Advancing the understanding of treponemal disease in the past and present

Baker, Brenda J.; Crane-Kramer, Gillian; Dee, Michael W.; Gregoricka, Lesley A.; Henneberg, Maciej; Lee, Christine; Lukehart, Sheila A.; Mabey, David C.; Roberts, Charlotte A.; Stodder, Ann L. W.

Published in:
American Journal of Physical Anthropology

DOI:
10.1002/ajpa.23988

Publication date:
2020

Received: 21 July 2019 | Revised: 4 December 2019 | Accepted: 5 December 2019

DOI: 10.1002/ajpa.23988

YEARBOOK OF PHYSICAL ANTHROPOLOGY ARTICLE

Yearbook of PHYSICAL ANTHROPOLOGY

WILEY

Advancing the understanding of treponemal disease in the past and present

Brenda J. Baker[1] | Gillian Crane-Kramer[2] | Michael W. Dee[3] | Lesley A. Gregoricka[4] | Maciej Henneberg[5,6] | Christine Lee[7] | Sheila A. Lukehart[8] | David C. Mabey[9] | Charlotte A. Roberts[10] | Ann L. W. Stodder[11] | Anne C. Stone[1] | Stevie Winingear[1]

[1]School of Human Evolution and Social Change, Arizona State University, Tempe, Arizona

[2]Department of Anthropology, State University of New York at Plattsburgh, Plattsburgh, New York

[3]Centre for Isotope Research, University of Groningen, Groningen, Netherlands

[4]Department of Sociology, Anthropology, and Social Work, University of South Alabama, Mobile, Alabama

[5]Biological Anthropology and Comparative Anatomy Unit, Adelaide Medical School, University of Adelaide, Adelaide, Australia

[6]Institute of Evolutionary Medicine, University of Zurich, Zurich, Switzerland

[7]Department of Anthropology, California State University Los Angeles, Los Angeles, California

[8]Department of Medicine/Infectious Diseases and Global Health, University of Washington, Seattle, Washington

[9]Communicable Diseases, London School of Hygiene & Tropical Medicine, London, UK

[10]Department of Archaeology, Durham University, Durham, UK

[11]Office of Archaeological Studies, The Museum of New Mexico, Santa Fe, New Mexico

Correspondence
Brenda J. Baker, Center for Bioarchaeological Research, School of Human Evolution and Social Change, Arizona State University, Tempe, AZ 85287-2402.
Email: bjbaker@asu.edu

Funding information
Private Donor, Grant/Award Number: CC0640/GR06564 to Brenda Baker; School for Advanced Research, Grant/Award Number: Research Team Seminar

Abstract

Syphilis was perceived to be a new disease in Europe in the late 15th century, igniting a debate about its origin that continues today in anthropological, historical, and medical circles. We move beyond this age-old debate using an interdisciplinary approach that tackles broader questions to advance the understanding of treponemal infection (syphilis, yaws, bejel, and pinta). How did the causative organism(s) and humans co-evolve? How did the related diseases caused by *Treponema pallidum* emerge in different parts of the world and affect people across both time and space? How are *T. pallidum* subspecies related to the treponeme causing pinta? The current state of scholarship in specific areas is reviewed with recommendations made to stimulate future work. Understanding treponemal biology, genetic relationships, epidemiology, and clinical manifestations is crucial for vaccine development today and for investigating the distribution of infection in both modern and past populations. Paleopathologists must improve diagnostic criteria and use a standard approach for recording skeletal lesions on archaeological human remains. Adequate contextualization of cultural and environmental conditions is necessary, including site dating and justification for any corrections made for marine or freshwater reservoir effects. Biogeochemical analyses may assess aquatic contributions to diet, physiological changes arising from treponemal disease and its treatments (e.g., mercury), or residential mobility of those affected. Shifting the focus from point of origin to investigating who is affected (e.g., by age/sex or socioeconomic status) and disease distribution (e.g., coastal/ inland, rural/urban) will advance our understanding of the treponemal disease and its impact on people through time.

KEYWORDS

archaeological biogeochemistry, archaeometry, genetics, human-pathogen co-evolution, paleopathology, syphilis, *Treponema pallidum*

1 | INTRODUCTION

Clinicians categorize human treponemal infections as pinta, yaws, bejel (also known as endemic syphilis), and syphilis (sexually acquired or congenital). Although pinta has not been documented for the past 20 years, there is no surveillance in regions where it was previously endemic; therefore, affected persons may exist in remote areas (Salazar & Bennett, 2014; Stamm, 2015). The relationship of pinta to the infections caused by *Treponema pallidum* subspecies, however, is little known. Treponemal infection has long been the topic of speculation concerning its origin, past distribution, clinical presentation, nature of the causative agent(s), and epidemiology of the currently recognized clinical phenotypes (e.g., Giacani & Lukehart, 2014; Kojima & Klausner, 2018; Mitjà et al., 2015). Because syphilis was perceived to be a new condition that suddenly appeared in Europe in the late 15th century, debate about its origin has persisted for more than five centuries (see reviews by Baker & Armelagos, 1988; Cook & Powell, 2012; Harper, Zuckerman, Harper, Kingston, & Armelagos, 2011), giving rise to the competing Columbian, Pre-Columbian, Unitarian, and Evolutionary hypotheses. Questions concerning the spread of infections caused by *T. pallidum* subspecies and their emergence in different parts of the world are still contested in anthropological (e.g., Cook & Powell, 2012; Zuckerman, 2016) and medical circles (e.g., Anteric, Basic, Vilovic, Kolic, & Andjelnovic, 2014; Karem & Pillay, 2014; Tampa, Sarbu, Matei, Benea, & Georgescu, 2014). As a result, "the history of treponematosis continues to be one of the most contentious issues in science" (Ortner, 2003:273).

This controversy persists in part because large expanses of the Old World, particularly Africa and Asia, have not been investigated as intensively as Europe and the Americas. A systematic (rather than incidental) evaluation of skeletal remains for evidence of treponemal disease in the Old World by multiple researchers familiar with its manifestations, and a thorough search of publications in the non-English literature in different regions, has never been conducted. Even in Europe, where there is a long history of paleopathological study, the quality of training in paleopathology is variable when compared to the study of normal variation in the skeleton (Buikstra & Roberts, 2012; also see Roberts, 1994:106). In contrast, skeletal evidence for the occurrence of treponemal infection in North America as well as the skeletal patterning of treponemal disease, its geographic distribution, and temporal depth, were examined by scholars in a 1998 American Association of Physical Anthropologists conference symposium that resulted in an edited volume on *The Myth of Syphilis* (Powell & Cook, 2005b). However, a similar treatment for South America is also needed. Additionally, research is complicated by the proliferation of publications advancing "possible" pre-Columbian evidence in Europe (e.g., Rissech et al., 2011) that are incomplete, lack any differential diagnosis, or ignore diagnostic criteria for skeletal and dental involvement (i.e., Hackett, 1976; Hillson, Grigson, & Bond, 1998). Site contextualization often is inadequate as well. Such publications detract from more secure studies (e.g., Mays, Crane-Kramer, & Bayliss, 2003), leading proponents of the New World origin (the Columbian hypothesis) to dismiss all pre-1493 evidence from the Old World (e.g., Zuckerman, Harper, & Armelagos, 2016). A review by Harper et al. (2011) is controversial due to the authors' assumptions and methods, including subjective application of "corrections" for marine contributions to diet to adjust radiocarbon dates for purportedly pre-Columbian sites in the Old World, and rejection of secure dating using standard archaeological methods (see Section 4.1 for details). While Harper et al.'s (2011) article renewed debate, it resolved little due to the limited understanding of treponemal disease patterns and the timing of their occurrence in much of the world.

Here, a group of scholars with differing areas of expertise (anthropological genetics, bioarchaeology, microbiology and immunology, paleopathology, radiocarbon dating, tropical and infectious medicine) and regional foci (including Africa, North and South America, Europe, Asia, Australia, and Pacific Rim) has come together to initiate development of a more holistic and systematic means of investigating the co-evolution of treponemal pathogens and humans through evaluation of the patterns of clinical and skeletal manifestations (including congenital transmission); pathogen genetics and phylogenetics; demographic, geographic, and temporal distribution; and the effects of mercury or other treatments on skeletal manifestations. Rather than focusing solely on the perennial question of who is to blame for the purported surge in sexually-acquired syphilis in 16th-century Europe, a more informed understanding of clinical variation in modern disease manifestations and the genetics of the subspecies of *T. pallidum* permits exploration of the co-evolution of the pathogen and its human hosts and testing of long-held hypotheses. Consideration of insights into the genetic variation present in *T. pallidum* and other treponemes, the phylogeny of causative organism(s), environmental effects on disease expression, and the accuracy of radiocarbon dating, calibration procedures, and correction for any marine component of the diet are crucial for our interpretations of skeletal patterning, deduced disease distribution, and temporal depth in paleopathology and bioarchaeology. All of these factors are essential for investigating the *global* distribution of treponemal infection and how (or whether) its manifestations may have changed over time in different geographic regions. Our principal goals, therefore, are to (1) outline the current state of research in specific relevant fields, (2) present recommendations to advance our understanding of treponemal disease and its impact on people in both the past and present in these areas, and (3) stimulate additional work.

2 | COMPETING HYPOTHESES

Four hypotheses have been advanced to explain the origin and distribution of treponemal infections affecting humans, collectively called treponematosis (per Hudson, 1946, 1958). These are the Columbian hypothesis, Pre-Columbian hypothesis, Unitarian hypothesis, and Evolutionary hypothesis. The first two hypotheses are based on geographic origin, while the last two concern the nature of the causative organism(s) and acknowledge that treponemal infection likely existed in both Old and New Worlds in antiquity.

The Columbian hypothesis is rooted in accounts by late 15th- to 16th-century chroniclers and physicians, such as Gonzalo Fernández

de Oviedo y Valdés (1547, 1851, 1959), Fray Bartholomé de Las Casas (1552, 1875–1876), Ruy Díaz de Ysla (1539), Ulrich von Hutten (1533), and Giralamo Fracostoro (1911 [1530]), describing the rapid spread of a newly recognized sexually transmitted disease through Europe. This hypothesis was articulated in the modern era initially by Bloch (1901, 1908) and promoted by Harrison (1959), Crosby (1969, 1972), and others. This hypothesis posits a New World origin of treponemal infection and transmission to Europe after the return of Christopher Columbus and his crew in 1493. Proponents emphasize the lack of evidence for treponematosis in Classical and Medieval European records as well as negative or inconclusive paleopathological evidence from the Old World.

The pre-Columbian hypothesis, promulgated first by Holcomb (1934, 1935), states that treponemal disease was present in the Old World before 1493 but was not distinguished from other conditions, including leprosy. The Unitarian hypothesis proposed by Hudson (1946, 1965) posits that pinta, yaws, bejel, and syphilis are caused by a single organism that produces different clinical manifestations depending upon climatic, social, and demographic factors. According to this hypothesis, the *Treponema* pathogen spread with humans out of Africa, so infection was present globally prior to 15th-century European contact with the Americas.

The Evolutionary hypothesis advanced by Hackett (1963; see also Cockburn, 1961) suggests that human treponemal disease likely arose from an animal infection in Afro-Asia. One potential phylogeny proposed by Hackett (1963:25) shows pinta as the earliest, global form from which mutations after 10,000 B.C. gave rise over time to yaws, bejel, then syphilis. In an alternative scenario also presented by Hackett (1963), pinta arose c. 15,000 B.C. from an ancestral form as a separate infection, then the yaws branch diverged from this ancestral form around 10,000 B.C., followed by the divergence of bejel, then syphilis from the yaws branch.

Although attempts have been made to explore evidence for or against certain hypotheses as originally articulated (e.g., Baker & Armelagos, 1988; de Melo, de Mello, Fraga, Nunes, & Eggers, 2010; Harper et al., 2008, 2011), they have not been tested sufficiently using multiple lines of evidence derived from epidemiology, genetics/genomics, archaeometry (including radiometric dating and analyses of stable isotopes and trace elements), and paleopathology. Evaluating these hypotheses, therefore, requires a review of the current state of research in multiple areas and consideration of factors that are necessary for contextualizing archaeological samples.

