PROTOCOL

Ivermectin for prevention and treatment of covid-19

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Update 27-02-2021: Differences between protocol and items reported in review:
Improvement and deterioration, as measured by were added as additional post-hoc outcomes as they were identified as being important and useful outcomes

Meta-analyses used inverse variance method rather than Mantel-Haentzel (MH) method for weighting. This was just for consistency across all outcomes. MH is used in various sensitivity analyses.

A systematic review is awaiting publication and results will be disseminated soon.

Background

Description of the condition

In countries across the world, hospitalisations and deaths from covid-19 have increased rapidly over recent months with total deaths now exceeding 2 million people (WHO Dashboard) These figures may be underestimates of the true burden of this disease as in many settings tests are not readily available. As a result of the pandemic, there has been increased pressure on health care systems, with greater increases in health care spending. For example, health care spending in the UK, has increased by an additional £48.3billion (The Health Foundation 2020).There is a unique challenge in responding to the covid-19 pandemic in low- and middle-income countries (LMICs) where there are limited resources, which results in poorer quality and availability of health care resources compared to high-income countries (Walker 2020). As such, finding evidence for treatments that are both clinically and cost effective are crucially important in the development of future management strategies for covid-19 in the context of different health care systems.

To date, very few treatments have been identified that have been demonstrated to reduce the burden of morbidity and mortality from covid-19. While corticosteroids are used in those with severe illness and have been shown to reduce mortality in severely ill hospitalised patients (Horby 2020), outpatient interventions that may prevent disease, reduce hospitalisations and reduce the numbers of people progressing to critical disease have been comparatively neglected in public policy (McCullough 2020).

Description of the intervention

Ivermectin is an anti-parasitic medication widely used in low- and middle-income countries LMICs to treat parasitic worm infections, scabies and lice (Barrow 2016; Conterno 2020). It is on the World Health Organisation's *Essential Medicines List* (WHO 2019). With total doses of ivermectin distributed apparently equalling one-third of the present world population (Nicolas 2020), ivermectin at the usual doses (0.2 mg/kg in scabies or strongyloidiasis) is considered extremely safe for use in humans (Banerjee 2020; Navarro 2020; WHO 2018b). It is suggested to avoid used in pregnancy and the first week of lactation. Due to its anti-parasitic, antiviral and anti-inflammatory properties, it has been noted to have an increasing list of medical indications (Kircik 2016).

Ivermectin's utility has expanded considerably over the last decade and, since April 2020, a large and growing database of observational and randomised studies of ivermectin use against covid-19 has been accumulating. There is preliminary evidence to suggest ivermectin may be a useful drug in the treatment and possibly prevention of covid-19 infection (Carvallo 2020; Chamie-Quintero 2021; Clancy 2021; Kory 2021). However, there is currently no comprehensive systematic review in this area. A review by the Front Line Covid-19 Critical Care Alliance (FLCCC) summarised findings from 27 studies on the effects of ivermectin for the prevention and treatment of covid-19 infection, which reports favourable results for ivermectin (Kory 2021) and another recent review found that ivermectin reduced deaths by 75% (Hill 2021). Certain South American countries, Indian states, and more recently Slovakia and other countries in Europe have implemented its use for covid-19 (Chamie-Quintero 2021; CGTH 2021; Trial Site News 2021; Bolivia 2020; Honduras 2021). However, the National Institute of Health in the US recently stated that "there are insufficient data to recommend either for or against the use of ivermectin for the treatment of covid-19" (NIH 2021).

How the intervention might work

Ivermectin has been shown to have antiviral activity against a wide range of RNA viruses and some DNA viruses including zika, dengue, yellow fever, sindbis, and others (Heidary 2020). A dominant mechanism of action of ivermectin as an anti-viral is believed to be a host-directed blocking of the nuclear import of viral proteins (Caly 2020; Heidary 2020). If imported into the host nucleus, these proteins play a key role in viral replication by suppressing the normal immune response to infection. Caly 2020 demonstrated that a single ivermectin treatment virtually obliterates the SARS-CoV-2 virus at 48 hours in vitro. Other mechanisms of action include virus-directed effects such as inhibition of SARS-CoV-2 3CLPro (3-Chymostrypsin-Like Protease) enzymatic activity. As the latter is essential for viral replication, it is considered an excellent target for anti-SARS drugs (Anand 2003; Mody 2021). Several anti-inflammatory effects have also been demonstrated (DiNicolantonio 2020). Candidate mechanisms thus span both the initial infectious disease stage, and the

later inflammatory stages. According to the FLCCC group, ivermectin is the sole therapeutic to have demonstrated utility at all stages of the complex clinical course of covid-19 (Kory 2021), from prophylaxis to critical care.

