CADTH COVID-19 PANDEMIC

COVID-19 CADTH Health Technology Review

Ivermectin for the Treatment and Prevention of COVID-19

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To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation II instrument
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
CI	confidence interval
COVID-19	novel coronavirus disease 2019
C_{max}	maximum plasma concentration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IC_{50}	half-maximal inhibitory concentration
NCCET	National COVID-19 Clinical Evidence Taskforce
NIH	National Institutes of Health
PCT	prophylactic chemotherapy
RCT	randomized controlled trial
RNA	ribonucleic acid
ROBINS-I	risk of bias in non-randomized studies of interventions
RT-PCR	reverse transcription–polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SR	systematic review

Key Messages

- The primary studies identified in this report, including those within the systematic review, were found to have high risk of bias. Therefore, the very low quality of evidence from these studies preclude the ability to draw any strong conclusions as to whether ivermectin could reduce all-cause mortality, improve clinical symptoms, hospitalization, and viral clearance in patients with COVID-19.
- Evidence on the cost-effectiveness of ivermectin for the treatment and prevention of COVID-19 was not identified.
- With the current evidence, the included guidelines do not recommend the use of ivermectin for the treatment of COVID-19.

Context and Policy Issues

The novel coronavirus disease 2019 (COVID-19) is caused by a ribonucleic acid (RNA) virus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] In late 2019, the virus originally emerged from Wuhan in the central Chinese province of Hubei and quickly spread around the world creating the current pandemic that has threatened the health care system, devastated the economy, and disrupted people's normal lives in all countries.[1] Most people infected with SARS-CoV-2 are asymptomatic and have mild symptoms, which allows the virus to spread more readily.[1] Among the general population

with a positive test for COVID-19, 20% to 75% were asymptomatic.[2] The disease is initially presented with flu-like symptoms such as fever, cough, sore throat, headache, fatigue, muscle pain, and chest pain.[1] Collective data from Wuhan, China, revealed that 80.9% of cases were mild, with flu-like symptoms; 13.8% were severe, with pneumonia; 4.7% required admission to the intensive care unit due to respiratory failure or organ failures.[1] To date, the COVID-19 pandemic has killed more than 2 million people worldwide, and more than 19,000 people in Canada.[3-5]

While vaccines are being rolled out, researchers around the world continue to search for the effective control and therapeutic treatment for COVID-19. In an effort to manage the pandemic, many older drugs that had been approved for other types of treatment have been repurposed as potential treatments for COVID-19, more than a dozen of which including ivermectin have been registered for clinical trials.[1]

Ivermectin is an antiparasitic drug and has been approved in Canada for the treatment of strongyloidiasis (a disease caused by infection with roundworm or nematode) and onchocerciasis (also known as river blindness, a disease caused by infection with a parasitic worm).[6] In addition to its antiparasitic properties, ivermectin has also been shown in in vitro studies to have an antiviral effect against a number of viruses including SARS-CoV-2.[7] A recent in vitro study has shown that a single dose of ivermectin given to the SARS-CoV-2 transfected cell line at 2 hours post-infection was able to inhibit by more than 90% viral RNA release and 99% cell-associated viral RNA at 24 hours post-infection.[8] By 48 hours post-infection, ivermectin was able to reduce viral RNA by about 5,000-fold compared with the control.[8] The half-maximal inhibitory concentration (IC_{50}) of ivermectin in this study was found to be between 2.2 and 2.8 μm.[8] Since then, there has been increasing interest in ivermectin for the treatment of COVID-19 and more than 50 clinical trials are ongoing to study the effect of ivermectin for SARS-CoV-2 infection in humans.[9]

The aim of this report is to review the clinical effectiveness and cost-effectiveness of ivermectin for the treatment and prevention of COVID-19. This report also aims to identify evidence-based guidelines regarding the use of ivermectin for the treatment and prevention of COVID-19.

Research Questions

1. What is the clinical effectiveness of ivermectin for the treatment and prevention of coronavirus disease (COVID-19)?
2. What is the cost-effectiveness of ivermectin for the treatment and prevention of COVID-19?
3. What are the evidence-based guidelines regarding the use of ivermectin for the treatment and prevention of COVID-19?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE and Embase via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of

Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ivermectin and COVID-19. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2018 and January 5, 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Individuals with confirmed or suspected COVID-19 or those at risk of infection
Intervention	Ivermectin (used as a treatment or as a prophylactic, alone or in combination with other therapies)
Comparator	Q1 and Q2: No treatment, placebo, standard care, other active treatments (e.g., remdesivir, dexamethasone) Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., mortality, length of hospital stay, clinical symptoms, viral load, safety [e.g., adverse events]) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained) Q3: Recommendations regarding best practices (e.g., place in therapy, treatment protocols, appropriate patient populations and clinical settings, guidance related to which formulations are appropriate)
Study designs	HTAs, SRs, RCTs, non-randomized studies, economic evaluations, and evidence-based guidelines

COVID-19 = novel coronavirus disease 2019; HTA = heath technology review; RCT= randomized controlled trial; SR = systematic review.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2018. Systematic reviews (SR) in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included SRs. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[10] for SRs, the Downs and Black checklist[11] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument[12] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 334 citations were identified in the literature search. Following the screening of titles and abstracts, 314 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant

publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 16 publications were excluded for various reasons and 6 publications met the inclusion criteria and were included in this report. These comprised 1 SR, 1 randomized controlled trial (RCT), 2 non-randomized studies, and 2 evidence-based guidelines. Appendix 1 presents the PRISMA[13] flow chart of the study selection.

A list of preliminary reports that have not been peer-reviewed and do not meet the inclusion criteria of this report are provided in Appendix 5.

Summary of Study Characteristics

The detailed characteristics of the included SR,[14] (Table 2) primary studies[15-17] (Table 3) and the National COVID-19 Clinical Evidence Taskforce (NCCET)[18] and the National Institutes of Health (NIH)[19] guidelines (Table 4), are presented in Appendix 2.

Study Design

The included SR[14] included 4 observational studies, 3 with a control arm and 1 without a control arm. The literature search was performed from 5 main databases from database inception to August 31, 2020. The risk of bias of the included studies was assessed using the risk of bias in non-randomized studies of interventions (ROBINS-I). The quality of the evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The random-effects model meta-analysis was used to provide the summary estimates.

The included primary studies comprised 1 RCT,[15] 1 retrospective chart review,[16] and 1 retrospective databases review.[17] The RCT[15] was a double-blind, parallel, 3-arm (1:1:1), placebo-controlled trial. One retrospective study[16] reviewed hospitalized patients charts between March 10th and 30th of 2020. Another retrospective study[17] conducted a database review of countries with routine mass drug administration of prophylactic chemotherapy (PCT). None of the studies reported sample size calculations to detect a clinically relevant treatment effect.

