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Prophylaxis against covid-19: living systematic review and network meta-analysis

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ABSTRACT

UPDATES

This is the second version (first update) of the living systematic review, replacing the previous version (available as a data supplement). When citing this paper please consider adding the version number and date of access for clarity.

OBJECTIVE

To determine and compare the effects of drug prophylaxis on severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (covid-19).

DESIGN

Living systematic review and network meta-analysis (NMA).

DATA SOURCES

WHO covid-19 database, a comprehensive multilingual source of global covid-19 literature to 4 March 2022.

STUDY SELECTION

Randomised trials in which people at risk of covid-19 were allocated to prophylaxis or no prophylaxis (standard care or placebo). Pairs of reviewers independently screened potentially eligible articles.

METHODS

After duplicate data abstraction, we conducted random-effects bayesian network meta-analysis. We assessed risk of bias of the included studies using a modification of the Cochrane risk of bias 2.0 tool and assessed the certainty of the evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach.

RESULTS

The second iteration of this living NMA includes 32 randomised trials which enrolled 25 147 participants and addressed 21 different prophylactic drugs; adding 21 trials (66%), 18 162 participants (75%) and 16 (76%) prophylactic drugs. Of the 16 prophylactic drugs analysed, none provided convincing evidence of a reduction in the risk of laboratory confirmed SARS-CoV-2 infection. For admission to hospital and mortality outcomes, no prophylactic drug proved different than standard care or placebo. Hydroxychloroquine and vitamin C combined with zinc probably increase the risk of adverse effects leading to drug discontinuation—risk difference for hydroxychloroquine (RD) 6 more per 1000 (95% credible interval (CrI) 2 more to 10 more); for vitamin C combined with zinc, RD 69 more per 1000 (47 more to 90 more), moderate certainty evidence.

CONCLUSION

Much of the evidence remains very low certainty and we therefore anticipate future studies evaluating drugs for prophylaxis may change the results for SARS-CoV-2 infection, admission to hospital and mortality outcomes. Both hydroxychloroquine and vitamin C combined with zinc probably increase adverse effects.

SYSTEMATIC REVIEW REGISTRATION

This review was not registered. The protocol established a priori is included as a supplement.

FUNDING

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Introduction

As of 10 August 2022, more than 584 million people have been infected with severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (covid-19); of these, more than 6.4 million have died.[1] Cases and deaths continue to rise as SARS-CoV-2 variants of concern (VOCs) become increasingly widespread. Because of vaccine hesitancy, contraindications to receiving the vaccine, potential reduced vaccine effectiveness against these VOCs, and waning immunity, drug and antibody prophylaxis, if effective, will be an important intervention against covid-19.[2] Drugs used as pre-exposure prophylaxis (PrEP) in high-risk populations and post-exposure prophylaxis (PEP) are effective and commonly used for other viruses, including HIV and hepatitis B.[3] If effective against covid-19, they could also have a monumental impact worldwide to prevent infection and attenuate disease, especially in those at high risk of death. Therefore, researchers around the world have enrolled participants in randomised trials of drugs and antiviral antibodies for prophylaxis against covid-19.

Clinicians, patients, guideline bodies, and government agencies face challenges in interpreting the results from trials that are being published at a rate never encountered previously. This environment necessitates well developed summaries that distinguish between trustworthy and untrustworthy evidence.

Living systematic reviews and network meta-analyses resolve an important limitation of traditional systematic reviews and network meta-analyses—that of providing an overview of the relevant evidence only at a specific point in time.[4] They require a continuous workflow, repeated analyses, and tailored peer-reviewed publication formats to index and link iterations over time. The ability of a living network meta-analysis to present a complete, broad, and up-to-date view of the evidence makes it ideal to inform the development of practice recommendations, ideally in the form of living clinical practice guidelines.[4-6] Network meta-analysis, rather than pairwise meta-analysis, provides useful information about the comparative effectiveness of treatments that have not been tested head-to-head. The lack of such direct comparisons is certain to limit inferences in the covid-19 setting; therefore, network meta-analysis is critical to inform the selection of the best drug among all alternative options. Moreover, the incorporation of indirect evidence can strengthen evidence in comparisons that were tested head-to-head.[7]

In this living systematic review and network meta-analysis, we compare the effects of drug prophylaxis for covid-19. This living network meta-analysis will—similar to our established living network meta-analyses on covid-19 treatments[8 9]—directly inform living WHO guidelines on drugs to prevent covid-19,[5 6] a collaborative effort between WHO and the MAGIC Evidence Ecosystem Foundation (www.magicevidence.org), inspired by the *BMJ* Rapid Recommendations.[10] This review will inform trustworthy, actionable, and living guidance to clinicians caring for people at risk of developing covid-19.

Methods

The protocol provides detailed methods of this systematic review (see supplementary file). We report this living systematic review following the guidelines of the preferred reporting items for systematic reviews and network meta-analyses (PRISMA) checklist.[11] A living systematic review is a cumulative synthesis updated regularly as new evidence becomes available.[4 12] The linked WHO living guideline methods team provided input on formulation of questions and other elements of data synthesis to allow evidence summaries to inform subsequent recommendations made by the Guideline Development Group.

Eligibility criteria

We included randomised trials of people at risk of covid-19 that compared drugs, therapeutic doses of vitamins, or antibodies for prophylaxis against one another or against no prophylaxis (placebo or standard care, as defined by the researchers), with no restriction on language of publication. We included studies addressing people pre- or post-exposure to covid-19 and at low risk (e.g. unexposed community member) or high risk (e.g. member of the same household with one or more positive cases, contact of index case, healthcare worker or long term care resident) for covid-19.

We excluded randomised trials published only as press releases and trials that evaluated vaccination, nutrition, and non-drug supportive care interventions. We synthesised randomised trials that evaluated drugs, and antibody and cellular therapies for treatment of covid-19 in separate living network meta-analyses.[8 9]

Information sources

We performed daily searches from Monday to Friday in the World Health Organization (WHO) covid-19 database for eligible studies—a comprehensive multilingual source of global literature on covid-19.[13] Before its merger with the WHO covid-19 database on 9 October 2020, we performed daily searches from Monday to Friday in the US Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies.[14] The database includes, but is not limited to the following: 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO covid-19 website, CDC covid-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints). The supplementary file includes the WHO literature search strategy, which is maintained and tested on an ongoing basis by two WHO research librarians and one US CDC research librarian.

We designed the daily searches to match the update schedule of the database and capture eligible studies the day of or the day after publication. To identify randomised trials, we filtered the results through RobotSearch, a validated and highly sensitive machine learning model.[15] We tracked preprints of randomised trials until publication and, when discrepant, updated data to match that in the peer-reviewed publication. When needed, we reconciled multiple versions of preprints, post-hoc analyses, corrections and retractions.

In addition, we searched six Chinese databases: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We adapted the search terms for covid-19 developed by the CDC to the Chinese language. For the Chinese literature search, we also included search terms for randomised trials. The supplementary file includes the Chinese literature search strategy. We stopped searching the Chinese databases on 20 February 2021 because they had not provided studies that meaningfully altered the evidence for any intervention.

We monitored living evidence retrieval services on an ongoing basis. These included the Living Overview of the Evidence (L-OVE) COVID-19 Repository by the Epistemonikos Foundation[16] and the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University.[17]

We searched all English information sources from 1 December 2019 to 4 March 2022, and the Chinese literature from conception of the databases to 20 February 2021.

Study selection

Using a systematic review software, Covidence,[18] following training and calibration exercises, pairs of reviewers independently screened all titles and abstracts, followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicated conflicts.

Data collection

For each eligible trial, following training and calibration exercises, pairs of reviewers extracted data independently using a standardised, pilot tested data extraction form. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), participant characteristics (country, age, sex, comorbidities), exposure characteristics (exposure status, exposure duration, high risk group) and outcomes of interest (means or medians and measures of variability for continuous outcomes and the number of participants analysed and the number of participants who experienced an event for dichotomous outcomes). Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a third party.

The review team selected outcomes of interest based on importance to people without covid-19, and these were informed by clinical expertise in the systematic review team and the linked guideline panel responsible for the WHO living guideline on drugs to prevent covid-19.[5] The panel, detailed in the guideline, includes unconflicted clinical experts and patient partners, and was recruited to ensure global representation. We rated outcomes from 1 to 9 based on importance to individuals without covid-19 (9 being most important), and we included any outcome rated 7 or higher by any panel member. This process resulted in choice of the following outcomes: laboratory confirmed SARS-CoV-2 infection; a composite of suspected, probable or laboratory confirmed SARS-CoV-2 infection; admission to hospital (within 28 days); mortality (closest to 90 days); adverse effects leading to discontinuation (within 28 days); and time to symptom resolution or clinical improvement in the subset of participants who became infected with SARS-CoV-2. For the linked WHO recommendation on hydroxychloroquine prophylaxis, we analysed drug-specific adverse effects from trials reporting on hydroxychloroquine versus standard care or placebo.[5]

Because of inconsistent reporting across trials, when possible, we preferentially extracted participant characteristics and outcome data for participants with a polymerase chain reaction (PCR) test that was negative for SARS-CoV-2 infection at baseline. If authors did not report data separately for those who were PCR-negative for SARS-CoV-2 infection at baseline, we extracted data from all participants, regardless of their PCR status at baseline.

