Alberta Health Services

COVID-19 Scientific Advisory Group

Ivermectin Evidence Review Update Oct 5, 2021, AHS Scientific Advisory Group

The AHS Scientific Advisory Group (SAG) and the COVID-19 Therapeutics Working Group continue to monitor new evidence on ivermectin. After review there continues to be insufficient evidence of benefit, and the previous recommendations continue to be upheld:

- At this time, ivermectin should not be prescribed or taken to **prevent or treat** COVID-19 (outside of a clinical trial, although SAG is currently not aware of ongoing trials in Alberta).

The SAG and the Therapeutics Working Group will continue to monitor and assess new evidence on ivermectin as it is published. Several high quality randomized controlled trials are being conducted to further study the use of ivermectin for COVID-19; this review and recommendations will be updated as new evidence comes to light.

Since the previous reviews, there were two significant updates on the evidence for ivermectin use in COVID-19 that SAG would like to comment on:

1. Guidelines and Evidence Review Update: Fraudulent Data Withdrawn
A recent Cochrane systematic review by Popp et al. (July 2021) is in alignment with AHS and other jurisdictions (including the US National Institutes of Health, the World Health Organization, Health Canada, and the US Food & Drug Administration. It concludes that the reliable evidence available to date does not support the use of ivermectin for treatment or prevention of COVID-19 (outside of well-designed randomized trials). The authors found that the available studies varied widely in the dosages used, the other medications included as comparators, and the outcomes examined, and that many of the studies were at high risk of bias (meaning any differences noted across groups were likely due to other factors).

This Cochrane review excluded a study (Elgazzar et al.) that contributes to the positive findings noted in some other meta-analyses. It should be noted that the Elgazzar et al. RCT, which reported results that were very favorable to ivermectin, has been withdrawn from the preprint server for possible data fraud, so any reviews or meta-analyses that include it are not valid. For details on the issues identified in the Elgazzar et al. study, please see the article published in Nature (some of the issues include duplicated patient records, patients whose records indicate they died before the study started, and phrases that were identical to other published work).

The SAG is aware that there has been considerable social media attention related to ivermectin as an effective therapy for COVID-19, in part due to the study by Elgazzar and meta-analyses using that study as well as other lesser quality observational trials with significant data issues including impossible numbers, unexplainable mismatches between trial registry updates and published patient demographics, and nonfeasible timelines. Given the ongoing investigation of these studies, more may be withdrawn over the coming months.

Concerns regarding the lack of assessment of quality of these studies have been published, stating that “relying on low-quality or questionable studies in the current global climate presents severe and immediate harms. The enormous impact of COVID-19 and the consequent urgent need to demonstrate the clinical efficacy of new therapeutic options provides fertile ground for

even poorly evidenced claims of efficacy to be amplified, both in the scientific literature and on social media. This context can lead to the rapid translation of almost any apparently favorable conclusion from a relatively weak trial or set of trials into widespread clinical practice and public policy."

2. Commentary on Ivermectin Use in Uttar Pradesh, India

Multiple social media sources have also reported that ivermectin might have been responsible for reducing COVID-19 cases in Uttar Pradesh, India, with claims that the low rate of new cases in spite of low vaccination rates in this region is related to distribution of ivermectin-containing medication kits. There are several potential issues with these lines of reasoning, including:

- Both observational trial data and "real world" data sources need careful evaluation using these key principles of review: expert peer review of evidence, assessment of errors in reporting, assessment of due scientific diligence, and careful consideration of confounders. These principles have not been applied to this data.
- This observational data is much lower quality evidence compared with randomized trials (which also can vary in quality and require assessment). There is variability in assessment of infection rates and outcome reporting at a population level, as well as confounding.
- Multiple sources suggest the infection rate and death toll of COVID-19 in India in general, and Uttar Pradesh in particular, has been underestimated and current transmission is likely lower because of post infection immunity in survivors given prior waves of the pandemic
    - India's death toll (and associated case counts) is estimated to be at least 7-13X higher than reported, suggesting actual population infection rates have been 60-70%, confirmed by seroprevalence data. Multiple resources indicate that cremations outstripped official death estimates considerably in this area.
    - A preprint analysis of excess mortality for India related to COVID-19 (which found up to 2% of the population died up to June, 2021) had to omit data from Uttar Pradesh because of significant reporting irregularities (including districts that reported NO deaths for months)
    - Public health seroprevalence data reported by the Center for Global Development suggested extreme underreporting of cases and deaths in Uttar Pradesh, and Indian Council of Medical Research data (reported by press release) showed 71% seroprevalence in Uttar Pradesh in spite of only 29% initial dose vaccinated in July.

It is also noted that many districts in India used ivermectin over a period in which the evidence was less clear, based on national guidelines, so regions cannot be compared based on use or non-use. Ivermection and hydroxychloroquine have recently been removed from the national COVID-19 guidelines in India for lack of efficacy.

In summary, this would suggest Uttar Pradesh had a devastating prior COVID-19 surge with high case rates and significant uncounted mortality, with current evidence of partial population immunity in people who survived COVID-19 infection and increasing numbers of vaccinated people.

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Major COVID-19 Guidelines and Manufacturers Statement Do Not Support Ivermectin Use, in Part Given Safety Concerns

As summarized in the Cochrane review, national and international guidelines regarding the use of ivermectin for the treatment or prevention of COVID-19 have been developed over the past 12 months. Recommendations from the WHO, updated 31 March 2021 (WHO 2021b); European Medicines Agency, updated 22 March 2021 (EMA 2021); Infectious Diseases Society of America, updated 13 February 2021 (IDSA 2021); and the COVID Management Guidelines India Group, updated 15 May 2021 (COVID Guidelines India 2021), concur that ivermectin should only be used for treatment of COVID-19 in the context of clinical trials. The EMA additionally advises against the use of ivermectin for prophylaxis outside RCTs (EMA 2021). The US NIH guidance updated on 11 February 2021 describes 'insufficient data' to permit a recommendation for or against the use of ivermectin for the treatment of COVID-19 (NIH 2021).

In addition it is notable that Merck, the manufacturers of ivermectin, have concluded that there is:

- "No scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies;
- No meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease, and;
- A concerning lack of safety data in the majority of studies."

Furthermore, Merck states that "We do not believe that the data available support the safety and efficacy of Ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information."

As noted in the SAG review that follows, the product monograph for Stromectol® oral ivermectin tablets reports that no fatalities have been observed in humans due to overdose of medical-grade ivermectin (Merck Canada Inc., 2020). Consumption of veterinary-grade ivermectin formulations, which contain ingredients not used in human medicines, most commonly results in rash, contact dermatitis, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea (Merck Canada Inc., 2020). The US Food & Drug Administration warns that "even the levels of ivermectin for approved human uses can interact with other medications, like blood-thinners. You can also overdose on ivermectin, which can cause nausea, vomiting, diarrhea, hypotension (low blood pressure), allergic reactions (itching and hives), dizziness, ataxia (problems with balance), seizures, coma and even death." They also warn that the doses used for animals are often highly concentrated because they are intended for use in large animals, and that these doses can be highly toxic for humans. Furthermore, many of the inactive ingredients found in products for animals are not intended for use in humans.

Several high quality randomized controlled trials are being conducted to further study the use of ivermectin for COVID-19; this review and recommendations will be updated as new evidence comes to light.

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Prescribing Ivermectin for COVID-19 is presently outside the usual standard of care and may pose increased risk (including potential medication adverse events); there is not a reasonable expectation of benefit based on current evidence. The College of Physicians and Surgeons of Alberta and the Alberta College of Pharmacy issued a joint statement on September 23 expressing concern over misinformation being spread by a small number of pharmacists and physicians about ivermectin. They noted that "there is no evidence that prescribing and dispensing ivermectin is beneficial but there is certainly significant risk of patient harm when ivermectin is used in the prevention and treatment of COVID-19" and concluded that "**ivermectin must not be prescribed or dispensed, in any form, for the prevention or treatment of COVID-19**" (emphasis in original).

COVID-19 Scientific Advisory Group
Rapid Evidence Report

Ivermectin in the Treatment and Prevention of COVID-19

February 2, 2021

A recent Cochrane review by Popp et al. supports the conclusions of this Scientific Advisory Group review. As of July 28, 2021, our conclusions continue to be consistent with current evidence. We are also monitoring the COVID-NMA evidence review page, which is being updated continually to add the results of new ivermectin trials, as well as other emerging literature on ivermectin.

In addition, a widely cited paper (Elgazzar, Hany, Youssef, Hafez, & Moussa, preprint) has been withdrawn for significant data irregularities and will be removed from the review, along with any meta-analysis that would be affected by its withdrawal.

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Physical distancing works

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Lay Summary

BACKGROUND

- Ivermectin is used to treat parasitic infections (such as intestinal worms or lice) in both humans and animals. Ivermectin is generally safe when used according to the label, but can cause mild side effects like nausea, diarrhea, fatigue, dizziness, and rash.
- Laboratory studies performed in monkey cells showed that ivermectin is able to stop the virus that causes COVID-19 from growing in cells. This raised interest in ivermectin as a potential treatment for COVID-19, even though many medicines that are effective in the laboratory are not effective when they are used in people.
- There is a lot of hype about ivermectin in social media, but it is still unclear if ivermectin actually prevents COVID-19 infection or is an effective treatment for COVID-19 because of the way studies have been done so far. This review summarizes the scientific research of ivermectin to provide guidance to public health officials and clinicians.

KEY FINDINGS

- The studies evaluating ivermectin treatment are not high enough quality to properly decide if ivermectin is useful or not. Most studies did not clearly describe the effect of the other medications given to patients or what other factors might influence their findings (“confounding”), did not have an adequate comparator group to assess if there was a difference in patients given ivermectin, or were too small to be sure that any effect of ivermectin seen was real.
- With respect to ivermectin's ability to prevent infection with COVID-19, four low quality studies showed that ivermectin may reduce the risk of COVID-19 infection; however, there were several confounding factors and we don’t know what else the study participants were doing that might have influenced their risk of infection. More studies are needed to show if ivermectin can be used to prevent infection.
- With respect to ivermectin's ability to treat people with COVID-19, seven studies that had a control group (ie. a group of participants that did not receive ivermectin) reported the effect of ivermectin on death from COVID-19. Four showed that deaths from COVID-19 went down, while three showed that deaths from COVID-19 were not affected. All seven studies were small and were of low or very low quality, so we can’t be sure that their findings were real. More studies are needed to show if ivermectin can be used to treat COVID-19.
- The available data on ivermectin purchasing in Alberta doesn’t clearly show us if it is being used for purposes other than parasitic infections (ie. for COVID-19).

RECOMMENDATIONS

- At this time, ivermectin should not be prescribed or taken to **prevent** COVID-19 outside of a clinical trial, as we need to establish whether it is truly useful.
- At this time, ivermectin should not be prescribed or taken to **treat** COVID-19 outside of a clinical trial, as we need to establish whether it is truly useful.
- Scientists in Alberta should support clinical trials of ivermectin to help clarify whether ivermectin is effective against COVID-19 or not.

Authorship and Committee Members

Name	Contribution
Rachael Erdmann	Writing (Primary and grey literature evidence extraction; Downs & Black assessment of primary evidence; draft preparation and revisions)
Sarah Andrews	Writing (collation and summarization of ongoing clinical trials; AMSTAR-2 critical appraisal of meta-analyses)
Lauren Seal	Librarian (Database searching and preliminary results screening)
Mark Yarema	Primary scientific reviewer
Lynora Saxinger, John Conly, Alastair Cribb	Secondary scientific reviewers
Braden Manns & Lynora Saxinger	Scientific Advisory Group chairs (oversight and leadership responsibility)
John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Marcia Johnson, Elizabeth MacKay, Andrew McRae, Melissa Potestio, Jeremy Slobodan, Brandie Walker, Nathan Zelyas	Discussion, revision, and approval of document

Topic: Ivermectin as prophylaxis and treatment for COVID-19

1. **What is the evidence for ivermectin as prophylaxis for COVID-19?**
2. **What is the evidence for ivermectin as a treatment for COVID-19?**
3. **Are there risks associated with the use of ivermectin for prophylaxis or treatment of COVID-19?**
4. **Does available data on utilization of accessible ivermectin products in Alberta suggest that it is being used in COVID-19?**

Context

- Ivermectin is a well-characterized drug that is used to treat parasitic infections in both humans and animals. Laboratory based studies have shown ivermectin can inhibit SARS-CoV-2 (the virus causing COVID-19) replication, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- Statements regarding ivermectin as a potential “miracle cure” for COVID-19 from Dr. Pierre Kory of the Front-Line Covid-19 Critical Care Alliance have attracted much attention on social media (e.g. NewsNOW from FOX, 2020). Subsequently, cautionary statements regarding the potential effectiveness of ivermectin were made by the FDA and NIH. Many drugs that show promise in laboratory based studies are not found to be effective in patients (Hay et al., 2014).
- The World Health Organization living guidelines for COVID-19 therapy from the British Medical Journal do not recommend ivermectin (Siemeniuek et al, 2020), and recently updated guidelines from the National Institutes of Health (as of 14 January 2021) state that there is insufficient evidence to “recommend either for or against ivermectin as a treatment for COVID-19” (National Institutes of Health, 2021). An ongoing analysis of RCT data rates ivermectin trials as having "very low" certainty evidence.
- As was seen with the interest in hydroxychloroquine use in the early stages of the COVID-19 pandemic, there are many ongoing clinical studies (of varying quality) to assess the effectiveness of ivermectin as a treatment for COVID-19.
- There are anecdotal reports of prescribers and patients in Alberta seeking medical-grade and veterinary-grade ivermectin for off-label use with which to treat COVID-19. Care providers in South America also show great enthusiasm for ivermectin as a treatment for COVID-19, despite the limited evidence base.

Key Messages from the Evidence Summary

- Ivermectin has been shown to inhibit viral replication *in vitro,* but at concentrations that may be unattainable with human therapeutic doses. Vero cells (a non-human cell line) infected with SARS-CoV-2 and treated with 5 µmol/L ivermectin at 2 hours post-infection showed a 5000X reduction in viral replication compared to untreated controls. However, the 100% inhibitory concentrations of ivermectin needed *in vitro* are approximately 50-55X higher than the maximum plasma concentration of ivermectin after an oral dose of 12 mg in adults.
- Studies evaluating ivermectin treatment are of inadequate quality for definitive assessment of ivermectin use in prophylaxis and therapy, with many studies involving incompletely described use of multiple other medications meant to manage symptoms and limit viral replication, inappropriate study design,

inadequate controls, short follow-up length, performance bias, small sample sizes and high risk of bias from confounding factors.