3 | EPIDEMIOLOGICAL AND GENETIC RESEARCH

Treponemes are spirochetes, which are spiral-shaped bacteria that may be free-living, commensal, or pathogenic for humans and other mammals. Clinical manifestations of yaws, bejel, and syphilis are well-known from mid-20th-century clinical studies of untreated infection (e.g., Gjestland, 1955; Grin, 1952; Hackett, 1951; Stokes, Beerman, & Ingraham, 1944) along with modern studies involving antibiotic treatment (see, for example, Ho & Lukehart, 2011; Mitjà et al., 2012; Scolnik et al., 2003). Advances in genetic and genomic studies are revolutionizing the study of treponemal infections by beginning to remove speculation and subjectivity from analyses of both clinical and paleopathological disease diagnoses.

3.1 | The nature of treponemal infection: Epidemiological evidence

Yaws, bejel, and syphilis are all transmitted by direct contact with infectious lesions. The disease is characterized by localized primary lesion(s) appearing at the site of transmission, dissemination of the bacteria throughout the body resulting in widespread lesions (the secondary stage), persistence during years of asymptomatic infection (latency), and the possible development of late (tertiary) destructive lesions of various organs, including bone. In all treponemal infections, patients vary widely in the severity of their clinical manifestations and in whether they progress to the late stage.

Although syphilis is often said to be differentiated from yaws and bejel by its sexual mode of transmission, it was recognized centuries ago that the agent of syphilis could infect fingers and other nongenital sites when exposed to body fluids of a contagious patient (Stokes et al., 1944). Although symptomatic neurological, cardiovascular, and congenital manifestations have been long recognized in syphilis, there is substantial evidence in the literature that these do occur, albeit less frequently, in yaws and bejel (e.g., Akrawi, 1949; Edington, 1954; Román & Román, 1986; Smith et al., 1971; see also Giacani and Lukehart, 2014; Lukehart & Giacani, 2014). Grin (1952), in his extensive study of bejel in the non-arid environment of Bosnia, also reported genital lesions and evidence of congenital infection. Two factors may be at play in the relative lack of recognition of these aspects of yaws and bejel. First, both yaws and bejel are usually transmitted in early childhood. By the time an infected individual reaches sexual maturity, the infection has been present for many years and may have resolved or progressed to the late latent stage in which pathogen load is low. Thus, even in syphilis, a pregnant woman with longstanding infection is much less likely to infect her fetus than a woman with early active infection (Richens, Mayaud, & Mabey, 2014:311; Stafford, Sánchez, & Stoll, 2019). Second, the varied and nonspecific signs of treponemal-related neurological and cardiovascular involvement may not be recognized in settings without trained medical personnel where yaws and bejel are most likely to occur. The inability to distinguish (clinically or pathologically) the lesions of the three historically designated treponemal "diseases" and their similar courses support the Unitarian hypothesis (Hudson, 1946, 1958).

3.2 | Genetic analyses of modern human Treponemes

The species *T. pallidum* is the causative agent of syphilis, bejel, and yaws (reviewed by Giacani & Lukehart, 2014). Because of the differing

epidemiology of these diseases, the agents were classified initially as separate species of *Treponema*. Following early genetic analysis showing near identity (Miao & Fieldsteel, 1980), they were reclassified as *T. pallidum* subspecies (*pallidum*, *pertenue*, and *endemicum*, respectively). These agents are morphologically identical, and full genome comparisons indicate that they have >99.8% DNA homology (Cejkova et al., 2012; Mikalová et al., 2010; Štaudová et al., 2014). Because there is no extant isolate from pinta, there is no genetic information; thus, its relationship to *T. pallidum* is unknown. Its causative agent, therefore, is still called *T. carateum*.

How to classify bacteria into taxonomic units and where to draw the line in terms of diversity among lineages (or whether such models are even useful) has been the subject of much debate (e.g., Achtman & Wagner, 2008; Doolittle & Papke, 2006; Krause & Whitaker, 2015). Konstantinidis & Tiedje (2004) suggested that an average nucleotide identity (ANI) of genome sequences among strains of >94% would correspond to a molecular species definition based on DNA–DNA reassociation experiments and on 16S rRNA sequence identity. Under this definition, the three agents, bejel, syphilis, and yaws, are clearly the same species, but what is a subspecies or ecotype? Are the so-called subspecies ecotypes that correspond to specific niches? If so, how much genetic exchange or niche shifting occurs? In addition, do the current strains (at least those for which genome sequences are available) simply reflect current, largely clonal lineages in ecological niches (i.e., genital, skin, and mucosal membranes) that shift over time?

Ecotypes are lineages or groups of bacteria that exploit a particular ecological niche such that periodic selective sweeps reduce diversity while fixing adaptive mutations or genetic elements, and this definition can be expanded to include populations where the genetic diversity is limited by genetic drift (Cohan & Perry, 2007). If adaptive selection defines each ecotype, then it is expected that there will be recognizable adaptive changes that associate with the ecological niche. While a few gene regions can be used to distinguish existing isolates (which may or may not hold as sample sizes increase), adaptive genetic differences have not been identified to distinguish the *T. pallidum* subspecies. Instead, strains of *T. pallidum* were first classed into species based on location of lesions on the body, then as subspecies based upon re-association kinetics of a single strain of *pallidum* and *pertenue* (Miao & Fieldsteel, 1980), and more recently as the result of phylogenetic analyses that have some limitations, as outlined below. This classification raises the question of whether *T. pallidum* subspecies (or ecotype) "boxes" are due to genetic drift and whether these categories are biologically meaningful or are just a convenience for the clinician. It is also unclear whether there are sufficient genomic data to evaluate which model of speciation or population subdivision best describes *T. pallidum*. Because of these challenges, in this section, our use of the terms yaws, bejel, and syphilis refers to classical clinical phenotypes.

Overall, genetic data from *T. pallidum* are limited. *T. pallidum* does not grow in artificial media and has only recently been grown in a complex tissue culture system (Edmonson, Hu, & Norris, 2018). Thus, there are not many strains of *T. pallidum*, particularly from nonvenereal infections, available for genome sequencing. Many early treponemal strain comparison analyses focused on the *T. pallidum* repeat (*tpr*) gene family (Centurion-Lara et al., 2006, 2013; Gray et al., 2006; Marra et al., 2010). However, evidence for recombination and gene conversion events has been detected in *T. pallidum*, particularly within the *tpr* gene family, thus confounding phylogenetic analyses (Gray et al., 2006; Grillová et al., 2019; Mikalová et al., 2017; Petrošová et al., 2012).

Today, ~150 full genomes of *T. pallidum* are available in public databases (Beale et al., 2019). Most of the available genomes are representatives of strains designated as *T. pallidum* subsp. *pallidum* because of the clinical phenotype from which they were derived. Because genome sequences for *T. pallidum* subspecies show less than 0.2% variation (Cejkova et al., 2012; Mikalová et al., 2010; Štaudová et al., 2014), this degree of genetic similarity necessitates full genome sequencing to obtain sufficient statistical power in phylogenetic analyses to resolve relationships fully. For example, initial phylogenetic analyses of *T. pallidum* using 21 genes showed poor resolution of branching patterns and low statistical support for internal nodes (Harper et al., 2008). The full genome sequences of strains classified as *T. pallidum* subsp. *pertenue* (Cejková et al., 2012) and *T. pallidum* subsp. *endemicum* (Štaudová et al., 2014) were published more than a decade after the first sequence of *T. pallidum* subsp. *pallidum* (Fraser et al., 1998). These data suggest that *endemicum* and *pertenue* subspecies are more closely related to each other than either is to *T. pallidum* subsp. *pallidum* (Arora et al., 2016). In addition to discerning the relationships among strains, genome data can be used to estimate divergence times, potentially providing insight into the origin of human treponemal infection. Bayesian analysis of 39 *T. pallidum* strains has pointed to a recent common ancestry of *T. pallidum* subsp. *pallidum* in A.D. 1744 (95% confidence interval: 1611–1854), notably well after the first reported syphilis epidemic in Europe (Arora et al., 2016:2). Arora et al. (2016) note, however, that this estimate reflects only extant *T. pallidum* lineages and likely would be pushed back in time if sequences from extinct strains were available. In addition, the geographical sources of the strains could introduce spurious structure into the phylogeny (i.e., subspecies samples used by Arora et al. [2016] for *pallidum* were almost exclusively from the U.S. and Europe, while *endemicum* strains were from the Middle East, and *pertenue* were from Africa and the Pacific Islands). Notably, there are few if any *pallidum* subspecies sequences from Africa and no *pertenue* sequences from South America.

Recognized virulence factors of *T. pallidum* include Tp0751 and the other extracellular matrix-binding proteins involved in attachment to host cells and dissemination, and the *Tpr* family that includes the antigenically variable TprK. Genes for these proteins are found in all three subspecies. Single nucleotide polymorphisms (SNPs) have been identified that support the subspecies classification of a number of isolates (Centurion-Lara et al., 2006), but none of these SNPs suggests a mechanism for explaining the purported differences used by clinicians to categorize infections as yaws, bejel, or syphilis. Interestingly, many of these SNPs are found in the members of the *tpr* gene family, which shows evidence of recombination and thus are excluded from

phylogenetic analyses. Despite the SNPs in the *tpr* genes, the functional virulence of the subspecies overlaps, because molecular analyses have identified clear examples where the clinical diagnosis and the expected subspecies gene signatures do not correlate. For example, these genetic signatures demonstrated that the historical Haiti B yaws strain, isolated in 1951 from an 11-year-old boy with "typical generalized frambesiform yaws" (Turner & Hollander, 1957:270), is actually a *T. pallidum* subsp. *pallidum* isolate (Centurion-Lara et al., 1998:1039; Nachvatal et al., 2014). More recently, reports of clinically diagnosed genital primary chancres, sexually transmitted and presumed to be syphilis, were shown to have been caused by *T. pallidum* subsp. *endemicum* (Grange et al., 2013; Kawahata et al., 2019; Mikalova et al., 2017; Noda et al., 2018). Thus, "molecular subspeciation" does not always correlate with the clinical manifestations or mode of transmission.

3.3 | Genetic analyses of nonhuman primate Treponemes

Wild primates (including chimpanzees, gorillas, baboons, macaques, sooty mangabeys, vervet and blue monkeys, and African green monkeys) have been observed with yaws-like and syphilis-like lesions; treponemal infection is supported in these animals by serological, bacteriological, or molecular evidence (Fribourg-Blanc & Mollaret, 1969; Chuma et al., 2018; Harper et al., 2012; Klegarth et al., 2017; Knauf et al., 2012, 2015, 2018). Of particular interest, olive baboons at Lake Manyara National Park in Tanzania were observed with ulcerative lesions in the anogenital region, suggesting sexual transmission, although molecular analyses of four gene regions (Knauf et al., 2012) and subsequent whole genome sequencing (Knauf et al., 2018) showed that the causative agent was most closely related to *T. pallidum* subsp. *pertenue*. Further, surveys of baboons at various national parks in Tanzania analyzed six gene regions and found that, while the Lake Manyara strain clustered with human strains of *T. pallidum* subsp. *pertenue*, the Serengeti National Park and Fribourg-Blanc strains were more basal to the human *T. pallidum* subspecies strains (Harper et al., 2012). In a survey of 85 individuals from six primate species, Chuma et al. (2019) analyzed two genes (*tp0548* and *tp0448*) and showed that strains, all classed as *T. pallidum* subsp. *pertenue* despite differing clinical phenotypes, appear to cluster based on geography rather than host species, which suggests that there has been transmission among primate species. These studies indicate that the nonhuman primate treponemes examined to date are most similar to *T. pallidum* subsp. *pertenue*, but additional full genome data are needed to understand the variable clinical presentations of *T. pallidum* subspecies across different taxa and the phylogenetic relationships among strains.

Until recently, only a single complete genome originating from a nonhuman primate treponeme had been sequenced. This genome, sequenced from the Fribourg-Blanc strain that was isolated multiple decades ago from a Guinea baboon (*Papio papio*), clusters with human *T. pallidum* subsp. *pertenue*, with only 117 SNPs and 11 indels (insertions and deletions) differentiating it from human strains of yaws (Zobaníková et al., 2013). Knauf et al. (2018) recovered partial and full genome *T. pallidum* sequence data from eight primates sampled during previous work (Knauf et al., 2012), including green monkeys (*Cercocebus sabaeus*), sooty mangabeys (*Cercocebus atys*) and baboons (*Papio anubis*) from locations in Tanzania, Senegal, the Gambia, and Ivory Coast. All clustered with previously sequenced *T. pallidum* subsp. *pertenue* lineages, with human and primate strains interspersed in a star-like pattern pointing to a rapid radiation. This clustering could indicate that treponemal infection is an heirloom disease that radiated rapidly among primates, but further research about strains affecting humans and nonhuman primates from the same areas would also help us understand the frequency of exchange (in the past as well as today).

