Ivermectin (IVM) is an antiparasitic drug that is approved by the Food and Drug Administration (FDA) for the treatment of onchocerciasis and strongyloidiasis. Ivermectin is not FDA-approved for the treatment of any viral infection. In general, the drug is well tolerated. It is currently being evaluated as a potential treatment for COVID-19.

**Clinical Data**

Updated: Two meta-analysis\(^{14,15}\) published in July 2021. See summary of analysis in the meta-analysis table below.

The results of several randomized trials and retrospective cohort studies of IVM use in patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports. There are no well-designed controlled trials that have been published to date. However, pilot studies, or retrospective chart review of patients treated with IVM show a trend to benefit viral load reduction or overall decrease in mortality. The evidence table summarizes studies that have reported shorter time to resolution of disease manifestations attributed to COVID-19, greater reduction in inflammatory markers, shorter time to viral clearance, or lower mortality rates in patients who received ivermectin than in patients who received usual care or placebo.

Ivermectin was widely distributed among 8 states in Peru. Peru has reported a dramatic decrease in case fatality rates, especially among patients over 60 years old.\(^6\) These data, despite studied as part of controlled trial, resulted in the Peruvian government approving IVM use by decree on in May 2020. As a result of this, *in vitro* data and small reports, IVM use has created much interest and controversy in the scientific community. See evidence table for a data analysis (Ref 10) of all countries that deployed prophylactic chemotherapy with ivermectin compared to no ivermectin.

A long-awaited, placebo controlled trial (IVERCOR-COVID-19)\(^{16}\) conducted in Argentina was published in July 2021 that evaluated whether ivermectin prevents hospitalization in patients who have been diagnosed with early COVID-19. Patients were randomized to treatment vs placebo within 48 hours of a positive test result. A total of 501 participants were enrolled and randomized. Dosing will be either 12 mg, 18 mg or 24 mg daily for 2 days, based on patient's weight (48-80kg; 81-110kg, or > 110 kg, respectively). Enrollment completion date was in February 2021. Although the primary endpoint of hospitalization due to COVID was lower in the ivermectin treated group, this was not statistically significant. Overall low hospitalization was a limitation to this study. There were also no statistically significant differences in secondary endpoints evaluated (invasive mechanical ventilation, time to hospitalization, and PCR test negativity). The dose used in the study may have been too short duration and it also did not select for high risk patients.
Key points:

- No individual trial published to date is large enough to draw conclusions to incorporate into standard practice.
- Combined data from the controlled trials shows consistent benefit, however possible study bias and variances in standard of care therapies should be considered.
### NATIONAL GUIDANCE RECOMMENDATIONS SUMMARY:

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| **FDA Statement** to consumers (3/5/2021) **FAQ** (4/26/2021) | • Issued statement against ivermectin use in COVID-19. | • The FDA has received multiple reports of patients who have required medical support and been hospitalized after self-medicating with ivermectin intended for horses.  
• The FDA has not reviewed clinical data regarding efficacy and safety when ivermectin is taken for prophylaxis or treatment of COVID-19. |
| **IDSA** (2/5/2021) | • The panel suggests against ivermectin in both inpatients and outpatients, unless in the context of enrollment in clinical trials. | • The panel determined the certainty of evidence to be low and a risk for bias and imprecision within published studies. |
| **NIH** (1/14/2021 7/8/2021 evidence update) | • The COVID-19 Treatment Guidelines Panel (the Panel) has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.  
• In some of the published studies, the authors reported shorter time to resolution of disease manifestations, greater reduction in inflammatory marker levels, shorter time to viral clearance, or lower mortality rates in the IVM group vs a comparator or placebo.  
• Some studies have shown no benefit or worsening of COVID.  
• Note the limitations in many of the published studies | • The sample size of most of the trials was small.  
• Various doses and schedules of ivermectin were used.  
• Some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms.  
• In addition to ivermectin or the comparator drug, in some studies patients also received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids), confounding assessment of the true efficacy or safety of ivermectin.  
• The severity of COVID-19 in the study participants was not always well described.  
• The study outcome measures were not always clearly defined. |

It should be noted that Guidelines Groups of these expert bodies have found ivermectin (compare to placebo or control) to reduce mortality based on > 15 clinical trials or reports. Since the quality of available evidence graded is low or very low and there are no large well designed, RCTs published, IVM prescribing for COVID-19 is discouraged outside of a clinical trial.
META-ANALYSIS

On July 20, 2021, the pre-print publisher of Research Square, retracted the largest, long-awaited Egyptian study enrolling because of data set anomalies found and plagiarism. The study was one of the largest ivermectin trials (400-patients) in the world, and had been included in two recent meta-analyses (Bryant et al. and Hill et al.) that received much attention for their positive results. The authors of the meta-analysis plan to re-evaluate their analysis, withdrawing the retracted study from the studies included.

