09%)	3 / 30 (10.00%)	/	NS
Reynolds 2020 [70]	Diuretics	Non-user	PrEP	Laboratory-confirmed infection	551 / 989 (55.71%)	5343 / 11605 (46.04%)	aOR: 0.90 (0.77-1.05)	NS
				Severe COVID-19 illness	120 / 551 (21.78%)	882 / 5343 (16.51%)	aOR: 0.95 (0.74-1.22)	NS
Anticoagulants								
Svensson 2021 [48]	Aspirin	Non-user	PrEP	ICU admission due to COVID-19	136 / 1086 (12.52%)	1103 / 10860 (10.16%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.97 (0.75-1.24)	NS
Botton 2022 [72]	Aspirin	Non-user	PrEP	Hospitalization for COVID-19	5573 / 1542840 (0.36%)	47227 / 29529802 (0.16%)	aHR: 1.03 (1.00-1.06)	**No**
				Death for COVID-19	1804 / 1542840 (0.12%)	10629 / 29529802 (0.04%)	aHR: 1.04 (0.98-1.10)	NS
Son 2021 [77]	Aspirin	Non-user	PrEP	Laboratory-confirmed infection	313 / 3825 (8.18%)	617 / 7650 (8.06%)	aOR: 1.02 (0.87-1.21)	NS
				Composite of complications	77 / 339 (22.71%)	58 / 339 (17.11%)	aOR: 1.07 (0.65-1.75)	NS
				Death	37 / 128 (28.91%)	31 / 128 (24.22%)	aOR: 0.76 (0.34-1.71)	NS
Svensson 2021 [48]	Warfarin	Non-user	PrEP	ICU admission due to COVID-19	17 / 1086 (1.57%)	150 / 10860 (1.38%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.96 (0.52-1.76)	NS
Fung 2021 [73]	Warfarin	Non-user	PrEP	COVID-19 diagnosis	11755 / 374299 (3.14%)	47251 / 1866576 (2.53%)	aHR: 0.88 (0.86-0.91)	**Yes**
				COVID-19 hospitalization	/	/	aHR: 0.95 (0.92-0.99)	**Yes**
				Death after a COVID-19 diagnosis	/	/	aHR: 0.82 (0.78-0.87)	**Yes**
Svensson 2021 [48]	NOAC	Non-user	PrEP	ICU admission due to COVID-19	45 / 1086 (4.14%)	474 / 10860 (4.36%)	/	NS
				Severe COVID-19 requiring mechanical ventilation	/	/	aOR: 0.70 (0.46-1.06)	NS
Khider 2020 [50]	Anticoagulant	Non-user	PrEP	Laboratory-confirmed infection	12 / 66 (18.18%)	3 / 30 (10.00%)	/	NS
Mancia 2020 [69]	OAC	Non-user	PrEP	COVID-19 diagnosis	643 / 6272 (10.25%)	2173 / 30759 (7.06%)	aOR: 1.16 (1.04-1.30)	**No**
Others								
Huh 2020 [49]	Camostat	Non-user	PrEP	Laboratory-confirmed infection	3 / 7341 (0.04%)	29 / 36705 (0.08%)	aOR: 1.14 (0.31-4.18)	NS
	Ciclesonide	Non-user	PrEP	Laboratory-confirmed infection	2 / 7341 (0.03%)	3 / 36705 (0.01%)	aOR: 4.96 (0.68-36.39)	NS
	Azithromycin	Non-user	PrEP	Laboratory-confirmed infection	11 / 7341 (0.15%)	103 / 36705 (0.28%)	aOR: 0.58 (0.30-1.12)	NS
				Severe disease among infected	3 / 878 (0.34%)	3 / 1927 (0.16%)	aOR: 2.03 (0.39-10.59)	NS