Why it is important to do this review

Development of new medicines takes years; therefore, existing medicines that can be re-purposed against covid-19 and that already have a strong safety profile through decades of use could play a critical role in ending the SARS-CoV-2 pandemic. Using re-purposed medicines may be especially important because it could take months for much of the world's population to get vaccinated, particularly among low- and middle-income country (LMIC) populations. Drug re-purposing has been proposed as an alternative to developing de-novo treatment for covid-19, given the costly and time-consuming process involved in developing and demonstrating safety of new technologies (Low 2020. Re-positioned drugs may offer a cost-effective pathway to treatment of covid-19; for example, the corticosteroid dexamethasone has been shown to be cost-effective in treating severe covid-19 infection cases (Jo 2020).

Ivermectin is a well-known medicine that is approved by the World Health Organization and the US Food and Drug Administration (FDA) for use as an anti-parasitic medication. That it has now been shown to have anti-viral and anti-inflammatory properties suggests that ivermectin's effect against SARS-CoV-2 needs a systematic review. Currently, ivermectin is commercially available and affordable in many countries globally (Banerjee 2020). A 2018 application for ivermectin use for scabies gives a price of $2.90 for 100 12 mg tablets (WHO 2018b). A therapeutic course of ivermectin for cases of covid-19 infection in India, for example, has been reported to cost less than PPP$ 53.93 for a dose of 12mg twice daily for 7 days (Vora 2020; PPP = purchasing power parity in 2021). This price for ivermectin represents that of a dosage at the upper-end of what has be used to treat covid-19 cases (Vora 2020). For these reasons, the exploration of ivermectin's potential effectiveness against SARS-CoV-2 has been stated of particular importance for settings with limited resources (Chaccour 2020). If demonstrated to be effective as a treatment for covid-19, the cost-effectiveness of ivermectin could potentially be considered against existing treatments and prophylaxes.

Priority Questions:

Question 1: Among people with covid-19 infection (P), what is the effect of ivermectin treatment (I) compared with no ivermectin (C) on important health outcomes (O)?

Question 2: Among people at higher risk of covid-19 infection (P), what is the effect of prophylactic ivermectin (I) compared with no ivermectin (C) on important health outcomes?

Objectives

To assess the effectiveness of ivermectin treatment among people with covid-19 infection (to address priority question 1) and as a prophylaxis among people at higher risk of covid-19 infection (to address priority question 2).

Safety will also be assessed in included randomised controlled trials (RCTs). However, since it is one of the World Health Organisation's *Essential Medicines* (WHO 2019) and is considered safe for use in humans (Banerjee 2020; Navarro 2020; WHO 2018), no assessment will be made beyond included RCTS.

Methods

Criteria for considering studies for this review

Types of studies

Prespecified eligibility criteria is as follows:

Study design

- Randomised controlled trials (RCTs)
- Quasi-RCTs
- Cluster-RCTs

Minimum study duration

Any time frame.

Types of participants

- For research question 1: People with mild, moderate, severe or critical covid-19 infection.
- For research question 2: People at higher risk of covid-19 infection, such as frontline workers and covid-19 contacts.

Special populations of interest are healthcare and other frontline workers, the elderly, and those with pre-existing health conditions.

Types of interventions

Intervention

- Oral ivermectin, administered as a minimum single dose of 6 mg.
    - Studies assessing ivermectin in combination with doxycycline or other medicines or supplements will be included.
    - Studies comparing different formulations, doses, and schedules of ivermectin will also be included.

Comparator(s)

- No ivermectin
    - placebo, or
    - another active treatment

Types of outcome measures

Primary outcomes

For Question 1: Ivermectin treatment vs control/comparator:

- Death from any cause

For Question 2: Ivermectin prophylaxis vs control:

- covid-19 infection

Secondary outcomes

For Question 1: Ivermectin treatment vs control/comparator:

- Time to PCR negativity, in days
- Time to clinical recovery, in days
- Admission to ICU
- Requiring mechanical ventilation
- Length of hospital stay, in days
- Admission to hospital
- Duration of mechanical ventilation
- Serious adverse events

For Question 2: Ivermectin prophylaxis vs control:

- Admission to hospital
- Death from any cause
- Serious adverse events

Studies will be included in the review irrespective of whether they measured outcome data that are reported in a way that allows us to include them in meta-analysis. We will also include studies that are otherwise eligible but may not necessarily report on the review's outcomes; these studies will be summarised in Characteristics of included studies tables. This will be done in case we miss any outcomes that are pertinent as new outcomes of importance may emerge given the changing nature of the pandemic. We will note any such analyses as post hoc and interpret accordingly.

