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# Ivermectin for preventing and treating COVID-19 (Protocol)

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[Intervention Protocol]

# Ivermectin for preventing and treating COVID-19

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and safety of ivermectin compared to standard of care, placebo, or any other proven intervention (1) for prevention of an infection with SARS-CoV-2 (post-exposure prophylaxis), and (2) for people with COVID-19 receiving treatment as outpatients or inpatients.

# BACKGROUND

## Description of the condition

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 11 March 2020, after spreading from China to more than 144 countries, the World Health Organization (WHO) declared a COVID-19 pandemic. Since then, over 108 million cases have been confirmed, including over 2.3 million deaths, with cases rising (WHO 2020a; WHO 2020b).

Available data suggest that at least one-third of SARS-CoV-2 infections are asymptomatic (Oran 2021). About 80% of infected cases developing symptoms show mild to moderate manifestation, including flu-like symptoms such as fever, cough, sore throat, and myalgia, as well as the almost pathognomonic loss of smell and taste. These are mostly manageable in ambulatory settings. Severe and critical cases (approximately 20%), with the need for ventilatory support or intensive medical care, are individually tragic and an unsustainable burden for entire healthcare systems. Age (over 60 years) and pre-existing co-morbidities are defined risk factors for a severe course of COVID-19 (Huang 2020; WHO 2020a). Chronic diseases - for example, cardiovascular disease, hypertension, diabetes, respiratory disease, and cancer - are associated with an increased risk of severe COVID-19 and death (Deng 2020; Williamson 2020).

Only 60% to 65% of people with COVID-19 who have been treated in a hospital intensive care unit survive, often with considerable consequential damage (Herrmann 2020; Prescott 2020). COVID-19 can lead to death due to a variety of causes, such as severe respiratory failure, septic shock, and multiple organ failure (WHO 2020a). The case fatality rate worldwide is currently estimated at 2.2% with large statistical fluctuations (less than 0.1% in Singapore up to 8.8% in Mexico, status February 2021) (Dong 2020). However, these varying rates should not be interpreted as markers for the quality of health care (Karagiannidis 2020), or the aggressiveness of different virus variants. These statistics are influenced by the average age of a population or of those infected, the quality and extent of local test strategies, as well as documentation and reporting systems (Kobayashi 2020). The gold standard for identifying infection is the reverse transcription polymerase chain reaction- (RT-PCR) based detection of viral ribonucleic acid (RNA) from a nasopharyngeal swab test, sputum, or tracheal secretion, with a sensitivity ranging from 70% to 98%, depending on pre-test probability (Watson 2020). Offering lower sensitivity but greater practicality and accessibility, antigen tests are receiving increasing attention, especially in point-of-care diagnostics of COVID-19.

The virus is highly contagious - especially the recently discovered variants - which makes it difficult to contain its spread in the community (WHO 2021). Currently, the only ubiquitously available measures to control virus spreading are non-pharmaceutical interventions, including restrictions of public life and social interactions, and strict hygiene. Research on prophylaxis of SARS-CoV-2 infection and treatment of COVID-19 is being carried out under great pressure worldwide. Evaluating the effectiveness of repurposed drugs represents one important strand of these research efforts. In this context, ivermectin - an antiparasitic intervention - has recently received a lot of attention, especially in South America and parts of Asia.

## Description of the intervention

Ivermectin is an antiparasitic agent belonging to the group of avermectins, originally a fermentation metabolite produced by the bacterium *Streptomyces avermitilis*. Ivermectin was introduced for medical use in 1982 and is effective against various types of nematodes and helminthes, and ectoparasites such as mites and lice. The mode of action is based on binding to specific cell membrane channels that only occur in invertebrates. Channel activation ultimately leads to blocked cell signal transmission through chloride-induced hyperpolarization. Consequently, parasites are paralysed and die, interrupting their reproduction cycle (Campbell 1983; Dourmishev 2005; Panahi 2015). Ivermectin is on the WHO List of Essential Medicines for its high effectiveness against human ectoparasite infestations (WHO 2019).

In animals and humans, the agent is easily resorbed by the mucosa or skin if taken orally or topically, respectively. As a lipophilic compound, it accumulates in fat and liver tissue from where it effuses and takes effect. Elimination is processed through bile and faeces. Ivermectin is widely used in veterinary medicine, but it is also approved for human parasitic diseases such as onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies in several countries (e.g. USA, Japan, France, Germany, Australia) (González-Canga 2008). The established dosing regimen ranges from 150 to 200 µg/kg administered orally, with a one- to two-dose administration generally being effective. Dosing is generally low because of the agent's high potency (Ashour 2019 ).