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<tr>
<th>AUTHORS/Country</th>
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<th>RESULTS</th>
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<tr>
<td>Bryant A, et al14, 2021</td>
<td>24 RCT met inclusion involving 3,406 participants ITT data was used for all analysis Authors of individual trials were contacted for clarity</td>
<td>Mortality was decreased with IVM with a RR of 62% vs no IVM Avg risk ration 0.38, 95% CI 0.19-0.73. These results were consistent among mild, moderate, and severe disease. Total of 15 trials included to assess mortality risk Moderate certainty Prophylaxis with IVM reduced COVID infection by an average of 86% (95% CI 79%-91%) – Low certainty Only 3trials Improvement/Deterioration – very low certainty Lack of benefit with IVM for need of mech ventilation Overall improvement favored IVM</td>
<td>NOTE: Differing doses used in studies was not evaluated or concluded. Authors found that most of the studies were self-funded by clinicians in the field. No obvious biases except potential bias in 2 trials total. Overall, evidence suggests that early IVM use may reduce morbidity and mortality from COVID-19 based on 1) reduction in infections when IVM is used for prophylaxis, 2) more favorable when IVM used for mild to moderate disease for any cause of death, 3) less deterioration.</td>
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<td>Hill, et al15, 2021</td>
<td>PRISMA Guidelines for literature review Primary: all-cause mortality (ITT- follow-up) Secondary: time to viral clearance, PCR negative at day 7; time to clinical recovery, mech vent; progress to hospitalization; days hospitalized. Included 24 RCTs. Total participants 3328. Dosing variations: Single dose: 9 trials</td>
<td>Individual report on inflammatory markers, 5 trials 4/5 trials – sig reduction in CRP vs control 1 trial reported sig reduced ferritin levels in the severe pt population/ no difference in mild to moderate disease. Another trial showed decreased ferritin on day 10. Two trials did not show a significant reduction in ferritin D-dimer2 studies showed significant decrease in d-dimer; one study did not (smaller sample size). Viral clearance: Appears to be a dose-dependent relationship with viral clearance. Studies that gave only on dose/day IVM had lower viral clearances.</td>
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FMCP 07/27/2021; 03/08/2021.lhr
Multi day dosing up to 7 days: 15 trials
Mild to moderate disease: 15 trials
Blinded (single or double sided) – 18 trials
Open – 6 trials

Most pronounced when IVM is given for 5 days or more and a dose of 0.4 mg/kg.
Mortality:
70% increased survival in the mild-moderate disease
No difference in mortality in participants with severe disease. It was noted that the number of deaths were small.
There were only 128 deaths reported in 11 clinical trials.

EVIDENCE

There are additional studies that have been conducted that are not included below – either because of design, or not published in full. The following studies are either most recent, most quoted or designed well enough to include.

<table>
<thead>
<tr>
<th>AUTHORS/Country</th>
<th>STUDY DESIGN AND REGIMEN</th>
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<tr>
<td>Lopez-Medina 13</td>
<td>RCT, DB single site in Cali, Columbia. Participants identified by random sampling from the state’s health dept electronic database of laboratory confirmed, COVID-19 and symptoms. Time period: July 15-Nov 30, 2020 Total of 476 adult patients identified who had • Mild disease • Symptoms ≤ 7 days • Inpatient or outpatient Ivermectin dose 300 mcg/kg of body weight daily for 5 days After enrollment by study nurse, patients were contacted by telephone for assessment and given treatment or identical placebo at home Primary Endpoint: time to resolution of symptoms within 21-day follow-up. Solicited ADR and serious ADRS also collected.</td>
<td>Median time to resolution: IVM gp: 10 days (9-13) Placebo gp: 12 days (9-13) Hazard ratio 1.07 (95% CI 0.87-1.32) P=0.53 Resolution of symptoms by day 21: IVM gp: 82% Placebo 79% Headache was the most common solicited adverse event reported in over 50% of patients. Serious adverse event was multiorgan failure – occurring in 4 patients total, 2 patients in each treatment group.</td>
<td>Authors conclude that a 5-day course of ivermectin compared with placebo, did not significantly improve time to resolution of symptoms for the treatment of mild COVID-19. Usual ivermectin dose is 150-200 mcg/kg 1. Other studies vary continuation for 2-5 days; or repeat x 1 at day 7. Patient self-administered treatment vs placebo and contacted by telephone for assessment. Reliability questionable. Ivermectin effect on decreasing viral load was not evaluated</td>
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<tr>
<td>Hellwig MD, Maia A. 10</td>
<td>GOAL: Collect data from countries that routinely deploy prophylactic chemotherapy (PCT) and determine if there is a correlation with SARS-CoV-2 incidence and ivermectin PCT. Observational Study - Data retrieval from</td>
<td>Countries with routine mass drug administration of prophylactic chemotherapy that included ivermectin have a significantly lower incidence of COVID-19 (p&lt; 0.05)</td>
<td>Ivermectin has the ability to inhibit replication of SARS-CoV-2 but the concentrations needed in humans doesn’t correlate with efficacy/safety. The authors hypothesize that there is an unknown mechanism that is efficacious at lower, safe dosages don’t</td>
</tr>
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</table>
• Prophylactic Chemotherapy (PCT) databank (WHO)
• Worldometer (Johns Hopkins) – count of COVID cases obtained