We will also produce a brief economic commentary (BEC) to summarise the available economic evidence relating to: 1) ivermectin as treatment and 2) ivermectin as prophylaxis for covid-19 infection.

Search methods for identification of studies

Electronic searches

An information specialist, (JP) designed all of the searches and will conduct them. These were informed and verified by a content expert (TL) and were independently peer reviewed by (ANS). The Medline search strategy is presented in Appendix 1. The search strategies in other electronic databases will be adapted accordingly. The following electronic databases will be searched:

- Medline from 1946 (for completeness but nothing should appear until 2019 in theory)
- Embase from 1980
- CENTRAL (latest issue)
- Cochrane covid-19 Study Register
- Chinese databases

We will perform a supplementary search to identify economic evaluation studies. The search will be conducted in Medline and Embase and limited to published studies from November 2019 to capture studies conducted since the initial outbreak of SARS-CoV-2. The search strategies that will be used to identify economic evidence can be viewed in Appendix 2. Following current guidance (Aluko 2020), the reference lists of the studies included in the main review will also be examined for any relevant economic data.

Searching other resources

We will search www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials for ongoing trials.

We will search the reference list of included studies, and of two other 2021 literature reviews that we are aware of on ivermectin (Kory 2021; Hill 2021). We have made initial contacts to experts in the field (Drs. Andrew Hill, Pierre Kory and Paul Marik) for information on new and emerging trial data but will follow these contacts up during the review process. This is a rapidly expanding evidence base so the number of trials are increasing quickly; as such, we will check for updates on ongoing trials regularly and perform hand searches as necessary.

Data collection and analysis

Selection of studies

Screening

All titles and abstracts retrieved by electronic searching will be downloaded to Endnote and duplicates will be removed. Two review authors (AB, TL, TD) with expertise in systematic reviewing will screen all titles and abstracts for eligibility. Full texts will also be reviewed by two reviewers (AB, TL, TD). Discrepancies will be resolved by consensus. Reasons for exclusion will be recorded for all studies excluded after full text review.

Inclusion of non-English language studies

Where possible, we will translate any reports of RCTs published in other languages than English.

Data extraction and management

We will abstract data using a pilot form which will be trialled by two reviewers (TL, TD, AB or GG) to record the following:

- Study design (including methods, location, sites, funding, study author declaration of interests, inclusion/exclusion criteria)
- Setting: hospital inpatient, outpatient
- Participant characteristics: disease severity, age, gender, co-morbidities, smoking, occupational risk
- Intervention characteristics: dose and frequency of ivermectin
- Comparator characteristics: dose and frequency of comparator
- Risk of bias items (see below)
- Length of follow-up
- Outcomes (as above) including numbers in each arm, definitions, unit of measurements, etc.

Data on outcomes will be extracted as below:

- For dichotomous outcomes (i.e. death from any cause, SAEs, etc), we will extract the number of participants in each treatment arm and the number of participants assessed at endpoint, in order to estimate a risk ratio.
- For continuous outcomes (i.e. length of hospital stay), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

If possible, we will extract data relevant to an intention-to-treat analysis, in which participants are analysed in groups to which they are assigned.

We will use Microsoft Excel to collate the data. If there is a conflict between data reported across multiple sources for a single study (e.g. between a published article and a trial registry record), we will email the authors for clarification. Differences between reviewers will be resolved by discussion.

Assessment of risk of bias in included studies

An assessment of risk of bias in each included RCT will be conducted by two reviewers (TL, TD, AB or GG) using the Cochrane risk of bias tool (Higgins 2019). Discrepancies will be resolved by discussion and, if necessary, involving a third reviewer. The risk of bias includes assessment of:

- sequence generation
- allocation concealment
- blinding (Assessment of blinding will be relevant to participants, health care personnel and outcome assessors)
- incomplete outcome data: We will record the proportion of participants whose outcomes were not reported at the end of the trial and will note whether loss to follow-up is not reported. We will code a satisfactory level of loss to follow-up for each outcome as:

    - Yes, if fewer than 20% of participants are lost to follow-up and reasons for loss to follow-up are similar in both treatment arms
    - No, if more than 20% of patients are lost to follow-up or reasons for loss to follow-up is different between treatment arms
    - Unclear if loss to follow-up is not reported
- selective reporting of outcomes
- other possible sources of bias

We will pay close scrutiny to unpublished reports and those of unpublished works and preprints that have not undergone formal peer review. If we can retrieve adequate information we will reach consensus in either making an appropriate risk of bias judgement in each domain for that trial or exclude is sufficient doubt as to whether it is truly an RCT.