Risk of bias within individual studies

For each eligible trial, reviewers, following training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0)[19] to rate trials at i) low risk of bias, ii) some concerns—probably low risk of bias, iii) some concerns—probably high risk of bias, or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered protocol; bias due to competing risks; and bias arising from early termination for benefit. We rated trials at high risk of bias overall if one or more domains were rated as probably high risk of bias or as high risk of bias and as low risk of bias if all domains were rated as probably low risk of bias or low risk of bias. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication by a third party.

Data synthesis

Summary measures

We summarised the effect of prophylactic drugs on laboratory confirmed infection and on laboratory confirmed, suspected, and probable infection using odds ratios (ORs) and corresponding 95% credible intervals (CrIs). Due to low number of events in most studies, we summarised all other dichotomous outcomes using risk differences (RDs) and corresponding 95% credible intervals (CrIs). To mitigate the risk of obtaining results with highly implausible and extremely imprecise effect estimates, the analyses included only prophylactic drugs with at least 100 participants or 20 events, regardless of the number of studies in which the drug was assessed or the number of participants who received the drug in each study.[9] The supplementary file presents results from a sensitivity analysis demonstrating that the estimated relative effects and their confidence intervals for comparisons between treatments with at least 100 patients or 20 events were similar regardless of whether or not treatments with fewer patients and events were included in the network meta-analysis. The analysis plan included, data permitting, adjustment for cluster randomisation.

Treatment nodes

We created nodes for each prophylactic drug (or combination of drugs), independent of dose or duration. Standard care and placebo arms across included trials were combined into a single node for analyses. We used the networkplot command of Stata version 15.1 (StataCorp, College Station, TX) to create network plots in which the inverse variance of the direct comparison was proportional to the thickness of lines between nodes and the number of participants randomised to the intervention was proportional to the size of nodes.[20]

Statistical analysis

For outcomes with sufficient data, we performed random effects network meta-analysis using the R package gemtc[21] and used three Markov chains with 100 000 iterations after an initial burn-in of 10 000 and a thinning of 10. Node splitting models provided methods to obtain indirect estimates and to assess local heterogeneity.[22] We performed analyses in RStudio version 3.5.3 (R Studio, Boston, MA, USA).[23] We chose a non-informative prior for the variance parameter and a uniform prior for the effect parameter.[24] Outcomes were analysed regardless of whether they were pre-specified in a protocol or trial registration. The foundational R codes are publicly available at https://github.com/covid19lnma/prophylaxis_NMA.

Certainty of the evidence

The grading of recommendations assessment, development, and evaluation (GRADE) approach for network meta-analysis provided the framework for assessing the certainty of evidence.[7 25] Two methodologists with experience in using GRADE rated each domain for each comparison and outcome separately and resolved discrepancies by discussion. Criteria for rating the certainty for each comparison and outcome as high, moderate, low, or very low, included considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence, and imprecision. When the credible interval suggested an effect, we used optimal information size to inform the GRADE rating for imprecision.[25] Judgments of imprecision for this systematic review were made using a minimally contextualised approach.[26] This minimally contextualised approach considers whether credible intervals include the null effect or when the point estimate is close to the null effect, whether the credible interval lies within the boundaries of small but important benefit and harm.

We rated the certainty of no important effect for the outcomes laboratory confirmed infection; suspected, probable or laboratory confirmed infection; admission to hospital; and mortality. Pending data from quantitative studies of patient values, we chose thresholds of small but important effects of 0.1% for mortality; 2% for adverse events leading to discontinuation and laboratory confirmed infection; 3% for suspected, probable, or laboratory confirmed infection; and 1% for admission to hospital. We rated the certainty that there is an increase or decrease in adverse effects leading to discontinuation using the null effect as a threshold. We created GRADE evidence summaries (Summary of Findings tables), developed in the MAGIC Authoring and Publication Platform (www.magicapp.org), to provide user friendly formats for clinicians and patients, and allow re-use in the context of clinical practice guidelines for covid-19, such as the WHO living guidelines.[5 6] Interim updates and additional study data will appear on our website (www.covid19lnma.com).

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for laboratory confirmed infection and suspected, probable, and laboratory confirmed infection—outcomes that were summarised as ORs. We used the median event rate in the standard care or placebo arms to calculate the baseline risk. We categorised the interventions from the most to the least effective using the minimally contextualised GRADE guidance to drawing conclusions from NMAs, which considers the effect estimates and the certainty of the evidence.[25]

Subgroup and sensitivity analysis

The analysis plan includes performing subgroup analyses of pre-exposure versus post-exposure studies, preprints versus peer-reviewed studies and high versus low risk of bias studies when there are at least two studies in each subgroup. We plan to perform network meta-regression to explore if duration of prophylactic drug use may modify the relative effect of the drug on adverse effects leading to discontinuation hypothesising that, if the drug is active at the time of exposure, it will have a greater relative effect. The linked independent WHO guideline panels may direct, in the future, additional subgroup analyses; in the first version, the panel provided direction to perform subgroup analyses by drug prophylaxis duration and dose. The Credibility of Effect Modification Analyses in randomised controlled trials and meta-analyses (ICEMAN) tool provides the methodology for, whenever statistical evidence of a subgroup effect exists, assessing subgroup hypothesis credibility.[27]

Patient and public involvement

As part of the WHO living guidelines and *BMJ* Rapid Recommendations initiative, patients participated in defining clinical questions and rating of importance of outcomes for this systematic review and are also involved in the interpretation of results and the generation of parallel recommendations.

Results

As of 4 March 2022, after screening 108 596 titles and abstracts and 1744 full texts, 32 unique randomised trials from 31 publications[28-58] that evaluated prophylactic drugs proved eligible (fig 1)—12 addressing hydroxychloroquine; two casirivimab combined with imdevimab; two ivermectin alone; two anti-SARS-CoV-2 immunoglobulin Y; two probiotic; and one each for hydroxychloroquine combined with tenofovir disoproxil fumarate/emtricitabine, ivermectin combined with iota-carrageenan, cilgavimab combined with tixagevimab, vitamin C combined with zinc, bamlanivimab, convalescent plasma, iota-carrageenan alone, vitamin C alone, povidone-iodine, silver nanoparticles, ramipril, melatonin, lopinavir-ritonavir, electrolysed water, dimethyl sulfoxide, and bromhexine hydrochloride. Searches of living evidence retrieval services identified six of these eligible randomised trials. We identified one randomised trial addressing vitamins and six randomised trials addressing antibodies as prophylaxis in people at risk for covid-19. The supplementary file includes a table of excluded full texts.

