Ivermectin for Prevention of COVID-19 Infection: A Systematic Review and Meta-analysis to Inform Clinical Guidelines

Protocol

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ABBREVIATIONS

Abbreviation	In full
ADR	Adverse Drug Reaction
AE	Adverse Event
BiRD	British Ivermectin Recommendation Development
BMI	Body mass index
CBA	Controlled before and after (study)
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CIC	Community Interest Company
COPD	Chronic Obstructive Pulmonary Disease
CRD	Centre for Reviews and Dissemination (NIHR)
DARE	Cochrane Database of Abstracts of Reviews of Effects
DET	Data Extration Table (in Excel)
EMA	European Medicines Agency
EPOC	Effective Practice and Organisation of Care
ESRD	End Stage Renal Disease
EU CTR	European Union Clinical Trials Register
FDA	Food and Drug Administration
FLCCC	Front Line COVID-19 Critical Care Alliance
GMC	General Medical Council (United Kingdom)
HART	Health Advisory and Recovery Team
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICC	Intracluster coefficient
ICTRP	International Clinical Trial Registry Platform
IHE	Institute of Health Economics
IPD	Individual Patient Data
IQR	Interquartile range
ITC	Indirect treatment comparison
ITS	Interrupted time series
ITT	Intention-to-treat
IVM	Ivermectin
LFT	Lateral flow test
MA	Meta-analysis
MeSH	Medical Subject Heading
mITT	Modified intention-to-treat
N/A	Non-applicable
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (England & Wales)
NIH	National Institutes for Health (USA)
NIHR	National Institute for Health Research (UK)
NMA	Network Meta-Analysis
NPI	Non-Pharmaceutical Intervention
OSF	Open Science Framework
PCR	Polymerase chain reaction
PD	Pharmacodynamic

Abbreviation	In full
PK	Pharmacokinetic
PLA	Placebo
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QA	Quality Assessment
QC	Quality Control
RCT	Randomised Controlled Trial
RR	Risk ratio
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Standard deviation
SR	Systematic Review
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
Wk	Week

1 ADMINISTRATIVE INFORMATION

1.1 Title

Ivermectin for Prevention of COVID-19 Infection: A Systematic Review and Meta-Analysis to Inform Clinical Guidelines

1.2 Protocol authors

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1.2.2 Contributions

Concept & objectives (EF, TL), drafting (KM), review (TL, AB, EF, RC)

Guarantor (KM)

1.3 Support

1.3.1 Sources, sponsor and roles

This systematic review (SR) is sponsored and funded by EbMCsquared CIC. EbMCsquared CIC developed the framework and objectives, designed the SR in order to answer the review questions, drafted the protocol and provided expert review. AB from Newcastle University (UK) and RC from University of Newcastle (Australia) provided expert review.

2 INTRODUCTION

2.1 Rationale/purpose

COVID-19 disease develops in susceptible people subsequent to infection with, and replication of, the SARS-CoV-2 virus. In addition to exposure level, infection risk at any time reflects the balance of protective and suppressive immune responses of the mucosal immune system.

Questions have been raised as to the duration of protection from infection provided by COVID-19 injections (1, 2) and concern voiced as to the sustainability of repeated boosters every three or four months, which could potentially result in problems with the immune response (3). Spacing of boosters over time, synchronised with the arrival of the cold season, has been advocated as an alternative (3).

Chemoprophylaxis - with ivermectin (IVM) or any other anti-viral prophylaxis - has not yet been evaluated by the World Health Organization (WHO) or by the National Institute for Health and Care Excellence (NICE) in the UK. Current recommendations from these bodies and from the Food and Drug Administration (FDA) in USA and the European Medicines Agency (EMA) are to not use IVM outside of clinical trials. In Australia the use of IVM for treatment or prevention of COVID-19 is not permitted.

Prophylaxis could be an additional pillar in the pandemic response as it could reduce both the spread and the incidence of acute COVID-19 (4). If prophylactic use of ivermectin (IVM) reduced the community case load, it could help optimise evidence-based protection as a counterpart to a vaccination strategy based on seasonal offers to the vulnerable (as practised for influenza). On a global basis, chemo-prophylaxis with cheap generics would have the potential to reach more people, more rapidly, than attempts at mass immunisation with experimental technologies which may be unavailable or unaffordable in many coutries.

A previous systematic review (SR) (5) with searches run April 25, 2021, identified three randomised controlled trials (RCTs) of IVM as prophylaxis for COVID-19 (6-8). The meta-analysis suggested that IVM reduced COVID-19 infection occurrence by an average of 86% (95% confidence interval 79%, 91%) (5), or by 87% (95% confidence interval 79%, 92%) (9) after removal of a disputed trial (7).

A new SR is proposed of published and unpublished RCT, non-RCT and observational evidence of IVM in the prevention of COVID-19, and, where infection control fails, the impact on subsequent hospitalisation and mortality, to inform clinical advice and policies.