Both included guidelines[18,19] were developed by multidisciplinary guideline committees, which consisted of health care professionals who were experts in the areas of interest. The guidelines used systematic methods to search for, select, and synthesize evidence. The recommendations in both guidelines were evidence-based and consensus based, and were rated based on the certainty and the strength of the evidence. The NCCET guideline[18] used the GRADE approach to assess and rate the quality of evidence, and the strength of recommendations was rated as “Strong for” for highest, or “Consensus statement” for lowest, quality of evidence. Each recommendation in the NIH guideline[19] was rated with a letter A, B, or C for strong, moderate, or weak, respectively, based on the quality of evidence. As the clinical information is quickly evolving, both guidelines are kept at a living status so that the recommendations are frequently updated based on the latest published research findings.

Country of Origin

The included SR was conducted by authors in India.[14] The included primary studies were conducted by authors from Bangladesh,[15] Spain,[16] and the US.[17] The included guidelines were conducted by authors from Australia[18] and the US.[19]

Patient Population

The included SR[14] included studies with adult hospitalized patients with mild (56%), moderate to severe (26%), symptomatic (14%), and asymptomatic (4%) cases of COVID-19. Patients in the included studies had a mean age of 53 years with about 60% being male. Most patients had 1 or more comorbidities like diabetes, hypertension, or bronchial asthma. A total number of 631 patients were included in the analysis.

The RCT[15] included 72 hospitalized adult patients with COVID-19. The COVID-19 severity status of included patients was not reported. The mean age of patients was 42 years and 46% were male. The mean duration of illness before assessment was 3.83 days. Patients with chronic illnesses, who were pregnant or lactating, were excluded from the study.

One retrospective study[16] reviewed the hospital charts of 26 patients diagnosed with COVID-19. The COVID-19 severity status of included patients was not reported. The mean age of patients was 49 years and 65% were male.

Another retrospective study[17] reviewed 2 publicly available databases of countries that routinely deployed mass drug administration of PCT including ivermectin to people. Information about PCT was obtained from the WHO data bank and the COVID-19 cases were obtained from Worldometer. Details of the patient populations was not reported in this study. Only cases among a subset of African countries were graphically reported.

The target populations in the NCCET[18] and the NIH[19] guidelines are people with diagnosed or suspected COVID-19. The intended users of both guidelines are health care workers responsible for the care of patients with COVID-19.

Interventions and Comparators

The SR[14] included studies comparing ivermectin as add-on therapy with usual care only (i.e., hydroxychloroquine and azithromycin, doxycycline, or N-acetylcysteine and atorvastatin). The dose of ivermectin varied between 150 and 200 mcg/kg body weight administered as a single dose. In one study, 13 patients received a second dose of ivermectin. The follow-up period was not reported.

The RCT[15] had 3 arms of comparison: ivermectin alone, ivermectin plus doxycycline, and placebo. In the ivermectin-alone group, patients were given 12 mg once daily for 5 days. In the ivermectin plus doxycycline group, patients were treated with 12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 hours for the next 4 days. The treatment regimen in the placebo group was not reported. Patients were followed up until the test result was negative.

The retrospective hospital chart review[16] compared ivermectin as add-on therapy to immune-suppressant drugs (i.e., corticosteroids or tocilizumab) and standard of care versus control. A single dose of ivermectin was administered at 200 mcg/kg body weight. All patients received hydroxychloroquine, azithromycin, and lopinavir/ritonavir. Patients were followed up 8 to 10 days after treatment.

The retrospective study[17] that reviewed databases of countries that routinely deployed mass drug administration compared different types of PCT for parasitic infections including PCT using ivermectin, PCT using other drugs, and no PCT. Dosages of ivermectin or other treatments were not reported.

The interventions considered in both guidelines[18,19] were corticosteroids, antiviral drugs, antimalarial drug, antiparasitic drug such as ivermectin, and many others.

Outcomes

The outcomes considered by the SR[14] were all-cause mortality, time to discharge from the hospital, time to viral clearance assessed by reverse transcription–polymerase chain reaction (RT-PCR), and clinical improvement assessed by the need for respiratory support.

The outcomes considered by the RCT[15] were time to viral clearance assessed by RT-PCR, clinical symptoms (i.e., fever, cough, and sore throat), duration of hospitalization, and all-cause mortality. Safety outcomes were adverse events and discontinuation of the study drug.

The post-treatment clinical and safety outcomes considered by retrospective chart review study[16] were viral clearance, symptom improvement, hospitalization, proportion of patients remaining in the intensive care unit, and serious adverse events.

The incidence of COVID-19, expressed as cases per 100,000 people, was the outcome of the retrospective databases review study.[17]

Both included guidelines[18,19] considered all the clinical and safety outcomes of the therapeutic management of patients with COVID-19.

Summary of Critical Appraisal

The detailed quality assessments of the included SR[14] (Table 5), primary studies[15-17] (Table 6), and guidelines[18,19] are presented in Appendix 3.

The included SR[14] was explicit in its research questions and inclusion criteria for the review, selection of study design for inclusion, and comprehensive literature search strategy. It was unclear if the study selection was performed in duplicate; however, 3 reviewers independently extracted and assessed the quality of data. The SR had a protocol published prior to the conducting of the review. The SR did not report the sources of funding of the studies included in their review and did not provide a list of excluded studies. The SR described the characteristics of the included studies in adequate detail, used appropriate techniques to assess the risk of bias of the included studies (i.e., ROBINS-I was used to assess the risk of bias in non-randomized studies), used appropriate methods to combine the results (i.e., random-effects model meta-analysis), accounted for the risk of bias in individual studies when interpreting or discussing the results, and reported conflicts of interest, as well as the source of funding received for conducting the review. Overall, the included SR was of high methodological quality.

The included RCT[15] clearly described the objective, the main outcomes, the intervention of interest, and the main findings. However, the study did not clearly describe the characteristics of the patients included in the study and it was unclear if the baseline characteristics were balanced between groups. Thus, residual confounding factors might not have been identified and controlled. Although the trial was a double-blind, controlled RCT, the lack of reporting about the method of random sequence generation and allocation concealment may introduce a high risk of selection bias. Performance and detection biases were minimized by the double-blind design of the trial. With a small sample size of patients (N = 72; 24 patients per group) enrolled from one hospital, it was unlikely that the participants were representative of the entire population from which they were recruited.

The study did not clearly describe statistical methods used in data analysis and did not perform sample size calculation to determine the number of participants needed to detect a clinically relevant effect. Overall, the methodological quality of the included RCT was very low.

The included retrospective chart review study[16] had several limitations regarding reporting, internal validity, external validity, and retrospective design. The study did not clearly describe the main outcomes in the method section, did not identify and adjust for confounders, and did not provide estimates of the random variability in the data (e.g., 95% confidence interval [CI]) for the main outcomes. The study sample size was small (N = 26; 13 patients per group), suggesting that the participants were likely not representative of the entire population from which they were recruited. Additionally, a sample size calculation was not performed and it remains unclear if the study was adequately powered to detect clinically meaningful differences. The study may have a high risk of selection bias, detection bias, and reporting bias. Overall, the methodological quality of this study was very low.