	Mycophenolate	Non-user	PrEP	Laboratory-confirmed infection	5 / 7341 (0.07%)	59 / 36705 (0.16%)	aOR: 0.51 (0.19-1.36)	NS
				Severe disease among infected	1 / 878 (0.11%)	1 / 1927 (0.05%)	aOR: 2.21 (0.13-37.06)	NS
	Amiodarone	Non-user	PrEP	Laboratory-confirmed infection	5 / 7341 (0.07%)	68 / 36705 (0.19%)	aOR: 0.41 (0.16-1.09)	NS
				Severe disease among infected	2 / 878 (0.23%)	2 / 1927 (0.10%)	aOR: 1.27 (0.17-9.69)	NS
Khider 2020 [50]	Central acting agent	Non-user	PrEP	Laboratory-confirmed infection	0 / 66 (0.00%)	1 / 30 (3.33%)	/	NS
Fillmore 2021 [51]	Disulfiram	Non-user	PrEP	Laboratory-confirmed infection	188 / 2233 (8.42%)	167139 / 941894 (17.74%)	aHR: 0.66 (0.57-0.76)	**Yes**
				ICU admission among infected	11 / 188 (5.85%)	7403 / 167139 (4.43%)	/	NS
				Mechanical ventilation	1 / 188 (0.53%)	959 / 167139 (0.57%)	/	NS
				Death	0 / 188 (0.00%)	5009 / 167139 (3.00%)	/	**Yes**
Liu 2020 [38]	Thymosin	Non-user	PrEP	Laboratory-confirmed and symptomatic COVID-19	2 / 101 (1.98%)	1 / 57 (1.75%)	/	NS
			PEP	Laboratory-confirmed and symptomatic COVID-19	3 / 277 (1.08%)	1 / 57 (1.75%)	/	NS
Zhou 2020 [46]	Melatonin	Non-user	PrEP	Laboratory-confirmed infection	/	/	aOR: 0.72 (0.56-0.91)	**Yes**
Garcia-Garcia 2022 [24]	Melatonin	Placebo	PrEP	Laboratory-confirmed infection	9 / 163 (5.52%)	4 / 151 (2.65%)	RR: 2.02 (0.64-6.45)	NS
Gendelman 2020 [42]	Colchicine	Non-user	PrEP	Laboratory-confirmed infection	7 / 1317 (0.53%)	64 / 13203 (0.48%)	/	NS
Cohen 2021 [19]	Bamlanivimab	Placebo	PrEP	Laboratory-confirmed infection and presence of mild or worse disease severity within 8 weeks	41 / 484 (8.47%)	73 / 482 (15.15%)	OR: 0.43 (0.28-0.68)	**Yes**
				Moderate or worse severity COVID-19 by Day 57	40 / 484 (8.26%)	68 / 482 (14.11%)	OR: 0.46 (0.29-0.73)	**Yes**
				Laboratory-confirmed infection by Day 29	87 / 484 (17.98%)	112 / 482 (23.24%)	OR: 0.66 (0.46-0.94)	**Yes**
				Death due to COVID-19	0 / 484 (0.00%)	4 / 482 (0.83%)	/	NS
Seet 2021 [20]	Povidone-iodine	Vitamin C	PrEP	Laboratory-confirmed infection within 42 days	338 / 735 (45.99%)	433 / 619 (69.95%)	RR: 0.66 (0.48-0.88)	**Yes**
				Acute respiratory symptoms	43 / 735 (5.85%)	69 / 619 (11.15%)	/	NS
				Symptomatic COVID-19	42 / 338 (12.43%)	64 / 433 (14.78%)	/	NS
				Pneumonia requiring hospitalization	0 / 735 (0.00%)	0 / 619 (0.00%)	/	NS
				Death	0 / 735 (0.00%)	0 / 619 (0.00%)	/	NS
Blanc 2021 [36]	Paracetamol	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 1.51 (0.82-2.84)	NS
	Antipsychotics	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 0.86 (0.38-1.90)	NS
	PPI	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 0.44 (0.23-0.82)	**Yes**

	NSAID	Non-user	PrEP	Laboratory-confirmed infection	/	/	OR: 7.31 (0.46-275.38)	NS
Huh 2020 [49]	NSAID	Non-user	PrEP	Laboratory-confirmed infection	1216 / 7341 (16.56%)	5864 / 36705 (15.98%)	aOR: 1.04 (0.97-1.12)	NS
				Severe disease among infected	255 / 878 (29.04%)	406 / 1927 (21.07%)	aOR: 1.53 (1.25-1.86)	**No**
Mancia 2020 [69]	NSAID	Non-user	PrEP	COVID-19 diagnosis	1036 / 6272 (16.52%)	4579 / 30759 (14.89%)	aOR: 1.06 (0.98-1.15)	NS
Sokhela 2022 [28]	Nitazoxanide	No intervention	PrEP	Laboratory-confirmed infection	100 / 240 (41.67%)	111 / 265 (41.89%)	RR: 1.21 (0.29-1.58)	NS
				Laboratory-confirmed and symptomatic COVID-19	23 / 240 (9.58%)	37 / 265 (13.96%)	RR: 0.83 (0.50-1.40)	NS
Stambouli 2022 [32]	Doxycycline	Placebo	PrEP	Laboratory-confirmed infection	5 / 56 (8.93%)	14 / 57 (24.56%)	/	**Yes**
	Doxycycline plus zinc	Placebo	PrEP	Laboratory-confirmed infection	5 / 59 (8.47%)	14 / 57 (24.56%)	/	
Mikhaylov 2022 [33]	Bromhexine hydrochloride	No intervention	PrEP	Laboratory-confirmed infection	2 / 25 (8.00%)	7 / 25 (28.00%)	/	NS
				Moderate COVID-19	0 / 25 (0.00%)	3 / 25 (12.00%)	/	NS
				Severe COVID-19 with hospitalization	0 / 25 (0.00%)	2 / 25 (8.00%)	/	NS
Fung 2021 [73]	Famotidine	Non-user	PrEP	COVID-19 diagnosis	13133 / 374299 (3.51%)	40984 / 1866576 (2.20%)	aHR: 1.12 (1.10-1.15)	**No**
				COVID-19 hospitalization	/	/	aHR: 0.94 (0.91-0.97)	**Yes**
				Death after a COVID-19 diagnosis	/	/	aHR: 1.00 (0.96-1.04)	NS