2.2 Objectives

- To identify randomised controlled trials (RCTs), non-RCTs and observational data of IVM alone or in combination with other agents as prophylaxis for COVID-19.
- To conduct a meta-analysis of the effectiveness of IVM in prevention of COVID-19 (i) among people at higher risk of infection – by virtue of higher exposure; or (ii) at higher risk of serious illness due to age, comorbidities or institutional setting, or (iii) in the general population, as a public health measure.
- To summarise the risk of bias in the available evidence and provide qualitative commentary.

2.3 Ivermectin in prevention of COVID-19

2.3.1 Recommended dose

The dose of IVM currently recommended (10) by the Front Line COVID-19 Critical Care (FLCCC) Alliance for chronic prevention is 0.2 mg/kg per dose (with or after a meal) twice per week. This is recommended to be continued while the community risk of COVID-19 is elevated.

For post-exposure prevention, IVM 0.4 mg/kg per dose (with or after a meal) is recommended (10), with one dose given and then a repeat dose given after 48 hours.

Other doses and schedules have been employed in studies (11, 12). Most involve 1-2 doses in the first week or two weeks, followed by weekly, fortnightly or monthly doses.

2.3.2 Concomitant treatments

Many expert groups recommend a “nutraceutical bundle” of vitamins, other natural products and minerals as general immune system support, though these are rarely controlled for in clinical trials. Other expert recommendations include dual anti-virals, both for efficacy reasons and potentially for avoidance of immune-escape variants (drug resistance) if used widely on a population scale (10, 12). Concomitant/adjuvant treatments will, therefore, be recorded where reported, and studies of IVM monotherapy or IVM in combination with other agents included.

2.3.3 Licensing status and international recommendations

IVM is listed by the World Health Organization (WHO) as an Essential Medicine (13) defined as: “*the minimum medicine needs for a basic healthcare system*”, albeit in the anti-parasitic indications only. The WHO does not currently recommend IVM treatment of COVID-19 outside of clinical trials, but the WHO guideline (14) did not look at IVM for prevention. It looked only at treatment of established infections.

IVM is licensed by the Food and Drug Administration (FDA) in the USA for oral use in humans as an anti-parasitic, against intestinal strongyloidiasis and onchocerciasis, and as topical treatment of head lice and rosacea. It is not yet approved for the prevention or treatment of COVID-19 outside of clinical trials.

In the UK, the National Institute for Health and Care Excellence (NICE) has similarly specified that IVM treatment of COVID-19 should only be used within clinical trials (15). Like the WHO, NICE has also ignored the use of IVM in prevention.

The European Medicines Agency (EMA) evaluated its use for the prevention and treatment of COVID-19 concluding it should not be used for COVID-19 except in well-designed clinical trials.

The legal framework governing prescription by licensed medical practitioners varies by jurisdiction. In the USA, medical practitioners may prescribe any FDA-licensed therapeutic, even outside of the original licensing “label”, at their clinical discretion, with the informed consent of the patient. In the UK, General Medical Council (GMC) guidelines and established law provide essentially similar legal freedom, though availability and National Health Service (NHS) policy in practice inhibits such use. Different situations may prevail in other jurisdictions.

3 METHODS

3.1 Methods overview

The systematic review (SR) will conform to the published requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (16). This protocol is developed in line with PRISMA-P (17). Key electronic database sources will include: Embase, via the Embase.com platform; the Cochrane Library databases (CENTRAL, CDSR); Medline, Medline InProcess and electronic publications ahead-of-print via PubMed; DARE (via CRD); Latin American and Caribbean Health Sciences Literature (LILACS) database; clinicaltrials.gov, World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) and the European Union Clinical Trials Register (EU CTR). Hand-searching: reference lists of included publications and of relevant, recent (2020+) SRs; pre-print servers MedRχiv, bioRxiv, Open Science Framework (OSF) preprints, Research Square and ResearchGate; Epistemonikos; the WHO COVID-19 database; and any supplemental search (e.g. searching via Google for a full text of a trial for which an abstract has been identified through the searches).

3.2 Research questions

What published or unpublished, randomised controlled trials (RCTs) of IVM in the prevention of COVID-19 have been conducted, or are ongoing?

What non-randomised controlled trials (non-RCTs) or uncontrolled trials (e.g. registry data/cohort studies, case-series or case-referent studies) of IVM in the prevention of COVID-19 have been conducted, or are ongoing?

What is the effectiveness of IVM in prevention of COVID-19 among people at higher risk of/from infection?

What dosages, frequencies (i.e. duration of effect) and adjuncts appear to be effective in use of IVM as chemo-prophylaxis ?

3.3 Eligibility criteria

The inclusion criteria are given in Table 1 below.

Table 1: PICOS inclusion criteria for Prophylaxis SR

Characteristic	Inclusion criteria
Population	Adults or children without diagnosed COVID-19 or SARS-CoV-2 infection at the time of enrollment General population or raised-exposure or at-risk. Raised-exposure populations include healthcare workers and those in institutional settings and household contacts of COVID-19 patients. At-risk populations include the elderly, care home residents, those with comorbidities (hypertensive diseases, heart disease and use of diuretics (18), immunocompromised status, male gender, ESRD and cognitive impairment (19), diabetes mellitus, central venous catheter/haemodialysis patients (20), and laboratory abnormalities such as raised neutrophil count, hypersensitivity C-reactive protein, creatinine kinase or blood urea nitrogen (21); decreased lymphocyte count or increased lactate dehydrogenase (22); etc.)

