South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: IVERMECTIN FOR PROPHYLAXIS OF COVID-19

Date: 25 January 2021

Research question: What is the effectiveness of ivermectin compared to no intervention to prevent COVID-19 in people at risk or those who are close contacts of suspected or confirmed cases?

Key findings

- We conducted a rapid review of clinical trials reporting on ivermectin for the prophylaxis of COVID-19 in people at risk of exposure or those who have contact with suspected or known cases of COVID-19.
- On 18 January 2021 we searched two electronic databases that scan all relevant sources regularly, including the clinical trial registries. We identified two trials that have reported results (a pre-print publication and a clinical trial registry record with results). There are 13 planned or ongoing trials listed in clinical trials registries.
- Two trials, both conducted in Egypt, included 448 participants who were contacts of people with COVID-19 or healthcare workers. Both trials were appraised as having high risk of bias due to reporting issues (Elgazzar *et al*. is a pre-print and Shouman *et al*. is a registry record). Both studies are at possible risk of selection bias. In addition, Shouman *et al*. was an open-label unblinded study and reported on subjective outcomes including COVID-19 symptom development and adverse events. Both studies reported low numbers of events and their small sample sizes limit our confidence that their results can inform a decision.
- Overall, the evidence for the benefits and harms of ivermectin for prophylaxis of COVID-19 remains uncertain. Ongoing trials may provide further evidence in this regard.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The NEMLC COVID-19 sub-committee suggests that ivermectin not be used routinely for COVID-19, except in the context of a clinical trial.
Rationale: The evidence for the use of ivermectin as prophylaxis of COVID-19 is insufficient to justify the inclusion of this medicine in guidelines at this time. Accordingly, we suggest that the option not be used until further evidence is generated and assessed.
Level of Evidence: Very low quality evidence

Review indicator: New high quality evidence of a clinically relevant benefit

Therapeutic Guidelines Sub-Committee of the COVID-19 Management Clinical Guidelines Committee: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish *(Chair)*, Helen Rees, Gary Reubenson *(Vice-Chair)*.

Note: Due to the continuous emergence of new evidence, the evidence review will be updated when more relevant evidence becomes available.

BACKGROUND

Coronavirus Disease 2019 (COVID-19) an infectious disease caused by 'Severe Acute Respiratory Syndrome Coronavirus 2' (SARS-CoV-2); was first identified in China in 2019, and has now spread worldwide.[1] As of 16 January 2021 the World Health Organization (WHO) reported approximately 92,506,811 confirmed cases of COVID-19 worldwide, including 2,001,773 deaths.[2] Currently (17 January 2021), in South Africa, it is reported that 1.33 million people have been infected with SARS-CoV-2 and over 36 000 deaths have been recorded.[Error! Bookmark not defined.]

Although COVID-19 vaccines started to be administered in the United Kingdom in December 2021,[3] access to these products in South Africa is only expected to start in 2021.[4] Currently there is a great deal of public interest in ivermectin, in South Africa and other countries, for both treatment and prevention of COVID-19. In laboratory studies, ivermectin has been shown to inhibit SARS-COV2 replication, raising the possibility that it might have a role in either treatment or prevention of COVID-19.[5,6]

Ivermectin is an antiparasitic medicine used for the treatment of animals and humans. The registered indications include tropical diseases such as filariasis and onchocerciasis. It has also been indicated for scabies and lice treatment. Products for use in animals are registered in South Africa in terms of the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947).[7] No products are registered in terms of the Medicines and Related Substances Act (Act 101 of 1965) at present, but individual patients have been enabled to access imported products in terms of section 21.

The National Essential Medicine List (NEMLC) COVID-19 Sub-committee is currently updating the rapid review of ivermectin for the treatment of COVID-19.[7,8]

The objective of this report is to review the evidence on safety and efficacy of ivermectin in the prophylaxis of COVID-19.

Eligibility criteria for review

Population: Persons at risk of contracting SARS-CoV-2; close contacts of confirmed or suspected COVID-19 cases.

Intervention: Ivermectin alone. No restriction on dose, frequency.

Comparators: No prophylaxis or placebo.