- Ivermectin has a favourable pharmacokinetic and safety profile when used according to label directions. Adverse events ascribed to ivermectin reported in the primary literature or the meta-analyses were non-severe and aligned with the side effects listed on the product monograph when used according to the medication label. The product monograph from Merck Canada advises against using ivermectin in pregnant women, children under 15 kg, and adults over 65 as the safety evidence is limited or has not yet been established however states that no fatalities or toxicity have been reported due to ivermectin overdose.
- A formal critical appraisal of the identified meta-analyses and included primary literature was undertaken. The meta-analyses were judged to be of critically low quality (Lawrie, 2021); low quality (Hill et al., preprint), and moderate quality (Padhy et al., 2020) after AMSTAR-2 assessment. The primary studies were assessed using the Downs & Black checklist. The majority of primary studies were assessed as fair quality (ie. they received a score of 14-18 out of a possible 32).
- For use in prophylaxis, the one meta-analysis containing two RCTs and two observational studies (Lawrie, 2021) was judged as critically low quality by AMSTAR-2 assessment; thus, the findings were not included in this review. The primary evidence was extracted and summarized with an additional observational study that was retrieved in the database search. All four studies show a significant reduction in COVID-19 infection in the intervention group; however, each study was at high risk of bias from confounding prevention behaviors.
- One preprint case control study in health care workers (Behera et al., preprint) suggested that ivermectin was independently associated with 73% reduced odds of COVID-19 infection (OR 0.27, 95%CI 0.15-0.51) and a history of exercise for more than one hour (as a proxy measure for inadequate social distancing) was an independent risk factor for COVID-19 infection (3.06 CI 1.18-7.93). In this study, HCWs were offered HQ prophylaxis after exposures for the initial period, and then ivermectin prophylaxis was offered, however, other workplace prevention measures instituted and changed, and the epidemic context over that time period are not described.
- For use as treatment, three meta-analyses were identified. Lawrie (2021) includes 9 RCTs and 3 observational studies; Padhy (2020) includes 4 observational studies, and Hill (preprint) includes 18 RCTs. The primary data was extracted and outcomes for mortality, intensive care unit (ICU) admission, or hospitalization were narratively summarized.
- Meta-analytic findings from Lawrie (2021) were excluded due its “critically low” AMSTAR-2 assessment (though the primary studies included within that metanalysis are considered herein. Padhy (2020) was assessed as moderate quality and Hill (preprint) was assessed as low quality. Both the observational data meta-analysis and the RCT meta-analyses reported that ivermectin reduces the odds of mortality with cautions regarding study quality and possible bias, and the magnitude of the effect varies significantly from OR 0.53 (95%CI: 0.29 to 0.96) in Padhy (2020) (includes three observational studies, no RCTs) to OR 0.2

(95%CI 0.12-0.52) in Hill (preprint) (includes six RCTs, no observational studies). The effect of publication bias on these findings is unclear.

- Eleven of 20 extracted primary studies (four of which are RCTs; one study (observational) was conducted in outpatients, and the remaining 10 studies (four RCTs, 6 observational) conducted in inpatients) reported on the effect of ivermectin on mortality, hospitalization, or ICU admission. In the studies that included a control group (seven out of eleven), four showed a reduced risk of death and three showed no effect from ivermectin treatment. These findings are uncertain due to high risk of bias from confounding, small sample sizes, poor controls and overall low quality of the evidence.
- With respect to question #3, no unique purchasing patterns of human-grade ivermectin were identified that might signal increased off-label use. Veterinary-grade ivermectin is not provincially regulated, so data could not be obtained in time for inclusion in this review. There is doubt that increased purchasing for off-label human use would be distinguishable above the normal background variation in veterinary supply. This was not pursued further as there is no recommendation for use outside or research at this time.

Committee Discussion

The committee generally agreed with the recommendations as presented however, every member expressed concern at the quality of the included meta-analyses and the relative importance placed on those findings. There was discussion about whether the Lawrie (2021) meta-analysis should be included at all due to extreme concerns about bias – as inclusion was felt to put the findings of the review at risk, but to exclude it reduces SAG transparency and could bolster sentiments that “the system” is suppressing evidence. To balance the need for transparency with an accurate assessment of the literature, revisions to the report were requested, including a formal assessment of the quality of the included meta-analyses and an independent assessment of the evidence from the primary literature (which now appears in this report).

There was some discussion of the relevance of information about the safety profile of ivermectin and the stability of ivermectin supply in Alberta. Since ivermectin is not being recommended for use, these considerations are rendered moot and could introduce confusion into the messaging of the report. To rectify this, supply information has been included in the practical considerations rather than the key messages, and the key message about safety has been integrated with the pharmacokinetic information.

Since the desired changes were substantial, the report was presented to the committee a second time for discussion. Upon second review by the committee, there was unanimous support for second iteration of the report as presented, with very minor adjustments. There was consensus on the recommendations and practical considerations.

Recommendations

1. At this time, ivermectin is not recommended for prophylaxis against COVID-19, outside of clinical trials

Rationale: The studies are of low quality so findings have considerable uncertainty around the effect size due to the shortcomings in study design and execution. Further research is necessary to confirm the effectiveness of ivermectin as COVID-19 prophylaxis.

2. At this time, ivermectin is not recommended for treatment of COVID-19 outside of a clinical trial.
   Rationale: Existing evidence on this topic is inconclusive due to low quality of the literature and mixed findings of the primary studies and meta-analyses. There is considerable uncertainty due to the shortcomings in study design and execution. Further research is necessary to confirm the role of ivermectin as an effective, clinically useful treatment for COVID-19.
3. We recommend Alberta investigators support clinical trials of ivermectin as possible to help establish the role of ivermectin in COVID-19.

Practical Considerations

- It is difficult to identify off-label use of ivermectin in Alberta. If this information is of further interest, an analysis of AHS administrative data and chart review from primary care services may provide a clearer picture of ivermectin prescribing.
- Pharmacy Services has confirmed that at this time there continues to be good access to supply of medical-grade ivermectin in Alberta. However, if high-quality evidence is published showing that ivermectin is an effective treatment for COVID-19 and can be used outside of clinical trials, ivermectin supply will need to be reassessed.

Research Gaps

- There have been no studies investigating ivermectin therapy against the standard of care in North American or European hospitals rather than as add on therapy.
- There has been no long-term follow-up of patients given ivermectin to see if the therapy affects persistent COVID-19 symptoms.

Strength of Evidence

Overall, the evidence for this topic is of very low to low quality. As with other clinical topics on COVID-19, the research on ivermectin is opportunistic and hastily done, with limited planning to minimize sources of bias. The body of evidence is at high risk of bias due to confounding, as many studies investigated ivermectin as add-on therapy to a cocktail of medications intended to manage symptoms and limit viral replication. Small sample sizes, performance bias, short follow-up time, inappropriate study designs, further limit the usefulness of the available evidence on ivermectin. Further, the evidence is not consistent for any outcome of COVID-19 treatment (such as PCR positivity, symptom resolution, days in hospital, or mortality).

The majority of studies are from Southeast Asia and Latin America, both regions with notably different healthcare systems, population health statistics and epidemic dynamics compared to Alberta. The natural history of COVID-19 does not appear to vary by region (although there is limited evidence) and severe outcomes have been linked to social determinants of health, age, and comorbidities rather than race or

ethnicity (Sorci et al., 2020). It is likely that the evidence on ivermectin, if valid, is applicable to the Alberta context.

Due to concerns about the evidence quality, a formal critical appraisal of the identified meta-analyses and included primary literature was undertaken. The meta-analyses were judged to be of critically low quality (Lawrie, 2021); low quality (Hill et al., 2021), and moderate quality (Padhy et al., 2020) after AMSTAR-2 assessment (Shea et al., 2017). Comments arising from the appraisal process are included in Table 9 in the appendix. These findings suggest that the meta-analytic results may not present an accurate summary of the evidence. To mitigate these issues, the results from the primary studies included in each meta-analysis were extracted and narratively synthesized to assess the clinical effectiveness of ivermectin against COVID-19.

Limitations of this review

This review is subject to some limitations. COVID-19 is a novel disease where the body of evidence is limited and changes rapidly. We sought the highest-quality evidence; however, the novelty of the question substantially affects the type of evidence that was available. This is a rapid review so the literature search was thorough but not systematic and it is likely that relevant studies were not identified. The primary evidence for this topic is still heavily dependent on pre-peer-reviewed literature – approximately half of the included primary studies were identified from the preprint server or from the trial results uploaded to Clinicaltrials.gov. It is likely that the body of evidence on this topic will be refined in the next months as the evidence is peer-reviewed.

Background

Ivermectin is an FDA- and Health Canada- approved antiparasitic medication that has human and veterinary applications. In humans, ivermectin is used to treat parasitic infections such as intestinal strongyloidiasis and onchocerciasis (Merck Canada Inc., 2020), and may be used to treat rosacea. Commercial formulations for human medicine were first launched in 1987 (Canga et al., 2008). Two formulations are available for use in humans in Canada: a 1% weight/weight cream (marketed as Rosiver by Galderma Canada) and a 3 mg tablet (marketed as Stromectol by Merck Canada). In veterinary medicine, ivermectin has broad applicability and is used as a broad spectrum antiparasitic agent, with systemic and pour-on applications (Food and Drug Administration, 2020a). Veterinary formulations are available as a large-volume pour-on product, oral paste, tablets, oral solutions, and injectables.

The pharmacokinetic profile of oral ivermectin, averaged from multiple studies, is shown in Table 1 below. Bioavailability and absorption varies by formulation (Canga et al., 2008; Muñoz et al., 2018). Ivermectin distributes widely across body systems and is excreted mainly in feces after being metabolized in the liver (Canga et al., 2008). A randomized study of 18 mg and 36 mg tablet dosing of ivermectin in healthy volunteers showed similar or higher C_{max} than the lower-dose tablet studies collected in Canga (2008) with similar time to C_{max}, but substantially longer elimination half-life and clearance than the lower dose tablets (Muñoz et al., 2018). These pharmacokinetics are not clearly understood. The healthy volunteers had no adverse events significantly associated with the treatment arms (Muñoz et al., 2018).

Table 1. Pharmacokinetic profile of oral ivermectin (adapted from Canga et al., 2008).

Dose	Absorption			Elimination	
	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2(abs)}$ (h)	$t_{1/2}$ (h)	Cl (/kg/day)
Healthy subjects					
6 mg (tablet) n=2 studies	21.7	4.5	1.1	11.9	5.9
12 mg (tablet) n=3 studies	34.6	6.3	2.0 (2 studies)	15.5	5.3 (2 studies)
18 mg (tablet) n=1 study	31.2	5.1	1.7	16.7	10.6
12 mg (solution) n=1 study	81	3.6	No data	No data	No data
12 mg (capsule) n=1 study	46	3.6	No data	No data	No data
150 µg/kg n= 3 studies	42.0	4.9 (1 study)	No data	36.6 (1 study)	4.70 (♂) 8.40 (♀) (1 study)
Onchocerciasis patients					
6 mg tablet n= 1 study	38.2	4.7	No data	54.5	3.1
150 µg/kg n=2 studies	45.2	5.4	No data	23.6 (3 studies)	No data

C $_{max}$ maximum plasma concentration; *t* $_{ma:}$ time to reach *C* $_{max}$; *t* $_{1/2abs}$ absorption half-life; *t* $_{1/2}$ elimination half-life; *Cl* total body clearance

Studies evaluating ivermectin as an antiviral agent have shown that it inhibits nuclear transport functions in ribonucleic acid (RNA) viruses such as human immunodeficiency virus (HIV), Dengue virus, and Zika virus (Caly et al., 2020). *In vitro*, ivermectin has been shown to be an effective inhibitor of SARS-CoV-2. Caly et al. (2020) showed 5000X reduction in viral replication in Vero/hSLAM cells treated with 5 µmol/L ivermectin at 2 hours post infection with SARS-CoV-2. This reduction equates to a 99.98% reduction in RNA in the supernatant and cell pellet, compared to control infections (Caly et al, 2020). Ivermectin was shown to inhibit 50% of SARS-CoV-2 replication (IC_{50}) at concentrations of approximately 2.5 µmol/L (Caly et al., 2020). No toxicity was observed in uninfected cells that were treated with ivermectin (Caly et al., 2020). The *in vitro* IC_{50} is approximately 50 X the peak plasma concentration after the approved oral dose of 12 mg (~165 mcg/kg) (Momekov & Momekova, 2020; Merck Canada Inc., 2020), and does not take into account the substantial protein binding of ivermectin *in vivo.* Higher doses have been safely administered, however it is unclear how these *in vitro* findings translate to human use in a clinical setting.

Summary of Evidence

In the original database search, 114 results were retrieved from the database search. The librarian searched Medline, PubMed, CINAHL, TRIP Pro, Google Scholar, Google, Clinicatrials.gov, United States Centers for Disease Control and Prevention, LitCOVID, World Health Organization, and MedRxiv for articles published in English between 2019-2021.

Eight records from the database search (two peer-reviewed, six preprint) were included in the narrative summary. These were: 1 peer-reviewed systematic review/meta-analysis (including 3 studies) was included); 3 randomized controlled trials (RCTs) were

included (3 were pre-review); 5 observational studies were included (4 were pre-review). Two additional meta-analyses, one preprint observational study, and six pieces of grey literature were *ad hoc* inclusions.

As described above, the included meta-analyses had substantial limitations due to their methodological quality. To rectify this, the data from the primary studies were extracted from the included meta-analyses due to concerns about their methodological quality.

When combined with the results from the database search, 24 primary records were included in the narrative synthesis. These consist of: 2 study result records from Clinicaltrials.gov (RCT); 11 RCTs (7 pre-review); 11 observational studies (5 were pre-review). Five clinical trials (included in Hill et al (2021)) did not have publicly available results. The quality of each primary study was assessed using the Downs & Black checklist (Downs & Black, 1998)

In addition to the primary literature, 38 ongoing clinical trials were identified and have been tabulated in the Appendix (table 3); the most promising trials are described in the Evolving Evidence section of this report.

1. What is the evidence for ivermectin as prophylaxis for COVID-19?

Evidence from secondary and grey literature

No grey literature was identified that addressed the use of ivermectin as a prophylactic agent for COVID-19.

The question of prophylaxis is addressed in the Lawrie (2021) meta-analysis; however, critical appraisal with the AMSTAR-2 tool (Shea et al., 2017) judged this article to be of critically low quality. AMSTAR-2 highlighted the meta-analysis' weakness in multiple critical domains such as adequacy of the literature search, consideration of risk of bias and publication bias. This appraisal suggests that the review should not be used to provide a comprehensive summary of available evidence on ivermectin. Four primary studies were included in the prophylaxis analysis by Lawrie (2021) (two RCT, two observational). The data from these studies has been extracted and narratively synthesized in the Primary Literature section below.

Evidence from the primary literature

Two studies were identified in the primary literature regarding ivermectin prophylaxis that were not included in the Lawrie (2021) meta-analysis.

Of these, only one is of sufficient quality to generate useful results (Behera et al., preprint). Aguirre-Chang & Trujillo Figueredo (preprint) administered 0.2 mg/kg ivermectin to SARS-CoV-2-negative contacts of confirmed COVID-19 cases. 7 of 40 participants were found to be seropositive for SARS-CoV-2 in the first three days of the study. 33 of 40 participants did not develop COVID-19 in the 21 days post-ivermectin administration; however, the study did not include a control group nor was the extent of the contact described. This study is very low quality and cannot be interpreted in the absence of a control group.

The findings from the remaining five studies are briefly described in Table 2 below. For a full description of each primary study, the evidence extraction table is included in the

appendix as Table 6. One study (Shouman, unpublished) has not yet publicly reported on the outcomes of interest so is not shown in table 2 (but is included in the full evidence extraction table).

Table 2. Primary studies reporting on ivermectin prophylaxis. One study was identified from the database search (Behera et al., preprint); the remaining four studies were included in Lawrie (2021). Full details of each study are included in Table 6 in the appendix.