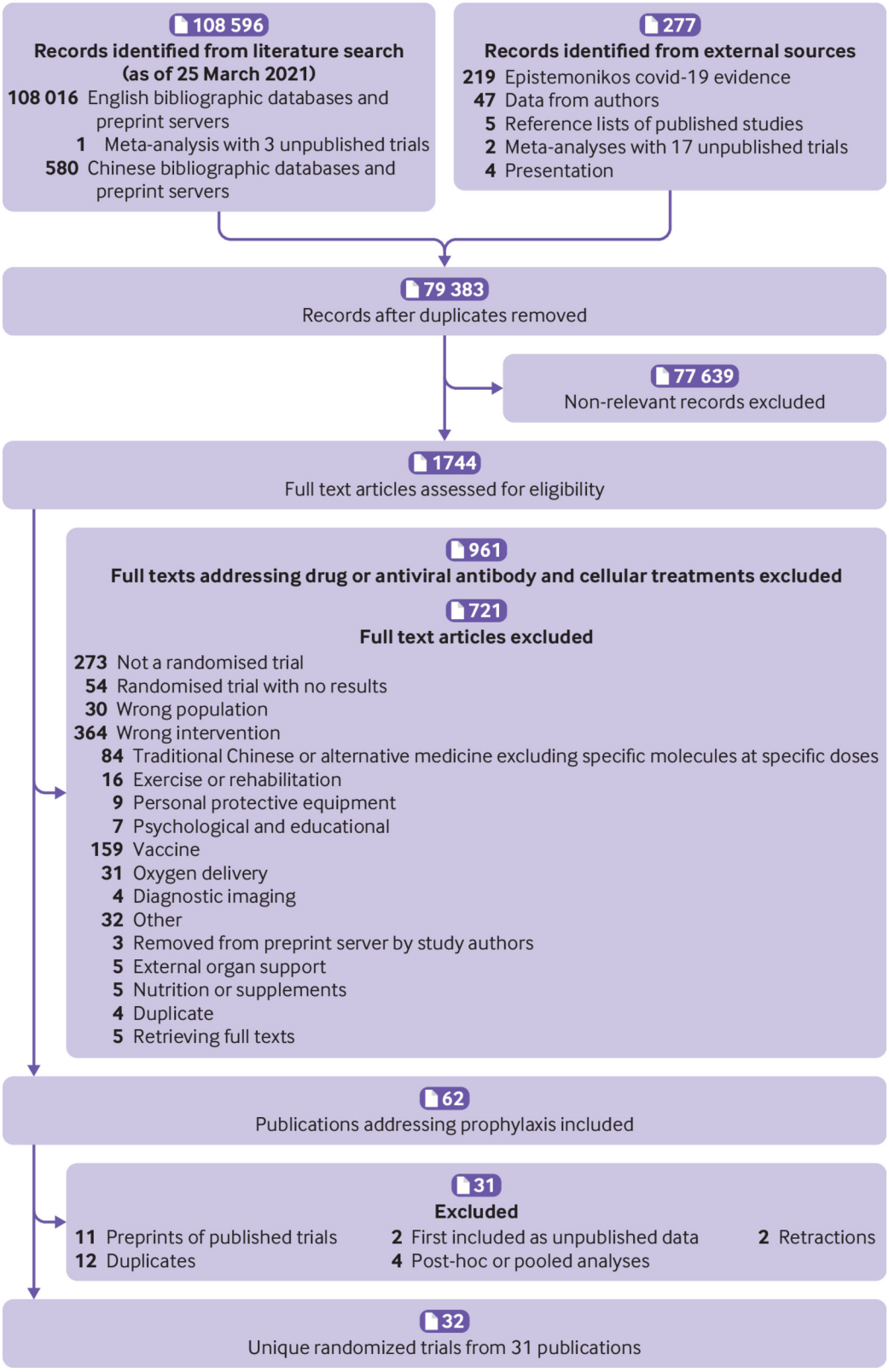

Fig 1 | Study selection

Of the 32 eligible randomised trials, 22 (69%) were published in peer reviewed journals and 10 (31%) only as preprint. All trials were published in English. Almost all trials were registered (31, 97%) and evaluated prophylactic drugs against standard care or placebo (30, 94%). Among the 27 randomised trials that reported covid-19 exposure status of participants, 18 evaluated prophylactic drugs in participants without documented exposure to covid-19 (pre-exposure) and seven evaluated prophylactic drugs in

participants with documented exposure to covid-19 (post-exposure). Two randomised trials evaluated prophylactic drugs in both participants pre-exposure and post-exposure to covid-19. Of the 21 trials for which the covid-19 vaccination status of the study population was reported or could be inferred, one was conducted among participants who received two doses of a covid-19 vaccine.[44] Table 1 presents the characteristics of the 32 included studies.

Table 1 | Study characteristics

Study	Publication status. Registration	No of participants	Country	Mean age	% Male	Exposure status	Vaccinated (%)	Treatments	Outcomes
Abella, 2020[28] PATCH	Published NCT04329923	132	United States	33	31.06	Pre-exposure	0*	Hydroxychloroquine; placebo	Mortality, infection with covid-19 (laboratory confirmed), admission to hospital, adverse effects leading to discontinuation
Almanza-Reyes, 2021[55]	Published NCT04894409	231	Mexico	34	35.06	NR	0*	ARGOVIT AgNPs	Infection with covid-19 (lab confirmed), adverse effects leading to discontinuation
Amat-Santos, 2020[41] RASTAVI	Published NCT03201185	102	Spain	83.3	56.86	Pre-exposure	0*	Rampiril; standard care	Mortality, infection with covid-19 (lab confirmed), admission to hospital
Barnabas, 2020[29]	Published NCT04328961	829	United States	39	40.2	Post-exposure	0*	Hydroxychloroquine; placebo	Infection with covid-19 (lab confirmed), admission to hospital
Boulware, 2020[30]	Published NCT04308668	821	United States, Canada	40	48.36	Post-exposure	0*	Hydroxychloroquine; placebo	Mortality, infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), admission to hospital, adverse effects leading to discontinuation
Chahla, 2021[42] Ivercar-Tuc	Pre-print NCT04701710	234	Argentina	38.5	42.73	Pre-exposure	NR	Iota-carrageenan; ivermectin	Infection with covid-19 (lab confirmed), adverse effects leading to discontinuation
Cohen, 2021[43] BLAZE-2	Published NCT04497987	1175	United States	52.8	25.26	NR	NR	Bamlanivimab	Mortality, infection with covid-19 (lab confirmed)
Fernández-Ferreiro, 2021[44]	Published NCT04756466	200	Spain	83.1	36.87	NR	100 (2 doses)	Loigolactobacillus coryniformis K8 strain	Mortality, infection with covid-19 (lab confirmed), adverse effects leading to discontinuation, time to symptom resolution
Figueroa, 2021[45] CARR-COV-02	Published NCT04521322	394	Argentina	38.6	24.87	Pre-exposure	0*	Iota-carrageenan	Mortality, infection with covid-19 (lab confirmed), admission to hospital, adverse effects leading to discontinuation
Frumkin, 2022[57]	Pre-print NCT04567810	24	Australia	25.2	54.2	Pre-exposure	NR	Anti-SARS-CoV-2 RBD IgY	Adverse effects leading to discontinuation
Frumkin, 2022[57]	Pre-print NCT04567810	24	Australia	26.6	25	Pre-exposure	NR	Anti-SARS-CoV-2 RBD IgY	Adverse effects leading to discontinuation
García-García, 2022[46] MeCOVID	Published NCT04353128	314	Spain	40	18.79	Pre-exposure	0*	Melatonin	Infection with covid-19 (lab confirmed), admission to hospital

Table 1 | Study characteristics *(Continued)*

Study	Publication status. Registration	No of participants	Country	Mean age	% Male	Exposure status	Vaccinated (%)	Treatments	Outcomes
Grau-Pujol, 2020[31]	Published NCT04331834	269	Spain	39.9	26.77	Pre-exposure	NR	Hydroxychloroquine; placebo	Infection with covid-19 (lab confirmed), adverse effects leading to discontinuation
Gutiérrez-García, 2021[47]	Published RPCEC00000357	170	Mexico	42.4	26.38	NR	0*	Neutral electrolysed water	Infection with covid-19 (lab confirmed), adverse effects leading to discontinuation
Hosseinzadeh, 2021[48]	Pre-print IRCT20200727048217N	232	Iran	37.2	37.93	Pre-exposure	NR	Dimethyl sulfoxide nasal spray	Infection with covid-19 (lab confirmed)
Isa, 2021[58]	Pre-print NCT04519437	969	United States	48	55.11	Pre-exposure	0	Casirivimab, imdevimab	Mortality, infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), adverse effects leading to discontinuation
Labhardt, 2021[49] COPEP	Pre-print NCT04364022	321	Brazil, Switzerland	39.7	50.63	Post-exposure	0	Lopinavir-ritonavir	Mortality, infection with covid-19 (lab confirmed)
Levin, 2021[50] PROVENT	Published NCT04625725	5197	Belgium, France, Spain, United Kingdom, United States	53.5	54	Pre-exposure	0	Cilgavimab, tixagevimab	Mortality, infection with covid-19 (lab confirmed, probable, and suspected)
McKinnon, 2021[32] WHIP COVID-19	Published NCT04341441	598	United States	44.9	41.87	Pre-exposure and post-exposure	0*	Hydroxychloroquine	Infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), admission to hospital
Mikhaylov, 2021[51]	Published NCT04405999	50	Russia	40.6	42	Pre-exposure	0	Bromhexine hydrochloride	Mortality, infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), admission to hospital, adverse effects leading to discontinuation
Mitja, 2020[33] BCN PEP-COV	Published NCT04304053	2525	Spain	48.7	27.05	Post-exposure	0*	Hydroxychloroquine	Mortality, infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), admission to hospital, adverse effects leading to discontinuation
Naggie, 2021[34] HERO-HCQ	Pre-print NCT04334148	1360	United States	43.7	34.66	Pre-exposure	NR	Hydroxychloroquine	Mortality, infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), adverse effects leading to discontinuation

Table 1 | Study characteristics *(Continued)*

Study	Publication status. Registration	No of participants	Country	Mean age	% Male	Exposure status	Vaccinated (%)	Treatments	Outcomes
O'Brien, 2021[52] Covid-19 Phase 3 Prevention Trial	Published NCT04452318	2475	United States, Romania, Moldova	42.9	45.9	Post-exposure	0	Casirivimab, imdevimab	Mortality, infection with covid-19 (lab confirmed), admission to hospital, adverse effects leading to discontinuation, time to symptom resolution
Polo, 2022[40] EPICOS	Pre-print NCT04334928	907	Bolivia, Spain, Venezuela	38.3	37.49	Pre-exposure	NR	Hydroxychloroquine, tenofovir disoproxil fumarate/emtricitabine	Infection with covid-19 (lab confirmed), admission to hospital, adverse effects leading to discontinuation
Rajasingham, 2020[35] COVID PREP	Published NCT04328467	1483	United States, Canada	41	48.82	Pre-exposure	0*	Hydroxychloroquine; placebo	Mortality, infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), admission to hospital
Rojas-Serrano, 2021[36] PHYDRA	Published NCT04318015		Mexico	31.1	44.1	Pre-exposure	0*	Hydroxychloroquine	Infection with covid-19 (lab confirmed), admission to hospital, adverse effects leading to discontinuation
Seet, 2021[37]	Published NCT04446104	2745	Singapore	33	100	Pre-exposure and post-exposure	NR	Hydroxychloroquine	Mortality, infection with covid-19 (lab confirmed), admission to hospital, adverse effects leading to discontinuation
Shoham, 2021[53]	Pre-print NCT04323800	180	United States	47	55	Post-exposure	0	Convalescent plasma	Mortality, infection with covid-19 (lab confirmed), admission to hospital
Shouman, 2021[56]	Published NCT04422561	340	Egypt	38.7	51.32	Post-exposure	0*	Ivermectin	Mortality, infection with covid-19 (lab confirmed, probable, and suspected)
Syed, 2021[38] CHEER	Published NCT04359537	200	Pakistan	30.6	54.5	Pre-exposure	NR	Hydroxychloroquine	Mortality, infection with covid-19 (lab confirmed), admission to hospital, adverse effects leading to discontinuation
Vijayaraghavan[39] HOPE	Pre-print CTRI/2020/05/025067	416	India	32.1	52.64	NR	NR	Hydroxychloroquine	Mortality, infection with covid-19 (lab confirmed or lab confirmed, probable, and suspected), admission to hospital, adverse effects leading to discontinuation
Wang, 2021[54]	Published	200	China	35.9	29.02	Pre-exposure	0*	Bactoblis oropharyngeal probiotic	Infection with covid-19 (lab confirmed)

*Inferred based on date range of patient enrolment when possible.

