

NIAID-Supported Research is Advancing the Response to Surging Syphilis Rates

U.S. syphilis incidence has increased since 2000, with an escalating toll in medically underserved populations.

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[Syphilis](#), a common sexually transmitted infection (STI) caused by the bacteria *Treponema pallidum*, is a centuries-old STI that can result in adult neurological and organ damage, as well as congenital abnormalities, stillbirths, and neonatal deaths.

Benzathine penicillin G (BPG) was introduced as syphilis treatment in the middle of the 20th century and led to a precipitous drop in disease burden, but *T. pallidum* continues to circulate in the global population, including in the United States. U.S. syphilis incidence has increased since 2000, marked by a sharp rise in reported [adult](#) and [congenital](#) cases since 2019 and, notably, an escalating toll in medically underserved populations.

There is currently a [shortage](#) of BPG, which is still one of only a few antibiotics known to effectively treat syphilis. There is no preventive vaccine and most syphilis testing is done in a laboratory setting, which prevents people from learning their status conveniently and in real time. More research is urgently needed to diversify the diagnostic, preventive, and therapeutic options available to alter the course of the growing public health threat of syphilis. NIAID supports a research portfolio to help address these areas of need, including studies featured at the recent STI & HIV World Congress in Chicago.

Updates from STI & HIV World Congress

The STI & HIV World Congress hosted presentations on new STI research, policy, and public health implementation issues, and was attended by a global community of scientists, policymakers, healthcare providers, advocates and community organizations. NIAID-supported studies and research priorities presented at the meeting included an update on syphilis vaccine development, an overview of strategies for enhanced penicillin allergy screening, exploratory research to identify new syphilis therapeutics, and the latest data and next steps to explore the utility of the antibiotic [doxycycline as post-exposure prophylaxis for syphilis and other STIs](#)—an approach commonly referred to as DoxyPEP:

- Lorenzo Giacani, PhD, from the University of Washington as well as Alloysius Gomez, B.Sc. and Simon Houston, PhD, from the University of Victoria described results from NIAID-supported syphilis vaccine studies, including preclinical (animal) research showing a vaccine containing [three different antigens](#)—a protein and peptides from the surface of *T. pallidum* bacteria—enabled animals to mount an immune response when they subsequently acquired syphilis, experiencing reduced severity of disease, but not full protection from infection. Dr. Houston shared how a laboratory team identified 95% of the approximately 1,000 proteins in *T. pallidum*. This discovery may enable scientists to select one or more of those proteins as targets for future vaccine candidates.
- Approximately 15% of people attending STI clinics report an allergy to penicillin, which prevents them from using the preferred BPG treatment. However, previous studies have shown more than 95% of people who self-reported penicillin allergy could safely use the antibiotic, according to allergy test results. Rebecca Lillis, MD, from the Louisiana State University School of Medicine, shared a validated process for determining penicillin allergy status in an STI care setting, which would enable providers to safely clear people who previously reported penicillin allergy for use of BPG.
- Given the limited known treatments for syphilis, Virginia Tech PhD candidate Kathryn Hayes presented results of a study to screen more than 100 β -lactams—antibiotics in the same class as penicillin—for their ability to kill *T. pallidum* bacteria or slow their growth. The team identified multiple β -lactams showing higher efficacy than BPG against *T. pallidum* in the laboratory, which may inform future research to develop new syphilis therapeutics.
- Multiple presenters addressed emerging NIAID-supported science on the use of DoxyPEP for STIs, including Connie Celum, MD, MPH, from the University of Washington-Fred Hutch, Annie Luetkemeyer, MD, from the University of California San Francisco, and Jenell Stewart, DO, MPH, from the University of Minnesota. Presenters reviewed the high efficacy of DoxyPEP in preventing syphilis, gonorrhea, and chlamydia among men who have sex with men and

transgender women, as well as the need to understand whether the lower efficacy observed in cisgender women to date may be due to lower acceptability of DoxyPEP in that population, which could pose a barrier to taking doxycycline as prescribed. Presenters underscored the need for further research and vigilance with respect to antimicrobial resistance and STI testing, the latter due to the potential for a [false negative test result](#) while someone is taking DoxyPEP.

Current and future NIAID syphilis research

In addition to the latest findings presented at the conference, new and ongoing NIAID-supported studies are helping to close gaps in the current syphilis response. To address the complicated and limited diagnostic tools currently available for syphilis, a new NIAID-supported [study](#) is enrolling volunteers at [all stages](#) of infection to provide laboratory samples for a biorepository of syphilis specimens. This biorepository will safely avail high-quality syphilis specimens for laboratories to use as they create new diagnostics. A new complementary [funding opportunity](#) will advance development of promising diagnostic technologies for congenital and adult syphilis.

The new [Syphilis in Pregnancy Study \(SIPS\)](#) is monitoring the outcomes of pregnant people diagnosed with and treated for syphilis, as well as the health outcomes of their infants. SIPS is expected to shed light on how adult and infant immune systems respond with effective treatment. Results may inform development of future vaccine concepts that could stimulate a similar immune response when a person is initially exposed to syphilis, thereby preventing infection.

In addition, NIAID funds [STI cooperative research centers \(CRCs\)](#) to advance the science related to numerous STIs, including development of syphilis vaccine concepts. In their pursuit of a syphilis vaccine, the CRCs are investigating the structure of proteins on the outer membrane (layer) of *T. pallidum* bacteria as potential vaccine targets and developing the tri-antigen vaccine that was featured at the STI & HIV World Congress. NIAID plans to fund new CRC awards in 2024.

Finally, in recognition of the limited treatment options for syphilis, the low-but-significant prevalence of penicillin allergy, and the current drug shortage, NIAID is [soliciting small business contract proposals](#) for identification of alternatives to BPG for syphilis treatment.

Syphilis is a serious public health challenge. Scientific discovery, research and development will continue to play a critical role in enabling an equitable and effective response to the syphilis surge.

References:

C Celum. STI biomedical prevention in 2023: Doxy PEP and Beyond. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Wednesday, July 26, 2023.

L Giacani. State of syphilis vaccine development. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Tuesday, July 25, 2023.

A Gomez. Syphilis vaccine development: Generating a stable and efficacious multi-epitope vaccine chimera through protein engineering. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Wednesday, July 26, 2023.

KA Hayes. A large-scale drug screen identifies novel therapeutics that target the syphilis pathogen *Treponema pallidum*. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Wednesday, July 26, 2023.

S Houston. *Treponema pallidum* Proteomic Analysis to Inform Syphilis Vaccine Development. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Wednesday, July 26, 2023.

A Luetkemeyer. Doxycycline Post-exposure prophylaxis (PEP) & PrEP for Syphilis Prevention. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Thursday, July 27, 2023.

RA Lillis. Validation of an Easy to Administer Algorithm to Define Penicillin Allergy Status in STI Clinic Outpatients. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Wednesday, July 26, 2023.

J Stewart. Self-reported adherence to event-driven doxycycline postexposure prophylaxis for sexually transmitted infection prevention among cisgender women. Presentation at the STI & HIV 2023 World Congress in Chicago, Illinois. Tuesday, July 25, 2023.

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