Outcomes: Positive SARS-CoV-2 (polymerase chain reaction) PCR on nasopharyngeal swab at chosen time point(s) after initiation of prophylaxis; development of COVID-19 infection, based on clinical diagnosis (PCR or rapid antigen test); duration of symptoms; proportion requiring hospitalisation; severity of disease; adverse reactions and adverse events.

METHODS

We conducted a rapid review based on the *a priori* methods developed for conducting rapid reviews (http://www.health.gov.za/covid-19-rapid-reviews/).[9] We systematically searching the Cochrane COVID-19 Study Register and Living Overview of the Evidence (LOVE) Platform for Covid-19 evidence on 18 January 2021. We did not restrict the type of study or language in our search, and also searched reference lists of the reviews retrieved. Where publications in languages other than English were retrieved, these were translated before a decision on their inclusion or exclusion was reached. Three reviewers (AG, TK & MR) reviewed titles and abstracts of the studies, using COVIDENCE, in line with the eligibility criteria for the review. Differences were resolved through discussion. Both systematic reviews (with or without meta-analyses) of randomised controlled trials (RCTs) and individual RCTs were included. We excluded observational studies, case reports, case control, case series, and narrative reviews. The search strategy is shown in Appendix 1. One reviewer extracted data which was checked by a second reviewer. Included studies are reported in Table 1 and excluded studies with the rationale for exclusion are summarised in Table 2. The narrative table of results was checked by all three reviewers.

For dichotomous outcomes we calculated the relative risk using an intention to treat approach to include all participants randomised. We conducted a grading of recommendations, assessment, development and evaluation (GRADE) assessment to establish the certainty of the evidence across each outcome, taking into account risk of bias, directness, consistency, precision, and other considerations such as publication bias to determine whether the confidence in the overall results was high, moderate, low or very low (Table 3).[10] The summary of findings table is shown as Table 4.

RESULTS

Results of search

The search identified 249 records. After the removal of 78 duplicates, the reviewers (AG, TK, MR) screened 171 records (titles and abstracts) and identified 20 potentially eligible studies. After reviewing the full text of the articles 17 papers were excluded: 11 were ongoing studies (from trial registers, with no results reported yet or trial report available); 2 were an incorrect/ineligible study design (observational), 2 were duplicate studies, and 2 were non-applicable reviews or commentaries.

Description of the studies

We identified one review by Kalfas *et al*.,[11] and two RCTs by Elgazzar *et al*.[12] and Shouman *et al*[13]. The review by Kalfas *et al*. included three studies on prophylaxis, of which one is the registry record for Shouman *et al*. reported below. The other two studies used ineligible study designs. This review was therefore not relied upon, as it offered less information than the individual RCTs.

We identified two individual RCTs. Elgazzar *et al*.[12] included both treatment and prevention groups and has only been reported in pre-print. This was a multi-centre trial conducted in Egypt between June and October 2020. In the prophylaxis arm, participants were household contacts and healthcare workers who had been exposed to COVID-19. It is not clear if exposure was to confirmed or suspected COVID-19 cases. In the prophylaxis arm 100 participants were allocated to each of two groups: ivermectin plus the use of personal protective equipment (PPE) versus PPE alone (see Table 1 for details). No detail was provided in the preprint about the baseline characteristics of the trial participants or the time from exposure to receiving ivermectin as prophylaxis.[12]

Shouman *et al.*[13] conducted an open-label RCT in participants who had contact with people with COVID-19. The protocol indicated that the sample size was based on identifying "family close contacts to 50 patients diagnosed as having COVID-19 by RT-PCR".[14] In the trial 228 participants were randomised to the ivermectin group and 112 to the control group between May and September 2020. There was no intervention in the control group, apart from observation. The trial results have not been published but have been documented on the trial registry site.

Effects of the intervention

See GRADE evidence profile in Table 3.