Adhering to recommended doses, ivermectin is generally well-tolerated. Adverse effects - which seem to arise partially from the rapid death of parasites, leading to hyperinflammation and anaphylactic reactions - include weakness, drowsiness, diarrhoea, nausea, and vomiting. In addition, ivermectin can cause fever and rash. Rare serious side effects can occur, such as vision problems, neurotoxicity, and liver damage (González-Canga 2008).

## How the intervention might work

An in vitro study showed that ivermectin can inhibit replication of the human-immunodeficiency-virus 1 (HIV-1), via inhibition of the interaction of virus proteins and a human cargo protein complex called importin (IMPα/β1) (Wastgaff 2012). Importin is used by viruses for nuclear import in order to initiate their replication process (Wastgaff 2012). Besides HIV-1, various other RNA viruses use importin as target protein, among them dengue virus, West Nile virus, and influenza. Several research groups have investigated ivermectin's efficiency on those pathogens (Goetz 2016; Tay 2013; Yang 2020). Although ivermectin showed some inhibitory potential for virus replication in vitro, there is no evidence of clinical effectiveness to date.

Before the COVID-19 pandemic, only two clinical trials had been registered on ClinicalTrials.gov (clinicaltrials.gov/) using ivermectin as an intervention for treatment of virus diseases. Only one of these had published results (Yamasmith 2018). In this small, single-centre study published as a conference abstract, ivermectin showed a shorter viral protein clearance time compared to placebo in people infected with dengue virus (Yamasmith 2018).

Another member of the beta-coronavirus family, SARS-CoV-1, which also causes respiratory failure, revealed similar dependence

on the IMPα/β1 interaction (Wulan 2015). The pathogen causing COVID-19, SARS-CoV-2, is also a RNA virus closely related to SARS-CoV-1. In 2020, ivermectin gained high interest as a promising therapeutic option against SARS-CoV-2, when Caly 2020 published their experimental study results showing that ivermectin inhibits the replication of SARS-CoV-2 in cell culture. So far, the only drugs shown to be clearly effective in COVID-19 treatment are targeting the immune response to a SARS-CoV-2 infection; for example, dexamethasone (RECOVERY 2021). Therefore, ivermectin's potential to restrict the disease's progression, or even its outbreak, indicates that it is possibly an effective antiviral agent. However, until showing success in human clinical trials with patient-relevant outcomes, these findings remain suggestive.

The molecular hypothesis of ivermectin's antiviral mode of action, explained above, suggests an inhibitory effect on virus replication in the early stages of the disease, indicating a benefit especially for people with mild or moderate disease. This possibility has also led to the idea of the possible preventive potency of ivermectin on infection with SARS-CoV-2 in individuals after exposure to a contagious contact, called post-exposure prophylaxis. In response to the early promising in vitro studies on ivermectin, mentioned above, a number of COVID-19 clinical trials have been initiated to investigate the prophylactic and therapeutic effects of ivermectin.

### Why it is important to do this review

Ivermectin is an inexpensive and widely used medicine, mainly in low- and middle-income countries with a high burden of parasitic diseases. The recently published in vitro studies, especially the results of Caly 2020, have led to great interest in ivermectin in many countries with high numbers of SARS-CoV-2 infections, including the USA and countries of South America and Asia. In South America in particular, people started liberally self-medicating with ivermectin, and the drug has become part of public health policies without reliable scientific data. For example, in May 2020, Bolivian and Peruvian health officials recommended ivermectin for the treatment of COVID-19 without supplying evidence. In Brazil, it was promoted as a preventive measure by municipalities (Rodríguez-Mega 2020). Due to the rapid increase in interest in ivermectin and the risk of abuse, the US Food and Drug Administration (FDA) discouraged the use of ivermectin intended for animals (FDA 2020).

The increased research interest in ivermectin has led to the registration of numerous trials in clinical trials registries worldwide. As of 18 February 2021, there were 57 trials registered on ClinicalTrials.gov (clinicaltrials.gov/) investigating ivermectin in various settings.