Twelve trials had multiple publication versions as preprints, trial registrations, or peer reviewed manuscripts.[31 33 35 36 38 42 45 47 50 51 55 56] One trial, not included in our network meta-analysis, published multiple iterations of their preprint that was subsequently retracted.[59] Of the included trials with multiple publication versions, four had discrepancies with patient baseline characteristics.[33 35 42 50] Five studies had discrepancies in terms of outcome reporting.[33 42 47 50 56] Four studies had discrepancies that affected risk of bias ratings.[33 35 50 56] The supplementary file presents additional study characteristics, participant characteristics, outcome data, and reporting differences between versions of study preprints and/or peer reviewed publications.

We performed the analyses on 9 May 2022 and included 24 randomised trials. On 22 November 2022, we updated our analyses to include the peer reviewed version of the PROVENT trial to support the WHO's recommendations for cilgavimab combined with tixagevimab.[50] Eight randomised trials addressing ramipril,[41] bromhexine hydrochloride,[51] convalescent plasma,[53] Loigolactobacillus corynormis K8 strain,[44] Bactoblis oropharyngeal probiotic,[54] neutralised electrolysed water,[47] and anti-SARS-CoV-2 RBD IgY,[57] and enrolling 926 participants in total, were not included in the network meta-analysis because they each enrolled less than 100 participants and observed less than 20 events in the prophylaxis arm. Since the molecule, rather than drug dose or duration of use, dictates the choice of nodes, the two active treatment arms in one three-arm trial were combined (hydroxychloroquine once weekly or twice weekly).[35] A post-hoc analysis with one of the analysed trials addressing hydroxychloroquine did not include information beyond what was already reported in the original peer reviewed publication of the trial.[30 60] Since the authors did not report the intracluster correlation coefficient, we could not adjust for cluster randomisation in one analysed trial addressing hydroxychloroquine.[33] We conducted a post-hoc sensitivity analysis omitting four cluster randomised trials (supplementary material).[29 33 37 49] Overall, inclusion of cluster randomised trials in our network meta-analysis improved the precision of effect estimates. However, our conclusions about the efficacy of investigated prophylactic interventions remained unchanged.

Risk of bias in included studies

Figure 2 summarises the assessment of risk of bias of the 32 included studies for each outcome. Thirteen studies proved at high risk of bias overall due to lack of blinding.[33 37-39 41 42 47-49 51 54-56] Of these 13 studies, eight had insufficient detail regarding allocation concealment,[38 41 42 47 51 54-56] and one terminated early due to benefit.[56] The supplementary material presents further details regarding the assessment of risk of bias.

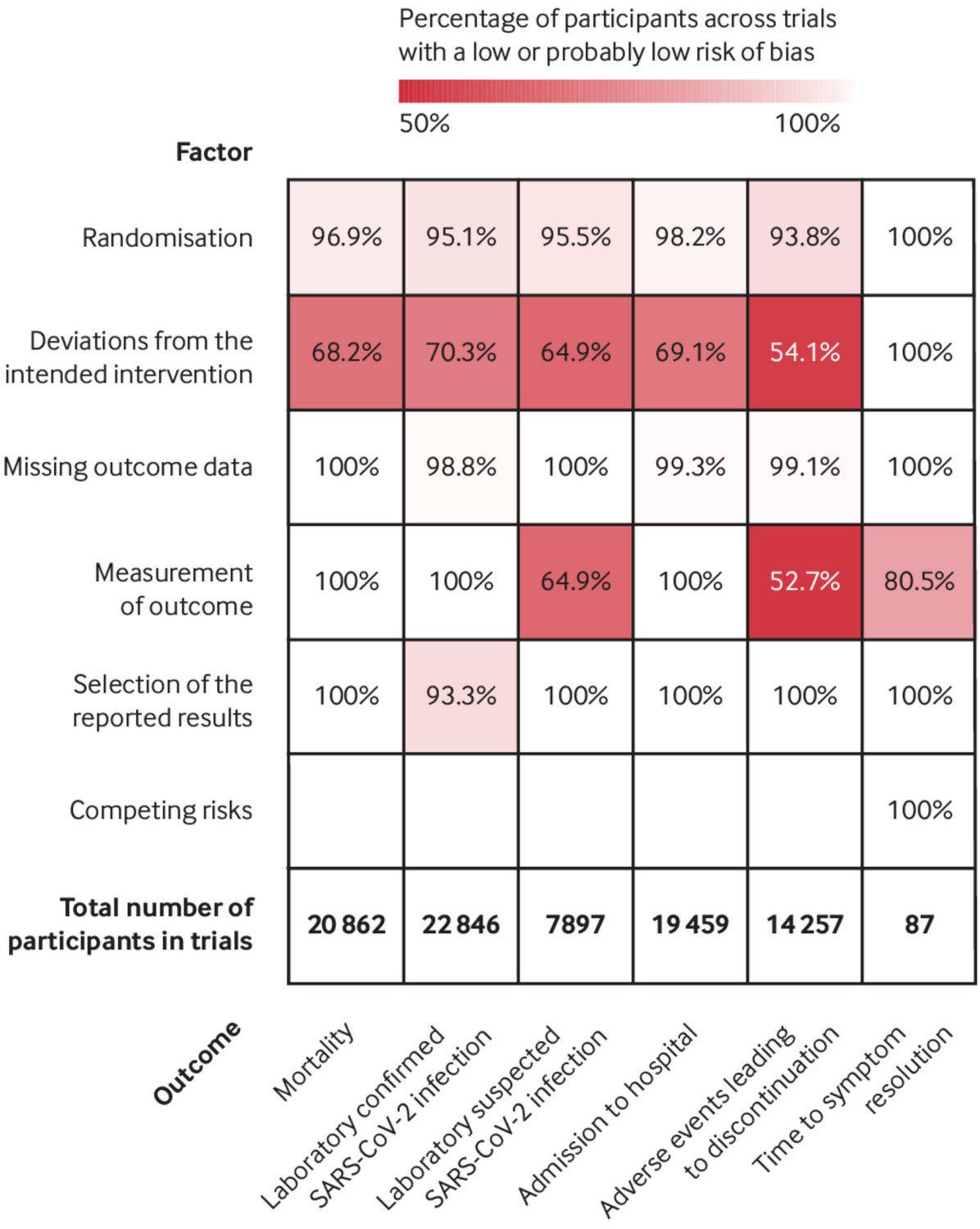

Fig 2 | Summary of risk of bias

Effects of the interventions

The supplementary material presents the network and forest plots depicting the interventions included in the network meta-analysis of each outcome. The supplementary file also presents detailed relative and absolute effect estimates, and certainty of the evidence for all comparisons and outcomes. We did not detect statistical incoherence in any of the comparisons or outcomes. Figure 3 presents a summary of the effects of prophylactic drugs on the

outcomes when compared with standard care/placebo, and we describe these results herein.