Outcomes:

1. Incidence of SARS-Cov2

a) Positive SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) after initiation of prophylaxis:
Elgazzar *et al.* – 2/100 participants in the ivermectin group were confirmed to be infected with SARS-CoV-2 compared to 10/100 in the control group.[12] Relative risk is 0.20 [95% CI 0.04 to 0.89]; very low certainty evidence - the certainty of the data is rated down for serious methodological limitations; very serious imprecision (low event rates and small sample size). As there is only one study, we cannot assess heterogeneity or publication bias.

b) Development of COVID-19 infection, based on clinical diagnosis (PCR or rapid antigen test):
Shouman *et al*. - 15/ 228 participants developed symptoms in the ivermectin group compared to 59/112 in the control group.[13] Relative risk is 0.12 [95% CI 0.07 to 0.21]; we rated the evidence as very low certainty due to very serious methodological issues as this is a subjective outcome in an open-label study; and imprecision due to low event rates and small sample size.

2. Duration of symptoms: no results reported

3. Proportion requiring hospitalization: no results reported

4. Adverse reactions and adverse events:
Elgazzar *et al*. – no results reported for this outcome.

Shouman *et al.* – 11/228 in the ivermectin group compared to 0/112 in the control group reported any adverse event (Risk ratio of 11.35 [95% CI 0.67 to 190.87]. Very low certainty evidence based on serious methodological limitations in the reported evidence and very serious imprecision.

CONCLUSION

Our review of the available trial evidence for ivermectin prophylaxis for COVID-19 found two trials with very low certainty evidence to inform a decision regarding any benefits or harms. Further trials are expected to inform this evidence base and this review will be updated when such data are available.

Reviewer(s): Dr M Reddy, Dr T Kredo, Mr A Gray

Declaration of interests: MR (Better Health Programme, South Africa) and TK (Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Department of Medicine, Stellenbosch University; TK is partly supported by the Research, Evidence and Development Initiative (READ-It). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies) have no interests to declare in COVID-19 prevention and treatment. AG (Division of Pharmacology, University of KwaZulu-Natal) declared Chairing of the Proposal Review Committee at UNITAID, which has supported research into ivermectin for malaria control.

Table 1: Characteristics of included trials

Randomised controlled studies:

Citation	Study design and methods	Population and setting	Intervention and comparison	Outcomes reported in trial	Quality appraisal
Elgazzar, Hany, Abo Youssef *et al*. Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic, 13 November 2020, PREPRINT (Version 1) available at Research Square https://doi.org/10.21203/rs.3.rs-100956/v1[12] Ethics Research Committee, Faculty of Medicine Benha University, Egypt (REC 96 /8 June 2020) Clinicaltrials.gov: NCT04668469	Methods: Multi-centre, no details of randomization reported. Duration: 8 June to 15 September 2020 Funding: None Declarations: The authors declare no competing interest	Country: Egypt (Benha and Kafrelsheikh University Hospitals; COVID-19 Isolation Hospitals) Sample size: n=200 health care and household contacts who formed a prevention group (n=400 in treatment group but not reported here) Sex: 28% females across 600 participants (not specified for the prophylaxis arm)	Prophylaxis: n=100 received a prophylactic dose of ivermectin 400 micrograms/kg single oral dose before breakfast to be repeated after one week in addition to personal protective equipment (PPE). Control: n=100 received only PPE Note: there were 4 other groups that explored treatment of COVID-19 in mild/moderate and severe cases.	Confirmed infected subjects by RT-PCR Confirmed infection in prevention group was reported as (2% (n=2/100) vs control group 10% (n=10/100).	**Risk of bias assessment** • Randomization: UNCLEAR RISK – no details in trial report • Allocation concealment: UNCLEAR RISK – no details • Blinding (participants, clinicians, outcome assessors): UNCLEAR RISK – no details • Attrition: none reported – LOW RISK • Selective outcome reporting (i.e., do they report planned outcome, registry number not found): HIGH RISK – no outcomes specified in registry record for this study component • **Other bias: n/a**
Shouman et al. Prophylactic Ivermectin in COVID-19 Contacts.[13] Zagazig University (Egypt) ClinicalTrials.gov. record: https://clinicaltrials.gov/ct2/show/NCT04422561	Methods: Randomized (but also described as sequential assignment), open label Duration: May (Study Start Date) to July 2020 September 2020 (Completion Date) Funding/Declarations: All Principal Investigators are employed by the organization sponsoring the study	Country: Egypt Sample size: n=340 (n=228 ivermectin and n=112 control group started the trial) Age: mean 38.72 years (SD 15.94) across 304 participants Sex: 48.7% females across 304 participants Loss to follow up: 25 in ivermectin group compared to 11 in control group	Prophylaxis: N=228 - Contacts received prophylactic ivermectin tablets 72 hours apart: 40-60 kg (15mg/day), 60-80kg (18mg/day) & >80kg (24mg/day) Control: Contacts only observed without prophylaxis	Primary Outcomes: Development of Symptoms (Fever, Cough, Sore Throat, Myalgia, Diarrhea, Shortness of Breath) [within 14 days after enrollment] history taking & clinical examination. 15/228 events in ivermectin group compared to 59/112 in control group Secondary Outcomes:	**Risk of bias assessment** • Randomization: UNCLEAR – no trial report available, and trial registry entry is contradictory • Allocation concealment UNCLEAR – no trial report available • Blinding (participants, clinicians, outcome assessors): High risk – open-label study • Attrition: UNCLEAR – (25/ 228) 11% in ivermectin group vs (11/112) 10% in control group. 10% loss to follow up in short term small study may impact results.