Reference	Study Design	Intervention	Comparator	Outcome	Downs & Black (1998) assessment
Alam et al, preprint	Non-randomized observational study (n=118)	Ivermectin 12mg every 4 weeks for 4 months	No prophylaxis, no placebo	73.3% participants in control group compared to 6.9% participants in the intervention group developed COVID-19 ($p<0.05$).	14 – poor/fair quality - unclear randomization - No placebo control - Risk of bias from confounding
Behera et al., preprint	Case-control (n= 372; 186 pairs)	Prophylaxis from ivermectin, HCQ, vitamin D, or any other interventions intended to prevent COVID-19	No prophylaxis	**Matched pair analysis:** Ivermectin is associated with the reduction of COVID-19 infection (OR 0.30, 95% CI, 0.16-0.53) **Multivariate regression:** Ivermectin is associated with fewer COVID-19 infections (OR 0.27, 95% CI, 0.15-0.51) after adjusting for risk and prophylactic activities	20 – Good quality - Measurement of outcomes not blinded - Potential for confounding due to unidentified prevention behaviors
Carvallo et al., 2020	Non-randomized observational trial Pilot n= 229 Multicentre trial n= 1195	Topical carrageenan + 1 drop ivermectin (0.6 mg/ml) every 4 hours daily for 14 days + PPE	PPE alone	**Pilot:** 0/131 in intervention group vs. 11/98 (11.1%) in control group tested positive for SARS-CoV-2 during the 5-week study period ($p<0.0001$). **Multicentre:** - 237/407 (58.2%) in control group compared to 0/788 in intervention group tested positive for COVID-19 over 3-month study period	15 – Fair - Risk of selection bias - Risk of confounding from other prevention behaviors - Staff characteristics not clearly described - Unclear adherence to treatment
Elgazzar et al., preprint	RCT (double-blind) (n= 200)	Ivermectin 0.4mg/kg single oral dose before breakfast to be repeated after one	PPE only	2% of Ivermectin-treated HCWs or household contacts had positive RT-PCR tests for COVID-19, compared to 10% of control	16 – Fair - Risk of confounding from unidentified prevention behaviours in control group

		week + PPE		contacts (PPE alone) ($p<0.05$)	

Synthesis of the Information Relating to Question 1

The primary evidence suggests that ivermectin may have some prophylactic activity against COVID-19; however, three of the four included studies use an observational methodology and can only show association, not causation (Alam et al., preprint; Behera et al., preprint; Carvallo et al., 2020). None of the studies were placebo controlled and are at risk of bias from confounding prevention behaviors, as participants were healthcare workers or household close contacts of confirmed COVID-19 case and possibly knew their risk of infection.

Downs & Black (1998) assessment of the of the study quality suggests that overall, the evidence is of low to moderate quality, with risk of bias from confounding, selection bias, unclear adherence to study protocols, and unclear blinding of assessors.

Taken together, these limitations reduce the certainty of the evidence presented here. Additional prospective, randomized, and blinded studies are needed to confirm the effectiveness of ivermectin as a prophylactic medication for COVID-19.

2. What is the evidence for ivermectin as a treatment for COVID-19?

Evidence from secondary and grey literature

Statements from reputable public health organizations unanimously state that there is not enough evidence to make conclusions about the clinical efficacy of ivermectin for treating COVID-19 (National Institutes of Health, 2021; Pan-American Health Organization, 2020; BC Centre for Disease Control, 2021; Food and Drug Administration, 2020b).

Three meta-analyses were identified for this review that describe ivermectin treatment: one in the database search (Padhy et al., 2020) and two *ad hoc* (Lawrie, 2021; Hill et al., preprint). The key characteristics of these analyses are listed in table 3 below.

Table 3. Key characteristics of identified meta-analyses reporting on ivermectin as treatment for COVID-19.

Reference	Number of RCTs	Number of observational studies	AMSTAR-2 quality assessment (Shea et al., 2017)	Key limitations
Padhy et al., 2020	0	4	Moderate	- Some limitations in methods reporting, but no critical flaws
Lawrie, 2021	9	3	Critically low	- Limitations in methods reporting - Literature search adequacy - No risk of bias consideration reported - No discussion of publication bias
Hill et al., preprint	18	0	Low	- Some limitations in methods reporting - No discussion of publication bias

As noted in the above section on prophylaxis, the critically low quality of Lawrie (2021) means that it should not be used in a comprehensive summary of evidence. The AMSTAR-2 assessment of Padhy (2020) highlighted the meta-analysis's one or two weakness but no critical flaws. This suggests that the review will provide an accurate

summary of the available evidence that was included in the review. For Hill (preprint), the meta-analysis' critical flaw was the limited discussion of publication bias within the included studies. This suggests that the review may not provide a comprehensive summary of the available evidence that was included in the review. The meta-analytic findings of Padhy (2020) and Hill (preprint) are narratively summarized below.

Padhy et al. (2020) pooled the data from three observational studies of standard care (SC) +/- ivermectin, (pooled n = 629). Because of the cocktail of medications administered as standard care and the risk of bias in outcomes and data measurement, the authors assessed each study to have an overall high risk of bias, resulting in very low certainty in the findings. Mortality was reduced in two out of three studies, suggesting the ivermectin treatment reduces the odds of death by 47% (OR= 0.53, 95%CI: 0.29 to 0.96) by random effects modelling (Padhy et al., 2020). All three included studies reported significant clinical improvement compared to usual therapy (assessed by the need for respiratory support until the available follow-up period) (OR=1.95, 95% CI: 1.09 to 3.49, P=0.02) (Padhy et al., 2020). Evidence for time to discharge and time to viral clearance was mixed or not reported.

Hill et al. (preprint) pooled18 RCTs (12 published or preprint, 6 unpublished) of ivermectin +/- standard care for treating COVID-19 (pooled n = 2282). As with Padhy (2020), the variability in ivermectin dosing, standard care regimens, severity of illness, and comparators makes it difficult to combine the primary data. Hill (preprint) reported on all-cause mortality, changes in inflammatory markers, and viral clearance. Six studies reported on survival and could be pooled - ivermectin was shown to reduce the odds of death by 75% (OR 0.25, 95%CI 0.12-0.52) by random effects modelling (Hill et al., preprint). Heterogeneity was moderate, with an I^2 value of 34%. This finding is uncertain, as publication bias was not reported by the study authors. The findings on inflammatory markers and viral clearance were not pooled in this analysis and their effect on clinically relevant metrics (such as survival, need for ventilation, or length of stay) is unclear.

Secondary literature is limited by the quality of the primary data. The primary studies in these meta-analyses all use different ivermectin dosage and timing schedules, different controls, and different standard care regimens. As with most COVID-19 treatment evidence, methodological heterogeneity makes combining primary data difficult. To mitigate this, the primary studies included in the three meta-analyses have been extracted and are presented in the Primary Literature section below.

Evidence from the primary literature

After extracting the primary studies from Padhy (2020), Lawrie (2021), and Hill (preprint), adding the eight primary studies from the database search, and removing duplicates and studies with no available data (5), 20 primary studies that address the question of ivermectin treatment were included. The findings from these 20 studies are briefly described in Tables 4 (RCTs) and Table 5 (observational studies) below. For a full description of each primary study, the evidence extraction table is included in the appendix as Table 6.

A variety of outcomes were reported in the primary literature. Often, they were subjective and dependent on individual characteristics (such as clinical improvement or symptom resolution), had limited clinical relevance (such as time to PCR negativity), or

are influenced by health system factors (such as hospital length of stay). Objective measures of treatment effectiveness ((hospitalization, intensive care unit (ICU) admission, or mortality) were less often reported, but offer a clearer picture of disease progression. To minimize the effect of subjective outcomes on the present review, only primary studies reporting an objective endpoint are described in table 4.

The ICON study (Rajter et al., 2020) which has driven much of the current interest in ivermectin for COVID-19 therapy, was a retrospective chart review of 280 patients, treated with (n=173) and without (n= 107) ivermectin in 4 Florida hospitals. Univariate analysis showed lower mortality in the ivermectin group, which persisted after multivariate analysis. Propensity matching also suggested lower mortality in the ivermectin group (OR 0.47, CO 0.22-0.99; p, 0.05), with ARR 11.2% and NNT of 8.9. This was a hypothesis generating, observational study and a major limitation is higher use of dexamethasone in the ivermectin group, which could drive much of the difference observed. In addition, timing bias is a possible issue, as the non-ivermectin group was identified in the initial weeks of the time period, and other treatments, and care pathways may have improved with greater acute care experience.

Overall, the primary studies are of poor/fair quality, such that it is difficult to draw conclusions with any certainty. Of studies that are designed with a comparator group, the evidence of ivermectin's effectiveness is mixed. Roy (preprint) shows that ivermectin had no effect on ICU admission or the need for mechanical ventilation. Camprubí et al. (2020), Hashim et al. (preprint), and Mahmud (unpublished) show no or non-significant effect on mortality, while Elgazzar et al. (preprint), Naiee et al. (preprint), Rajter et al. (2020), and Roy et al. (preprint) show that ivermectin can reduce the risk of death. These findings, however are at high risk of bias from confounding due to the cocktail of therapies often used as standard care and are often poorly controlled, as standard care is administered according to physician discretion rather than a firm protocol.

Synthesis of the Information Relating to Question 2

Taken together, the primary and meta-analytic findings are inconclusive. While the meta-analyses suggest that ivermectin may have an effect on COVID-19 mortality, the primary evidence is mixed and of low certainty due to the risk of bias from confounding, small sample sizes, poor controls and overall low quality of the evidence. Additional prospective, randomized, and blinded studies are needed to confirm the effectiveness of ivermectin as a treatment for COVID-19.

Table 4. Primary RCTS reporting on objective measures (hospitalization, ICU admission, or mortality) of ivermectin treatment. All RCTs identified in the database search that were included at least one of the three meta-analyses. Full details of each study are included in Table 6 in the appendix.

Reference	Study Design	Intervention	Comparator	Outcome	Downs & Black (1998) assessment
Elgazzar et al., preprint Included in Hill and Lawrie	RCT (double-blind) (n=400) Hospitalized participants	**Group I:** Mild/moderate COVID-19; 4 days ivermectin 0.4 mg/kg (max 24 mg), once daily + SC **Group II:** Mild/moderate COVID-19; HCQ (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days) + SC **Group III:** Severe COVID-19; 4 days ivermectin 0.4 mg/kg (max 24 mg), once daily + SC **Group IV:** Severe COVID-19; HCQ (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days) + SC	Active intervention with HCQ (Groups II and IV)	- The mortality rate was Significantly reduced in ivermectin-treated patient groups I& III (0.0% & 2% respectively) versus HCQ treated groups II & IV (4% & 20%) ($p<0.001$)	16 – Fair - Risk of confounding from standard care - No standard care treatment comparator
		Azithromycin 500mg OD for 6 days, Paracetamol 500mg PRN, vitamin C 1gm OD, Zinc 50 mg OD, Lactoferrin 100mg sachets BID, Acetylcysteine 200mg t.d.s & prophylactic or therapeutic anticoagulation if D-dimer > 1000			

Reference	Study Design	Intervention	Comparator	Outcome	Downs & Black (1998) assessment
Hashim et al., preprint Included in Hill, Lawrie, and Database results	RCT (open-label) (n=140) Hospitalized participants	Standard care + ivermectin 200ug/kg PO per day for two days, and in some patients who needed more time to recover, a third dose 200ug/kg PO per day was given 7 days after the first dose. Doxycycline as needed.	Standard care only	- Mortality: 0/11 (0%) in ivermectin-Doxycycline group compared to 6/22 (27.27%) in control group for patients with severe COVID-19 (P=0.052) - Mortality: 0/48 (0%) in ivermectin-Dox group and 0/48 (0%) in control group for patients with mild/moderate COVID-19 (n.s.)	16 – Fair - Intervention not standardized (performance bias) - High risk of bias from confounding due to cocktail of therapies for standard care - Small sample size
		Standard care: - Acetaminophen 500mg on need - Vitamin C 1000mg twice/ day - Zinc 75-125 mg/day - Vitamin D3 5000IU/day - Azithromycin 250mg/day for 5 days - Oxygen therapy/ C-Pap if needed - Dexamethasone 6 mg/day or methylprednisolone 40mg twice per day, if needed			
Mahmud et al. Unpublished Included in Hill	RCT (double-blind) (n=400) Hospitalized participants	Ivermectin 6 mg stat and Doxycycline 100 mg twice daily for 5 days + Standard Care	Standard care	All cause mortality: ivermectin+Dox: 0/183 (0%) Placebo: 3/180 (1.67%) (no stats)	19 – Good - Confounding from standard care - Study results only; no interpretation from authors
		Standard Care: Paracetamol, Vitamin D, Oxygen if indicated, Low molecular weight heparin, dexamethasone if indicated			
Naiee et al., preprint Included in Hill and Lawrie	RCT (double-blind) (n=180) Hospitalized participants	Standard care + I: Single dose ivermectin (200mcg/kg, 1 pill/day) II: Three low interval doses of ivermectin (200, 200, 200 mcg/Kg , 3 pills in 1, 3 and 5 interval days)	SC alone Placebo + SC	Mortality: I: 0% II: 10% III: 0% IV:3.3% SC: 16.7% P+SC: 20%	18 – Fair - Potential confounding from standard care -Small sample size

Reference	Study Design	Intervention	Comparator	Outcome	Downs & Black (1998) assessment
		III: Single dose ivermectin (400mcg/Kg, 2 pills per day) IV: three high interval doses of ivermectin (400, 200, 200 mcg/Kg, 4 pills in 1, 3 and 5 interval days).		- Comparison of all ivermectin arms to all control arms suggests that ivermectin contributes to a risk difference of death of 15% (95% CI -25.3 – 14.7) (RR 0.18 0.06-0.55)	
		Standard Care: oral hydroxychloroquine (HCQ) 200mg/kg twice per day as standard regimen and a heparin prophylaxis in combination with supplemental oxygen.			
Roy et al., preprint Included in Hill and Database results	RCT (double-blind) (n=112) Hospitalized participants	Ivermectin 12 mg on day 1 and day 2 of admission plus standard care	Placebo + standard care	- 1.8% (n=1) in the intervention arm needed invasive ventilation compared to 8.8% (n=5) in the placebo arm (n.s.) - 9.1% (n=5) of the patients in the intervention arm and 10.5% (n=6) in the placebo arm required ICU care (RR 0.9, 95% CI 0.3 to 2.7, p=0.798). - In-hospital mortality was 6.9% (n=4) in the placebo arm as opposed to 0/55 deaths in the intervention arm	22 – Good - confounding from standard care - High risk of performance bias - small sample sizes
		Standard care: HCQ, steroid, enoxaparin, antibiotic, remdesivir (if necessary), convalescent plasma (if necessary), tocilzumab (if necessary)			

Table 5. Primary observational studies reporting on objective measures (hospitalization, ICU admission, or mortality) of ivermectin treatment. Three studies were identified in the database search (Carvallo et al., preprint; Morgenstern et al., preprint; and Camprubí et al., 2020) that were not included at least one of the three meta-analyses. Full details of each study are included in Table 6 in the appendix.

