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UP adds ivermectin to its COVID-19 protocols without evidence that the drug works

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A box of the drug ivermectin, made by Biogaran, is pictured on the counter of a pharmacy in Paris, France, on 28 April 2020. Experts have warned against using the drug to control COVID-19 at the population level till clinical trials prove its efficacy. BENOIT TESSIER / REUTERS

COVID-19

(/covid-19)

The government of Uttar Pradesh has pushed the use of an antiparasitic drug called ivermectin as both, a treatment for and prophylaxis against COVID-19. However, the recommendation has no scientific basis yet—there have been no trials that prove that it works against the novel coronavirus. In fact, scientists at the World Health Organisation warned (https://iris.paho.org/handle/10665.2/52372) against using ivermectin to treat COVID-19 since existing studies on its efficacy "have a high risk of bias, very low certainty of the evidence, and that existing evidence is insufficient to draw a conclusion on benefits and harms." The US Food

and Drug Administration said (https://www.fda.gov/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals#:~:text=Q%3A%20What%20is%20ivermectin%20approved%20for%20in%2) drug was not approved for prevention or treatment of COVID-19 and that additional testing was needed. Notably, the union ministry of health and family welfare has neither recommended the drug for treatment of COVID-19 patients, nor issued any advisory against its use.

But state government-run hospitals in Uttar Pradesh have prescribed the drug as part of their protocol to treat mild and moderate cases of COVID-19. Moreover, rapid response teams—teams of doctors who assess asymptomatic patients—have been charged with distributing the drug to people in home quarantine and primary and secondary contacts of confirmed cases.

Researchers at the Kitasato Institute in Japan and the US-based pharmaceutical company Merck and Co first formulated ivermectin in the 1970s. It was deemed an important development in veterinary medicine because it was potent against internal and external parasites and in boosting animal health. The drug was subsequently found to be effective in the treatment of human diseases such as river blindness, lymphatic filariasis, and scabies. “In some countries, the drug has also been formulated for topical treatment in the form of a shampoo against head lice,” Dr Carlos Chaccour, a health researcher with the Barcelona Institute of Global Health, said. “In a few Latin American countries, oral dosage of the drug has been approved to treat head lice as well.”

Chaccour has studied the drug for more than a decade and warned against its use in treating COVID-19 at a population level. He has also closely monitored the mass misuse of ivermectin in Latin American countries such as Peru, where thousands of people started using veterinary ivermectin when the supply for human-use ivermectin fell. Many reportedly suffered side effects (https://www.the-

scientist.com/news-opinion/surgisphere-sows-confusion-about-another-unproven-covid19-drug-67635), including stomach ailments, tremors, panic attacks and painful blisters. A recent article (https://www.nejm.org/doi/full/10.1056/NEJMc1917344?query=featured_home), "Serious Ivermectin Toxicity and Human ABCB1 Nonsense Mutations", published in *The New England Journal of Medicine* analysed how a single dose of ivermectin, formulated for human use, caused a 13-year-old boy with an unusual genetic condition to develop encephalopathy and slip into a coma.

Uttar Pradesh's focus on ivermectin is reminiscent of the unreasonable attention given to hydroxychloroquine, a drug approved for treatment of malaria, in the early days of the pandemic. In fact, the state government approved ivermectin as a supplementary COVID-19 medicine and replaced hydrochloroquine in its official treatment protocol. On 9 August, Amit Mohan Prasad, the state's additional chief secretary for health and medicine, issued an order that instructed chief medical officers in all districts to incorporate ivermectin in COVID-19 treatment protocols. The chief medical officers in turn circulated the updated protocol to government hospitals and recommended ivermectin, along with the antibiotics azithromycin and doxycycline and the anti-inflammatory drug paracetamol. The protocol advised patients to take 200 micrograms of ivermectin per kilogram of their weight, up to a dose of 12 milligrams per day. According to this metric, an adult weighing 60 kilograms should take a dose of 12 milligrams of ivermectin per day.

The 9 August protocol was limited to infected individuals, who were under home quarantine, and mild to moderately-ill patients in hospitals. However, ten days later, RP Singh, the chief medical officer of Lucknow, issued an order asking all primary and secondary contacts of COVID-19 patients to take up to 12 milligrams of the medicine on the first and seventh day after their contact with a confirmed COVID-19 patient. The order, issued in Hindi, claimed that "*utt tablet kaafi had tak COVID-19*

mahamari se bachne mein madadgar hai"—the tablet is helpful in saving one from the COVID-19 pandemic to a large extent.

