Ivermectin

RECOMMENDATION

We recommend against the use of ivermectin as COVID-19 prophylaxis for the general population. *(Very low quality of evidence; Strong recommendation)*

We recommend against the use of ivermectin for COVID-19 as post exposure prophylaxis for household contacts of confirmed COVID- 19 patients *(Very low quality of evidence; Strong recommendation)*

We recommend against the use of ivermectin for COVID-19 as prophylaxis for healthcare workers. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

The studies included in the review have very serious or high risk of bias. In particular, the study by Elgazzar et al. (2021) had a very low overall quality of evidence due to the risk of bias and serious imprecision from the wide 95% confidence interval (CI). The Shoumann et al. (2021) study also has a serious validity issue due to the premature termination of the control group, and lack of pretermination protocol, thus leading to selective reporting. Lastly, the results of the Chahla et al. (2021) study also have validity issues due to the presence of a co-intervention in the treatment arm. These methodologic limitations leads to uncertainty in the effects of ivermectin.

The panel recognized the high likelihood for its misuse or overuse and the concomitant false sense of security. The panel also stressed that there is a need to have concrete evidence on safety, as well as on the appropriate dose and dosing frequency, which the current very low quality evidence did not provide. Another issue raised was that only a compassionate special permit (CSP) has been granted to two specific hospitals that applied for the permit, despite the current registration of ivermectin products as veterinary treatment for internal and external animal parasites. Hence, there may be legal implications when a positive recommendation to use it as a prophylaxis is issued. The human-grade ivermectin, on the other hand, is still applying for emergency use authorization (EUA) from the Philippine Food and Drug Administration. Considering the vaccine hesitancy of the public, a concern was raised by the panel that if a recommendation to an alternative to the vaccine as prophylactic agent will be made, then people may opt not to get vaccinated, undermining the national vaccination program of the government.

Should ivermectin be used as COVID-19 prophylaxis for the general population?

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Key Findings

Three very low quality randomized controlled trials (RCT) were found on the use of ivermectin as COVID-19 prophylaxis. Both RCTs showed indirect evidence for the general population, and were also found to have very serious risk of bias particularly on blinding, incomplete outcome, and selective reporting. One RCT showed lower rates of developing COVID-19 related symptoms. Another RCT showed lower RT-PCR-confirmed COVID-19 infection rates in the ivermectin group compared to non-intervention group. Thirdly, one RCT revealed a lower rate of RT-PCR-confirmed COVID-19 in the ivermectin group, however, the administration of a co-intervention in this group poses serious validity issues in the outcome of interest. Mild adverse events were reported such as gastrointestinal upset, fatigue, sleepiness, pruritus, numbness, and burning sensation, all of which did not necessitate discontinuation of therapy.

Introduction

Ivermectin, an anti-parasitic agent used for onchocerciasis and lymphatic filariasis, is currently being investigated as treatment and prophylaxis for COVID-19 due to its potential anti-viral effect against SARS-CoV-2 [1-3]. In an *in vitro* study by Caly *et al*. [4], SARS-CoV-2 infected cells that were treated with ivermectin two hours after infection were found to have a 99.98% reduction in viral RNA load on real-time polymerase chain reaction (RT-PCR) after 48 hours. It has been hypothesized that ivermectin inhibits importin $\alpha/\beta 1$-mediated transport of viral proteins into the host's cell nucleus, which is also the proposed mechanism of action of ivermectin in other RNA viruses. Given the promising *in vitro* findings and known safety profile of ivermectin, several clinical trials are now in progress to determine if this repurposed drug may be of significant value in controlling COVID-19 transmission.

Review Methods

Literature search was conducted on electronic databases and clinical trial registries (PubMed, CENTRAL, ClinicalTrials.gov, medRxiv.org, bioRxiv.org, covid-nma.com, COAP Living Evidence on COVID-19, Chinese and EU Clinical Trial Registry), and UpToDate on March 16-18 and April 21, 2021. Terms such as "COVID-19", "ivermectin", "prophylaxis" or "prevention" were used during the search. No limitation on language was set. Further review of references of retrieved studies was also done to check for other possible articles.

Studies that involved administration of ivermectin to high-risk contacts of COVID-19 patients such as household members and healthcare workers were included. Study outcomes included were development of COVID-19 infection or symptoms, and adverse events. Any studies that solely involved administration of ivermectin as treatment for COVID-19 patients were excluded.