Reference	Study Design	Intervention	Comparator	Outcome	Downs & Black (1998) assessment
Bhattacharya et al., preprint Included in Padhy	Case series (n=148) Hospitalized participants	Standard care (unclear) + ivermectin (single dose) + Atorvastatin (10 mg daily) + N-acetyl-cysteine	None	2 of 148 patients treated with Standard of Care + ivermectin + Atorvastatin + N-acetyl-cysteine died during the trial (fatality rate of 1.35% which is below national average)	7 – poor - High risk of bias due to confounding - Minimal description of methods - Small sample size - No blinding - No statistical analysis - Does not describe standard care
Camprubí et al., 2020 Included in database results	Non-randomized observational study (n=26) Hospitalized participants	Ivermectin at 200 µg/kg, single dose	No ivermectin treatment	- A higher proportion of patients receiving ivermectin required ICU admission (ICU) (69%) than patients who did not receive ivermectin (38%)	13 – poor - High risk of confounding due to immunosuppressive therapy - Risk of selection bias - Small sample size - No statistical analysis
		All patients received azithromycin and HCQ; all but one patient received lopinavir/ritonavir			
Carvallo et al., preprint Included in database results	Non-randomized observational trial (n=167) Hospitalized participants	IDEA protocol dependent on severity. Ivermectin + dexamethasone + antithrombotic + ventilation	None	- Only 1 of the 32 moderate / severe patients died, and the remaining 31 patients did not worsen - Overall mortality of patients treated according to IDEA protocol was 0.59% (1 death in 167 treated cases). Estimated overall mortality rate in Argentina is approximately 2.1% (official data)	15 – fair - Very poor controls - Does not show that ivermectin specifically affects mortality - High risk of confounding - no statistical analysis
Gorial et al., preprint	Non-randomized	Ivermectin 200 Mcg single dose at the	Matched historical controls	- There were two patients died in the non ivermectin	18 – Fair

Reference	Study Design	Intervention	Comparator	Outcome	Downs & Black (1998) assessment
Included in Padhy and database results	observational trial (n=140) Hospitalized participants	admission + standard care	treated with standard care	group (2/71) compared to the Ivermectin group (0/16) (no statistical analysis)	- Confounding from standard care - Small sample size - Poor statistical reporting
		HCQ 400mg BID for the first day then 200mg BID for 5 days plus AZT 500mg single dose in the first day then 250mg for 5 days			
Morgenstern et al., preprint Database results	Retrospective observational study (n=3099) Outpatient and hospitalized participants	Ivermectin at 0.4mg / kg, orally (PO) in a single dose in the ER; Additional doses and other medications not standardized	None	- Authors list the hospitalization and ICU outcomes, but do not assess the effect of ivermectin - Total mortality of outpatients and hospitalized patients treated with ivermectin, was 1.2%, well below the average 3% reported in most series and overall mortality worldwide	11 – poor - Treatment not standardized - High risk of confounding in hospitalised patients - No comparator group
Rajter et al., 2020 Included in Lawrie, Padhy and database results	Non-randomized trial (n=280) Hospitalized participants	Usual care + At least one oral dose of ivermectin at 200 µg/kg in addition to usual clinical care. A second dose could be given at the discretion of the treating physician at day 7 of treatment.	Usual care alone	- For the unmatched cohort, overall mortality was significantly lower in the ivermectin group than in the usual care group (15.0% vs 25.2% for ivermectin and usual care, respectively; P=.03) - In the matched cohort, ivermectin was associated with an absolute risk reduction of 11.2% (95% CI, 0.38%-22.1%) - Multivariate analysis suggests that ivermectin is associated with reduced odds of mortality (OR 0.27 (0.09-0.80) p<.03)	21 – good - Ivermectin treatment not standardized - Potential confounding from usual care - Potential for timing bias
		Usual care: hydroxychloroquine, azithromycin, or other medications was at the discretion of the treating physicians; oxygen and ventilation support applied as needed (not specifically described)			

3. Are there risks associated with the use of ivermectin for prophylaxis or treatment of COVID-19?

Evidence from secondary and grey literature

Adverse events were identified in the Lawrie (20201) meta-analysis. They were not found to be significant, possibly due to the confounding effect of the therapies used as standard care. Esophagitis due to doxycycline was specifically named in Lawrie (2021), although the author does not go into detail to compare the safety profile of ivermectin and doxycycline. No adverse events were reported in Padhy et al. (2020).

The product monograph for Stromectol® oral ivermectin tablets reports that no fatalities or toxicity have been observed in humans due to overdose of medical-grade ivermectin (Merck Canada Inc., 2020). Consumption of veterinary-grade ivermectin formulations most commonly results in rash, contact dermatitis, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea (Merck Canada Inc., 2020).

The safety of ivermectin in pregnant women, children under 15 kg, and adults over 65 is limited or has not yet been established. Breast-feeding mothers should only be offered ivermectin if the benefit to the mother outweighs the risk to the infant (Merck Canada Inc., 2020).

Side effects from ivermectin treatment for strongyloides and onchocerciasis include (but are not limited to) muscle/joint pain, lymph node swelling and tenderness, and skin rash (all due to Mazzotti-type reactions in onchocerciasis patients) (Merck Canada Inc., 2020). Of note, these side effects are noted when ivermectin is used according to the medication label; there is limited evidence for safety in off-label dosing regimens.

Evidence from the primary literature

Some adverse events were reported in the primary literature, however, those ascribed to ivermectin affected very few study participants and were not severe. All are listed These include nausea, diarrhea, burning sensation, heartburn, abdominal pain, fatigue/lethargy, tingling/numbness, sleepiness, dizziness, rash (Shouman, unpublished; Krolewiecki et al., preprint; Mahmud, unpublished; Chowdhury et al., 2020; Chachar et al., 2020; Chaccour et al., preprint) Carvallo et al. (preprint) reported one case of gastric ulcer during their study, however, the patient had a history of ulcers and the event was ascribed to the dexamethasone treatment.

Synthesis of the Information Relating to Question 3

The evidence identified for this review suggests that ivermectin is safe for use as prophylaxis and treatment of COVID-19, however, the evidence for safety in high doses is limited at best.

4. Does available data on utilization of accessible ivermectin products in Alberta suggest that it is being used in COVID-19?

There are limited data available that might signal increased use of ivermectin products in Alberta. Figure 1 below shows the number of discrete patients by year and month that have filled a prescription for Stromectol in Alberta (raw data obtained from personal communication with L. Svenson). Although there is a large increase in prescriptions in

December of both 2019 and 2020, there is no significant difference between the data for the two years (p=0.14). However, as this medication is frequently used in returned travelers with tropic acquired parasite infections, which could be the reason for the seasonality seen in 2019, there should not be a travel signal in 2020 given restrictions related to the pandemic, which suggests possible use in COVID-19.

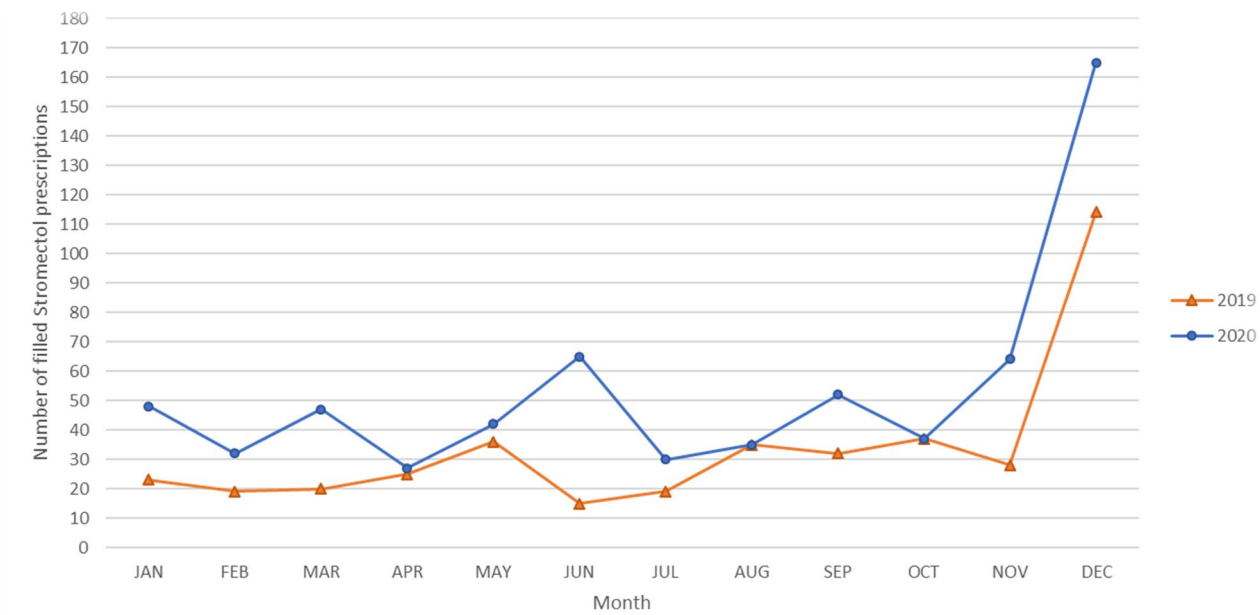

Figure 1. Number of discrete prescriptions for Stromectol filled in Alberta in 2019 and 2020. The counts are unique patients within a month and not across. Across the 2 years of data, there were 881 distinct patients, filling 1,149 prescriptions

Provincial Pharmacy Operations in AHS report that medical supply of ivermectin in Alberta is stable (as of January 2021). No supply issues have been reported from Merck Canada (personal communication). Figure 2 shows the number of four-packs of ivermectin – 3 mg tablets purchased by acute care sites in Alberta from April 2020 to December 2020. No obvious pattern emerges from the data. Purchasing does not appear to be related to the number of COVID-19 cases in the Calgary, Edmonton, and North Zones; rather, surface analysis suggests that purchasing in the Calgary Zone is bulk and scheduled, while purchasing in Edmonton Zone (includes the Royal Alexandra Hospital, the University of Alberta Hospital, and the Misericordia hospital) and North Zone (St. Therese Health Centre) occurs on an as-needed basis that may be related to the farming season and people spending summer holidays in lakes. However, the purchasing data does not show how the medications are being used at the site – this would require an in-depth analysis of the administrative data or a chart review.

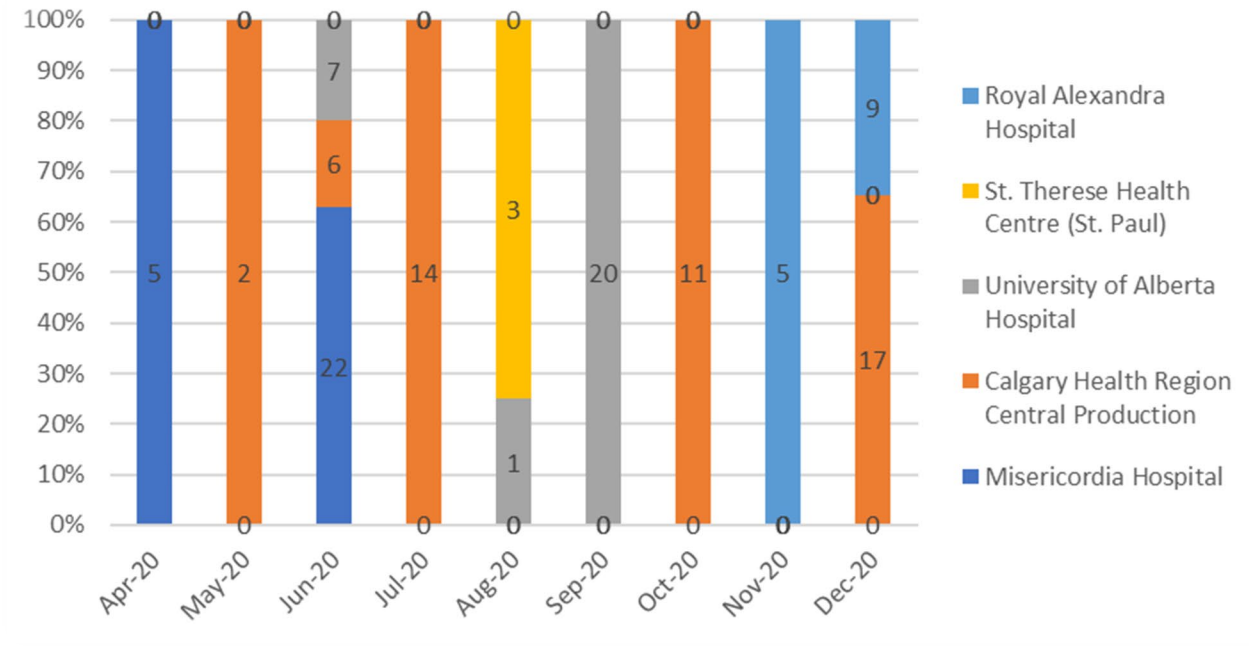

Figure 2. Number of 4-packs of ivermectin-3mg purchased by acute care sites in Alberta Health Services between April and December 2020.

Veterinary drug products are not sold or regulated through the Alberta Government, so it is difficult to obtain purchasing and prescribing data for veterinary ivermectin. The public health veterinarians in Alberta suggest that any increase in purchases for off-label human use would be imperceptible compared to the background due to the volumes of medication already used in agriculture (personal communication with K. Lehman and H. Keshwani).

Synthesis of the Information Relating to Question 4

The available data does not show an increase in ivermectin purchasing related to COVID-19 prevalence in the province, however, purchasing patterns do not show how the medication is utilized. Veterinary medications are not overseen by the province, so it is difficult to discern increased purchasing of off-label human use compared to normal veterinary use. More investigation is needed to identify if purchasing and utilization patterns can signal off-label use of ivermectin for COVID-19.

Evolving Evidence

Given the ongoing social media attention and hype that ivermectin has received, there are many ongoing clinical trials to determine the clinical effectiveness of ivermectin in COVID-19 prophylaxis and treatment. It is likely that this review will require updating when the results from the ongoing clinical trials are released.

There are 38 ongoing clinical trials registered to clinicaltrials.gov that are researching ivermectin as prophylaxis or treatment for COVID-19. Of the 38 trials, there are 31 randomized controlled trials (RCT), four non-randomized interventions trials, and three observational trials. Six trials explore the efficacy of ivermectin tablets in preventing the development of COVID-19 or COVID-19 symptoms in healthy adults, family members of

COVID-19 patients, and health workers. The remaining 32 clinical trials' primary purpose is to use ivermectin alone or in combination with other interventions as a treatment for COVID-19. Of the treatment trials, 18 specified the degree of severity for COVID-19 in its participant inclusion criteria, which includes: 14 trials for participants with mild to moderate COVID-19, two trials for participants with severe cases of COVID-19, and another two trials for asymptomatic COVID-19 patients. How COVID-19 severity was assessed was not always reported, nor was it uniform across who did report on it.

These ongoing trials frequently combine ivermectin with other drugs, including: aspirin, heparin and enoxaparin, corticosteroids, zinc, Nigella Sativa, losartan, hydroxychloroquine, favipiravir, azithromycin, nitazoxanide, doxycycline, cholecalciferol. Ivermectin delivery is most often in the form of a tablet, but alternative delivery methods such as nasal spray, oral drops, and sub-cutaneous injection were also researched. Ivermectin dosage is most often dependent on the patient's weight, with clinical trials varying their delivery and dosage schedule from single doses to continuous doses over weeks. The clinical trials monitored patients between the ranges of seven days up to three months. This fairly short window of time and little follow up after trial completion limits insights on ivermectin's impact on long-term cases of COVID-19. A full listing of the ongoing clinical trials is included in Table 7 in the Appendix. There are four notable clinical trials (described below) that have the potential for generating high-quality evidence at their conclusion. Studies with available results were compared with the database search to ensure that they were captured in the strategy or in the included meta-analyses.

Clinical Trial NCT04529525 (refer to #12 in Table 7) is a prospective, randomized, quadruple-blind, placebo-controlled study conducted by the Ministry of Public Health of the Province of Corrientes, Argentina to assess ivermectin as a treatment for COVID-19. Participants (n = 500) include adults (over 18 years of age) who have a PCR confirmed COVID-19 diagnosis that do not require hospitalization at the time of diagnosis. Participants will receive a daily dose of either a weight-based dose of ivermectin or a placebo for 30 days. The need for hospitalization due to COVID-19 during the trial period is the primary outcome being assessed, with time to hospitalization, use of invasive mechanical ventilation, dialysis, all-cause mortality, negative PCR tests, and ivermectin safety being secondary outcomes.

Clinical trial NCT04602507 (refer to #16 in Table 7) is randomized, quadruple-blind clinical trial, carried out by CES Clinic, Medellin-Colombia to assess ivermectin as a COVID-19 treatment for severe patients. The investigators will randomize 100 participants with severe COVID-19 (based on criteria of the National Institute of Health and the Colombian Consensus) into two groups. Experimental group will receive oral ivermectin (400 µg/kg in a single dose) in addition to standard management and the Control group will receive placebo plus standard management. The primary outcome being assessed is the admission to intensive care unit within the clinical trial period (21 days) and secondary outcomes including: length of stay, mortality rate, length of stay in ventilator, and adverse effects of ivermectin.

Clinical trial NCT04405843 (refer to #26 in Table 7) is a quadruple-blind, placebo controlled, randomized clinical trial by Centro de Estudios en Infectogía Pediatrica to evaluate the efficacy of ivermectin in preventing progression of early stages of COVID-19 in adult participants. Participants (n= 476) are split into two groups.The experimental group will receive ivermectin (300µg/kg) daily for five days and the control group will receive a placebo drug. The primary outcome being assessed is the time until symptoms resolve within the trial (21 days) with secondary outcomes including clinical condition check-ins throughout the trial, adverse events, duration of fever, and proportion of participants who discontinue intervention.