The included retrospective database review study[17] also had several limitations regarding reporting, internal validity, external validity, and retrospective design. The study did not provide the characteristics of the populations or countries investigated and the dosages or treatment durations of ivermectin. Confounding factors were not identified and adjusted as the comparisons were made between different countries. The study did not report the sample sizes and the authors acknowledged that sizes of the 3 samples varied greatly. No actual numerical values and the random variability in the data for the main outcome were reported. The study may have a high risk of selection bias and detection bias. Overall, the methodological quality of this study was very low.

Both included guidelines[18,19] were explicit scope and purpose (i.e., objectives, health questions, and populations), and had clear presentation (i.e., specific and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). Regarding stakeholder involvement, the guidelines clearly defined target users and the development groups included individuals from all relevant professional groups; however, it was unclear if the views and preferences of the target populations were sought in the NIH guideline.[19] For rigour of development, both guidelines explicitly reported details of systematic searches for evidence, criteria for selecting evidence, strengths and limitations of the body of evidence, methods of formulating the recommendations, and health benefits, side effects, and risks in formulating the recommendations. Both guidelines were posted on its website and were regularly updated based on the latest published research findings and evolving clinical information. For applicability, the guidelines were explicit in terms of facilitators and barriers to application, advice and/or tools on how the recommendations can be put into practice, and monitoring and/or auditing criteria. It was unclear if the resource (cost) implications of applying the recommendations have been considered. For editorial independence, the guidelines reported that the funding bodies had no influence on the content of the guidelines. The competing interests of the guideline development group members were reported. Overall, both included guidelines were of high methodological quality.

Summary of Findings

The main findings and authors' conclusions of the SR[14] (Table 8), primary studies[15-17] (Table 9), and guidelines[18,19] are presented in Appendix 4.

Clinical Effectiveness of Ivermectin

All-Cause Mortality

The meta-analysis of data from 3 observational studies in the SR[14] showed a significant reduction in all-cause mortality with ivermectin (200 mcg/kg, single dose) as add-on treatment compared to usual care only, such as hydroxychloroquine and azithromycin, doxycycline, or N-acetylcysteine and atorvastatin. The overall pooled odds ratio was 0.53 (95% CI 0.29 to 0.96); P = 0.04. It was estimated that ivermectin was associated with 54 fewer deaths per 1,000 (95% CI, 3 fewer to 85 fewer). The quality of the evidence was very low, as judged by authors of the SR.

The RCT[15] found no deaths during the course of the study in any of the ivermectin alone, ivermectin plus doxycycline, and placebo groups.

Clinical Improvement

The meta-analysis of data from 3 observational studies in the SR[14] showed that adding ivermectin (200 mcg/kg, single dose) resulted in a significant clinical improvement assessed by the need for respiratory support compared to usual care only, such as hydroxychloroquine and azithromycin, doxycycline, or N-acetylcysteine and atorvastatin. The overall pooled odds ratio was 1.95 (95% CI, 1.09 to 3.49); P = 0.02. It was estimated that ivermectin was associated with 61 more patients improved per 1,000 (95% CI, 12 more to 91 more). The quality of the evidence was very low, as judged by authors of the SR.

The results from the RCT[15] showed no significant differences between a 5-day course of ivermectin alone (12 mg once daily for 5 days) and placebo or between ivermectin plus doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 hours for the next 4 days) and placebo in the proportion of patients who had improvement in fever (P = 0.09; P = 0.35), cough (P = 0.23; P = 0.18), and sore throat (P = 0.09; P = 0.35) from the day of enrolment to 5-day post-treatment.

The retrospective chart review study[16] found no significant difference between add-on ivermectin therapy (200 mcg/kg) group and the control group in clinical improvement 8 to 11 days after treatment (69.2% versus 76.9%; P > 0.999). Clinical improvement was not defined in this study.

Hospitalization

The SR[14] included 3 studies comparing ivermectin add-on therapy (200 mcg/kg, single dose) to non-ivermectin groups for hospitalization. Meta-analysis was not possible because of the different data reported. One study found that the ivermectin group had a significantly lower mean time of hospital stay than the non-ivermectin groups (7.62 ± 2.75 days versus 13.22 ± 5.90 days; P = 0.00005). The other 2 studies found no significant difference in time to discharge from hospital between groups.

The RCT[15] found no significant differences in the mean duration of hospitalization between a 5-day course of ivermectin alone (12 mg once daily for 5 days) and placebo (9.6 days versus 9.7 days; P = 0.93) or between ivermectin plus doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 hours for the next 4 days) and placebo (10.1 days versus 9.7 days; P = 0.93).

The retrospective chart review study[16] found no significant differences between the add-on ivermectin therapy (200 mcg/kg) group and the control group in the proportion of patients

discharged from the hospital (53.8% versus 46.1%; P = 1.000), no significant differences in the proportion of patients who remained in hospital (30.8% versus 30.8%; P = 1.000), or stayed in the intensive care unit (15.4% versus 23.1%; P = 1.000) after 8 to 11 days of treatment.

Time to Viral Clearance

The SR[14] included 2 studies having time to viral clearance as an outcome. In one study, the median time to viral clearance was significantly lower in the ivermectin group compared to the non-ivermectin group (7 days versus 12 days; P = 0.001). The other study did not find any significant difference between the 2 groups.

The findings of the RCT[15] showed that the mean duration for viral clearance (i.e., negative test) was significantly shorter for the 5-day ivermectin group (9.7 days; 95% CI, 7.8 to 11.8 days) compared to placebo (12.7 days; 95% CI, 11.3 to 14.2 days); P = 0.02. Similarly, the proportion of patients at risk for COVID-19 (i.e., remaining positive test) was significantly reduced in the 5-day ivermectin group on day 7 (P = 0.03) and day 14 (P = 0.02) compared to placebo. There was no significant difference for viral clearance between a single dose of ivermectin plus doxycycline and placebo (P = 0.27).

The retrospective chart review study[16] found no significant difference between ivermectin and the control groups in the proportion of patients remaining positive in the COVID-19 test performed between 3 and 5 days after treatment (38.5% versus 30.8%; P = 1.000).

Incidence of COVID-19

The retrospective databases review study[17] found that countries that deployed mass drug administration of PCT with ivermectin had a significantly lower incidence of COVID-19 compared to countries with no PCT (P < 0.01). Similarly, a subset of African countries that routinely used ivermectin in their PCT against parasitic infections had significantly lower incidences of COVID-19 compared to countries with no PCT (P ≤ 0.05). There was a statistically significant correlation between PCT with ivermectin and a lower incidence of COVID-19 (P = 0.017) among African countries.

Adverse Events

The RCT[15] reported no serious drug-related adverse events in all patients. The retrospective chart review study[16] found no significant difference in the proportion of patients having severe adverse events between groups.

