

## On the Origin of Syphilis and Contemporary Views of Disease Dynamics

Kevin L. Karem\* and Allan Pillay

Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, USA

\*Corresponding author: Kevin L. Karem, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, USA, Tel: 4046391598; E-mail: [kkarem@cdc.gov](mailto:kkarem@cdc.gov)

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### Abstract

Despite effective treatment availability for nearly a century, syphilis remains a global public health problem with significant social and economic impact. Over 500 years after the first reports of this sexually transmitted infection, questions remain regarding its origins, relationship to other infectious agents and effective control measures. Studies addressing origins of syphilis and non-syphilitic treponemes provide content to questions of evolution and emergence, however, many questions remain. Disease dynamics of syphilis are embedded in social behaviors and contribute heavily to propagation of this ancient disease. Discussions on the origins of syphilis and disease dynamics are presented.

**Keywords:** Syphilis; Treponemes; Genomics; Origins; Treatment

### Introduction

Despite syphilis being a disease of antiquity, diagnosis and treatment remains problematic globally due to a complex biologic pathogen/host relationship and the spread of the disease embedded in human behavior. First documented as an independent disease in 1495, the origin of syphilis has been ambiguous for over 500 years. In the past century, there have been several approaches to investigate the origins of syphilis, but without definitive outcome [1-15]. A viable syphilis control option became available in the 20th century with the discovery of penicillin, leading to cost effective and safer treatment compared to prior use of mercury- and arsenic-containing compounds. However, despite the availability of antibiotics that can successfully treat syphilis, the disease waxes and wanes at various times and among certain social groups or settings, due in part to risky sexual behavior, a complex clinical presentation (multiple clinical stages including a latent stage where there are no clinical signs), diagnostic challenges and spontaneous healing or unnoticed lesions resulting in failure to seek clinical care or sexual partners not being referred for treatment [16-17]. Disease ecology of syphilis is highly dependent on human behavior and epidemiology remains the hallmark for surveillance of disease severity, transmission and intervention programs. Here we address contemporary aspects of the origin, control and treatment measures, and modern views of disease ecology of syphilis.

### Origin

Historically, controversy surrounds the origin of syphilis (*Treponema pallidum subsp. pallidum*) which is based on two theories, the Columbian and the pre-Columbian. The Columbian theory suggests that explorers in the late 1400s carried the disease back to Europe from the “New World” and triggered the first documented outbreak of syphilis in Naples during the invasion by King Charles VIII’s army in 1495 [1-5]. This view dominated thoughts on the subject until the 20<sup>th</sup> century when scientists began to recognize the similarities in clinical presentation between syphilis and other diseases

such as leprosy, and proposed that syphilis existed in pre-Columbian Europe but was not recognized as a separate disease until 1495 (pre-Columbian hypothesis) [6-10]. The clinical similarities to other diseases resulted in Sir William Osler referring to syphilis as “the great imitator” in the 19<sup>th</sup> century. The origin of syphilis remains unclear due to the lack of documented cases prior to 1495 and the contradiction of Columbian and pre-Columbian theories. These contrasting theories rely on documentation of the Naples outbreak and the coincidental timing with new world exploration.