Clinical trial NCT04527211 (refer to #30 in Table 7) is a randomized, multicenter, quadruple-blind, placebo-controlled clinical trial by Javeriana University to determine the effectiveness and safety of ivermectin as a COVID-19 prophylactic treatment for health workers. The 550 participants will be split into two groups: the experimental group will receive ivermectin (200 µg/kg) every week for seven weeks and the control group will receive a placebo for seven weeks. The primary outcome that will be assessed is the development of COVID-19 during the trial (eight weeks), while the secondary outcomes include seroconversion, hospitalization, ICU requirement, and safety of the intervention.

Appendix

Primary Evidence Extraction Table

Table 6. Characteristics and findings of primary literature included in Lawrie (2021), Padhy (2020), Hill (preprint), and identified in the database search.

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
Ahmed et al., 2020	RCT; double-blind	- Adults hospitalized with lab-confirmed SARS-CoV-2 infection - Average of 3.83 days post-illness onset - n = 72	- oral ivermectin alone (12 mg once daily for 5 days) (n=24) - oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days) (n=24)	- Placebo (n=24)	Does not describe outcomes of interest (mortality, hospitalization, ICU admission)	18 = Fair - Selection bias (all hospitalized patients, ~4 days post-symptoms) - Potential conflict due to funding source - Unclear if usual care was part of treatment regimen - Small sample size	Treatment
Alam et al., 2020	Prospective observational trial	- Healthy adults (> 21 years) working as healthcare providers in COVID-19 isolation wards - n = 118	- Prophylactic dose of ivermectin 12mg every 4 weeks for 4 months (n=58)	No prophylaxis; no placebo (n=60)	- 54 (93.1%) participants in experimental group remained healthy despite being exposed to COVID-19 RT-PCR positive patients - 44 out of 60 participants (73.3%) belonging to the control group emerged symptomatic at different phases of the study period and tested positive for COVID-19 in RT-PCR [26.6% remained healthy] - 73.3% participants in control group were positive for COVID-19, whereas only 6.9% the experimental group were diagnosed with COVID-19 ($p < 0.05$).	14 = low fair - Unclear if participants were randomized - Control group did not receive a placebo so blinding is impossible - Did not adjust for confounding factors - Small sample size	Prophylaxis
Asghar et al. Unpublished	No results available (used in Hill et al., preprint)						

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
Babalola et al. preprint	RCT; double-blind	Adult patients with lab-confirmed COVID-19, either asymptomatic or mild/moderate symptoms - n = 62	- Ivermectin 6mg (given every 84 hours) for two weeks (n= 21) - Ivermectin 12mg (given every 84 hours) for 2 weeks (n= 21) - Some patients required concomitant medications such as dexamethasone, enoxaparin, and supplemental oxygen. - Supplemental medications included zinc, ascorbic acid, vitamin D and Azithromycin	Lopinavir / ritonavir daily for 2 weeks (n=20)	Does not report outcomes of interest (mortality, hospitalization, ICU admission)	18 = Fair - Small sample size - Risk of bias due to confounding	Treatment
Behera et al., preprint	Case-control	- Cases were HCWs who were diagnosed as positive for COVID-19 by Reverse Transcription Polymerase Chain Reaction (RT-PCR) - Controls were defined as HCWs who were diagnosed as negative for COVID-19 by RT-PCR with a similar risk of exposure to COVID-19 - n= 186 pairs, matched for profession, gender, age, and date of diagnosis (372 participants)	Exposure was defined as the prophylaxis viz., ivermectin and or/ (HCQ) and or/ vitamin C and or/ other interventions taken for the prevention of COVID-19	No prophylaxis	- In the matched pair analysis, ivermectin prophylaxis (OR 0.30, 95% CI, 0.16-0.53) was associated with the reduction of COVID-19 infection - In the multivariate conditional logistic regression model 2, ivermectin prophylaxis (OR 0.27, 95% CI, 0.15-0.51) was associated with a reduction of COVID-19 infection after adjusting for COVID duties, type of household, physical activity, vitamin-C prophylaxis and HCQ prophylaxis	20 = Good - Measurement of outcomes was not blinded - Potential for confounding, but is accounted for - Healthcare workers may have different attitudes toward COVID-19 protection than the general population	Prophylaxis
Bhattacharya et al., preprint	Retrospective case series	Adult inpatients with lab-confirmed COVID-19 - n = 148	Standard of care (unclear; includes antivirals, anti-inflammatories and antioxidants) plus ivermectin single dose, Atorvastatin 10mg daily and injection N-acetyl-	None	- 2 of 148 patients treated with Standard of Care + ivermectin + Atorvastatin + N-acetyl-cysteine died during the trial (fatality rate of 1.35% which is below national average)	7 = Poor - High risk of bias due to confounding - No comparator to draw conclusions - Minimal description of methods	Treatment

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
			cysteine, irrespective of disease severity			- small sample size - No blinding - No statistics - Does not describe standard care	
Camprubí et al., 2020	Retrospective non-randomized observational study	Hospitalized patients with COVID-19 (not all lab-confirmed) receiving immunosuppressive therapy for COVID-19 (n= 26)	Ivermectin at 200 µg/kg, single dose (n=13) All patients received azithromycin and hydroxychloroquine; all but one patient received lopinavir/ritonavir	No ivermectin treatment (n=13)	- a higher proportion of patients in the ivermectin group required admission to an intensive care unit (ICU) (69% vs 38% in the non-ivermectin group)	13 = Poor - High risk of confounding due to immunosuppressive therapies - small sample size	Treatment
Carvallo et al., 2020	Prospective observational trial	HCWs with no COVID-19 symptoms and negative swabs for SARS-CoV-2 Pilot: n=229 Multicenter: n=1195	1 spray of topical carrageenan + 1 drop ivermectin (0.6 mg/ml) on the tongue (5X daily [every 4 hours]/ 14 days) + PPE Pilot: n=131 Multicenter: n= 788	PPE Alone Pilot: n=98 Multicenter: n= 407	**Pilot**: - 0/131 in intervention group tested positive for SARS-CoV-2 during 14-day treatment period or 3 weeks post-completion - 11/98 (11.1%) in control group tested positive during the 2-week intervention or 3 weeks post-completion - Transmission rate in the treated group is statistically significantly lower in the treated group ($p < 0.0001$). **Multicenter study:** - 237/407 in control group tested positive for COVID-19 over 3 month study period - 0/788 in intervention group tested positive for COVID-19 over 3-month study period	15 = Fair - Risk of selection bias - Risk of confounding from other prevention behaviors (impossible to blind intervention group) - Staff characteristics not clearly described - Adherence to treatment not analysed	Prophylaxis
Carvallo et al., preprint	Prospective observational trial	Lab-confirmed cases of COVID-19 in individuals over 5 years old, with any severity (n=167)	**For Mild COVID:** Ivermectin: 24 mg on days 0 and 7 Dex: none	None	- Only 1 of the 32 moderate/severe patients died, and the remaining 31 patients did not worsen - Overall mortality rate of patients treated according to IDEA protocol	15 = Fair - No control group - Data does not show that the	Treatment

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
		Mild COVID-19: 135 Moderate-severe: 32	Antithrombotic: Aspirin 250-mg tablet once daily for at least 30 days Ventilation: no **For moderate COVID:** Ivermectin: 36 mg on days 0 and 7 Dex: 4- mg injection daily Antithrombotic: Aspirin 250-mg tablet once daily for at least 30 days Ventilation: Low Flow Washed Oxygen or Oxygen Concentrator **For Severe COVID:** Ivermectin: 48 mg via gastric cannulae on days 0 and 7 Dex: 4- mg injection daily Antithrombotic: Enoxaparin 100 UI/kg (ca. 1 mg/kg) daily Ventilation: Mechanical Ventilation		was 0.59 % (1 death in 167 treated cases). As a comparison, estimated overall mortality rate in Argentina is approximately 2.1 % (official data by September 2nd, 2020) - an ad hoc control group of 12 patients were hospitalized in Eurnekian hospital in the same period but did not receive IDEA treatment. Three of them died, thus presenting a mortality rate of 25 %	regimen improves disease progression - High risk of confounding	
Chachar et al., 2020	RCT (open-label)	Adults with mild lab-confirmed COVID-19; outpatient treatment (n=50)	Ivermectin 12mg stat and then 12 mg after 12 hours and 12mg after 24 hours (n=25)	No treatment (n=25)	Does not report on outcomes of interest (mortality, hospitalization, ICU admission) - 32% of patients (n=8) patients in treatment group reported heartburn as an adverse event	17 = fair - Clinical improvement is subjective	Treatment
Chaccour et al. preprint	Pilot RCT (double-blind)	Adults presenting to Emergency with mild lab-confirmed COVID-19, no more than 3 days post-symptom onset; (n=24)	Ivermectin (400 mcg/kg) single oral dose (n=12)	Placebo (n=12)	- No patient from either group progressed to severe disease. - Patients in the ivermectin group reported more patient-days of dizziness (7 vs 1) and blurred vision (24 vs 1) (the blurred vision report is from a single patient who had undiagnosed presbyopia)	27 = Excellent - Small sample size	Treatment

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
Chowdhury et al., 2020	RCT (open-label)	Adults with lab-confirmed, asymptomatic or mild-moderate COVID-19 (n=116)	Ivermectin 200µgm/kg single dose + Doxycycline 100 mg BID for 10 days (n=60)	Hydroxychloroquine 400 mg 1st day then 200mg BID for 9 days + Azithromycin 500 mg daily for 5 Days (n=56)	Does not report outcomes of interest (mortality, hospitalization, ICU admission) - Adverse events: 23% of Intervention group reported lethargy, nausea, or vertigo	20 = Good - Possible selection bias	Treatment
Elgazzar et al., preprint	RCT (double-blind)	**Treatment**: Adults with lab-confirmed mild, moderate, or severe COVID-19 (n=400) **Prophylaxis**: Adult healthcare and household contacts of COVID-19 cases (n=200) The study participants were block randomized into groups of 100.	**Group I:** Mild/moderate COVID-19; 4 days ivermectin 0.4 mg/kg (max 24 mg), once daily + SC **Group II:** Mild/moderate COVID-19; HCQ (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days) + SC **Group III:** Severe COVID-19; 4 days ivermectin 0.4 mg/kg (max 24 mg), once daily + SC **Group IV:** Severe COVID-19; HCQ (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days) + SC **Group V:** Pre- or post-exposure contacts; prophylactic dose of ivermectin 0.4mg/kg single oral dose before breakfast to be repeated after one week + PPE **Standard Care:** Azithromycin 500mg OD for 6 days, Paracetamol 500mg PRN, vitamin C 1gm OD, Zinc 50 mg OD, Lactoferrin 100mg sachets BID , Acetylcysteine	**Group VI:** Pre- or post-exposure contacts, PPE only	- The mortality rate was significantly reduced in ivermectin-treated patients groups I& III (0.0% & 2%, respectively) versus Hydroxychloroquine treated groups II & IV (4% & 20%, respectively) ($p<0.001$) - 2% of ivermectin-treated HCWs or household contacts had positive RT-PCR tests for COVID-19, compared to 10% of control contacts (PPE alone) ($p<0.05$)	16 = Fair - Risk of confounding from standard care - Risk of confounding from unidentified prevention behaviours in control group	Prophylaxis and Treatment

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
			200mg t.d.s & prophylactic or therapeutic anticoagulation if D-dimer > 1000				
Gorial et al., preprint	Pilot RCT (open-label)	Adults with mild-moderate lab-confirmed COVID-19, enrolled consecutively (n=87)	- Ivermectin 200 Mcg single dose at the admission day as add-on therapy to Iraqi Ministry of Health protocol for treatment of mild to moderate COVID-19 [HCQ 400mg BID for the first day then 200mg BID for 5 days plus AZT 500mg single dose in the first day then 250mg for 5 days] (n=16)	- Matched historical controls of patients treated with HCQ and AZT (n=71)	- No side effects identified - There were two patients died in the non ivermectin group (2/71) compared to the ivermectin group (0/16) (no stats given)	18= Fair - Confounding from standard care - Small sample size	Treatment
Hashim et al., preprint	RCT (open-label)	Adolescent and adult COVID-19 patients with mild, moderate, severe, or critical disease - symptomatic for no more than three days for mild-moderate cases, no more than two days after being severe cases, and no more than one day after being critical cases (n=140)	Standard care + ivermectin 200ug/kg PO per day for two days, and in some patients who needed more time to recover, a third dose 200ug/kg PO per day was given 7 days after the first dose. Doxycycline 100mg capsule PO every 12h per day was given for 5-10 days, based on patient improvement. (n=70: 48 mild, 11 severe, 11 critical)	Standard Care only (n=70: 48 mild, 22 severe)	- Mortality: 0/11 (0%) in ivermectin-Doxycycline group compared to 6/22 (27.27%) in control group for patients with severe COVID-19 (P=0.052) - Mortality: 0/48 (0%) in ivermectin-Dox group and 0/48 (0%) in control group for patients with mild/moderate COVID-19 (n.s.)	16 = Fair - Intervention not standardized (performance bias) - High risk of bias from confounding due to cocktail of therapies for standard care - Small sample size	Treatment
			Standard care: - Acetaminophen 500mg on need - Vitamin C 1000mg twice/ day - Zinc 75-125 mg/day - Vitamin D3 5000IU/day - Azithromycin 250mg/day for 5 days - Oxygen therapy/ C-Pap if needed - Dexamethasone 6 mg/day or methylprednisolone 40mg twice per day, if needed				

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
Khan et al., 2020	Case series	Adult patients with lab-confirmed COVID-19, consecutively presenting for testing and admitted to hospital (n=325)	Ivermectin 12mg within 24-h after hospital admission, plus standard care (n=248)	Standard care only (n=133)	- No reported adverse events - Significantly fewer ivermectin-treated patients required intensive care management (0.9% vs. 8.3%) - mortality rate was significantly lower in the ivermectin group than SC (0.9% vs. 6.8%; P<0.05)	19 = Good - Limited detail - Confounding due to standard care	Treatment
			Standard care: Provided as required and included antipyretics for fever, anti-histamines for cough, and antibiotics to control secondary infection				
Krolewiecki et al., preprint	Pilot RCT (open-label)	Adults with lab-confirmed COVID-19, less than 5 days post-symptom onset, hospitalized for moderate disease (n= 45)	Ivermectin 0.6 mg/kg/day for 5 days (n= 15)	No ivermectin treatment (n=30)	Does not report outcomes of interest (mortality, ICU admission, hospitalization) - The most frequent adverse event and the only experienced by more than 1 case in the ivermectin group was rash in 3 (10%) cases (all mild, self-limited and lasting approximately24 h) - A single serious adverse event (SAE) was reported in the trial in a patient in the ivermectin group with hyponatremia, but other literature suggests that this is not due to ivermectin.	24 = Excellent - Small sample size - Viral load does not necessary correlate to clinical significance or outcomes	Treatment
Mahmud et al. Unpublished	RCT (double-blind)	Adults with mild-moderate lab-confirmed COVID-19 (n=400)	Ivermectin 6 mg stat and Doxycycline 100 mg twice daily for 5 days + Standard Care (n=200)	Placebo: Standard Care (n=200)	All cause mortality: ivermectin+Dox: 0/183 (0%) Placebo: 3/180 (1.67%) (no stats) - Adverse events (Only in ivermectin+Doxy group): Erosive esophagitis 2/183 (1.09%) Non-ulcer dyspepsia: 7/183 (3.83%)	19 = Good - Confounding from standard care - Study results only; no interpretation from authors	Treatment
			Standard Care: Paracetamol, Vitamin D, Oxygen if indicated, Low molecular weight heparin, dexamethasone if indicated				
Mohan et al. Unpublished	No results available (used in Hill et al., preprint)						
Morgenstern et al., preprint	Retrospective observational study	Mild, moderate, severe, and critical patients with probable	- Outpatients (mild COVID) were administered ivermectin at 0.4mg / kg, orally (PO) in a single dose in the ER and	No control/comparator group	- Of the patients treated as outpatients, 16 (0.59%) subsequently merited hospitalization in the COVID-19	11 = poor - Treatment not standardized	

