Evidence check

23 December 2020

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Ivermectin and COVID-19

Evidence check question

Is ivermectin effective in the treatment of COVID-19?

In brief

- Currently, there are insufficient data to support the use of ivermectin for prophylaxis or treatment of COVID-19.
    - There was insufficient evidence to include ivermectin in the 17 December 2020 release of the BMJ living systematic review on drug treatments; however, three randomised controlled trials will be included in the next update inclusion. (1-4)
    - The 17 December 2020 update for the World Health Organization guideline on drugs for COVID-19 does not include ivermectin.(5)
- While there is evidence of in vitro activity of ivermectin on infected cells, the necessary concentrations for in vivo effect are unlikely to be attainable in humans.(6)
- The Pan American Health Organisation, the World Health Organization regional office for the Americas, published a report in June 2020 that stated studies on ivermectin were found to have a high risk of bias, very low certainty of the evidence, and that the existing evidence is insufficient to draw a conclusion on benefits and harm.(7)
- While a more recent systematic review found a statistically significant effect on mortality and symptoms, the quality of evidence was very low.(8)
- There is continuing interest particularly in the Americas, India, and Bangladesh in the use of ivermectin prophylactically and therapeutically.(9-12)
- Emerging evidence from randomised controlled trials is mixed.
    - High dose ivermectin showed no reduction in viral load at day five.(2)
    - Patients receiving ivermectin plus standard care reported improvement in laboratory and severity parameters.(3)
    - A phase 2 clinical trial showed a decrease in hospitalisation and duration of low oxygen saturation with adjunct ivermectin treatment.(4)

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  - A three-arm randomised controlled trial of a five-day course of ivermectin reported that changes in patient symptoms were not clinically significant compared with placebo.(12)

- In the USA, the Front Line COVID-19 Critical Care Alliance advocates for further study of ivermectin.(9, 13) However, the US Food and Drug Administration released advice on 16 December 2020 that ivermectin is not approved for the prevention or treatment of COVID-19. (14)

Limitations

The evidence on ivermectin is still emerging and most of the available evidence is of low quality.

Background

Ivermectin is an antiparasitic medicine. It works by binding to glutamate-gated chloride ion channels to alter chloride channel function; and by acting as a gamma-aminobutyric acid agonist in the parasite. This leads to parasite paralysis and death. In recent years, ivermectin has shown antiviral activity against a broad range of viruses in vitro.

In Australia, oral ivermectin is indicated for the treatment of:

- onchocerciasis (river blindness)
- intestinal strongyloidiasis
- crusted scabies (in conjunction with topical therapy)
- human sarcoptic scabies when prior topical treatment has failed or is contraindicated.(15)

When taken orally, ivermectin has a good safety profile with low adverse effects.(15)

Table 1: Usual therapeutic doses of oral ivermectin for adults with indicated conditions (15)

Condition	Dose
Onchocerciasis	150µg/kg as a single dose
Scabies	200µg/kg Classic or typical scabies: two doses (day 1 and second dose between day 8 and day 15) Crusted scabies (ivermectin in combination with a topical scabicide): two doses for mild cases (day 1 and second dose between day 8 and day 15) Moderate to severe cases may require more than three doses.
Strongyloidiasis	200µg/kg as a single dose

Methods (Appendix 1)

An initial search conducted on 20 August 2020 was supplemented by an update on 21 December 2020.

- PubMed was searched using (COVID-19 AND ivermectin) AND LitCTREATMENT[filter]
- Google was searched using ivermectin AND COVID-19

