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Ivermectin and COVID-19: What's Going On?

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[**This document is a part of a series of discussion notes addressing fundamental questions about the COVID-19 crisis and response strategies. These documents are based on the best scientific information available and may be updated as new information comes to light.**]

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Photo: Kate Holt / Sightsavers (Community Eye Health). Community distribution of ivermectin for the treatment of onchocerciasis in Nigeria.

Ivermectin is an **antiparasitic agent** with **a broad efficacy spectrum**. **Merck**, the company that originally developed the drug decided to donate as much ivermectin as needed for the treatment and control of river blindness and lymphatic filariasis in an initiative known as the **Mectizan Donation Program** (MDP). This programme has distributed more than 4 billion treatments over the past 30 years (see *Figure 1*). Ivermectin is also licensed for the treatment of strongyloidiasis and scabies in some countries[1].

Given its broad spectrum of activity, ivermectin has been extensively studied and, like many other drugs, has shown have partial efficacy against targets **beyond its primary indication**. The drug is known to inhibit the replication of several RNA viruses including dengue, for which there are some recent results available[2].

Ivermectin has, however, also been in the spotlight as an example of the risks of **rushed** and **scientifically unfounded debates** in the response to crises such as the coronavirus pandemic. This policy brief offers an account of that episode and extracts some lessons that could be useful in the future ●

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[1] More details on the history of ivermectin at Questions and Answers about Ivermectin and COVID-19. Carlos Chaccour, ISGlobal, updated on December 2020.

[2] More details on ivermectin's antiviral properties at Questions and Answers about Ivermectin and COVID-19. Carlos Chaccour, ISGlobal, updated on December 2020.

1. The Origin of the Problem: Two Opposing Reactions Based on Scant Data

> "On the basis of the *in vitro* data and a preprint (non-peer reviewed paper) that was later retracted, as well as local experience with the drug, several countries in Latin America included ivermectin in their national guidelines for COVID-19 management."

In April 2020, Caly et al. published results from *in vitro* experiments showing that ivermectin **inhibits the replication of SARS-CoV-2** at relatively high concentrations. This caused two opposing reactions among the scientific community, health authorities and the general public, neither supported by much evidence:

• **Outright dismissal:** On the one hand, many scientists dismissed ivermectin altogether as a potential COVID-19 treatment on the basis of pharmacokinetic modelling (a technique that predicts how much drug will reach certain tissues or fluids) and the doses required to reach antiviral drug concentrations in the lungs (based on Caly's results)[3].

• **Advocacy and widespread use:** On the other hand, on the basis of the *in vitro* data and a preprint (non-peer reviewed paper) that was later retracted, as well as local experience with the drug, **several countries in Latin America** included ivermectin in their national guidelines for COVID-19 management: Peru and Bolivia in early May 2020, certain areas of Brazil in June, and Venezuela in July[4] •

Figure 1. Treatments approved by the Mectizan Donation Program 1988-2019 (in millions).
Since Mectizan was first donated in 1988, more than 4 billion Mectizan treatments have been approved by MDP for the elimination of onchocerciasis and lymphatic filariasis.
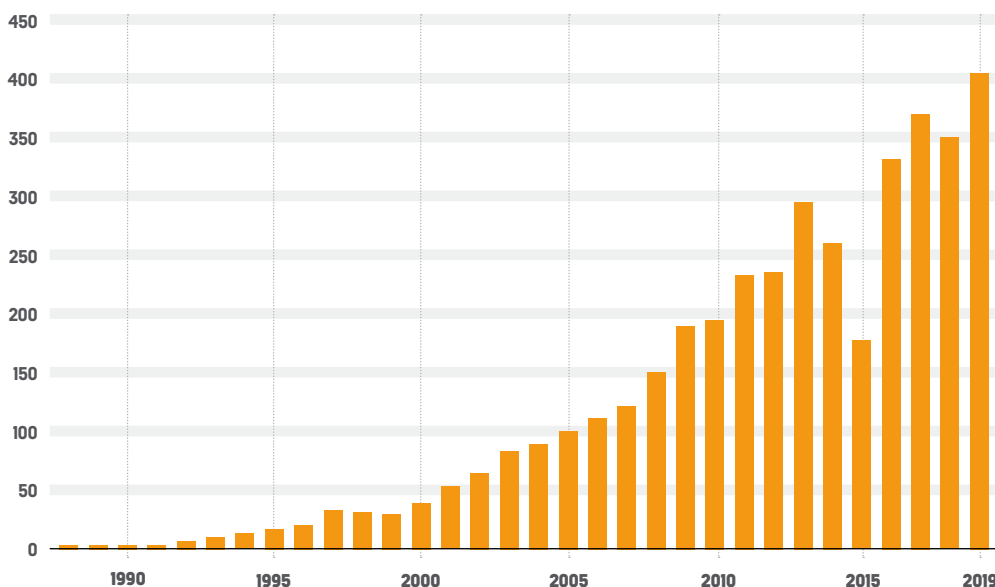
Source: Mectizan Donation Program. 2019 Annual Highlights.