	Laboratory confirmed SARS-CoV-2 infection	Suspected, probable, or laboratory confirmed SARS-CoV-2 infection	Admission to hospital[3]	Mortality[4]	Adverse effects leading to drug discontinuation[5]	Time to symptom resolution or clinical improvement
Baseline risk[1]	65 per 1000	77 per 1000	3 per 1000	0 per 1000	22 per 1000	
Minimal important difference[2]	20 per 1000	30 per 1000	10 per 1000	1 per 1000	20 per 1000	1 day
ARGOVIT AgNPs	-63 (-66 to -54)				0 (-17 to 17)	
Bamlanivimab	-24 (-50 to 24)			-2 (-34 to 30)		
Casirivimab, imdevimab	-53 (-62 to -40)	-72 (-78 to -59)	-3 (-34 to 28)	0 (-22 to 21)	0 (-2 to 1)	
Cilgavimab, tixagevimab	-48 (-62 to -17)		-4 (-35 to 27)	-1 (-30 to 28)		
Dimethyl sulfoxide nasal spray	-57 (-67 to -21)					
Hydroxychloroquine	-2 (-18 to 19)*	-10 (-28 to 10)	-2 (-6 to 2)*	0 (-3 to 2)*	6 (2 to 10)	
Hydroxychloroquine, tenofovir disoproxil fumarate/emtricitabine	-25 (-52 to 26)		-5 (-34 to 24)		34 (-13 to 81)	
Iota-carrageenan	-51 (-65 to -9)		0 (-32 to 32)	0 (-30 to 30)	-5 (-27 to 17)	
Iota-carrageenan, ivermectin	-56 (-65 to -36)				0 (-17 to 17)	
Ivermectin	54 (-22 to 173)	-74 (-77 to -68)	-3 (-36 to 30)	-2 (-25 to 21)		
Lopinavir-ritonavir	-12 (-55 to 90)			-2 (-34 to 30)		
Melatonin	95 (-30 to 363)		0 (-33 to 33)			
Povidone-iodine	-6 (-45 to 62)		-3 (-36 to 30)	-2 (-31 to 27)	20 (6 to 33)	
Tenofovir disoproxil fumarate/emtricitabine	-5 (-44 to 62)		-5 (-34 to 23)		46 (-2 to 94)	
Vitamin C	82 (-10 to 220)		-3 (-36 to 30)	-1 (-31 to 27)	46 (27 to 65)	
Vitamin C, zinc	-3 (-44 to 67)		-3 (-36 to 30)	-1 (-31 to 27)	69 (47 to 90)	

Footnotes

1. The expected risk of each outcome with standard care. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care
2. Minimal important differences were used to support judgements of imprecision
3. Due to low event rate, this outcome was analyzed as a risk difference
4. Due to low event rate, this outcome was analyzed as a risk difference
5. Due to low event rate, this outcome was analyzed as a risk difference

*Best estimate of effect was obtained from direct evidence

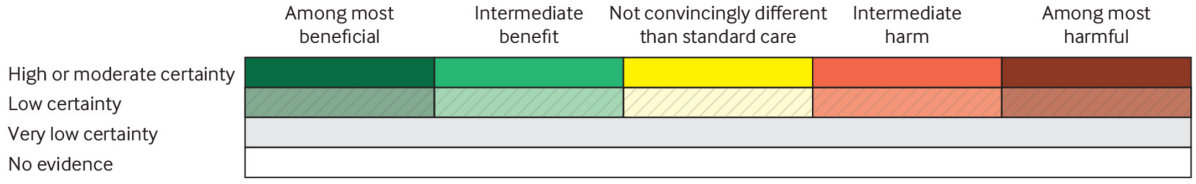

Fig 3 | Summary of effects of interventions compared with standard care

Laboratory confirmed SARS-CoV-2 infection

Twenty three trials with 22 164 participants who were PCR-negative at baseline reported on laboratory confirmed SARS-CoV-2 infection and were included in random effects bayesian network meta-analysis (fig 3). Sixteen different prophylactic drugs were included: the three most common were hydroxychloroquine (5000 participants), cilgavimab combined with tixagevimab (3441 participants), and casirivimab combined with imdevimab (1482 participants). Cilgavimab combined with tixagevimab may reduce the risk of laboratory confirmed SARS-CoV-2 infection (risk difference 48 fewer per 1000, 95% credible interval 62 fewer to 17 fewer; low certainty evidence). Casirivimab combined with imdevimab reduced the risk of laboratory confirmed infection in populations in which it was studied (53 fewer per 1000 participants, 95% credible interval 62 fewer to 40 fewer); however, certainty that it reduces infection is very low because of very serious indirectness (laboratory evidence suggests that it is ineffective against the omicron variant of concern (the predominant circulating SARS-CoV-2 variant at the time of publication)). Compared with standard care/placebo, hydroxychloroquine probably has trivial to no effect (2 fewer per 1000, 18 fewer to 19 more; moderate certainty evidence), and bamlavimab may have trivial to no effect (24 fewer per 1000, 50 fewer to 24 more; low certainty evidence). There was insufficient evidence to know if any other prophylactic drug reduces the risk of laboratory confirmed SARS-CoV-2 infection.

Suspected, probable, or laboratory confirmed SARS-CoV-2 infection

Eight trials with 7847 participants reported on the composite of suspected, probable, or laboratory confirmed SARS-CoV-2 infection and were included in random effects bayesian network meta-analysis (fig 3). Three different prophylactic drugs were included: hydroxychloroquine (3600 participants), casirivimab combined with imdevimab (729 participants), and ivermectin (203 participants). Compared with standard care/placebo, hydroxychloroquine probably has trivial to no effect (10 fewer per 1000, 28 fewer to 10 more; moderate certainty evidence). There was

insufficient evidence to know if ivermectin and casirivimab combined with imdevimab reduce the risk of the composite of suspected, probable, or laboratory confirmed SARS-CoV-2 infection.

Hospital admission

Fifteen trials with 19 444 participants reported on hospital admission and were included in random effects bayesian network meta-analysis (fig 3). Eleven different prophylactic drugs were included: the three most common were hydroxychloroquine (4498 participants), cilgavimab combined with tixagevimab (3641 participants), and casirivimab combined with imdevimab (1311 participants). Hydroxychloroquine probably has trivial to no effect on hospital admission (2 fewer per 1000, 6 fewer to 2 more; moderate certainty evidence). Low certainty evidence suggests the following prophylactic drugs may have trivial to no effect on hospital admission: cilgavimab combined with tixagevimab (4 fewer per 1000, 35 fewer to 27 more), hydroxychloroquine combined with tenofovir disoproxil fumarate/emtricitabine (5 fewer per 1000, 34 fewer to 24 more), iota-carrageenan (0 difference per 1000, 32 fewer to 32 more), melatonin (0 difference per 1000, 33 fewer to 33 more) and tenofovir disoproxil fumarate/emtricitabine (5 fewer per 1000, 34 fewer to 23 more). We are very uncertain about the effect of all other drugs on admission to hospital (very low certainty evidence).

Mortality

Fifteen trials with 20 624 participants reported on mortality and were included in random effect bayesian network meta-analysis (fig 3). Ten different prophylactic drugs were included: the three most common were hydroxychloroquine (4104 participants), cilgavimab combined with tixagevimab (3461 participants) and casirivimab combined with imdevimab (2040 participants). Compared with standard care/placebo, hydroxychloroquine has trivial to no effect on mortality (0 difference per 1000, 3 fewer to 2 more; high certainty evidence). Low certainty evidence suggests that bamlanivimab, cilgavimab combined with tixagevimab, and iota-carrageenan may have trivial to no effect on mortality. There was insufficient evidence to know if casirivimab combined with imdevimab, ivermectin, lopinavir-ritonavir, povidone-iodine, vitamin C, or vitamin C combined with zinc reduce the risk of mortality.

Adverse effects leading to drug discontinuation

Fifteen trials with 13 447 participants reported adverse effects leading to drug discontinuation and were included in random effect bayesian network meta-analysis (fig 3). Ten different prophylactic drugs were included: the three most common were hydroxychloroquine (3535 participants), casirivimab combined with imdevimab (2040 participants) and povidone-iodine (735 participants). Hydroxychloroquine (6 more per 1000, 2 more to 10 more) and vitamin C combined with zinc (69 more per 1000, 47 more to 90 more) probably increase the risk of adverse effects leading to drug discontinuation (moderate certainty evidence). Low certainty evidence suggests that the risk of adverse effects leading to drug discontinuation may be increased by povidone-iodine (20 more per 1000, 6 more to 33 more) and vitamin C (46 more per 1000, 27 more to 65 more). Silver nanoparticles, iota-carrageenan, iota-carrageenan combined with ivermectin, and tenofovir disoproxil fumarate/emtricitabine (prophylactic drugs for which there is moderate certainty evidence) probably have trivial to no effect on adverse effects leading to drug discontinuation. Low certainty evidence suggests casirivimab combined with imdevimab and hydroxychloroquine combined with tenofovir disoproxil fumarate/emtricitabine may have trivial to no effect on adverse effects leading to drug discontinuation.

Time to symptom resolution or clinical improvement

Among two trials that reported on time to symptom resolution or clinical improvement in the subset of participants that developed SARS-CoV-2 infection, different prophylactic drugs were assessed precluding meta-analysis. Further, neither trial met the sample size criteria for network meta-analysis.

Subgroup analysis

Extremely low event rates and consistency between trials precluded investigation of subgroup effects by exposure status, publication status and risk of bias.

Discussion

This living systematic review and network meta-analysis provides a comprehensive overview of the evidence for prophylaxis against covid-19 up to 4 March 2022 and directly informs WHO living guidelines on drugs to prevent covid-19.[5] The second iteration of this living network meta-analysis includes evidence evaluating 16 different prophylactic drugs; of which, none provided convincing evidence of a reduction in the risk of laboratory confirmed SARS-CoV-2 infection. Cilgavimab combined with tixagevimab, an anti-SARS-CoV-2 antiviral, may reduce the risk of laboratory confirmed SARS-CoV-2 infection, but certainty was low. Study results addressing admission to hospital and mortality provide no evidence to at least moderate certainty evidence—none of which supports any benefit. Prophylactic drugs which probably increase adverse effects include hydroxychloroquine and vitamin C combined with zinc (moderate certainty evidence).