Abbreviations: PrEP, pre-exposure prophylaxis; PEP, post-exposure prophylaxis; HCQ, hydroxychloroquine; PPE, personal protective equipment; LPV/r, lopinavir/ritonavir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; PPI, proton pump inhibitors; OAD, oral antidiabetic drugs; CCB, calcium channel blockers; TZD, thiazolidinediones; NSAID, non-steroidal anti-inflammatory drug; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitor; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SGLT-2 inhibitors, sodium-glucose co-transporter-2 inhibitors; NOAC, new oral anticoagulants; RT-PCR, reverse transcription-polymerase chain reaction; HRCT, high-resolution computed tomography; CT, computed tomography; NS, not significant

Fig S1 Traffic light plot of risk of bias assessment of RCTs by RoB 2.0

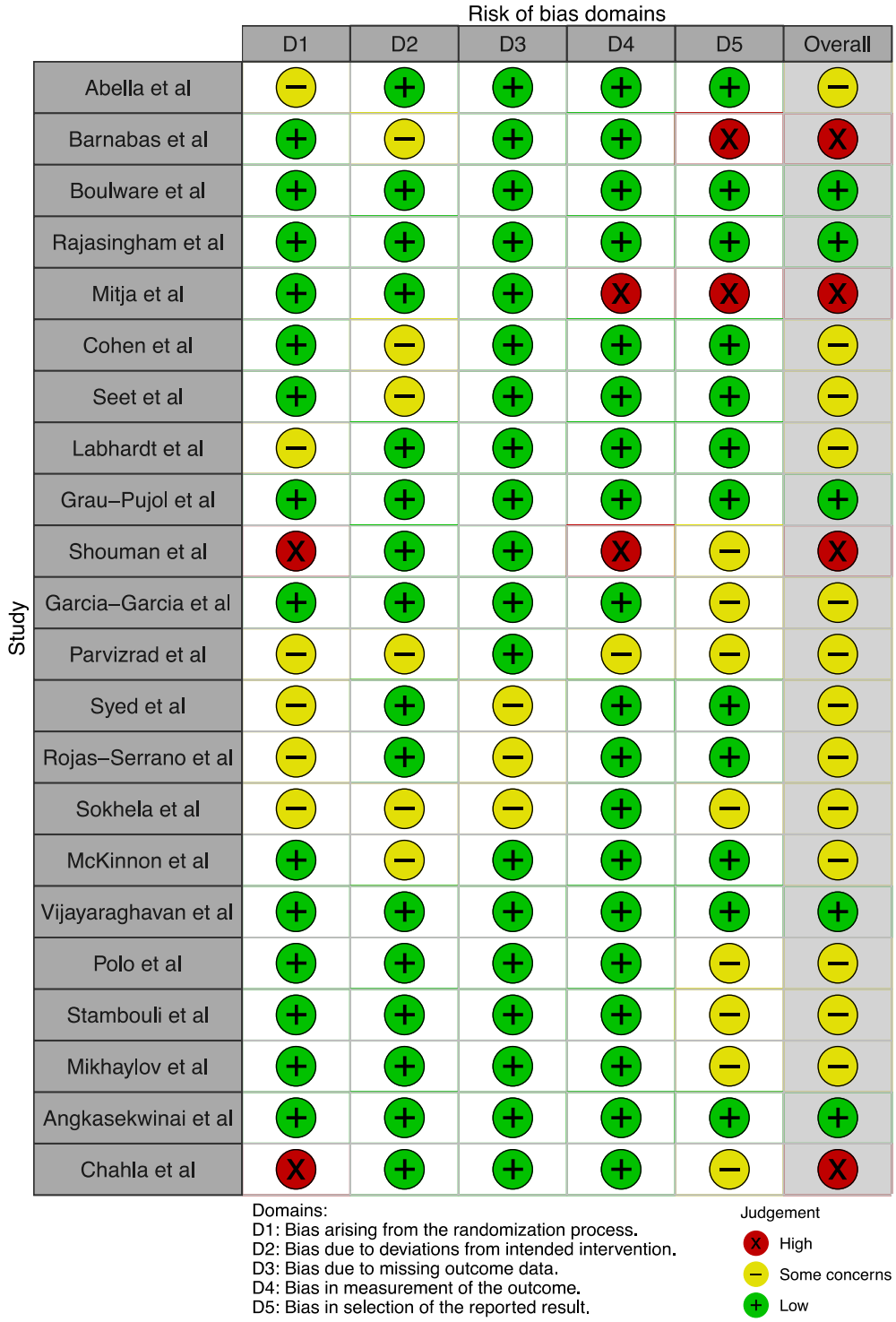


Fig S2 Summary plot of risk of bias assessment of RCTs by RoB 2.0

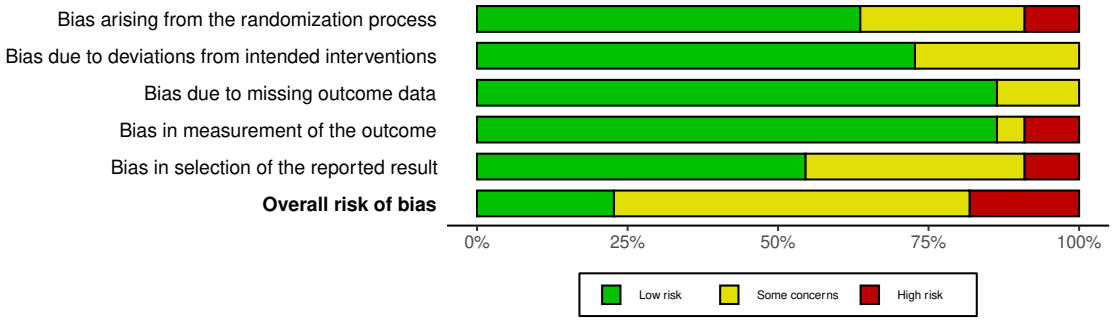


Fig S3 Traffic light plot of risk of bias assessment of non-randomized studies by ROBINS-I

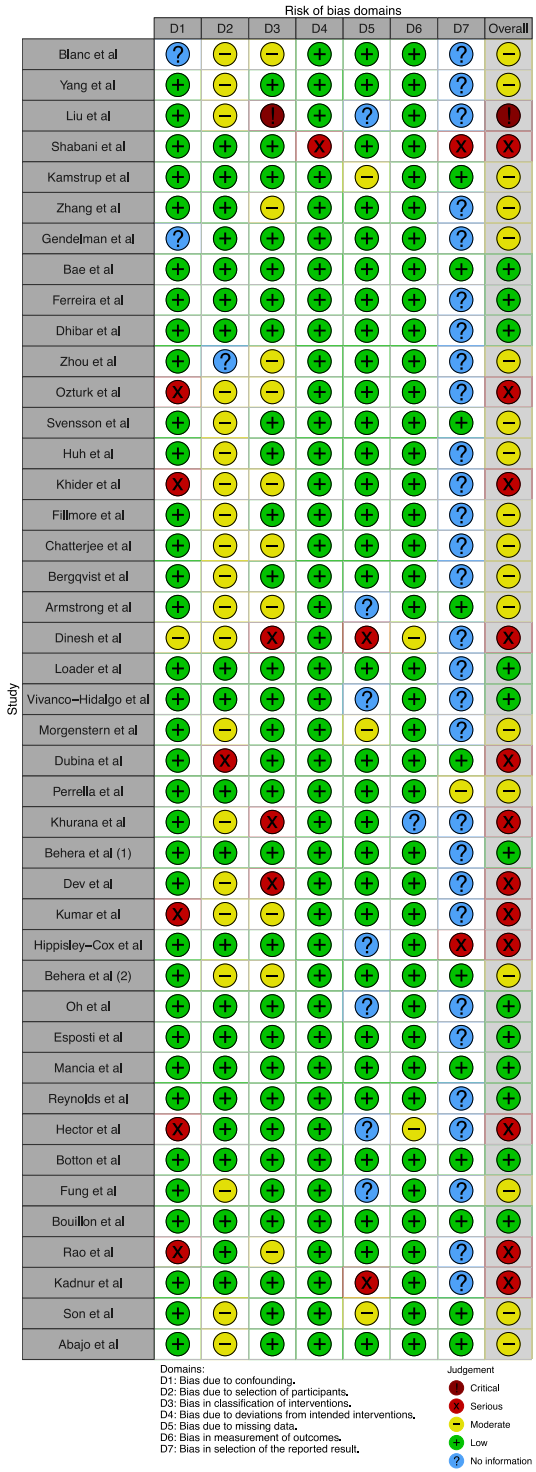


Fig S4 Summary plot of risk of bias assessment of non-randomized studies by ROBINS-I