Characteristic	Inclusion criteria
Interventions/ comparators	IVM, as monotherapy or in combination with another product or other products, administered as pre-exposure or post-exposure prophylaxis at a recommended dose, dose frequency and duration of schedule. Any form of IVM is eligible, i.e. tablet, intranasal spray, etc. Comparators: normal NPI precautions used in relevant setting, or other potentially active chemo-prophylaxes, PLA or none (for case series, registry data, etc)
Outcomes	At least 1 prespecified outcome reported, as a 1ry or 2ry outcome, out of: • Presence of COVID-19 infection (symptoms, positive test result or investigator-defined) • Seroconversion by antibody test with or without symptomatic Covid-19 • Incidence of cases / secondary cases within a specified time interval up to 32 days (one calendar month plus one day) since the last prophylactic treatment • Adverse effects of treatment • Compliance with prophylactic treatment • Hospitalisation • Deaths from COVID-19
Study design	Prospective parallel design RCTs with active or PLA controls Quasi-RCTs and cluster-RCTs Other controlled clinical trials (interventional, prospective, non-RCT) Prospective registry studies (including retrospective analyses of prospectively collected data) / case series Prospective or retrospective cohort studies Case-control studies+ (case-referent, case-cohort, case-base, case-control) Controlled before-and-after studies Interrupted time series
Date limits	Unlimited. However, the vast majority of data is from 2020-2021
Country limits	Unlimited
Linked abstracts	Abstracts linked to a full publication will be included if they have unique data
Publication type	Original articles (full text or abstracts). Abstracts are includable if clearly eligible and if have usable data. Letters, if they contain details about relevant studies Errata
Languages	Any foreign language paper with an English abstract will be included at 1st stage screening if sufficient information is present in the English abstract to suspect that the eligibility criteria are met.
Ongoing and unpublished studies	Ongoing studies will be sought via registry searches Unpublished studies are eligible for inclusion Studies in press are eligible for inclusion

Abbreviations: AE, Adverse Event; ESRD, end-stage renal disease; HRQoL, Health-Related Quality of Life; ITC, indirect treatment comparison; NMA, network meta-analysis; NPI, non-pharmaceutical intervention; PLA, placebo; RCT, Randomised Controlled Trial; SR, Systematic Review;
+ Case-control studies are anticipated to be included in the qualitative write-up only, not in the meta-analysis

The exclusion criteria and codes are given in Table 2. Citations excluded at first pass (after abstract/title review) are tagged ‘e1’. Citations excluded at second pass (after full-text review) are tagged ‘e2’.

Table 2: Clinical SR exclusion criteria with rationale (according to hierarchy for exclusion)

Characteristic	**Exclusion code & criterion**	**Explanatory notes**
Publication type	e1 pub: Publication type not of interest	e.g. editorials, commentaries or letters (if not providing details on methods, results or commentary of relevant studies), notes, protocol-only articles

Characteristic	Exclusion code & criterion	Explanatory notes
		(except where providing methodological detail for studies with results).
Duplicate	e1 dup: Duplicate/copy	Exact duplicates or copy abstracts, for example where the content is almost identical. If there are discrepancies in the actual data reported, then both will be retained and the discrepancy noted
Linked abstract	e1/e2 child: Linked abstract or sub-study with no unique data	To be determined at 1st or 2nd stage screening
Languages	e2 lang: Full text in language outside of language capabilities*	The search strings are not limited by language. During screening, foreign language articles with insufficient information in the English abstract or without an abstract, or with an abstract in a language outside of the reviewers' language capabilities*, will have the full text obtained and added to the Endnote file. Those in a language within the reviewers' capabilities will be assessed in the usual way at 2nd pass. Those in languages outside of the reviewers' capabilities will be excluded at 2nd pass, tagged and listed in the report for transparency as a paper for which the eligibility could not be established.
Population	e1/e2 pop: COVID-19 already diagnosed at study entry	
Interventions / comparators	e1/e2 comp: No intervention/comparator of interest	The prophylactic regime does not include IVM. IVM given as treatment for pre-established COVID-19
Sample size	e1 size	Total study sample, N<30 patients (≥30 is includable). Prophylaxis studies will need a large sample size to be considered of relevant quality.
Study design	e1/e2 design: Cross-sectional survey Chart/record review Modelling studies Qualitative studies	
	Case reports	Case series (n>30) may be relevant but not individual case reports
	PK/PD study only	No outcome of interest
	Non-systematic reviews	Any particularly interesting clinical-type reviews may be noted for discussing in the report. However, in general non-systematic reviews will be excluded.
	SRs/MAs/NMAs/ITCs	Relevant 2020+ SRs and MAs are kept in after 1st stage screening for cross-referencing purposes but will be excluded after 2nd stage screening, except if MA/ITC data not available elsewhere
	Post-hoc pooled analyses	To avoid the same data being included twice. The original trials going in to the pooled analysis, if relevant, will be included, but the pooled analysis would be excluded
	Economic analyses or budget impact	Clinical outcomes only

