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The bad science and poor ethics of Patanjali's Coronil research

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Ramdev along with the union health minister Dr Harsh Vardhan and Nitin Gadkari during the release of research papers on Patanjali Coronil medicine for Covid-19 in February. RAJ K RAJ / HINDUSTAN TIMES

COVID-19

(/covid-19)

On 19 February, Patanjali Ayurved, the packaged consumer goods company founded by self-styled yoga guru Baba Ramdev, announced the publication of a research paper on its COVID-19 medicine called Coronil. Doctors across India strongly protested both the manner in which the announcement was made—Harsh Vardhan, the union health minister, presided over it—and the company's claim that the research showed Coronil was effective against COVID-19. Three days after the event, the Indian Medical Association issued a press release that said Patanjali's claims amounted to "blatant deceiving of the people of the country." A month later, the *Pune Mirror* reported (https://punemirror.indiatimes.com/pune/crime/criminal-case-against-patanjali-on-coronil/articleshow/81556528.cms), a law student in Pune filed a criminal case against Ramdev and Acharya Balkrishna, the chairman of Patanjali Ayurved and an author of the Coronil study, on

grounds of cheating, criminal conspiracy, and a malignant act likely to spread infection of disease dangerous to life.

On 4 February, the journal *Phytomedicine* published (https://www.sciencedirect.com/science/article/pii/S0944711321000362?via%3Dihub) a paper describing a randomised control trial testing the efficacy of Patanjali's Coronil kit. The study was authored by employees of Patanjali and doctors from the National Institute of Medical Sciences, a private medical college in Rajasthan. The kits consist of Coronil tablets made from ayurvedic herbs *ashwagandha*, *giloy* and tulsi. It also includes Patanjali's *swasari vati*, which a mixture of more than a dozen medicinal herbs that is supposed to treat colds and coughs, and *anu taila,* which is another mixture of herbs pressed into an oil which the Patanjali website claims has "multifarious benefits." The study's purpose was to evaluate "the impact of traditional Indian Ayurvedic treatment regime on asymptomatic patients with COVID-19 infection."

The team conducted a double-blind randomised control trial. This means that volunteers were randomly assigned to either the treatment arm (in which they received medicines from the Coronil kit) or the placebo arm. Neither the research team nor volunteers themselves knew which arm they were in. The study's endpoints were to test viral loads through RTPCR on days one, three and seven. The trial also tested levels of two types of proteins secreted by the immune system called cytokines —interleukin-6 or IL-6 and tumor necrosis factor alpha or TNF-α—in the patients' blood. In severe COVID-19 infections, sensitive immune systems have been found to respond in the form of cytokine storms that can produce severe, even fatal effects. Patanjali's study also measured the levels of high sensitivity C-reactive protein or hs-CRP, which is produced by the liver when there is inflammation in the body.

According to the results, by day seven of the trial, hundred percent of the people in the treatment arm recovered compared to 60 percent in the placebo arm. Recovery was not measured by an eradication of symptoms

alone but by virological clearance, which is when patients were clear of all virus as confirmed by RTPCR tests.

I spoke with two medical experts who have closely evaluated the study and found major methodological flaws, which in turn make the study's results contentious. Cyriac Abby Philips, a hepatologist at Kerala's Ernakulam Medical Centre, who has been closely monitoring the scientific claims made in favour of Coronil, told me that the foremost flaw was the relatively small sample size of 95 patients. "The authors have not calculated the sample size required to adequately prove efficacy and safety," he said. The study included only 95 patients of which 45 were in the treatment arm and 50 were in the placebo arm. A larger sample size leaves less room for error, while a smaller sample size can amplify a false result. Jammi Nagaraj Rao, an independent public health physician and epidemiologist who served over 25 years in the United Kingdom's National Health Service, further explained the problems of too small a sample size. "For example, if you see a positive trend due to the medical intervention and if it is consistent in a larger sample size, there is less of a chance of it being a false trend or an outlier," he said. Conversely, a small sample size limits the chance of investigators observing an unexpected result. "This is what we call the type 2 statistical error, which is an error of omission. In a smaller sample size, one might miss out on results which they might have observed in a bigger sample," Rao added. To put trial sizes into context, the World Health Organization's trial (https://www.nejm.org/doi/full/10.1056/NEJMoa2023184) to test four repurposed antiviral drugs enrolled 11,330 hospitalised COVID-19 patients from 405 hospitals across 30 countries. Pfizer tested its vaccine on more than 43,000 participants randomised into intervention and placebo arms for its phase two and three trials.

