

Syphilis in Maria Salviati—16th Century Royalty

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Antonio Fornaciari, a postdoctoral fellow in history of medicine and paleopathology at the University of Pisa in Italy. We'll be discussing a case of syphilis in a royal woman in 16th century Florence.

Welcome, Dr. Fornaciari.

[Antonio Fornaciari] Welcome, hi Sarah. Thank you for having me.

[Sarah Gregory] So what is syphilis?

[Antonio Fornaciari] Syphilis is an infectious disease, sexually transmitted, caused by the bacteria *Treponema pallidum*. Syphilis...it's a very important disease also for the history of the past. Syphilis has 4 stages: primary, secondary, latent, and tertiary. The signs and symptoms of syphilis vary, depending which of the 4 stages is present. The primary stage classically appears with a single chancre, a painless and firm—and only itchy—skin ulceration, usually between 1 centimeter and 2 centimeter in diameter. Also, there may be multiple throat chancres. Chancres appear at the site of infection on external genitals or in the rectum but can also occur on the lips and in the mouth.

In secondary syphilis, approximately 4 to 10 weeks after the primary infection, a reddish rash occurs which frequently involves the trunk and the extremities. All these lesions harbor bacteria and are infectious. There are many also...these sores in the mouth or vagina. The acute symptoms usually resolve after 3 or to 6 weeks. In latent syphilis, which can last for years, there are few or no symptoms. It develops after secondary syphilis. And the latent phase of syphilis can last many years after which, without treatment, approximately 15 to 40% of people can develop tertiary syphilis. Without treatment, a third of infected people develop tertiary disease. People with tertiary syphilis are not infectious. This disease, this stage of disease, is more frequently diagnosed by the paleopathologist in ancient human bones because the bones are affected by typical lesions on cranium and on the long bones.

Another form of syphilis is congenital syphilis. Congenital syphilis that which is transmitted during pregnancy or during birth with huge risks if contracted before pregnancy outcome, with deformities or stillbirths or death in newborns. Some typical dental defect in juvenile individuals help the paleopathologist in the diagnosis of congenital syphilis on skeletal remains.

Syphilis also has been known as the great imitator or the great pretender, as it may cause symptoms similar to many other diseases. However, syphilis typically follows a progression of stages that can last for weeks, months, or even years.

[Sarah Gregory] Okay. So, you mentioned sexually transmitted and congenital, but what specifically are the ways a person usually gets syphilis?

[Antonio Fornaciari] Yes. People catch the disease through sexual direct intramucosal contact by vaginal, anal, or oral sex with an individual with the disease. Syphilis is passed from person to person through direct contact with a syphilitic chancre. Another possibility is the so-called "congenital syphilis." A pregnant woman with the disease can transmit it through the placenta to the fetus, or at birth to the neonate.

[Sarah Gregory] Do we know how long people have been getting syphilis?

[Antonio Fornaciari] Yes. Venereal syphilis first emerged in Europe at the end of the 15th century. Really, the origin of the disease is one of the greatest issues in the history of medicine and in paleopathology. There are many different theories about the origin of syphilis. The first is the Columbian theory. Columbian theory holds that syphilis was endemic in the Americas and was transmitted to sailors of Columbus by the native population of the Hispaniola island. Hispaniola island actually is Haiti and San Domingo in the Caribbean area. And the disease...the disease arrived in Europe with the return of Columbus with his crews of sailors from the Americas in arriving in 1493. But other scholars hold that syphilis was already present in Europe before the Columbian expedition. But they hold that in Greek and ancient text and by ancient physicians, the disease was confused with other conditions, like leprosy, for instance.

There's also another theory—so called an Italian hypotheses—that syphilis is a single organism that is *Treponema*, caused different clinical manifestations depending upon climatic, social, and demographic factors, producing the clinical manifestation named pinta, yaws, bejel, and syphilis. For this theory, the pathogen spread out of Africa with humans prior to the 15th century. As you can see, the debate is very complex and, at the moment, there are still archeological finds, human remains with typical lesion of syphilis and treponematosis, that will help us to find a definitive solution.