Characteristic	Exclusion code & criterion	Explanatory notes
	analyses	
	In vitro studies or animal studies	Human in vivo only. However, preclinical studies of interest will be tagged for noting in the report among the excluded studies.
Outcomes	e1/e2 out: No outcome of interest Baseline only data	Paper does not report at least one outcome of interest
Date limits	e1/e2 date: 2020 for SRs/MAs Unlimited for original studies	Most recent and relevant SRs to be reference-checked

Abbreviations: 1st, first; 2nd, second; e1, excluded on abstract screening; e2, excluded on full paper screening; ITT, Intention-To-Treat; MA, meta-analysis; mITT, modified ITT; ITC, indirect treatment comparison; NMA, network meta-analysis; PD, pharmacodynamics; PK, pharmacokinetic; PP, per protocol; RCT, Randomised Controlled Trial; SR, Systematic Review; wk, week
* English, French, German, Hungarian, Italian, Polish, Portuguese and Spanish.

3.4 Information sources

Electronic databases

The electronic databases to be searched for the Prophylaxis SR are in Table 3, with further sources in Table 4.

Table 3: Information sources – electronic databases – for clinical SR

Database	Platform
Embase	Embase.com
MEDLINE, MEDLINE In-Process and e-publications ahead-of-print	PubMed interface http://www.ncbi.nlm.nih.gov/pubmed/http://www.ncbi.nlm.nih.gov/pubmed/
Cochrane library CDSR	http://onlinelibrary.wiley.com/cochranelibrary/search/
Cochrane library CENTRAL	http://onlinelibrary.wiley.com/cochranelibrary/search/
LILACS	https://lilacs.bvsalud.org/en/

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; LILACS, Latin Amercian and Caribbean Health Sciences Literature

Table 4: Information sources – CRD database, registries and preprint servers

Database	Platform	Search terms
DARE, now hosted by CRD	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp	Any field: ivermectin
US NIH registry & results database	https://clinicaltrials.gov	Advanced search In Condition or disease: COVID-19 In Other terms: prophylaxis or prevention In Interventions/Treatment: Ivermectin
WHO ICTRP registry	https://trialsearch.who.int/AdvSearch.aspx	Advanced search In Title: prevention OR prophylaxis In Condition: COVID-19 OR SARS-CoV-2 In Intervention: ivermectin Recruitment status: select ALL Search to be repeated to look for trials in children

Database	Platform	Search terms
EU CTR	https://www.clinicaltrialsregister.eu/ctr-search/search	COVID-19 AND ivermectin
Epistemonikos	https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d/advanced-search	Advanced search in COVID Evidence ivermectin AND prophylaxis
MedRχiv, bioRxiv	https://www.biorxiv.org/	ivermectin, prophylaxis or prevention, COVID-19 OR SARS-CoV-2 terms in title or abstract
OSF	https://osf.io/preprints/	ivermectin AND (prophylaxis OR prevention)
ResearchGate	https://www.researchgate.net/search/publication	ivermectin AND (prophylaxis OR prevention) AND (COVID-19 OR SARS-CoV-2)
Research Square	https://www.researchsquare.com/	ivermectin within COVID-19 preprints only
WHO COVID-19 database	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/advanced/?lang=en	Advanced search (tw:(ivermectin)) AND (tw:(prevention OR prophylaxis)) AND (tw:(covid-19 OR sars-cov-2)) Medline and Embase hits excluded prior to export.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; EU CTR, European Union Clinical Trials Registry; ICTRP, International Clinical Trials Registry Platform; NIH, National Institutes of Health (USA); OSF, Open Science Framework

Further hand-searching

- Bibliographic reference lists of included papers.
- Bibliographic reference lists of the most recent and comprehensive systematic reviews and meta-analyses from 2020 identified during screening.
- Unpublished data reported on clinicaltrials.gov or other trial registry
- Google hand-searching – for full texts of relevant abstract-only data from electronic screening

Study authors will be contacted for missing outcome data and de-identified individual patient data (IPD) requested where available under local data protection, ethical and other legal clearances. Lack of IPD will not exclude any study from inclusion.

3.5 Search strategy

General method

The search strings use Emtree Medical Subject Heading (MeSH) terms and broad free-text terms, using a specific method developed and recommended by Wichor Bramer[a], a biomedical information specialist in Erasmus MC, Rotterdam, to create high-quality and thorough searches in Embase.com.

Population terms in search strings

The population terms are based on the covid-relevant terms used in the literature search conducted for the NICE COVID-19 rapid guideline: managing the long-term effects of COVID-19 (NG188). Additions to these terms were made to provide a comprehensive range of terms including potential printing errors.

Search filters

[a] http://www.slideshare.net/wichor

We have not applied study design-specific filters, as a wide range of study types may be employed in studies of prophylaxis. Instead, we have used a bespoke filter to identify studies examining prophylaxis/prevention.