The second major flaw in the study was with the endpoints. All clinical studies should have a well-defined endpoint. The primary endpoint of a study is the result that points to the most significant question the trial is

trying to answer. In the Coronil study, this endpoint was viral clearance. “Here, the authors have only measured viral clearance, which is not equal to resolution of disease,” Philips. Viral clearance denotes the absence of virus in the body and resolution of disease refers to an end of all symptoms. A more valuable clinical endpoint for the study is to measure the time it takes for symptoms to resolve and for patients to feel healthy again. “For an acute disease like COVID-19, looking at recovery time, reduced mortality rate, reducing the need for intensive care—these are the endpoints that matter,” Rao said. “Viral clearance occurs on its own through the passage of time, but medical intervention should intend to save lives here.” Most clinical trials for COVID-19 therapy, such as the recovery trial (https://www.recoverytrial.net/results) in the UK which tests various repurposed drugs and therapies on patients, seek reduction in mortality rates in hospitalised patients as a primary endpoint.

Rao admitted that there was some value in measuring viral clearance in patients after a medical intervention for epidemiological purposes. “It will help reduce overall infectivity in the population I suppose,” he said. “In diseases like typhoid and tuberculosis this was important, because often people weren’t allowed to assimilate back in society until they were clear of the infection completely, even if their symptoms had receded.” However, for the current pandemic, India’s public health strategy does not focus on eradicating viral load. “Each individual needs to wear masks and practice social distancing. We all have to assume that any of us can be a carrier of the infection and take precautions accordingly. So, the focus is not so much on killing the virus, but on making sure fewer people die from the disease,” Rao explained.

Another reason why viral clearance is not a great marker for the ayurvedic treatment’s efficacy is that the study only recruited asymptomatic COVID-19 patients. Rao argued that asymptomatic patients, whether in the treatment or the placebo group, had mild infections and were bound to clear the virus from their systems without medical intervention. “It is a vague endpoint,” Rao emphasised. “How do

we know that all the patients enrolled in the trial would have tested negative at the end of day seven anyway, without any ayurvedic intervention?" To illustrate this point, let us imagine that you are in the first car at a traffic intersection waiting for the light to turn green. Behind your car is a truck honking at you while the light is red. After half a minute, green comes on, you put your car in gear and move ahead. You would have done this regardless of honking from behind. But the truck driver thinks his persistence with the horn is what made you move. The Coronil study only established that the medicine is as effective as the truck in our analogy. Coronil was claiming to push the COVID-19 infection along a path that it would have naturally taken anyway.

It was also unclear when each of the enrolled asymptomatic patients was first exposed to the virus. Each patient was possibly enrolled while they were at different stages of the disease. So, day three for one patient, could actually be day seven for another. This error is called lead-time bias. "Such inclusion could falsely give us the impression that patients on treatment improved earlier than the ones receiving placebo," Philips said.

If the trial investigators had decided to enroll symptomatic patients, then the day on which symptoms showed up could have been the standardised day one. "The convention is to always use symptomatic patients," Rao

said. “With asymptomatic patients there is no way of knowing when exactly they contracted the disease. Some of the patients enrolled in the trial might have a lead in terms of having contracted the virus much before the others. This also means that this patient will shed their viral load before others. Suppose most of the patients in the intervention arm have this lead, then there is a chance that the trial is boasting of a false positive result.”

The secondary endpoints were levels of IL-6, TNF-α and hs-CRP, all which are markers of the extent of inflammation. According to the paper, these were measured to assess the effect of the Ayurvedic regime on inflammation. “Not only is it unusual for asymptomatic patients to have high levels of cytokines, but also the fact that due to the lead time bias, each patient will have different levels of IL-6 to begin with,” Rao pointed out.

The study acknowledged that “IL-6 was found to be reduced in the treatment group, although the reduction was not statistically significant in comparison to the placebo group, most likely, due to small sample size”. Despite this concession, the paper concluded that “average fold changes in serum levels of hs-CRP, IL-6 and TNF-α in the treatment group were respectively, 12.4, 2.5 and 20 times lesser than those in the placebo group at day 7”. In other words, the authors implied that the rate of increase in inflammatory markers were much less in the treatment group as compared to the placebo group. Philips said that using any of the inflammatory markers as secondary endpoints was misguided. “These are soft endpoints because they do not have a specific association with a COVID-19 infection, they can occur due to any serious injury, stress or infection in the body. The levels of these markers alone cannot reveal anything regarding how sick a patient is,” he explained. In other words, even when levels of these inflammatory markers are low in the patient’s body, it does not suggest that the patient has recovered. Reciprocally, if someone has high levels of such markers in their body, it does not necessarily suggest that they have a severe COVID-19 infection.

“The problem is not necessarily that these markers were measured, but that these weren’t complimented with clinical and radiological endpoints,” Philips continued. A clinical endpoint would be a resolution of symptoms or decreased number of days under intensive care, but since the trial enrolled only asymptomatic patients, it could not assess such clinical endpoints. A radiological endpoint such as a computed tomography or CT scan of the lungs could be a useful end point to study even asymptomatic patients. However, the Patanjali study did not include any data on CT scans of enrolled patients.