This search strategy yielded 49 articles in PubMed. Studies cited in meta-analyses and systematic reviews by Kory *et al.* [5], Bryant *et al.* [6] and the British Ivermectin Recommendation Development [7] were also searched. After removing duplications, eight full-text articles were retrieved. Only three RCTs were included in the review after assessing for eligibility and methodology (Appendix 1). The six articles excluded in the review were case control and cohort studies, mostly involving healthcare workers [1-3,8-10].

Results

The three completed RCTs were by Elgazzar *et al.* [11], Shoumann *et al.* [12], and Chahla *et al.* [13] (Appendix 1). The multi-center double-blind study by Elgazzar *et al*. (preprint article) involved populations of COVID-19 patients (n = 400), and their household contacts and healthcare workers (n = 200), aiming on determining the efficacy and safety of ivermectin both as treatment and prevention of COVID-19 infection [11]. The household contacts and healthcare workers recruited for prophylaxis groups (ivermectin group and non-intervention group) had baseline negative RT-PCR results. Only the outcomes of these prophylaxis groups were included in this review. The study by Chahla *et al.* [13] recruited healthcare and non-healthcare (administrative) personnel from local healthcare centers (n = 234). The intervention group received a combination of ivermectin and iota-carrageenan, while the control group had no prophylaxis. COVID-19 diagnosis for each group was confirmed by RT-PCR. Lastly, the randomized open-label trial by Shoumann *et al.* [12] recruited asymptomatic household contacts (n = 340) of RT-PCR-confirmed COVID-19 patients. Recruitment was based on normal body temperature and lack of symptoms, and not on negative RT-PCR results, unlike the two RCTs. Only four symptomatic participants in ivermectin group and 12 symptomatic participants in non-intervention group underwent RT-PCR testing, which all had positive results. The study did not discuss the reasons for participant withdrawal.

The overall risk of bias was deemed to be very serious. The study by Elgazzar *et al.* [11] had blinding issues due to absence of placebo in the control group, unclear allocation concealment, and selective reporting of results due to unavailable data on adverse events. No baseline and outcome data on the subgroups (household contacts and healthcare workers) were presented. Shoumann *et al.* [12] also lacked blinding and had unclear allocation concealment. Per protocol analysis was made due to exclusion of drop-outs. Furthermore, the premature termination of the control group due to perceived high protective effect of ivermectin was another source of serious bias. Chahla *et al.* [13] also had issues on blinding and allocation concealment similar to the two RCTs. Administration of a co-intervention in the ivermectin group poses a serious risk of bias as well.

All three studies determined the COVID-19 infection rate as primary outcome within 14-day follow-up period after contact [11-13]. Results were not pooled since the studies had variable outcome definitions (RT-PCR confirmed COVID-19 vs presence of COVID-19 symptoms). The study by Elgazzar *et al.* [11] showed that the rate of developing RT-PCR confirmed COVID-19 was 2% in ivermectin group compared to 10% in non-intervention group (RR 0.2, 95% CI 0.05 to 0.89). There were no available data on the subgroup analysis between healthcare workers and household contacts. Although with significant protection in the ivermectin group, the confidence interval was wide, and the risk of bias for this study was deemed to be very serious as mentioned above.

Similarly, Chahla *et al.* [13] looked into the number of patients who tested positive with RT-PCR for COVID-19. However, since a co-intervention in the form of iota-carrageenan spray was also used in the treatment arm, we decided not to combine its results with the earlier study. The incidence of RT-PCR confirmed COVID-19 in the ivermectin plus iota-carrageenan group was 3.4% compared to 21.4% in the control group (RR 0.16, 95% CI 0.06 to 0.45). The study's very serious risk of bias may have also affected the frequency of outcomes.

The second outcome was the development of COVID-19 related symptoms as reported by Shoumann *et al.* [12] Statistically significant difference between the two groups in favor of ivermectin prophylaxis group (7.4% vs 58.4%, p <0.001) was reported (RR 0.13, 95% CI 0.08 to 0.21). Despite showing clear benefit, the results should be interpreted with caution due to its very serious risk of bias as mentioned above, and its methodological inconsistencies. The study did not use the gold standard test (RT-PCR) both as baseline and as confirmatory test for majority of participants, and prematurely terminated the control arm. The symptom-based approach in COVID-19 diagnosis of Shoumann *et al.* might have missed an unknown number of asymptomatic carriers.