Cost-Effectiveness of Ivermectin

No studies regarding the cost-effectiveness of ivermectin for the treatment and prevention of COVID-19 were identified; therefore, no summary can be provided.

Guidelines Regarding the Use of Ivermectin for the Treatment and Prevention of COVID-19

The NCCET guideline[18] does not recommend ivermectin for the treatment of COVID-19 ("Not recommended") based on very low-quality evidence.

The NIH guideline[19] also recommends against the use of ivermectin for the treatment of COVID-19 (A, strong recommendation) based on level III evidence (i.e., expert opinion).

Limitations

Although the included SR[14] was well-conducted, the included primary studies provided very low-quality evidence. They were primarily small observational in design, with potential confounders. Of the included primary studies in the SR, 3 have not been peer-reviewed (i.e., preprints) and one study had no control arm. Meta-analysis was performed with 3 studies,2 of which were preprints. The RCT[15] and the retrospective chart review study[16] had small sample sizes to draw any solid conclusions and potential confounders were not identified and adjusted in the analysis, thus providing low-quality evidence. The retrospective database review study[17] was poorly conducted, with potential confounders and imbalanced sample sizes among groups. The period of investigation was short (i.e., a few months in 2020) to accurately determine an association between the incidence of COVID-19 and prophylactic chemotherapy. The evidence provided from this study was also of very low quality. The collected limitations of the included studies in this report preclude any definitive conclusions regarding the use of ivermectin for the treatment and prevention of COVID-19. The findings are therefore not generalizable to the Canadian context. Likewise, the included guidelines[18,19] currently do not recommend ivermectin for the treatment of COVID-19 because of the lack of strong evidence. Of note, the dose of ivermectin used in the included studies, which was the approved dose for parasitic infections, may not provide sufficient bioavailability against SARS-CoV-2 as shown in the in vitro study;[8,20] that may be one of the reasons that the effectiveness of ivermectin for COVID-19 treatment was not consistently observed in the included studies. The IC_{50} of ivermectin in the in vitro study was 2.2 to 2.8 μM, which is more than 35 times the maximum plasma concentration (C_{max}) after a fasted oral administration of an approved dose of ivermectin for the treatment of parasitic infections (i.e., 150 to 200 mcg/kg), reaching a C_{max} of 0.033 μM in the plasma and 0.087 μM in the lung.[20] Even with 10 times higher than the approved dose, the predicted Cmax in the lung was 0.820 μM, which is much lower than the in vitro IC_{50}.[20] Doses of ivermectin used in the included studies in this report were between 150 to 200 mcg/kg or 12 mg single dose; thus, the bioavailability of ivermectin may be far less compared to that observed in vitro against SARS-CoV-2 and the likelihood of a positive result of ivermectin in a trial is low with the approved dose. Novel formulations using microtechnology- and nanotechnology-based systems have been proposed to optimize ivermectin's bioavailability and to effectively inhibit SARS-CoV-2 in vivo.[21]

Conclusions and Implications for Decision- or Policy-Making

One SR[14] and 3 primary studies (one RCT[15] and two observational studies[16,17]) were included to address the clinical effectiveness of ivermectin for the treatment and prevention of COVID-19. No studies regarding the cost-effectiveness of ivermectin for the treatment and prevention of COVID-19 were identified. Two well-conducted guidelines — one from Australia[18] and one from US[19] — were identified. The primary studies identified in this report including those within the SR were found to have high risk of bias, thus producing a very low quality of evidence that preclude the ability to draw any strong conclusions as whether ivermectin could reduce all-cause mortality, improve clinical symptoms and hospitalization, and enhance viral clearance in patients with COVID-19. The decision for the use of ivermectin to treat COVID-19 is currently discouraged by the included guidelines due to lack of strong evidence. It is possible that the inconsistency in the observed efficacy of ivermectin in recent human studies was in part due to insufficient concentration of the drug reached in the plasma of patients when the approved dose for parasitic infections was

used to treat COVID-19. Well-conducted, dose-response trials are needed to provide reliable conclusions regarding the benefit and harms of ivermectin for the treatment and prevention of COVID-19. Until then, interpretations of existing evidence in this report should be taken with caution.

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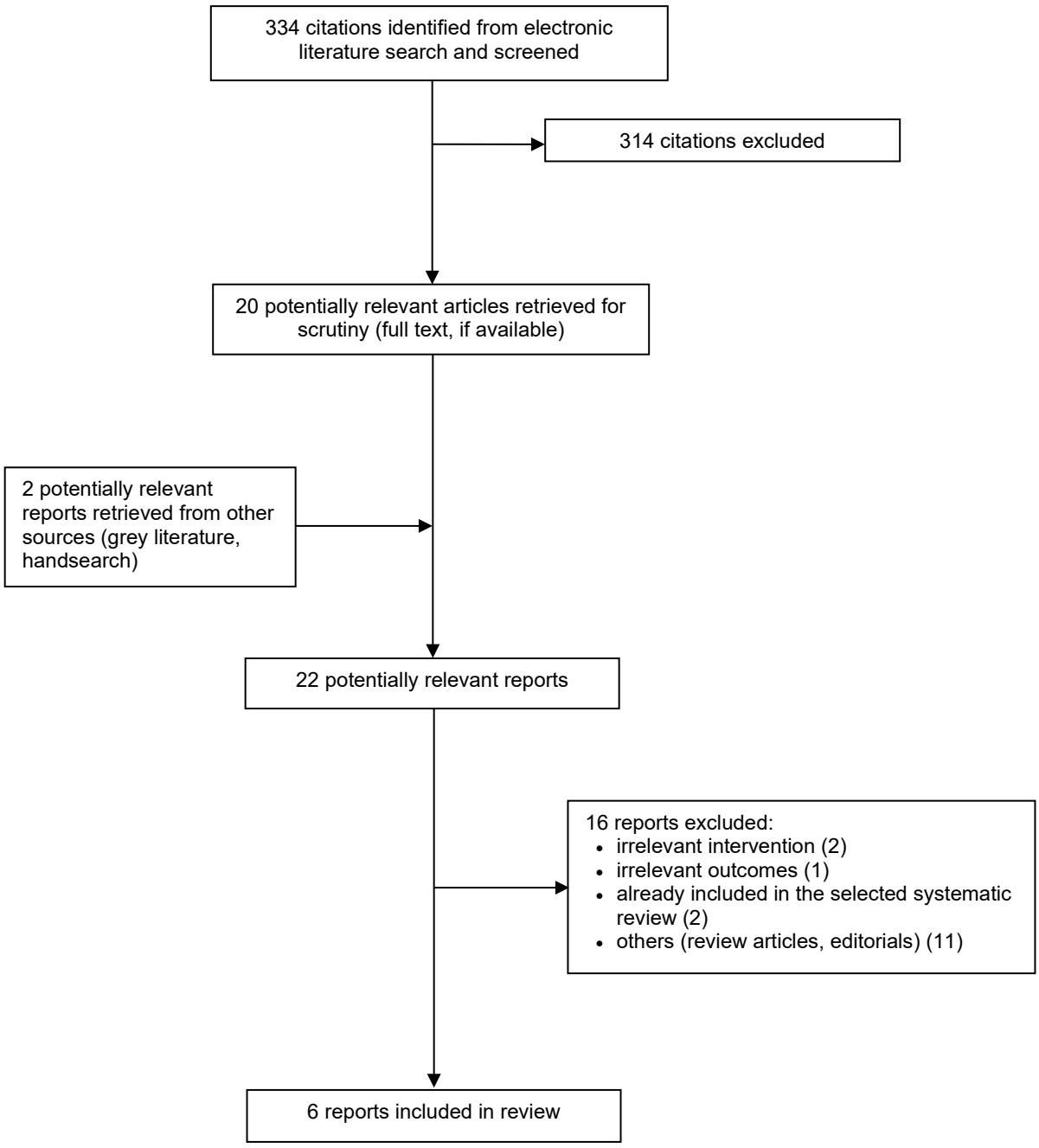
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