Date limits

Individual studies are unlimited by date. SRs/NMAs/ITCs will have their bibliographies checked from 2020 onwards but are unlimited by the strings.

Search string construction

The search string combines:

COVID-19 terms AND IVM terms AND prophylaxis terms

We have not used the usual method for excluding non-human studies, as pre-clinical data of interest will be tagged for comment in the report.

Embase/medline search string

The search string for Embase/Medline in Embase.com is in Table 5. Search hits for each set of search terms will be recorded in the report.

Table 5: Search string for Embase/Medline via Embase.com

No.	Search	Hits
1	'coronavirus disease 2019'/exp OR 'coronavirus infection':de OR 'severe acute respiratory syndrome'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp OR covid*:ab,ti OR coronavirus*:ab,ti OR 'corona virus':ab,ti OR coronovirus*:ab,ti OR 'corono virus':ab,ti OR coronavirinae*:ab,ti OR 'corona virinae':ab,ti OR 'sars virus':ab,ti OR sarsvirus:ab,ti OR 'severe acute respiratory syndrome*':ab,ti OR 'severeacute respiratory syndrome*':ab,ti OR 'severeacuterespiratory syndrome*':ab,ti OR 'severeacuterespiratorysyndrome*':ab,ti OR 'severe acuterespiratory syndrome*':ab,ti OR 'severe acuterespiratorysyndrome*':ab,ti OR 'severe acute respiratorysyndrome*':ab,ti OR cov:ab,ti OR ncov:ab,ti OR ncovid*:ab,ti OR '2019 ncov*':ab,ti OR 2019ncov*:ab,ti OR '19 ncov*':ab,ti OR 19ncov*:ab,ti OR ncov2019*:ab,ti OR 'ncov 2019*':ab,ti OR ncov19*:ab,ti OR 'ncov 19*':ab,ti OR 'hcov 19*':ab,ti OR hcov19*:ab,ti OR 'hcov 2019*':ab,ti OR hcov2019*:ab,ti OR '2019 novel*':ab,ti OR ncov*:ab,ti OR 'n cov':ab,ti OR 'sars cov 2*':ab,ti OR 'sarscov 2*':ab,ti OR 'sarscov2*':ab,ti OR 'sars cov2*':ab,ti OR sarscov19*:ab,ti OR 'sars cov19*':ab,ti OR 'sarscov 19*':ab,ti OR 'sars cov 19*':ab,ti OR sarscov2019*:ab,ti OR 'sars cov2019*':ab,ti OR 'sarscov 2019*':ab,ti OR 'sars cov 2019*':ab,ti OR sars2*:ab,ti OR 'sars 2*':ab,ti OR sarscoronavirus2*:ab,ti OR 'sars coronavirus 2*':ab,ti OR 'sarscoronavirus 2*':ab,ti OR 'sars coronavirus2*':ab,ti OR sarscoronovirus2*:ab,ti OR 'sars coronovirus 2*':ab,ti OR 'sarscoronovirus 2*':ab,ti OR 'sars coronovirus2*':ab,ti OR 'corvid-19':ab,ti OR corvid19:ab,ti OR '2019 novel':ab,ti OR 2019novel:ab,ti	**246556**
2	'ivermectin'/exp OR ivermectin*:ab,ti OR stromectol*:ab,ti OR mectizan*:ab,ti OR ivermax*:ab,ti OR avermectin*:ab,ti OR dihydroavermectin*:ab,ti OR cardotek*:ab,ti OR revectina*:ab,ti OR quanox*:ab,ti OR diapec*:ab,ti OR ivermectol*:ab,ti OR ivexterm*:ab,ti OR mk933:ab,ti OR 'mk 933':ab,ti	**15676**
3	'prevention'/exp OR prevent*:ab,ti OR prophyla*:ab,ti OR protect*:ab,ti OR chemoprophyla*:ab,ti OR chemoprevent*:ab,ti	**4010436**
4	#1 AND #2 AND #3	**319**

Cochrane search string

CENTRAL and CDSR are searched with the following string (Table 6).

