The Nossa Senhora Aparecida cemetery in Manaus, Brazil, where many COVID-19 victims are buried. The city's clinical trial with chloroquine started in late March, when cases had begun to explode. MICHAEL DANTAS/AFP VIA GETTY IMAGES

'It's a nightmare.' How Brazilian scientists became ensnared in chloroquine politics

By Lindzi Wessel | Jun. 22, 2020 , 5:30 PM

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Now that several big trials have shown disappointing results, hope has faded that chloroquine or hydroxychloroquine might be miracle drugs against COVID-19. But for one group of researchers in Brazil, the story is far from over.

In April, a team led by Marcus Lacerda, a clinical researcher at the Heitor Vieira Dourado Tropical Medicine Foundation in Manaus, Brazil, published a study showing chloroquine can increase mortality in COVID-

19 patients. Since then, they have been accused of poisoning their patients with a high dose of chloroquine just to give the drug—praised by U.S. President Donald Trump and his Brazilian counterpart Jair Bolsonaro—a bad name. Social media attacks, defamatory articles, death threats, and even a legal inquiry into the group's work have left Lacerda and his team stressed and exhausted.

Other scientists have watched the public spectacle with dismay. But some agree that about half of the patients in the trial received such a high dose Kremsner of the University of Tübingen in Germany, who is using far lower doses in two trials of hydroxychloroquine. Others say Lacerda and his colleagues took a calculated risk at a time when the optimal dose for SARS-CoV-2, the virus that causes COVID-19, was still under debate. "It's clearer now that you wouldn't have gone for that dose," says Nicholas White, a veteran malaria researcher at Mahidol University in Bangkok who helped design the Recovery trial in the United Kingdom, which included a hydroxychloroquine arm. "But at that time, I think it was a legitimate choice."

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Lacerda started the trial in late March, at a time when coronavirus cases in Manaus were growing explosively and scientists had promising results from chloroquine and hydroxycholoroquine in test tube studies and small, nonrandomized clinical studies. (Lacerda chose chloroquine because it's widely available as a malaria treatment in Brazil.) The plan was to recruit 440 patients and give half of them 600 milligrams (mg) of chloroquine twice a day over a 10-day period—a total of 12 grams. The other half received 900 mg for 1 day followed by 450 mg for 4 days, a total of 2.7 grams.

When the trial's independent data safety monitoring team saw the number of deaths in the high-dose group rise rapidly, they alerted the researchers and asked for that arm to be stopped. Of 81 patients enrolled at the time, seven in the high-dose group had died, versus four in the low-dose group. By the times the results were published, those numbers had risen to 16 and six, respectively. Two patients from the high-dose group developed dangerous cardiac arrhythmias before death, a known side effect from chloroquine, and warning signs for future heart trouble were more common in the high-dose group. An 11 April

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preprint about the results was covered by international media outlets, including *The New York Times*.

On 14 April, Michael James Coudrey, CEO of a U.S. marketing company whose website says he offers "social media and 'digital information warfare' services to political candidates," tweeted accusations that the researchers had overdosed their patients and used them as "guinea pigs" in a study conducted "so irresponsibility I can't even believe it." Three days later, Eduardo Bolsonaro, the Brazilian president's son, tweeted out a similar message, including an article that called the researchers "left-wing medical activists" and included their past social media posts in support of certain political candidates and sporting rainbow flag profile frames as proof. The article framed the study, which was later published in *JAMA Network Open*, as an attempt to "disparage the drug that the Bolsonaro government approved as effective for treating COVID-19." Soon, death threats against the researchers and their families started to come in.

Then came the inquiry from the federal prosecutor's office—the first such investigation of a medical study approved by an ethical review board, according to the research team's lawyers. A Brazilian official announced the investigation on Twitter and posted a nine-page document that asked Lacerda's team to justify everything from their choice of chloroquine to why the study didn't focus on patients in earlier stages of COVID-19. Many of the questions centered on how the dose was determined and whether patients in the study experienced cardiac problems. The investigation is ongoing.

