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COVID-19 CRISIS

# Are anti-malarial drugs the answer to COVID-19?

**About IPR**

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In a Press Conference at the White House, US President Trump was perhaps guided by the ancient search by humans for the elixir of life. Or maybe it was the urgent situation caused by the pandemic. True to form, he jumped the gun by declaring that a cure had been found for the coronavirus. He said that hydroxychloroquine and chloroquine can combat the new virus and that FDA had approved them to treat COVID-19[1].

Within hours, stocks of these two medicines disappeared from shelves, especially in countries where these are sold over the counter. In Nigeria, three people became sick from overdose. In Arizona, one man died because he took a product with these contents, but which was not made for humans[2]. Mr. Trump is known to shoot from the hip, but this time it was about a matter of life and death. And at least in one case, death came unwarranted.

Soon after, the head of US Federal Drug Administration denied that his organization had cleared use of the medicines to cure COVID-19. FDA would wait for a fuller report from clinical trials[3]

[1] ABC News, Trump announces potential 'game changer' on drugs to treat novel coronavirus, but FDA says more study is needed, 20 March 2020, also Forbes, Forbes, Updated: Trump says FDA Approved Anti-Malaria Drug Chloroquine To Test As Coronavirus Treatment

[2] The Guardian, Arizona man dies after attempting to take Trump coronavirus 'cure', 24 March 2020

[3] Bloomberg News, Trump Touts Drug That FDA Says Isn't Yet Approved for Virus

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New York state governor also said that a study would begin shortly. On 20 March 2020, as medicine stores ran out of stock, Pakistan's Drug Regulatory Authority notified them as a prescription drug and stipulated that a record be kept of their use.

In the fight against COVID-19, the two drugs are not without promise. Yet, the data is still weak about their direct effect on COVID-19. Let us look at the evidence.

In Marseilles, France a study that is still on going, has released preliminary indication about the efficacy of hydroxychloroquine. Experts consider it promising and certainly a possible cure, but it is too early for them to be put to use against the new virus. To know why some experts are not convinced, we must step back to see what makes a clinical trial[4].

For FDA approval in the US, a clinical trial must go through three stages. A small sample to see early efficacy of the drug and to rule out safety concerns. If that shows promise, a mid-sized sample refines the results. Then the third stage with a large sample size confirms the findings. Of the drugs that enter stage two, 27.5% get FDA approval. Of the drugs entering stage 3, 63% get to the market[5].

For the trials to be reliable, a drug must go through a controlled experiment. That means the experiment must have two groups. The total sample is made up of people that fall within a certain criteria.

[4] Several sources for this and succeeding Para. 1. Stat News, Why President Trump is at odds with his medical experts 22 March, 2. Medscape, COVID-19: Could Hydrochloroquine Really Be An Answer 25 March, 3. Contagion Live, How Does Hydrochloroquine and Azithromycin Combination Therapy Measure Up for COVID-19 Treatment? 4. Center for Disease Control Information for Clinicians on Therapeutic Options for COVID-19 Patients 5. Healio, Hydroxychloroquine for COVID-19? Experts discuss its promise, risks amid reports of shortages, 23 March,

[5] Stat News, Why President Trump is at odds with his medical experts 22 March 2020

One group would get the medicine, the other would not, or get a placebo. The other requirement is that during the trial period just one variable should be different between the two groups[6]. They get the same treatment, but one group gets the drug the other does not. The selection of who gets it and who doesn't is entirely random, like the flip of a coin. Also, to make it further reliable, it should be a blind trial. That is the doctors, keen to find a cure for a malady, must not know who has received the drug and who has not. Also, the test must happen several times for reliability and in increasing sample sizes.

None of these conditions apply to the Marseilles test. It was 'hastily designed even by the standards of Phase 1 studies"[7]. Also, it was not a controlled test, nor was the selection random or the test blind. A varied group got the drug and the results from day 3 to day 6 was compared with patients who did not. These other patients were in several hospitals in the same city in different conditions. The number of patients given the drug was 26.

Of these, six had to leave the experiment. Three went to the ICU, all PCR positive. One had adverse reaction to the drug and opted out. One died, though by then had tested negative. And one healed and went home. That patient also tested negative. There is no data about them, and they are considered as though they were not part of the group. Add to that add one more complication. Six of the remaining 20 were given an antibiotic along with the hydroxychloroquine.

So far, doctors running the clinical trial have used just one indicator to assess efficacy. They have taken day 3 to day 6 blood samples to see presence of virus. There was "strong reduction in viral load" in blood. However, they have not so far shown clinical results, that is how the patient is doing in terms of health. The results are in vitro, meaning that they are test tube results. There is no in vivo, or living organism results.

The experiment has split the world of experts who study disease. While some applaud the finding, others cast doubt on the experiment's method. US senior official Dr. Anthony Fauci called the result 'anecdotal', as reported by CNN[8]. He said the study was not done in a controlled environment. Nothing about the medicine can be certain until a proper clinical trial takes place. The drug has promise, but more needs

[6] Khan Academy, Controlled experiments, How scientists conduct experiments and make observations to test hypotheses.