Results will be presented in both a risk of bias graph and a risk of bias summary. Results of meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We will use the following measures of the effect of treatment:

- For dichotomous outcomes (e.g. death from any cause, SAEs), we will use the risk ratio
- For continuous outcomes, we will use the mean difference (MD) or standardised mean difference (SMD) as appropriate. Continuous outcome data for length of hospital stay and time to recovery will be standardised to the same unit of measurement (i.e. days) so the need to use SMD is unlikely.

Unit of analysis issues

We will consider interventions that comprised multiple doses of ivermectin as a single intervention and subgroup when necessary. None of our outcomes should be time-dependent (e.g. measured at a particular time point since these are relatively short term outcomes given nature of the virus and intention of the interventions).

We will also include cluster randomised controlled trials (cluster-RCTs). If the analysis accounts for the cluster design then a direct estimate of the desired treatment effect will be extracted e.g. RR plus 95% CI. If the analysis does not account for the cluster design, we will extract the number of clusters randomised to each intervention, the average cluster size in

each intervention group and the outcome data, ignoring the cluster design, for all participants in each group. We will then use an external estimate of the intracluster coefficient (ICC) to estimate a design effect to inflate the variance of the effect estimate (Higgins 2019). It will then enter the data into RevMan 5.4 and combine the cluster randomised trials with individually randomised trials in the same meta-analysis.

Dealing with missing data

We will not impute missing data for any of the outcomes.

Contacting study authors

Authors of trials will be contacted for missing outcome data and for clarification on study methods, if possible, and for trial status for ongoing trials. We are aware that many studies will be in preprint form or not in peer review journals yet, so we will request full and transparent information on trial conduct including risk of bias confirmation as well as details on participants' populations, interventions and outcomes if necessary. We will follow Cochrane guidelines and recommendations on the need to include these data from unpublished studies to attempt to reduce publication bias and selective reporting of outcomes (Higgins 2019).

Assessment of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the I^2 statistic (I^2 ≥60% was considered substantial heterogeneity) (Higgins 2003), by a formal statistical test to indicate statistically significant heterogeneity (Deeks 2001) and, if possible, by subgroup analyses (see below). If there is evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported.

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects if more than 10 trials are included in the analysis. If there is evidence of small-study effects, publication bias will be considered as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models (Higgins 2019).

Data synthesis

If sufficient clinically similar trials are available, we will pool their results in meta-analyses. We will use forest plots to display the results of the data syntheses.

- For dichotomous outcomes, the risk ratios will be pooled.
- For continuous outcomes, the MD or standardised mean difference (if appropriate) will be pooled

Trials with multiple treatment groups are discussed above, but in the unlikely event the 'shared' comparison group was divided into the number of treatment groups and comparisons made between each treatment group, the split comparison group were treated as independent comparisons.

We will meta-analyse data using the random effects model (DerSimonian 1986). Results will use Mantel-Haentzel method for weighting.

Where interventions differed to any degree or there was other substantial heterogeneity the results were reported in a narrative.

Subgroup analysis and investigation of heterogeneity

Where possible, we will perform subgroup analyses grouping trials by:

- Disease severity, namely mild, moderate, severe and any disease
- Inpatients vs outpatients
- Single dose vs multiple doses

Sensitivity analysis

We will perform sensitivity analysis by excluding trials which do not confirm adequate methods of randomisation for treatment assignment and allocation concealment. We will also perform sensitivity analysis for other aspects that may put a trial at high risk of bias and trials creating unexplained heterogeneity as outlined above in Assessment of heterogeneity and trials identified in subgroup analysis.

Grade and Summary of findings

All outcomes will be assessed independently by two review authors (TD and AB) using the GRADE approach (Schünemann 2019; GRADE 2020), which ranks the quality of the evidence. Results will be presented in a summary of findings table for treatment and prophylaxis outcomes (Appendix 4). Any differences will be resolved by discussion with the wider group. We will use Cochrane Effective Practice and Organisation of Care guidance to interpret the evidence (EPOC 2015).