Results

Table 1. Peer-reviewed evidence

Source	Summary
Peer reviewed sources	
Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens Momekov, et al. 2020 (6) June 2020	• Literature survey analysed the published dose regimens and human exposure data for ivermectin, following clinically relevant (150-800µg/kg) or excessive dosing (up to 2000µg/kg). • The broad-spectrum antiparasitic agent ivermectin has been very recently found to inhibit SARS-CoV-2 in vitro and proposed as a candidate for drug repurposing in COVID-19. • The available pharmacokinetic data from clinically relevant and excessive dosing studies indicate that the SARS-CoV-2 inhibitory concentrations are not likely to be attainable in humans.
The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19 Schmith, et al. 2020 (16)	• Brief report, simulation study. • Simulations were conducted using an available population pharmacokinetic model to predict total (bound and unbound) and unbound plasma concentration-time profiles after a single and repeat fasted administration of the approved dose of ivermectin (200µg/kg), 60mg, and 120mg. • Plasma ivermectin concentrations of total (bound and unbound) and unbound concentrations do not reach the half maximal inhibitory concentration, even for a dose level 10 times higher than the approved dose. • Conclusions: the likelihood of a successful clinical trial using the approved dose of ivermectin is low. Combination therapy should be evaluated in vitro.
The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro Caly, et al. 2020 (17)	• In vitro study. • To test the antiviral activity of ivermectin towards SARS-CoV-2, authors infected Vero/hSLAM cells with SARS-CoV-2 isolate Australia/VIC01/2020 at an multiplicity of infection of 0.1 for 2 hours, followed by the addition of 5µM ivermectin. • At 24 hours, there was a 93% reduction in viral RNA present in the supernatant (indicative of released virions) of samples treated with ivermectin compared to the vehicle dimethyl sulfoxide. • By 48 hours this effect increased to an approximately 5000-fold reduction of viral RNA in ivermectin-treated compared to control samples, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 hours.

Source	Summary
Peer reviewed sources	
	• Conclusions: this report alongside the known-safety profile, demonstrates that ivermectin is worthy of further consideration as a possible SARS-CoV-2 antiviral.
The SARS-CoV-2 Ivermectin Navarra-ISGlobal Trial (SAINT) to evaluate the potential of ivermectin to reduce covid-19 transmission in low risk, non-severe COVID-19 patients in the first 48 hours after symptoms onset: a structured summary of a study protocol for a randomized control pilot trial Chaccour, et al. 2020 (18)	• Study protocol. • Single centre, double-blind, randomised, placebo-controlled, superiority trial with two parallel arms (SAINT). • The primary objective is to determine the efficacy of a single dose of ivermectin, administered to low risk, non-severe COVID-19 patients in the first 48 hours after symptom onset reduces the proportion of patients with detectable SARS-CoV-2. • The population for the study will be patients with a positive nasopharyngeal swab polymerase chain reaction (PCR) test for SARS-CoV-2, with non-severe COVID-19 disease, and no risk factors for progression to severity. • Ivermectin will be administered to the treatment group at a 400µg/kg dose. The control group will receive placebo. • Eligible patients will be allocated in a 1:1 ratio using a randomisation list, generated by the trial statistician, in blocks of four to ensure balance between the groups. • The sample size is 24 patients: 12 participants will be randomised to the treatment group and 12 participants to the control group.
Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen Heidary, et al. 2020 (19)	• Comprehensive review on PubMed, reference lists were also considered. • Several studies reported antiviral effects of ivermectin on RNA viruses such as Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, avian influenza A, porcine reproductive and respiratory syndrome, human immunodeficiency virus type 1, and SARS-CoV-2. • Some studies showing antiviral effects of ivermectin against DNA viruses such as equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus 1. • Conclusions: Ivermectin plays a role in several biological mechanisms, therefore it could serve as a potential candidate in the treatment of a wide range of viruses including COVID-19.
Role of ivermectin in the prevention of COVID-19 infection among	• A hospital-based matched case-control study to explore the association between ivermectin prophylaxis and development of

Source	Summary
Peer reviewed sources	
healthcare workers in India: A matched case-control study Behera, et al. 2020 (10) (Pre-print)	COVID-19 infection among healthcare workers, conducted from September to October 2020. • Ivermectin prophylaxis was taken by 77 controls and 38 cases. • Two-dose ivermectin prophylaxis was associated with 73% reduction of COVID-19 infection among healthcare workers for the following one month (0.27, 95% confidence interval (CI), 0.15-0.51), those who were involved in physical activity for more than an hour per day were more likely to contract COVID-19 infection (3.06 95% CI, 1.18-7.93). • Conclusions: two-dose ivermectin prophylaxis at a dose of 300µg/kg body weight with a gap of 72 hours was associated with a 73% reduction of COVID-19 infection among healthcare workers in the following one month. This is an intervention worth replicating at other centres until a vaccine is available.
Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ICON study Rajter, et al. 2020 (20)	• Retrospective chart review of patients as four health hospitals in Florida, with confirmed COVID-19, treated with (n=173) or without (n=107) ivermectin (n=280 total). • Most patients in both groups also received hydroxychloroquine, azithromycin, or both. • Univariate analysis showed lower mortality in the ivermectin group (15.0% vs 25.2% p=0.03). • Mortality also was lower among ivermectin-treated patients with severe pulmonary involvement (38.8% vs 80.7% p=0.001). • No significant differences were found in extubation rates (36.1% vs 15.4% p=0.07) or length of stay. • After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant. • Conclusions: ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement.
Quantitative proteomics reveals a broad-spectrum antiviral property of ivermectin, benefiting for COVID-19 treatment Li, et al. 2020 (21)	• This study aimed to identify ivermectin-related virus infection pathway alterations in human ovarian cancer cells. • A total of 4447 ivermectin-related proteins were identified in ovarian cancer cells treated with and without ivermectin with stable isotope labelling by amino acids in cell culture based quantitative proteomics.