3.4 | Recovery and analysis of ancient human Treponemes

Several researchers have worked to recover ancient treponemal DNA from skeletal remains with diagnostic lesions of treponemal infection. Assessment of the relationships of these ancient pathogens to extant strains could help identify the distribution of *Treponema* species and the extent of variation of *T. pallidum* in past populations, and would be particularly useful for shedding light on the debate about the origin of syphilis and the perceived European epidemic in the early 16th century. Early studies of ancient pathogen DNA focused on small segments of DNA and used polymerase chain reaction (PCR) methods followed by fragment analysis, cloning, or Sanger sequencing (Harkins & Stone, 2014). Such research was challenging and results were often questioned because it was difficult to identify contamination by modern sources. Other challenges included co-extraction of inhibitors with the DNA, the limiting amount of starting DNA template, DNA damage, and the small size of the targeted sequence (Handt, Höss, Krings, & Pääbo, 1994; Pääbo, 1989). For example, the sequence of the PCR fragment reflects an average of all the molecules amplified (unless PCR products are cloned, and clones are sequenced separately) and does not allow damage pattern assessment. New techniques such as targeted capture and next-generation sequencing methods have revolutionized ancient DNA analyses, allowing capture of complete genome sequences and the assessment of damage patterns, DNA fragment sizes, and the percentage of contaminating molecules (e.g., Stone & Ozga, 2019).

Initial studies of ancient *Treponema* DNA also suffered from some of the same issues as other early studies of ancient DNA. Kolman, Centurion-Lara, Lukehart, Owsley, & Tuross (1999) used immunological analyses as well as DNA analyses (specifically PCR targeting the 5′ flanking region of the *tpp*15 gene, followed by RFLP analysis using Eco47III of a SNP that is diagnostic for *T. pallidum* subsp. *pallidum*) to confirm its presence in a skeleton approximately 240 years old from Easter Island that exhibited lesions consistent with treponemal disease. In some subsequent studies (Barnes & Thomas, 2005; Bouwman & Brown, 2005), investigators were not able to recover

T. pallidum DNA from ancient bones and questioned Kolman and coworker's prior work accordingly. Bouwman & Brown (2005) analyzed 27 bones with pathological lesions consistent with syphilis. They were unable to detect the pathogen using PCR and noted that pathogen load was likely very low by the time bony changes were visible, as Von Hunnius Yang, Eng, Waye, & Saunders (2007) demonstrated later. In exploring the survival of bacterial pathogen DNA in bones, Barnes & Thomas (2005) analyzed bone samples from eighteenth- and twentieth-century individuals, some of whom were medically documented to have been infected with *Treponema pallidum*. Their research showed no reproducible evidence of surviving pathogen DNA. At the time they emphasized the need to understand better how pathogen DNA survives in archaeological bones.

To address questions about the preservation of *T. pallidum* DNA in archaeological human remains, von Hunnius et al. (2007) used two lab rabbits with different stages of syphilis infection to test whether various tissues (including bone) showed evidence of the pathogen. They also examined 15 archaeological human bone and tooth samples from individuals showing lesions indicative of syphilis, or with historical documentation or medical reports showing a syphilis diagnosis. Despite the use of five different PCR assays targeting *T. pallidum*, none of the human bone samples yielded positive results. Only the bone from the rabbit in the primary, acute stage of infection (i.e., soon after initial infection) tested positive, while those from the rabbit in the latent/chronic stage (with healed lesions) did not. Thus, von Hunnius et al. (2007) concluded that, by the time tertiary skeletal lesions are evident, it is likely that the pathogen load in bones is very low. This work suggested that *T. pallidum* DNA will be challenging to detect in the archaeological record.

Tackling the problem of low pathogen load, Montiel et al. (2012) hypothesized that infants with congenital syphilis (CS) who died soon after birth would have higher systemic bacterial loads. Thus, their efforts to obtain ancient *T. pallidum* sequences focused on bone samples from such individuals, who are potentially identifiable from skeletal changes associated with CS. To test this hypothesis, Montiel et al. (2012) extracted DNA from four neonates with pathological lesions suggestive of CS who were buried in a crypt dating from the 16th to 17th centuries in southwestern Spain. They used PCR to amplify two DNA fragments and identified sequences identical to those found in *T. pallidum* for two individuals. Unfortunately, the *tpp15* sequences that they analyzed are identical among the subspecies and further analyses to assess the evolutionary placement of these strains have not yet been performed.

Subsequently, Prümers, Trautmann, Trautmann, Lösch, & Pusch (2012) used PCR analysis of a fragment of the *T. pallidum polA* gene on teeth from 30 individuals of 123 excavated from the precontact site of Loma Salvatierra in Bolivia (up to 25 individuals were reported to have treponemal disease). They obtained positive results from seven individuals, but the sequence in this segment of the *T. pallidum* genome is identical among the three subspecies. Guedes et al. (2018) also used PCR of fragments of three genes (*polA*, *tpp15* and *tpp47*) to assess whether treponemal infection was present in 25 individuals from a colonial (17th–19th century) church and cemetery contexts in Rio de Janeiro, Brazil. Two individuals produced positive results for the *tpp15* PCR (one from each context) and sequence results from a female young adult suggest that she was infected with *T. pallidum* subsp. *pallidum*. Additional research is needed to confirm PCR results from these studies and to recover sufficient genome data for phylogenetic and evolutionary analyses.

More recently, using improved methods for extracting short DNA fragments developed by Dabney et al. (2013), along with targeted DNA enrichment and whole genome sequencing using next-generation sequencing technology, Schuenemann et al. (2018) successfully recovered *T. pallidum* genomes from skeletal remains of two infants and a neonate with presumed CS interred in a historic cemetery in Mexico City. Three genomes were recovered, two of which cluster with extant strains of *T. pallidum* subsp. *pallidum* consistent with CS, as expected. The genome from the third infant clusters with *T. pallidum* subsp. *pertenue* strains that are assumed to cause yaws. Though these genomes cannot shed light on the geographical origins of syphilis, they demonstrate that *pertenue* and *pallidum* clades coexisted in the Americas at this time, that both caused infections in infants, and that it is possible to recover ancient *T. pallidum* lineages.

DNA is not the only biomolecule that may provide insight into the evolutionary history and spatial distribution of *T. pallidum*. Recently, the study of ancient proteins (i.e., paleoproteomics) and lipids has also been applied to questions about health and disease in ancient humans. Such analyses have been used previously to address a range of questions in paleontology and archaeology, and they have the advantage of often obtaining results in environments or time periods that are beyond DNA preservation (Cappellini et al., 2018). Most proteomic assessments of human pathogens have targeted the oral cavity. For example, Warinner et al. (2014) examined the oral microbiome in people from Medieval Germany using DNA and protein analyses and detected many oral commensals and pathogens including *Treponema denticola*, which has been linked to periodontal disease. To investigate immune activity, Sawafuji et al. (2017) used shotgun proteomics of ribs from eight individuals and found suggestions of an immune response related to infectious disease. Though these methods have not been used to identify or assess individuals with *T. pallidum*, proteomics could provide insight into this pathogen and immune responses to it.

3.5 | Evaluation of origin models from a genetic perspective

In order to evaluate the competing hypotheses concerning the origin of treponemal disease in humans, we turn to the body of currently available genetic data. Schuenemann et al. (2018) constructed a *T. pallidum* phylogeny using whole genome data, and the resultant topology clusters into the commonly described subspecies, though the clinical phenotypes from which they are derived are not always consistent. A basic model of this topology is shown in Figure 1a. This branching pattern (shown in red) represents relationships between the known, predominately extant *T. pallidum* strains and includes

relatively few yaws or bejel-like strains. In Figure 1b, representing the Columbian hypothesis, the assumption is that syphilis stemmed from an American treponeme and either arose in the Americas and subsequently spread into Europe, or that it evolved into syphilis quickly after being brought to Europe. Under this hypothesis, new data (shown in black) should show that some form of early American treponemal disease would be most closely related to modern syphilis strains. In Figure 1c, for the pre-Columbian hypothesis, we expect that syphilis strains were present in Eurasia and/or Africa prior to contact with the Americas. Thus, the Eurasian/African treponemal lineages

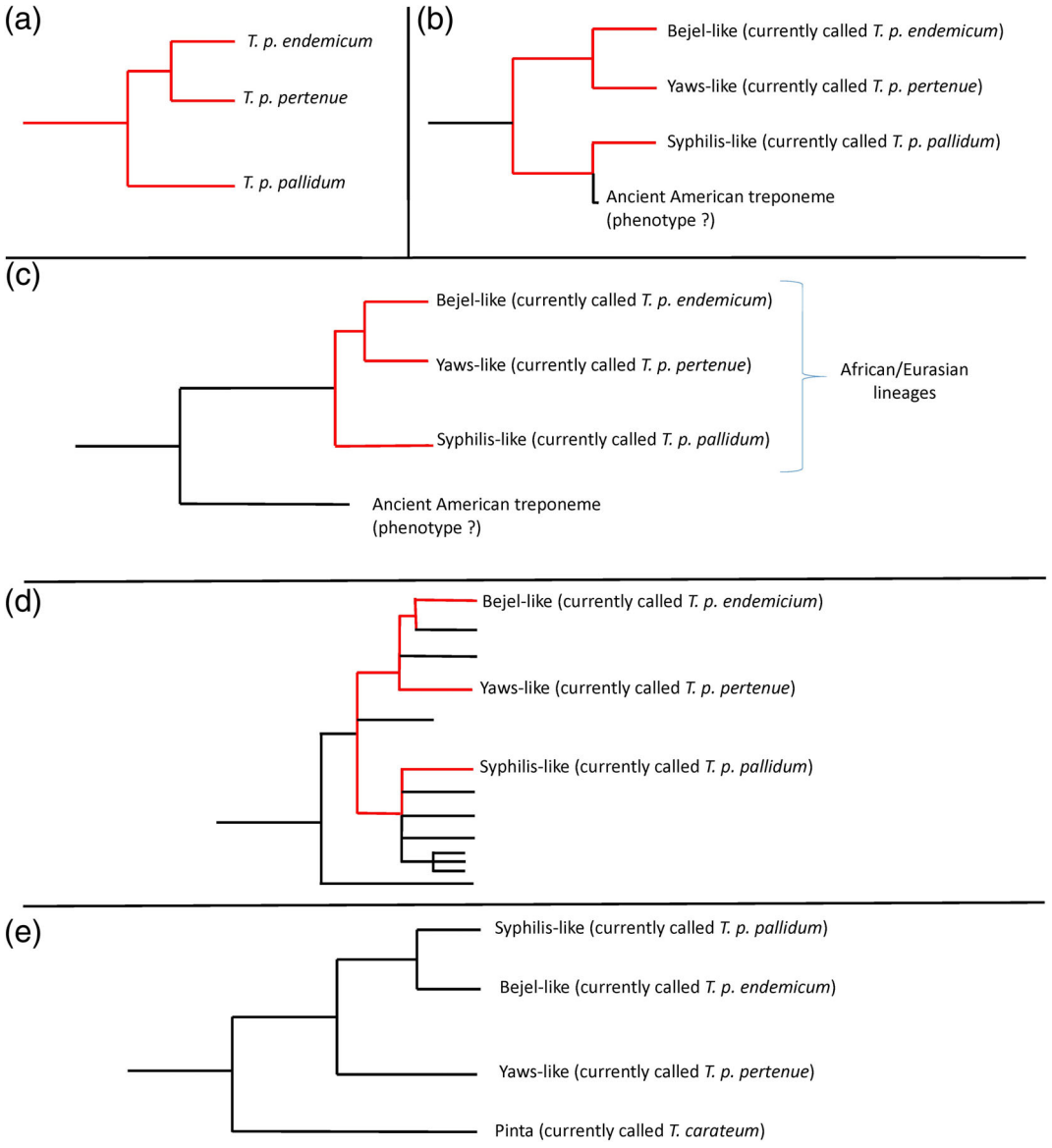

FIGURE 1 Tree topology and origin hypotheses. Based on recent phylogenetic analysis using genome-wide data, the various *Treponema pallidum* strains are presumed to be related as shown in Tree (a). This tree topology is highlighted in red. Trees (b–e) illustrate the expected tree topology given the assumptions of the four hypotheses on the origins of *T. pallidum* and treponemal infection. In three of four trees, the known branch pattern (in red) can be observed. In these models, branch lengths are not to scale. (a) Phylogenetic analyses of the limited genomic data available for *T. pallidum* yield a tree topology that groups bejel and yaws-like strains to the exclusion of syphilis-like strains (Schuenemann et al., 2018). (b) Under the Columbian hypothesis, a treponemal pathogen circulating in the Americas was imported into Europe after contact. This imported organism gave rise to the syphilis-like strains of *T. pallidum* that are circulating today. (c) The Pre-Columbian hypothesis postulates that human treponemal diseases, including syphilis, were present in Africa/Eurasia prior to contact with the Americas. Under this model, the Afro-Eurasian and American strains of *T. pallidum* diverge into separate clades. This/these American *T. pallidum* strains may or may not have been replaced by Afro-Eurasian strains. (d) Under the Unitarian hypothesis, it is expected that the clear definition of "subspecies" clades will dwindle as more genomic data become available. (e) The Evolutionary hypothesis, as advanced by Hackett (1963), suggests that pinta and yaws-like strains emerged prior to syphilis and bejel-like strains. In the resultant phylogeny, syphilis and bejel-like strains are more closely related to one another than to other treponemal strains. This model is not supported by currently available genomic data