Citation	Study design and methods	Population and setting	Intervention and comparison	Outcomes reported in trial	Quality appraisal
				Development of COVID [within 14 days after enrollment] Confirmed by swab. No results reported All-cause mortality – no events Serious adverse events – no events Adverse events – 11 in ivermectin group vs 0 in control group	• Selective outcome reporting UNCLEAR – no full trial report available yet •Other bias: n/a

Table 2. List of Excluded Studies

Full Reference	Title	Affiliation /Authors	Reason for Exclusion	Trial End Date for Ongoing Trails/ Unpublished Results
Kumar et al., 2020. Ivermectin in the prevention of covid-19. ICTRP. http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=45156&EncHid=&modid=&compid=%27,%2745156det%27	Ivermectin in the prevention of covid-19	DVFM	Ongoing study	Date of First Enrollment (India) = 10/07/2020 Estimated Duration of Trial = 1 Year
Federal University of Pernambuco; Clinical Research Institute Scinet. Study on the effects of using ivermectin to prevent COVID-19 in an adult population in Brazil isrctn.com. http://www.isrctn.com/ISRCTN90437126	Study on the effects of using ivermectin to prevent COVID-19 in an adult population in Brazil	Federal University of Pernambuco; Clinical Research Institute Scinet	Ongoing study	30/06/2021
Fundacia Assistencial Matua Terrassa. 2020. Study of the efficacy of ivermectin in the treatment and prevention of COVID-19 ICTRPEU Clinical Trials Register (EU-CTR). https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001994-66/ES	Study of the efficacy of ivermectin in the treatment and prevention of COVID-19	Fundacia Assistencial Matua Terrassa	Ongoing study	Not Listed
Akam Tejarat Fartak Company. Farasoo.2 2020. Evaluation of prophylaxis induced by ivermectin in populations exposed to COVID-19 patients. Iranian Registry of Clinical Trials. https://www.irct.ir/trial/51999	Evaluation of prophylaxis induced by ivermectin in populations exposed to COVID-19 patients	Akam Tejarat Fartak Farasoo Company	Ongoing study	Expected recruitment end date: 30/12/2020 Trial completion date: Not Listed
Maria de los Angeles Peral de Bruno Prophylaxis Covid-19 in Healthcare Agents by Intensive Treatment with Ivermectin and Iota-carrageenan. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04701710	Prophylaxis Covid-19 in Healthcare Agents by Intensive Treatment with Ivermectin and Iota-Carrageenan	Maria de los Angeles Peral de Bruno	Ongoing study	Actual Study Completion Date: 31/12/2020 No results posted
National University Hospital, Singapore. A Preventive Treatment for Migrant Workers at High-risk of Covid-19 ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04446104	A Preventive Treatment for Migrant Workers at High-risk of Covid-19	National University Hospital, Singapore	Ongoing study	Actual Study Completion Date: 31/08/2020
Javeriana University. 2020. Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in Colombian Health Personnel. ClinicalTrials.gov. at:https://www.clinicaltrials.gov/ct2/show/NCT04527211	Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in Colombian Health Personnel	Javeriana University	Ongoing study	Estimated Study Completion Date: 16/12/2020 No results posted
Instituto de Efectividad Clínica y Sanitaria. 2020. Ivermectin for COVID-19. http://www.iecs.org.ar/publicacion/?id=18749.	Ivermectin for COVID-19	Instituto de Efectividad Clinnica y Sanitaria	Foreign Language – Did not meet PICO (treatment review)	
Pan American Health Organization. Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews. Rapid Review, 23 May 2020 Pan American Health Organization. https://iris.paho.org/handle/10665.2/52719	Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews. Rapid Review, 23 May 2020	Pan American Health Organization	No trial data included	