Several studies describe ivermectin's positive effect on resolution of mild COVID-19 symptoms or describe a reduction of inflammatory marker levels or shorter time to viral clearance, while other studies indicate no effect or even a negative effect on disease progression. Many studies are already summarised in existing systematic reviews, meta-analyses and guidelines (Hill 2021; NIH 2021; Padhy 2020). It has to be kept in mind that many available meta-analyses and reviews, as well as most of the underlying original studies, have not yet been published in peer-reviewed journals and are only available on preprint servers without any supervising authority. Given the pace of the pandemic, it is important and welcome to make new scientific findings immediately available. But non-peer-reviewed results have to be handled with care and should not be used as the basis for clinical decisions and recommendations. Methodological limitations in the design of original studies, data integrity, and potential conflicts of interests have to be critically appraised when judging trial results. Many reviews and meta-analyses of ivermectin for COVID-19 are not reliable due to insufficient methodologic accuracy and quality.

As of February 2020, the efficacy and safety of ivermectin for COVID-19 treatment and prophylaxis are still subject to debate. The most recent Association of the Scientific Medical Societies in Germany (AWMF) guideline recommends against the use of ivermectin as antiviral treatment (German AWMF Guideline 2021), while in February 2021, the US National Institutes of Health (NIH) revised their COVID-19 treatment guidelines from a recommendation 'against the use of ivermectin' to 'cannot recommend either for or against the use of ivermectin', giving clinicians leeway in individual case decision-making (NIH 2021).

This review aims to provide a complete evidence profile, based on current Cochrane standards, for ivermectin with regard to efficacy and safety for post-exposure prophylaxis and treatment of COVID-19.

## OBJECTIVES

To assess the efficacy and safety of ivermectin compared to standard of care, placebo, or any other proven intervention (1) for prevention of an infection with SARS-CoV-2 (post-exposure prophylaxis), and (2) for people with COVID-19 receiving treatment as outpatients or inpatients.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomized controlled trials (RCTs) only, as this is the best study design for evaluating the efficacy of interventions (Higgins 2020a). We will exclude non-standard RCT designs, such as cluster-randomized and cross-over trials (Higgins 2020b). These designs are not appropriate in this context, since the underlying cause of COVID-19 is an infection with the SARS-CoV-2 virus and the medical condition evolves over time.

We will include full-text journal articles published in PubMed-indexed and non-indexed journals, preprint articles, results published in trial registers, and abstract publications. All studies, especially preprint articles that have not been peer-reviewed, must report robust and valid data on study design, participants' characteristics, interventions, and outcomes, to be eligible for inclusion. We will categorize studies in question as ‘awaiting classification’ until the authors publish further information or clarify certain questions.

We will not apply any restrictions on the language of publication of the articles.

#### Types of participants

##### *Treatment of COVID-19 with ivermectin*

We will include studies in participants with confirmed SARS-CoV-2 infection (RT-PCR or antigen testing), regardless of age, gender, ethnicity, disease severity, and setting (in- and outpatients).

***Prevention of SARS-CoV-2 infection***

We will include studies investigating participants that are not infected with SARS-CoV-2 at enrolment, but are at high risk of developing the infection (e.g. post high-risk exposure), regardless of age, gender, ethnicity, disease severity, and setting (in- and outpatients). Participants may be hospitalized for reasons other than COVID-19. Eligible trials must report on the history of previous SARS-CoV-2 infections or serologic evidence in included participants. A previous history of SARS-CoV-2 infection will not be an exclusion criterion.

We will exclude studies investigating ivermectin for prevention and treatment of other viral diseases.

### Types of interventions

All doses and regimens of ivermectin are eligible and will be pooled for the primary analysis. Dosing schemes will be considered and categorized into recommended (up to 0.2 mg/kg orally, single dose) and high doses (> 0.2 mg/kg orally, single dose or with higher frequency) and analysed in subgroup analyses.

We will compare ivermectin to no treatment, placebo or to any other active pharmacological comparator with proven efficacy for prevention or treatment of COVID-19. For dexamethasone, it has been shown that mortality from COVID-19 was lower among people who were randomized to receive dexamethasone than among those who received the usual standard of care (RECOVERY 2021; Siemieniuk 2020). Remdesivir showed some benefit for people hospitalized with COVID-19, though to a lesser extent (Beigel 2020). Co-interventions (standard of care) are allowed but must be comparable between groups.

We will create these comparisons:

- ivermectin versus placebo or no treatment; and
- ivermectin versus active pharmacological intervention with proven efficacy.

### Types of outcome measures

We will analyse different outcomes for the use of ivermectin for treatment of people with COVID-19 in inpatient and outpatient settings, and for the prevention of SARS-CoV-2 infection. If studies are eligible for inclusion regarding design, population, intervention, and comparator, but do not report outcomes of interest, they cannot be included for meta-analysis. However, we will summarize descriptively reported outcomes for all included studies in an additional table.