These findings are consistent with those reported in a meta-analysis of hydroxychloroquine prophylaxis against no prophylaxis, which did not find any statistical evidence of a benefit with hydroxychloroquine prophylaxis for the patient-important outcomes of SARS-CoV-2 infection, hospital admission, and death.[61] The study, which included fewer randomised trials for hydroxychloroquine than our systematic review, concluded that hydroxychloroquine is likely to increase the risk of adverse effects.[61] Further, our data are consistent with two meta-analyses[62 63] and one network meta-analysis[9] of ivermectin as treatment for covid-19. In contrast to other meta-analyses, we rated the certainty as very low due to serious risk of bias and very serious imprecision.[62 63] The finding that vitamin C combined with zinc probably increases adverse effects is consistent with evidence regarding vitamin C and zinc as treatment for covid-19—both can cause gastrointestinal intolerance.[64 65]

The risk of death is much lower in people at risk of covid-19 compared with those diagnosed with covid-19.[9] Similarly, the risk of SARS-CoV-2 infection varies depending on pre- or post-exposure status and setting. Therefore, prophylactic research necessitates large trials and/or a focus on the highest risk populations to detect a possible benefit on outcomes of most importance to patients. Thus far, the cumulative evidence has been underpowered to detect differences in mortality. Further, rare but important harms may not be detected with randomised trials unless they enrol a large sample size, diligently follow up participants to ascertain these outcomes, or include patients at greater risk. Guideline panels, which independently rate the certainty of the evidence, therefore have to consider the trade-offs between concluding probably no benefit and meaningful adverse effects, and waiting for more precise data. For example, the WHO living guidelines issued a strong recommendation against hydroxychloroquine for prophylaxis in covid-19.[5]

Strengths and limitations of this review

This second iteration incorporates the most up-to-date evidence on prophylactic drugs for covid-19, including vitamins and antiviral antibodies. It adds to our living systematic review on drugs for covid-19 and directly informs the WHO living guidelines, together constituting major innovations in the evidence ecosystem.[5] Since the first iteration, one trial addressing ivermectin and showing large positive effects was retracted.[59] The living nature of our systematic review and network meta-analysis enables the exclusion of retracted data from this second iteration and between subsequent iterations if needed. Further, since 4 March 2022, we identified 15 new randomised trials to include in the subsequent iteration of this living systematic review and network meta-analysis.[66-80]

The search strategy was comprehensive with explicit eligibility criteria and no restrictions on the language of publication. To ensure expertise in all areas, our team includes clinical and methods experts who have undergone training and calibration exercises for all stages of the review process. In order to avoid spurious findings, we prespecified that we would only analyse interventions to which at least 100 people had been randomised or 20 events have been observed. Eight randomised trials of ramipril,[41] bromhexine hydrochloride,[51] convalescent plasma,[53] *Loigolactobacillus corynormis* K8 strain,[44] Bactoblis oropharyngeal probiotic,[54] neutralised electrolysed water,[47] and anti-SARS-CoV-2 RBD IgY[57] were therefore omitted from the network meta-analysis.[9]

The GRADE approach provided the structure for rating certainty of evidence and interpreting the results considering absolute effects. To rate the GRADE domain of imprecision, we prespecified thresholds of effect that most would consider small but important. In the absence of empirical data, these thresholds represent our collective experience but are, to a large extent, arbitrary. People placing a larger or smaller value on certain outcomes may reasonably make different inferences about the certainty of evidence for no important effect. For example, people who consider that the smallest important effect in mortality is increasing or reducing 4 per 1000 or more deaths, would not rate down the certainty of the evidence due to imprecision and conclude that hydroxychloroquine does not have an effect on this outcome (that is, high certainty).

With regard to the limitations of this review, one cluster randomised trial did not report the design effect or the intracluster correlation coefficient itself necessary to calculate the design effect, precluding adjustment in analyses—potentially leading to falsely narrow credible intervals.[33] Cluster sizes were, however, small, making substantial bias unlikely.

The living nature of our systematic review and network meta-analysis could amplify publication bias, because studies with promising results are more likely to be published and are published sooner than studies with negative results. Given the failure of hydroxychloroquine trials to show benefit, this is not a concern for hydroxychloroquine. We include these data, regardless of publication status and risk of bias, because of the urgent need for information and because so many of the studies on covid-19 are published first as preprints.

A limitation of the evidence to date is lack of blinding, which might introduce bias through differences in co-interventions between randomisation groups, especially when measuring the outcomes clinically suspected and probable infection, and adverse effects leading to discontinuation of the drug. We chose to consider the treatment arms that did not receive an active experimental drug (that is, placebo or standard care) within the same node: it is possible that unblinded standard care groups may have received systematically different co-interventions or changed their personal protective behaviours when compared with groups randomised to receive a placebo. Laboratory confirmation mitigates risk of bias from lack of blinding in outcome measurement; however, the availability of diagnostic testing differs across health systems, warranting the additional use of a symptomatic case definition for infection. This was the case for the majority of participants, including healthcare workers, enrolled in one study in the United States, which risked overestimating incidence of infection by using a symptomatic definition for infection.[30 81]

A limitation of the evidence for anti-SARS-CoV-2 antivirals is its applicability to people at risk of covid-19 today and in the future. The participants in the randomised trials that evaluated bamlanivimab, casirivimab combined with imdevimab, and cilgavimab combined with tixagevimab were at risk of being infected with SARS-CoV-2 strains that are different from those in widespread circulation today. At the time of publication, the WHO guideline panel no longer recommends using any of these antiviral antibodies because the currently circulating SARS-CoV-2 strains (omicron lineages and sublineages) are resistant to them. Any benefit for these antibodies, particularly cilgavimab combined with tixagevimab, is almost certainly overstated in our network meta-analysis. For that reason, our GRADE certainty is lower because of very serious concerns about indirectness.

Much of the evidence remains very low certainty, and we anticipate that future studies evaluating drugs for prophylaxis may substantially change the results, particularly for outcomes of laboratory confirmed SARS-CoV-2 infection and mortality. We will periodically update this living systematic review and network meta-analysis. The changes from each iteration will be highlighted for readers, and the most updated version will be the one available in the publication platform. Previous iterations will be archived in the supplementary material. This living systematic review and network meta-analysis is accompanied by an interactive infographic and a website for users to access the most updated results in a user friendly format (https://app.magicapp.org/public/guideline/L6RxYL, www.covid19lnma.com).

Conclusions

This living systematic review and network meta-analysis on prophylactic drugs for covid-19 reports results for 16 different prophylactic drugs—none of which provide convincing evidence of a reduction in the risk of SARS-COV-2 infection, admission to hospital, or mortality. However, both hydroxychloroquine and vitamin C combined with zinc probably increase adverse effects. Because much of the evidence remains uncertain, we anticipate future studies evaluating drugs for prophylaxis may substantially change the results of our network meta-analysis.

What is already known on this topic

- Effective prophylaxis for covid-19 could have a global impact in preventing infection and attenuating disease
- This is the second iteration of our living network meta-analysis on prophylaxis for covid-19

What this study adds

- Review of 21 of 32 randomised trials (66%), 18 162 of 25 147 participants (75%), 16 of 21 prophylactic drugs (76%)
- Of 16 drugs analysed, none showed convincing evidence of a reduction in the risk of laboratory confirmed SARS-CoV-2 infection caused by the viral strains circulating at the time of publication

- Study results evaluating 13 different prophylactic drugs were analysed for admission to hospital and mortality—none of which support any benefit
- Both hydroxychloroquine and vitamin C combined with zinc probably increase adverse effects

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RACS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The infographic and MAGICapp decision aids (available at www.magicapp.org/) were created to facilitate conversations between healthcare providers and patients or their surrogates. The MAGICapp decision aids were co-created with people who have lived experience of covid-19.

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Data sharing: No additional data available.

1 Johns Hopkins University. Coronavirus Resource Center. 2020 https://coronavirus.jhu.edu/map.html.

2 Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions. 2021. www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html.

3 Krakower DS, Jain S, Mayer KH. Antiretrovirals for primary HIV prevention: the current status of pre- and post-exposure prophylaxis. *Curr HIV/AIDS Rep* 2015;12:-38. . doi: 10.1007/s11904-014-0253-5 pmid: 25600106

4 Vandvik PO, Brignardello-Petersen R, Guyatt GH. Living cumulative network meta-analysis to reduce waste in research: A paradigmatic shift for systematic reviews? *BMC Med* 2016;14:. . doi: 10.1186/s12916-016-0596-4 pmid: 27025849

5 Lamontagne F, Agoritsas T, Siemieniuk R, etal. A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021;372:. doi: 10.1136/bmj.n526 pmid: 33649077

6 Agarwal A, Rochwerg B, Lamontagne F, etal. A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:.pmid: 32887691

7 Puhan MA, Schünemann HJ, Murad MH, etalGRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:. doi: 10.1136/bmj.g5630 pmid: 25252733

8 Siemieniuk RA, Bartoszko JJ, Díaz Martinez JP, etal. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. *BMJ* 2021;374:. doi: 10.1136/bmj.n2231 pmid: 34556486

9 Siemieniuk RAC, Bartoszko JJ, Ge L, etal. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:. doi: 10.1136/bmj.m2980 pmid: 32732190

10 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:. doi: 10.1136/bmj.i5191 pmid: 27680768

11 Hutton B, Salanti G, Caldwell DM, etal. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:-84. doi: 10.7326/M14-2385 pmid: 26030634

12 Elliott JH, Synnot A, Turner T, etalLiving Systematic Review Network. Living systematic review: 1. Introduction-the why, what, when, and how. *J Clin Epidemiol* 2017;91:-30. doi: 10.1016/j.jclinepi.2017.08.010 pmid: 28912002

13 World Health Organization. Global research on coronavirus disease (COVID-19). www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov

14 The Stephen B. Thacker CDC Library. COVID-19 Research Articles Downloadable Database: U.S. Centers for Disease Control and Prevention (CDC); 2020 www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html.