First author, publication year, country, funding	Objectives, types and numbers of primary studies included quality assessment tool, databases and search date	Patient characteristics	Interventions and comparators	Outcomes and follow-up
Padhy et al. (2020)[14] India Funding: Not reported	Objective: To determine the therapeutic potential of ivermectin for the treatment of COVID-19 as add-on therapy Total 4 observational studies (N = 631 patients); 3 with control arm and 1 without control arm Quality assessment tool: ROBINS-I Grade of evidence: GRADE was used to assess the quality of the evidence Databases: PubMed, Embase, the Cochrane Library, SCOPUS, and Web of Science from their dates of inception to August 31, 2020 Data analysis: Random-effects meta-analysis	Adult patients with mild and moderate-to-severe cases of COVID-19 Comorbidities: Most patients had one or more comorbidities such as diabetes, hypertension, or bronchial asthma COVID-19 severity status: Mild, moderate-to-severe, asymptomatic, symptomatic Mean age: 53.3 years % Male: 59.5	Ivermectin (n = 397) • 233 mild cases • 104 moderate-to-severe cases • 11 asymptomatic • 49 symptomatic No ivermectin (n = 234) • 121 mild cases • 57 moderate-to-severe cases • 14 asymptomatic • 42 symptomatic Ivermectin dose: 200 mcg/kg, single dose. In one study, 13 patients received second dose of ivermectin Other therapies: hydroxychloroquine and azithromycin, doxycycline, or N-acetylcysteine and atorvastatin	Primary outcome: • Mortality Secondary outcomes: • Time to discharge • Clinical improvement (assessed by the need for respiratory support) • Viral clearance (assessed by RT-PCR) Follow-up: NR

COVID-19 = novel coronavirus disease 2019; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NR = not reported; ROBINS-I = risk of bias in non-randomized studies of interventions; RT-PCR = reverse transcription–polymerase chain reaction.

Table 3: Characteristics of Included Primary Clinical Studies

First author, publication year, country, funding	Study design and analysis	Population characteristics	Intervention and comparator(s)	Clinical outcomes and follow-up
Ahmed et al. (2020)[15] Bangladesh Funding: Beximco Pharmaceutical Ltd., Bangladesh	Double-blind, parallel, 3 arms (1:1:1), placebo-controlled RCT Statistical analysis: Reported 95% CI and P values Sample size calculation: NR	Hospitalized adult patients diagnosed positive for COVID-19 (N = 72) COVID-19 severity status: NR Exclusion: Patients with chronic illnesses, were pregnant, or lactating	• Ivermectin alone (n = 24; 12 mg once daily for 5 days) • Ivermectin + doxycycline (n = 24; 12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 hours for the next 4 days)	Primary outcomes: • Time required for viral clearance (assessed by RT-PCR) • Remission of fever (≥ 37.5oC) and cough within 7 days Secondary outcomes: • Failure to maintain an SpO2 > 93%

First author, publication year, country, funding	Study design and analysis	Population characteristics	Intervention and comparator(s)	Clinical outcomes and follow-up
		Mean age: 42 years % Male: 46 Mean duration of illness before assessment: 3.83 days	• Placebo (n = 24; treatment not reported)	• Duration of hospitalization • All-cause mortality Safety: • AEs • Discontinuation of the study drug Follow-up: Until test-negative
Camprubi et al. (2020)[16] Spain Funding: The authors declared that they did not receive any specific funding	Retrospective chart review between March 10th and 30th 2020 in a hospital clinic in Barcelona, Spain Statistical analysis: Categorical variables were compared using chi-square test or Fisher's exact test; continuous variables were compared using Mann-Whitney-Wilcoxon test Sample size calculation: NR	Hospitalized patients diagnosed positive for COVID-19 (N = 26) COVID-19 severity status: NR Mean age: 43 years (41 to 49 years) in ivermectin group; 54 years (48 to 58 years) in control group % Male: 69.2% in ivermectin group; 61.5% in the control group	• Ivermectin (n = 13; 200 mcg/kg, single dose, plus immune-suppressant drugs such as corticosteroids or tocilizumab, and standard or care) • Control n = 13; (immune-suppressant drugs, and standard or care All patients received hydroxychloroquine, azithromycin, lopinavir/ritonavir	• Severe AEs • Positive test after 3 to 5 days of treatments • Improvement after 8 to 11 days of treatments • Discharged after 8 to 11 days of treatments • Remained in hospital after 8 to 11 days of treatments • Remained in ICU after 8 to 11 days of treatments
Hellwig and Maia (2020)[17] US Funding: NR	Retrospective databases review of data from countries that routinely deploy PCT using drugs including ivermectin From 2 publicly available databases, countries were grouped into 3 categories: those had ivermectin in their PCT, PCT treatment without ivermectin, and no PCT Statistical analysis: significance was adjusted using the Bonferroni method Sample size calculation: NR	NR	• Ivermectin in PCT • Other PCT • No PCT	Incidence of COVID-19

AE = adverse event; COVID-19 = novel coronavirus disease 2019; ICU = intensive care unit; NR = not reported; PCT = prophylactic chemotherapy; RCT = randomized controlled trial; RT-PCR = reverse transcription–polymerase chain reaction; SpO_2 = oxygen saturation.