Anyway, in Europe, the sexual and social behavior of the end of the 15th century was particularly favorable to the spread of the disease. In 1495 in Italy, we are the first to spread a description of the disease, and in 1496, incidents were already widespread throughout the entire Italian peninsula.

[Sarah Gregory] Is it very contagious? You mentioned one form that was not, but generally is it very contagious?

[Antonio Fornaciari] Yes, yes. It's very contagious, and sexual transmission and through the birth transmission lane. Studies have showed the attack rate of syphilis within 30 days of sexual exposure to someone with syphilis is about 16% to 30%. Syphilis can also be transmitted congenitally when *Treponema* transfers to the placenta of an infected woman and infect the fetus. And syphilis can be transmitted through transfused blood. While bloodborne transmission risk is nearly nonexistent in high-income countries, it persists in low and middle-income countries. In pregnant women, untreated syphilis—if acquired during the four years before delivery—can lead to the infection of the fetus in up to 80% of cases and then result in stillbirth or infant death in up to 40% of cases.

[Sarah Gregory] Are there treatments?

[Antonio Fornaciari] Yes, syphilis can be cured with the right antibiotics. But it's important that therapy begins at the early stages of the disease, because syphilis is easy to cure in its early stages. The right antibiotic is benzathine penicillin G, administered intramuscularly for persons with primary, secondary, or latent syphilis. The same antibiotic is used and recommended by CDC for pregnant women. Antibiotics will kill the syphilis bacterium and prevent further damage, but it will not repair damage already done. Of course, someone who receives syphilis treatment must abstain from sexual contact with new partners until the syphilis sores are completely healed.

[Sarah Gregory] If so many people were getting it before there were antibiotics, why didn't it kill off the human population?

[Antonio Fornaciari] Yes, when syphilis appeared in Europe in the late 15th century, the disease killed many people. And it's difficult to have an estimation of the data, but there were certainly hundreds of thousands. And during the modern age, syphilis was an endemic disease in Europe and very serious—until the advent of penicillin in 1943, it constituted a major health problem—but certainly, after the first pandemic phase, after the third decade of the 16th century, seems that this virulence and probably also its lethality helped to create. The disease came into barns with the horses, and this also represented an advantage for the pathogen. Furthermore, being a sexually transmitted disease, not all of humanity was subject to contracting the disease, because some categories of individuals having no sexual relation avoided contagion and those that had more exposive behavior and attitude.

[Sarah Gregory] Syphilis seems to be reemerging as a worrisome disease. Tell us about that.

[Antonio Fornaciari] Yes. Syphilis is reemerging not only in developing countries but also in the western world. In general, in recent years a new increase has occurred in the incidence of sexually transmitted diseases, among which syphilis occupies a prominent place. For example, in the USA, in 2000–2001, the national rate of reported primary and secondary syphilis cases was the lowest rate since reporting began in 1941. However, syphilis rate has increased almost every year since 2001 up to a rate of 10.8 cases in a 100,000 population in 2018. This increase was largely attributable to the increase among men, and in particularly among men who have sex with men. However, in the last 5 years, the rate has increased among both men and women, and the syphilis rate among women has almost tripled. And the increase in syphilis among women is a particular concern because it's associated with a striking and concurrent increase in congenital syphilis.

Europe...Europe experienced a similar trend until 2017. In 2018, the increase seems to have halted. Anyway, syphilis continues to cause morbidity and mortality worldwide. While syphilis infection is easily identifiable and treatable, rates of syphilis infection continues to increase among select populations in high-income countries and remain at endemic levels in low- and middle-income countries. Each year, there are an estimated 6 million new cases of syphilis globally in persons aged from 15 to 49 years. The strategy of the World Health Organization prioritized the elimination of congenital syphilis by implementing syphilis screening and treatment among pregnant women. But syphilis continues to persist among men who have sex with men and other groups who tend to have multiple sex partners and could likely return in the orthodox sexual population without public health vigilance.