diverged from the American lineages 5,000–20,0000 years ago (depending on whether treponematosis was transported by first Americans or subsequent Arctic migrations or both). If that were the case, then we would expect ancient American treponemes to be basal to the current Eurasian/African strains (which have shallow branches and therefore recent node dates as shown by Arora et al. 2016). The phenotype(s) of this/these American treponemes are unknown, as they may have been replaced by African/Eurasian lineages after contact. At the time of the African/Eurasian vs. American *T. pallidum* split, the clinical phenotype could have been yaws-like or not. Studies of ancient *T. pallidum* DNA, as well as a better understanding of the phenotypic characteristics, are needed to clarify this divergence. According to the Unitarian hypothesis (Figure 1d), new lineages (shown in black) are expected to be identified by sequencing of additional geographically diverse *T. pallidum* strains; however, these would not necessarily cluster by clinical phenotype as typically expected. Some recently sequenced or identified strains (including Haiti B and the venereal *endemicum* strains) are discrepant in "subspecies" and clinical phenotype but, as noted above, additional genome data from a broader geographic sampling are needed. As shown in Figure 1, currently available genetic data fail to answer questions about the origins of treponemal infection because of the vast amount of unexplored variation within *Treponema pallidum*. One conclusion is clear, however: the Evolutionary model (depicted in Figure 1e), which posits that yaws-like strains should be basal to syphilis- and bejel-like strains, does not fit the current phylogeny. More basal strains not represented in this phylogeny could have a yaws-like phenotype; however, in addition to making this model somewhat accurate, it would ultimately support the Unitarian hypothesis where phenotype and strain relationships are not tightly linked (i.e., there is homoplasy in clinical phenotypes). The remaining hypotheses about the origins of syphilis require additional data to be tested.

3.6 | Future prospects in the genetics of *Treponema*

Genetic data can provide insight into our understanding of the biology and evolutionary history of *Treponema*, including the pathogens that cause infection in humans and nonhuman primates. For the reasons discussed above, phylogenetic analyses currently fail to strictly support or refute most of the hypotheses of treponemal infection origins. The exception is the refutation of the Evolutionary hypothesis, at least by the *current* phylogeny. The clinical and genetic analyses briefly described here do show preliminary support for the Unitarian hypothesis, because there is increasing evidence that clinical presentations of treponemal disease are not strictly linked to the infecting "subspecies." Thus, the phylogenetic separation of the treponemal genomes into groups may better be described as clades of one species, rather than as subspecies. However, to address the hypotheses about the origin and antiquity of syphilis in depth, more genome data from both modern and past strains of *T. pallidum* are required.

Specifically, there is a need to sample modern treponemes strategically and recover full genomes from a more representative cross section of the genus. Doing so necessitates collaboration with clinicians to obtain samples from currently affected individuals in poorly sampled regions of the world, and with pathologists to sample archived material, including bone and soft tissue retained in medical collections. This work would enable a clearer assessment of the relationships among strains and the mutation rate of the pathogen, as well as the extent to which recombination and gene conversion affect phylogenetic signals in the genome. Ideally, such sampling would include detailed descriptions of the clinical manifestations and epidemiological context, including the source of the infection and route of transmission, in addition to descriptions of any tissue samples that were examined by a pathologist. This information would assist in confirming or refuting the correlation of genotype to the mode of transmission and clinical manifestations. Additional outgroup genome sequences, as well as that of *T. carateum*, the causative agent of pinta, would aid in a broader understanding of treponemes and their evolution. Because the same organisms can infect many primates, uncovering the diversity of *T. pallidum* and related treponemes in other species may be important for assessing how these organisms have adapted to primates (and other mammals) and could lead to a deeper understanding of shared biology and evolutionary environments. The fact that the Nichols strain of *T. pallidum* can infect humans, rabbits, and nonhuman primates, resulting in virtually identical clinical and pathological findings, suggests that mammalian immune systems interact with *T. pallidum* in similar ways and that *T. pallidum* can find permissive environments in a wide variety of mammalian bodies. Such information also is critical to current efforts to develop a treponemal vaccine and eradicate yaws (as noted by Chuma et al. [2018] and Knauf et al. [2018]; see WHO [2012]), a disease that in 2014 remained endemic in at least 13 countries (Mitja et al., 2015).

4 | ARCHAEOMETRY AND ARCHAEOLOGICAL BIOGEOCHEMISTRY

Chronology has long been central to debates concerning the evolution and spread of treponemal disease (Crosby, 1969; Williams, 1932). Key to establishing timing of disease in different areas of the globe, radiocarbon dating has often been used to establish archaeological site dates but has been dismissed by some (e.g., Harper et al., 2011) due to issues concerning the contribution of freshwater or marine resources to the diet of individuals showing lesions that are associated with a diagnosis of treponemal infection. Corrections for any reservoir effect that could affect a radiocarbon date must be done carefully and in conjunction with stable isotope analyses. Stable isotope analyses and other methods in archaeological biogeochemistry are now used regularly to assess much more than diet (e.g., see Bentley, 2006; Pederzani & Britton, 2018; and Reitsema, 2013). These methods can contribute substantial information concerning pathophysiology of affected individuals, mobility of affected individuals and the

treponemal pathogens they carry with them, plus information concerning potential treatment (e.g., with arsenic or mercury).

4.1 | Establishing chronology in studies of past treponemal disease

The debate about the Columbian hypothesis has overshadowed many investigations into the evolution of treponemal disease, and its influence has been particularly marked on studies addressing the timing of its dispersion (Baker & Armelagos, 1988; Harper et al., 2011). For example, some historical investigations have tried to address at the level of weeks, or even days, whether members of Columbus's returning crew could have been present in Naples, Italy, during the widely reported outbreak of syphilis in 1494–1495 (Brown et al., 1970; Luger, 1993). Archaeological information, especially radiocarbon (^{14}C) dates, has been viewed through the same lens. Some early Old World evidence of treponemal disease has been dismissed for want of ^{14}C dates, even where there were reliable dates based on artifacts and stratigraphy (e.g., the remains from a Megalithic site near Agripalle, India, are among those Harper et al. [2011:123] deem to lack "strong evidence of a pre-Columbian date" despite their deposition in cist and urn burial complexes associated with ceramics and iron artifacts dated to the 1st to 2nd centuries B.C. [Rao, Vasulu, & Rector Babu, 1996:50]). Other evidence, conversely, has been questioned for underplaying the statistical uncertainty in ^{14}C dates (Harper et al., 2011). Here, we regard the Columbian/Pre-Columbian debate as something of a false dichotomy, which at times has impeded objective chronological analysis. The following passages recommend how best to treat new and existing archaeological dating information, focusing particularly on the application of ^{14}C dating.

4.1.1 | Archaeological context and dating

A brief defense of traditional archaeological dating based on material culture and site stratigraphy must first be made. For contexts in the Common Era, especially in Europe and the ancient Near East, assignments made on such grounds by experienced excavators are rarely overturned by chronometric measurements. One example is provided by Cole & Waldron (2012), who rebutted the scoring system used by Harper et al. (2011:105), which prioritizes radiocarbon dates as the "minimum level of proof necessary for assigning an individual of the pre-Columbian period." This scheme was noted by Cole & Waldron (2012) to lead Harper et al. (2011:Table 1) to give lower scores to Count Gottfried von Cappenberg's known dates of birth and death and question the dating of the Anglo-Saxon Apple Down 152 skeleton based on artifactual evidence. Cole & Waldron (2012) demonstrated how artifacts of this period provide more precise dating than ^{14}C date ranges. A radiocarbon date subsequently obtained for the Apple Down individual by Cole & Waldron (2014) yielded a calibrated date of A.D. 427–624 (99.7% probability), supporting the original estimate of cemetery use from the late fifth or early sixth century to the late seventh century derived from grave goods (Cole & Waldron, 2010:73). Another key example is a child with CS from ancient Nicaea, in modern Turkey (Erdal, 2006), a diagnosis widely considered unequivocal by paleopathologists including Harper et al. (2014:121). Although no ^{14}C dates were obtained during this excavation, Erdal (2006) described in detail how the affected skeleton was discovered in strong stratigraphical relationships with other human remains that could be assigned securely to the 13th century A. D. by both historical and artifactual evidence, including coins found *in situ*. Nonetheless, as with Apple Down 152, the date of the skeleton was deemed uncertain by Harper et al. (2011) on the grounds that no radiocarbon analyses had been conducted.

4.1.2 | Best practices for radiocarbon dating

The versatility and precision of ^{14}C dating make it the most appropriate scientific technique for understanding the spatiotemporal trajectory of treponemal disease. Nonetheless, it also harbors certain shortcomings. For example, it can rarely resolve the order of events separated by less than about 50 years. The greatest challenges arise where plateaus occur in the calibration curve (reference used for conversion of ^{14}C results to calendar years). At these times, most notably the mid-first millennium B.C. and late second millennium A.D., events that are centuries apart sometimes cannot be distinguished. Further aspects of ^{14}C dating of relevance to the issue at hand are sample selection, reservoir effects, and Bayesian modeling.

The most common reason ^{14}C dates diverge from ages expected on archaeological or historical grounds is poor sample selection (Pettitt, Davies, Gamble, & Richards, 2003; Waterbolk, 1971). Flawed sampling often stems from a lack of understanding of what ^{14}C results actually denote. A ^{14}C date represents an estimate of when the original organism, from which the sample was obtained, ceased incorporating carbon from its environment. This date may differ significantly from the historical or archaeological context within which the item was found. Durable materials such as shell, wood, and even bone are generally the most problematic because they can lie unused, be refashioned, and even be handed down as heirlooms, before final deposition. Shell and bone may also be affected by reservoir effects (see below). For such reasons, high-precision ^{14}C studies usually employ short-lived terrestrial plant samples (Bayliss, 2009; Bruins, van der Plicht, & Mazar, 2003; Manning et al., 2006). Typical materials include charred cereal grains, which represent both anthropogenic activity and only a single year's growth, plant-based basketry, matting, clothing, and writing materials such as papyri (Dee et al., 2012). Where plant materials are analyzed, there is clearly scope for a discrepancy to arise between the age of the sample and any related human remains. However, it has been repeatedly demonstrated that plant-based items directly associated with skeletal evidence tend to provide the most accurate ^{14}C results. A key example of this approach was a wide-ranging ^{14}C study of dynastic Egypt (Bronk Ramsey et al., 2010) in which more than 200 seed, linen, and basketry samples were used to produce a ^{14}C-based chronology that concurred very closely with historical estimates.