Contemporary science has investigated human remains to identify syphilitic lesions associated with the different timelines and the appearance of the disease in the old versus new worlds. Limitations in assessments of the origin of syphilis include variations in the scientific method used. For example, documentation of bone lesions may provide possible evidence of syphilis in anthropologic specimens; however, these may not be exclusive to syphilis. Likewise, the variations in dating of specimens are highly dependent on the methods used. These limitations were addressed in detail by Harper and colleagues through detailed analysis of the scientific data available. This careful assessment indicates a lack of evidence to support the presence of syphilis in the “Old World” prior to the 1495, thus supporting a New World origin for the disease [3]. Recent research provides evidence regarding the origin of syphilis geographically and chronologically. A phylogenetic approach was performed in 2008 using 26 geographically distinct *Treponema* isolates to assess 21 genomic regions for relatedness of *T. pallidum subsp. pallidum* (syphilis) to the non-venereal treponemes (*T. pallidum subsp. pertune* and *T. pallidum subsp. endemicum*), the agents of yaws and bejel, respectively [4]. These data support the closest genetic relative of syphilis being yaws-causing *T. pallidum subsp. pertune* strains from South America, thus supporting the Columbian theory of syphilis origin in the new world. However, there are limitations to this study with respect to the number of strains assessed and limited genomic regions used in the analysis, as well as definitive links to syphilis treponemes in the new world. Also, the analysis does not provide a chronologic assessment of when treponemes may have first emerged. Harper et al. and others before proposed that *T. pallidum* arose in the old world as a non-venereal infection and was disseminated

throughout Europe and the Middle East prior to migrating to North America with humans in the form of yaws, then reintroduced to Europe with exploration of the Americas as the progenitor to modern syphilis strains around 1495 [2,4]. Reports of high morbidity and virulence of syphilis during the outbreaks in 1495 suggest that initially syphilis strains were highly virulent, which may have limited the transmission due to obvious and painful disease (lower sexual promiscuity during active disease) and over time has become, through selective adaptation, a more mild illness with a greater chance of being maintained in transmission cycles. This makes sense from a microbiological perspective as the less virulent strains of a microbe are often preferentially perpetuated in the host species. Nevertheless, Harper and colleagues' conclusions, while supported by these data, remain only part of the story regarding origin of syphilis. Another view of the origin of syphilis is presented using phylogenetic and paleopathological data [5] using a combination of molecular analysis data with pre-Columbian evidence of treponemal infections (yaws, bejel, venereal and congenital syphilis) to make predictions of the evolutionary rate of change for treponemes compared to human migration to North America 5000-16,500 years before present (ybp) [5]. In fact, the authors conclude that syphilis emerged approximately 5000 ybp based on genomic rate of change comparable to other bacteria. This approach does not refute Columbian origin, but suggests discrimination between emergence of syphilis and either introduction to Europe or observation of syphilis as an independent disease in 1495. The latter suggests that syphilis origins are evolutionarily 500-600 years old, while the cumulative evidence suggests the etiologic agent of syphilis is much older. While this analysis provides conclusive results on the origin of syphilis, these studies highlight the power of genomic analysis particularly when paired to other measures of scientific assessment such as anthropology and paleopathology. While the conclusions from these two studies are not mutually exclusive of one another, it is clear that whole genomic sequencing of more treponemes will provide additional support regarding the origin of syphilis. Overall, the story of research to define the origin of syphilis has been reviewed extensively recently [6]. Other studies on leprosy and smallpox in the past decade also used a combination of approaches such as evolutionary studies, epidemiology, disease ecology and phylogenetics to assess the origins of these ancient diseases [18,19]. Multidisciplinary approaches may also provide insight into attributes of convergent or divergent evolution and natural selection of other ancient human pathogens.

## Control and Treatment

First described in 1495, syphilis has undergone dynamic changes in both therapeutic options as well as behavior adaptation to remain a global problem in the 21<sup>st</sup> century. The control of syphilis was viewed as a real possibility in the mid-20<sup>th</sup> century due to the effectiveness of penicillin and the World Health Organization published a monograph in 1957 [20] in which it states: "Penicillin has rendered the control of the treponemal diseases a practical possibility for the first time; their complete elimination is now no longer a fantastic objective." While the authors acknowledged that such an achievement would require intelligent and patient application of knowledge for even partial control, the implications are clearly reflective of total elimination based on the success of treatment in the mid-20<sup>th</sup> century. Despite this optimism and the low cost of antibiotics, the complexity of syphilis clinical presentation, difficulty to diagnose infection depending on the stage of disease, and changes in human sexual behavior have favored the propagation of the disease and adaptation of the syphilis pathogen

to new niches. There remain inexpensive and available treatment options globally, including use of Benzathine penicillin and in the presence of penicillin allergy Doxycycline or Tetracycline may be used as describe [21].