[Sarah Gregory] So, besides Western Europe and the United States, are there geographic locations where it's more endemic than others?

[Antonio Fornaciari] Yes, syphilis is widespread all over the world. But of course in low- and middle-income countries syphilis has remained endemic. General population prevalence data on syphilis are mostly limited to high-income countries. Especially among low- and middle-income countries, currently available data likely underestimates the true burden of syphilis due to poor documentation and underreporting. Most country-representative data come from studies conducted among women after their first antenatal care visit and reported by the World Health Organization. Countries in Latin America, Africa, and Southeast Asia are most affected, while high-income countries have concentrated epidemics of syphilis in specific, select populations—for example, men who have sex with men, transgenders, and sex workers. And this is a big problem for...worldwide.

[Sarah Gregory] Give us a brief rundown of syphilis in the 16th century.

[Antonio Fornaciari] After the 1494 invasion of Italy by the army of Charles VIII, King of France, venereal syphilis had a pandemic spread in Italy and Europe. The end of the 15th century and the first half of the 16th centuries are very terrible time periods for Italy. Italy was a battleground between French, Spanish, and Italian lords in general, including the Pope. And as we have seen, the origin of the disease is...is still unclear. For us, it was already present in Europe, perhaps arrived from the Americas, imported by the crew of Columbus. But what is certain is that it's spreading through the years. The first written records of an outbreak of syphilis occurred in 1495 in Naples, Italy, during the siege of the city defended by French and besieged by the Spaniards. And since it was claimed to have been spread by French dukes, it was...it was initially called "the French disease" by the people of Naples, and the "Neapolitan disease" by the French. And sure, nobody liked having his name associated with the disease. In 1530, the name syphilis was first used by the Italian physician and poet Girolamo Fracastoro as the title of his Latin poem describing the ravages of the disease in Italy, titled "Syphilis sive morbus gallicus," in Latin, of course; "Syphilis or the French disease" is the translation. The social and cultural context of this period can explain the spread of syphilis. In renaissance Italy experienced an increasing rate of change: new contact between populations, migration from other countries, and above all, a time of greater sexual liberty. The prostitution among the troops and the civilians in led the spread of the disease. And syphilis, for its sexual connotation, embodied the concept of divine ill-punishment in the early pandemic and violent phase of syphilis had an impressive impact on European society.

Contemporary physicians quickly acknowledged that the infection had been transmitted through sexual intercourse. The first phase—the first phase of the new disease—was very aggressive, with ulcerations followed by pustules and sores all over the face and body with joint pain and pruritis. And after some years, syphilis changed from an acute and debilitating disease into a less severe chronic infection with the classical chronicization to three stages, probably because the selection of the less virulent strain of the bacterium represented an evolutionary advantage for the pathogen. And then after the second or third decade of the 16th century, it seems that this virulence, and probably also its lethality have decreased. Also, syphilis, throughout the modern age and until the advent of penicillin, constituted a major health problem.

[Sarah Gregory] Now tell us about Maria Salviati. She was the person you spoke of in your historical review for EID. Who was she, what was discovered about her, and how was it discovered?

[Antonio Fornaciari] Maria Salviati was an important historical figure. She was the granddaughter of Lorenzo de' Medici, named "the Magnificent," a nephew of the Pope Leo X. She was born in Florence in 1499 and in 1516 she married Giovanni de' Medici, named "of the Black Bands." Giovanni belonged to the collateral branch of the Medici family, but was one of the most famous captains of mercenary troops of the time. Giovanni died of gangrene and septicemia in 1526 by complications resulting from an injury and amputation of his right leg after a battle, leaving his wife a widow at the age of 27. Maria never remarried. Cosimo, the son of Maria and Giovanni, was Duke of Florence from 1537. Maria died in 1543 from the complication of tertiary syphilis, which we discovered with our study of her skeleton. Since no historical data finding the diagnosis of the disease was known, in 2012, we exhumed the skeletal remains of Maria. The bones were in an excellent state of preservation. We examined the skeleton microscopically and performed a radiographic and computed tomography scan. The

anthropological study of the skeleton revealed a female of 40-45 years of age with a stature of 1.56 meters. We detected many lytic lesions on the skull. Two circular depressions, ectocranial depressions, on the frontal bone, elliptical in shape, with a central destructive focus and a reactive compact bone formation on the margins. Furthermore, the cranial vault on the parietal bones showed several osteolytic lesions in the form of depressed areas with fine scar lines radiating inside the shallow depressions. Computer tomography examination confirms the lytic and reparative nature of the lesions, and the presence of superficial circumvallated cavitation with radial scars is pathognomonic of cranial syphilis, technically called caries sicca, typical of tertiary syphilis.

[Sarah Gregory] Would you give us some historical context about the Medicis, including Maria?

[Antonio Fornaciari] Medici were an important family, one of the Florence most powerful banking families and one of the most important of the Italian Renaissance—bankers and politicians, patrons of the arts. For example, they were patrons of Boticelli and Michelangelo Buonarroti. And in the first half of the 16th century, from Medici there were two popes: Leo X and Clement VII. The cousin of Maria, the Duke of Florence, Alexander de' Medici was killed in 1557, and Maria used her family connections to get involved in the discussion to decide the next Duke of Florence. She played a key role in getting her son, Cosimo, elected. And Cosimo would then be able to unify the rule of Tuscany under his control, and to be nominated Grand Duke by the Pope. Cosimo gave rise to the Grand Duke Medici branch, which ruled Tuscany until 1757.

[Sarah Gregory] Tell us how you went about examining Maria's bones. What kind of tests were done on it and such?

[Antonio Fornaciari] I participated in the Medici project together with my colleagues from the paleopathology division of the University of Pisa. This is an important paleopathological project, started in 2004, involving the study of the bodies of the Medici skeletal remains, of all the Medici family—preserving the Medici chapter in Florence. I initially participated as... as an archaeologist, specializing in funerary archaeology. Then I also worked with colleagues on the paleopathological and historical medical study. The study of Maria Salviati and Giovanni of the Black Bands was sponsored by the Italian Society of Orthopedics and Traumatology. The opening of the tombs of de' Medici was a very delicate operation due to the historical and artistic value of the contents. The Medici chapels are today one of the most important museums in Florence. They host absolute masterpiece of the artistry, such as the funerary monuments of some of the Medici sculpted by Michelangelo Buonarroti. And for the study... for the study, we set up a temporary lab in the Medici chapel and we performed x-ray exams of the findings in the Florentine Hospital of Santa Maria Nuova, always with the assistance of restorers and the staff and superintendents of the Ministry of Cultural Heritage of Florence.

[Sarah Gregory] Do you think she was actually diagnosed with syphilis at the time? You mention in your review that she may have been hiding it from her doctors. Why would she do that?

[Antonio Fornaciari] Yes. In the last... in the last three years of her life, many symptoms of severe illness were described in letters sent by the court physician to Duke Cosimo, including abundant recurring bleeding from the rectum, rectal and perianal ulcers, headaches, and abdominal cholic. Today, by relating these symptoms to skeletal... skeletal lesions, it is possible to make a diagnosis of tertiary syphilis with cranial and probably colorectal localization. Symptoms such as frequent fever and headache, abdominal cholic, rectal and perianal ulcers are very compatible with tertiary syphilis but were not attributed to syphilis by the physicians of the

time. Also today, really, in clinical medicine anal syphilis could be easily misdiagnosed as cancer or advanced stage hemorrhoids.

One hypothesis is that the contemporary physician might have correctly diagnosed and recognized Maria Salviati's disease but concealed the sexual component of the infection. Another hypothesis that Maria Salviati, who never allowed the physicians to inspect her genitals—we know this from the private documents of Medici archives—may have hidden the symptoms of her disease out of modesty. A further explanation, based on political reasons, is that the mother of Duke Cosimo I could not appear to be affected by venereal syphilis, to avoid corrupting the image of the Medici family that the son Cosimo was trying to promote in these years among the royal rank. The fact that in her last years of life Maria was always portrayed with a veil might indicate her intention to hide the syphilitic skin lesions. In her final years, Maria had a very withdrawn life, possibly to conceal the signs of the illness and certainly for the social complications caused by her recurrent anal hemorrhages. However, we have no report that she was marginalized from the ducal court. Instead, she was held in high regard as the mother of the reigning duke. In the famous portrait painted by Bronzino in the year of her death, she appears veiled and in widow's clothes, as if to hide the signs of the illness.

[Sarah Gregory] Are there any ideas about how Maria contracted her syphilis? Is there much written about syphilis among noble women of that time? Or any historical writings about syphilis in women during the 16th century?

[Antonio Fornaciari] It...it is difficult of course to speculate on how Maria Salviati contracted the disease. But she's likely to have been infected by her husband Giovanni before his death in 1526, and more probably after the birth of her son Cosimo in 1519. Indeed, the historical sources do not reveal any detail about a possible infection of the child, nor do the skeletal remains of the first Grand Duke of Tuscany show any signs of congenital syphilis. The lifestyle of Giovanni of the Black Bands was characterized by intense sexual extramarital affairs, with lovers and with prostitutes, as witnessed by many documents of the time preserved in the archives of Florence. The skeleton of Giovanni de' Medici does not reveal any lesion of syphilis, probably because he died at the young age of 28 years, before the development of the tertiary stage of the disease.

Syphilis affected many members of the aristocracy—many noblemen, and particularly captains of the troops. Famous are the cases of Cesare Borgia, the Duke Valentino, and the son of Pope Alexander VI, who had to wear a leather mask covering half of his face, disfigured by syphilis. For noblewomen, we have much less historical information and documents. Noblewomen were at risk for contracting sexually transmitted diseases caused by the lifestyle of their husbands. And probably, syphilis is likely to have been more widespread among the noblewomen of the Renaissance than is attested by the written sources. In some cases, paleopathology revealed some hidden illness of the Italian noblewomen, as in the case of Maria of Aragon, Marquess of Vasto and wife of Alfonso d'Avalos. In the artificial mummy of Maria of Aragon, the histologic, immunohistochemical, and ultrastructural study of a cutaneous ulcer of the left arm led to the direct identification of *Treponema pallidum* and the diagnosis of tertiary...tertiary venereal syphilis. The biographic sources report that Maria of Aragon periodically spent time at the Agnano Baths, near Naples, probably to treat a skin disease with the sulfuric waters. However, in the written sources, there is no mention of any possible syphilitic...syphilitic infection affecting the noblewoman, who was famous at the time for her beauty and cultural refinement. Syphilis, that was not a reason of particular shame for men and sovereigns, princes and gentlemen, was instead jealousy concealed by noblewomen as a “secret illness” that often did not seep outside of

the private apartments. This attitude reveals a disparity of perception and of mentality, symptomatic of gender discrimination in the Renaissance society.

[Sarah Gregory] Is catching syphilis preventable?

[Antonio Fornaciari] Yes. The risk of sexual transmission of syphilis can be reduced by using a latex or polyurethane condom. But also, condom does not completely eliminate the risk; the abstinence from sexual conduct with an infected person is the best prevention. Also, in the Italian Renaissance, because it was already a well-known fact at the time that syphilis was transmitted sexually, noblewomen with syphilitic partners refused to have sexual intercourse with their husband. At that time, this was of course a prerogative of elite married women who could exercise high self-care and power of choice. Another...another problem is with congenital syphilis. Congenital syphilis in newborn can be prevented by screening mothers during early pregnancy and treating those who are infected.

[Sarah Gregory] How do you think this historical review impacts current public health? Are there any guidelines or practices we should learn from it?

[Antonio Fornaciari] Paleopathology offers a source for increasing the diagnosis of infection in the past and for understanding the social and cultural impact of infectious diseases in ancient populations. Theoretically, the models obtained can be compared with what happens today with emerging and reemerging diseases and can serve to refine the systems of prevention and fight against future infection outbreaks. But I don't know if this paleopathological and historical study particularly could have a positive impact on current public health. Unfortunately, history is often not a teacher for people. But in my opinion, this study can provide an important lesson about the source of contagiousness inside the family, and about the gender differences in the perception of the disease and about the gender discrimination. In many...in many countries, social control of maids and women and cultural barriers probably do not allow to diagnose early and prevent sexual transmitted disease—a big problem in the early treatment, for example, of congenital syphilis.

[Sarah Gregory] You work in the field of paleopathology. That sounds extremely interesting to me. Tell us what it is and what you do.

[Antonio Fornaciari] Paleopathology is the study of ancient disease directly through the human remains of the past, skeletons and mummies. It is a medical and historical discipline at the same time, intrinsically multidisciplinary. For paleopathology, human remains are biological archives to be read by applying all the most modern biomedical science technologies. But to be able to recover the finds—digging up them in an archeological or historical site and then to contextualize them—you need refined archeological and historical skills. The ability to bring man's past closer make it, in my opinion, a discipline extremely fascinating and an exciting field of study. A paleopathological team is therefore composed of several specialists—archeologists, paleoanthropologists, historians, and of course pathologists, and also other medical specialties such as biology, paleogenetics, or molecular research. I am, in particular, an archaeologist with strong interest in osteoarcheology and in the history of medicine of the Middle Ages and of the Renaissance.

[Sarah Gregory] I wonder about this a lot, and I'm sure other people do. Also, is it possible to catch a disease from old remains, like plague from the 1600s or something, if a body was dug up that had it?

[Antonio Fornaciari] Yes, it's possible. Also, plague is an example of a pathogen that doesn't hide directly in the bones. But it's possible to detect ancient pathogens, as for example, *Yersenia pestis*, which is the bacterium, no, that caused the plague, by the paleogenetics research on ancient DNA. Many scholars, many paleogenetics can obtain directly from the bones, from the teeth, the DNA of the pathogen. Because the DNA of the pathogen is preserved inside, for example, the part of the...inside of the teeth where the teeth are more linked to...to circulation of blood.

[Sarah Gregory] But can you get the disease from old bones? Not diagnose it, but actually get it? Like, get plague?

[Antonio Fornaciari] Like...like plague from the old bone? Yes, it's possible. It depends on the...also from the preservation state of the bones, because ancient pathogens are very delicate and not so easy to find a good preservation state of ancient pathogens. But it's possible.

[Sarah Gregory] Well that must be slightly worrisome when you're digging up bones. What do you enjoy most about your work?

[Antonio Fornaciari] Probably the direct contact with the remains of the past. The...the ability to interrogate them and get answers is extremely fascinating for me. It is a way to touch history. The data of the paleopathological study opens new perspective of knowledge and it is a real privilege for me, which I thank my professor and my colleagues and companions of paleopathological adventures.

[Sarah Gregory] Well, thank you so much for taking the time to talk with me today, Dr. Fornaciari.

[Antonio Fornaciari] Thank you to you. Thank you for having me.

[Sarah Gregory] And thanks for joining me out there. You can read the June 2020 historical review, Syphilis in Maria Salviati (1499–1543), Wife of Giovanni de' Medici of the Black Bands, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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