^{14}C dates on organisms that have acquired a substantial amount of their carbon from marine or aquatic environments are liable to be older than expected due to the reservoir effect (see Lanting & van der Plicht, 1998; Stuiver et al. 1986). This issue also can affect results from collagen, the fraction of human bone most commonly extracted for dating, if the diet of the individual concerned contained a significant quantity of fish or mollusks (Lanting & van der Plicht, 1998). It should be emphasized, however, that reservoir effects in humans are usually the exception rather than the rule. The issue is often first suspected when a date turns out to be much older than expected; however, the presence of reservoir effects can also be inferred from other physical and analytical data. Firstly, any archaeological evidence for extensive consumption of aquatic resources (e.g., fish bones, shell middens) should be considered. Secondly, collagen stable isotope ratios, δ^{13}C and δ^{15}N, which are obtained as a by-product of the ^{14}C dating process, become notably elevated when a marine dietary effect is present (De Niro & Schoeninger, 1983). Freshwater-derived offsets are not so easily identified in this manner, but their occurrence is comparatively rare, and any claim they are present should be substantiated by solid archaeological evidence. Where compelling archaeological or stable isotope evidence exists for a marine reservoir effect, corrections may be applied to the affected ^{14}C dates. The basic rationale involves adjusting the ^{14}C measurement in proportion to the observed enrichment in ^{13}C. The best practices for implementing marine reservoir corrections were reviewed by Cook et al. (2015). When making a correction, it is always advisable to obtain local "end-member" values for δ^{13}C; that is, δ^{13}C results on collagen from individuals with wholly terrestrial and marine diets. Doing this work makes it possible to estimate the marine intake of any given individual at the site. However, data for end-members are sometimes difficult to obtain, so it is also common to use approximations. The results of Arneborg et al. (1999) of −21.0‰ (δ^{13}C, wholly terrestrial) and −12.5‰ (δ^{13}C, wholly marine) are often used for this purpose. Once the marine proportion of the diet is estimated, this value may be incorporated into the calibration of the ^{14}C measurement in programs such as OxCal (Bronk Ramsey, 1995). OxCal also allows for the inclusion of any further uncertainty, such as the 10% recommended by Cook et al. (2015). Notwithstanding, ^{14}C dates should not be subjected to reservoir corrections unless the supporting evidence, described above, is observed.

In recent years, considerable progress has been made with compound-specific ^{14}C dating (see Deviese et al., 2019; McCullagh, 2010). This approach involves a more exacting form of sample pretreatment. Instead of simply purifying a bulk fraction like proteins or lipids, a specific molecule is isolated and spectroscopically characterized, before it is dated. For human bone, the amino acid hydroxyproline is often the compound of choice. It has already been shown that isolating hydroxyproline can enable even the most tightly bound curatorial contaminants on bone samples to be eliminated (Deviese et al., 2019; Marom, McCullagh, Higham, Sinitsync, & Hedges, 2012). Meanwhile, for pot residues, specific fatty acids that are diagnostic of foodstuffs, such as milk (Dunne et al., 2012), have also been directly dated. Further research on pot residues has involved distinguishing terrestrial from potentially reservoir-affected marine and aquatic compounds (Craig et al., 2011). Nonetheless, compound-specific dating has yet to offer a means by which diet-derived reservoir effects on human bone may be bypassed or negated. Thus, it is unlikely to assist greatly with issues relating to the origin and spread of treponemal infection.

The final aspect of modern ^{14}C analysis that is relevant to intricate chronological issues like the origin and propagation of treponemal infection is Bayesian statistical modeling (Bayliss, 2009; Bronk Ramsey, 2009; Buck, Litton, & Smith, 1992). This procedure allows the calendar date ranges generated by ^{14}C measurements to be greatly refined by mathematically combining them with relative chronological information, such as stratigraphy. The enormous site of St. Mary Spital, London, was the subject of a rare but important example of the application of Bayesian modeling to the history of treponemal disease. Here, precise absolute dates were obtained for the sequence of archaeological phases at the site (Sidell, Christopher, & Bayliss, 2007). Moreover, the historical and stable isotopic evidence obtained was commensurate with diets that were relatively low in fish. The overall findings showed that there was a rise in treponemal infection in the late 15th century, in keeping with historical accounts at this time. However, it also indicated that evidence of treponemal disease was present in phases that dated as early as the 13th century (Walker, Powers, Connell, & Redfern, 2015). Such studies represent the cutting edge of what is now possible in radiocarbon dating and should provide the blueprint for future chronological analyses of treponemal disease.

4.2 | Using archaeological biogeochemistry in investigating treponematosis

In addition to the use of stable isotope analyses to assess the potential marine contribution to the diet for accurate calibration of radiocarbon dates, as described in the preceding section, such analyses contribute to our understanding of the physiological impact of disease on the skeleton and provide information on human migration and, therefore, the mobility of the pathogen under study. New techniques in this field also may help identify individuals who have undergone treatment with agents such as mercury.

4.2.1 | Isotopes and pathophysiology

The impact of pathological conditions on isotope values in human skeletal remains has not been extensively studied, largely due to the destructive nature of biogeochemical sampling and the desire to preserve the integrity of bones exhibiting pathological lesions. While pathophysiological changes influencing isotope fractionation are more likely to be detected in rapidly-forming soft tissues often unavailable to bioarchaeologists, such as skin or hair (e.g., Mekota, Grupe, Ufer, & Cuntz, 2006; Wheeler, Williams, Beauchesne, & Dupras, 2013), chronic conditions such as untreated treponemal disease may similarly exhibit distinctive isotope values incorporated into the skeleton, particularly in newly-formed bone lesions (Katzenberg & Lovell, 1999). Modified

human isotope values, possibly resulting from altered protein metabolism or negative nitrogen imbalance evidenced by ^{13}C- and ^{15}N-enrichment in bone collagen, have been detected previously by sampling human bone collagen with evidence of osteomyelitis, periostitis, osteopenia, and anemia in a handful of isotopic studies (Katzenberg & Lovell, 1999; Olsen et al., 2014; Olsen, von Heyking, Grupe, White, & Longstaffe, 2018; White & Armelagos, 1997), although differences between lesion and non-lesion sites were typically less than one per mil (Katzenberg & Lovell, 1999; Olsen et al., 2010, 2014, 2018).

Few isotopic studies of bone collagen have included individuals diagnosed with suspected treponematosis (Dent, 2017; Mays, Crane-Kramer, & Bayliss, 2003; Mays, Vincent, & Meadows, 2010; Rissech et al., 2011; Santos, Gardner, & Allsworth-Jones, 2012; Schwarz, Skytte, & Rasmussen, 2013); even fewer have sought to compare these values directly with other bones or individuals exhibiting no signs of the disease to discern any potential pathophysiological effects associated with treponemal infection (Salesse, Kaupová, Brůžek, Kuželka, & Velemínský, 2019). Slightly lower $\delta^{13}C_{col}$ values (0.3–0.4‰) noted among 19th-century people with syphilis, relative to unaffected individuals, were attributed to either prescribed dietary change or to nutritional stress—possibly resulting in endogenously-formed nonessential amino acids derived from nonprotein sources depleted in ^{13}C—but not to the pathophysiology of the disease itself (Salesse et al., 2019). Nitrogen isotope values in the same group remained unchanged (Salesse et al., 2019). Oxygen isotope values from hydroxyapatite also have the potential to be modified by disease due to imbalances during respiration or modified basal metabolic rates; however, ^{18}O depletion associated with anemia identified in one human study was attributed not to pathophysiological change but to changes in diet (Carroll, Inskip, & Waters-Rist, 2018). To date, no comparable studies using oxygen isotope analysis have been performed on individuals exhibiting signs of treponemal disease. Subsequently, it remains uncertain whether treponemal infection would consistently affect isotope fractionation in detectable ways, particularly as human plasticity against stressors may circumvent the physiological effects of disease (Reitsema, 2013).

As preliminary studies have demonstrated that pathophysiological changes to bone result in only minor modifications to isotope values that may be impossible to differentiate from an altered diet (e.g., Salesse et al., 2019) or nutritional stress (e.g., Fuller et al., 2005), should future directions include more experimental studies that directly sample suspected treponemal lesion sites? Additional investigations would likely improve our understanding of how treponemal infection physiologically affects the body as reflected in modified biogeochemical signatures, particularly if sampling of both lesion and non-lesion (control) areas on the same bone is possible (Katzenberg & Lovell, 1999). Lesion sites are comprised of newly remodeled bone containing isotope values more recently incorporated into skeletal tissues (Katzenberg & Lovell, 1999), in contrast with non-lesion sites where cortical bone turnover occurs at a much slower rate and–depending on the element–may exhibit isotope values averaged over the last 10–30 years of life (Hedges, Clement, Thomas, & O'Connell, 2007). Nevertheless, such sampling strategies would be unlikely to aid directly in a differential diagnosis specific to treponematosis.

Furthermore, sampling these lesions directly when so little change has been identified isotopically would unnecessarily damage precious paleopathological individuals whose lesions could yield additional information as novel methods are developed in the future. In lieu of direct lesion sampling, then, it may be more productive to consider sampling unaffected areas of bone elsewhere on the skeleton from individuals exhibiting treponemal disease. Prior studies experimenting with sampling bone from unaffected areas in close and/or distant proximity to a pathological lesion have revealed variable differences in isotope values relative to lesion sites (e.g., Katzenberg & Lovell, 1999; Olsen et al., 2014), suggesting that, in at least some cases, the isotope values of unaffected bone may be influenced by chronic pathological conditions. For instance, dietary changes associated with nutritional stress or starvation have been observed in avian (Hobson, Alisauskas, & Clark, 1993) and archaeological human bone (Wheeler et al., 2013) and dentin (Beaumont & Montgomery, 2016) samples, producing higher nitrogen isotope values as a result of catabolic processes of protein recycling. Consequently, a compromise in which sampling is performed on unaffected compact bone from individuals with suspected treponemal infection would facilitate the continued study of the physiology of this disease using biogeochemical techniques without lesion destruction. In particular, unaffected areas of cortical bone that experience higher turnover rates more similar to those found at active lesion sites—such as large entheses, or sites of muscle attachment (Schlecht, 2012)—may produce isotope values reflective of more recent pathophysiologically influenced fractionation that would be more comparable to lesions themselves (Rasmussen et al., 2013).

4.2.2 | Human migration and pathogen mobility

The temporal and geographic spread of infectious disease was and continues to be interconnected intimately with patterns of interaction, mobility, and migration (Greenaway & Castelli, 2018; Richards & Montgomery, 2012; WHO, 2018). Subsequently, establishing the origins and movements of past individuals will affect the ways in which we interpret disease prevalence by revealing potentially underlying social forces and exchange networks that contributed to its transmission (Richards & Montgomery, 2012; Roberts et al., 2012; Schrenk, Gregoricka, Martin, & Potts, 2016). Beyond historic records and archaeological evidence documenting such movements, radiogenic ($^{87}Sr/^{86}Sr$, $^{206}Pb/^{204}Pb$), and stable ($\delta^{18}O$, $\delta^{34}S$) isotopes in human skeletal tissues enable bioarchaeologists to directly evaluate residential mobility in the past (Bentley, 2006).

The best-known attempt to examine the relationship between treponemal infection dispersal and human mobility comes from Roberts et al. (2012), who analyzed the tooth enamel of skeletons (n = 12) with and without treponemal lesions from Medieval Hull, a port city in England and well-known hub of foreign trade, for radiogenic strontium and stable oxygen isotope ratios. Hypothesizing that infected individuals may have had nonlocal origins, their data instead revealed four individuals were nonlocal but only one had treponemal lesions. There were no patterns found between geographic origins and

isotope values, suggesting that nonlocals were not more likely to advance the transmission of treponemal infection in England, and that those infected could have contracted the condition in England itself, not elsewhere. Roberts et al. (2012) warn, however, that because syphilis is a chronic condition that takes years before it affects bone (and that bony changes occur only in ~8–20% of people when left untreated; Resnick and Niwayama, 1995), it remains possible that individuals without lesions in this study still may have had this condition. Similar results were obtained for a young woman with treponemal lesions from Blackfriars in Gloucester, England (Roberts, 1994), whose strontium and oxygen isotope ratios were consistent with others from the site; additionally, lead isotope values indicated that she grew up in western Britain and so likely contracted the infection there, and not outside of the country (Budd, Millard, Chenery, Lucy, & Roberts, 2004; Montgomery, 2002).

More work is necessary to assess the promise of such analyses. In particular, the use of techniques such as multi-tissue or intra-tooth/serial sampling are integral to exploring individual life histories more closely (Beaumont & Montgomery, 2016; Eerkens & Bartelink, 2013; Gregoricka, Sheridan, & Schirtzinger, 2016), thereby enabling bioarchaeologists to better track disease acquisition and/or transmission through refining at what stages of the life course individual mobility and migration may have taken place among those exhibiting treponemal lesions. As these techniques do not involve the destruction of treponemal lesions themselves, such analyses provide another valuable facet of inquiry from which we might learn more about the lives and lifestyles of those affected. Multi-isotope studies (in which two or more isotope values from the same skeletal tissue are measured; e.g., $^{87}Sr/^{86}Sr$ and $\delta^{18}O$) are also encouraged to ensure more reliable assessments of residential mobility, as single measures may be influenced unknowingly by environmental or cultural factors such as the use of fertilizers, regionally-specific seasonal changes to precipitation and/or evaporation, and even beverage preparation and storage techniques (Bentley, 2006; Brettell, Montgomery, & Evans, 2012; Price et al., 2009). Best practices should include detailed evaluations of local isotope bioavailability to establish baseline values against which human ratios may be evaluated, typically by analyzing faunal, plant, or water samples.