3 Groups – noted that the sizes of the three groups vary greatly
• PCT deployed in countries, ivermectin included
• PCT deployed in countries, ivermectin NOT included
• PCT not deployed in country

Time
April 2020; Because SARS-CoV-2 was being detected in new countries almost daily, calculations were updated and new countries affected were added several times throughout May 2021.

Prophylactic use of ivermectin against parasitic infections is most common in Africa and these data show that the reported correlation is highly significant both when compared among African nations as well as in a worldwide context (p=0.017).

Individual dosages generally varied between 150 μg and 200 μg per kilogram of body weight, there seemed to be no notable difference in COVID-19 incidence among recipients of different dosages.

Ahmed S. et al. 1
2020 in Dhaka, Bangladesh

RCT, DB, Goal: to evaluate the rapidity of viral clearance and safety of a 5-day course of
• ivermectin 12 mg PO daily x 5 days (n=24), vs

Virological clearance occurred earliest in the ivermectin x 5 days group (9.7 days) compared to Placebo (12.7 days) p=0.02.
The ivermectin + doxy arm virological clearance was not statistically improved over placebo group p=0.27.

The results provide potential benefit of early intervention with ivermectin in adult patients with early COVID-19.
Presumably, the faster viral clearance at disease onset may prevent significant immune system involvement.
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<tr>
<td>Kory P, et al. 2021</td>
<td>Protocol of individual drugs/dose criteria based on severity of disease, O2 requirements, ICU, etc. MATH: methylprednisolone + ascorbic acid + thiamine + heparin+ • Vit D3 5000 IU/day • atorvastatin • melatonin • zinc • famotidine • therapeutic plasma exchange GOAL: to study the efficacy of the MATH+ protocol with “supportive care only”, AND against other novel proposed treatment approaches Formation of patient registry</td>
<td>Authors summarize their protocol of MATH+ and the evidence supporting the efficacy of ivermectin in the prophylaxis and treatment. Most of data are from pilot or case series. Reports show patients who received early (usually single doses) of 0.4 mg/kg</td>
<td>MATH+ protocol not studied. So many variables, it is unclear how ivermectin adds to the other unproven but theoretical therapies.</td>
</tr>
<tr>
<td>Chaccour C, et al 2021</td>
<td>RCT, DB, single center, parallel arm</td>
<td>Initially, there was no difference in proportion of PCR positives between the groups for genes E and N in the same order of magnitude.</td>
<td>A larger trial is warranted to evaluate the positive trend in symptom</td>
</tr>
<tr>
<td>AUTHORS/Country</td>
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<td>RESULTS</td>
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| Spain           | Goal: to evaluate the efficacy of a single ivermectin dose in reducing transmission of SARS-CoV-2 when administered early. A reduction of at least 50% in proportion of positives desired. | • The median viral load for both genes was lower at days 4 and 7 post in the ivermectin group 3-fold lower at day 4 to around 18-fold lower at day 7, p > 0.05.  
• There was a marked reduction in anosmia/ hyposmia, reduction in cough  
• A trend to lower viral loads, lower IgG | Improvement in the treatment group compared to placebo.  
There is a need to evaluation ivermectin treatment with disease severity, inflammation and antibody titers.  
The results raise questions about the possible mechanism of ivermectin in COVID-19. Ivermectin may downregulate the expression of pro-inflammatory genes; it may have an effect on the nicotinic receptor; the mechanism may be immunomodulatory. |  
Ivermectin was associated with lower mortality as part of treatment of COVID-19 patients, especially in patients who required higher inspired O2 or ventilator support.  
Study not powered to detect difference in mortality from hydroxychloroquine treatment.  
Authors note that there may have been preferential treatment of more severe patients with ivermectin. There may have been a treatment timing bias. |  
Appropriate dosing of ivermectin for this indication is not known. |  |