***Primary outcomes***

**Ivermectin for treating COVID-19 in the inpatient setting**

- All-cause mortality up to 28 days.
- Clinical status, assessed by need for respiratory support with standardized scales (e.g. WHO Clinical Progression Scale (Marshall 2020), hereafter referred to as the WHO scale) up to 28 days. If the study has not used a standardized scale to assess the status of the participants, we will categorize their status according to the WHO scale with the information provided by the study. Clinical status is a complex outcome with substantial heterogeneity. We will pool data only if clinically reasonable (see the list of specific outcomes below). When only a few studies are available that report different outcomes in terms of clinical status, we will describe the results narratively.
  * Improvement of clinical status
    - ☐ Weaning or liberation from invasive mechanical ventilation in surviving participants (i.e. WHO scale ≤ 6, if ≥ 7 at baseline).
    - ☐ Ventilator-free days (ventilator-free defined as WHO scale ≤ 6).
    - ☐ Duration of liberation from invasive mechanical ventilation.
    - ☐ Liberation from supplemental oxygen in surviving participants (i.e. WHO scale ≤ 4, if ≥ 5 at baseline).
    - ☐ Duration of liberation from supplemental oxygen.
  * Worsening of clinical status
    - ☐ Need for invasive mechanical ventilation (i.e. WHO scale = 7 to 9, if ≤ 6 at baseline).
    - ☐ Need for non-invasive mechanical ventilation or high flow (i.e. WHO scale = 6, if ≤ 5 at baseline).
    - ☐ Need for oxygen by mask or nasal prongs (i.e. WHO scale = 5, if ≤ 4 at baseline).
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with at least one event within 28 days.

**Ivermectin for treating COVID-19 in the outpatient setting**

- All-cause mortality up to 28 days.
- Admission to hospital.
- Clinical status, assessed by need for respiratory support with standardized scales (e.g. WHO Clinical Progression Scale (Marshall 2020)) up to 14 days. If the study has not used a standardized scale to assess the status of the participants, we will categorize their status according to the WHO scale with the information provided by the study. Clinical status is a complex outcome with substantial heterogeneity. We will pool data only if clinically reasonable (see the list of specific outcomes below). When only a few studies are available that report different outcomes in terms of clinical status, we will describe the results narratively.
  * Development of moderate to severe clinical COVID-19 symptoms (defined as WHO scale ≥ 6)
    - ☐ Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow (i.e. WHO scale ≥ 6, severe disease):
      - ○ need for invasive mechanical ventilation (i.e. WHO scale = 7 to 9);
      - ○ need for non-invasive mechanical ventilation or high flow (i.e. WHO scale = 6).
    - ☐ Need for hospitalization with or without supplemental oxygen (i.e. WHO scale = 4 to 5, moderate disease):
      - ○ need for oxygen by mask or nasal prongs (i.e. WHO scale = 5);
      - ○ need for hospitalization without oxygen therapy (i.e. WHO scale = 4).
  * Symptom resolution (i.e. WHO scale = 1)
    - ☐ Number of participants with symptoms resolved
    - ☐ Duration of symptom resolution
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with at least one event within 14 days.

**Ivermectin for preventing SARS-CoV-2 infection**

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days.
- Development of clinical COVID-19 symptoms at 14 days; assessed in accordance with individual items of the WHO Clinical Progression Scale (Marshall 2020). If the study has not used a standardized scale to assess the status of the participants, we will categorize their status according to the WHO scale with the information provided by the study.
  * Uninfected (WHO scale = 0)
  * Ambulatory mild disease (WHO scale = 1 to 3)
  * Hospitalized with moderate disease (WHO scale = 4 to 5)
  * Hospitalized with severe disease (WHO scale = 7 to 9)
  * Death (WHO scale = 10)
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with at least one event within 14 days.

**Timing of outcome measurement**

We expect that included studies will measure several outcomes – including clinical status, SARS-CoV-2 infection, and adverse events – at different time points. For inpatient setting outcomes, the main time point of interest will be 28 days after randomization. For outpatient setting and prevention trials outcomes, the main time point of interest will be 14 days after randomization, with the exception of mortality (28 days). If only a few studies have contributed data to an outcome, we will pool different time points, provided the studies have produced valid data and pooling is clinically reasonable. If sufficient data are available, we will group the measurement time points of eligible outcomes into those measured directly after treatment (up to 7 days), medium-term outcomes (up to 14 days), and longer-term outcomes (28 days or more).