Brief economic commentary

We will develop a brief economic commentary (BEC) based on current methods guidance (Aluko 2020). The (BEC) will summarise the availability and core findings of full economic evaluations (cost-utility analyses, cost-effectiveness analyses and cost-benefit analyses) of ivermectin compared to alternatives regimens for 1) treatment and 2) prophylaxis of SARS-CoV-2. Findings from studies conducted in all settings globally will be considered.

Aluko 2020

Aluko P, Graybill E, Craig D, Henderson C, Drummond M, Wilson ECF, et al.. Chapter 20: Economic evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors.. Cochrane Handbook for Systematic Reviews of Interventions (version 61): Cochrane; 2020. 2020.

Anand 2003

Anand K, Ziebuhr J, Wadhwani P, Mesters J R, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. Science 2003;300:1763-1767.

Banerjee 2020

Banerjee K, Nandy M, Dalai CK, Ahmed SN. The Battle against covid 19 Pandemic: What we Need to Know Before we "Test Fire" Ivermectin. Drug Res (Stuttg) June 19, 2020;70(08):337-340 (Accessed January 26 2021). [DOI: 10.1055/a-1185-8913; Other: https://www.thieme-connect.de/products/ejournals/abstract/10.1055/a-1185-8913]

Banka 2015

Banka G, Edgington S, Kyulo N, et al.. Improving Patient Satisfaction. J. Hosp. Med 2015;8:497-502. [DOI: doi:10.1002/jhm.2373; Other: ; Other:]

Barrow 2016

Barrows NJ, Campos RK, Powell ST, Prasanth KR, Schott-Lerner G, Soto-Acosta R, et al. A Screen of FDA-Approved Drugs for Inhibitors of Zika Virus Infection. Cell Host & Microbe July 28, 2016 (Accessed January 26 2021). [DOI: 10.1016/j.chom.2016.07.004]

Beer 2021

Beer AE. covid-19 Linked to Devastating Pregnancy Complications. https://www.24-7pressrelease.com/press-release/478930/covid-19-linked-to-devastating-pregnancy-complications 27 Jan 2021;Accessed 1 Feb 2021.

Bennet 2020

Bennett P, Noble S,Johnston S, Jones D, Hunter R. covid-19 confessions: a qualitative exploration of healthcare workers experiences of working with covid-19. BMJ Open 2020;10:e043949.

Bernigaud 2021

Bernigaud C, Guillemot D, Ahmed-Belkacem A, Grimaldi-Bensouda L, Lespine A, Berry F, et al. Oral ivermectin for a scabies outbreak in a long-term–care facility: Potential value in preventing COVID-19 and associated mortality? British Journal of Dermatology (in press);https://doi.org/10.1111/bjd.19821.

Bolivia 2020

Bolivia Ministry of Health. Ministerio de Salud autoriza uso de ivermectina contra el COVID-19 bajo protocolo. https://www.minsalud.gob.bo/4157-ministerio-de-salud-autoriza-uso-de-ivermectina-contra-el-covid-19- bajo-protocolo;.

Brown 1998

Brown KR. Changes in the use profile of Mectizan: 1987–1997. Annals of Tropical Medicine and Parasitology 1998;92(suppl 1):61-64.

Caly 2020

Caly L, et al. Antiviral Res 2020;178(104787).

Carvallo 2020

Carvallo H, Hirsch RR, Farinella ME. Safety and efficacy of the combined use of ivermectin, dexamethasone, enoxiparin and aspirin against covid-19. MedRxiv September 2020;(Accessed 27 January 2021). [DOI: https://doi.org/10.1101/2020.09.10.20191619].

Castañeda-Sabogal 2021

Castañeda-Sabogal A, Chambergo-Michilot D, Toro-Huamanchumo CJ, Silva-Rengifo C, Gonzales-Zamora, Barboza JJ. Outcomes of Ivermectin in the treatment of covid-19: a systematic review and meta- analysis. https://www.medrxiv.org/content/10.1101/2021.01.26.21250420v1.full.pdf 2021;Accessed 28/1/2021.

CGTH 2021

The Complete Guide to Health. https://www.thecompleteguidetohealth.com/Ivermectin.htmlAccessed 6/2/2021.

Chaccour 2020

Chaccour C, Casellas A, Matteo A, Pineda I, Fernandez-Montero A, Castillo P, et al. The effect of early treatment with ivermectin on viralload, symptoms and humoral response in patientswith mild covid-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. Research squareAccessed 6/2/2021.

Chamie-Quintero 2020

Chamie J. Real-World Evidence: The Case of Peru. Causality between Ivermectin and COVID-19 Infection Fatality Rate. https://www.researchgate.net/publication/344469305 2020;Accessed 1 February 2021.