[7] Op. Cit. 4

[8] YouTube, Gupta stunned by Trump-Fauci difference at briefing, 21 March 2020, statement in presence of President Trump by Dr. Anthony Fauci, Director National Institute of Allergy and Infectious Diseases

to be done to confirm it. Plus, practitioners must know appropriate dosage and probable side effects.

It is encouraging because it is relatively cheap, has generics available, and has FDA approval already for other purposes. Over many years, enough is known about its side effects and properties. Another experiment in China, supported by government and with a sample size of 100, reportedly shows positive results. These too are in vitro results. That study is ongoing, and the data is not out yet[9].

Side effects is a concern. The first is that it is premature. Use of the drug could come at the expense of another treatment. If hydroxychloroquine doesn't work the cost in terms of lives lost would be high. Even for malaria, not everyone tolerates the drug well. It has cardiac effects as well as affects the eye. The heart's rhythm changes with its use. Lastly, the drug interacts with other medicines.

All of this means that while hydroxychloroquine is a possible cure for COVID-19, it would be several weeks before it is mainstreamed for treatment, if at all. Even today, hospitals use it for severe cases. An FDA provision for compassionate use in serious cases allows this. In France also, some hospitals have used it. The Punjab government has allowed its use in critical cases. And that is fine as it will be done under supervision[10].

Why does South Asia and Africa show such few cases?

This leads us to more relevant territory. There is a view, and not without validity, that perhaps low incidence in South Asia is because of widespread use of chloroquine for malarial treatment. The chloroquine may have built immunity among the people of South Asia against COVID-19 also

This is an important observation. For nations with weak health systems, in fact, it could be a lifeline. But clearly the governments of South Asia have not come around to the idea. They have made no study yet of the reasons the virus is slow to spread here, or whether Resochin is a possible cure or has built our immunity. Karachi University has studied structure of the virus, and has seen that its version in Pakistan is a mutation.

No global or South Asian expert has considered immunity a possible source for the slow proliferation. In his interview to Indian TV 'India Today', eminent virologist

[9] Clinical Infectious Diseases (online journal), 9 March 2020

[10] Dawn, Punjab govt approves malaria drug for critically ill Covid-19 patients, updated 31 March 2020

Dr. Ian Lipkin of Columbia University, when asked why India had such few cases, said India is early on the curve. He suggested that the number of cases would rise in the days to come. Other reasons were low testing and not reporting of mild cases[11]. Dr. David Nabarro, WHO Special Envoy for COVID-19 gave the same message in another interview[12].

Yet, by all estimates the cases are few. One would think that South Asia's population size, weak health services and cramped living condition should have meant more cases.

Let us look at the evidence about possible immunity against COVID-19 because of use of malaria drugs. A known source of immunity against a disease are vaccines. Until a few years ago, the world did not have a malaria vaccine. The one it has now is not effective. So, there is no support for long-term immunity against Malaria. Drugs for Malaria, consumed in large amounts in South Asia, serve two purposes. They prevent or they cure. It is not clear if their effect lasts after many years of ingestion. Besides the same person can have malaria twice. So, clearly the previous drug does not give long lasting immunity. US Center for Disease Control gives half-lives for several anti-malaria drugs. They range from two days to two weeks. After this period, the body contains half the strength of the drug's starting dose[13].

**Half-lives of selected antimalarial drugs**

| Drug | Half life |
|---|---|
| Atovaquone | 2–3 days |
| Chloroquine | 6–60 days |
| Doxycycline | 12–24 hours |
| Mefloquine | 2–3 weeks |
| Primaquine | 4–7 hours |
| Proguanil | 14–21 hours |
| Tafenoquine | 2 weeks |

[11] YouTube, World's Top Virologist Dr. Ian Lipkin Speaks On Fighting Coronavirus Crisis | India Today Exclusive, 12 March 2020

[12] YouTube, WHO Envoy, Dr. David Nabarro On India's Fight Against COVID-19 | News Today With Rajdeep Sardesai, 26 March 2020