In terms of adverse events, Chahla *et al.* [13] had no reported adverse events. Elgazzar *et al.* [11] did not mention results on adverse events in the preprint article. However, through email correspondence, the author revealed that only minor side effects were observed such as upper gastrointestinal upset, insomnia, and pruritus; no major side effects developed necessitating discontinuation of the drug. Similarly, Shoumann *et al.* [12] reported mild side effects in 11 (5.4%) subjects in the ivermectin group. Symptoms included diarrhea (1.5%), nausea (1%), fatigue (1%), sleepiness (0.5%), abdominal pain (0.5%), heart burn (0.5%), numbness (0.5%), and burning sensation (0.5%). Though the side effects were mild, statistical analysis showed significant difference (p = 0.018) between the ivermectin group and non-intervention group. These symptoms were similar to the known adverse events from systemic administration of ivermectin as anti-parasitic agent [14].

Recommendations from Other Groups

As of this writing, certain agencies have recommended against the use of ivermectin as COVID-19 prophylaxis. In particular, the European Medicine Agency [15] has concluded that the currently available data have not been found to be sufficient to support the use of ivermectin for COVID-19 outside of clinical trials. Other groups such as Infectious Diseases Society of America [16], and Alberta Health Services COVID-19 Scientific Advisory Group [17] have expressed similar recommendations in their latest guidelines on COVID-19 management, citing presence of confounding factors and very low to low certainty of evidence. The National COVID-19 Clinical Evidence Taskforce of Australia [18] has not yet made recommendations on this topic due to insufficiency of well-designed clinical trials. The guideline development group of the World Health Organization [19] has not issued a statement on ivermectin as COVID-19 prophylaxis stating that the topic is not included in the scope of the guidelines.

The US Food and drug Administration (FDA) [20] and Philippine FDA [21] both have not approved the use of ivermectin for COVID-19 prevention. However, as of April 17, 2021, the Philippine FDA

has granted a compassionate use permit to use Ivermectin as COVID-19 treatment to two unnamed hospitals [22,23].

Research Gaps

Majority of the nine ongoing RCTs on ivermectin as COVID-19 prophylaxis in various trial registries have started recruitment, and will be completed as early as April 2021 (Appendix 4). Additionally, two RCTs have already been completed on registry, but all have yet to publish or release their preliminary results (Appendix 3)

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Appendix 1. Table of Included Studies

Study (RCTs)	Population, n	Intervention	Control	Outcome
Elgazzar *et al.,* 2021 (preprint)	health care and household contacts of COVID-19 patients; Age 18-80 years n = 200	Ivermectin 0.4 mg/kg BW single oral dose, and another dose after 1 week	No Ivermectin, only usual standard precautions and PPE	Primary outcome: • Prevention of COVID-19 (RT PCR confirmation) Secondary outcome: • Adverse events
Shoumann *et al.,* 2021	asymptomatic household contacts of confirmed RT-PCR COVID-19 index case; Age ≥ 16 years n = 340	Ivermectin 0.225-0.375 mg/kg: 15 mg/day per orem for subjects 40-60 kg BW; 18 mg/day for 60-80 kg; 24 mg/day for >80 kg, given on D1 and D3 from diagnosis day	No Ivermectin, only usual standard precautions and PPE	Primary outcome • Prevention of COVID-19 by D14 of follow-up (symptom-based) Secondary outcomes: • Occurrence of disease before 14 days • Drug side effects
Chahla *et al.*, 2021	Personnel who perform patient care and administrative tasks (healthcare and non-healthcare personnel) n = 234	Ivermectin 12mg/tab PO every 7 days, + Iota-carrageenan 6 oral sprays per day, for 4 weeks	No Ivermectin or carrageenan, only usual standard precautions and PPE	Primary outcome: • Prevention of COVID-19 (RT PCR confirmation) Secondary outcome: • Adverse events