Source	Summary
Peer reviewed sources	
	• Pathway network analysis revealed four statistically significant antiviral pathways, including human cytomegalovirus, Epstein–Barr virus, human papillomavirus, and HIV1 infection pathways. • Compared with the reported 284 SARS-CoV-2/COVID-19-related genes from GencLip3, authors identified 52 SARS-CoV-2/COVID-19-related protein alterations when treated with and without ivermectin. • Molecular complex detection analysis of protein–protein network identified three hub modules, including cytokines and growth factor family, mitogen-activated protein kinase and G-protein family, and human leukocyte antigen class proteins. • Gene ontology analysis revealed 10 statistically significant cellular components, 13 molecular functions, and 11 biological processes. • Conclusions: the broad-spectrum antiviral property of ivermectin is beneficial for COVID-19 treatment in the context of predictive, preventive, and personalised medicine in virus-related diseases.
Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19 DiNicolantonio, et al. 2020 (22)	• Editorial. • Article described early mice studies of Ivermectin. • Article describes two retrospective pre-publication reports in hospitalised patients with COVID-19, some of whom received treatment with ivermectin. • Rajter et al, have reported that, in univariate analysis, mortality in 173 patients receiving one or more doses of ivermectin was significantly lower than in 107 patients not so treated (15% vs 25.2%, p=0.03); after multivariate adjustment for pertinent covariates, this mortality difference was confirmed. • Gorial et al included16 patients who received ivermectin had hospital stays averaging 7.62 days, lower than the average hospital stays of 71 patients not receiving ivermectin (13.22 days; p=0.00005). Two patients died in the control group, none in the ivermectin group. • Conclusions: as the impact of ivermectin on antiviral immunity has not been studied, it is unclear whether it would be prudent to withhold its use until later-stage COVID-19.
Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating	• Narrative review on a three-part prevention, diagnostic, and treatment plan for COVID-19. • Only prevention and treatment relevant to ivermectin have been extracted below.

Source	Summary
Peer reviewed sources	

controlled randomized trials
 	
Horowitz, et al. 2020 (23)
	• Regarding the second part of the plan, prevention:
	  ○ ivermectin has been published to have antiviral properties against COVID-19
	  ○ a randomised trial of ivermectin, and/or nutraceuticals that has been published to support immune function could be beneficial.
	• Regarding the third part of the plan, treatment:
	  ○ other potential treatments being considered are ivermectin
	  ○ an international, multicentre observational case-controlled study in 1,408 patients with COVID-19 (half of whom received ivermectin) demonstrated a lower in-hospital mortality (1.4%) in the treatment group, versus an 8.5% mortality in the non-treatment group).

The battle against COVID 19 pandemic: what we need to know before we "test fire" ivermectin Banerjee, et al. 2020 (24)	• Narrative review reflecting on past use of ivermectin. • In the past two years, efficacy study in animal models of pseudorabies and Zika virus was found to be favourable and unfavourable respectively. • Only one clinical study evaluated the drug in dengue virus infection without any clinical efficacy. • Research on earlier SARS-CoV to which SARS-CoV-2 is closely related, shows that the virus possesses a well-developed system to interact with the host nuclear import pathway. • The proposed mechanism of drug action, by inhibiting the importin family of nucleus-cytoplasmic transporters along with favourable pharmacokinetics, warrants exploration of its role in COVID-19. • At the time of this publication, there were two health organisations recruiting participants in placebo controlled interventional trials and three other trials enlisted to start recruitment.
Clinically approved antiviral drug in an orally administrable nanoparticle for COVID-19 Surnar, et al. 2020 (25)	• In vitro animal cell study. • Aims: to test if ivermectin packaged in an orally administrable nanoparticle could serve as a vehicle to deliver a more potent therapeutic antiviral dose and investigate its efficacy to decrease expression of viral spike protein and its receptor angiotensin-converting enzyme 2. • Ivermectin dose: not applicable, not tested in human patients. • Results: the ivermectin nanoformulation was able to decrease expression of viral spike protein and its receptor angiotensin-