Table 4: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
NCCET (2020)[18]						
Intended users: Individuals responsible for the care of people with COVID-19 Target population: People with diagnosed or suspected COVID-19	Clinical management and care of people with suspected or confirmed COVID-19	Clinical efficacy and safety outcomes related to treatments, chemoprophylaxis, and care of patients with COVID-19	Key clinical questions in the management and care of people with COVID-19 were identified. Systematic methods were used to search for evidence, selection, and synthesis.	The risk of bias was assessed using the Cochrane Risk of Bias 2.0 assessment tool for RCTs, and the ROBINS-I risk of bias assessment tool for non-RCTs. The GRADE approach was used for assessing and rating the quality of evidence. The strength of the recommendation was rated based on the level of certainty of the evidence.[a]	The Evidence Review Team drafted the initial recommendations, which were then discussed, revised, and agreed on by the relevant guideline panels, approved by the Guideline Leadership Group, and endorsed by the Steering Committee. The guideline panels consisted of clinicians with clinical expertise relevant to the specific aspect(s) of care.	The guideline recommendations were reviewed and approved by a Steering Committee that was comprised of a representative from each of the member organizations the Chair of the National Guidelines Leadership Group and a representative of Cochrane Australia (Taskforce Secretariat).
NIH (2020)[19]						
Intended users: Health care workers who care for patients with COVID-19 Target population: Patients with COVID-19	Therapeutic management and care of patients with COVID-19	All clinical outcomes and safety related to the treatment and care of patients with COVID-19	Systematic methods were used to search for evidence and selection. Available data were critically reviewed and synthesized to develop recommendations.	Evidence was assessed based on the source of data, the study design, the quality and suitability of the methods, the number of participants, and the effect sizes. Each recommendation was rated with 2 letters: a letter (A, B, or C) indicates the strength of the recommendation[b] and a Roman numeral (I, II, or	Recommendations were developed by working groups of panel members with expertise in the area of each section. The working groups were responsible for reviewing and synthesized the available data. Recommendations were made based on	The panel members include representatives from federal agencies, health care and academic organizations, and professional societies. The guidelines are continuously updated based on the latest published research findings and evolving clinical information.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
				III) indicates the quality of the evidence[c]	scientific evidence and expert opinion.	

COVID-19 = novel coronavirus disease 2019; GRADE = The Grading of Recommendations Assessment, Development and Evaluation; NCCET = National COVID-19 Clinical Evidence Taskforce; NIH = National Institutes of Health; RCT = randomized controlled trial; ROBINS -I = risk of bias in non-randomized studies of interventions.

[a] Strength of Recommendation:

Strong for: Moderate- to high-certainty evidence suggests that benefits in critical outcomes clearly outweigh the reported harms.

Strong against: Moderate- to high-certainty evidence suggests harms outweigh benefits.

Conditional for: Moderate- to high-certainty evidence suggests equivalent benefits and harms, patients would mostly want to receive the practice, and there is no significant resources implication in doing so.

Conditional against: Moderate- to high-certainty evidence suggests equivalent benefits and harms, but there is expected large variation in patients' preference to receive this practice or important resource implications.

Consensus statement: Evidence is absent or of insufficient certainty.

[b] Strength of Recommendation:

A: Strong recommendation for the statement.

B: Moderate recommendation for the statement.

C: Optional recommendation for the statement.

[c] Quality of Evidence for the Recommendation:

I: One or more randomized trials with clinical outcomes and/or validated laboratory end points.

II: One or more well-designed, non-randomized trials or observational cohort studies.

III: Expert opinion.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Quality Assessment of Systematic Review Using AMSTAR 2 Checklist[10]

Item	Padhy et al. (2020)[14]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes (A protocol was written according to PRISMA-P guidelines and registered in PROSPERO)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes (RCTs and observational studies reporting the use of ivermectin as add-on therapy in COVID-19 patients in the English language)
4. Did the review authors use a comprehensive literature search strategy?	Yes (5 databases were used)
5. Did the review authors perform study selection in duplicate?	Unclear (Not reported)
6. Did the review authors perform data extraction in duplicate?	Yes (3 reviewed authors independently and extracted and assessed the quality of the data)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Yes (Patient characteristics and dosages of treatment were described in adequate detail)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (ROBINS-I was used to assess the risk of bias in non-randomized studies)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes (Cochrane Program Review Manager 5.3 software was used for the meta-analysis. Random-effects modelling was used for data synthesis)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No (This was due to the limited number of included studies whose quality was very low)
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes (I^2 values were provided for statistical heterogeneity)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Not applicable (Only 3 studies were included in the meta-analysis)

Item	Padhy et al. (2020)[14]
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes (The authors declared that there was no conflict of interest)

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; COVID-19 = novel coronavirus disease 2019; PICO = Population, Intervention, Comparator, Outcomes; PRISMA-P = Preferred Reporting Items for Systematic review and Meta-Analysis Protocols; RCT = randomized controlled trial; ROBINS-I = risk of bias in non-randomized studies of interventions.

Table 6: Quality Assessment of Clinical Studies Using the Downs and Black Checklist[11]

Item	Ahmed et al. (2020)[15]	Camprubi et al. (2020)[16]	Hellwig and Maia (2020)[17]
Reporting			
1. Is the hypothesis/aim/objective of the study clearly described?	Yes (Determined the rapidity of viral clearance and safety of ivermectin among adult hospitalized patients with COVID-19)	Yes (Evaluated the efficacy of standard doses of ivermectin in severe COVID-19 patients)	Yes (Compared the incidence of COVID-19 between countries with routine mass drug administration of prophylactic chemotherapy with and without ivermectin)
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes (Outcomes were well described in the Methods section)	No (Outcomes were only reported in the Results section)	Yes (Main outcome was incidence of COVID-19)
3. Are the characteristics of the patients included in the study clearly described?	No (Only mean age, gender, and duration of illness before assessment were provided)	Yes	No (Only incidence was searched from databases)
4. Are the interventions of interest clearly described?	Yes (Dosage and duration of treatment of ivermectin were provided)	Yes (Dosage of treatment of ivermectin were provided)	No (No description on treatment dosage or duration of ivermectin)
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	No (Details of patient characteristic were not clearly described)	No (List of principal confounders was not provided)	No
6. Are the main findings of the study clearly described?	Yes	Yes	Yes
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes (95% CI was provided)	No (No standard error, standard deviation, or CI was reported)	No (No standard error, standard deviation, or CI was reported)
8. Have all important adverse events that may be a consequence of the intervention being reported?	No (Only mentioned that none of the patients had serious adverse events)	No (Only reported severe adverse events)	No
9. Have the characteristics of patients lost to follow-up been described?	NA (No patients lost to follow-up)	NA (Retrospective study)	NA (Retrospective study)