Appendix 2. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	no Ivermectin	Relative (95% CI)	Absolute (95% CI)		
Development of RT-PCR confirmed COVID-19 (Elgazzar 2021)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	2/100 (2.0%)	10/100 (10.0%)	**RR 0.2000** (0.0450 to 0.8898)	**80 fewer per 1,000** (from 96 fewer to 11 fewer)	⨁◯◯◯ VERY LOW	
Development of RT-PCR Confirmed COVID-19 (Chahla 2021)												
1	randomised trials	very serious [e]	not serious	serious [b]	not serious	none	4/117 (3.4%)	25/117 (21.4%)	**RR 0.1600** (0.0575 to 0.4455)	**179 fewer per 1,000** (from 201 fewer to 118 fewer)	⨁◯◯◯ VERY LOW	
Development of COVID-19 related symptoms (Shoumann 2021)												
1	randomised trials	very serious [d]	not serious	serious [b]	not serious	none	15/203 (7.4%)	59/101 (58.4%)	**RR 0.1265** (0.0757 to 0.2115)	**510 fewer per 1,000** (from 540 fewer to 461 fewer)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Unclear allocation concealment, incomplete reporting of results (article was only a preprint), no data on breakdown of household contacts and healthcare workers

b. Indirect evidence for the general population

c. Wide confidence interval

d. The study by Shoumann demonstrated high risk of bias in terms of blinding, selective reporting and incomplete outcome data. Subjects recruited did not undergo baseline RT-PCR tests to confirm that they were indeed COVID negative. Most participants in both groups who were diagnosed to have COVID-19 infection also did not undergo confirmatory RT-PCR tests, and were only diagnosed based on presence of symptoms. The non-intervention group was also prematurely stopped due to the perceived high protective efficacy of Ivermectin by the researchers.

e. Lack of blinding, allocation concealment, co-intervention bias

Appendix 3. Table of Completed Unpublished Studies (no preprint available)

Study	Population/Setting	Intervention	Control	Outcomes	Status
A Preventive Treatment for Migrant Workers at High-risk of COVID-19 NCT04446104 Randomized Open-label trial Author: National University Hospital, Singapore	Men residing in dormitory Ages 21-69 years 4257 participants Singapore	Arm 1: Hydroxychloroquine Arm 2: Ivermectin Arm 3: Zinc/Vit C Arm 4: Povidone-iodine throat spray Arm 5: Vitamin C	-	Primary: Laboratory-confirmed COVID-19 Secondary: 1. Acute respiratory illness in treatment arms 2. Febrile respiratory illness in treatment arms 3. Rate of hospitalization for COVID-19 and non-COVID-19 related indications 4. Rate of O2 supplementation 5. Duration of O2 supplementation and mechanical ventilation 6. Length of hospital stay 7. Rate of laboratory-confirmed COVID-19 8. Adverse events and serious adverse events 9. Drug discontinuation due to adverse events	Completed, no available results Completion date: August 31, 2020
Evaluation of prophylaxis induced by ivermectin in populations exposed to COVID-19 patients IRCT20200408046987N3 Randomized trial	Healthy individuals exposed directly and constantly with COVID-19 patients Ages 18-65 years Iran	Ivermectin	Placebo	Primary: 1. Percentage of patients in family members 2. Duration of Illness 3. Severity of Illness Secondary: 1. Considering the drug side effects 2. IgA 3. IgM 4. IgG	Completed Completion date: December 30, 2020

Author: Gheibi				5. Duration of illness with recheck of RT-PCR	

Appendix 3. Table of Ongoing Studies

Study	Population/Setting	Intervention	Control	Outcomes	Status
Efficacy of Nano-Ivermectin Impregnated Masks in Prevention of Covid-19 Among Healthy Contacts and Medical Staff NCT04723459 Randomized Open-label trial	Health care personnel and family contact of confirmed COVID-19 cases Ages 18 years and older Estimated: 150 participants Egypt	Ivermectin mask	Ordinary Mask	Primary: 1. Number of persons who complain of any suspected symptoms (within 14 days after enrolment) Secondary: 1. Number of persons who are diagnosed as COVID-19 patients (within 21 days of enrolment)	Recruiting Estimated Completion Date: February 28, 2021 (not yet updated in registry)
Comparative Study of Hydroxychloroquine and Ivermectin in COVID-19 Prophylaxis NCT04384458 Randomized open-label trial	Professionals working in areas of high exposure and high risk of transmission of COVID-19 Ages 18-70 years Estimated: 400 participants Brazil	Ivermectin	Hydroxychloroquine	Primary: 1. Proportion of participants positive for COVID-19 (post-intervention at day 52) Secondary: 1. Participants who developed mild, moderate, or severe forms of COVID-19 (proportion according to severity) 2. Measurement of QT interval 3. Widening of corrected QT interval or with changes in heart rate on ECG 4. Comparison of hematological and biochemical parameters 5. Occurrence of adverse events 6. Assessment of COVID-19 symptom severity 7. Proportion of participants who	Recruiting Estimated completion date: April 2021