Full Reference	Title	Affiliation /Authors	Reason for Exclusion	Trial End Date for Ongoing Trails/ Unpublished Results
Eurnekian Public Hospital Usefulness of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19. ClinicalTrials. https://www.clinicaltrials.gov/ct2/show/NCT04425850	Usefulness of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19	Eurnekian Public Hospital	Observational Study (Ineligible study design)	Actual Study Completion Date: 10/08/2020
Lagos University Teaching Hospital. 2020. Does ivermectin cure and/or prevent COVID-19? ICTRPISRCTN.org. http://www.isrctn.com/ISRCTN40302986.	Does ivermectin cure and/or prevent COVID-19?	Lagos University Teaching Hospital	Ongoing study	October 2020
Phatak et al., Department of Community Medicine. 2020. Prophylactic Ivermectin in COVID 19 Contacts ICTRPClinical Trials Registry - India (CTRI). http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=46676&EncHid=&modid=&compid=%27,%2746676det%27.	Prophylactic Ivermectin in COVID 19 Contacts	Department of Community Medicine	Ongoing study	Date of First Enrollment (India) 31/08/2020 Estimated Duration of Trial = 6 Months
Marra LP; Oliveira Jr HA; Medeiros FC; Brito GV; Matuoka JY; Parreira PCL; Bagattini AM; Pachito DV; Riera R. Ivermectin for COVID-19: rapid systematic review. Esta revisão rápida (rapid review methodology) foi produzida por meio de uma ação colaborativa entre a Unidade de Avaliação de Tecnologias em Saúde do Hospital Alemão Oswaldo Cruz (UATSHAOC) e Núcleo de Avaliação de Tecnologias em Saúde do Hospital Sírio-Libanês (NATS-HSL). https://docs.bvsalud.org/biblioref/2020/06/1099488/rs_rapida_ivermectina_covid19_06_05_20-1.pdf.	Ivermectin for COVID-19: rapid systematic review	Marra LP; Oliveira Jr HA; Medeiros FC; Brito GV; Matuoka JY; Parreira PCL; Bagattini AM; Pachito DV; Riera R	No additional data included	
Fundació Assistencial Mútua Terrassa. Randomised clinical trial of ivermectin for treatment and prophylaxis of COVID-19. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001994-66/ES	Randomised clinical trial of ivermectin for treatment and prophylaxis of COVID-19	Fundació Assistencial Mútua Terrassa	Ongoing study	Not listed
Behera et al., 2020. Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study medRxiv https://www.medrxiv.org/content/10.1101/2020.10.29.20222661v1.full	Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study	Priyamadhaba Behera; Binod Kumar Patro; Arvind Kumar Singh; Pradnya Dilip Chandanshive; Ravikumar S R; Somen Kumar Pradhan; Siva Santosh Kumar Pentapati; Gitanjali Batmanabane; Biswa Mohan Padhy; Shakti Bal; Sudipta Ranjan Singh; Rashmi Ranjan Mohanty	(Ineligible study design)	