Table 6: Search string for CENTRAL and CDSR via Cochrane Library

No.	Search	Hits
1	MeSH descriptor: [COVID-19] explode all trees	**918**
2	MeSH descriptor: [Coronavirus Infections] this term only	**668**
3	MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees	**367**
4	MeSH descriptor: [SARS-CoV-2] explode all trees	**599**
5	(covid* OR coronavirus* OR "corona virus" OR coronovirus* OR "corono virus" OR coronavirinae* OR "corona virinae" OR "sars virus" OR sarsvirus OR "severe acute respiratory syndrome*" OR "severeacute respiratory syndrome*" OR "severeacuterespiratory syndrome*" OR "severeacuterespiratorysyndrome*" OR "severe acuterespiratory syndrome*" OR "severe acuterespiratorysyndrome*" OR "severe acute respiratorysyndrome*" OR Cov OR ncov OR "n cov" OR ncovid* OR "2019 nCoV*" OR 2019nCoV* OR "19 nCoV*" OR 19nCoV* OR nCoV2019* OR "nCoV 2019*" OR nCoV19* OR "nCoV 19*" OR "HcoV 19*" OR HCoV19* OR "HcoV 2019*" OR HCoV2019* OR "SARS CoV 2*" OR "SARSCoV 2*" OR "SARSCoV2*" OR "SARS CoV2*" OR SARSCov19* OR "SARS Cov19*" OR "SARSCov 19*" OR "SARS Cov 19*" OR SARSCov2019* OR "SARS Cov2019*" OR "SARSCov 2019*" OR "SARS Cov 2019*" OR SARS2* OR "SARS 2*" OR SARScoronavirus2* OR "SARS coronavirus 2*" OR "SARScoronavirus 2*" OR "SARS coronavirus2*" OR "CORVID-19" OR CORVID19 OR "2019 novel" OR 2019novel):ti,ab,kw	**9159**
6	#1 OR #2 OR #3 OR #4 OR #5	**9159**
7	MeSH descriptor: [Ivermectin] explode all trees	**447**
8	(ivermectin* OR stromectol* OR mectizan* OR Ivermax* OR avermectin* OR dihydroavermectin* OR cardotek* OR revectina* OR quanox* OR diapec* OR ivermectol* OR ivexterm* OR mk933 OR "mk 933"):ti,ab,kw	**850**
9	#7 OR #8	**850**
10	MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees	**237**
11	MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees	**81**
12	(prevent* OR prophyla* OR protect* OR chemoprophyla* OR chemoprevent*):ti,ab,kw	**287451**
13	#10 OR #11 OR #12	**287451**
14	#6 AND #9 AND #13	**47**
15	#14 in Cochrane Reviews, Trials	**46**

Pubmed search string

The PubMed string is given below, to capture Medline, in-process or e-publications ahead of print (Table 7).

Table 7: Search string for Medline, Medline in-process and e-publications via PubMed

No.	Search	Hits
1	"COVID-19"[mh] OR "Coronavirus Infections"[Mesh:NoExp] OR "Severe Acute Respiratory Syndrome"[mh] OR "SARS-CoV-2"[mh]	**138,894**
2	covid*[tiab] OR coronavirus*[tiab] OR "corona virus"[tiab] OR coronovirus*[tiab] OR "corono virus"[tiab] OR coronavirinae*[tiab] OR "corona virinae"[tiab] OR "sars virus"[tiab] OR sarsvirus[tiab] OR "severe acute respiratory syndrome*"[tiab] OR "severeacute respiratory syndrome*"[tiab] OR "severeacuterespiratory syndrome*"[tiab] OR	**221,750**

No.	Search	Hits
	"severeacuterespiratorysyndrome*"[tiab] OR "severe acuterespiratory syndrome*"[tiab] OR "severe acuterespiratorysyndrome*"[tiab] OR "severe acute respiratorysyndrome*"[tiab] OR Cov[tiab] OR ncov[tiab] OR "n cov"[tiab] OR ncovid*[tiab] OR "2019 nCoV*"[tiab] OR 2019nCoV*[tiab] OR "19 nCoV*"[tiab] OR 19nCoV*[tiab] OR nCoV2019*[tiab] OR "nCoV 2019*"[tiab] OR nCoV19*[tiab] OR "nCoV 19*"[tiab] OR "HcoV 19*"[tiab] OR HCoV19*[tiab] OR "HcoV 2019*"[tiab] OR HCoV2019*[tiab] OR "SARS CoV 2*"[tiab] OR "SARSCoV 2*"[tiab] OR "SARSCoV2*"[tiab] OR "SARS CoV2*"[tiab] OR SARSCov19*[tiab] OR "SARS Cov19*"[tiab] OR "SARSCov 19*"[tiab] OR "SARS Cov 19*"[tiab] OR SARSCov2019*[tiab] OR "SARS Cov2019*"[tiab] OR "SARSCov 2019*"[tiab] OR "SARS Cov 2019*"[tiab] OR SARS2*[tiab] OR "SARS 2*"[tiab] OR SARScoronavirus2*[tiab] OR "SARS coronavirus 2*"[tiab] OR "SARScoronavirus 2*"[tiab] OR "SARS coronavirus2*"[tiab] OR "CORVID 19"[tiab] OR CORVID19[tiab] OR "2019 novel*"[tiab] OR 2019novel[tiab]	
3	#1 OR #2	**230,015**
4	"Ivermectin"[mh] OR "avermectin H2B1b"[Supplementary Concept] OR "22,23-dihydroavermectin B(1)a"[Supplementary Concept]	**6,938**
5	ivermectin*[tiab] OR stromectol*[tiab] OR mectizan*[tiab] OR Ivermax*[tiab] OR avermectin*[tiab] OR dihydroavermectin*[tiab] OR cardotek*[tiab] OR revectina*[tiab] OR quanox*[tiab] OR diapec*[tiab] OR ivermectol*[tiab] OR ivexterm*[tiab] OR mk933[tiab] OR "mk 933"[tiab]	**7,705**
6	#4 OR #5	**9,546**
7	"prevention and control"[Subheading] OR "Pre-Exposure Prophylaxis"[mh] OR "Post-Exposure Prophylaxis"[mh]	**1,383,171**
8	prevent*[tiab] OR prophyla*[tiab] OR protect*[tiab] OR chemoprophyla*[tiab] OR chemoprevent*[tiab]	**2,472,625**
9	#7 OR #8	**3,272,725**
10	#3 AND #6 AND #9	**113**

3.6 Data items

Variables for which data will be sought will include at least the following.