				discontinue study intervention 8. Proportion requiring hospital care 9. Proportion requiring mechanical ventilation	
Exploratory Ph I Trial of the Active IMP in Healthy Volunteers in Relation to COVID-19 NCT04632706 Randomized Double-Blind, Placebo-controlled Trial	Healthy male with negative RT-PCR test for SARS-CoV 2 Ages 18-45 years Estimated: 24 participants United Kingdom	Ivermectin 50 mcg/kg, 75 mcg/kg, 100 mcg/kg doses	Placebo	Primary: 1. Maximum plasma concentration (Cmax) 2. Time to reach Cmax (Tmax) 3. Trough Plasma Concentration 4. Area under the plasma concentration-time curve from zero to 24 hrs 5. Area under the plasma concentration-time curve from zero to 48 hrs 6. Apparent Terminal Half-life Secondary: 1. Number of participants with treatment emergent adverse events 2. Number of participants with abnormal ECG 3. Number of participants with abnormal clinical neurological exam 4. Number of participants with abnormal urine and/or blood test 5. Number of participants with abnormal physical exams	Recruiting Estimated completion date: May 2021
Prevention and Treatment for COVID-19 associated severe	Cohort 1: -Index case ≥ 5 years with confirmed COVID-19 mild	Ivermectin	Placebo	Primary: 1. Cohort 1 Index Case: Percentage of patients with COVID-19	Recruiting Estimated completion

Pneumonia in the Gambia (PaTS-COVID) NCT04703608 Single-Blinded Randomized Trial	disease or moderate pneumonia -Household contacts Cohort 2: Individuals ≥ 12 years with suspected or confirmed COVID-19 associated severe pneumonia Ages ≥ 5 years Estimated: 1200 participants Gambia			2. Cohort 1 Household contacts: Percentage of HH members that get infected with COVID-19 3. Cohort 2: Percentage of COVID-19 associated severe pneumonia patients Secondary: 1. Days from recruitment to virological clearance 2. Days from recruitment until clinical recovery 3. IgG 4. HH contacts IgG 5. Percentage of HH members infected that develop COVID-19 symptoms	date: July 2022
Effectiveness and Safety of Ivermectin for the Prevention of COVID-19 Infection in Colombian Health Personnel (IveprofCovid19) NCT04527211 Randomized multi-center trial	Health care worker, with negative COVID-19 serological antibody test Age ≥ 18 years Estimated: 550 participants Colombia	Ivermectin	Placebo	Primary: Clinical development of COVID-19 Secondary: 1. Seroconversion 2. Hospitalization requirement 3. ICU Requirement 4. Safety of the intervention	Not yet recruiting Estimated completion date: December 16, 2020
Prophylactic Ivermectin in COVID 19 Contacts CTRI/2020/08/027282	Healthy contacts of COVID-19 patients Ages 18-70 years India	Ivermectin	Placebo	Primary: Episodes and severity of symptoms of respiratory tract infection Secondary:	Not yet recruiting

Randomized Trial				1. Requirement of treatment for symptoms 2. Incidence of COVID-19 3. Analysis of adverse events	
Ivermectin in the prevention of COVID-19 CTRI/2020/06/026232 Randomized trial	Healthy volunteers with high chances of exposure to COVID-19 patients Age ≥ 18 years India	Ivermectin	Placebo	Primary: Clinical development of COVID-19 Secondary: 1. Seroconversion 2. Hospitalization requirement 3. ICU Requirement 4. Safety of the intervention	Recruiting Estimated completion date: July 2022
Study of the effects of using ivermectin to prevent COVID-19 in an adult population in Brazil ISRCTN90437126 Randomized trial	Healthy volunteer Ages ≥ 18 years Brazil	Ivermectin	Placebo	Primary: COVID-19 case diagnosis Secondary: 1. Clinical status of COVID-19 2. Incidence of severe COVID-19 3. Rate of adverse events 4. Hospitalization 5. Deaths	Recruiting Estimated completion date: June 30, 2021
Randomized clinical trial of ivermectin for treatment and prophylaxis of COVID-19 2020-001994-66 Randomized trial	Contacts of symptomatic COVID-19 patients Ages 18-64 years 229 participants Spain	Ivermectin	Placebo	Primary: Incidence of secondary cases of COVID-19 Secondary: 1. Morbidity and mortality at 28 days 2. Analytical values at 0, 7, 12, 21 days	Ongoing