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	converting enzyme 2. Targeted nanoparticle delivered ivermectin was able to inhibit the nuclear transport activities mediated through proteins such as importin α/β1 heterodimer as a possible mechanism of action.
Ivermectin treatment may improve the prognosis of patients with COVID-19 Khan, et al. 2020 (11)	• Retrospective controlled trial with 248 patients with SARS-CoV-2 infection confirmed by PCR of nasal swabs to assess the clinical efficacy of ivermectin in COVID-19 patients. • Setting is Bangladesh, April to June 2020. • 115 patients received ivermectin plus standard care, while 133 received only standard care. • Ivermectin dose: ivermectin was given once at dose of 12mg within 24 hours after hospital admission. • Results: ivermectin seemed to control the course of the disease in patients with COVID-19. None of the ivermectin-treated patients showed progressive pathology, such as pneumonia or cardiovascular complications. On the other hand, 9.8% of standard care patients developed pneumonia and 1.5% had ischemic stroke. Significantly fewer ivermectin-treated patients required oxygen inhalation (9.6% ivermectin group vs 45.9% standard care group), developed respiratory distress (2.6% vs 15.8%), or needed antibiotic treatment (15.7% vs 60.2%) and intensive care management (0.9% vs 8.3%). Patients receiving ivermectin became SARS-CoV-2 negative more quickly (median 4 days vs 15 days; 95% CI, 8.97-10.59; p<0.001). The ivermectin-treated patients also had shorter hospital stays (median 9 days vs 15 days; 95% CI, 5.09-7.51; p<0.001). The mortality rate was significantly lower in the ivermectin group than standard care (0.9% vs 6.8%; p<0.05). There was no adverse events or complications reported from patients using ivermectin.
A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness Ahmed, et al. 2020 (12)	• Three-arm randomised controlled trial of oral ivermectin vs ivermectin plus doxycycline vs placebo to determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients. • 72 patients were enrolled, with 24 patients per study arm. • Ivermectin dose: oral ivermectin alone was 12mg once daily for 5 days. Combination ivermectin plus doxycycline was 12mg ivermectin single dose and 200mg stat doxycycline day 1 followed by 100mg 12 hourly for next 4 days. • Results: virological clearance was earlier in the 5-day ivermectin treatment arm vs the placebo group (9.7 days vs 12.7 days;

Source	Summary
Peer reviewed sources	
	p=0.02); but not with the ivermectin plus doxycycline arm (11.5 days; p=0.27). Changes in patient symptoms were not statistically significant for fever (p=0.35 and 0.09), cough (p=0.18 and 0.23) or sore throat (p=0.35 and 0.09) in the ivermectin plus doxycycline and the 5-day ivermectin groups when compared with placebo. There were no severe adverse drug events recorded in the study.
A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin Hellwig, et al. 2020 (26)	• Aims: Should ivermectin be used prophylactically against SARS-CoV-2? • Study characteristics: retrospective data analysis of national databases. Collected data from, mainly African, countries that routinely deploy prophylactic chemotherapy using various drugs including ivermectin. • Ivermectin dose: varied • Results: Countries with routine mass drug administration of prophylactic chemotherapy including ivermectin have a significantly lower incidence of COVID-19.

Inhaled route and anti-inflammatory action of ivermectin: Do they hold promise in fighting against COVID-19?
Mittal, et al. 2020 (27)
	• Narrative review.
	• What is the role of inhaled ivermectin in COVID-19? Can ivermectin be used as anti-inflammatory agent in COVID pneumonia?
	• Ivermectin dose: varied.
	• Results
	  ○ There is no current human trials evidence for the role of inhaled ivermectin in COVID-19.
	  ○ The authors note that there are 33 clinical trials registered with clinicaltrials.gov evaluating the role of oral, parenteral or nasal ivermectin in COVID-19.
	  ○ There is no current human trials evidence for the role of ivermectin as an anti-inflammatory agent in COVID-19

Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19): a structured summary of a study protocol for a randomized controlled trial Vallejos, et al. 2020 (28)	• Randomised controlled trial protocol. IVERCOR-COVID19 will be a single-centre, prospective, randomised, double-blind, parallel group (1:1 ratio), placebo-controlled study. Setting will be Argentina. • To assess the efficacy of ivermectin in addition to standard treatment compared to standard treatment alone in reducing hospitalisations in the COVID-19 patient population. • Ivermectin dose: patients who are randomised to ivermectin will receive the dose according to their weight (patients up to 80kg will

Source	Summary
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	receive 2 tablets of 6mg ivermectin; patients with more than 80kg and up to 110kg will receive 3 tablets of 6mg of ivermectin; patients weighing more than 110kg will receive 4 tablets of 6mg ivermectin) the day they enter the study and the same dose 24 hours after the first dose. • Results: no results yet.
Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis Padhy, et al. 2020 (8)	• Systematic review and meta-analysis to assess the therapeutic potential of ivermectin for the treatment of COVID-19 as add on therapy. • Ivermectin dose: varied. • Results: o 629 patients were included from four included studies and all patients were COVID-19 reverse transcription PCR positive. Among them, 397 patients received ivermectin along with usual therapy. o The random effect model showed the overall pooled odds ratio to be 0.53 (95% CI: 0.29 to 0.96) for the primary outcome (all-cause mortality) which was statistically significant (p=0.04). o Similarly, the random effect model revealed that adding ivermectin led to significant clinical improvement compared to usual therapy (odds ratio=1.98, 95% CI: 1.11 to 3.53, p=0.02). o However, this should be inferred cautiously as the quality of evidence is very low. Currently, many clinical trials are ongoing, and definitive evidence for repurposing this drug for COVID-19 patients will emerge only in the future.
Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients Camprubi, et al. 2020 (29)	• Retrospective study identifying hospitalised patients diagnosed with SARS-CoV-2 infection receiving ivermectin between 10 and 30 March 2020 in a hospital clinic in Barcelona, Spain. • Evaluated clinical and microbiological outcomes of 13 patients with confirmed SARS-CoV-2 severe infection receiving standard doses of ivermectin in comparison with a similar group of patients not receiving ivermectin. • Ivermectin dose: used dosage as for treating strongyloides stercoralis (receiving immunosuppressant drugs such as corticosteroids or tocilizumab) for COVID-19 patients, which was ivermectin 200µg/kg, single dose, following standard hospital procedures. Note that in the ivermectin group, 5 (38.5%) patients

Source	Summary
Peer reviewed sources	
	were treated with tocilizumab, 3 (23.1%) with high doses of steroids, 3 (23.1%) with both tocilizumab and steroids, and 2 (15.3%) with tocilizumab, steroids and anakinra. • Results: No relevant differences in microbiological or clinical outcomes were observed between groups. SARS-CoV-2 PCR from nasopharyngeal swabs performed between 3 and 5 days after receiving ivermectin resulted positive in 5 out of 13 patients in the ivermectin group (38.5%), and 4 out of 13 in the non-ivermectin group (30.8%, p>0.999). A remarkable clinical improvement was observed in 9 (69.2%) participants receiving ivermectin and in 10 (76.9%) of the non-ivermectin group, with no differences between groups (p >0.999), 8 to 11 days after ivermectin treatment (or equivalent time in the non-ivermectic group).
Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis Szente Fonseca, et al. 2020 (30)	• Retrospective patient chart review. • A large health maintenance organisation, in Brazil allowed physicians to prescribe antiviral medications immediately at presentation, and prednisone starting on day 6 of symptoms to treat pulmonary inflammation. They implemented this COVID-19 protocol for outpatients and studied 717 consecutive SARS-CoV-2-positive patients age 40 years or older presenting at the emergency rooms. • Ivermectin was only given for discharged patients, and in combination with other drugs. The COVID-19 protocol included (all as oral medications), as chosen by doctors and patients: hydroxychloroquine as first-line treatment, if used (400mg twice day 1, 400mg daily days 2-5), prednisone (1mg/kg daily for 5 days, maximum 80mg/day, no taper), azithromycin (500mg daily for 5 days), ivermectin (12mg daily for 2 days), plus symptom relievers. Zinc sulfate, oseltamivir and nitazoxanide were also available to be prescribed but were used infrequently. • Results: ivermectin, azithromycin and oseltamivir did not substantially reduce hospitalisation risk further (in addition to hydroxychloroquine, prednisone or both).
Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial Krolewiecki, et al. 2020 (2)	• A pilot, randomised, controlled, outcome-assessor blinded clinical trial with the goal of evaluating the antiviral activity of high dose ivermectin in COVID-19 patients. • Eligible patients were adults (aged 18 to 69 years) with mild or moderate reverse transcription PCR confirmed infection within five days of symptoms onset.