4.2.3 | Detecting mercurial and arsenic treatments

Prior to antibiotics, Western historic records outline the use of a variety of therapies and medications to treat treponemal disease, including arsenic, bismuth salts, guaiacum (an aromatic wood), and mercury (O'Shea, 1990; Quétel, Braddock & Pike, 1990; Swiderski, 2008; Tampa, et al., 2014). Mercurial treatments had been in use since at least the Medieval period in Europe to treat many conditions (Hudson, 1961; Norn, Permin, Kruse, & Kruse, 2008; O'Shea, 1990; Parker, 1860; Quétel et al., 1990; Rosebury, 1971; Sartin & Perry, 1995; Swiderski, 2008), with even earlier documented experimentation and usage among the Greeks, Romans, and later among Arab and Persian populations in the Middle Ages (Norn et al., 2008; Thomann, 2015). Physicians treated patients with various mercurial methods, ranging from ointments/salves/frictions to fumigation/inhalation, injection, and oral medications (O'Shea, 1990; Quétel et al., 1990). Mercury (Hg) itself was typically dispensed as mercuric chloride ($HgCl_2$), calomel (Hg_2Cl_2), and cinnabar (HgS) for treatments (O'Shea, 1990; Quétel et al., 1990). Although the popularity of certain remedies appears to have shifted over time, mercurial treatments had by the 17th century become a favored therapy for those with syphilis (Quétel, 1990). Dosages were correspondingly modified over time, as high doses of mercury in the late 15th and 16th centuries gave way to lower dosages with reduced toxicity (O'Shea, 1990; Quétel et al., 1990; Siena, 2004); nevertheless, this general trend was likely complicated by sex- and status-based access to treatment (Siena, 2001; Zuckerman, 2017).

In addition to mercury, and despite recognition as a potent poison for many millennia, low doses of arsenic (As) had simultaneously been employed as a topical treatment for skin conditions by the ancient Greeks and Romans, and continued to be used–particularly between the 18th and 20th centuries–to alleviate a variety of ailments, including psoriasis, asthma, fevers, headaches, anemia, rheumatism, malaria, cholera, leukemia, pellagra, and treponemal disease (Jolliffe, 1993; Swiderski, 2008). Despite the development of less toxic and more effective arsenic-based treatments for syphilis such as Salvarsan (arsphenamine) in the early 20th century, mercury continued to be favorably used, often topically applied in combination with injected Salvarsan, and was even recognized as a cheaper alternative to antibiotics after the widespread adoption of penicillin in the mid-1940s (Jolliffe, 1993; O'Shea, 1990; Swiderski, 2008). Using inductively-coupled plasma mass spectrometry (ICP-MS), arsenic has been detected in the bones and hair of archaeological skeletons and mummies examined for evidence of metallurgical practices such as copper smelting (Oakberg, Levy, & Smith, 2000) as well as contamination from the natural environment (Arriaza et al., 2010). Arsenic thus provides a potentially useful analytical tool for examining its medicinal applications among past populations.

Because of the popularity of mercury and arsenic in treating treponemal disease for many centuries, it stands to reason that identifying these heavy metals in the skeletal tissues of those afflicted with the disease may provide an additional means by which to approach a differential diagnosis in skeletal remains from the past. Because these elements replace trace amounts of calcium within bone hydroxyapatite, they hold great potential for identifying individuals with treponematosis, even when pathological changes to bone have not occurred (Ávila, Mansilla, Bosch, & Pijoan, 2014; Lee, Kim, & Kwon, 2005; Rasmussen et al., 2015). Nevertheless, it is recognized that both mercury and arsenic were used to treat conditions beyond treponemal disease (Jolliffe, 1993; Swiderski, 2008), including leprosy (Demaitre, 2007:264). Therefore, such interpretations should be accompanied by other forms of supporting bioarchaeological evidence (e.g., treponemal lesions identified elsewhere at the site/region) and archaeological and historical contextual information. Moreover, while far less has been recorded on non-Western treatment strategies for treponematosis and other skin lesions, traditional remedies made from plants with known medicinal properties were used, including the *mūtokia* plant in Kenya (Dawson,

1987), a variety of plants in Uganda (Ssegawa & Kasenene, 2007); Indian tobacco, milkweed, and Solomon's Seal among indigenous groups in North America (Hutchens, 1992; Mooney, 1891); and sarsaparilla in South Asia (Hutchens, 1992). Subsequently, trace elemental analyses of mercury and arsenic will only be useful for certain regions and time periods.

Following a preliminary study by Yamada et al. (1995), in the last decade, bioarchaeologists have attempted to evaluate mercury (Hg) levels in bone and surrounding soils using various analytical techniques, including ICP-MS (Tucker 2007; Walser, Kristjánsdóttir, Gowland, & Desnica, 2018), laser ablation ICP-MS (LA-ICP-MS; Kępa et al., 2012), advanced mercury analyzer (AMA; Rasmussen et al., 2008), atomic absorption spectroscopy (AAS; Rasmussen et al., 2013, 2015), and pXRF (Zuckerman, 2016, 2017). However, it remains unclear how reliable results are from more recently developed instrumentation such as pXRF relative to established ICP-MS analyses of bone, as x-ray depth, complex microstructures, and diagenetic change can substantially affect pXRF results (Byrnes & Bush, 2016; Shugar & Mass, 2012). Additionally, "internally consistent" pXRF data are often presented without accompanying calibration curves developed using international reference standards or other reference materials, resulting in data that may be precise but not necessarily accurate, or valid but unreliable, and that correspondingly do not permit these results to be tested by others (Craig et al., 2007; Nazaroff, Prufer, & Drake, 2009; Speakman & Shackley, 2012:1435).

Due to these limitations, more experimental studies are necessary to develop standardized methods of the best practice for bioarchaeological applications involving instrumentation that can aid in the identification of mercury and arsenic in the skeleton. This research should include taking dual measurements (i.e., analysis using both ICP and pXRF; Bergmann, 2018) as well as using international standards or references to develop and improve calibrations for pXRF instrumentation (Speakman & Shackley, 2012). In taking such measures, bioarchaeologists will not only enhance our understanding of heavy metal uptake into the skeleton but also verify the reliability and comparability of elemental analysis on varying instruments. Research involving the uptake and distribution of Hg into skeletal systems is already underway, including an excellent experimental evaluation by Rasmussen et al. (2013) using AAS to identify variable Hg concentrations between cortical and trabecular bone, as well as finding cortical Hg concentration uniformity across both intra- and inter-element sampling for a single individual. Continued research on tissue uptake and instrumentation reliability is warranted to assess mercury treatment for treponemal disease in the past.

In addition, while substantial Hg contributions from environmental or occupational exposure are typically rare, they may complicate interpretations of intentional, medicinal uptake to treat conditions such as treponemal disease, particularly in areas with active volcanoes where atmospheric concentrations of mercury may be naturally high (Walser et al., 2018); when used in the manufacturing various items including hats, mirrors, lamps, and shoes (Katz & Krenkel, 1972; Lee, 1968); and where foods high in methylmercury, such as seafood, are consumed (Iyengar & Woittiez, 1988; Sheehan et al., 2014). Subsequently, control samples—including from surrounding soils, faunal bone, as well as other human skeletons with no outward expression of treponemal disease—must be analyzed alongside those individuals diagnosed with treponematosis to ensure that exogenous sources of mercury are not mistaken for treatment (Kępa et al., 2012; Rasmussen et al., 2013; Walser et al., 2018; Zuckerman, 2016). Moreover, as unaffected human skeletons may still represent victims of treponematosis who were treated with mercury but whose bones never developed diagnostic lesions, alternate controls (soil, faunal), as well as greater numbers of control human samples, are recommended (Wood et al., 1992; Zuckerman, 2017; see also section 6.3.5).

5 | USE OF DOCUMENTARY AND ICONOGRAPHIC EVIDENCE

Until the past several decades, much of the debate surrounding the origins and evolution of syphilis has relied almost exclusively upon documentary evidence. The foundations of both the Columbian and Pre-Columbian hypotheses lie upon a documentary pedestal, which has led to biased and often misleading conclusions (Baker & Armelagos, 1988; Crane-Kramer, 2001; Crosby, 1969; Dutour, Pálfi, Bérato, & Brun, 1994; Hackett, 1963; Harrison, 1959; Holcomb, 1934, 1935; Hudson, 1961, 1968; Luger, 1993; Powell & Cook, 2005b; Rosebury, 1992). In the absence of skeletal remains, literary material becomes a vital and essential resource; however, the dialogue has been dominated by a Western European perspective, with the nature of the original sources being problematic on many levels.

How do we move forward in the investigation of treponemal infection in terms of written, iconographic, and oral history evidence? While Europeans have devoted an enormous amount of literature to the origin of syphilis, most of the world has been essentially silent. Few written descriptions of the disease can be found in the literature of Asia, Africa, the Pacific, and the Americas. Descriptions of possible evidence of the disease complex in early texts from these regions are vague and difficult to interpret. Retrieving information from many regions of the world where no written language existed or where most people were largely illiterate is more challenging, but important resources can be found in the realms of both iconography and oral history. For example, pathography provides a valuable study of the artistic representation of the disease experience and has the added benefit of often reflecting the experiences of the general population rather than the elite (Giuffra & Fornaciari. 2018; Grmek, 2018). Sites like the church of St. Mary's in Kraków, Poland, where Veit Stoss created a large altar between 1477 and 1489 in which two sculpted faces show characteristics of CS (Grzegorczyk, Grzegorczyk, & Grzegorczyk, 2016), provide an important visual commentary of contemporary disease experience and perceptions.

The analysis of folklore, or vernacular culture, is a theoretically rich field, where scholars such as Guy Beiner have provided a sophisticated methodology for the investigation of oral/written data (Babcock, 1978; Bacchilega, 2012; Beiner, 2007; Burke, 2004, 2016;

Dundes, 2005; Finnegan, 2003; Rosenberg, 1986; Trouillot, 1995). This research emphasizes the importance of investigating both the oral and written stories, proverbs, riddles, and superstitions that can inform us about life in the past (Beiner, 2007). While there are significant challenges to the analysis of oral vernacular culture, it has the potential to contribute important new information about the presence of treponemal infection in the distant past. Such research will stimulate the development of new questions and provide a transformative new perspective on the human/disease experience throughout time and space. These tales often represent important oral recollections of actual historic events as experienced by the *volk* (the people, or folk) and constructed in a collective oral statement.

Further information regarding the presence of disease in the past can be accessed through an examination of indigenous botanical knowledge applied to the treatment of disease, which is often orally transmitted wisdom. Traditional peoples have a sophisticated knowledge of the plant species in their environments and have developed an array of medicinal uses for a variety of different plant species. The nomenclature associated with indigenous plant names and the traditional application of this botanical knowledge to the treatment of disease is a potential source of fruitful information. The ancient and geographically widespread nature of treponemal infection suggests that references to its treatment may be found in the pharmacopoeia of past or extant indigenous populations (see also Section 4.2.3).

Treponemal infection, particularly syphilis, has been a reviled and feared disease for centuries. This status marks syphilis as an issue for social commentary, not only through written documents, but also through artistic representations, and oral tales in many guises. It is time not only to reevaluate with a critical eye the written documents used to investigate the origins of treponemal infection, but also to include more fully the hitherto ignored but important sources of evidence—the pathographic and oral representations. The inclusion of these new data may play a significant role in illuminating the presence of the disease in areas without written language and may provide information regarding the disease experience of the majority of the population.

6 | PALEOPATHOLOGY

Most researchers would agree with Erdal's (2006:16) assertion that "[t]here is hardly any subject as controversial as syphilis in palaeopathology." The origin, evolution, and history of treponemal infection remains controversial, due in part to the variable quality of published data from skeletal analyses, including the use of a range of criteria for diagnosis and varying adherence to accepted criteria. Compared to many other parts of the world, a preponderance of work has been devoted to treponemal disease in North America (see Baker & Armelagos [1988]; Powell & Cook [2005b]; Williams, [1932] for extensive treatments of New World evidence). Less attention has been paid to the Old World in general, where data on treponemal disease in archaeological skeletal remains are concentrated in modern European countries, with limited evidence reported thus far in Africa, Australia, or much of Asia (Baker & Armelagos, 1988; Brothwell, 2005; Dutour et al., 1994; Harper et al., 2011; Meyer et al., 2002; although see Webb [1995:135–160] on Australia). The current status of evidence is reviewed briefly below.