Prasad told me, "The decision to begin using ivermectin was made by an expert committee. There is evidence that the drug is helpful in combating the virus, hence we are using it as part of our treatment protocol." However, Prasad refused to reveal the names of the members of the expert committee. He also refused to comment further on any scientific study or evidence on the basis of which the state government decided to add ivermectin to its protocols.

Dr D Himanshu, who is in charge of a COVID-19 isolation unit at the King George's Medical University in Lucknow, said that the government decided to incorporate ivermectin on the basis of observations made by doctors in Agra. Himanshu acknowledged the lack of concrete evidence. No one has completed a randomised controlled trial, or RCT—the recognised gold standard for a drug trial—to determine the safety and efficacy of ivermectin for COVID-19 patients. But he defended its use as emergency supplementary treatment. "Since the pandemic struck us, we have been repurposing medication on a trial basis without any concrete evidence," he said. "Neither hydroxychloroquine nor other drugs like Tamiflu used for treating swine flu were proven to be efficacious or safe when we began using them." Tamiflu is a brand name of the antiviral medicine oseltamivir. Himanshu also claimed that the amount of ivermectin that the government protocols prescribed were safe for human intake.

Dr Agam Vora, a pulmonologist and lead author of a white paper (https://pubmed.ncbi.nlm.nih.gov/32825892/) titled, *Ivermectin as a potential therapy for COVID 19,* published in the *Indian Journal of Tuberculosis* in July, claimed that in emergent situations like this pandemic, scientists do not have time to conduct vast and time consuming clinical trials. "We have been safely using ivermectin in epidemics in the past such as for malaria in 2005 and swine flu as well,"

he said while speaking to me and added that he trusted affordable, off-label medicines, such as hydroxychloroquine and ivermectin. "I for one believe in using hydroxychloroquine as a prophylactic for COVID-19 and use it regularly."

Hydroxychloroquine was touted as effective treatment and prophylaxis for COVID-19 early in the pandemic. However, it was removed from treatment protocols around the world after studies showed it had no significant impact on the disease and was could potentially harm a person's cardio-vascular health.

Studies unrelated to COVID-19 show that ivermectin is safe for human consumption in limited doses. For instance, one study (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30163-4/fulltext) to test ivermectin's use against malaria published in *The Lancet Infectious Diseases* in June 2018 proved that doses of up to 600 micrograms per kilogram of body weight can be safely administered to humans subjects for a short course. Chaccour said, "A dose of 200 microgram per kg of ivermectin is tolerated well by the human body for a short period of time." However, no study has proved that ivermectin works against the SARS-CoV2 virus. "Currently there is very limited and inconclusive evidence that ivermectin can treat or prevent COVID-19," Dr Andrew McLachlan, head of school and dean of pharmacy at the University of Sydney wrote in an email to me. "The available trials are low quality and inconclusive."

A study (https://www.sciencedirect.com/science/article/pii/S0166354220302011) titled, *The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro*, generated some excitement when it was published in early April. But the study by scientists at Australia's Monash University went only as far to show that ivermectin could curb replication of SARS-CoV2 in monkey cells *in vitro*—inside a test tube. McLachlan, who is not

associated with the study, pointed out in an article (https://theconversation.com/ivermectin-is-still-not-a-miracle-cure-for-covid-19-despite-what-you-may-have-read-144569) for *The Conversation* that its process required concentrations of ivermectin that were well above the recommended doses for humans. In other words, a safe dose of ivermectin was unlikely to kill the SARS-CoV2 virus in the human body.

Still, the Monash University study was received with such enthusiasm that Dr Mike Bray, editor-in-chief of the medical journal *Antiviral Research* that published the study, wrote a letter (https://www.sciencedirect.com/science/article/pii/S0166354220302199) on 21 April which said that "Despite the authors' cautious conclusion that ivermectin 'warrants further investigation for possible benefits in humans,' the paper has excited widespread interest on medical and veterinary websites, which often incorrectly describe the drug as a treatment or cure for COVID-19." Bray also pointed to the US FDA's warning (https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans) to people against self-medicating with ivermectin.