Brazilian researchers worry the legal inquiry from a federal prosecutor's office could set a dangerous precedent in a nation already beset by attacks on science. "Today it's [Lacerda], tomorrow it's anyone else," says Mauro Schechter, an infectious disease researcher at the Federal University of Rio de Janeiro, Rio de Janeiro. "It was quite outrageous the way things developed," adds Adauto Castelo, an infectious disease researcher at the Federal University of São Paulo, São Paulo.

Tricky position

But there has been a real scientific debate about what an appropriate dose might be. Chloroquine is highly effective against malaria—unless resistance emerges—but test tube studies suggest much higher levels may be needed for the drug to block viruses. Both chloroquine and hydroxychloroquine are known to be toxic at high doses, but most information on toxicity comes from studies on suicides and accidental poisonings, where the dose was often not precisely known.

That put clinical researchers in a tricky position, White says. Go too low and you might miss the lifesaving activity of the drug. Go too high and you might endanger your patients.

Lacerda went very high. The 12 grams given to participants in his high-dose arm approached two times what was used in Recovery trial, which didn't show a benefit from hydroxychloroquine, and in the World Health Organization's Solidarity trial, which didn't see a benefit either and ended its hydroxychloroquine arm on Wednesday. At least two hydroxychloroquine trials—one of 150 patients in Shanghai and a study

at the University of Pennsylvania—went slightly over Lacerda's total, but most studies used far less.

The participants in Lacerda's trial were also given two to three other medications, including azithromycin, which shares chloroquine's propensity to cause heart problems. It's hard to evaluate just how harmful the high-chloroquine doses may have been, says James Watson of Mahidol University, who has attempted to model the toxicity of various dosing regimens.

"I'm sure that it's going to be a very nice scientific discussion," Lacerda says, adding that the criticisms of the high dose didn't start until politics got involved. "Some people will be against that dose, some people will be in favor of that dose, and, unfortunately, I was the one who had the bad luck to be the first one to try the high dose. I probably will have to pay the price for that forever."

White maintains Lacerda and his team made a reasonable choice at the time of their trial. But Kremsner says both Recovery and Lacerda's trial were "a dangerous undertaking." Two trials in Germany he leads—one in hospitalized patients and one in milder cases at home—use 3.3 grams over 7 days as the maximum dose . David Boulware of the University of Minnesota, Twin Cities, who led a study of hydroxychloroquine as a prophylactic drug in people exposed to the virus, says he wouldn't be comfortable with Lacerda's high dose either, but says the decision was "not crazy," particularly given the "desperate times" of a pandemic without alternative treatment. (Boulware's own study, which came up empty-handed, gave subjects 2.9 grams over 3 days.) "I think it would be reckless if they had no monitoring plan," Boulware says. "There was a monitoring plan, they did stop the trial early, and they didn't hide their results—they published them to try to warn others."

Intense strain

Part of Lacerda's problem is that he appeared unaware that the dose was very high. In the preprint, the team justified the high dose in part by pointing to an expert consensus coming from Guangdong province in China that recommended using 500 mg of chloroquine phosphate twice daily—seemingly in the same ballpark as the 600 mg the Brazilian team used. Lacerda also discussed the consensus in the *New York Times* story and again in a 20 April written statement defending his study.

But the comparison was off. A dose of chloroquine base, the nomenclature used by Lacerda, is 67% more potent than an equal dose of cloroquine phosphate, which the Chinese authors used. Lacerda said the mistake came when writing the preprint, after the trial was completed. He says the team did a wide literature review before making its dose decision and that the Guangdong dose was just one factor in their choice. Lacerda is still under intense strain from the fallout. "It's a nightmare," he told *Science* in a video call. For weeks he hasn't been able to stop worrying that "my whole career is gone" or agonizing over the death threats against his family. "The day someone tells in your social media, that they're going to kill your children to make you suffer the way you made other people suffer, you will understand what I've been through," he says.

With reporting by Kai Kupferschmidt.

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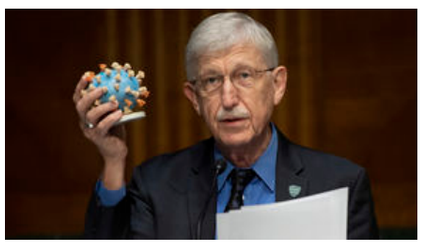

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