Table 3. GRADE evidence profile

Question: Ivermectin compared to no treatment or placebo for prevention of COVID-19
Setting: Public health sector in South Africa
Bibliography: Elgazzar *et al*.; Shouman *et al.*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	no treatment or placebo	Relative (95% CI)	Absolute (95% CI)		
Incidence of COVID-19 (PCR proven) (assessed with: PCR SARS-COV2)												
1 (Elgazzar)	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	2/100 (2.0%)	10/100 (10.0%)	**RR 0.20** (0.04 to 0.89)	**80 fewer per 1,000** (from 96 fewer to 11 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Incidence of COVID-19 (development of symptoms) (follow up: 14 days; assessed with: History and examination at 14 days)												
1 (Shouman)	randomised trials	very serious [d]	not serious	serious [b]	not serious	none	15/228 (6.6%)	59/112 (52.7%)	**RR 0.12** (0.07 to 0.21)	**464 fewer per 1,000** (from 490 fewer to 416 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Duration of symptoms - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Hospitalisation - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse events												
1 Shouman	randomised trials	very serious [e]	not serious	not serious	very serious [c]	none	11/228 (4.8%)	0/112 (0.0%)	**RR 11.35** (0.67 to 190.87)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations
a. Rated down by one level for serious risk of bias. Unclear reporting regarding sample selection and blinding, and mismatch with registry record and results regarding outcomes for this study component (prevention).
b. Rated down by one level for indirectness. One small study, in one study population may not be applicable to our setting. Elgazzar duration of follow up unclear; in Shouman duration of follow up is 14 days which may not be applicable in public sector programmes with intention to prevent exposure for longer duration.
c. Rated down by two levels for imprecision. Wide confidence interval, very low event rates, very small sample size. Does meet requirements for optimal information size (i.e. adequate sample size).
d. Rated down by two levels for serious methodological limitations. Evidence only available in the clinical trial registry record. Unable to assess what was done in the trial in absence of a trial report/ publication. Unblinded, which would affect the subjective outcome of 'development of symptoms'.
e. Rated down by two levels for serious methodological limitations. Evidence only available in the clinical trial registry record. Unable to assess what was done in the trial in absence of a trial report/ publication. Unblinded, which would affect the subjective outcome assessment regarding adverse events.

Table 4. Ivermectin compared to no treatment or placebo for prevention of COVID-19

Patient or population: prevention of COVID-19
Setting: Public health sector in South Africa
Intervention: ivermectin
Comparison: no treatment or placebo

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment or placebo	Risk difference with ivermectin
Incidence of COVID-19 (PCR proven) assessed with: PCR SARS-COV2	200 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 0.20** (0.04 to 0.89)	100 per 1,000	**80 fewer per 1,000** (96 fewer to 11 fewer)
Incidence of COVID-19 (development of symptoms) assessed with: History and examination at 14 days follow up: 14 days	340 (1 RCT)	⊕◯◯◯ VERY LOW [b,d]	**RR 0.12** (0.07 to 0.21)	527 per 1,000	**464 fewer per 1,000** (490 fewer to 416 fewer)
Duration of symptoms - not reported	-	-	-	-	-
Hospitalisation - not reported	-	-	-	-	-
Adverse events	340 (1 RCT)	⊕◯◯◯ VERY LOW [c,e]	**RR 11.35** (0.67 to 190.87)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Rated down by one level for serious risk of bias. Unclear reporting regarding sample selection and blinding, and mismatch with registry record and results regarding outcomes for this study component (prevention).
b. Rated down by one level for indirectness. One small study, in one study population may not be applicable to our setting. Elgazzar duration of follow up unclear; in Shouman duration of follow up is 14 days which may not be applicable in public sector programmes with intention to prevent exposure for longer duration.
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e. Rated down by two levels for serious methodological limitations. Evidence only available in the clinical trial registry record. Unable to assess what was done in the trial in absence of a trial report/ publication. Unblinded, which would affect the subjective outcome assessment regarding adverse events.