6.1 | Diagnosing treponemal disease in human skeletal remains

General standards for recording pathological lesions in human remains exist (e.g., Buikstra & Ubelaker, 1994:Chapter 10; Roberts, 2017b; Roberts & Connell, 2004), as well as helpful volumes on paleopathology (e.g., Buikstra, 2018). Osteological database programs (e.g., Osteoware, https://osteoware.si.edu/; the Wellcome Osteological Research Database [WORD], accessed via https://www.museumoflondon.org.uk/collections/other-collection-databases-and-libraries/centre-human-bioarchaeology/about-osteological-database with methods delineated in Powers, 2012) also incorporate coding for pathology. Certain projects also have developed paleopathological recording systems (e.g., Steckel et al., 2018). Because some of these recording standards are not specific enough or focus on parts of the skeleton, however, lesions important for recognizing a particular condition, such as treponemal disease, may be overlooked, particularly if the analyst is not familiar with them (see Stodder [2012] for a review of issues concerning data analysis in paleopathology). For example, the codebook used for recording skeletal data in the Global History of Health Project (European module) focused on the cranial, nasopharyngeal, and tibial diaphyseal lesions expected for treponemal disease, but osteoperiostitis was also considered relevant (Steckel et al., 2018:14–15, 30–31; https://economics.osu.edu/sites/economics.osu.edu/files/Codebook-01-24-11-em.pdf; Steckel et al., 2018:Chapter 14). Due to the scale of this project, specific details concerning characteristics of lesions to be recorded were not provided, apart from caries sicca on the cranium—to a certain extent. Thus, it is important to recognize various aspects involved with analysis that affect the nature of the resulting data and their usefulness in the larger sphere of the global history of human health and, on the smaller scale, interpretations of the health of individuals, communities, and populations. A standard protocol must be built on realistic expectations of what skeletal and dental changes we are likely to see in imperfectly preserved human remains, especially in concert with the clinically documented frequency (or infrequency) of specific lesion types that characterize treponemal disease.

Much is known about skeletal lesions that arise in the secondary and tertiary stages of treponemal disease. Primary clinical studies (e.g., Akrawi, 1949; Csonka & Pace, 1985; Freedman & Meschan, 1943; Gerstl et al., 2009; Gjestland, 1955; Grin, 1952; Hackett, 1951; Mitjà, Hays, Ipai, Wau, & Bassat, 2011, Mitjà et al., 2011; Murray, Merriweather, Freedman, & de Villiers, 1956; Willcox, 1951) and recent overviews (e.g., Antal, Lukehart, & Meheus, 2002; Farnsworth & Rosen, 2006; Giacani & Lukehart, 2014; Koff & Rosen, 1993; Marks, Solomon, & Mabey, 2014; Meheus, 2005) include substantial information on skeletal lesions, their frequencies and patterning, and similarities among yaws, bejel, and syphilis. Paleopathologists, however, do

not always consult these sources, or use them selectively, and studies of diagnostic skeletal manifestations associated with documented treponemal disease such as those described by Hackett (1976) and Hillson et al. (1998) are sometimes ignored in favor of heavily criticized methods such as SPIRAL (Rothschild and Rothschild, 1995). Thus, little consistency currently exists in the differential diagnosis of treponematosis and the standards to which such diagnoses are held.

Because many of the lesions characteristic of treponemal disease are also found in other conditions, they have low specificity (i.e., the lesion occurs in multiple diseases). Lesions also differ in sensitivity, or the proportion of affected individuals who exhibit the lesion (Frangos, Lavranos, & Frangos, 2011; Hackett, 1976:102–103; Zuckerman et al., 2016). Periosteal reaction, for example, has low specificity but high sensitivity and, by itself, is not diagnostic of any specific condition (see Roberts, 1994:107; Weston, 2008, 2009, 2012). A particular type of lesion, therefore, must have high specificity, or be pathognomonic, to be useful as a diagnostic indicator. A pathognomonic lesion is one that occurs only in a single condition; such lesions, however, often have very low sensitivity so very few people develop it in their skeletons.

In treponemal infection, skeletal lesions occur in only the secondary and tertiary stages of disease (Grin, 1952:17–30; Hackett, 1951:9; Resnick & Niwayama, 1995:2496–2501). Age of onset (primary infection) for yaws is typically in children less than 15 years of age, between ages 2 and 15 for bejel, and in older age groups for syphilis (Giacani & Lukehart, 2014:Table 1). Periosteal reaction and osteitis affect the long bones and proximal phalanges in the secondary stages of both yaws and bejel (Grin, 1952; Hackett, 1951; Giacani & Lukehart, 2014). Approximately 10% of untreated patients with yaws develop tertiary lesions (Giacani & Lukehart, 2014). Gummatous lesions produce gangosa (posteriorly located perforated palate and nasal cavity changes, including saddle nose) in tertiary yaws (Hackett, 1951). Periosteal new bone formation of the rhinomaxillary region causes goundou in secondary and tertiary yaws (Hackett, 1951; Mafart, 2002). Chronic periosteal new bone formation on the anterior tibia also produces saber shin. Tertiary skeletal manifestations of yaws, bejel, and syphilis are all quite similar (e.g., Akrawi 1949; Grin 1952:19*ff*.; Hackett 1951:181–182), including gangosa, goundou, and saber shins. Cranial lesions beyond those involving the readily observable rhinomaxillary region are rarely reported in the clinical literature.

In CS, 10 to 30% of those affected develop the diagnostic Hutchinson's incisors and Moon's molars (Hillson et al., 1998; Lipski & Przylipiak, 1959; Svejda, 1952). Mulberry, or Fournier's, molars occur in CS, but they are not diagnostic because they also develop in other conditions (Hillson et al., 1998; Iouannou, Sassani, Henneberg, & Henneberg, 2015; Iouannou, Henneberg, & Henneberg, 2017). Beyond these dental alterations, macroscopically observable skeletal lesions in both early (onset under 2 years of age) and late (age 3–30 years) stages of CS are indistinguishable from those observed in other forms of treponemal infection (see, for example, Crissey & Denenholz, 1984; Rasool & Govendor, 1989), with the possible exception of Higoumenakis' sign of the clavicle (Frangos et al., 2011). Extensive clinical studies show that the radiologically detectable lesions associated with CS (including Wegner's sign and Wimberger's sign) are age-related and ephemeral (Brion et al., 1991; Crissey & Denenholz, 1984:156–157; McLean, 1931; Rasool & Govender, 1989).

Clinical studies also demonstrate that, like sexually acquired syphilis, transplacental transmission can occur in yaws and bejel, resulting in miscarriage, stillbirth, or CS (e.g., Akrawi, 1949:118; Grin, 1952:31–32; review by Román and Román, 1986). Despite the demonstrated occurrence of congenital transmission in yaws and bejel, CS is typically conceived as a proxy for the presence of sexually acquired syphilis in a mother (e.g., Harper et al., 2011:102).

Because clinical studies rely on radiographic evidence to document bone lesions, it is essential in developing diagnostic criteria to observe skeletons from people with documented treponemal infection, preferably in patients who were not treated. Publications in 1976 by two medical doctors, Cecil J. Hackett and R. Ted Steinbock, are landmarks in this endeavor. Prior to Hackett's (1976) work, the only alteration identified as pathognomonic of syphilis was caries sicca, initially described as manifesting nodular lesions by Virchow in 1896 and subsequently by Williams in his 1932 review (Hackett 1976:19–20). Hackett (1976) elaborated on these changes, creating a series of line drawings illustrating the sequence of destruction and healing. Hackett (1976:63–66) also added healed nasopalatine destruction as a diagnostic cranial lesion, which he differentiated from changes found in leprosy. For the infracranial skeleton, a thickened cortex with focal destruction (superficial cavitation that does not penetrate beyond the original cortex) was also deemed diagnostic, but additional changes in long bones that Hackett (1976:103–104) found suggestive were designated "on trial" as diagnostic criteria until they could be tested further.

Surprisingly, these "on trial" criteria have not been tested using other identified skeletal collections in different geographical regions as Hackett (1976) recommended. Confirmation of these less severe infracranial manifestations would aid the diagnosis of treponemal disease and re-evaluation of published evidence. Because Hackett (1976) used European museum collections, predominantly pathological anatomy assemblages on which to develop diagnostic criteria, it is likely that only the most severe and fatal examples of syphilis in the skeleton were considered. Additionally, skulls were typically separated from other bones that were selectively retained, limiting observation of lesion patterning (e.g., unilateral or bilateral occurrence) throughout the skeleton. No examples of yaws or bejel were included in these collections, although Hackett (1976:102–104; Appendix IX) did examine collections of archaeological skeletons in Australia and the United States to test the diagnostic criteria on undocumented remains.

Skeletal patterning of lesions was a major emphasis for Steinbock (1976), who introduced the skeletal diagrams showing affected bones and areas of bones that are now commonly used in paleopathology. This work, however, promoted the idea that yaws, bejel, and syphilis could be distinguished based on the frequency of particular skeletal elements affected (e.g., cranial vault more commonly affected in syphilis, and tibiae in yaws). Contrary to this suggestion, however, Steinbock (1976:111, 139, 143) stated several times that the lesions produced are identical.

Based on the idea that the frequency of a lesion type could differentiate yaws, bejel, and syphilis, Rothschild & Rothschild (1995) advanced the SPIRAL technique. This method involves recording Yes or No for six criteria: "**S**aber shin without periostitis, **P**repubescent, **I**nvolvement of tibia unilaterally, **R**outinely affected hand or foot, **A**verage number of bone groups affected ≥ 3, **L**acking periostitis but flattened" (Rothschild & Rothschild, 1995:Table 4). This work is problematic on several levels (see the thorough critiques by Cook & Powell, 2005:469-474, 2012; and Heathcote et al., 1998). Briefly, Rothschild & Rothschild (1995) used four skeletal samples in their study, three of which were archaeological; the fourth was a documented collection for which only individuals identified as having had syphilis were included. Furthermore, they provide no clear descriptions or images to demonstrate the changes they consider, so their work cannot be replicated by other investigators. The circularity of SPIRAL, therefore, obviates its use for diagnosing treponemal infection and calls into question publications that use this method.

Harper et al. (2011) contributed an ordinal scoring system following Hackett's (1976) diagnostic criteria in a manner originally suggested by Powell & Cook (2005b:6), which categorizes involvement as pathognomonic, strongly suggestive, or "consistent with but not specific" to the disease in question. This scoring system is a more objective, standardized approach for recording skeletal lesions reflecting treponemal infection. This system does not appear to have been adopted in most recent publications. Unfortunately, some of the supposedly diagnostic criteria on which their scores of 2 on a 3-point scale for CS lack specificity (e.g., mulberry molars) or any diagnostic value (e.g., flared scapulae, which were discarded as useful discriminators by clinical investigators long ago). The scoring criteria in Harper et al. (2011) thus need refinement.

Preservation, of course, also will affect the ability to make a diagnosis. We suggest that individuals with at least one tibia, and one other long bone, or with the cranium preserved, are minimally observable for the presence or absence of treponemal disease. Even where these bones are preserved, significant abrasion of the cortex may preclude close observations of change on the bone surface. Lesions should be recorded as present, absent, or unobservable on the long bones, the bones of the hands and feet, and the axial skeleton, including observation of diaphyseal thickening, nodes or localized expansions, periosteal new bone formation, striations or vascular markings, osteolytic or resorptive lesions, and bowed diaphyses. On the cranium, the caries sicca sequence should be scored, including stellate scars or shallow crater lesions on the vault bones, and resorptive lesions with sclerosis in the nasomaxillary area. Table 1 lists the skeletal changes typically associated with treponemal infection and their diagnostic weight, expressed as consistent with treponemal infection, strongly indicative of treponemal infection, and pathognomonic. Weighted diagnostic systems have been advanced for other conditions (e.g., scurvy; see Brickley & Ives, 2008; Snoddy et al., 2018). The observations in Table 1 form the basis for the suggested approach to recording the presence (and absence) of treponemal disease (a recommended recording form for keying an investigator into these alterations is included in Supporting Information).