Hospital treatment guidelines were available but prescribing was at the discretion of the prescribing physician.  
Total charts = 280  
173 tx’d ivermectin  
Received at least one dose of 200 mcg/kg, orally.  
A second dose could be prescribed at day 7, at the physician’s discretion.  
107 did not receive ivermectin (usual care)  
Primary Endpoint  
All cause in-hospital mortality | Mortality rates:  
Overall the ivermectin gp had significantly lower mortality the usual care gp (15% vs 25.2%, p=0.03).  
Ivermectin-tx’d with severe pulmonary involvement Mortality 38.8% vs 60.7%, respectively, P = 0.001).  
In a matched cohort, the absolute risk reduction from ivermectin was 11.2% (95% CI, 0.38%-22.1%). The number need to treat was 8.9 to prevent one death.  
No difference found in extubation rates. |  
Ivermectin was associated with lower mortality as part of treatment of COVID-19 patients, especially in patients who required higher inspired O2 or ventilator support.  
Study not powered to detect difference in mortality from hydroxychloroquine treatment.  
Authors note that there may have been preferential treatment of more severe patients with ivermectin. There may have been a treatment timing bias.  
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</tr>
</thead>
</table>
| **Secondary Endpoints** | • Mortality with pulmonary involvement  
• Extubation rates  
• LOS  

Inclusion  
Laboratory confirmed SARS-CoV-2  
Enrollment March 15-May 11, 2020  
Adult patients only  

Usual treatment care may have included:  
hydroxychloroquine treatment  
Corticosteroids  
Azithromycin  

Severity of pulmonary involvement assessed (severe vs non-severe). Severe pulmonary involvement defined as = FiO₂ ≥ 50%, high flow nasal O₂, noninvasive ventilation, or mechanical ventilation. |  
Progression:  
4.28% of all and 9% (severe) progressed to more severe disease in the ivermectin group vs 10% (all) and 31.8% (severe) in the control group (p>0.05). In subanalysis, progression was lowered if ivermectin given within the first two days of severe stage.  

Mortality: Was 0% in mild-moderate and 18% in severe Covid for the ivermectin group vs 0% and 27.3%, respectively (p=0.052)  

Mean time to recovery:  
For the ivermectin group it was 6.34, 20.27 and 24.13 for the mild-moderate, severe, and critical patients respectively versus 13.7 and 24.25 in the mild-moderate and severe patients treated with stand care, respectively (p < 0.01). | Ivermectin with doxycycline significantly reduced the time to recovery. The combination also decreased progression to more severe disease. Mortality was also reduced but bordering significance. |

| Hashim et al. 2020  
Iraq | RCT  
COVID-19 pts (n=70)  
ARM 1  
Ivermectin 200 mcg/kg/d x 2-3 days plus doxycycline 100 mg BID x 5-10 days  
Severe disease (n=11)  
Critical patients (n=11)  
ARM 2: Usual Care (MATH + regimen above)  
Mild/moderate (n=48)  
Severe disease (n=22)  
Critical patients (n=0)  
Endpoints:  
• Time to recover  
• Progression of disease  
• Mortality |  
Endpoint:  
Progression:  
4.28% of all and 9% (severe) progressed to more severe disease in the ivermectin group vs 10% (all) and 31.8% (severe) in the control group (p>0.05). In subanalysis, progression was lowered if ivermectin given within the first two days of severe stage.  

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**Abbreviations:** DB=double blind; H/A=headache; LOS=length of stay; RCT=randomized controlled trial; tx’d=treated;
ADDITIONAL KEY POINTS TO CONSIDER

Ivermectin (Stromectol®)
- Available as a 3-mg oral tablet.
- Tablets should be taken on an empty stomach with water.

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<th>PARASITIC INFECTIONS</th>
<th>COVID-19</th>
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| **USUAL ADULT DOSE**   | 150-200 mcg/kg | • Ref 1: 12 mg x 1 (with doxycycline); or 12 mg x 5 days. -
|                       |           | • Ref 3: 400 mcg/kg single dose; may repeat at day 7
| Common Adverse Events |          | • 200 mcg/kg 2-3 days with doxy 5 days |
| *From Package Insert of listed side effects occurring ≥ 3%* | Varies depending on parasite treated: | |
|                       | • Skin rash or itching | |
|                       | • Lymph node enlargement/tenderness | |
|                       | • Dizziness | |
|                       | • Diarrhea | |
|                       | • Joint or muscle pain | |
|                       | • Lightheadedness | |
|                       | • Peripheral edema | |
|                       | • tachycardia | |
| Precaution            | May make bronchial asthma worse | |
|                       | Elevation of liver enzymes and bilirubin | |
| Cost                  | 12 mg x 1 = $13.40 (GPO) | 12 mg x 1 dose = $13.40 (GPO); Repeat in 7 days = $27
|                       | OR 12 mg x 5 days = $66.65 (GPO) | |
| Efficacy              | Intestinal strongyloidiasis | Pilot study in mild Covid-19 may decrease viral load; may hasten improvement of anosmia/hyposmia and cough
|                       | Onchocerciasis | For more severe patients, may decrease overall mortality |
Select References:


