Syphilis transmission networks and antimicrobial resistance in England uncovered using genomics

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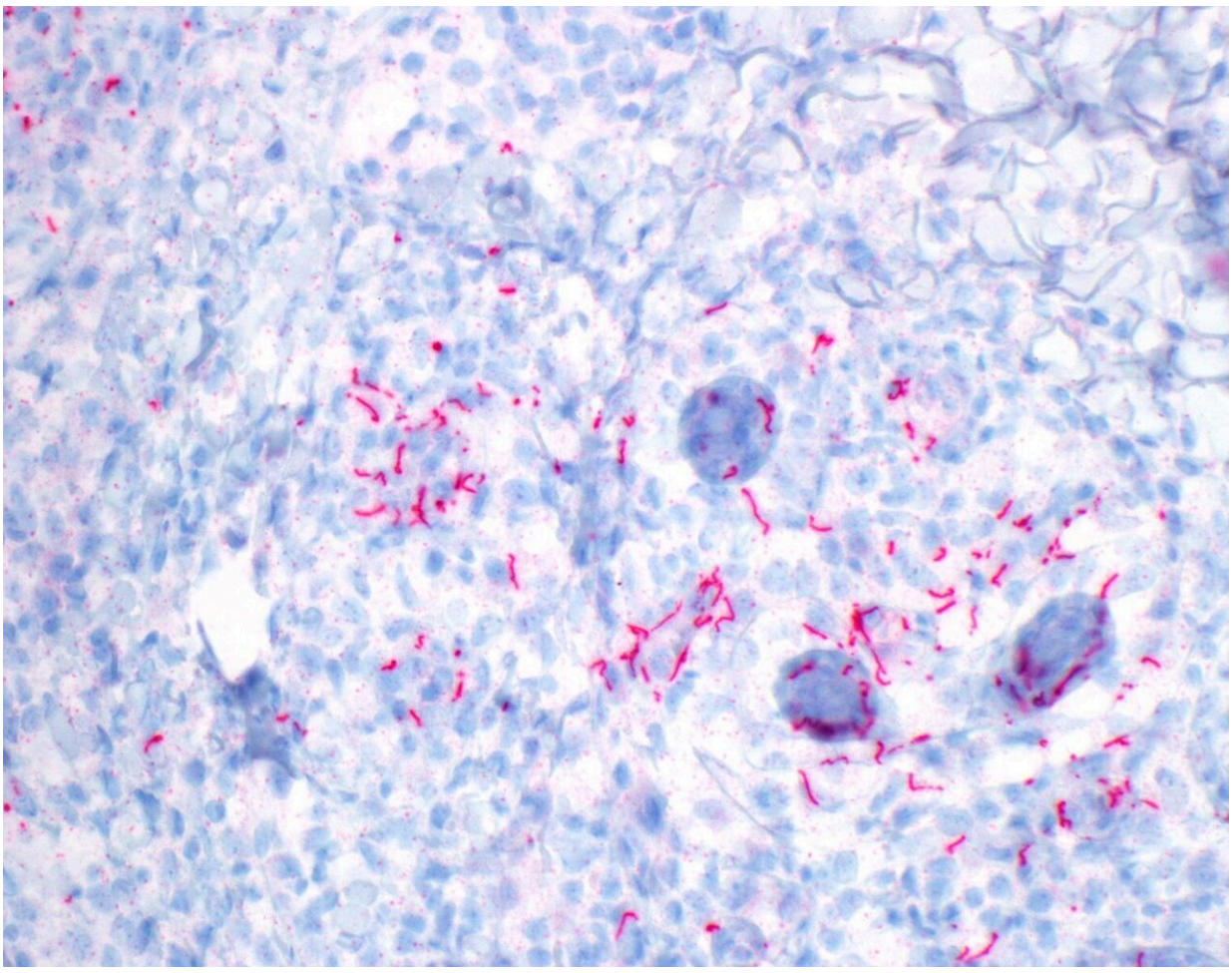

Photomicrograph of skin biopsy showing secondary syphilis. Spirochete organisms are stained bright red by the Treponema pallidum immunohistochemical stain. 400x magnification. Credit: Jerad M. Gardner, MD,

Scientists have used genomics to reveal distinct sexual networks for syphilis transmission, defined geographically or by sexual preference, among a background of wider circulation in England. They also show a presence of drug resistance in the majority of cases.

By grouping closely related strains of the bacterium that causes syphilis—Treponema pallidum—researchers demonstrate how a large number of cases are linked together.

Researchers from the Wellcome Sanger Institute and their collaborators at the UK Health Security Agency (UKHSA) sequenced 237 whole genome samples and integrated this with epidemiological data to map the bacterium's evolution and spread through a population. They show distinct transmission chains between individuals as well as significant resistance to a commonly prescribed class of antibiotics in England.

The findings, published in *The Lancet Microbe*, help demonstrate the utility of genomics to understand syphilis transmission patterns, revealing information beyond what standard epidemiological surveillance data can provide.

Unpacking STI trends using genomic surveillance could help identify high-risk areas or populations and inform targeted public health strategies to break the chains of transmission. The findings warrant further investigation into the role of genomics across different settings and STI-causing bacteria.

Cases of syphilis have tripled in the past decade in England, increasing from 2,648 diagnoses in 2010 to 7,982 in 2019. The increases are

thought to be partially fostered through overlapping sexual networks of gay, bisexual and other men who have sex with men (GBMSM) as well as women. While routine epidemiological data provide insights into the current rise in syphilis rates, it struggles to show how the bacterium circulates within a population at national and regional levels.

For example, a group of clustered syphilis cases—close in time and proximity—could represent a single outbreak and chain of transmission, but could also be the result of separate co-circulating networks.

Syphilis is a sexually transmitted infection caused by the bacterium, Treponema pallidum (T. pallidum). While the genomes of T. pallidum are highly conserved compared to other bacterial pathogens—as they tend to transmit more frequently than they mutate—subtle differences can still exist as it spreads through a population. By comparing how genetically related T. pallidum samples are between individuals with a syphilis diagnosis, scientists hope to pinpoint the source of syphilis outbreaks and construct networks that capture its spread.

In this new study, researchers from the Wellcome Sanger Institute and their collaborators set out to test the use of genomic surveillance to resolve local transmission chains for T. pallidum and better understand the genomic landscape for syphilis in England.

The team combined anonymized patient demographic and epidemiological data with whole genome sequencing analysis of T. pallidum genomes from 237 patients diagnosed with syphilis in England between 2012 and 2018. By comparing the bacterial genomes from different individuals, researchers were able to identify single letter changes in the DNA—known as single nucleotide polymorphisms (SNPs)—to distinguish one strain, or sublineage of T. pallidum from another.

Researchers identified multiple features of transmission networks of T. pallidum in England, affecting GBMSM and heterosexuals at national and regional levels. They were able to make inferences of recent transmission based on how related—identical or highly similar—T. pallidum genomes were across different individuals. These inferences were later verified by epidemiological data.

While previous work has grouped T. pallidum lineages separated by many years with a large number of SNPs, the new study goes down to the identical gene level with zero SNPs, indicating recent transmission. This never-seen-before resolution could allow public health authorities to map syphilis spread in an ongoing outbreak.

The researchers' analysis of T. pallidum genetic diversity also highlights the extent of drug resistance in England. Many of the 237 genome samples sequenced were resistant to macrolides, a class of antibiotics commonly used to treat many STIs. The work therefore aids in public health policy around safeguarding ineffective use of antibiotics as part of antimicrobial resistance (AMR) stewardship efforts and informs best treatments for patients.

Dr. Mathew Beale, first author of the study and senior staff scientist at the Wellcome Sanger Institute, said, "The COVID-19 pandemic has reimagined what scale is possible in genomic surveillance and this study capitalizes on that, providing important background information on how fast the genomes of T. pallidum evolve as syphilis spreads through a population."

"We should explore with future sampling work whether these evolutionary baselines are representative and if the approach can be used robustly in settings outside of England. Syphilis genome diversity is poorly understood in countries where STI control programs are most needed."

Dr. Helen Fifer, senior author and lead microbiologist for bacterial sexually transmitted infections at the UK Health Security Agency, said, "We are seeing record levels of STIs including syphilis."

"Genomics provides yet another tool in our toolbox for understanding chains of transmission of syphilis and predicting response to treatments. We must also focus on readily available prevention strategies and STI services, such as condoms, including information about their limitations, effective follow-up of people with new STI diagnoses and self-monitoring for symptoms when necessary."

Professor Nicholas Thomson, senior author and program leader from the Wellcome Sanger Institute and the London School of Hygiene & Tropical Medicine, said, "In many ways, syphilis is tricky to track with genomic surveillance given how slowly it mutates. The fact that we have demonstrated the usefulness of analyzing both different and identical bacterial genomes to help make inferences about sexual transmission is exciting."

"In other STIs such as gonorrhea, chlamydia and human immunodeficiency virus (HIV) we may be able to cluster strains into direct transmission events, confirming patient-patient contact. While its use will need to be investigated further, genomic surveillance could provide a step change in our ability to understand and inform surveillance, prevention, and treatment strategies for a broad range of STIs."

Dr. Ana Cehovin, Senior Research Manager, Infectious Disease at Wellcome, said, "Genomic surveillance is an invaluable tool for understanding how diseases are spreading, what populations are at increased risk and which strains are developing drug resistance. Using this knowledge, we can spot outbreaks or incidences of drug resistance earlier, and therefore take action to protect at-risk communities."

"This study shows the importance of building trusted relationships and close collaboration between researchers and public health agencies, to enable a quick response to changes in disease transmission and spread and target interventions and treatments more effectively. Similarly, realizing the potential of genomic surveillance to identify and monitor drug resistance can help decision makers to implement necessary mitigation measures to control the spread of resistant strains, reducing the chance of disease escalation and protecting at-risk communities."

More information: M. A. Beale et al, Genomic epidemiology of syphilis in England: a population-based study, *The Lancet Microbe* (2023). DOI: 10.1016/S2666-5247(23)00154-4.
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