### *Secondary outcomes*

**Ivermectin for treating COVID-19 in the inpatient setting**

- Serious adverse events, defined as number of participants with at least one event within 28 days.
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 28 days (WHO 2012).
- Admission to intensive care unit (ICU).
- Duration of hospitalization.
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, and at 3, 7, and 14 days.

**Ivermectin for treating COVID-19 in the outpatient setting**

- Serious adverse events, defined as number of participants with at least one event within 14 days.
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 28 days (WHO 2012).
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, and at 3, 7, and 14 days.

**Ivermectin for preventing SARS-CoV-2 infection**

- All-cause mortality up to 28 days.
- Admission to hospital.
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 28 days (WHO 2012).

**Timing of outcome measurement**

We expect that included studies will measure several outcomes – including serious adverse events, quality of life, and viral clearance – at different time points. We will analyse different time points for viral clearance separately due to the dynamic course of the viral load. For other inpatient setting outcomes, the main time point of interest will be 28 days after randomization. For other outpatient setting and prevention trials outcomes, the main time point of interest will be 14 days after randomization, with the exception of mortality (28 days). If only a few studies have contributed data to an outcome, we will pool different time points, as long as the studies have produced valid data and pooling is clinically reasonable. If sufficient data are available, we will group the measurement time points of eligible outcomes into those measured directly after treatment (up to 7 days), medium-term outcomes (up to 14 days) and longer-term outcomes (28 days or more).

## Search methods for identification of studies

### Electronic searches

The Information Specialist (MIM) will conduct systematic searches of the following sources and will not place restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
  * Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates;
  * MEDLINE (PubMed), daily updates;
  * Embase, weekly updates;
  * ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
  * World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates; and
  * medRxiv (www.medrxiv.org), weekly updates.
- Web of Science Core Collection (from 1 January 2020 onwards):
  * Science Citation Index Expanded (1945-present);
  * Emerging Sources Citation Index (2015-present).
- Preprint servers:
  * medRxiv (www.medrxiv.org/search);
  * ResearchSquare (www.researchsquare.com/browse).

For detailed search strategies, see Appendix 1.

We will not conduct separate searches of the databases required by the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards (Higgins 2021), since these databases are already being regularly searched for the production of the CCSR. For greater precision, we will search the Web of Science database from 1 January 2020 onwards. We will search all other resources without date limits.

### Searching other resources

We will search the reference lists of included studies, systematic reviews, and meta-analyses to identify other potentially eligible studies or ancillary publications. We will contact the investigators

of included studies to obtain additional information on the retrieved studies.

We will search for grey literature, which we define as searching trials registries such as ClinicalTrials.gov and WHO ICTRP contained in the CCSR, as well as searching preprint servers. In addition, we will search the website c19ivermectin.com/, which lists studies related to ivermectin and COVID-19.

## Data collection and analysis

### Selection of studies

We will perform study selection in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2020). Two review authors (SW, MP) will independently screen titles and abstracts of identified records. We will retrieve full-text articles and independently assess eligibility of the remaining records against predefined eligibility criteria. We will resolve discrepancies through discussion between the review authors. We will include studies irrespective of whether measured outcome data are reported in a 'usable' way. We will collate multiple reports of the same study, so that the study, rather than the report, is the unit of interest in the review.

We will document the study selection process in a PRISMA flow diagram with the total number of studies included, ongoing, excluded, and awaiting classification. We will list the reasons for exclusion and awaiting classification in the 'Characteristics of excluded studies' and the 'Characteristics of studies awaiting classification', respectively.

### Data extraction and management

Two review authors (SW, MP) will independently extract data using a standardized data extraction form, including details of the study, participants, intervention, comparator, and outcomes. If necessary, we will try to obtain missing data by contacting the authors of relevant articles. At each step of data extraction, we will resolve any discrepancies through discussion between the review authors.

### Assessment of risk of bias in included studies

We will assess the risk of bias in the included studies using the Cochrane 'Risk of bias' tool 2 (RoB 2) (Higgins 2020c; Sterne 2019). The effect of interest is the effect of assignment at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat effect'). We will assess the risk of bias for all results (outcomes) reported in the included studies that we have specified as outcomes for the current review and that will contribute to the review's 'Summary of findings' table.

Two review authors (SW, MP) will independently assess the risk of bias of all results. We will resolve any disagreements through discussion with a third review author.