Source	Summary
Peer reviewed sources	
	• 45 patients were randomised in a 2:1 ratio to standard of care plus oral ivermectin at 0.6mg/kg/day for five days versus standard care. The primary endpoint was viral load reduction in respiratory secretions at day five. • There was no difference in viral load reduction between groups but a significant difference in reduction was found in patients with higher median plasma ivermectin levels (72% interquartile range 59-77) versus untreated controls (42% interquartile range 31-73) (p=0·004).

Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic
Elgazzar et al. 2020 (3)
	• A multicentre randomised controlled clinical trial to evaluate the anti-parasitic medication efficacy of ivermectin plus standard care (azithromycin, vitamin C, zinc, lactoferrin, acetylcystein and prophylactic or therapeutic anticoagulation if D-dimer >1000) in the treatment of mild or moderate and severely ill cases with COVID-19, as well as prophylaxis of healthcare and/or household contacts in comparison to the hydroxychloroquine plus standard treatment.
	• 600 subjects divided into six groups.
	  ○ Group 1: 100 patients with mild or moderate COVID-19 received a 4 day course of ivermectin 400µg/kg body weight maximum four tablets (6mg per tablet) once daily before breakfast plus standard of care as issued by Egyptian protocol of COVID-19 treatment.
	  ○ Group 2: 100 patients with mild or moderate COVID-19 infection received hydroxyxholorquine (400mg every 12 hours for one day followed by 200mg every 12 hours for five days) plus standard care.
	  ○ Group 3: 100 patients with severe COVID-19 infection received a four day course of ivermectin 400µg /kg body weight maximum four tablets (6mg per tablet) once daily before breakfast plus standard care
	  ○ Group 4: 100 patients with severe COVID-19 infection received hydroxyxholorquine (400mg every 12 hours for one day followed by 200mg every 12 hours for nine days) plus standard care.
	  ○ Group 5: 100 patient contacts, healthcare workers or household members, received a prophylactic dose of ivermectin 400µg /kg single oral dose before breakfast to be repeated after one week in addition to personal protective equipment.

Source	Summary
Peer reviewed sources	
	○ Group 6: 100 patient contacts, healthcare workers or household members, received only personal protective equipment. • Patients who received standard care plus ivermectin reported substantial improvement in laboratory and severity parameters; total lymphocytes count, lymphocyte (%),C-reactive protein, D-dimer, and reverse transcription PCR conversion days (6.4±2.1, 32.4±6.8, 4.8±2.1, 94.8±48.6, 0.54±0.06 and, 5±1, respectively) compared to group 2, treated by standard care, (7.1±2.3, 28.2±3.9, 8.3±3.6, 98.4±54.8, 0.68±0.21 and, 10±4, respectively) one week after starting treatment ($p<0.001$). • The prognosis of the disease reported a significant improvement in groups which received ivermectin plus standard care (groups 1 and 3, 99% and 94% respectively) compared to those received hydroxychloroquine plus standard care only (groups 2 and 4, 74% and 50% respectively), (p-value <0.001). The mortality rate significantly reduced in ivermectin treated patients group 1 and 3 (0.0% and 2%, respectively) versus hydroxychloroquine groups 2 and 4 (4% and 20%, respectively).
Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial Niaee et al. 2020 (4)	• Randomised, double-blind, placebo-controlled, multicentre, phase 2 clinical trial was designed at five hospitals to determine the efficient dose of ivermectin for 45 days, with 180 mild to severe hospitalised patients with confirmed COVID-19 infections. • Participants were randomly allocated to six arms including common regimen based on Iran health ministry (hydroxychloroquine 200mg/kg twice per day), placebo plus common regime, single dose ivermectin (200µg/kg, one pill per day), three low interval doses of ivermectin (200µg/kg each, three pills, in one, three and five day intervals), single dose ivermectin (400µg/kg, two pills per day), and three high interval doses of ivermectin (400, 200 and 200µg/kg, four pills, in one, three and five day intervals). • Complete blood count evaluation of the patients among the standard and placebo and ivermectin treated (arms three to six) showed that ivermectin had a good effect on blood biomarkers and improved other clinical parameters such as absolute lymphocyte count, C-reactive protein, thrombocyte count, erythrocyte sedimentation rate, lactate dehydrogenase, blood urea nitrogen, and creatinine. A decrease in hospitalisation and low oxygen saturating terms was significant in ivermectin treated 1-4 arms compared to the two untreated controls (p=0.006 and p=0.025 respectively).