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[3] Some of the reasons why it was important to conduct trials with a safe drug for a disease without specific treatment are discussed at Questions and Answers about Ivermectin and COVID-19. Carlos Chaccour, ISGlobal, updated on December 2020.

[4] See more details about early approvals in Latin America at Ivermectin and COVID-19: How a Flawed Database Shaped the Pandemic Response of Several Latin-American Countries. Carlos Chaccour, ISGlobal, updated on June 2020.

2. Ongoing and Completed Trials

> **"The differences between the studies carried out have resulted in a very heterogeneous matrix from which it is difficult to extract conclusions. Moreover, since only a small fraction of the registered studies have published results, the literature may be affected by a publication bias."**

Since 2020, at least 60 trials with Ivermectin for COVID-19 have been registered at ClinicalTrials.gov, 19 of which have been completed. These studies differ in a number of ways:
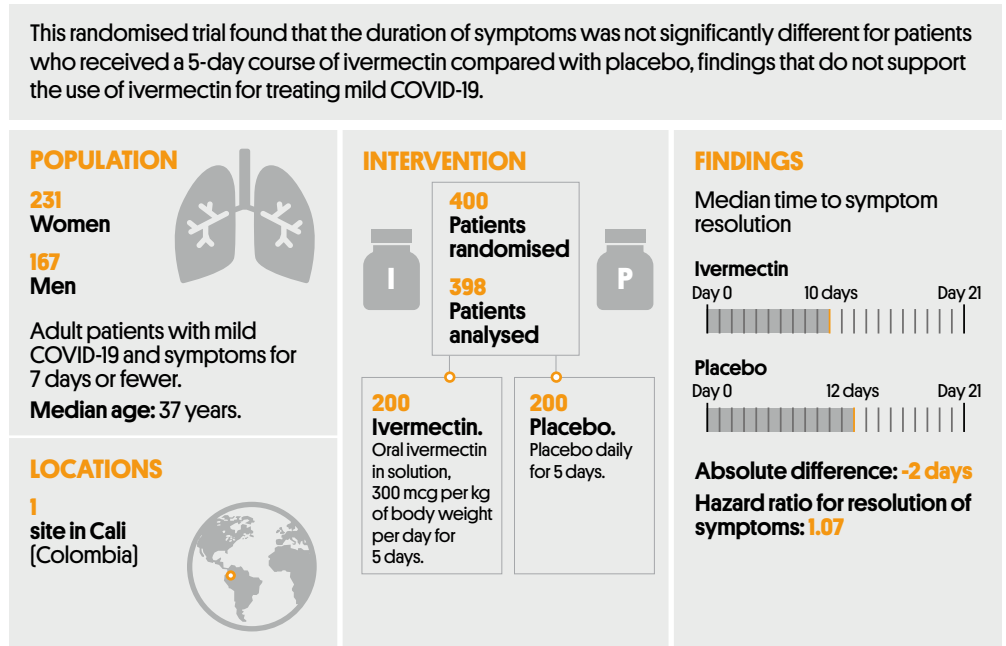
• Different **potential indications** have been tested (prophylaxis, "early treatment" and "late treatment").

• Therefore, the **timing of treatment initiation** has been different (pre-exposure, post-exposure, after confirmed infection, or after confirmed severe disease).

• Different **dosages** have been tested (ranging from a single dose of 150 mcg/kg to a 5-day regimen of 1200 mcg/kg).

• **The study designs** used include case series, case-control studies, non-randomized and randomized trials (all having different randomization and blinding strategies), as well as varying comparators and outcome measures.