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
		or confirmed COVID-19 (n=3099)	Azithromycin 500mg PO per day for 5 days, with follow-up - Hospitalized patients (moderate – critical COVID) were administered ivermectin PO at 0.3mg / kg, days 1 and 2, and the dose was repeated on days 6 and 7. They were given Azithromycin 500mg PO daily, for 7 days. If D-dimer greater than 1,000 ng / ml or an increase of 50% from the initial value, they were started with Enoxaparin at 1mg / kg subcutaneously, every 12 hours. Patients who required oxygen received Dexamethasone at 0.1mg / kg PO per day, maximum 10mg per day, for 10 days (or Methylprednisolone at an equivalent dose)		area room with 0 (0%) deaths and 2 of them (0.08%) required hospitalization in the ICU, of which 1 died (0.04%) - 411 patients (13.3%) were hospitalized, including patients initially treated on an outpatient basis and later merited hospitalization - In the COVID-19 ICU, 111 patients (27%) were hospitalized, representing, 3.6% of the cases originally treated in ER - Total mortality adding up outpatients and hospitalized patients treated with ivermectin, was 1.2%, well below the average 3% reported in most series and overall mortality worldwide - No adverse events or severe side effects reported	- High risk of confounding in hospitalised patients - No comparator group	
Naiee et al., preprint	RCT (double-blind)	Adults with mild, moderate or severe lab-confirmed COVID-19, admitted to hospital (n=180) n=30 in each group	I: Single dose ivermectin (200mcg/kg, 1 pill/day) II: Three low interval doses of ivermectin (200, 200, 200 mcg/Kg , 3 pills in 1, 3 and 5 interval days) III: Single dose ivermectin (400mcg/Kg, 2 pills per day) IV: three high interval doses of ivermectin (400, 200, 200 mcg/Kg, 4 pills in 1, 3 and 5 interval days).	Standard Care alone (n=30) Placebo + SC (n=30)	- No adverse effects Mortality: I: 0% II: 10% III: 0% IV:3.3% SC: 16.7% P+SC: 20% - Comparison of all ivermectin arms to all control arms suggests that ivermectin contributes to a risk difference of death of 15% (95% CI -25.3 – 14.7) (RR 0.18 0.06-0.55)	18 = Fair - Potential confounding from standard care -Small sample size	Treatment
			Standard Care: oral hydroxychloroquine (HCQ) 200mg/kg twice per day as standard regimen and a				

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
			heparin prophylaxis in combination with supplemental oxygen.				
Okumuş et al. Unpublished	Results not publicly available yet (included in Hill et al., preprint)						
Podder et al., 2020	RCT (open-label)	Adults with mild-moderate lab-confirmed COVID-19, <7 days since symptom onset Consecutive enrollment (n=62)	Usual care + single dose of ivermectin 200 mcg/kg on day 1 (n=30)	Usual care (n= 32)	Does not report outcomes of interest (mortality, ICU admission, hospitalization)	17 = Fair - Small sample size - Potential confounding from usual care and from patient characteristics	Treatment
			Usual care: all COVID-19 cases received symptomatic treatment which include antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hrs for seven days)				
Raad et al. Unpublished	Results not publicly available yet (included in Hill et al., preprint)						
Rajter et al., 2020	Non-randomized trial	Adults hospitalized for lab-confirmed COVID-19; characterized as “severe” or “non-severe” (n=280)	At least one oral dose of ivermectin at 200 µg/kg in addition to usual clinical care. A second dose could be given at the discretion of the treating physician at day 7 of treatment. (n= 173)	Usual care (n= 107)	- For the unmatched cohort, overall mortality was significantly lower in the ivermectin group than in the usual care group (15.0% vs 25.2% for ivermectin and usual care, respectively; P = .03) - In the matched cohort, ivermectin was associated with an absolute risk reduction of 11.2% (95% CI, 0.38%-22.1%) - Multivariate analysis suggests that ivermectin is associated with reduced odds of mortality (OR 0.27 (0.09-0.80) p<.03)	21= good - ivermectin treatment not standardized - Potential confounding from usual care - Potential for timing bias	Treatment
			Usual care: hydroxychloroquine, azithromycin, or other medications was at the discretion of the treating physicians; oxygen and ventilation support applied as needed (not specifically described)				
Rezai et al. Unpublished	Results not publicly available (included in Hill et al., preprint)						
Roy et al., preprint	RCT (double-blind)	Adults with mild, moderate or severe lab-confirmed COVID-19 admitted to hospital	Ivermectin 12 mg on day 1 and day 2 of admission plus standard care (n=55)	Placebo plus standard care (n=57)	- Only 1.8% (n=1) in the intervention arm needed invasive ventilation compared to 8.8% (n=5) in the placebo arm (n.s.)	22= Good - potential confounding from standard care	Treatment

Reference	Study design	Population	Intervention / Exposure	Controls / Comparators	Outcomes	Quality (D&B score; sources of bias)	Notes
		(n=112)	Standard care: HCQ, steroid, enoxaparin, antibiotic, remdesivir (if necessary), convalescent plasma (if necessary), tocilzumab (if necessary)		- 9.1% (n=5) of the patients in the intervention arm and 10.5% (n=6) in the placebo arm required ICU care (RR 0.9, 95% CI 0.3 to 2.7, p=0.798). - In-hospital mortality was 6.9% (n=4) in the placebo arm as opposed to 0/55 deaths in the intervention arm		
Shouman et al. Unpublished	RCT (open-label)	Adolescents (16yrs +) and adults who are household contacts of a confirmed COVID-19 case (n-= 340)	Ivermectin tablets: 40-60 kg (15mg/day) 60-80kg (18mg/day) >80kg (24mg/day) (n= 228)	No intervention N= 112	- PCR confirmation of COVID-19 infection not reported - No serious adverse events reported - Not serious adverse events: Nausea (2/203), diarrhea (3/203), burning sensation (1/203), heart burn (1/203), abdominal pain (1/203), fatigue (2/203), tingling/numbness (1/203), sleepiness (1/203)	- Study results only, no interpretation from authors	Prophylaxis
Spoorthi & Sasank, 2020	Non-randomized trial	Adults with mild-moderate lab-confirmed COVID-19 (n=100)	Ivermectin 200mcg/kg single dose + doxycycline 100 mg BID for 7 days (n=50)	Placebo (n=50)	Does not report outcomes of interest (mortality, ICU admission, hospitalisation) - Side effects: diarrhea, vomiting, pruritis, can't be ascribed specifically to ivermectin	17 = fair - Small sample size - Poor description of study methods	

List of Ongoing Clinical Trials

Table 7. List of Ongoing Clinical Trials of Ivermectin against COVID-19

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
1	USEFULNESS of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19 (IVERCAR) NCT04425850 Eurnekian Public Hospital, Buenos Aires, Argentina	Observational (cohort) Prevention	Combination Product: Iota carrageenan nasal spray and ivermectin oral drops (used as buccal drops) Topical application in the nose and oral cavity	Control group: Standard prophylactic measures and PPE only.	**Primary:** Number of Infected Subjects **Secondary:** Adverse Events Other Than Those Resulting From Contagion or Disease Progression [Time Frame: 28 days]	Healthy adults	Results available
2	The Efficacy of Ivermectin and Nitazoxanide in COVID-19 Treatment NCT04351347 Tanta University, Egypt	RCT (parallel assignment) Treatment	Two experimental groups: Ivermectin Nitazoxanide with ivermectin (Alenia)	Control group: standard treatment.	Number of patients with improvement or died [Time Frame: 1 month]	All ages with COVID-19	
3	Sars-CoV-2/COVID-19 Ivermectin Navarra-ISGlobal Trial (SAINT) NCT04390022 Barcelona Institute for Global Health, Spain	RCT (parallel assignment) Treatment	Ivermectin Single dose of STROMECTOL® tablets at 400mcg/kg	Control group: placebo tablets	**Primary:** Proportion of Patients With a Positive SARS-CoV-2 PCR [Time Frame: 7 days post-treatment] **Secondary:** (1) Median Viral Load, (2) Fever and Cough Progression (3) Seroconversion at Day 21, (4) Proportion of Drug-related Adverse Events, (5) Levels of	Ages 18 – 65, exclude those with co-morbidities.	Results available Double blind

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
					IgG, IgM and IgA, (6) Frequency of Innate Immune Cells, (7) Frequency SARS-CoV-2-specific CD4+ T and and CD8+ T Cells (8) Results From Cytokine Human Magnetic 30-Plex Panel 4[Time Frames: variable, up to 21 days]		
4	Safety and Efficacy of Ivermectin and Doxycycline in Treatment of Covid-19 NCT04551755 Bangladesh Medical Research Council (BMRC)	RCT (parallel assignment) Treatment	Ivermectin and Doxycycline: Tab Ivermectin (6mg): 12mg first dose then one more dose of 12mg after 12 hours Cap. Doxycycline (100mg): 1+0+1 after meal for 10 days. To be taken with half glass of water and sit up for 20 minutes	Control group: Placebo tab with standard symptomatic and supportive treatment	(51) Time to outcome measure of fever (<100.40F) and cough, (2) Negative RT-PCR test on day 5 of treatment [Time Frame: 10 days]	Adult participants with mild cases of COVID-19 Excludes comorbidities	Follow up six weeks after patient recovery Triple blind (Participant, Care Provider, Investigator)
5	Randomized Phase IIA Clinical Trial to Evaluate the Efficacy of Ivermectin to Obtain Negative PCR Results in Patients With Early Phase COVID-19 (SAINT-PERU) NCT04635943 Lima, Peru	RCT (parallel assignment) Treatment	Daily dose of 300 mcg/kg ivermectin during three (3) consecutive days	Control group: Placebo oral drop solution	**Primary:** Proportion of patients with a positive SARS-CoV-2 PCR. [Time Frame: 7 days post-treatment] **Secondary:** (1) Median Viral Load, (2) Fever and Cough Progression (3) Seroconversion at Day 21, (4) Proportion of Drug-related Adverse Events, (5) Levels of	Non-severe COVID-19 patients in the first 96 hours after symptoms onset Women of child bearing age may participate if they use a safe contraceptive method for the	Triple blind (Participant, Investigator, Outcomes Assessor)

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
					IgG, IgM and IgA, (6) Frequency of Innate Immune Cells, (7) Frequency SARS-CoV-2-specific CD4+ T and and CD8+ T Cells (8) Results From Cytokine Human Magnetic 30-Plex Panel, (9) Presence of intestinal helminths [Time Frames: variable, up to 21 days]	entire period of the study.	
6	Prophylactic Ivermectin in COVID-19 Contacts NCT04422561 Zagazig, Sharkia, Egypt	Interventional (sequential assignment) Prevention	Ivermectin Tablets (two doses 72 hours apart)	Control Group: no prophylaxis	Primary: Development of Symptoms (Fever, Cough, Sore Throat, Myalgia, Diarrhea, Shortness of Breath) Secondary: Development of COVID [Time Frame: within 14 days after enrollment]	Ages 16 – 70 years, who have had family contact of a confirmed COVID-19 case	Results available
7	Outpatient Use of Ivermectin in COVID-19 NCT04530474 Philadelphia, Pennsylvania, United States	RCT (parallel assignment) Treatment	Ivermectin tablet (Single dose of 0.15-2 mg/kg/dose to a maximum of 12 mg)	Control Group: single dose of placebo pills	Clinical Improvement [Time Frame: 28 days]	Adults who display symptoms highly suspicious for COVID-19. Excludes participants with co-morbidities.	Triple blind Participation does not require COVID-19 confirmation
8	Max Ivermectin-COVID 19 Study Versus Standard of Care Treatment for	Interventional (non-randomized, crossover assignment)	Ivermectin 200 to 400mcg per kg body weight on day 1 and day 2 along with standard treatment of the hospital protocol	Control group: treatment as per hospital protocol for COVID 19s	Effect of ivermectin on eradication of virus. [Time Frame: 3 months]	Confirmed case of COVID-19 at Max Hospitals, aged 18-75.	

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
	COVID 19 Cases. A Pilot Study NCT04373824 New Delhi, Delhi, India	Treatment				Excludes patients who are critically sick.	
9	Ivermectin-Azithromycin-Cholecalciferol (IvAzCol) Combination Therapy for COVID-19 (IvAzCol) NCT04399746 Mexico City, Mexico	Intervention (non-randomized, parallel assignment) Treatment	Combination: Ivermectin (6mg once daily in day 0,1,7 and 8) plus Azithromycin (500mg once daily for 4 days) plus Cholecalciferol (400 IU twice daily for 30 days).	Control group (participants who refused treatment)	**Primary:** Viral clearance **Secondary:** (1) Symptoms duration (2) SpO2 (oxygen saturation), (3) SpO2/FiO2 (Oxygen Saturation (SpO2)/Fraction of Inspired Oxygen (FiO2) Ratio) [Time Frame: 14 days]	Ages 18-90, confirmed mild case of COVID-19 with symptoms of respiratory illness, cough, fever.	
10	Ivermectin, Aspirin, Dexamethasone and Enoxaparin as Treatment of Covid 19 (IDEA) NCT04425863 Buenos Aires, Argentina	Observational (cohort) Treatment	Combination and dosage of treatment depends on participant severity: Mild cases cohort: Ivermectin 5 MG/ML oral solution, Aspirin 250 mg tablets. Moderate cases cohort: Ivermectin 5 mg/mL oral solution, Dexamethasone 4-mg injection, Aspirin 250 mg tablets. Severe cases cohort: Ivermectin 5 MG/ML oral solution, Dexamethasone 4-	No control group	(1) Patients Who Improved Their Condition or Did Not Worsen it, (2) ICU-treated Patients After 2-week Treatment, (3) Mortality, (4) Patients Needing Drug Dose Adjustment, (5) Adverse Events [Time Frame: varied, ranging 7 – 30 days]	Ages 5 and older with a positive COVID-19 oral/nasal swab results	

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
			mg injection, Enoxaparin injection. Inpatient treatment with mechanical ventilation in ICU.				
11	Ivermectin vs Combined Hydroxychloroquine and Antiretroviral Drugs (ART) Among Asymptomatic COVID-19 12Infection (RA-COVID19) NCT04435587 Bangkok Noi, Bangkok, Thailand	RCT (parallel assignment) Treatment	Combination of oral ivermectin 600mcg/kg/day once daily for 3 days and Zinc sulfate (100mg/tab) 2 tab every 12 hours for 3 days	Active Comparator: Combination of (1) Day1 hydroxychloroquine 400mg bid, then 200mg bid on Day 2-5, and (2) Darunavir/ritonavir (400/100mg) every 12 hours for 5 days, and (3) Zinc sulfate (100/tab) 2 tab every 12 hours for 5 days	**Primary:** (1) Adverse event rates (2) Efficacy for shortening duration of SAR-CoV2 detection by PCR **Secondary:** Antibody detection rates [Time Frame: weekly after treatment until 4th week]	Adult participants with PCR confirmed COVID-19, who are asymptomatic or only demonstrate upper respiratory symptoms such as runny noses	Single blind (outcome assessor)
12	Ivermectin to Prevent Hospitalizations in COVID-19 (IVERCORCOVID19) NCT04529525 Corrientes, Argentina	RCT (parallel assignment) Treatment	Ivermectin: The dose of ivermectin in patients depends on the weight of the patient	Control group: Placebo	**Primary:** Percentage of Hospitalization of medical cause in patients with COVID-19 in each arm **Secondary:** (1) Time to hospitalization, (2) Use of invasive mechanical ventilation support, (3) Time to invasive mechanical ventilation support, (4) Dialysis, (5) All-cause mortality, (6) Negative of the swab at 3±1 days and 12±2 days after entering the study, (7) Incidence of Treatment-	Adult participants who had PCR confirmed cases of COVID-19, excludes patients requiring hospitalization at the time of diagnosis. Women of childbearing age, they must be using a contraceptive method of proven	Quadruple blind (Participant, Care Provider, Investigator, Outcomes Assessor)