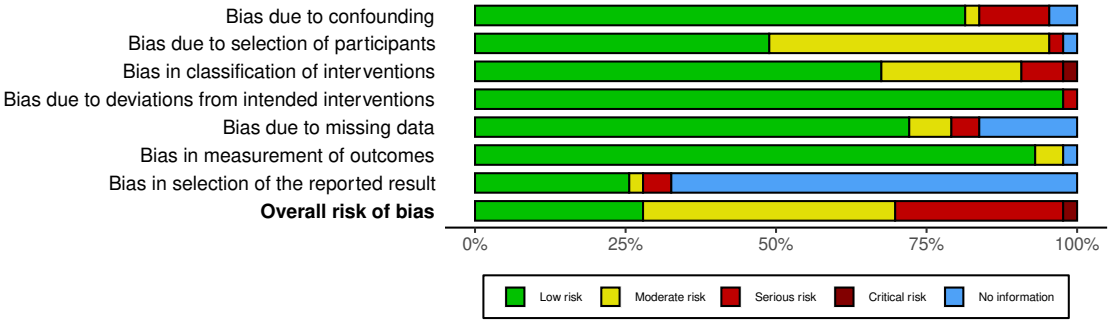


Fig S5 Funnel plot (publication bias) of HCQ studies on laboratory-confirmed infection

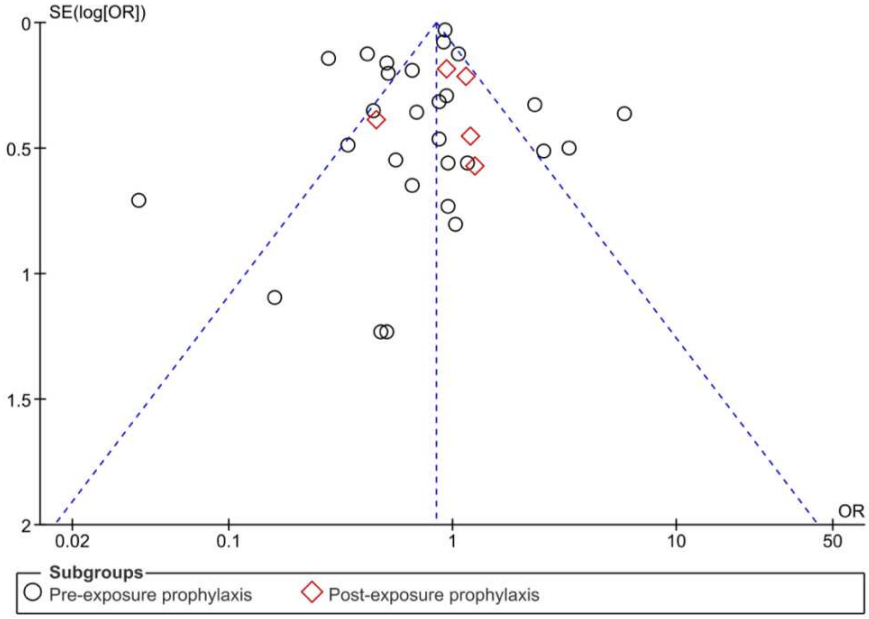
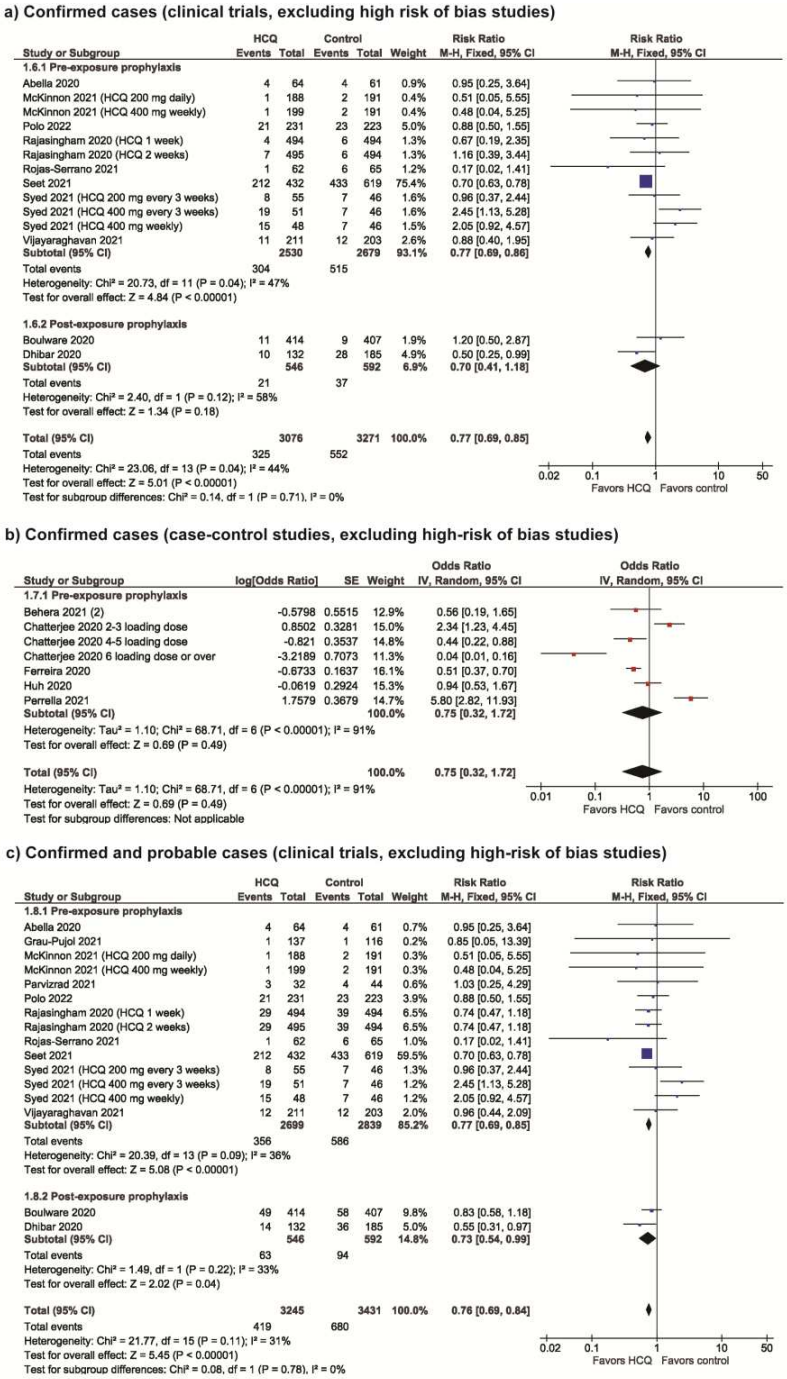