Item	Ahmed et al. (2020)[15]	Camprubi et al. (2020)[16]	Hellwig and Maia (2020)[17]
10. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	Yes (Actual P values were reported)	Yes (Actual P values were reported)	Yes (Actual P values were reported)
External validity			
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear (Only 72 hospitalized patients were enrolled)	Unclear (Only 26 hospitalized patients were enrolled)	Unclear (Not reported)
12. Were the subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear	Unclear	Unclear (Not reported)
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of the patients receive?	Yes (Treatment was conducted in hospital)	Yes (Treatment was conducted in hospital)	NA (Database search for incidence)
Internal validity – bias			
14. Was an attempt made to blind study subjects to the intervention they have received?	Yes (Double-blind)	NA (Retrospective study)	NA (Retrospective study)
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes (Double-blind)	NA (Retrospective study)	NA (Retrospective study)
16. If any of the results of the study were based on “data dredging”, was this made clear?	Yes (No retrospective unplanned subgroup analyses were reported)	NA (Retrospective study)	NA (Retrospective study)
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes (Follow-up was carried out until test-negative)	NA (Retrospective study)	NA (Retrospective study)
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes
19. Was compliance with the intervention/s reliable?	NA (Treatment was carried out in hospital)	NA (Treatment was carried out in hospital)	NA (Retrospective study)
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes
Internal validity – confounding (selection bias)			
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes (Both groups were recruited from the same hospital)	Yes (Both groups were from the same hospital)	No (Comparison between different countries)
22. Were study subjects in different intervention groups (trial and cohort studies) or were the cases and controls	Yes (During the pandemic)	Yes (Between March 10th and 30th 2020)	Yes (During the pandemic)

Item	Ahmed et al. (2020)[15]	Camprubi et al. (2020)[16]	Hellwig and Maia (2020)[17]
(case-controls studies) recruited over the same period of time?			
23. Were study subjects randomized to intervention groups?	Yes (RCT)	No	No
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Unclear (There was no report on concealment allocation)	NA (Retrospective study)	NA (Retrospective study)
25. Was the adequate adjustment for confounding in the analyses from which the main findings were drawn?	Probably no (Patient characteristics were not clearly described)	No (No adjustment for confounding factors in the analyses)	No (No adjustment for confounding factors in the analyses)
26. Were losses of patients to follow-up taken into account?	NA (No loss to follow-up)	NA (Retrospective study)	NA (Retrospective study)
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Unclear (Sample size calculation was not provided)	Unclear (Sample size calculation was not provided)	Unclear (Sample size calculation was not provided)

CI = confidence interval; COVID-19 = novel coronavirus disease 2019; NA = not applicable; RCT = randomized controlled trial.

Table 7: Quality Assessment of Guidelines Using AGREE II[12]

Item	NCCET (2020)[18]	NIH (2020)[19]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Unclear
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Unclear (The guideline was posted on its website)	Unclear (The guideline was posted on its website)

Item	NCCET (2020)[18]	NIH (2020)[19]
14. A procedure for updating the guideline is provided.	Yes	Yes
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes
20. The potential resource (cost) implications of applying the recommendations have been considered.	Unclear	Unclear
21. The guideline presents monitoring and/or auditing criteria.	Yes	Yes
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

AGREE II = Appraisal of Guidelines for Research & Evaluation II.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings in Included Systematic Review

Main Study Findings	Authors' Conclusions
Padhy et al. (2020)[14]	
Ivermectin (20 mcg/kg, single dose) versus non-ivermectin All-cause mortality (3 studies): • OR (95% CI) = 0.53 (0.29 to 0.96); I^2 = 0%; P = 0.04 • RD (95% CI) = 54 fewer per 1,000 (3 fewer to 85 fewer) • Quality of evidence: very low Clinical improvement (3 studies): • OR (95% CI) = 1.95 (1.09 to 3.49); I^2 = 0%; P = 0.02 • RD (95 % CI) = 61 more per 1,000 (from 12 more to 91 more) • Quality of evidence: very low Time to discharge from the hospital (3 studies; no MA due to different data reported): • 1 study: 7.62 ± 2.75 days in ivermectin group versus 13.22 ± 5.90 days in non-ivermectin group; P = 0.00005 • Other 2 studies: No significant difference in time to discharge between groups Time to viral clearance (2 studies): • 1 study: 7 days in ivermectin group versus 12 days in ivermectin group; P = 0.001 • Another study: No significant difference between groups	*"Ivermectin is an established drug with a long history of clinical use and with minimal safety concern. Recent observational studies have reported the effectiveness of this drug as add-on therapy in patients with COVID-19. Our meta-analysis also supports this finding and suggests the modest utility of ivermectin in reducing all-cause mortality and improving clinical outcomes. Currently, many clinical trials are ongoing, and definitive evidence for repurposing this drug for COVID-19 patients will emerge only in the future."*[14] (p. 468)

CI = confidence interval; COVID-19 = novel coronavirus disease 2019; MA = meta-analysis; OR = odd's ratio; RD = risk difference.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusions
Ahmed et al. (2020)[15]	

Ivermectin alone (12 mg once daily for 5 days) versus ivermectin + doxycycline versus placebo
 	
Time required for virological clearance:
• Ivermectin alone: 9.7 days (95% CI, 7.8 to 11.8 days); P = 0.02 compared with placebo
• Ivermectin + doxycycline: 11.5 days (95% CI, 9.8 to 13.2 days); P = 0.27 compared with placebo
• Placebo: 12.7 days (95% CI, 11.3 to 14.2 days)
• Ivermectin alone versus placebo:
  ○ On day 7: HR (95% CI) = 4.1 (1.1 to 14.7); P = 0.03
  ○ On day 14: HR (95% CI) = 2.7 (1.2 to 6.0); P = 0.02
• Ivermectin + doxycycline versus placebo:
  ○ On day 7: HR (95% CI) = 2.3 (0.6 to 9.0); P = 0.22
  ○ On day 14: HR (95% CI) = 1.7 (0.8 to 4.0); P = 0.19
 	
Fever:
• At enrolment, proportion of patients had fever:
  ○ Ivermectin alone: 77.3% (17/22)
  ○ Ivermectin + doxycycline: 73.9% (17/23)
  ○ Placebo: 82.6% (19/23)
	"Although the study sample was too small (n = 72) to draw any solid conclusions, the results provide evidence of the potential benefit of early intervention with the drug ivermectin for the treatment of adult patients diagnosed with mild COVID-19."[15] (p. 216)

Main Study Findings	Authors' Conclusions

• At day 7, proportion of patients had no fever:
  ○ Ivermectin alone: 100% (17/17); P = 0.35 compared with placebo
  ○ Ivermectin + doxycycline: 94.1% (16/17); P = 0.09 compared with placebo
  ○ Placebo: 84.2% (16/19)
 	
Cough:
• At enrolment, proportion of patients who had cough:
  ○ Ivermectin alone: 81.8% (18/22)
  ○ Ivermectin + doxycycline: 82.6% (19/23)
  ○ Placebo: 65.2% (15/23)
• At day 7, proportion of patients whose coughing had subsided:
  ○ Ivermectin alone: 61.1% (7/18); P = 0.18 compared with placebo
  ○ Ivermectin + doxycycline: 63.2% (7/19); P = 0.23 compared with placebo
  ○ Placebo: 40% (9/15)
 	
Sore throat:
• At enrolment, proportion of patients with sore throat:
  ○ Ivermectin alone: 18.2% (4/22)
  ○ Ivermectin + doxycycline: 13% (3/23)
  ○ Placebo: 17.4% (4/23)
• At day 7, proportion of patients whose sore throats had subsided:
  ○ Ivermectin alone: 75% (3/4); P = 0.35 compared with placebo
  ○ Ivermectin + doxycycline: 33.3% (1/3); P= 0.09 compared with placebo
  ○ Placebo: 75% (3/4)
 	