15 Marshall IJ, Noel-Storr A, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying Randomized Controlled Trials: An evaluation and practitioner's guide. *Res Synth Methods* 2018;9:-14. doi: 10.1002/jrsm.1287 pmid: 29314757

16 Epistemonikos Foundation. Living evidence repository for COVID-19. 2020. https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d.

17 Norwegian Institute of Public Health. NIPH systematic and living map on COVID-19 evidence 2020. 2020. www.nornesk.no/forskningskart/NIPH_mainMap.html.

18 Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia.

19 Sterne JAC, Savović J, Page MJ, etal. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:. doi: 10.1136/bmj.l4898 pmid: 31462531

20 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8:e76654. . doi: 10.1371/journal.pone.0076654 pmid: 24098547

21 gemtc: Network meta-analysis using Bayesian methods. R package version 0.8-4 version, 2020.

22 van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods* 2016;7:-93. doi: 10.1002/jrsm.1167 pmid: 26461181

23 Roever C. Bayesian random-effects meta-analysis using the bayesmeta R package. *J Stat Softw* 2020;93:-51doi: 10.18637/jss.v093.i06 .

24 Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat Med* 2015;34:-98. doi: 10.1002/sim.6381 pmid: 25475839

25 Brignardello-Petersen R, Bonner A, Alexander PE, etalGRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol* 2018;93:-44. doi: 10.1016/j.jclinepi.2017.10.005 pmid: 29051107

26 Brignardello-Petersen R, Florez ID, Izcovich A, etalGRADE working group. GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework. *BMJ* 2020;371:. doi: 10.1136/bmj.m3900 pmid: 33177059

27 Schandelmaier S, Briel M, Varadhan R, etal. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020;192:-6. doi: 10.1503/cmaj.200077 pmid: 32778601

28 Abella BS, Jolkovsky EL, Biney BT, etalPrevention and Treatment of COVID-19 With Hydroxychloroquine (PATCH) Investigators. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med* 2021;181:-202. doi: 10.1001/jamainternmed.2020.6319 pmid: 33001138

29 Barnabas RV, Brown ER, Bershteyn A, etalHydroxychloroquine COVID-19 PEP Study Team. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection: a randomized trial. *Ann Intern Med* 2021;174:-52. doi: 10.7326/M20-6519 pmid: 33284679

30 Boulware DR, Pullen MF, Bangdiwala AS, etal. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020;383:-25. . doi: 10.1056/NEJMoa2016638 pmid: 32492293

31 Grau-Pujol B, Camprubí-Ferrer D, Marti-Soler H, etal. Pre-exposure prophylaxis with hydroxychloroquine for COVID-19: a double-blind, placebo-controlled randomized clinical trial. *Trials* 2021;22:. doi: 10.1186/s13063-021-05758-9 pmid: 34781981

32 McKinnon JE, Wang DD, Zervos M, etal. Safety and tolerability of hydroxychloroquine in health care workers and first responders for the prevention of COVID-19: WHIP COVID-19 Study. *Int J Infect Dis* 2022;116:-73. doi: 10.1016/j.ijid.2021.12.343 pmid: 34954095

33 Mitjà O, Corbacho-Monné M, Ubals M, etalBCN-PEP-CoV2 Research Group. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. *N Engl J Med* 2021;384:-27. doi: 10.1056/NEJMoa2021801 pmid: 33289973

34 Naggie S, Milstone A, Castro M, etal. Hydroxychloroquine for pre-exposure prophylaxis of COVID-19 in health care workers: a randomized, multicenter, placebo-controlled trial (HERO-HCQ).*medRxiv* 2021:2021.08.19.21262275doi: 10.1101/2021.08.19.21262275 .

35 Rajasingham R, Bangdiwala AS, Nicol MR, etalCOVID PREP team. Hydroxychloroquine as pre-exposure prophylaxis for coronavirus disease 2019 (COVID-19) in healthcare workers: a randomized trial. *Clin Infect Dis* 2021;72:-43. doi: 10.1093/cid/ciaa1571 pmid: 33068425

36 Rojas-Serrano J, Portillo-Vásquez AM, Thirion-Romero I, etal. Hydroxychloroquine for prophylaxis of COVID-19 in health workers: A randomized clinical trial. *PLoS One* 2022;17:e0261980. doi: 10.1371/journal.pone.0261980 pmid: 35139097

37 Seet RCS, Quek AML, Ooi DSQ, etal. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial. *Int J Infect Dis* 2021;106:-22. doi: 10.1016/j.ijid.2021.04.035 pmid: 33864917

38 Syed F, Hassan M, Arif MA, etal. Pre-exposure prophylaxis with various doses of hydroxychloroquine among healthcare personnel with high-risk exposure to COVID-19: a randomized controlled trial. *Cureus* 2021;13:e20572. doi: 10.7759/cureus.20572 pmid: 35103151

39 Tirupakuzhi Vijayaraghavan BK, Jha V, Rajbhandari D, etalHOPE Investigators. Hydroxychloroquine plus standard personal protective equipment versus personal protective equipment alone for the prevention of laboratory-confirmed COVID-19 infections among healthcare workers: a multi-centre parallel-group randomised controlled trial from India. *BMJ Open* 2022;12:e059540. doi: 10.1136/bmjopen-2021-059540 pmid: 35649613

40 Polo R, García-Albéniz X, Terán C, etalEPICOS. Daily tenofovir disoproxil fumarate/emtricitabine and hydroxychloroquine for pre-exposure prophylaxis for COVID-19: a double-blind placebo-controlled randomized trial in healthcare workers. *Clin Microbiol Infect* 2023;29:-93. doi: 10.1016/j.cmi.2022.07.006 pmid: 35940567

41 Amat-Santos IJ, Santos-Martinez S, López-Otero D, etal. Ramipril in high-risk patients with COVID-19. *J Am Coll Cardiol* 2020;76:-76. doi: 10.1016/j.jacc.2020.05.040 pmid: 32470515

42 Chahla RE, Medina Ruiz L, Ortega ES, etal. A randomized trial - intensive treatment based in ivermectin and iota-carrageenan as pre-exposure prophylaxis for covid- 19 in healthcare agents.*medRxiv* . 2021:2021.03.26.21254398doi: 10.1101/2021.03.26.21254398 .

43 Cohen MS, Nirula A, Mulligan MJ, etalBLAZE-2 Investigators. Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. *JAMA* 2021;326:-55. doi: 10.1001/jama.2021.8828 pmid: 34081073

44 Fernández-Ferreiro A, Formigo-Couceiro FJ, Veiga-Gutierrez R, etal. Effects of *Loigolactobacillus coryniformis* K8 CECT 5711 on the immune response of elderly subjects to COVID-19 vaccination: a randomized controlled trial. *Nutrients* 2022;14:. doi: 10.3390/nu14010228 pmid: 35011103

45 Figueroa JM, Lombardo ME, Dogliotti A, etal. Efficacy of a nasal spray containing iota-carrageenan in the postexposure prophylaxis of COVID-19 in hospital personnel dedicated to patients care with COVID-19 disease. *Int J Gen Med* 2021;14:-86. doi: 10.2147/IJGM.S328486 pmid: 34629893

46 García-García I, Seco-Meseguer E, Ruiz-Seco P, etal. Melatonin in the prophylaxis of SARS-CoV-2 infection in healthcare workers (MeCOVID): a randomised clinical trial. *J Clin Med* 2022;11:. doi: 10.3390/jcm11041139 pmid: 35207411

47 Gutiérrez-García R, De La Cerda-Ángeles JC, Cabrera-Licona A, Delgado-Enciso I, Mervitch-Sigal N, Paz-Michel BA. Nasopharyngeal and oropharyngeal rinses with neutral electrolyzed water prevents COVID-19 in front-line health professionals: A randomized, open-label, controlled trial in a general hospital in Mexico City. *Biomed Rep* 2022;16:. doi: 10.3892/br.2021.1494 pmid: 34987795

48 Hosseinzadeh A, Emamian MH, Tavakolian A, etal. Application of nasal spray containing dimethyl sulfoxide (DSMO) and ethanol during the COVID-19 pandemic may protect healthcare workers: A randomized controlled trials.*medRxiv* . 2021:2021.07.06.21259749.