Study characteristics: NCT number/trial identifiers, phase, population, setting (hospital or community), country, drug class, study design, number of patients, treatment arms, total study duration, pre-defined subgroups, matching, case definition, methods to control for confounding for each analysis (particularly for non-RCTs), time period/dates over which participants recruited, further aspects to assess risk of bias

Population characteristics: defining the included study population, e.g. healthcare workers, contacts of household cases, elderly, care home residents, etc.

Exposure description: how exposure is defined/measured, severity of index case(s), duration of exposure to index case(s) or to population with significant prevalence

Treatment characteristics: previous treatment(s), IVM dose, frequency, duration and route, adjunct/concomitant treatments (including over-the-counter treatments), combination treatments

Baseline participant characteristics for index case(s) and contact cases: for each arm e.g. patient characteristics, prior treatment, mean (SD) age, median (IQR) age, n (%) within different age categories, % female, co-morbidities, height, weight, body mass index (BMI)/obesity, metabolic syndrome, serum 25-hydroxyvitamin D level, other potential

confounding factors, if reported, for contracting infection or for poor outcome once infected (e.g. physical activity >1 hour per day, immune compromised, chronic obstructive pulmonary disease (COPD), hypertensive disease, heart disease, use of diuretics, ESRD, cognitive impairment, diabetes mellitus, central venous catheter/haemodialysis patients, neutrophil count, C-reactive protein, creatinine kinase, blood urea nitrogen, lymphocyte count, lactate dehydrogenase), severity of index case(s), duration of follow-up after taking IVM

Compliance: Dosing and compliance with IVM/treatments (treatment interruptions, treatment withdrawals, planned:actual dosing intensity, study withdrawals)

Efficacy and safety outcomes (follow-up period, data timepoints/ranges, adjusted and unadjusted outcomes, factors adjusted for): incidence of appearance of symptoms related to COVID-19 infection, incidence of detection of COVID-19 by PCR/LFT tests, severity of symptoms, seroconversion (antibody test), hospitalisation, death and time-to-event measures for any of these outcomes

Adverse effects of treatment (AEs), treatment-related AEs (adverse drug reactions (ADRs)), serious adverse events (SAEs), treatment-related SAEs (SADRs)

Analysis dataset: intention-to-treat (ITT), modified intention-to-treat (mITT), per protocol (PP), etc.

3.7 Quality assessment

This SR will use established risk of bias tools recommended for Health Technology Appraisal submissions.

RCTs

The Cochrane risk of bias tool for randomised trials (RoB 2, 22 August 2019 version), which includes assessment at the trial level and at the outcome level(23).

Non-randomised studies

From the Internal validity of non-randomised studies (NRS) on interventions (EUnetHTA v1.0 July 2015)(24), the ACROBAT-NRSI will be used to assess comparative NRS, for example, cohort studies and case-control studies.

Case series/registry data

Twenty-item case series quality assessment (QA) checklist from the Institute of Health Economics (IHE) (25) with the following additional items considered if required:

- From the NICE 8-item tool, the question concerning ‘Are outcomes stratified? (e.g. by disease stage, abnormal test results, patient characteristics)’
- From McGill’s QA chapter(26): Is the study based on a representative sample selected from a relevant population? Are the criteria for inclusion explicit? Did all individuals enter the study at a similar point in their disease progression? Was follow-up long enough for important events to occur? Were outcomes assessed using objective criteria or was blinding used? If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors? For long-term safety considerations, it is important to consider the adverse reaction evidence in light of the likely exposure duration to pharmacological therapy(27).

3.8 Study records

Data management

Results from the database searches will be downloaded via Endnote into an online tool for screening, Rayyan: http://rayyan.qcri.org

This will be used to manage citation screening during first pass (abstract and title review stage).

Papers retained for second pass (full paper review stage) will be exported to an Excel file for further review. Second pass papers will also be tagged in Endnote (i2s).

If there is a conflict between data reported across multiple sources for a particular study (e.g. between a full text published article and a registry record), the authors will be contacted. If no reply is received, the published data will be extracted and the discrepancy noted in a comment, except in the case where the published data are clearly incorrect.

Selection process

Abstracts are screened by one senior reviewer (KM). As per good practice, we will produce a table counting citations excluded at abstract stage (e1) by exclusion reason. In the instance of borderline eligibility cases a precautionary principle will be applied and these will be accepted into second pass.

Full texts are first sought within Endnote (full text automated search). Full texts not available via Endnote or open access online are viewed via DeepDyve.com.[b] Those unavailable via DeepDyve will be requested via Desk Reprints or other subscription service.