Failure to maintain SpO_2:
• None of the enrolled patients required oxygen
 	
Mean duration of hospitalization:
• Ivermectin alone: 9.6 days (95% CI, 7.7 to 11.7 days); P = 0.93 compared to placebo
• Ivermectin + doxycycline: 10.1 days (95% CI, 8.5 to 11.8 days); P = 0.93 compared to placebo
• Placebo: 9.7 days (95% CI, 8.1 to 11.0 days)
 	
Safety
• No serious drug-related AEs
• No death	

Camprubi et al. (2020)[16]	

Ivermectin (20 mcg/kg, single dose) versus control:
 	
• Other severe AEs:
  ○ Ivermectin: 4 (30.8%); Control: 3 (23.1%); P = 1.000
• Positive test 3 to 5 days after treatment:
  ○ Ivermectin: 5 (38.5%); Control: 4 (30.8%); P = 1.000
• Improvement 8 to 11 days after treatment:
  ○ Ivermectin: 9 (69.2%); Control: 10 (76.9%); P = 1.000
• Discharged 8 to 11 days after treatment:
  ○ Ivermectin: 7 (53.8%); Control: 6 (46.1%); P = 1.000
• Hospitalized 8 to 11 days after treatment:
  ○ Ivermectin: 4 (30.8%); Control: 4 (30.8%); P = 1.000
	"No relevant differences in microbiological or clinical outcomes were observed between groups."[16] (p. 4)

Main Study Findings	Authors' Conclusions
• ICU 8 to 11 days after treatment: ○ Ivermectin: 2 (15.4%); Control: 3 (23.1%); P = 1.000	
Hellwig and Maia (2020)[17]	

PCT with ivermectin versus other PCT versus no PCT
 	
• Countries around the world that had included ivermectin in their PCT had significantly lower incidences of COVID-19 (cases per 100,000) compared to countries with no PCT.
  ○ On 15 April 2020; adjusted P < 0.01
  ○ By 15 June 2020; adjusted P < 0.001
• Among African countries, those that routinely used ivermectin in their PCT against parasitic infections had significantly lower incidences of COVID-19 compared to countries with no PCT (P ≤ 0.05).
• There was a statistically significant correlation between PCT with ivermectin and lower incidence of COVID-19 (P = 0.017) among African countries.
• No statistical comparison was made between PCT with ivermectin and other PCT.
	"It is important to note that the hypothesis that ivermectin might have a prophylactic effect against SARS-CoV-2 is merely based on a rather strong correlation. On the other hand, this correlation has grown increasingly stronger in the worldwide data set earlier this year and then been independently replicated within the African dataset later in the summer. Both remain highly significant, suggesting that there may be a causal connection, which is also suggested by other recent findings reported in the literature."[17] (p. 4)

AEs = adverse events; CI = confidence interval; COVID-19 = novel coronavirus 2018; HR = hazard ratio; ICU = intensive care unit; PCT = prophylactic chemotherapy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SpO_2 = oxygen saturation.

Table 10: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
NCCET (2020)[18]	
"Do not use ivermectin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval."[18] Supporting evidence: • Evidence came from 3 randomized trials that compared ivermectin with standard care in 287 adults with COVID-19. Two studies are only available as preprints that have not been peer-reviewed. • The authors of the guidelines were uncertain regarding the clinical efficacy (mortality, rate of viral clearance, time to clinical recovery, and length of hospital stay) and safety (adverse or serious adverse events) of ivermectin.	Quality of evidence: very low Strength of recommendation: not recommended
NIH (2020)[19]	
*"The COVID-19 Treatment Guidelines Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial"*[19] (p. 95) Supporting evidence: • Ivermectin is not approved for the treatment of any viral infection, including COVID-19 infection. The FDA issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans. • A retrospective study that has not been peer-reviewed analyzed the use of ivermectin in patients with COVID-19. Consecutively admitted patients who were admitted to 4 hospitals in Florida received at least 1 dose of ivermectin of 200 mcg/kg (n = 173) or received usual care (n = 103). Most patients in each group received hydroxychloroquine and azithromycin. The study found that patients in the ivermectin group had significantly lower all-cause mortality (OR = 0.27; P = 0.03) compared to the usual care group, without a significant difference in the hospital length of stay or the proportion of ventilated patients who were	Quality of evidence: III Strength of recommendation: A

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
successfully extubated between groups. The mortality benefit appeared to be limited to the subgroup of patients with severe disease.	

COVID-19 = novel coronavirus disease 2019; NCCET = National COVID-19 Clinical Evidence Taskforce; NIH = National Institutes of Health; OR = odd's ratio.

Appendix 5: Preliminary Reports — Not Peer-Reviewed

1. Hashim HA, Maulood MF, Rasheed AM, et al. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq **[non peer-reviewed preprint]**. medRxiv; 2020: doi: 10.1101/2020.10.26.20219345. https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1. Accessed 2021 Feb 1.
2. Behera P, Patro BK, Singh AK, et al. Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: a matched case-control study **[non peer-reviewed preprint]**. medRxiv; 2020: doi: 10.1101/2020.10.29.20222661. https://www.medrxiv.org/content/10.1101/2020.10.29.20222661v1. Accessed 2021 Feb 1.
3. Carvallo HE, Hirsch RR, Farinella ME. Safety and efficacy of the combined use of ivermectin, dexamethasone, enoxaparin and aspirin against COVID-19 **[non peer-reviewed preprint]**. medRxiv; 2020:doi: 10.1101/2020.09.10.20191619. https://www.medrxiv.org/content/10.1101/2020.09.10.20191619v1. Accessed 2021 Feb 1.
4. Morgenstern J, Redondo JN, De Leon A, et al. The use of compassionate ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of COVID-19 at the Medical Center Bournigal and the Medical Center Punta Cana, Rescue Group, Dominican Republic, from May 1 to August 10, 2020 **[non peer-reviewed preprint]**. medRxiv; 2020: doi: 10.1101/2020.10.29.20222505. https://www.medrxiv.org/content/10.1101/2020.10.29.20222505v1. Accessed 2021 Feb 1.
5. Cadeginani FA, Goren A, Wambier CG, McCoy J. Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly reduced symptoms compared to known outcomes in untreated patients **[non peer-reviewed preprint]**. medRxiv; 2020: doi: 10.1101/2020.10.31.20223883. https://www.medrxiv.org/content/10.1101/2020.10.31.20223883v1. Accessed 2021 Feb 1.
6. Soto-Becerra P, Culquichicon C, Hurtado-Roca Y, Araujo-Castilo RV. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru **[non peer-reviewed preprint]**. medRxiv; 2020: doi: 10.1101/2020.10.06.20208066. https://www.medrxiv.org/content/10.1101/2020.10.06.20208066v3. Accessed 2021 Feb 1.