IN DEPTH

A trial aims to test messenger RNA vaccines for COVID-19 in pregnant Africans, like this woman receiving a sonogram at an AIDS care center in South Africa.

CREDITS: (PHOTO) AP PHOTO/DENIS FARRELL; (DATA) COVID-19 PREVENTION NETWORK

COVID-19

'Landmark' African vaccine trial faces impasse

Pfizer and Moderna have been unwilling to participate in key test of their mRNA vaccines

By **Jon Cohen**

The questions are urgent, and the funding is in place. But a highly anticipated, $130 million clinical trial, meant to test the efficacy of the novel messenger RNA (mRNA) vaccines for COVID-19 against a key variant of the pandemic coronavirus as well as in people living with HIV and pregnant women, is stalled. It is ready to launch in eight countries in sub-Saharan Africa, yet neither maker of the vaccines, Pfizer and Moderna, wants to participate—or even provide their vaccines.

A group of prominent HIV advocates and activists in South Africa has written a letter complaining about the delay to U.S. government officials, including Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), which agreed to pay for the study. They stress that COVID-19 strikes people living with HIV especially hard, and that dangerous variants of SARS-CoV-2 evolve in them because many have weakened immune systems. "We believe this will be a landmark study for this region and ... the world," they wrote. "We respectfully ask that you do all in your power to enable this study to take place."

The efficacy trial could yield answers in as little as 12 weeks given the rapid spread of SARS-CoV-2 in the region. "This is the most important yet-to-be-done study" in the entire portfolio of adult COVID-19 vaccine trials funded by the U.S. government to date, says Lawrence Corey of the Fred Hutchinson Cancer Research Center, who helped organize the trial.

The trial aims to follow up on hints that mRNA vaccines, which code for the coronavirus' spike protein, can protect against a variant first seen in South Africa, originally called B.1.351 and now dubbed Beta under the World Health Organization's new naming system. The variant, widespread in Africa, escapes critical antibody responses in lab studies, and non-mRNA vaccines have shown lower efficacy against it (see table, left). Two of those vaccines, from Novavax and Johnson & Johnson, also appeared to offer only modest, if any, protection in people with HIV. "We have a real problem with HIV-infected individuals," says Glenda Gray, who heads the South African Medical Research Council, the study's sponsor. And whether current COVID-19 vaccines protect pregnant women remains uncertain, as initial efficacy trials excluded them.

The new trial was organized by the COVID-19 Prevention Network, which Corey co-leads; CoVPN previously staged efficacy trials of the Moderna vaccine and four other candidates developed under the U.S. government's multibillion-dollar Operation Warp Speed program. Positive results would

Beta testing

Some COVID-19 vaccines may be compromised in Africa because Beta, a variant of SARS-CoV-2 that can escape key antibody responses, is widespread there. The Pfizer messenger RNA (mRNA) vaccine did best in an African trial, but it was small.

COMPANY	VACCINE TYPE	U.S./U.K./ BRAZIL EFFICACY*	SOUTH AFRICA EFFICACY*
Johnson & Johnson	Adenovirus vector	72%	57%
Novavax	Protein	89%	49%
AstraZeneca	Adenovirus vector	70%	11%
Pfizer	mRNA	95%	100%
Moderna	mRNA	94%	Unknown

*Efficacy measured for symptomatic COVID-19, not severe disease

strengthen the case that mRNA vaccines, now scarce in the developing world, should be more widely available. But a Pfizer spokesperson says it considers the study unnecessary because evidence shows its vaccine works well against the Beta variant, and it has an international study underway in pregnant women.

When the trial designers turned to Moderna, the company initially said it would provide its mRNA vaccine, although it wanted the trial to compare the current version with another under development. Then, a few weeks ago as the trial was preparing to launch, Moderna began to back out. The company and its would-be collaborators say a complex mix of liability concerns, Moderna's reluctance to have its scientists help with required oversight known as pharmacovigilance, and concerns about the design of the study led to the change of heart.

Some of the trial organizers suspect business considerations factor in, too. Both firms may be wary that new data, if negative, would complicate getting full approval for their vaccines, which so far have only received emergency use authorizations.

Science's COVID-19 reporting is supported by the Heising-Simons Foundation.

The proposed trial would involve 14,000 people in South Africa, Eswatini, Botswana, Zimbabwe, Malawi, Zambia, Uganda, and Kenya, where adult HIV prevalence ranges from 4.5% to 27%. Half the participants in the study, dubbed CoVPN 3008, would receive two doses of the current Moderna vaccine. The others would receive placebo shots initially. But as soon as clear evidence emerged that the current vaccine protects against COVID-19 at the African sites, the placebo group would be offered a new "bivalent" vaccine Moderna has developed. It contains mRNA for the original spike as well as mRNA for the slightly mutated version in Beta.