In vitro experiments, such as the Monash study, are one step in a long process of determining a drug's safety and efficacy. "You see, in a petri dish there is no immune system," said Chaccour, the researcher from the Barcelona Institute of Global Health. "In a petri dish, the ratio of viral load to cells could be much higher, so there is no knowing how this will work in a human, and this is why we need to conduct proper clinical trials." Chaccour added that it might be safe to prescribe an ivermectin dose of 12 mg per day at the individual level, but the drug could cause great harm when taken prescribed as protocol at a population level. He referred to Peru where the government's promotion of ivermectin led to excessive self-medication and allegedly a black market for the drug. Chaccour has written an analysis

(https://www.isglobal.org/en/healthisglobal/-/custom-blog-portlet/ivermectin-and-covid-19-how-a-flawed-database-shaped-the-covid-19-response-of-several-latin-american-countries/2877257/0)about how a flawed database claiming to prove ivermectin efficacy in treating COVID-19 shaped the pandemic response in Latin America. His analysis refers to an observational study (https://www.isglobal.org/documents/10179/6022921/Patel+et+al.+2020+version+1.pdc3e-4593-a075-db96f4536e9d) by scientists in the US who based their research on data from Surgisphere, an American healthcare analytics company, and claimed that ivermectin reduced SARS-CoV2 viral RNA drastically within 48 hours. The study was published in the *Social Science Research Repository*in April but later retracted as scientists, including Chaccour, pointed out various discrepancies in the database that formed the basis of the research. "The fact remains that even in times of the pandemic, rigorous scientific research needs to be conducted before a medicine is prescribed to the masses," Chaccour said.

Chaccour is part of a team that is conducting a double blind RCT to test the safety and efficacy of ivermectin in COVID-19 patients, using a dosage of 400 micrograms per kilogram, which is about 24 milligrams of ivermectin for an adult weighing 60 kilograms. In a double blinded study, neither participants nor researchers are aware of who is administered the drug and who is administered the placebo. Double blinded RCTs are the most rigorous forms of testing drugs. According to the Indian Council of Medical Research's Clinical Trials Registry, currently 11 interventional studies to test the efficacy of ivermectin in COVID-19 treatment have been registered in India, all of which are yet to recruit subjects. Out of the eleven, six are RCTs. Under normal circumstances, most regulatory authorities approve drugs only after robust results from RCTs. However, during the pandemic, governments have approved medication for emergency use without waiting for results from such methodical trials.

The danger of Uttar Pradesh's promotion of ivermectin is also due to the fact that it is cheap and easily available. "In the past week, the sale of ivermectin has surged," Diwakar Singh, head of the Uttar Pradesh Chemists' Association, said. "People are buying the drug in bulk, for themselves and their family members. I have brought some home for my family as well." Singh also said that Vermact 12 mg, the brand name for ivermectin manufactured by the pharmaceutical company Mankind Pharma, was the most popular off label brand amongst buyers. In August, Mankind Pharma released a poster (https://pbs.twimg.com/media/EguF759UwAAVyjB?format=jpg&name=medium) on social media detailing UP's protocol for administering ivermectin as a prophylactic for "all healthcare workers and persons who came in close contact to COVID-19 patients" and as treatment for asymptomatic and mild COVID-19 patients. The poster carried the branding of another of Mankind's ivermectin formulations called Bandy Plus that was approved for deworming. The poster also carried a disclaimer at the bottom that it was "for the knowledge upgradation of healthcare professionals" and that the company did not promote off-label use of Bandy Plus.

According to a news report (https://www.hindustantimes.com/lucknow/lucknow-admin-to-set-up-kiosks-for-distribution-of-ivermectin-tablets/story-YNDN2GIdWHf7EsDgZQbmNL.html) on 22 August, the Uttar Pradesh government was planning to set up 40 kiosks across Lucknow to distribute ivermectin tablets to asymptomatic patients in the city, free of cost. The report said that these kiosks were likely to be set up at entry and exit points across the city, including bus stands, railways station, the airport and highway entries and exit. KP Singh, additional district magistrate for Lucknow, told me that the plan for kiosks had been put on hold but that rapid response teams would continue mass distribution of ivermectin to asymptomatic patients and contacts of patients. "It has proven to be effective in treating asymptomatic patients and the dose of

12 mg per day is now prescribed widely by our government doctors as well," Singh claimed.

While Uttar Pradesh promotes ivermectin widely, it has no system in place to curb unsupervised self-medication by people hoping to protect themselves and their families. A doctor of internal medicine from a government hospital in Lucknow who did not want to be identified said in a telephonic conversation, "It is yet another arbitrary decision made by the government. We received an order and we have complied."

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