Fig S6 Meta-analysis of the effect of HCQ prophylaxis excluding high risk of bias studies on (a) laboratory-confirmed SARS-CoV-2 infection in clinical trials; (b) laboratory-confirmed SARS-CoV-2 infection in case-control studies; (c) laboratory- or clinical-confirmed SARS-CoV-2 infection in clinical trials



Search strategy

No	Database	Key term
1	PubMed	(SARS-CoV-2 [Mesh] OR COVID-19 [Mesh] OR coronavirus [Mesh] OR SARS-CoV-2 [tiab] OR COVID [tiab] OR coronavirus [tiab] OR "2019 nCoV" [tiab]) **AND** ("Pre-Exposure Prophylaxis" [Mesh] OR "Post-Exposure Prophylaxis" [Mesh] OR "Primary Prevention" [Mesh] OR "Chemoprevention" [Mesh] OR "Drug Repositioning" [Mesh] OR "prevention and control" [Subheading] OR prophyla* [tiab] OR chemoprophyla* [tiab] OR chemoprevent* [tiab] OR prevent* [tiab] OR pre-expos* [tiab] OR post-expos* [tiab] OR preexpos* [tiab] OR postexpos* [tiab] OR reposition* [tiab] OR repurpos* [tiab]) **AND** ("COVID-19/drug therapy" [MAJR] OR antimalarials [Mesh] OR hydroxychloroquine [Mesh] OR chloroquine [Mesh] OR amodiaquine [Mesh] OR "antiviral agents" [Mesh] OR emtricitabine [Mesh] OR tenofovir [Mesh] OR lopinavir [Mesh] OR ritonavir [Mesh] OR darunavir [Mesh] OR ribavirin [Mesh] OR nelfinavir [Mesh] OR "anti-retroviral agents" [Mesh] OR "anti-bacterial agents" [Mesh] OR doxycycline [Mesh] OR azithromycin [Mesh] OR anisomycin [Mesh] OR immunotherapy [Mesh] OR interferons [Mesh] OR anticoagulants [Mesh] OR "adrenal cortex hormones" [Mesh] OR thymosin [Mesh] OR glucocorticoids [Mesh] OR ivermectin [Mesh] OR bromhexine [Mesh] OR famotidine [Mesh] OR colchicine [Mesh] OR metformin [Mesh] OR "hydroxymethylglutaryl coa reductase inhibitors" [Mesh] OR "proton pump inhibitors" [Mesh] OR povidone-iodine [Mesh] OR "protease inhibitors" [Mesh] OR "anti-inflammatory agents" [Mesh] OR "antihypertensive agents" [Mesh] OR niclosamide [Mesh] OR "antipsychotic agents" [Mesh] OR "antidepressive agents" [Mesh] OR clomipramine [Mesh] OR chlorpromazine [Mesh] OR promethazine [Mesh] OR "antiparasitic agents" [Mesh] OR antimalarial* [tiab] OR hydroxychloroquine [tiab] OR chloroquine [tiab] OR amodiaquine [tiab] OR antiviral* [tiab] OR nitazoxanide [tiab] OR emtricitabine [tiab] OR tenofovir [tiab] OR lopinavir [tiab] OR ritonavir [tiab] OR favipiravir [tiab] OR umifenovir [tiab] OR arbidol