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
					Emergent Adverse Events [Safety and Tolerability] [Time Frame: through study completion, an average of 30 days]	efficacy and safety	
13	Ivermectin Nasal Spray for COVID19 Patients NCT04510233 Tanta, Gharbia, Egypt	RCT (parallel assignment) Treatment	Two experimental groups: Ivermectin administered as nasal spray (one ml in each nostril two times daily) Ivermectin administered orally (one tablet 6 mg three times daily) for 72 hours plus the standard care of COVID-19 cases.	Control group: standard care	PCR of SARS-Cov2 RNA [Time Frame: 14 days]	Ages 18 – 60, with mild to moderate COVID-19 cases.	
14	Ivermectin in Treatment of COVID-19 NCT04445311 Zagazig, Sharkia, Egypt	RCT (parallel assignment) Treatment	Ivermectin with standard care	Control group: standard care	**Primary:** time to be symptoms free **Secondary:** (1) hospitalization, (2) Mechanical ventilation, (3) length of stay, (4) mortality	Ages 18-70 with COVID-19	
15	Ivermectin In Treatment of COVID 19 Patients NCT04425707 Cairo, Egypt	RCT (parallel assignment) Treatment	Two experimental groups: Ivermectin will be administered alone	Control group: standard care alone	**Primary:** to evaluate the role of ivermectin as a line of treatment for COVID 19 **Secondary:** To assess the rate of viral clearance in	Adult participants with Asymptomatic, mild cases and moderate cases of COVID-19	

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
			Ivermectin will be administered in addition to standard care		comparison to other treatment protocols. [Time Frame: 2 months]		
16	Ivermectin in Adults With Severe COVID-19. NCT04602507 Medellín, Antioquia, Colombia	RCT (parallel assignment) Treatment	Ivermectin 400 µg/kg (2 drops per kg) orally in a single dose plus routine care offered in the hospital	Control group: routine care offered in the hospital plus placebo orally (2 drops per kg) in a single dose.	**Primary:** Admission to the intensive care unit. **Secondary:** (1) Hospital length of stay, (2) mortality rate, (3) ICU length of stay, (4) Length of stay in ventilator time, (5) Adverse effects of ivermectin [Time Frame: 21 days]	Adult participants with severe COVID-19, less than 14 days since onset of symptoms	Quadruple blind (Participant, Care Provider, Investigator, Outcomes Assessor)
17	Ivermectin for Severe COVID-19 Management NCT04646109 Afyonkarahisar, Turkey	RCT (crossover assignment) Treatment	Ivermectin 200 mcg/kg/day for five days with -hydroxychloroquine (2x400mg loading dose followed by 2x200mg, po, 5 days) + favipiravir (2x1600mg loading dose followed by 2x600mg maintenance dose, po, total 5 days) + azithromycin (first day 500mg followed by 4 days 250mg/day, po, total 5 days)	Control group: Hydroxychloroquine, favipiravir and azithromycin (HFA) standard treatment protocol were given	**Primary:** (1) Gender distribution, (2) Age distribution, (3) Percentage of patients with accompanying diseases, (4) Percentage of patients with baseline clinical symptoms, (5) Body temperature means, (6) Heart rate means, (7) Respiratory rate means, (8) Respiratory rate means, (9) Systolic and diastolic pressure means, (9) Clinical response, (10) Changes in SpO2 values, (11) Changes in PaO2/FiO2, (12) Changes in serum lymphocyte counts, (13) Changes in PNL/L, (14) Changes in serum ferritin levels, (15) Changes in serum D-dimer levels, (16) Genetic	Adult participants with severe COVID-19 diagnosis	Results available

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
					examination of haplotypes and mutations that cause function losing for ivermectin metabolism, (17) Treatment-Related Adverse Events as Assessed by CTCAE v4.0 [Time Frame: At the first 5 days of study] **Secondary:** (1) Clinical response, (2) mortality, (3) Changes in SpO2 values, (4) Changes in PaO2/FiO2, (5) Changes in serum lymphocyte counts, (6) Changes in PNL/L, (7) Changes in serum ferritin levels, (8) Rate of COVID-19 Polymerase Chain Reaction (PCR) test negativity (9) Treatment-Related Adverse Events as Assessed by CTCAE v4.0 [Time Frame: From the 6th day of study to the 10th day of study]		
18	Ivermectin Effect on SARS-CoV-2 Replication in Patients With COVID-19 NCT04381884 Salta, Argentina	RCT (parallel assignment) Treatment	Ivermectin (IVER P®) 600 µg / kg / once daily plus standard care.	Control group: standard care	**Primary:** Reduction in SARS-CoV-2 viral load [Time Frame: 1 - 5 days] **Secondary:** (1) Number of patients with partial or complete response in COVID-19 clinical symptoms (2)	Ages 18 – 69, who are hospitalized with COVID-19 5 days before participating in the trial	

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
					Number of patients with worsening in the clinical condition, (3) Number of patients with adverse events as a measure of safety and tolerability, (4) ivermectin concentrations measured in plasma, (5) Evaluation of reactivity of the antibodies against SARS-CoV-2 [Time Frame: varied, up to 1 month]	Excludes severe COVID-19 cases and patients with comorbidities	
19	Ivermectin and Nitazoxanide Combination Therapy for COVID-19 NCT04360356 Tanta, Gharbia, Egypt	RCT (parallel assignment) Treatment	Combination of ivermectin 200 mcg/kg once orally on empty stomach plus Nitazoxanide 500 mg twice daily orally with meal for 6 days	Control group: standard care (oxygen via ventilators)	Primary: to evaluate the role of ivermectin as a line of treatment for COVID 19 Secondary: To assess the rate of viral clearance in comparison to other treatment protocols. [Time Frame: 2 months]	Ages 18-65, symptomatic patients with PCR confirmed COVID-19	Double blind (participant, investigator)
20	Ivermectin as a Novel Therapy in COVID-19 Treatment NCT04403555 Tanta, Gharbia, Egypt	RCT (parallel assignment) Treatment	Ivermectin plus standard of care treatment Dose 2 tablets 12mg per day for 4 days	Control group: standard care	The number of patients with improvement or mortality [Time Frame: 1 month]	COVID-19 patients	
21	Inhaled Ivermectin and COVID-19 (COVID-19) NCT04681053 Mansoura, Egypt	Interventional Non-randomized (parallel assignment)	Three experimental groups: Received both oral and inhaled ivermectin in	Control group: standard care	**Primary:** Rate of virological cure by Rt -PCR for COVID -19 using ivermectin when compared to standard treatment	Adults with mild to moderate PCR confirmed COVID-19 diagnosis	

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
		Treatment	addition to the standard of care. Received oral ivermectin in addition to the standard of care Received inhaled ivermectin in addition to the standard of care		**Secondary:** resolution of pneumonia [Time Frame: throughout the study completion up to one year (for every case must be done after 2 weeks from the start of treatment).]	Excludes those with comorbid conditions	
22	Hydroxychloroquine and Ivermectin for the Treatment of COVID-19 Infection NCT04391127 Mexico	RCT(parallel assignment) Treatment	Ivermectin 12 mg or 18mg (weight dependent) PO every 24 hours for one day. Subsequently this group will take two tablets of placebo 12 hrs after ivermectin ingestion and then one tablet of placebo each 12 hrs per 4 more days. Hydroxychloroquine: 400 mg PO every 12 hours for one day. Subsequently 200 mg every 12 hours per 4 more days. (only for patients with QTc < 500 ms)	Control group: Two tablets of placebo PO every 12 hours for one day. Subsequently one tablet of placebo every 12 hours per 4 more days.	**Primary:** (1) Mean days of hospital stay, (2) Rate of Respiratory deterioration, requirement of invasive mechanical ventilation or dead, (3) Mean of oxygenation index delta [Time Frame: Three months] **Secondary:** Mean time to viral PCR negativization [Time Frame: 5, 14, 21 and 28 days after the first positive PCR]	Ages 16 – 90, hospitalized with COVID-19 or suspected COVID-19 pneumonia	Double blind (Participant, Care Provider)
23	Efficacy, Safety and Tolerability of Ivermectin in Subjects Infected With SARS-CoV-2 With or Without	RCT (parallel assignment) Treatment	Ivermectin 12 mg / day for 3 days, in combination with paracetamol therapy	Placebo of ivermectin 12 mg / day for 3 days, in combination with standard paracetamol	Participants with a disease control status defined as no disease progression to severe. [Time Frame: 14 days]	Adults with asymptomatic, or with mild symptoms who are taking	Singe blind (care provider)

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
	Symptoms (SILVERBULLET) NCT04407507 Zapopan, Jalisco, Mexico		(500 mg QID) for 14 days	therapy (500 mg QID) for 14 days		outpatient treatment of the disease	
24	Efficacy of Subcutaneous Ivermectin With or Without Zinc and Nigella Sativa in COVID-19 Patients (SINZ-COVID-PK) NCT04407507 Lahore, Punjab, Pakistan	RCT(parallel assignment) Treatment	Three experimental groups: Sub-cutaneous injection ivermectin 200ug/kg body weight once every 48 hourly plus standard care Sub-cutaneous injection ivermectin 200ug/kg body weight once every 48 hourly with 80mg/Kg/day Nigella Sativa plus standard care Sub-cutaneous injection ivermectin 200ug/kg body weight once every 48 hourly with 20mg Zinc Sulphate 8 hourly plus standard care	Placebo drug plus standard care	**Primary:** qRT-PCR [Time Frame: 144 hours] **Secondary**: Severity of symptoms [Time Frame: 14 days]	Adults with a mild COVID-19 diagnosis, BMI 18-28 kg/m	Quadruple blind (Participant, Care Provider, Investigator, Outcomes Assessor)
25	Efficacy of Ivermectin in COVID-19 NCT04392713	RCT(parallel assignment) Treatment	Participants will be administered ivermectin (12 mg) with standard chloroquine regimen	Control group: only receive chloroquine as per existing policy of hospital	**Primary:** Negative PCR [Time Frame: 144 hours]	Ages 15 – 65, in good general health with no or mild to moderate symptoms of	

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
	Lahore, Punjab, Pakistan				**Secondary:** Need for mechanical ventilation [Time Frame: 4 weeks]	PCR confirmed COVID-19.	
26	Efficacy of Ivermectin in Adult Patients With Early Stages of COVID-19 (EPIC Trial) NCT04405843 Colombia	RCT(parallel assignment) Treatment	Ivermectin, 300 micrograms / kg, once daily for 5 days	Placebo	**Primary:** Time until resolution of symptoms **Secondary:** (1) Clinical condition on day 2, 5, 8,11, 15, 21, (2) Proportion of subjects with additional care, (3) Proportion of subjects who die, (4) Duration of additional care, (5) adverse events, (6) Proportion of subjects who discontinue intervention, (7) time to event, (8) duration of fever [Time Frame: 21 days]	Adults with PCR or antigen detected confirmed COVID-19 diagnosis and beginning of symptoms in the past 7 days	Quadruple blind (Participant, Care Provider, Investigator, Outcomes Assessor)
27	Efficacy and Safety of Ivermectin for Treatment and Prophylaxis of COVID-19 Pandemic NCT04668469 Benha, Egypt	RCT (parallel assignment) Treatment	Ivermectin plus standard care in Mild/Moderate COVID-19 Ivermectin plus standard care and steroids in Sever COIVD-19	Active comparator: hydroxychlorquine plus standard care in Mild/Moderate COVID-19	**Primary:** (1) number of participants with improvement of clinical condition (symptoms and signs), (2) Reduction of recovery time, hospital stay days and mortality rate **Secondary:** improvement of laboratory investigations and 2 consecutive negative PCR tests taken at least 48 hours apart. [Time Frame: 3 months]	Ages 18 – 80, with COVID-19	Triple (Participant, Care Provider, Investigator) Treatment was terminated at any time by a multidisciplinary team if a serious side effect occurred, which was attributed to the medications used
28	Efficacy and Safety of Ivermectin and	RCT (parallel assignment)	Two experimental groups:	3 placebo tablets	**Primary:** (1) Virological clearance, (2) Remission of	Ages 18-65, PCR COVID-19	Double blind

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
	Doxycycline in Combination or IVE Alone in Patients With COVID-19 Infection. NCT04407130 Bangladesh	Treatment	200 mcg/kg (12 mg tablet) ivermectin (IVERA) single dose and 200 mg stat doxycycline day-1 followed by 100mg doxycycline 12hrly for 4 day (i.e. day2-day5)+ Placebo one tablet D2-5 Ivermectin - 200 mcg/kg (12 mg tablet) once per day D1-D5 + Placebo two tablets D1 followed by Placebo one tablet D2-5		fever, (3) Remission of cough [Time Frame: within 7 days after enrollment] **Secondary:** (1) Patients requiring oxygen, (2) Patients failing to maintain SpO2 >93% despite oxygenation, (3) Number of days on oxygen support, (4) Duration of hospitalization, (5) All causes of mortality [Time Frame: within 14 days after enrollment]	confirmed diagnosis, at the enrollment having at least one of the following symptoms: Temp 37.5 C or above, Cough, Sore throat, Duration of illness ≤ 7 days, SpO2 >94%	
29	Effectiveness of Ivermectin and Doxycycline on COVID-19 Patients NCT04591600 Iraq	RCT (parallel assignment) Treatment	Ivermectin 200ug/kg PO per day for two days, and in some patients who needed more time to recover, a third dose 200ug/kg PO per day was given 7 days after the first dose. Doxycycline 100mg capsule PO every 12h per day was given for 5-10 days, based on the clinical improvement of patients.	Control group: standard care	**Primary:** (1) Mortality rate, (2) rate of progression disease **Secondary**: time to recovery [Time Frame: Up to 8 weeks]	Ages 16 – 86, COVID-19 patients at any stage of this disease	Single blind
30	Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in	RCT (parallel assignment) Prevention	Oral administration of ivermectin 200 mcg/kg	Placebo every week for seven weeks	**Primary:** Clinical development of covid-19 disease during the intervention period	Adults health works, COVID-19 negative	Quadruple blind

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
	Colombian Health Personnel (IveprofCovid19) NCT04527211 Cali, Valle Del Cauca, Colombia		every week for seven weeks		**Secondary:** (1) seroconversion, (2) hospitalization requirement, (3) intensive care unit requirement, (4) safety of the intervention [Time Frame: 8 weeks]		
31	Early Treatment With Ivermectin and LosarTAN for Cancer Patients With COVID-19 Infection (TITAN) NCT04447235 SAo Paulo, Brazil	RCT (parallel assignment) Treatment	single dose of 12mg of ivermectin on the day of the confirmed diagnosis of COVID-19, followed by losartan 50mg orally once daily for 15 consecutive days	Participants receive placebo	**Primary:** Incidence of severe complications due COVID-19 infection **Secondary:** (1) Incidence of Severe Acute Respiratory Syndrome, (2) adverse events, (3) overall survival [Time Frame: 28 days]	Adults with biopsy-proven diagnosis of previous cancer and diagnosed with active malignancy, with PCR confirmed COVID-19 diagnosis. Excludes severe conditions	Double blind (Participant, Care Provider)
32	COVidIvermectin: Ivermectin for Treatment of Covid-19 (COVER) NCT04438850 Italy and Spain	RCT (sequential assignment) Treatment	Two experimental groups: Ivermectin 600 µg/kg daily for 5 consecutive days (I_600) + placebo Ivermectin 1200 µg/kg daily at empty stomach with water for 5 consecutive days	Placebo	**Primary:** (1) SADR, (2) viral load **Secondary:** (1) trend viral load, (2) clinical resolution, (3) viral clearance, (4) virological clearance, (5) hospitalization rate, (6) severity score [Time Frame: varied, Day 7-30]	Adults with COVID-19 with a severity score < 3	Quadruple blind (Participant, Care Provider, Investigator, Outcomes Assessor)