This has resulted in a very heterogeneous matrix from which it is **difficult to extract conclusions**. Moreover, since only a small fraction of the registered studies have published results, the literature may be affected by a publication bias (a phenomenon in which only positive results are published while negative findings are not), as the apparently negative results of a recent large trial in Colombia suggest ●

Figure 2. **Report in *JAMA* on the effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19.**
*This data has just been made public and has not yet been subjected to post-publication peer review.

This randomised trial found that the duration of symptoms was not significantly different for patients who received a 5-day course of ivermectin compared with placebo, findings that do not support the use of ivermectin for treating mild COVID-19.

POPULATION

231 Women

167 Men

Adult patients with mild COVID-19 and symptoms for 7 days or fewer.
Median age: 37 years.

LOCATIONS

1 site in Cali (Colombia)

INTERVENTION

400 Patients randomised

398 Patients analysed

200 Ivermectin. Oral ivermectin in solution, 300 mcg per kg of body weight per day for 5 days.

200 Placebo. Placebo daily for 5 days.

FINDINGS

Median time to symptom resolution

Ivermectin
Day 0   10 days   Day 21

Placebo
Day 0   12 days   Day 21

Absolute difference: -2 days
Hazard ratio for resolution of symptoms: 1.07

Source: Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19 A Randomized Clinical Trial. *JAMA*. Published *online* 4 March 2021.

3. Emerging Data

Nonetheless, the results of several trials do point towards a **potential effect** but this needs to be confirmed before widespread clinical or public health use is considered. The following are some of the **key trials**:

a) Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19

The most recent publication is the report of a large trial assessing the effect of ivermectin on the symptoms of patients with **mild COVID-19** (see *Figure 2*). **The findings of this study do not support its use in this setting**. This data has just been made public and has not yet been subjected to post-publication peer-review.

b) Clinical trial of ivermectin plus doxycycline for the treatment of confirmed COVID-19 infection

A double-blind, randomised, placebo-controlled trial with **400 patients**. This study found a **clinical benefit** in ambulatory and hospitalised patients with **mild to moderate COVID-19**.

c) Antiviral effect of high-dose ivermectin in adults with COVID-19: A pilot randomised, controlled, open label, multicentre trial

A pilot, randomized controlled trial with **45 patients**. This study found a **correlation** between ivermectin levels in the blood of COVID-19 patients and the rate of **viral decay**.

d) The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial

ISGlobal's own trial conducted in partnership with the Clínica Universidad de Navarra: the SARS-CoV-2 Ivermectin Navarra-ISGlobal Trial **(SAINT)**. This pilot, double-blind, placebo-controlled trial with **24 patients** found that a single dose of 400 mcg/kg given within 72 hours of onset of **fever** or **cough** had an **impact on viral load**, rate of viral decay and symptoms (specifically **anosmia**) as well as on the antibody titres of treated patients (see *Figure 3*).

e) Anti-COVID-19 efficacy of ivermectin in the golden Syrian hamster

An elegant study from the Institut Pasteur found reduced anosmia (olfactory loss) in hamsters treated with a single dose of either 400, 200 or 100 mcg/kg of ivermectin upon SARS-CoV-2 infection ●

Daily proportion of individuals with anosmia/hyposmia (total/partial loss of the sense of smell) for a 28 day follow up.