Control and potential eradication of infectious diseases are dictated by several specific factors including limited host range (or a single host); safe, effective and cheap treatment or vaccination; and globally synchronized efforts to eliminate the disease. All these factors were in place and were exploited during the eradication of smallpox in the 20<sup>th</sup> century through a global program lead by the US. Unlike smallpox, syphilis is effectively treated but there isn't a vaccine, and has a public health impact that engages health professionals globally.

Despite having some hallmarks for successful eradication, syphilis remains a global public health problem particularly in the unborn. Congenital syphilis continues to be a plague in developing countries due the difficulty of diagnosing congenital syphilis due to the lack of optimal diagnostic capabilities and limited aspects of health care for women. In 2013, The World Health Organization published global guidance for validation of the elimination of mother to child transmission (EMTCT) of HIV and syphilis [22] which highlights congenital transmission as one aspect of these diseases that threatens the future generations in affected areas. Despite the lack of coordinated efforts in some regions, inadvertent global use of antibiotics in the past century has likely contributed to the decline in tertiary syphilis cases [17]. This "collateral treatment" phenomenon appears to have been effective in the absence of antimicrobial resistance to penicillin in the syphilis pathogen.

Successful treatment and control of syphilis may be impacted by different factors, including availability of effective diagnostic tests, antibiotics for treatment and understanding behavioral contributions to spread. Diagnostics remains dependent on a complex algorithm requiring two separate tests in various formats and order [22]. The value of the duel test algorithm is confirmation of acute infection, while the disadvantage is the capacity to perform these tests on a global scale. Confounding diagnostics in a disease with varying clinical presentation may lead to poor levels of early diagnosis and surveillance for epidemiologic purposes. Beyond diagnostics, behavioral and social impact on syphilis has been substantial [16,17]. The spread of the disease may be simplified as "sexual" transmission; however, changes in human social and sexual behaviors have resulted in increasing disease incidence in recent years. Syphilis was targeted for potential elimination in the United States in 2000 as rates reached a nadir but have increased since that time corresponding to an increase mainly among men who have sex with men. Overall syphilis rates among women increased between 2005 and 2008 and then declined, reflecting changes in rates among black women.

Biologically, research on syphilis has been limited due to the absence of an *in vitro* growth system to propagate treponemes, thereby making basic research more difficult and costly due to the need for *in vivo* growth methods. This has led to the use of laboratory strains for research that have been passaged numerous times in laboratory animals. While still useful for research studies, these "lab" strains may not represent pathogenic strains circulating in humans at any given time. Clinical isolation and propagation of the syphilis bacterium is done for research purposes only due to the need for animal facilities, which limits the study and tracking of pathogenic strains. The limited number of isolates available worldwide has hampered the extensive comparison of genomes and phenotypic characteristics of isolates. This limitation includes non-venereal treponemes which could

provide more information on the origin of treponemal disease and the divergence of *T. pallidum subsp. pallidum* from the etiologic agents of non-endemic treponematoses.

## Conclusion

Syphilis disease ecology is exclusively dependent on human behaviors, and control efforts are largely dependent on ongoing surveillance of the disease, improved and/or timely diagnosis, and effective intervention programs. Transmission dynamics are complex as they are embedded in human sexual behaviors. Epidemiology of syphilis is well studied and advances in this science continue to track incidence and prevalence based on changes in behaviors and in public health activities to facilitate education and compliance with best practices. Advances in diagnostic capacity and effectiveness may provide improved public health impact regarding global control of syphilis, and whole genomic sequencing may shed more light on the origin of syphilis, as well as other treponemes. Until then, the capacity to control this ancient disease requires advances in education and compliance with best practices for diagnostic screening and treatment.

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