Then there are the results. The perfect recovery rate of hundred percent and the absence of any reported adverse event is very rare, even impossible, in a carefully conducted clinical trial. “I can see how the hundred percent recovery rate arises from the fact that they had a flawed trial design, where the endpoint is viral clearance and there is a lead time bias, but it is hard to believe that no patient reported adverse events or side effects,” Rao said. Even patients in the placebo arm of trials often report side effects and symptoms. “Not because the placebo causes these side effects, but because if you ask patients to report any symptoms, they will have observed at least some physical manifestation or change in their body which they find unusual,” Rao said. The absence of reported adverse events, according to Rao, was more a sign of a poorly designed and implemented trial protocol, than evidence for the safety of the ayurvedic medicine.

“Without good study power and sample calculation and specifically including adverse events as a secondary end point, one will tend to miss drug-related side effects,” Philips said. The study claims that the “Ayurvedic medicines studied in this trial fit well with this requirement: these are safe without any observed side-effects, can be distributed *en mass* and are effective against asymptomatic to mild cases.” Philips said that Patanjali’s Coronil kit included substances with known side effects. A study on *ashwagandha*, a medicinal plant which is a key ingredient in

the Coronil tablet, published in the journal Liver International in February 2020, showed (https://pubmed.ncbi.nlm.nih.gov/31991029/) how the medicine can cause liver injury and toxicity. In December of 2020, Philips had tweeted (https://twitter.com/drabbyphilips/status/1338512692747796480) results of a test he had conducted on the Coronil tablet, which revealed that the medicine contained higher than recommended levels of lead and cadmium. "*Ashwagandha* has been shown to cause severe liver toxicity in combination with other herbs in polyherbal formulations," Philips reiterated to me. "*Swasari Ras* alone or in combination with the other components of Coronil kit are not studied on tissue lines, small animals and in humans adequately to assess their safety. Also, the pharmacokinetics and pharmacodynamics of this combination in humans remain unknown. Hence direct use in humans as part of this study was very unethical."

Despite the inadequacies in the paper, government representatives explicitly endorsed the Coronil kit. In the 19 February press conference, Ramdev was flanked by two senior union ministers: Harsh Vardhan, the health minister and Nitin Gadkari, the minister for micro, small and medium enterprises. Endorsing the product and the Patanjali's research paper, Vardhan said, "Using this modern and scientific mechanism to re-establish Ayurveda's relevance in the world is a proud moment for India."

Many sections of the medical community objected to the ministers' presence at the press conference. In their letter (https://twitter.com/just1doctorwala/status/1363744925641183232/photo/2)criticising the false claims made by Patanjali, the IMA also condemned Vardhan's endorsement. The letter said that the health minister, being a doctor himself, had violated the code of ethics according to which a physician should not give any person an endorsement, approval or recommendation for any drug or medicine. The IMA demanded an explanation from Vardhan and claimed they would write to the National

Medical Commission seeking suo moto explanation for Vardhan's blatant disrespect towards the Medical Council's code of conduct.

"Code of conduct or not, this explicit endorsement by the government makes me very uncomfortable," Rao said. "How can government officials espouse such a treatment, which has not even been clinically established?"

At the same press conference, Patanjali announced that the Central Drugs Standard Control Organisation granted Coronil a certificate of pharmaceutical product or a CoPP after the paper was published. India's guidelines for granting CoPP are based on the World Health Organization's guidelines on Good Manufacturing Practices (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/gmp) for medicinal products. This certificate allows Patanjali to export Coronil to more than 158 countries. Various news portals inaccurately reported (https://www.youtube.com/watch?v=MBJpx-hzWdw&feature=emb_title&ab_channel=News18India) that the WHO had "approved" or "certified" Coronil as treatment for COVID-19. Such rumours were fuelled by a number of identical tweets (https://www.boomlive.in/fact-check/false-claims-go-viral-about-patanjalis-coronil-approved-by-who-12061) stating that "Patanjali has made history in the field of Ayurveda as Coronil has been recognised by WHO as First Evidence based medicine for Corona." The WHO was quick to dismiss the rumours, tweeting (https://twitter.com/WHOSEARO/status/1362755186112880646) that it had "not reviewed or certified the effectiveness of any traditional medicine for the treatment of COVID-19." I wrote multiple emails to WHO's regional office for South East Asia that monitors public health in India asking what they think about the promotion of alternative therapies as treatment of COVID-19 in general and of Patanjali's study in particular. I received no response till the time this story was published.

Patanjali's poorly designed study and loud promotion of Coronil casts a shadow on more substantive and relevant research into Ayurveda and other traditional medicine. MS Valiathan, a renowned cardiologist who has authored several articles and books on Ayurveda and a former president of the Indian National Science Academy has studied the convergence of modern biology and ayurveda as a scientific discipline. He told me that it was possible to hold clinical research in Ayurveda to the standards of modern science. "We need to design good clinical trials to test these products," he said. "There is a lot to gain from this school of medicine, but we can't just rely on anecdotal evidence and faith any more. Research in Ayurveda should be modelled on the current standard of clinical research."

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