Chamie-Quintero 2021

Chamie-Quintero J, Hibberd J, Scheim DE. Covid-19 case fatalities and total deaths with and without ivermectin treatment in different states in Peru. Open Science Foundation(Accessed January 26 2021). [Other: https://osf.io/ydc2p/]

Chesler 2021

Chesler DL. Letter to Dr Bray at the National Institutes of Health. Personal communication.

Clancy 2021

Clancy R. covid-19: A realistic approach to community management. https://quadrant.org.au/opinion/qed/2021/01/covid-19-a-realistic-approach-to-community-management/ 17 Jan 2021.

Collins 2004

Collins K. Profitable gifts: a history of the Merck Mectizan donation program and its implications for international health. Perspecttive in Biology and Medicine 2004;47(1):100-9.

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Conterno LO, Turchi MD, Corrêa I, Monteiro de Barros Almeida RA. Anthelmintic drugs for treating ascariasis. Cochrane Database of Systematic Reviews 2020 (Accessed January 26 2021);(4). [DOI: 10.1002/14651858.CD010599.pub2]

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Deeks JJ, Altman DG, Bradburn MJ. Chapter 15: Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd edition. London: BMJ Publication Group, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-88.

DiNicolantonio 2020

DiNicolantonio JJ, Barroso J, McCarty, M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage covid-19. Open Heart 2020;7:e001350.

EPOC 2015

Cochrane Effective Practice and Organisation of Care (EPOC). EPOC resources for review authors. 2015. epoc.cochrane.org/epoc-specific-resources-review-authors (accessed 6 July 2016).

Fesler 2021

Fesler ML, Stricker RB. Pre-exposure prophylaxis for covid-19 in pregnant women. Int J Gen Med 2021;14:279-284.

Galehdar 2020

Galehdar N, Kamran A, Toulabi T, Heydari H. Exploring nurses' experiences of psychological distress during care of patients with covid-19: a qualitative study. BMC Psychiatry 2020;20:489.

GRADE 2020

The GRADE Working Group. GRADE 2020 (Accessed January 26 2021). [Other: www.gradeworkinggroup.org]

GRADE-DECIDE 2016

DECIDE. The DECIDE Project; 2016. http://www.decide-collaboration.eu/.

Harvey 2020

Harvey D, Kueper M. Improving Patient Experience During the covid-19 Pandemic: One Family's Reflections. J. Hosp. Med December 2020;(Accessed 26 January 2021). [Other: https://www.journalofhospitalmedicine.com/jhospmed/article/231557/hospital-medicine/improving-patient-experience-during-covid-19-pandemic-one]

Hector September 15, 2020 (Accessed 27 January 2021)

Hector Eduardo Carvallo, Roberto Raul Hirsch, Maria Eugenia Farinella. SAFETY AND EFFICACY OF THE COMBINED USE OF IVERMECTIN, DEXAMETHASONE, ENOXAPARIN AND ASPIRIN AGAINST covid 19. medRxiv September 15, 2020 (Accessed 27 January 2021). [DOI: https://doi.org/10.1101/2020.09.10.20191619]

Heidary 2020

Heidary H & Gharebaghi R.. J. Antibiotics 2020;73:593-602.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.

Higgins 2019

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Hill 2021

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Honduras 2021

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Horby 2020

Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalised patients with Covid-19 - preliminary report. NEJM July 17, 2020;(Accessed 26 January 2021). [DOI: 10.1056/NEJMoa2021436; Other: https://www.nejm.org/doi/10.1056/NEJMoa2021436]

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Jo 2020

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King CL. Is ivermectin safe in pregnancy – Comment. Lancet Global Health 2020;8:e12-13.

Kircik 2016

Kircik LH, Del Rosso JQ, Layton AM, Schauber J. Over 25 Years of Clinical Experience With Ivermectin: An Overview of Safety for an Increasing Number of Indications. March 2016 (Accessed January 26 2021);15(3). [Other: https://jddonline.com/articles/dermatology/S1545961616P0325X]

Kory 2021

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Internal sources

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External sources

No sources of support provided

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Contributions of authors

Andrew Bryant and Theresa Lawrie co-wrote the draft of the protocol with input from other authors. All authors reviewed and approved the final version.

Declarations of interest

Andrew Bryant declares no conflicts of interest.

Theresa Lawrie declares no conflicts of interest.

Therese Dowswell declares no conflicts of interest.

Scott Mitchell declares no conflicts of interest.

