

## The role of Ivermectin in COVID -19 |management, issues and challenges

**Running Title:** Ivermectin and COVID-19

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### Dear editor

Why was Ivermectin not mentioned by the medical community in the treatment of COVID-19? In a pandemic, emergency physicians don't have time to wait for validated studies before we try something.

An example of a sentence that we hear a lot from parents of children in the community:

Here are so many facts to question now: The COVID-19 mandatory injection for children, now going into effect nationwide has me shuddering! Where are the national baseline tests for antibodies for these kids, before they must have this experimental vaccine? It is still experimental people! (Until now, drugs widely used under the mandatory three-year data study by the FDA, are deemed experimental).

In the last two years, humans have witnessed a deadly catastrophe called the Corona virus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has turns to a pandemic all around the world. Despite the importance of vaccination, more efficient drugs are required to treat or manage coronavirus disease-19.

According to the Centers for Disease Control and Prevention, 150,000-200,000 new cases of COVID-19 are reported in the United States every day. In the United States, COVID-19 causes more than 2000 deaths a day and more than 300,000 deaths since January 2020(1). Many drugs, including Hydroxychloroquine, have been introduced for treatment, but clinical trials have shown multiple side effects and less benefit in treating the disease with this drug (2).

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According to World Health Organization's (WHO), Ivermectin is one of the essential drugs, which is approved by the US Food and Drug Administration in 1981 (3).

The dose is 0.2 mg/kg. Ivermectin comes in 3 mg tablets in the United States. In an average person, a reasonable dose is 15 mg per day times for five days.

Ivermectin can inhibit SARS CoV 2 replication in vitro, lead to off-label use. Previously, this drug was investigated as a therapeutic choice for viral infections. Evidence suggested some in vitro Ivermectin activity against a broad range of viruses, including HIV, dengue, influenza, and Zika virus. The possible mechanism of action of Ivermectin is through inhibition of importin  $\alpha/\beta$ 1-mediated nuclear import of viral proteins. Wagstaff et al., reported that Ivermectin was a potent in vitro inhibitor of SARS-CoV-2, and revealed that it led to 99.8% reduction in viral RNA after 48 h. Based on Clinical Trials.gov, at the present there are 37 studies which are investigating the usefulness of Ivermectin in COVID-19 (<https://clinicaltrials.gov>) (4- 5).

We made a comparison between Ivermectin and other drugs in the treatment of COVID-19:

In addition to the mechanism of action of different drugs between this drug and Hydroxychloroquine, other aspects also show the superiority of this drug. For example, side effects such as irreversible retinal damage, QT prolongation, myopathy, Hydroxychloroquine-related neuropathy are not seen in patients taking this pill. In addition, this tablet treatment regimens may be more cost-effective. Therapy regimen with a

combination of hydroxychloroquine and azithromycin is approximately 5-6 times more expensive than the Ivermectin regimen. The same can be said of patented antiviral drugs, which are priced at exorbitant prices. Another valuable issue to address is the overuse of Hydroxychloroquine in the management of Covid-19 patients, which may reduce drug supply and increase demand due to standard treatment for patients with autoimmune diseases (6).

In one study, researchers used docking and molecular dynamics simulations to discover the mechanism of action of Ivermectin and Doxycycline in inhibiting SARS-CoV-2. They showed that a combination of Ivermectin and Doxycycline may increase load clearance by inhibiting virus entry. Viruses exert this effect by targeting different functional viral proteins. Both drugs bind significantly to SARS-CoV-2 proteins, but this pill has better binding properties than Doxycycline (7).

We note that this tablet, Based on the evidence that it may act as an antiviral, could be used to treat patients with coronavirus. In this respect, its potential use outside the framework of a clinical trial or research protocol for unlabeled drugs that evaluate its efficacy and safety cannot be ruled out. But there are some important key points about previous studies:

1. The sample size in previous studies was small.
2. Some studies were mini or small clinical trial.
3. It may be bias in these studies.
4. There are no systematic review on previous surveys.

5. WHO guide line don't confirm it for COVID-19 management.

Although we found nearly 34 articles about positive effect of Ivermectin on prophylaxis and treatment of COVID-19 but because of loss of a comprehensive and reliable meta-analysis study on this subject, we don't suggest this medicine for COVID-19 treatment. In addition, the latest guide line don't introduce it We think that this medicine may show considerable action if administered for the treatment of COVID-19.

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