The RoB 2 tool considers these domains:

- bias arising from the randomisation process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We will assess the RoB 2 domains using the recommended signalling questions and these response options:

- yes;
- probably yes;
- probably no;
- no; or
- no information.

RoB 2 algorithms map responses to signalling questions. We will use the proposed algorithm after verification to reach a risk of bias judgement, and assign one of three levels to each domain:

- low risk of bias;
- some concerns; or
- high risk of bias.

Similarly, we will reach an overall risk of bias judgement for a specific outcome by considering all domains resulting in one of the three judgement options described above. Overall low risk of bias of the trial result is assumed when all domains are assessed as low risk; some concerns of bias is assumed when the trial result is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain; overall high risk of bias of the trial result is assumed when the trial is judged to be at high risk of bias in at least one domain for this result or when it is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result (Higgins 2020c).

We will use the RoB 2 Excel tool (available on the website www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2) to implement RoB 2. We will store the full RoB 2 data (e.g. completed Excel tool) in an online repository.

The primary analysis will include only those studies which have low risk or some concerns of bias. High risk of bias studies will be included in a secondary analysis to assess the impact on the results.

### Measures of treatment effect

For dichotomous outcomes, we will record the number of events and the number of analysed participants in the intervention and control groups. We will use the risk ratio (RR) with 95% confidence interval (CI) as effect measure.

For continuous outcomes, we will record the mean, the standard deviation (SD), and the number of analysed participants in the intervention and control groups. If the standard deviation is not reported, we will use standard errors, confidence intervals, or P values to calculate the standard deviation with the formulas described in Higgins 2020d. If studies report data as median with interquartile range (IQR), we will assume that the median is similar to the mean when sample sizes are large and the distribution of the outcome is similar to the normal distribution. In these cases, the width of the interquartile range will be approximately 1.35 SDs (Higgins 2020d). We will use the mean difference (MD) with 95% CI as effect measure.

We will consider effect estimates of dichotomous outcomes with the range of the 95% CIs not crossing 1 and continuous outcomes with the range of the 95% CIs not crossing 0 as statistically significant effect estimates. A statistically significant effect does not necessarily mean that the estimated effect is clinical

relevant. We will assess the clinical relevance of the effect size separately and report it transparently.

### Unit of analysis issues

The unit of analysis for this review is the individually randomized participant.

In studies with multiple intervention groups, we will combine groups if reasonable (e.g. study arms with different doses of ivermectin). If it is not reasonable to pool the groups, we will split the 'shared' comparator group to avoid double-counting of participants.

### Dealing with missing data

There are many potential sources of missing data in a systematic review or meta-analysis, which can affect the level of studies, outcomes, summary data, individuals, or study-level characteristics (Deeks 2020). Incomplete data can introduce bias into the meta-analysis, if they are not missing at random. We will address all sources of missing data. Missing studies may be the result of reporting bias and we will address this as described in the Assessment of reporting biases section. Missing outcomes and summary data may be the result of selective reporting bias; missing individuals may be the result of attrition from the study or lack of intention-to-treat analysis. We will address these sources of missing data using the RoB 2 tool (Assessment of risk of bias in included studies). If data are incompletely reported, we will contact the study authors to request additional information.

### Assessment of heterogeneity

We will use the descriptive statistics reported in the 'Characteristics of included studies' table to assess whether the studies within each pairwise comparison are homogenous enough, with respect to study and intervention details and population baseline characteristics, that the assumption of homogeneity might be plausible. In case of excessive clinical heterogeneity, we will not pool the findings of included studies.

We will measure statistical heterogeneity using the $Chi^2$ test and the $I^2$ statistic (Deeks 2020), and the 95% prediction interval (PI) for random-effects meta-analysis (IntHout 2016). The prediction interval helps in the clinical interpretation of heterogeneity by estimating what true treatment effects can be expected in future settings (IntHout 2016). We will restrict calculation of a 95% PI to meta-analyses with four or more studies (≥ 200 participants), since the interval would be imprecise when a summary estimate is based on only a few small studies. We will use the open-source statistical software R package meta to calculate 95% PIs (Meta 2021). We will declare statistical heterogeneity if the P value is less than 0.1 for the $Chi^2$ statistic, or the $I^2$ statistic is equal to or greater than 40% (40% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity, Deeks 2020), or the range of the 95% PI reveals a different clinical interpretation of the effect estimate compared to the 95% CI.

### Assessment of reporting biases

We will seek to identify all research that meets our predefined eligibility criteria. Missing studies can introduce bias to the analysis. We will search for completed non-published trials in trials registers, contact authors to seek assurance that the results will be made available, and classify them as 'awaiting classification' until the results are reported. We will report the number of completed non-published trials.

When there are 10 or more relevant studies pooled in a meta-analysis, we will investigate risk of reporting bias (publication bias) in pairwise meta-analyses using contour-enhanced funnel plots. If funnel plot asymmetry is suggested by a visual assessment, we will perform exploratory analyses (e.g. Rücker's arcsine test for dichotomous data and Egger's linear regression test for continuous data) to further investigate funnel plot asymmetry. A P value of less than 0.1 will be considered as the level of statistical significance. We will analyse reporting bias using the open-source statistical software R package meta (Meta 2021).

### Data synthesis

The primary analysis will include only those studies that have low risk or some concerns of bias according to the assessment with RoB 2. We will include high risk of bias studies in a secondary analysis to assess the impact on the results (Sensitivity analysis).

We will analyse trials with different intentions of ivermectin use and different participant populations separately, as follows.

- Treatment of COVID-19 in the inpatient setting: participants with confirmed SARS-CoV-2 infection.
- Treatment of COVID-19 in the outpatient setting: participants with confirmed SARS-CoV-2 infection.
- Prevention of SARS-CoV-2 infection (post-exposure prophylaxis): participants at high risk of developing the infection.

We will create these comparisons:

- ivermectin versus placebo or no treatment; and
- ivermectin versus active pharmacological intervention with proven efficacy.

We will perform meta-analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020).

If clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will pool the data in meta-analysis. When meta-analysis is feasible, we will use the random-effects model as we assume that the intervention effects will be related but will not be the same for the included studies. For dichotomous outcomes, we will perform meta-analyses using the Mantel-Haenszel method under a random-effects model to calculate the summary (combined) intervention effect estimate as a weighted average of the intervention effects estimated in the individual studies. For continuous outcomes, we will use the inverse-variance method.

We will use the RevMan Web software for meta-analyses (RevMan Web 2020).

### Subgroup analysis and investigation of heterogeneity

For ivermectin used as treatment for COVID-19 in the inpatient setting, we will perform a subgroup analysis independent of heterogeneity for the following characteristic.

- Severity of condition at baseline (moderate (WHO 4 to 5) versus severe disease (WHO 6 to 9) as defined by the WHO Clinical Progression Scale).

For ivermectin used to prevent SARS-CoV-2 infection, we will perform a subgroup analysis independent of heterogeneity for the following characteristic.

- Studies including participants with a previous history of SARS-CoV-2 infection versus studies including only participants without a previous history of infection.

We will investigate heterogeneity by visual inspection of the forest plot and by subgroup analysis to calculate RR or MD in conjunction with the corresponding CI for each subgroup. We will perform subgroup analyses, if statistical heterogeneity is present ($P < 0.1$ for the $Chi^2$ test of heterogeneity, $I^2 \geq 50\%$, or a different clinical conclusion of 95% CI versus 95% PI). We will perform subgroup analyses to investigate heterogeneity only if enough studies are available (at least 10 studies per outcome). Otherwise, details of the intervention and age of the population will be reported for each study in the footnotes of the forest plot.

We will perform subgroup analyses to investigate heterogeneity for the following characteristics.

- Ivermectin used as treatment (inpatients and outpatients):
  * Details of the intervention (recommended versus high dose);
  * Age (children versus adults).
- Ivermectin used for prevention:
  * Dose of ivermectin (recommended versus high);
  * Mode of exposure (e.g. working place, nursing home) and burden of exposure (e.g. living in a high-risk area, high-risk medical contact) in prevention studies;
  * Confirmation of SARS-CoV-2 infection (RT-PCR versus antigen testing; for the outcome 'SARS-CoV-2 infection').

**Sensitivity analysis**

We will use sensitivity analyses to proof the robustness of the meta-analyses. We will exclude:

- non-peer reviewed studies (including preprint articles);
- studies reporting data as median instead of mean for continuous outcomes.

Additionally, we will perform a secondary analysis including studies with outcomes judged as overall high risk of bias to assess the impact of those studies on the results.

**Summary of findings and assessment of the certainty of the evidence**

We will present the main results of the review in Summary of findings tables, including a rating of the certainty of evidence based on the GRADE approach. We will follow current GRADE guidance as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020).