Appendix 1: Search strategy

Database:	**Cochrane COVID-19 Study Register** **https://covid-19.cochrane.org/**
Date:	**18 January 2021**
Search Strategy:	**Ivermectin OR mectizan OR equalan OR stromectol OR ivomec**
Number of studies numbers:	**100 studies**
Database:	**LOVE Platform https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=aile**
Date:	**18 January 2021**
Search Strategy: (see below)	
Number of studies numbers:	**149 articles**

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ x *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low certainty evidence based on small sample sizes and low event rates, methodological issues with the reports available *(possible publication bias if negative studies are not being shared in reports yet)*
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☒ x Moderate ☐ Small ☐ None ☐	The trials report a large reduction in incidence of COVID-19 in the intervention compared to the control group. PCR-confirmed cases reported in Elgazzar *et al*. and development of symptoms reported in Shouman *et al*.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ x *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low event rates from one study that was not blinded. Evidence very uncertain.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ x None ☐	More adverse events reported when participants were taking ivermectin. No serious adverse events or fatalities reported.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒ x	The available evidence is uncertain whether desirable effects outweigh desirable outcomes.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☒ x	No SAHPRA-registered ivermectin-containing product for human use is registered in South Africa. Some compounding is being done locally, which is also legally questionable. No single exit price or state tender price is therefore available. To date, a small number of patients have been given s21 approval to import the registered oral solid dosage (marketed as Stromectol® by Merck)
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☒ x	The resource requirements are uncertain, as the potential number of persons who might be offered prophylaxis is unknown.

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [x] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	No study data on this, however, emerging ivermectin interest groups are supportive of this treatment and anecdotal data regarding use of ivermectin by health care practitioners and their prescription to patients for both treatment and prevention. In the absence of available ivermectin for human use, concerns regarding safety are not captured.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [x]	Access remains a challenge with no available ivermectin for human use in South Africa. If this became available, access should be possible in all sectors and at all levels of the health system, depending on affordability and availability.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	25 January 2021	TK, AG, MR	There is currently insufficient evidence to support routine use of ivermectin as prophylaxis for COVID-19; may be used in a clinical trial setting.

REFERENCES:

[1] Covid-19 Online Resource and News Portal. About COVID-19 (Coronavirus). https://sacoronavirus.co.za/information-about-the-virus-2/
[2] World Health Organisation. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/
[3] BBC News. Covid-19 vaccine: First person receives Pfizer jab in UK. https://www.bbc.com/news/uk-55227325
[4] Covid-19 Online Resource and News Portal. What does South Africa's COVID vaccine roll-out plan say? https://sacoronavirus.co.za/2021/01/12/what-does-south-africas-covid-vaccine-roll-out-plan-say/
[5] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020 Jun;178:104787. https://pubmed.ncbi.nlm.nih.gov/32251768/
[6] Hellwig MD, Maia A. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin. Int J Antimicrob Agents. 2021 Jan;57(1):106248. doi: 10.1016/j.ijantimicag.2020.106248.
[7] South African Health Products Regulatory Authority (SAHPRA). 6 January 2021. SAHPRA'S Guidance on the Use of Ivermectin in the Prophylaxis or Treatment of Covid-19. https://www.sahpra.org.za/news-and-updates/sahpras-guidance-on-the-use-of-ivermectin-in-the-prophylaxis-or-treatment-of-covid-19/.
[8] National Essential Medicine List (NEMLC) COVID-19 Sub-committee (South African National Department of Health). Ivermectin Rapid Evidence summary, 21 December 2020. http://www.health.gov.za/covid-19-rapid-reviews/
[9] South African Department of Health. 2020. National Essential Medicines List Therapeutic Guidelines Subcommittee on Covid-19 Terms of Reference. http://www.health.gov.za/covid-19-rapid-reviews/
[10] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-926. https://pubmed.ncbi.nlm.nih.gov/18436948/
[11] Kalfas et al., 2020. The Therapeutic Potential of Ivermectin for Covid-19: A Review of Mechanisms and Evidence. MedRxiv, 4 December 2020. https://www.medrxiv.org/content/10.1101/2020.11.30.20236570v1
[12] Elgazzar, Hany, Abo Youssef et al. Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic, 13 Research Square , November 2020. https://doi.org/10.21203/rs.3.rs-100956/v1
[13] Shouman et al. 2020. Prophylactic Ivermectin in COVID-19 Contacts. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04422561.
[14] Shouman et al., 2020. Protocol: Use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contacts with Patients of COVID-19. https://clinicaltrials.gov/ct2/show/NCT04422561