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
33	Comparative Study of Hydroxychloroquine and Ivermectin in COVID-19 Prophylaxis NCT04384458 Fortaleza, Ceará, Brazil	RCT (parallel assignment) Prevention	Oral ivermectin dosage guidelines based on participant body weight, once on day for 2 consecutive days. This dose schedule should be repeated every 14 days for 45 days associated with 20 milligrams twice on day of active zinc	Active comparator: Oral hydroxychloroquine 400 mg twice a day on day 1, one 400 mg tablet on day 2, 3, 4, and 5. For the following 45 days active zinc will be taken twice daily and one 400 mg hydroxychloroquine tablet every 5 days	**Primary:** Proportion of participants who tested positive for SARS-CoV-2. **Secondary:** (1) Participants who developed mild, moderate, or severe forms of COVID-19, (2) Measurement of the QT interval, (3) Widening of the corrected QT interval or with changes in heart rate on the ECG, (4) Comparison of hematological and biochemical parameters, (5) Occurrence of adverse events, (6) Assessment of COVID-19 symptom severity, (7) Proportion of participants who discontinue study intervention, (8) Proportion of participants who required hospital care, (9) Proportion of participants who required mechanical ventilation [Time Frame: Post-intervention at day 52]	Ages 18 – 70, Health professionals working in areas of high risk for COVID-19 exposure and transmission.	
34	Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection	RCT (parallel assignment) Treatment	Ivermactin 6 mg 2 tab stat, cap Doxycycline 100 mg 1 cap BD 5 days	Placebo and standard treatment	**Primary:** (1) Number of Patients With Early Clinical Improvement, (2) Number of Participants With Late Clinical Recovery [Time Frame: 7, 12 days]	Adults with mild to moderate COVID-19	Results available Double (Participant, Investigator)

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
	NCT04523831 Bangladesh				**Secondary:** (1) Number of Patients Having Clinical Deterioration, (2) Number of Patients Remain Persistently Positive for RT-PCR of Covid-19 [Time Frame: 1 month, 14 days]		
35	A Study to Compare the Efficacy and Safety of Different Doses of Ivermectin for COVID-19 (IFORS) NCT04431466 São Carlos, São Paulo, Brazil	RCT (parallel assignment) Treatment	Four experimental groups for ivermectin: 100mcg / kg PO single dose 100mcg / kg PO on the first day, followed by 100mcg / kg PO after 72h Ivermectin 200mcg / kg PO single dose 200mcg / kg PO on the first day, followed by 200mcg / kg PO after 72h	Control group: standard treatment	**Primary:** Time to undetectable SARS-CoV-2 viral load in the nasopharyngeal swab **Secondary:** (1) Viral load variation in the nasopharyngeal swab, (2) Time to undetectable SARS-CoV-2 viral load in the nasopharyngeal swab, (3) Proportion of patients with undetectable SARS-CoV-2 viral load in the nasopharyngeal swab, (4) Proportion of patients with clinical improvement. [Time Frame: 7 after intervention]	Adults with COVID-19	
36	A Preventive Treatment for Migrant Workers at High-risk of COVID-19 NCT04446104	RCT (parallel assignment) Prevention	Four experimental groups: hydroxychloroquine tablet 400mg loading dose, followed by 200mg daily for 42 days	Active Comparator: Vitamin C tablet 500mg daily for 42 days	**Primary:** Laboratory-confirmed COVID-19 in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine)	Men residing in dormitory aged 21-60 years	

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
	Singapore		Ivermectin tablet 12mg single dose zinc tablet 80 mg/vitamin C 500mg daily for 42 days povidone-iodine throat spray (3 times daily) for 42 days		**Secondary:** (1) Acute respiratory illness in treatment arms, (2) Febrile respiratory illness in treatment arms, (3) Rate of hospitalization for COVID-19 and non-COVID-19 related indications in treatment arms, (4) Rate of oxygen supplementation and mechanical ventilation in treatment arms, (5) Duration of oxygen supplementation and mechanical ventilation in treatment arms, (6) Length of hospital stay in treatment arms, (7) Rate of laboratory-confirmed COVID-19 in treatment arms, (8) Adverse events and serious adverse events in control arm (Vitamin C), (9) Drug discontinuation due to adverse events in control arm (Vitamin C) [Time Frame: At the end of study dosing, which is day 42]		
37	A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh Bangladesh	Observation (case-only)	Ivermectin 200µgm/kg single dose + Doxycycline 100mg BID for 10days	Active comparator: Hydroxychloroquine 400mg first day then 200mg BID for 9days + Azithromycin 500mg daily for 5Days.	(1) Number of participants with "treatment success" determine by a negative RT PCR for COVID19, and (2) Number of participants with "adverse effects" determined by the existence of the pharmacological side effects	Ages 16 to 80 years, COVID-19 patients with mild to moderate severity	Results posted

	Trial Name/ NCT / Jurisdiction	Study Design	Intervention	Comparator(s)	Primary and Secondary Outcomes	Population	Notes
					of the particular drug during treatment. [Time Frame: 02/05/2020 to 05/06/2020]		
38	Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19 NCT04429711 Ramat-Gan, Israel	RCT (parallel assignment) Treatment	Ivermectin Oral Product 3mg Capsules, 12-15mg/ day for 3 days	Control group: placebo	(1) viral clearance at day 6, (2) viral shedding duration, (3) symptoms clearance time [Time Frame: Outcome will be determined till 14 days post intervention]	Ages 18 – 80, molecular confirmation of COVID-19.	Quadruple blind (Participant, Care Provider, Investigator, Outcomes Assessor)

List of Abbreviations

AHS: Alberta Health Services
C_{max} : maximum plasma concentration
CI: confidence interval
Cl : total body clearance
COVID-19: Coronavirus Disease 2019
FLCCC: Front Line COVID-19 Critical Care Alliance
HCQ: hydroxychloroquine
HIV: human immunodeficiency virus
ICU: intensive care unit
kg: kilograms
mg: milligrams
OR: Odds Ratio
PCR: polymerase chain reaction
RCT: randomized controlled trial
RNA: ribonucleic acid
RR: Risk Ratio
SARS-CoV-2: Sudden Acute Respiratory Syndrome – Coronavirus – 2
$t_{½}$: elimination half-life
$t_{1/2abs}$: absorption half-life
t_{ma}: time to reach C_{max}
µg: micrograms
µM: micromolar (µmol / litre)

Methods

Literature Search

A literature search was conducted by Lauren Seal from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published from 2019-2021, and included: Medline, PubMed, CINAHL, TRIP Pro, Google Scholar, Google, Clinicatrials.gov, United States Centers for Disease Control and Prevention, LitCOVID, World Health Organization, and MedRxiv. The full search strategy is included further in the appendix below. Briefly, the search strategy involved combinations of keywords and subject headings relating to the following concepts:

- COVID-19 / SARS-CoV-2
- Ivermectin

Articles identified by KRS in their search were pre-screened by the librarian and relevant articles were forwarded for further screening. Articles were first screened by title and abstract against the inclusion/exclusion criteria listed in Table 8 below. 114 articles were identified by KRS with references and abstracts provided for further review. 9 articles were identified *ad hoc* by the review team. 67 articles were excluded from the review in accordance with the inclusion/exclusion criteria stated below. Of the 54 included articles, 38 were ongoing clinical trials, 6 were grey literature, and 9 were primary literature.

Table 8. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- Any patient population - COVID-19 - Human study - Any intervention including ivermectin - Any comparator - Any outcome - Clinical Trial registered with clinicaltrials.gov - Systematic review +/- metanalysis, RCT (randomized & non-randomized), Observational studies, Case Report/Series - Published 2019-Current - English language - Any jurisdiction	- Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions - Respiratory viruses outside β-coronavirus family (eg. flu, RSV, adenovirus, rhinovirus) - Drugs other than ivermectin (incl. others in the avermectin family) - Non-human *in vivo* study - *In vitro* or *in silico* study - Editorial, commentary, narrative review, study protocol, conference abstract, poster - Referenced in an included meta-analysis

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

As described in the body of this report, the meta-analyses were assessed for quality with the AMSTAR-2 tool (Shea et al., 2017). The comments and score from the appraisal are included in Table 9 below.

Table 9. Critical appraisal comments and score for Lawrie (2021), Hill (preprint) and Padhy (2020).

Meta-analysis	Score	AMSTAR-2 Summary (Shea et al., 2017)
Lawrie (2020)	Critically Low	Did not explicitly state that the review methods were established before the review was conducted. Nor did the author use comprehensive literature search strategies (multiple databases, provided key word searches, etc.). The authors stated their inclusion of only RCTs and OCTs was due to other methodologies high risk for bias. While a colleague checked the data extraction, only one author performed the study selection and data extraction.

		The author provided a table to summarize the included studies that provided brief information on country, design (RCT or OCT), sample size, ivermectin dose and frequency, and risk of bias. There was no list of excluded studies or justification for the exclusions. The author reported that this meta-analysis did not receive funding for this work. The authors did not assess the potential impact of risk of bias in the individual studies on the results of the meta-analysis. Although a GRADE approach was used, there was no discussion of publication bias and the potential impact on the results. The author reported no conflicts of interest.
Padhy (2020)	Moderate	Research question and inclusion criteria included all PICO components (population, intervention, comparator, and outcome). Systematic review was registered, and protocol was written according to PRISMA-P guidelines. Authors did not explain why they were only including RCT and observational studies. Authors used partial comprehensive search strategies by searching multiple databases, exploring literature from references, and provided key word search strategies, search trials, justified publication restrictions. However, there was no mention of a consultation with experts within the field. There were three authors that performed the data extraction, but the number of authors to perform the study selection was not reported. There was no list of excluded studies or justification for the exclusions. There was a table the described the included studies in detail, including its patient characteristics, primary outcomes, secondary outcomes, country, and additional notes. The authors used a satisfactory risk of bias assessment for the included studies (ROBINS I). There was no reporting on whether this meta-analysis was funded. Authors utilized a GRADE approach to evaluate the quality of evidence which, as mentioned in the discussion, was determined to be very low quality. The authors reported no conflicts of interest.
Hill	Low	Components of PICO were mentioned in the inclusion criteria. Systematic review protocol was written according to PRISMA guidelines. Authors did not explain why they were only including RCT. There was a partial comprehensive literature search as there use of more than two databases, provided key words, justified restrictions, consulted experts and searched trial registries. However, there was no mention of a search of reference lists of studies included. There were two authors that performed the data extraction, but the number of authors to perform the study selection was not reported. There was no list of excluded studies or justification for the exclusions. The meta-analysis separates the included studies into two tables (ivermectin trials dosing on day 1 only and ivermectin trials with multi-day dosing) which described the studies: country, sample size, daily dose, duration, patients, intervention arm, comparator arm. Authors used a satisfactory risk of bias assessment for the included studies (Cochrane Risk of Bias Tool). The impact of the risk of bias for individual studies was not discussed. However, in the limitations section, Hill outlined the impact the limited quality of research could have on the evidence as a whole. There were no reported tests for publication bias for

		the included documents. No conflict of interests was reported. Funding was provided by Unitaid.

Table 10 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (Urwin, Gavinder & Graziadio, 2020; Viswanathan et al, 2012; Wynants et al., 2020; Brouwers et al., 2010).

Table 10. Narrative overview of the literature included in this review.

	Description
Volume	In the evidence review: 1 systematic review/meta-analysis was included (0 were pre-review); 3 RCTs were included (3 were pre-review); 5 observational studies were included (4 were pre-review). 6 pieces of grey literature from reputable sources were included. 38 registered clinical trials were included. Background information: 1 human pharmacokinetic study; 1 experimental *in vitro* study, 1 narrative review.
Quality	Overall, the evidence for this topic is of low-moderate quality. As with other clinical topics on COVID-19 the research is often opportunistic and hastily done, with limited planning to minimize sources of bias. The body of evidence is at high risk of confounding, as many studies investigated ivermectin as add-on therapy to a cocktail of medications to manage symptoms and limit viral replication. Small sample sizes, performance bias, short follow-up time, inappropriate study designs, further limit the usefulness of the available evidence on ivermectin.
Applicability	The majority of studies are from Southeast Asia and Latin America, both regions with notably different healthcare systems, population health statistics and epidemic dynamics compared to Alberta. However, ethnic and racial backgrounds have not been shown to be strong risk factors for COVID-19. It is likely that the evidence is applicable to the Alberta context. There was a sufficient body of evidence regarding COVID-19 for this topic; it was unnecessary to use evidence from other β-coronaviruses or respiratory viruses.
Consistency	The evidence is not consistent for any outcome of COVID-19 treatment (PCR positivity, symptom resolution, days in hospital, mortality.

Search Strategy

Medline/PubMed

1 exp Coronavirus/ or Coronavirus Infections/ or coronaviru*.mp. or "corona viru*".mp. or ncov*.mp. or n-cov*.mp. or "novel cov*".mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-CoV-2.mp. or SARSCoV-2.mp. or SARSCoV2.mp. or SARSCoV19.mp. or SARS-Cov-19.mp. or SARSCov-19.mp. or SARSCoV2019.mp. or SARS-Cov-2019.mp. or SARSCov-2019.mp. or "2019 ncov".mp. or 2019ncov.mp. or "severe acute respiratory syndrome*".mp. or "severe acute respiratory disease*".mp. or Severe Acute Respiratory Syndrome/ (90960)

2 Middle East Respiratory Syndrome Coronavirus/ (1458)

3 "middle east respiratory syndrome".mp. (2952)

4 mers.mp. (5593)

5 mers-cov.mp. (2350)

6 SARS Virus/ (3738)

7 Severe Acute Respiratory Syndrome/ (5405)

8 SARS.mp. (36366)

9 sars-cov.mp. (28489)

10 "severe acute respiratory syndrome".mp. (44304)

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (96278)

12 exp Ivermectin/ (6482)

13 ivermectin.mp. (8411)

14 stromectol.mp. (7)

15 eqvalen.mp. (1)

16 ivomec.mp. (109)

17 MK-933.mp. (13)

18 mectizan.mp. (153)

19 12 or 13 or 14 or 15 or 16 or 17 or 18 (8426)

20 11 and 19 (87)

21 limit 20 to (yr="2019 -Current" and english) (86)

CINAHL

S1 (MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR ("2019 ncov" OR 2019ncov OR Hcov*)) OR (COVID-19 OR COVID19 OR COVID-2019 OR COVID2019) OR (SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR

SARS-COV-2019 OR SARSCOV-2019) OR (MH "Severe Acute Respiratory Syndrome) OR "severe acute respiratory syndrome*" OR "severe acute respiratory disease*") 37,600

S2 (MH "SARS Virus") 355

S3 (MH "Middle East Respiratory Syndrome") OR (MH "Middle East Respiratory Syndrome Coronavirus")

659

S4 MERS OR mers-cov OR SARS OR sars-cov 4,729

S5 S1 OR S2 OR S3 OR S4 39,142

S6 ivermectin OR stromectol OR eqvalen OR ivomec OR MK-933 OR mectizan 15

Trip/Google Scholar/Google Advanced/clinicaltrials.gov/CDC

(covid-19 OR sars-cov-2 OR coronavirus OR "corona virus" OR "middle east respiratory syndrome" OR mers OR sars OR "severe acute respiratory syndrome") AND (ivermectin OR stromectol OR eqvalen OR ivomec OR "MK-933" OR mectizan) from:2019

LitCovid/WHO Database

(ivermectin OR stromectol OR eqvalen OR ivomec OR "MK-933" OR mectizan)

medrxiv

"(covid-19 OR sars-cov-2 OR coronavirus) AND (ivermectin OR stromectol OR eqvalen OR ivomec OR "MK-933" OR mectizan)" and posted between "01 Jan, 2019 and 11 Jan, 2021"

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