		[tiab] OR darunavir [tiab] OR ribavirin [tiab] OR nelfinavir [tiab] OR alisporivir [tiab] OR antiretroviral* [tiab] OR antibacterial* [tiab] OR antibiotic* [tiab] OR doxycycline [tiab] OR azithromycin [tiab] OR anisomycin [tiab] OR dalbavancin [tiab] OR oritavancin [tiab] OR immunotherap* [tiab] OR immune-therap* [tiab] OR antibod* [tiab] OR interferon* [tiab] OR thymosin* [tiab] OR anticoagulant* [tiab] OR corticosteroid* [tiab] OR glucocorticoid* [tiab] OR ivermectin [tiab] OR bromhexine [tiab] OR famotidine [tiab] OR colchicine [tiab] OR metformin [tiab] OR statin* [tiab] OR "proton pump inhibitor*" [tiab] OR povidone-iodine [tiab] OR "protease inhibitor*" [tiab] OR antifibrotic* [tiab] OR antiinflammtory* [tiab] OR anti-inflammatory* [tiab] OR antihypertensive* [tiab] OR anti-hypertensive* [tiab] OR niclosamide [tiab] OR antipsychotic* [tiab] OR antidepress* [tiab] OR clomipramine [tiab] OR chlorpromazine [tiab] OR promethazine [tiab] OR antiparasitic* [tiab] OR "angiotensin-converting enzyme inhibitors" [Mesh] OR “angiotensin converting enzyme inhibitors” [tiab] OR "angiotensin receptor antagonists" [Mesh] OR “angiotensin receptor blockers” [tiab] OR "adrenergic beta-antagonists" [Mesh] OR “beta blocker” [tiab] OR "calcium channel blockers" [Mesh] OR “calcium channel blockers” [tiab] OR aspirin [Mesh] OR aspirin [tiab] OR insulin [Mesh] OR insulin [tiab] OR bamlanivimab [Mesh] OR bamlanivimab [tiab]) **AND** ("Clinical Trial" [Publication Type] OR "clinical trials as topic" [Mesh] OR "observational studies as topic" [Mesh] OR "cohort studies" [Mesh] OR "case-control studies" [Mesh] OR "cross-over studies" [Mesh] OR "clinical trial" [tiab] OR "observational" [tiab] OR cohort [tiab] OR follow-up [tiab] OR longitudinal* [tiab] OR "prospective stud*" [tiab] OR "retrospective stud*" [tiab] OR case-control [tiab] OR random* [tiab] OR RCT [tiab] OR cross-over [tiab] OR crossover [tiab] OR "test negative*" [tiab] OR trial [ti]) **NOT** (Review [tiab] OR "systematic review" [Publication Type] OR Letter [Publication Type] OR Editorial [Publication Type] OR Comment [Publication Type] OR News [Publication Type] OR "in vitro" [ti])

		Filters: Publication date from 1st January 2020 to 28th September 2022, language in English
2	Embase	**#1** 'sars cov 2'/exp OR 'covid 19'/exp OR coronavirus/exp OR ('sars cov 2' OR coronavirus OR '2019 nCoV'):ab,ti **#2** 'pre-exposure prophylaxis'/exp OR 'post-exposure prophylaxis'/exp OR 'primary prevention'/exp OR 'chemoprevention'/exp OR 'chemoprophylaxis'/exp OR 'drug repositioning'/exp OR (prophyla* OR chemoprophyla* OR chemoprevent* OR prevent* OR pre-expos* OR post-expos* OR preexpos* OR postexpos* OR reposition* OR repurpos*):ab,ti **#3** 'antimalarial'/exp OR antimalarial*:ab,ti OR 'hydroxychloroquine'/exp OR hydroxychloroquine:ab,ti OR 'chloroquine'/exp OR chloroquine:ab,ti OR 'amodiaquine'/exp OR amodiaquine:ab,ti OR 'antiviral'/exp OR antiviral*:ab,ti OR 'nitazoxanide'/exp OR nitazoxanide:ab,ti OR 'emtricitabine'/exp OR emtricitabine:ab,ti OR 'tenofovir'/exp OR tenofovir:ab,ti OR 'lopinavir'/exp OR lopinavir:ab,ti OR 'ritonavir'/exp OR ritonavir:ab,ti OR 'favipiravir'/exp OR favipiravir:ab,ti OR 'umifenovir'/exp OR umifenovir:ab,ti OR 'arbidol'/exp OR arbidol:ab,ti OR 'darunavir'/exp OR darunavir:ab,ti OR 'ribavirin'/exp OR ribavirin:ab,ti OR 'nelfinavir'/exp OR nelfinavir:ab,ti OR 'alisporivir'/exp OR alisporivir:ab,ti OR 'antiretrovirus agent'/exp OR antiretrovir*:ab,ti OR 'antibacterial'/exp OR antibacterial*:ab,ti OR 'antibiotics'/exp OR antibiotic*:ab,ti OR 'doxycycline'/exp OR doxycycline:ab,ti OR 'azithromycin'/exp OR azithromycin:ab,ti OR 'anisomycin'/exp OR anisomycin:ab,ti OR 'dalbavancin'/exp OR dalbavancin:ab,ti OR 'oritavancin'/exp OR oritavancin:ab,ti OR 'immunotherapy'/exp OR immunotherap*:ab,ti OR 'immune therapy'/exp OR 'immune therap*':ab,ti OR 'antibody'/exp OR antibod*:ab,ti OR 'interferon'/exp OR interferon*:ab,ti OR 'thymosin'/exp OR thymosin*:ab,ti OR 'anticoagulant'/exp OR anticoagulant*:ab,ti OR 'corticosteroid'/exp OR corticosteroid*:ab,ti OR 'glucocorticoid'/exp OR