Ivermectin
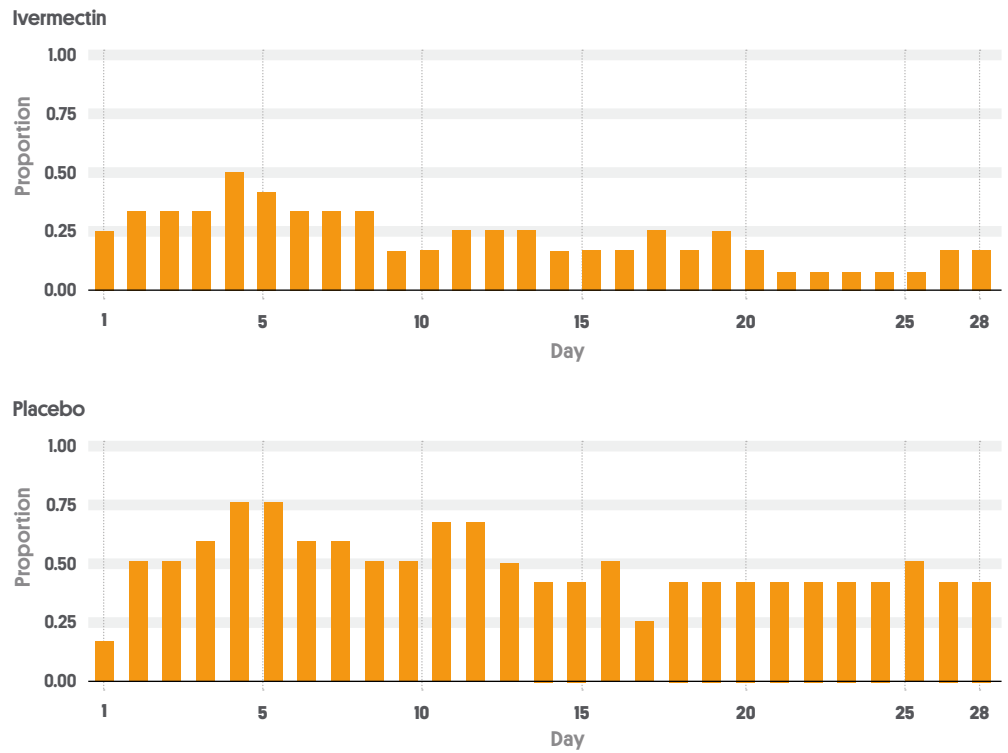
Placebo

Source: The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. *The Lancet*. 19 January 2021.

Evidence Reviews and Compilations (Some Contested)

"Several groups have conducted reviews of the evidence from published and unpublished data. This has led to mixed messages and caused confusion in the general public, fuelling conspiracy theories and sometimes leading to contradictory recommendations and statements from national authorities and international groups."

Several groups have conducted reviews of the evidence from published and unpublished data. This has led to **mixed messages** and caused **confusion** in the general public, fuelling conspiracy theories and sometimes leading to contradictory recommendations and statements from national authorities and international groups.

The Front Line COVID-19 Critical Care Alliance (FLCCC) has played a key role in sparking a second wave of international interest in ivermectin for the treatment of COVID-19. This group of front line and critical care physicians **summarised the evidence available** on COVID-19 treatment or prophylaxis with ivermectin and generated their own **clinical protocols**.

That review is, however, affected by several **potential problems** as it contains **very heterogeneous data**, some of it with **high risk of bias**, such as the ecological studies and the so-called "real world evidence". The **ecological studies** assess the relationship of COVID-19 dynamics at population level with the level of ivermectin use in said populations. The results of this type of analysis are **subject to the influence of other concurrent factors** (lockdown restrictions, mask wearing, quality of hospital care), which can give rise to serious misconceptions. The **testimony of Dr. Pierre Kory** in the US senate on December 8, 2020 has been broadly publicised and led to a renewed global interest in the potential use of ivermectin in COVID-19.

The FLCCC not only claims that the current evidence supports the large-scale roll-out of ivermectin, but also asserts that conducting further research on this topic would be unethical given the "overwhelming" evidence on efficacy. These seem to be **exaggerated claims** given the heterogeneity of the data and the doubts raised about the quality of the evidence reviewed, considering they cited a study with **apparently fraudulent**

Surgisphere **data** on ivermectin in early versions of their COVID-19 management protocols. The review was provisionally accepted for publication by *Frontiers in Pharmacology* but was later removed after questions were raised about the integrity of the manuscript, prompting a media statement by the journal on the subject.

Additional confusion has been sown by **several ongoing meta-analyses** reporting conflicting results. One of these was commissioned by Unitaid and carried out by Dr. Andrew Hill, a senior visiting Research Fellow in the Pharmacology Department at Liverpool University. Since Unitaid is hosted by the World Health Organisation, several news outlets claimed that WHO/PAHO had actually commissioned Hill's meta-analysis and recommended ivermectin. This erroneous assertion proliferated on social media, prompting PAHO to clarify the issue.

There is indeed a **WHO-led meta-analysis** on this topic currently underway, which was announced at this press conference on February 15, 2020. That study **will assess the certainty and the risks** based on multiple studies, some with a small sample size. The methodology is the same as that used for all living clinical guidelines produced to date. A time frame of four to six weeks was mentioned in this press conference. Other, independent, meta-analyses have been published with varying levels of quality and differing results.

Throughout this period, proponents and opponents have engaged in **heated debates** on social media and amplified the discussion many-fold, sometimes with vicious **attacks** and even **threats** directed at the people highlighting the need for proper evidence (including members of the ISGlobal team) ●

5. Latest Developments

"In recent months, several countries have included the drug in their national therapeutic guidelines. This is the real problem currently facing the international community: implementation in the field without clear guidelines on doses or regimens solid evidence of efficacy or, even more worryingly, of safety for this particular indication."

