

Finally, hope for a syphilis vaccine

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Credit: National Cancer Institute

Despite efforts to eradicate it, syphilis is on the rise. Until now, most health agencies focused on treating infected people and their sex partners but new discoveries may make a vaccine possible, UConn Health researchers report in the 12 June issue of *mBio*.

The World Health Organization estimates that 10.7 million people between the ages of 15 and 49 had [syphilis](#) in 2012, and about 5.6 million people contract it every year. In the U.S., its prevalence is

growing, particularly among men who have sex with men. In many developing nations, it is growing among women sex workers and their clients.

For a long time, [health agencies](#) have tried to eliminate syphilis by treating people who contract it, tracking down the patients' recent sex partners, treating them and their partners, until the healthcare workers found everyone who could have been exposed to the disease. But this method is limited by people's willingness and ability to reveal their sexual contacts. It's also limited by the difficulty diagnosing syphilis.

"Syphilis is the great imitator; it can look like hyper pigmentation, or other conditions," says Dr. Juan C. Salazar, chair of pediatrics at UConn Health and physician-in-chief at Connecticut Children's Medical Center.

And, the sexually transmitted disease poses serious [health](#) consequences. Syphilis is the second leading cause of stillbirth and miscarriage worldwide and, if left untreated, it can cause strokes, dementia, and other neurological disease.

Salazar was born in Colombia, where, in the city of Cali, about seven percent of young, sexually active people have evidence of syphilis.

About 15 years ago, he introduced UConn Health researchers to a group of health care professionals at CIDEIM, an infectious disease research institute in Cali, and they started an ongoing relationship: UConn Health researchers received access to a large population of patients for their studies, and the Cali clinicians and researchers received high-level training in recognizing and treating syphilis.

UConn Health personnel often visit Cali, and researchers from CIDEIM have come to UConn Health to train in advanced laboratory techniques in immunology and molecular biology. It's a good exchange, and it's

helped fuel breakthroughs like the one the researchers discuss in their recent mBio paper.

Syphilis is hard to study because, unlike many disease causing bacteria, it cannot be grown in a lab dish or in mice. Besides humans, the only animal commonly found in laboratories that is susceptible to syphilis is the rabbit. But rabbits clear syphilis infections quickly, so new rabbits must be infected regularly to maintain a strain of *Treponema pallidum*, the syphilis-causing bacteria.

The second reason syphilis is hard to study is because the bacteria causes the disease is so delicate. Most disease causing bacteria are pretty tough—you can wash them, dry them, and then look at their exteriors in great detail under a microscope. *T. pallidum* doesn't survive that rough treatment. It tends to break open and spill its guts, making a mess, and also making it impossible to figure out which proteins are supposed to be on the outside of the bacteria.

And those proteins on the outside of the bacteria are key—they are how our immune system recognizes bacterial invaders. They are how vaccines work, too. The search to find and identify these proteins in syphilis has taken a long, long time. *T. pallidum* was first identified in 1905, but until now, no one has been able to figure out which proteins it sports on its [outer membrane](#).

Researchers have tried all kinds of tricks. When genetic analysis became available, they started looking at *T. pallidum*'s genetic code, in hopes that the genes for its exterior proteins would look like the genes other bacteria have. But *T. pallidum* is part of the spirochete phylum of bacteria—they're spiral shaped and weird, about as closely related to other bacteria as we are to invertebrates.

Just about the only easy thing about *T. pallidum*'s genetic code is its size:

it has only about 1,000 genes, total. That's small. Small enough for a human to analyze.

When UConn Health microbiologists Justin Radolf and Melissa Caimano began analyzing the genetics of the syphilis bacteria they collected from patients in Colombia, as well as the syphilis samples sent to them by collaborators in San Francisco and the Czech Republic, they began to notice that the strains from different places were very similar. Not many genes differed. And that makes sense—in an organism with such a small genetic code, every gene must be essential. The genes would only mutate into a different form if it was a matter of life and death. And what controls life and death for *T. pallidum*?

"They're mutating to avoid the immune system," Radolf says. Radolf and Caimano's team suspected that these mutating genes coded for the proteins they were looking for. So they began testing them. They used a computer modeling program to model the proteins these genes would make, and see if those proteins had the characteristic barrel shape that bacteria use for proteins on their outer membranes. It turned out that many of them did.

The researchers then actually made the proteins and tested whether they folded into that barrel shape in real life. And then finally, they made antibodies for the proteins and showed that these antibodies did indeed attach to the exteriors of intact *T. pallidum* bacteria. This meant they'd found their marks—the proteins were there.

Of course, proteins that mutate a lot to hide from the immune system aren't good candidates for a vaccine. For a vaccine, you want the opposite; proteins that are always the same in every syphilis [bacteria](#). So the final step in the team's work was to go back through *T. pallidum*'s [genetic code](#) to find genes that coded for proteins in the outer membrane that never changed, using the genes they'd already found as clues.

"You want the best candidate outer membrane [protein](#) for a vaccine, the one that varies the least," says Caimano.

They found them, and now the researchers plan to use them to immunize rabbits to prove they could work as a vaccine. They're also looking for even more diverse types of syphilis.

The UConn Health researchers will be collaborating with researchers at the University of North Carolina to enroll patients in Guangzhou, China, and Lilongwe, Malawi to make sure the syphilis they've been studying is representative of syphilis worldwide. If the proteins they've identified really do end up becoming a vaccine, they want it to benefit as many people as possible.

"Every time you go into a developing country, you need to leave something of benefit to the healthcare providers and their patients," Salazar says. Even better if a vaccine comes out of it that benefits the entire world.

Provided by University of Connecticut

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