Table 2. Evidence from grey literature

Source	Summary
Grey literature sources	
Recommendation regarding the use of ivermectin as a treatment for COVID-19, 22 June 2020 Pan American Health Organization, 2020 (7)	• A recent study reported that ivermectin was successfully used in vitro for the treatment of SARS-CoV-2 in experimentally infected cells, and two preprint publications reported observational clinical studies on the apparent utility of ivermectin to treat patients with COVID-19 needing mechanical ventilation. • None of these studies was peer-reviewed nor formally published and one study was later retracted. • The Pan American Health Organization compiled an evidence database of potential COVID-19 therapeutics for which a rapid review was conducted of all COVID-19 in vitro (lab) and in vivo (clinical) human studies published from January to May 2020. • The review concluded that the studies on ivermectin were found to have a high risk of bias, very low certainty of the evidence, and that the existing evidence is insufficient to draw a conclusion on benefits and harms. • Though the effectiveness of ivermectin is currently being evaluated in various randomized clinical trials, the World Health Organization excluded ivermectin from its co-sponsored solidarity trial for COVID-19 treatments. • The *Mectizan® (ivermectin) Expert Committee Statement on Potential Efficacy of Ivermectin on COVID-19* emphasised that the laboratory results showing efficacy of ivermectin to reduce viral loads in laboratory cultures, at dosage levels far beyond those approved by the US Food and Drug Administration for treatment of parasitic diseases in humans, are not sufficient to indicate that ivermectin will be of clinical benefit to reduce viral loads in COVID-19 patients. • Chaccour et al. caution against using in vitro findings as more than a qualitative indicator of potential efficacy and emphasize that 'due diligence and regulatory review are needed before testing ivermectin in COVID-19'.
The ethics of COVID-19 treatment studies: too many are open, too few are double-masked Aronson, et al. 2020 (31)	• The Centre for Evidence-Based Medicine review on ethics of COVID-19 treatment studies included the following reference. • The US Food and Drug Administration issued a warning to the American public not to rush out and buy ivermectin formulated for treating parasitic infections in animals, following the publication of a preprint describing the effects of ivermectin on SARS-CoV-2 in a laboratory petri dish.

Source	Summary
Grey literature sources	
Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19 Kory, et al. 2020 (9)	• Front Line COVID-19 Critical Care Alliance update from 18 December 2020. • Ivermectin, an anti-parasitic medicine, has highly potent antiviral and anti-inflammatory properties against SARS-CoV-2 and COVID-19. • This conclusion is based on the increasing study results reporting effectiveness, not only within in vitro and animal models, but in numerous clinical trials.
COVID-19 update: invermectin Rezaie, 2020 (32) (REBEL-EM COVID-19)	• Evidence review: does ivermectin demonstrate efficacy in prophylaxis and treatment of COVID-19?, published on 16 December 2020. • Evidence for the use of ivermectin is based on in vitro, prophylaxis, clinical, safety, and large-scale epidemiologic studies (heterogenous populations in multiple different settings). • Many of the trials thus far are methodologically flawed without enough information about baseline demographics, multiple primary outcomes, soft or subjective outcomes, convenience samples, and unclear definitions. • A valid concern in evaluating the literature is that many of the trials have not yet passed the peer review process and are in pre-print format. • Although ivermectin is cheap, readily available, with a fairly safe side effect profile, based on the evaluation of the literature above, at this time, ivermectin should not be recommended outside of a clinical trial to ensure we get a true answer of effect.
FAQ: COVID-19 and ivermectin intended for animals U.S. Food and Drug Administration, 2020 (14)	• Content current as of 16 December 2020. • There are approved uses for ivermectin in people and animals, it is not approved for the prevention or treatment of COVID-19.

Appendix

PubMed search terms

- PubMed was searched using (COVID-19 AND ivermectin) AND LitCTREATMENT[filter]

Google search terms

- Ivermectin COVID-19", first 10 pages

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