Tony Tham declares no conflict of interest.

Edmund Fordham declares no conflicts of interest.

Sarah Hill declares no conflict of interest.

Appendices

1 MEDLINE search strategy

1. exp Ivermectin/
2. (stromectol* or mectizan* or soolantra* or sklice* or ivermectin* or ivomec or acarexx or bimectin* or cardomec or equimectrin or eqvalan or heartgard* or hyvermectin or Ivermax or noromectin or oramec or pandex or phoenectin or stromectal or uvemec or vermic or vetmec or zimecterin).ti,ab,kw.
3. (Dihydroavermectin* or "cardotek-30" or "CCRIS 8839" or "EINECS 274-536-0" or "L 640471" or "MK 933" or "MK-0933" or "UNII-8883YP2R6D" or "agri-mectin").ti,ab,kw.
4. 1 or 2 or 3
5. exp Severe Acute Respiratory Syndrome/
6. covid-19.mp.
7. covid.mp.
8. SARS-CoV-2.mp.
9. severe acute respiratory syndrome coronavirus 2.mp.
10. 2019-nCoV.mp.
11. 2019 novel coronavirus.mp.
12. Wuhan coronavirus.mp.
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 4 and 13

2 Economic Medline search strategy

1. exp Ivermectin/
2. stromectol*.ti,ab,kw.
3. mectizan*.ti,ab,kw.
4. soolantra*.ti,ab,kw.
5. sklice*.ti,ab,kw.
6. ivermectin*.ti,ab,kw.
7. ivomec*.ti,ab,kw.
8. acarexx*.ti,ab,kw.
9. bimectin*.ti,ab,kw.
10. cardomec*.ti,ab,kw.
11. equimectrin*.ti,ab,kw.
12. eqvalan*.ti,ab,kw.
13. heartgard*.ti,ab,kw.
14. hyvermectin*.ti,ab,kw.

15. Ivermax*.ti,ab,kw.
16. noromectin*.ti,ab,kw.
17. oramec*.ti,ab,kw.
18. pandex*.ti,ab,kw.
19. phoenectin*.ti,ab,kw.
20. stromectal*.ti,ab,kw.
21. uvemec*.ti,ab,kw.
22. vermic*.ti,ab,kw.
23. vetmec*.ti,ab,kw.
24. zimecterin*.ti,ab,kw.
25. Dihydroavermectin*.ti,ab,kw.
26. cardotek-30.ti,ab,kw.
27. CCRIS 8839.ti,ab,kw.
28. EINECS 274-536-0.ti,ab,kw.
29. L 640471.ti,ab,kw.
30. MK 933.ti,ab,kw.
31. MK-0933.ti,ab,kw.
32. UNII-8883YP2R6D.ti,ab,kw.
33. agri-mectin.ti,ab,kw.
34. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. Coronavirus Infections/
36. covid-19/
37. SARS-CoV-2/
38. covid-19.rs.
39. severe acute respiratory syndrome coronavirus 2.os.
40. (2019 nCov or nCov 2019 or nCov 19).tw,kf.
41. (coronavir* or corona vir*).tw,kf.
42. covid.mp.
43. covid19.tw,kf.
44. ("SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2").mp.
45. ("SARS coronavirus 2" or "SARS-like coronavirus" or "Severe Acute Respiratory Syndrome Coronavirus-2").mp.
46. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 34 and 46
48. economics/
49. exp "costs and cost analysis"/
50. cost of illness/
51. exp health care costs/
52. economic value of life/
53. exp economics medical/
54. exp economics hospital/
55. economics pharmaceutical/
56. exp "Fees and Charges"/
57. (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.

58. (expenditure$ not energy).tw.
59. (value adj1 money).tw.
60. budget$.tw.
61. exp Cost-Benefit Analysis/
62. (cost* adj3 (effectiv* or utilit* or benefit* or evaluat* or consequence*)).ti,ab,kw.
63. (CEA or CUA or CBA or CCA).ti,ab,kw.
64. 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63
65. 47 and 64

3 Data extraction form

Review Title: Ivermectin for prophylaxis and treatment of covid-19

Review ID: **Study ID**: **Reference ID:**

Person/s extracting data: Date of date extraction: Year of study publication:

Study citation:

Other publications from same study:

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes No Unclear	Location in text or source *(pg /fig/table/other)*
Type of study			
Participants			
Types of intervention			
Types of comparison			
Types of outcome measures			

INCLUDE EXCLUDE

Reason for exclusion

Notes:

DO NOT PROCEED IF STUDY IS EXCLUDED FROM REVIEW

Methods

Design:

Country:

Accrual dates:

Trial reg:

Funding:

Declaration of interests:

Participants

No. randomised:

No. analysed:

Inclusion/exclusion criteria:

Age:

Gender:

Co-morbidities:

Smokers:

Severity of covid-19 infection (in treatment setting):

[List anything else]

Interventions/study arms

Arm 1:

Arm 2:

Outcomes (please underline review outcomes):

Risk of Bias assessment

See Chapter 8 of the Cochrane Handbook (Higgins 2019). Additional domains may be added for non-randomised studies.