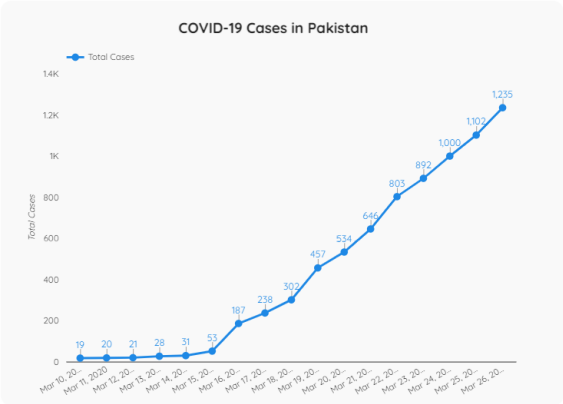
[13] CDC, The Disease, What is Malaria

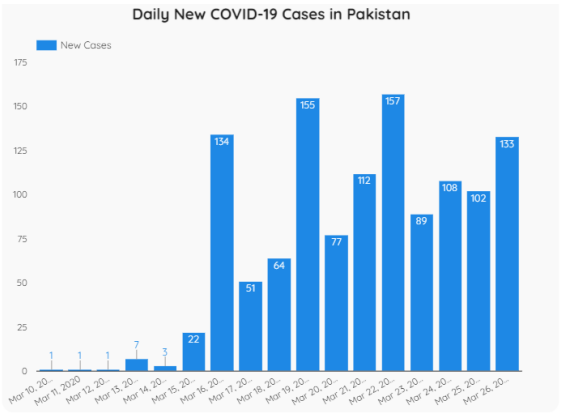
CDC's same paper says that in tropical countries some people may build immunity against malaria. That comes from frequent and regular exposure to the mosquito that bears the malaria parasite. Exposure to malaria parasites can build immunity against malaria.

But does that immunity transfer to COVID-19? There is no evidence to suggest so. That logic would run like this. Because anti malaria drug may possibly be a cure for COVID-19, a person immune to the malaria parasite should have immunity against the new virus. That is not very convincing.

Also, it would be a dangerous assumption to make given the explosive nature of the pandemic. It is a leap of logic to get there. It is a leap that is worth studying and exploring, though not acting upon yet.

Meanwhile there are things that Pakistan must continue to do. The trajectory of the disease in Pakistan is disturbing if not alarming[14].




Pakistan is in partial lockdown, which should help. Congregations in mosque still take place. And it takes one exception to break the benefit of many days of social distancing. A lockdown is the minimum we can do, given that the quality and quantity of our health capacity is such that a breakdown would ensue, if we don't.

[14] GoP, http://covid.gov.pk/stats/pakistan 27 March 2020 @ 3 PM

Because of the similarity of our environment, we may take cue from a study of what India should do.

Indian American expert Ramanan Laxminarayan is both an economist and an epidemiologist. He knows India well. He also knows how diseases spread. He is director of the Center for Disease Dynamics, Economics & Policy in Washington and a senior scholar at Princeton. Working with the Indian Council for Medical Research, he estimated that 300 to 500 million will be infected in India, of whom 30 to 50 million would be serious cases. Now with the lockdown in place in India, that number will go down sharply. Strict social distancing could bring the numbers down by 70%. Yet, about a million people would still need to be hospitalized. That would stretch India's capacity. He says that India's present estimate of a few hundred cases is way below actual. This is because of very low testing and mild cases.

India, he says has about six weeks until early May to get its act together. That is when virus will be in full force in the country. India has that brief window "to create an enormous, affordable and easily available testing infrastructure". The country must "intensify efforts to identify the sick, trace their contacts and isolate them". By then also, India must have enough "quarantine facilities and intensive-care beds".

His paper also counsels quickly setting up "temporary COVID-19 treatment facilities" and procuring needed equipment, especially test kits. Health workers would need personal protective equipment. And there should be enough hospital beds, oxygen-flow masks and ventilators. Failure to do so he fears, would exact "a heavy toll"[15].

An earlier report by this Institute gave similar recommendations and pointed at the consequences of not doing so[16].

The message from WHO DG is the same. While a lockdown is commendable, he called for "aggressive measures to find, isolate, test, treat and trace'. He said it is "the best and fastest way out"[17].

So, we may not yet assume that South Asians are immune to COVID-19. Coming back to Pakistan, outbreak of the disease is may occur in a few weeks. If that happens, there would be a collapse of our systems with high human and economic costs. By any benchmark, Pakistanis are poorly provided. We have one doctor to a

[15] New York Times, What India Needs to Fight the Virus, 27 March 2020

[16] IPR, Is the forecast for Corona Virus as bleak as they say? March 2020

[17] India Today, Lockdown not enough to eradicate Covid-19 pandemic: WHO, 26 March 2020.

thousand and 0.6 hospital beds to a 1,000. Health workers do not have enough protective gears. Testing capacity is low and ventilators few. Their count vary from 700 to 1,700, but many are not working.

The time to act is now. We need to take clear and decisive actions to identify, trace, test, isolate and treat. In the coming days and weeks, we must build the capacity of which we are woefully short. There is no magic solution. As Dr. Fauci said in a CNN interview "you don't make the timeline, the virus does"[18].

We must improvise isolation units, equip hospitals, and set up makeshift facilities in public spaces. We must make every effort to import or produce protection that our health workers need as well as oxygen masks and ventilators. And we must import testing equipment as well as try to replicate them here.

This Institute's earlier report referred above says "This is the time to reinstate trust of government in the eyes of the people. Decisions taken in crisis shows the mettle of a leader. There is no running away from difficult choices. One takes them today, or the whole nation must live with the consequences of weak decision making"[19].

[18] YouTube, CNN Dr. Fauci: You don't make the timeline, the virus does, 26 March
[19] IPR, Is the forecast for Corona Virus as bleak as they say? March 2020, Page 22