Two review authors (SW, MP) will assess the certainty of evidence, considering risk of bias, inconsistency, imprecision, indirectness, and publication bias. We will use the overall RoB 2 assessment and sensitivity analyses to inform the risk of bias judgement underlying the assessment of the certainty of evidence.

We will create separate Summary of findings tables for the use of ivermectin with different intentions (e.g. prevention of SARS-CoV-2 infection and treatment of people with COVID-19 in inpatient and outpatient settings) and for different comparisons with regard to the intervention and comparator, respectively. The Summary of findings tables will include the following outcomes.

For use of ivermectin with intention to treat COVID-19 in the inpatient setting:

- All-cause mortality up to 28 days.
- Clinical deterioration or improvement of symptoms up to 28 days, assessed as need for respiratory support.
- Adverse events (any grade) up to 28 days.
- Quality of life up to 28 days.
- Duration of hospitalization.
- Viral clearance at 7 days.

For use of ivermectin with intention to treat COVID-19 in the outpatient setting:

- All-cause mortality up to 28 days.
- Clinical deterioration or improvement of symptoms up to 14 days, assessed as need for respiratory support.
- Any adverse events (any grade) up to 14 days.
- Quality of life up to 14 days.
- Admission to hospital.
- Viral clearance at 7 days.

For use of ivermectin with intention to prevent SARS-CoV-2 infection:

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days.
- Development of clinical COVID-19 symptoms up to 14 days; assessed in accordance with the WHO Clinical Progression Scale.
- All-cause mortality up to 28 days.
- Quality of life up to 14 days.
- Adverse events (any grade) up to 14 days.
- Admission to hospital at day 14.

The GRADE assessment will result in one of four levels of certainty and these express our confidence in the estimate of effect (Balshem 2011).

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate the true effect is likely to be substantially different from the estimate of effect.

We will use the MAGICapp to create Summary of findings tables (MAGICapp).

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# APPENDICES

## Appendix 1. Search strategies

### Cochrane COVID-19 Study Register

**Search string:** ivermectin* OR stromectol* OR mectizan* OR "MK 933" OR MK933 OR eqvalan* OR soolantra* OR sklice* OR stromectal* OR ivomec*

**Study characteristics:**
1) "Intervention assignment": “Randomised” OR
2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover" AND "Unclear"

### Web of Science Core Collection (Advanced search)

#1. TI=(ivermectin* OR stromectol* OR mectizan* OR "MK 933" OR MK933 OR eqvalan* OR soolantra* OR sklice* OR stromectal* OR ivomec*) OR AB=(ivermectin* OR stromectol* OR mectizan* OR "MK 933" OR MK933 OR eqvalan* OR soolantra* OR sklice* OR stromectal* OR ivomec*)

#2. TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR"SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel

coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR"SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3. #1 AND #2

#4. TI=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

#5. #3 AND #4, Indexes=SCI-EXPANDED, ESCI Timespan=2020-2021

**medRxiv (Advanced search)**

for abstract or title "ivermectin AND randomized" (match all words)
for abstract or title "ivermectin AND randomised" (match all words)
for abstract or title "ivermectin AND randomly" (match all words)
for abstract or title "ivermectin AND groups" (match all words)

**ResearchSquare**
**Abstract:** ivermectin

**Article Type:** Research Article

## HISTORY

Protocol first published: Issue 4, 2021

## CONTRIBUTIONS OF AUTHORS

Maria Popp (MP): methodological expertise, conception, and writing the protocol.

Miriam Stegemann (MS): clinical expertise and advice, and proofreading the protocol.

Maria-Inti Metzendorf (MIM): search strategy design and writing the protocol.

Peter Kranke (PK): clinical expertise and advice, and proofreading the protocol.

Patrick Meybohm (PM): clinical expertise and advice, and proofreading the protocol.

Nicole Skoetz (NS): methodological expertise and advice, conception, and writing the protocol.

Stephanie Weibel (SW): methodological expertise and advice, conception, and writing the protocol.

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Miriam Stegemann (MS) has no known conflicts of interest to declare.

Maria-Inti Metzendorf (MIM) has no known conflicts of interest to declare.

Peter Kranke (PK) has no known conflicts of interest to declare.

Patrick Meybohm (PM) has no known conflicts of interest to declare.

Nicole Skoetz (NS) has no known conflicts of interest to declare.

Stephanie Weibel (SW) is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project, which was paid to the institution).

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- Liverpool School of Tropical Medicine, UK

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