Full papers are reviewed by two reviewers independently in a blinded fashion. Discrepancies will be discussed and resolved. If a paper remains borderline a third appropriate reviewer will adjudicate and the paper discussed with other authors. As per good practice we will produce a table of citations excluded at full text stage (e2) with full rationale for exclusion.

The screening process will be summarised in a PRISMA flow diagram.

3.9 Data collection process

Data collection is via a pilot-tested Data Extraction Table (DET), in Excel (KM and EF).

Data are extracted by as follows:

- Data / text entries and risk of bias assessment will be entered by one reviewer and QC'd by a second independent reviewer.
- QC comments and replies are recorded automatically in a temporary log. QC notes remain within the file.

3.10 Endnote file

An Endnote file will be prepared containing all references from the SR, any background references from this protocol, & papers (SRs/NMAs) used for cross-referencing purposes.

Registry records and other hand-searched citations will also be added. Parent (main paper), linked (related papers) and registry records will be tagged with the relevant study name.

[b] DeepDyve.com is a subscription service providing view-access to many full text papers)

3.11 BiBTeX database

A BiBTeX database will also be established.

3.12 Statistical considerations

Measures of treatment effect

We will use the risk ratio (RR) as the measure of treatment effect for dichotomous outcomes. A hazard ratio (HR) will be presented for any time-to-event outcomes.

Unit of analysis issues

We will consider interventions that comprise multiple doses of ivermectin as a single intervention and subgroup when necessary.

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. risk ratio (RR) plus 95% confidence interval (CI).
- If the analysis does not account for the cluster design, if available data permit, before combining the cluster randomised trials with individually randomised trials in the same meta-analysis in RevMan 5.4, the RR reported from the cluster-RCT would be adjusted as follows: we would 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 would then use an external estimate of the intracluster coefficient (ICC) to estimate a design effect to inflate the variance of the effect estimate (28).
- If suitable IPD are available, appropriate adjustment would be made to account for clustering effects.

Handling data from controlled before and after studies and interrupted time series

We will handle data and analysis of controlled before and after (CBA) and interrupted time series (ITS) studies following guidance from the Cochrane Effective Practice and Organisation of Care (EPOC) group. In particular, this group has led in the worldwide development of SR methodology for ITS designs.

Dealing with missing data

We will not impute missing data for any of the outcomes. Authors of studies will be contacted for missing outcome data and for clarification on study methods, if possible, and for study status for ongoing trials or studies. We are aware that many studies will be in preprint form or not yet in peer reviewed journals, so we will request full and transparent information on study 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 (28).

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) (29), by a formal statistical test to indicate statistically significant heterogeneity (30) 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 (28).

Data synthesis

If sufficient clinically similar studies 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, risk ratios (RR) will be pooled. For time-to-event outcomes, we will pool hazard ratios (HR).

IPD will be requested from authors. If data permit, a propensity-score matching analysis using IPD will be conducted. Stratification into high risk and low risk would be attempted, using patient characteristics, such as age (≥ 65 yrs vs <65 yrs), obesity, co-morbidities present or not, immune compromised or not, COPD present or not, etc.

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

If necessary, methods to account for zero events in either or both groups/arms will also be followed using approach used in a previous SR (5).

We will meta-analyse data using the random effects model (31). Results will use Mantel-Haentzel method for weighting. Where interventions differ to any degree or if there is other substantial heterogeneity the results will be reported in a narrative.

Subgroup analysis and investigation of heterogeneity

Where possible, we will perform the following pre-specified subgroup analyses grouping studies by:

- Pre-exposure prophylaxis versus post-exposure prophylaxis subgroups
- RCTs versus non-randomised studies (unadjusted, risk-adjusted or propensity-matched non-randomised)
- Single initial dose in first 7 days versus double initial dose inside 7 days
- IVM dose frequency (weekly, fortnightly, monthly)
- Active comparators versus NPI-only comparators

Further post-hoc subgroup analyses, dependent on data availability, will be performed on an exploratory basis.

Sensitivity analysis

For included RCTs, if data permit, we will perform sensitivity analysis by excluding studies which do not confirm adequate methods of randomisation for treatment assignment or allocation concealment. More generically, sensitivity analyses defining subsets of data, wherein particular studies at high risk of bias may be excluded to ascertain their influence on the results.

Grade and Summary of findings

All outcomes will be assessed independently by two review authors (TL and AB) using the GRADE approach, which ranks the quality of the evidence. Results will be presented in a summary of findings table for prophylaxis outcomes. Any differences will be resolved by discussion with the wider group.

4 FUNDING SOURCES

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5 DECLARATIONS OF INTEREST

The authors have no conflicts of interest to declare.

Other disclosures: Some authors were members of the British Ivermectin Recommendation Development (BiRD) panel “Evidence to Decision” event convened on 20 February 2021 (TL, EF, AB). Mr. Bryant and Dr. Lawrie were members of the steering group and did not vote. Dr. Fordham was an ordinary member of the panel. BiRD continues as a public information activity managed by EbMCsquared, a non-profit Community Interest Company.

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