Ever since the **second wave of interest in ivermectin for the treatment of COVID-19** was sparked by the FLCCC in December 2020, several countries have included the drug in their national therapeutic guidelines. This is the **real problem** currently facing the international community: implementations in the field without clear guidelines on doses or regimens, solid evidence of efficacy or, even more worryingly, of safety for this particular indication. The **most recent approvals and recommendations** include Slovakia (January 27, 2021), South Africa (January 27, 2021), Zimbabwe (January 28, 2021) and the Czech Republic (Prime Minister's announcement on March 2, 2021).

These recent approvals have triggered a second wave of **statements from international organizations** and even from Merck, the original manufacturer of ivermectin. The US National Institutes of Health has updated its statement on ivermectin use as follows: "there are **insufficient data** to recommend either for or against the use of ivermectin for the treatment of COVID-19". This is a **balanced statement** that appropriately reflects the current state of the evidence. The **FDA** already published a letter and FAQs about the use of ivermectin for COVID-19 (specifically veterinary formulations) in 2020. Nonetheless, the **misuse of veterinary ivermectin formulations** continues, as evidenced by reports of an uptick in calls to poison control centres linked to the drug.

The original manufacturer, **Merck**, has issued a statement citing the **lack of any scientific basis** for the use of ivermectin in the treatment of COVID-19 and raising concerns on the **dearth of safety data** in many of the trials. The **Mectizan Donation Program**, responsible for distributing ivermectin to hundreds of millions of people every year for the control of river blindness and lymphatic filariasis, has also reminded partner countries that the donated product is to be used solely for these two neglected tropical diseases.

Some of the **expected consequences** of this surge in demand without clear guidance on indication, dosage or regimens are beginning to appear. Most worrying is the circulation of low-quality formulations in South Africa that include **undeclared and potentially dangerous substances**, such as benzodiazepines, antiplatelet agents and even anticonvulsants. The same report also warns of **profiteering**, with some formulations sold at ZAR 1000 (US$ 68), way above the usual price. Experience with antimalarials teaches us that when anti-infective drugs become very profitable, counterfeit formulations do not take long to enter the market. In the case of ivermectin, the question is whether or not **counterfeits** are already in circulation ●

6. Lessons for the Debate on COVID-19

"Scientific rigour and an open mind are both essential for the rational evaluation of the available, emerging and future data."

There is evidence to suggest a potential role for ivermectin in the management of COVID-19, but there is **no definitive data** on the safety or efficacy of the drug in this indication or on the doses/regimen required. Scientific rigour and an open mind are both essential for **the rational evaluation** of the available, emerging and future data. Ivermectin is a live-saving medication for millions of people affected by neglected tropical diseases worldwide every year. While its potential as treatment for COVID-19 is of great interest, unexpected negative consequences can occur with misguided approvals, recommendations or roll-out.

The **lessons learned** include:

- There is a need for scientific rigour in the evaluation of potential emerging drug-based strategies against COVID-19.

- At the same time, there is a need for humility and an open mind since quality science does not necessarily come only from high-income countries.

- The debate on a certain topic can only start once there is **appropriate evidence**. Any debate before this happens is just polarization or even **politicization** and does not really serve to advance the field.

- On **social media**, advocates and opponents of a strategy can create more noise than knowledge and contribute to premature or uninformed actions by policy makers or the general public.

- Early guidance from **key opinion leaders**, **funders** and **health authorities** could help to establish uniform systems and protocols for testing new interventions ●

TO LEARN MORE

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• Un ensayo clínico proporciona resultados alentadores sobre el uso de la ivermectina para reducir la transmisión viral en pacientes con COVID-19 leve. Clínica Universidad de Navarra. 19 January 2021.

• López-Medina E et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19 A Randomized Clinical Trial. *JAMA*. Published *online* 4 March 2021. doi:10.1001/jama.2021.3071

• A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021;372:n526. 2 de marzo de 2021. doi: https://doi.org/10.1136/bmj.n526

• Chaccour C and Vilasanjuan R. Infodemic: How Has the Epidemic of Misinformation Affected the Response to COVID-19? ISGlobal. Series COVID-19 and response strategy. 22 September 2020.