Ethicists long have debated whether vaccine trials should include placebos once a proven product exists, but Linda-Gail Bekker, a South African researcher who helped design CoVPN 3008, notes the study received approvals from multiple bodies after intensive ethical reviews. At the moment, says Bekker, who is director of the Desmond Tutu HIV Centre, "There is no vaccine for most people" in the region, and trial participants will likely receive doses earlier than most Africans. If participants become eligible for any authorized COVID-19 vaccine during the trial, they will be encouraged to drop out.

Gray is surprised that Moderna is balking. NIAID worked closely with the company to design its vaccine, and Warp Speed gave the firm $1.5 billion for related R&D and efficacy trials. (Pfizer did not receive government support to develop or test its vaccine.) "This is a request from the U.S. government to a drug company to help answer a critical question," Gray says. "It just seems weird."

Moderna, however, says it wants to move on to assessing its new formulation. "We believe science and public health will be better served by investigating the safety and efficacy of a multivalent vaccine, which includes the sequence against B.1.351," a spokesperson said. "We are in active discussions with potential investigators in Africa to conduct such a study." But Gray and other leaders of the planned study say the company also expressed concern to them about liability for vaccine side effects and staffing the required pharmacovigilance effort.

The case for the new trial remains strong, they add. Tantalizing results from a small South African trial of the Pfizer vaccine suggested mRNA vaccines might work well against the Beta variant: Only nine people, all in the placebo group, developed symptomatic COVID-19 among the 800 participants. But a bigger study is critical for both science and policy, Corey says. "Having data showing the efficacy of mRNA in this region provides the hard facts that excluding these countries from access [to this type of vaccine] is medically inappropriate."

Trial organizers hope a deal can still be reached with Moderna. They note that in theory, the U.S. government could assume liability and provide the trial with the vaccine. A U.S. government official familiar with the negotiations says the hitch is the Public Readiness and Emergency Preparedness Act, which indemnifies COVID-19 vaccine manufacturers but only in the United States. Amending the act to provide international indemnity would require action at the highest government levels. Alternatively, the South African government could indemnify the company, and Gray says such negotiations are underway.

Even if the mRNA vaccine trial launches and proves that the current Moderna vaccine works against the Beta variant, Gray predicts that Moderna and Pfizer will still move forward with reformulated vaccines targeting different variants as well as the original virus. And that could lead to a windfall for the African continent, as rich countries embrace the new formulations. "There would be a whole lot of [original] mRNA vaccine lying around that nobody wants," she envisions. "There'd be all these stashes of it all over the place, and we could acquire it cheaper." ■

PLANETARY SCIENCE

NASA missions to test idea of a watery past for Venus

Climate models suggest Earth's sister planet was once cool, wet, and habitable

By **Paul Voosen**

When NASA announced last week it would spend $1 billion developing two new missions to Venus—the agency's first visits in decades to Earth's hothouse twin—planetary scientists were elated, and not just because a long wait had ended. A dramatic shift in thinking about the planet over the past few years has made a visit even more enticing. Venus was once thought to have boiled off all its water almost as soon as it was born 4.5 billion years ago, turning into the parched, hostile world of today. But many scientists now think Venus might have kept expansive oceans for billions of years—a nearly perfect setting for life.

The missions, to arrive late this decade, are equipped to look for signs of that water—and clues to why Venus ultimately declined into an inferno. If their findings support the new picture, Mars, the longtime hope for discovering signs of ancient extraterrestrial life, will have a rival. "Why look at Mars, which had water for 300 million years, when Venus had water for 3 billion years?" asks Darby Dyar, a planetary scientist at Mount Holyoke College who is deputy principal investigator for one of the new missions, VERITAS (Venus Emissivity, Radio Science, InSAR, Topography, and Spectroscopy).

Early visits to Venus cemented the picture of a dead, waterless planet when they detected no sign of oxygen in its thick carbon dioxide (CO_2) atmosphere, which keeps its surface at a lead-melting 460°C. Venus likely started out with plenty of water, as it formed from roughly the same building

IMAGE: NASA GSFC; CI LABS/MICHAEL LENTZ AND OTHERS

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Science **372** (6547), 1135-1136.
DOI: 10.1126/science.372.6547.1135