		glucocorticoid*:ab,ti OR 'ivermectin'/exp OR ivermectin:ab,ti OR 'bromhexine'/exp OR bromhexine:ab,ti OR 'famotidine'/exp OR famotidine:ab,ti OR 'colchicine'/exp OR colchicine:ab,ti OR 'metformin'/exp OR metformin:ab,ti OR 'statin'/exp OR statin*:ab,ti OR 'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR 'povidone iodine'/exp OR 'povidone iodine':ab,ti OR 'protease inhibitor'/exp OR 'protease inhibitor*':ab,ti OR 'antifibrotic agent'/exp OR antifibrotic*:ab,ti OR 'antiinflammatory agent'/exp OR antiinflammat*:ab,ti OR anti-inflammat*:ab,ti OR 'antihypertensive agent'/exp OR antihypertensi*:ab,ti OR 'niclosamide'/exp OR niclosamide:ab,ti OR 'antipsychotics'/exp OR antipsychotic*:ab,ti OR 'antidepressant agent'/exp OR antidepress*:ab,ti OR 'clomipramine'/exp OR clomipramine:ab,ti OR 'chlorpromazine'/exp OR chlorpromazine:ab,ti OR 'promethazine'/exp OR promethazine:ab,ti OR 'antiparasitic agent'/exp OR antiparasitic*:ab,ti OR ('angiotensin converting':ab,ti AND ('enzyme'/exp OR enzyme:ab,ti) AND ('inhibitors'/exp OR inhibitors:ab,ti)) OR 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'dipeptidyl carboxypeptidase inhibitor':ab,ti OR 'angiotensin receptor antagonist'/exp OR 'angiotensin receptor antagonist':ab,ti OR 'beta adrenergic receptor blocking agent'/exp OR 'beta adrenergic receptor blocking agent':ab,ti OR 'calcium channel blocking agent'/exp OR 'calcium channel blocking agent':ab,ti OR 'acetylsalicylic acid'/exp OR 'acetylsalicylic acid':ab,ti OR aspirin:ab,ti OR 'insulin'/exp OR 'insulin':ab,ti OR 'bamlanivimab'/exp OR 'bamlanivimab':ab,ti
		#4
		'clinical trial'/exp OR 'observational study'/exp OR 'cohort analysis'/exp OR 'case control study'/exp OR 'randomized controlled trial'/exp OR 'test negative design'/exp OR 'cross-over study'/exp OR ('clinical trial*' OR observational OR cohort OR follow-up OR longitudinal* OR 'prospective stud*' OR 'retrospective stud*' OR 'case control' OR random* OR RCT OR 'test negative' OR cross-over OR crossover):ab,ti OR trial*:ti
		'clinical study'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'crossover procedure'/de OR 'observational study'/de OR 'pilot

		study'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/de OR 'test negative design'/de **#5** review:ab,ti OR letter:it OR 'conference abstract':it OR editorial:it OR news:it OR 'animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de OR 'systematic review'/de (#1 AND #2 AND #3 AND #4 NOT #5) AND [2020-2022]/py

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5, Table S1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	PROSPERO protocol
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Table S2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure S1-S4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table S3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 10-12 Figure 2-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure 2-5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figure S6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12
	23b	Discuss any limitations of the evidence included in the review.	Page 12-15
	23c	Discuss any limitations of the review processes used.	Page 15
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 16
Competing interests	26	Declare any competing interests of review authors.	Page 17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/