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes*	Location in text or source *(page/fig/table/other)*

	where available with explanatory comments)
Random sequence generation *(selection bias)*	
Allocation concealment *(selection bias)*	
Blinding of participants and personnel *(performance bias)*	Outcome group:
(if separate judgement by outcome(s) required) Blinding of outcome assessment *(detection bias)*	Outcome group: Outcome group:
(if separate judgement by outcome(s) required) Incomplete outcome data *(attrition bias)*	Outcome group: Outcome group:
(if separate judgement by outcome(s) required) Selective outcome reporting? *(reporting bias)*	Outcome group:
Other bias	
Notes:	

Additional information requested

Information requested:

From:

Date:

Response:

Outcomes for main analysis

	Outcome Measures (Dichotomous)	Total number of participants in study =			
		Intervention group		Control group	
		Total no. in group =		Total no. in group =	
		events	total	events	total
	Primary				
1	Death (mild to moderate Covid)				
	Death (severe Covid)				
	Death (any Covid, if severity not specified)				
2	covid-19 infection (prevention studies)				
	Secondary				
3	Admission to ICU				
4	Mechanical ventilation				
5	Admission to hospital (prevention studies)				
6	Admission to hospital (treatment studies)				
7	Improvement				
8	Deterioration				
9	Severe adverse events				

	Outcome Measures (Continuous)	Total number of participants in study =					
		Intervention group			Control group		
		Total no. in group =			Total no. in group =		
		mean	SD	total	mean	SD	total
	Secondary						
1	Recovery time to -ve PCR (outpatient)						
	Recovery time to -ve PCR (inpatient – mild to mod)						
	Recovery time to -ve PCR (inpatient – severe Covid)						
2	Clinical recovery time (outpatient)						

Clinical recovery time (inpatient) – mild to mod)

Clinical recovery time (inpatient – severe Covid)

3 Length of hospital stay (mild to mod Covid)

Length of hospital stay (severe Covid)

Length of hospital stay (any Covid, if severity not specified)

4 Duration of mechanical ventilation

General conclusions

Very brief summary of study authors main findings/conclusions:

Notes

Exclusion after data extraction

Reasons for exclusion: (study design? participants? interventions/ outcomes? attrition? bias?)

Dates:

Date entered into RevMan and by whom?

Date checked and by whom?

This form was adapted from "Good practice templates" developed by the Cochrane Editorial Resources Committee http://training.cochrane.org/authors/presentations/collecting-data

4 Summary of Findings dummy tables

Summary of findings: ivermectin for covid-19 treatment

Ivermectin compared with no ivermectin for treatment of covid-19 **infection**

Patient or population: Participants with covid-19 **infection**

Settings: Any

Intervention: Ivermectin treatment

Comparison: Control which included no ivermectin treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (RCTs)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No	Ivermectin				

	ivermectin	
Death from any cause		NNT will be calculated if appropriate
Recovery time to negative PCR test (days)		
Time to clinical recovery (days)		
Admission to ICU		
Need for mechanical ventilation		
Length of hospital stay (days)		
Admission to hospital		
Duration of mechanical ventilation		
Serious adverse events		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **MD:** Mean Difference; RCT: Randomised controlled trial; NNT: number needed to treat; ICU: intensive care unit; PCR: polymerase chain reaction.

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

2 Summary of findings: ivermectin for covid-19 prophylaxis

Ivermectin compared with no ivermectin for prophylaxis of covid-19 infection

Patient or population: Participants without covid-19 infection (healthy population)

Settings: Any

Intervention: Ivermectin treatment aimed at prevention of covid-19 **infection**

Comparison: Control which included no ivermectin treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (RCTs)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No ivermectin	Ivermectin				
covid-19 infection						NNT will be calculated if appropriate
Admission to hospital						
Death from any cause						
Serious adverse events						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; RCT: Randomised controlled trial; NNT: number needed to treat.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.