49 Labhardt ND, Smit M, Petignat I, etal. Efficacy of lopinavir-ritonavir prophylaxis for individuals exposed to SARS-CoV-2: The COPEP pragmatic open-label, cluster randomized trial.*SSRN* 2021doi: 10.2139/ssrn.3878828 .

50 Levin MJ, Ustianowski A, De Wit S, etalPROVENT Study Group. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for prevention of Covid-19. *N Engl J Med* 2022;386:-200. doi: 10.1056/NEJMoa2116620 pmid: 35443106

51 Mikhaylov EN, Lyubimtseva TA, Vakhrushev AD, etal. Bromhexine hydrochloride prophylaxis of COVID-19 for medical personnel: a randomized open-label study. *Interdiscip Perspect Infect Dis* 2022;2022:4693121. doi: 10.1155/2022/4693121 pmid: 35103059

52 O'Brien MP, Forleo-Neto E, Musser BJ, etalCovid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV antibody combination to prevent Covid-19. *N Engl J Med* 2021;385:-95. doi: 10.1056/NEJMoa2109682 pmid: 34347950

53 Shoham S, Bloch EM, Casadevall A, etal. Randomized controlled trial transfusing convalescent plasma as post-exposure prophylaxis against SARS-CoV-2 infection.*medRxiv* 2021doi: 10.1101/2021.12.13.21267611 .

54 Wang Q, Lin X, Xiang X, etal. Oropharyngeal probiotic ENT-K12 prevents respiratory tract infections among frontline medical staff fighting against COVID-19: a pilot study. *Front Bioeng Biotechnol* 2021;9:646184. doi: 10.3389/fbioe.2021.646184 pmid: 34249878

55 Almanza-Reyes H, Moreno S, Plascencia-López I, etal. Evaluation of silver nanoparticles for the prevention of SARS-CoV-2 infection in health workers: In vitro and in vivo. *PLoS One* 2021;16:e0256401. doi: 10.1371/journal.pone.0256401 pmid: 34411199

56 Shouman WM, Hegazy AA, Nafae RM, etal. Use of ivermectin as a potential chemoprophylaxis for COVID-19 in Egypt: a randomised clinical trial. *J Clin Diagn Res* 2021doi: 10.7860/JCDR/2021/46795.14529 .

57 Frumkin LR, Lucas M, Scribner CL, etal. Egg-derived anti-SARS-CoV-2 immunoglobulin Y (IgY) with broad variant activity as intranasal prophylaxis against COVID-19: preclinical studies and randomized controlled phase 1 clinical trial.*medRxiv* 2022:2022.01.07.22268914.

58 Isa F, Forleo-Neto E, Meyer J, etal. Repeat subcutaneous administration of REGEN-COV in adults is well-tolerated and prevents the occurrence of COVID-19.*medRxiv* 2021:2021.11.10.21265889doi: 10.1101/2021.11.10.21265889 .

59 Elgazzar A, Eltaweel A, Youssef SA, Hany B, Hafez M, Moussa H. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic.*Research Square* 2020.

60 Lofgren SM, Nicol MR, Bangdiwala AS, etal. Safety of hydroxychloroquine among outpatient clinical trial participants for COVID-19.*medRxiv* 2020:2020.07.16.20155531doi: 10.1101/2020.07.16.20155531 .

61 Lewis K, Chaudhuri D, Alshamsi F, etalGUIDE Group. The efficacy and safety of hydroxychloroquine for COVID-19 prophylaxis: A systematic review and meta-analysis of randomized trials. *PLoS One* 2021;16:e0244778. doi: 10.1371/journal.pone.0244778 pmid: 33406138

62 Padhy BM, Mohanty RR, Das S, Meher BR. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis. *J Pharm Pharm Sci* 2020;23:-9. doi: 10.18433/jpps31457 pmid: 33227231

63 Castañeda-Sabogal A, Chambergo-Michilot D, Toro-Huamanchumo CJ, Silva-Rengifo C, Gonzales-Zamora J, Barboza JJ. Outcomes of ivermectin in the treatment of COVID-19: a systematic review and meta-analysis.*medRxiv* 2021:2021.01.26.21250420doi: 10.1101/2021.01.26.21250420 .

64 Weismann K, Jakobsen JP, Weismann JE, etal. Zinc gluconate lozenges for common cold. A double-blind clinical trial. *Dan Med Bull* 1990;37:-81.pmid: 2192839

65 Thomas S, Patel D, Bittel B, etal. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. *JAMA Netw Open* 2021;4:e210369. doi: 10.1001/jamanetworkopen.2021.0369 pmid: 33576820

66 Jolliffe DA, Holt H, Greenig M, etal. Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomised controlled trial (CORONAVIT). *BMJ* 2022;378:e071230. doi: 10.1136/bmj-2022-071230 pmid: 36215226

67 Ahanchian H, Ranjbar A, Reihani H, etal. Synbiotic for prevention of SARS-Cov2 infection in high risk hospital staffs: A randomized controlled trial. *Open J Nurs* 2021;11. doi: 10.4236/ojn.2021.115025.

68 Tolouian R, Moradi O, Mulla ZD, etal. Bromhexine, for post exposure COVID-19 prophylaxis: a randomized, double-blind, placebo control trial.*SSRN* 2021. https://ssrn.com/abstract=3989849doi: 10.2139/ssrn.3989849.

69 Stambouli N, Driss A, Gargouri F, etalOD-doxy-PNV-COVID-19 Trial. COVID-19 prophylaxis with doxycycline and zinc in health care workers: a prospective, randomized, double-blind clinical trial. *Int J Infect Dis* 2022;122:-8. doi: 10.1016/j.ijid.2022.06.016 pmid: 35724828

70 Balmforth D, Swales JA, Silpa L, etal. Evaluating the efficacy and safety of a novel prophylactic nasal spray in the prevention of SARS-CoV-2 infection: A multi-centre, double blind, placebo-controlled, randomised trial. *J Clin Virol* 2022;155:105248. doi: 10.1016/j.jcv.2022.105248 pmid: 35952426

71 Hosseini B, Tremblay CL, Longo C, etal. Prevention of COVID-19 with oral vitamin D supplemental therapy in essential healthcare teams (PROTECT): ancillary study of a randomised controlled trial.*Research Square* 2022. doi: 10.21203/rs.3.rs-1588325/v1 .

72 Rodriguez-Blanque R, Sánchez-García JC, Cobos-Vargas Á, etal. Evaluation of the effect of *Loigolactobacillus coryniformis* K8 CECT 5711 consumption in health care workers exposed to COVID-19. *Front Nutr* 2022;9:962566. doi: 10.3389/fnut.2022.962566 pmid: 35990320

73 Sokhela S, Bosch B, Hill A, etal. Randomized clinical trial of nitazoxanide or sofosbuvir/daclatasvir for the prevention of SARS-CoV-2 infection. *J Antimicrob Chemother* 2022;77:-12. doi: 10.1093/jac/dkac266 pmid: 35953881

74 Wischmeyer P, Tang H, Ren Y, etal. Efficacy of probiotic treatment as post-exposure prophylaxis for COVID-19: a double-blind, placebo controlled randomized trial.*Research Square* 2022doi: 10.21203/rs.3.rs-1930760/v1 .

75 Bath PM, Skinner CJC, Bath CS, etalfor BEET-Winter Investigators. Dietary nitrate supplementation for preventing and reducing the severity of winter infections, including COVID-19, in care homes (BEET-Winter): a randomised placebo-controlled feasibility trial. *Eur Geriatr Med* 2022;13:-55. doi: 10.1007/s41999-022-00714-5 pmid: 36385690

76 Imsuwansri T, Jongthitinon T, Pojdoung N, etal. A randomized, placebo-controlled trial of a nasal spray solution containing broadly potent neutralizing antibodies against SARS-CoV-2 variants in healthy volunteers.*medRxiv* . 2022:2022.10.04.22280574doi: 10.1101/2022.10.04.22280574 .

77 Karonova TL, Chernikova AT, Golovatyuk KA, etal. Vitamin D intake may reduce SARS-CoV-2 infection morbidity in health care workers. *Nutrients* 2022;14:. doi: 10.3390/nu14030505 pmid: 35276863

78 Mair MJ, Maj-Hes A, Nussbaumer-Pröll A, etal. Prophylactic treatment with oral azithromycin in patients with cancer during the COVID-19 pandemic (OnCoVID): a randomized, single-blind, placebo-controlled phase 2 trial. *Infect Agent Cancer* 2023;18:. doi: 10.1186/s13027-023-00487-x pmid: 36782325

79 van Helmond N, Brobyn TL, LaRiccia PJ, etal. Vitamin D3 supplementation at 5000 IU daily for the prevention of influenza-like illness in healthcare workers: a randomized clinical trial.*medRxiv* 2022:2022.09.16.22280047.

80 Villasis-Keever MA, López-Alarcón MG, Miranda-Novales G, etal. Efficacy and safety of vitamin D supplementation to prevent COVID-19 in frontline healthcare workers. a randomized clinical trial. *Arch Med Res* 2022;53:-30. doi: 10.1016/j.arcmed.2022.04.003 pmid: 35487792

81 Guyatt GH, Oxman AD, Vist G, etal. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64:-15. doi: 10.1016/j.jclinepi.2010.07.017 pmid: 21247734