Defining the extent of completeness and degree of preservation that makes an individual skeleton observable for the presence or absence of treponemal disease is a more complex task. The documentation of observability of each skeletal change in a bone or element group (e.g., long bones), combined with the use of a clearly defined, but not overly rigid threshold of observability for each individual, are the essential foundations for identifying treponemal disease in a skeletal sample. If the caries sicca sequence is the only universally accepted pathognomonic change, then any skeleton without a well-preserved cranium could be unobservable. At the opposite extreme, use of criteria like SPIRAL potentially could deem an individual who is represented by only a single tibia observable. Clearly, the appropriate course is between these extremes. Recording such lesions in the entire skeletal assemblage being analyzed is, of course, necessary for investigating the paleoepidemiology of treponemal infection beyond simply counting people with pathognomonic lesions.

Of major import is determining which, if any, combinations of bony changes with high and lower specificity can together provide a confident diagnosis of treponemal disease. This issue relates to the significance attached to the more generalized changes on long bones. As Hackett (1976:89) laments, "There is unfortunately no 'accredited' diagnosis, such as Virchow's caries sicca, to provide a starting point for diagnostic criteria of syphilis in long bones." Long bone changes that may also occur in other conditions (i.e., have moderate specificity), likely include those that Hackett calls diagnostic criteria "on trial." Systematic recording of such "on trial" lesions is nevertheless important, not only for differential diagnosis of specific pathological conditions, but for gauging the extent of treponemal disease in a past community. Avoiding overdiagnosis of a condition is desirable. Limiting the diagnosis of treponematosis to pathognomonic lesions, however, will underestimate the number of affected individuals. Paleoepidemiology, as delineated by Boldsen & Milner (2012), presents a potential approach for building on Hackett (1976). The probabilistic models developed for other conditions, including leprosy (Boldsen, 2001; Boldsen & Milner, 2012) and tuberculosis (Pedersen, Milner, Kolmos, & Boldsen, 2019), take such an approach. Similar work is needed to move forward with a less restrictive, yet still conservative, method of quantifying treponematosis in past populations.

6.2 | Current status of New World evidence for treponemal disease

Evidence of treponemal disease in North American skeletal remains has been described since the 1870s (Jones, 1876) and soon after was reported in Central (e.g., Gann, 1901) and South America (Parrot, 1879:698). The occurrence of this disease in the Americas prior to European contact is well-established and has been reviewed thoroughly multiple times (e.g., Baker & Armelagos, 1988; Powell & Cook, 2005b; Williams, 1932). Consequently, this evidence will not be treated extensively here. Additional publications over the past 15 years, however, are increasing our understanding of disease distribution and the components of communities affected.

TABLE 1 Recording treponemal infection: systematic observations (present, absent, unobservable) and diagnostic status of skeletal changes

Element	Skeletal changes	Status	Citation
Nose and palate			
Palate	Abnormal porosity, resorption/perforation.	C/P	Hackett (1976:63-66)
Nasal cavity	Resorption, smooth lateral walls.	C/P	Hackett (1976:63-66)
Palatal and nasal bones	Extensive palatal and nasal resorption with healing.	P	Hackett (1976:63-66); Manchester (1994:80)
Rhinomaxillary area	New bone formation.	C	Hackett (1976:63-66)
Frontal and parietal bones: Hackett's sequence of cranial lesions			
Hackett 1,2. Clusters of pits. One or more clusters of pits in defined areas.		ST	Hackett (1976:31)
Hackett 3. Superficial cavities with concave walls, sharp edges; base of cancellous bone.		ST	Hackett (1976:31)
Hackett 4. Circumvallate cavities surrounded by a depression or wall-like ridge; minor endocranial changes.		ST	Hackett (1976:31)
Hackett 5. Radial scars: lines radiate from the center outward; new bone fills shallow depression; rim around margin eventually flattens; there may be endocranial bone formation.		ST	Hackett (1976:31)
Hackett 6. Serpiginous (irregular) cavities with irregular sharp margins and concave walls. They appear to spread, especially healing over in one portion while continuing to advance in another.		P	Hackett (1976:42)
Hackett 7. Nodular cavitation: sharp rims, rounded; nodules separated by open superficial cavities.		P	Hackett (1976:42)
Hackett 8. Caries sicca: healed stage; nodules are larger/crowd together; endocranially, bone changes do not develop the gross irregularities of the ectocranial surface. Serpiginous and nodular cavitation and caries sicca changes usually cover the whole frontal and most of the parietal bones, with the sutures, usually spared.		P	Hackett (1976:42)
Dental changes			
Incisors	Hutchinson incisors (usually bilateral). Peg/screw-driver shaped tooth with crescentic notch at the incisal edge. Congenital syphilis.	P	Hillson, Grigson, & Bond (1998); Ioannou, Henneberg, & Henneberg (2017:198)
First permanent molars	Moon's Molars M1 s: Dome-shaped, with small clustered cusps. Congenital syphilis.	P	Hillson, Grigson, & Bond (1998); Ioannou, Henneberg, & Henneberg (2017:198); Moon (1885:459)
First permanent molars	Mulberry/Fournier Molars Many nodules or tubercles on the occlusal surface. Congenital syphilis.	C	Hillson, Grigson, & Bond (1998); Iouannou, Henneberg, & Henneberg (2017)
Any teeth	Mercury treatment: expanses of pitted, rugged or missing enamel.	ST	Iouannou et al. (2015, 2017); Iouannou, Hunt, & Henneberg (2017), Radu & Soficaru (2016)
Infracranial changes			
Clavicle	Higoumenakis' sign: expanded medial end. Late sign of congenital syphilis, appears after 15 years.	C	Frangos et al. (2011)
Thoracic or lumbar vertebrae	Aortic aneurysm (outward bulge of a blood vessel wall caused by weakening): resorption defect, lateral aspect (usually left) of one or more vertebral bodies (could occur in thoracic/lumbar vertebrae). Tertiary treponematosis.	C	Castro et al. (2016); Roberts & Buikstra (2019:391)
Articular surfaces of knee, ankle, hip, and elbow joints	Charcot Joint: destruction of the articular surface, usually bilateral, with severe eburnation and new bone formation; represents absent sensation. Tertiary stage/neurosyphilis.	C	Hackett (1976:106); Steinbock (1976:136)
Hand and foot bones	Dactylitis (inflammation of a finger or toe): diaphyseal enlargement of one or more metacarpals or metatarsals, or phalanges.	ST	Rasool & Govender (1989)
Long bones: shape changes, surface changes, bone formation, and destruction			
Periosteal reaction (pitting/porosity/new bone formation); many bones can be affected, with longitudinal striae and/or plaques (new bone formation).		C	Hackett (1976:76-77)

(Continues)

TABLE 1 (Continued)

Element	Skeletal changes	Status	Citation
Enlarged diaphysis with a thickened cortex throughout the bone.		C	Hackett (1976:101)
Enlarged diaphysis with anteroposterior bending (as in "sabre shin").		ST	Hackett (1976:101)
Enlarged bone with smooth healed (lamellar bone) areas and a mix of striation and rippling. Unilateral.		C	Hackett (1976:82)
Enlarged bone with smooth healed (lamellar) bone areas and a mix of striation and rippling. Bilateral. "Diagnostic criterion on trial."		ST	Hackett (1976:82, 86)
Node(s): local, clearly defined, enlargements of bone; single or multiple; associated with a rugose surface (rippling and/or trabeculation); no bone destruction. Unilateral.		C	Hackett (1976:85)
Node(s): local enlargements of bone; single or multiple; associated with a rugose surface (rippling and/or trabeculation); no bone destruction. Bilateral. "Diagnostic criterion on trial."		ST	Hackett (1976:87-88)
Node(s): local enlargements of bone; single or multiple; rugose surface (rippling and/or trabeculation), and focal superficial cavitation. Unilateral.		ST	Hackett (1976:93-95)
Node(s): local enlargements of bone; single or multiple; rugose surface (rippling and/or trabeculation), and focal superficial cavitation. Bilateral.		P	Hackett (1976:93-95)
Osteomyelitis (cloaca, sequestrum, involucrum, and enlarged bone). Secondary to treponemal infection.		C	Hackett (1976:91-93; 95-96)
Radiological signs of early congenital syphilis (must be distinguished from taphonomic damage)			
Tibiae in newborns and infants.	Wimberger's sign: localized bilateral metaphyseal destruction of the medial proximal ends. Early congenital syphilis. Ephemeral.	P	Ghadouane et al. (1995); McLean (1931); Rasool & Govender (1989)
Long bone metaphyses in newborns and infants	Wegner's sign: metaphyseal destruction with saw-tooth erosion. Early congenital syphilis. Ephemeral.	P	Brion et al. (1991); Ghadouane et al. (1995); Greenberg & Bernal (1992); McLean (1931)
Long bones and other elements newborns and infants	Severe periostitis with cloaking. Early congenital syphilis. Ephemeral.	C	McLean (1931); Rasool & Govender (1989)
Long bones and other elements newborns and infants	Diffuse rarefaction or destruction. Early congenital syphilis. Ephemeral.	C	Brion et al. (1991); McLean (1931); Rasool & Govender (1989)

Abbreviations: C, consistent with treponemal infection but not pathognomonic; ST, strongly suggestive; P, pathognomonic.

With the publication of systematic regional reviews in *The Myth of Syphilis* (Powell & Cook, 2005b), additional research (largely from the eastern and midwestern U.S.) has considered environmental, cultural, and temporal differences in the distribution of treponemal disease. For example, Hutchinson & Richman (2005) examined 25 skeletal series with a total of 2,410 individuals across coastal and mountainous zones of Florida, North Carolina, Alabama, and Tennessee for evidence of cranial and dental lesions associated with treponemal disease from the Archaic period (8000–1000 B.C.) to the protohistoric period (A.D. 1500–1600). They found minimal regional differences, but disease frequency increased through time, as noted by several contributors to Powell & Cook (2005b; e.g., Baker, 2005; Powell, Jacobi, Danforth, & Eisenberg, 2005; Wilson, 2005; and detailed in the summary chapter by Cook & Powell, 2005). These results support Baker & Armelagos's (1988:719) conclusion that high frequencies of treponemal disease would "reflect population nucleation, particularly where sociopolitical organization allowed for widespread exchange of material goods and infectious diseases." Similar patterning has been established in west-central Illinois (e.g., Cook, 2005; Mosher, Smith, Albrecht, & Salaka, 2013) and in Tennessee, where Smith (2006) demonstrated that treponemal disease was infrequent in Archaic period remains from the western Tennessee River Valley but increased in more sedentary Early Woodland (500 B.C.–A.D. 0) communities even though subsistence continued to be based on gathering and hunting. Further work by Smith & Betsinger (2013) demonstrated differences in treponemal disease frequency in Late Woodland horticultural versus more sedentary Late Mississippian agricultural groups in East Tennessee, and a lower frequency among elites compared to nonelites (Smith, Betsinger, & Williams, 2010; see also Betsinger & Smith, 2019:245). Treponemal disease frequency, thus, may be related to more than population size and density or degree of sedentism, including factors such as sociopolitical organization, physical structure of settlements, or ethnic differences (Betsinger, Smith, Thorson, & Williams, 2017). Continuing explorations of these factors in other regions of North America and other parts of the globe are crucial to unraveling the effects of treponemal disease on past communities.

6.3 | Current status of Old World evidence for treponemal disease

In attempting to synthesize skeletal data for treponemal disease for the Old World, the published literature was surveyed for papers on

treponematosis (primarily in *American Journal of Physical Anthropology*, *HOMO*, *International Journal of Osteoarchaeology*, and *International Journal of Paleopathology*), along with Google Scholar searches in several languages, and evidence presented in Dutour et al. (1994). Because Europe has received the most intensive investigation, we specifically targeted this region to evaluate whether our understanding of treponemal disease has changed in the early 21st century. To ensure comprehensive coverage, people working in every European country were contacted for additional information that may exist in unpublished gray literature reports, in local or regional publications (e.g., bioarchaeological and archaeological journals), or through observations on recently excavated skeletons that have not been published yet (through personal communications). Contacts included some scholars working in commercial (contract) archaeology. We also considered unpublished reports, conference abstracts, and research theses to be of potential use in such an endeavor, contrary to Harper et al. (2011:105), because their assumption that "[t]he possibility of overlooking a credible case appears relatively small" is incorrect in our collective experience. Other synthetic bioarchaeological studies have critically reviewed gray literature (e.g., Roberts and Cox, 2003), demonstrating the utility of its inclusion. It was not feasible, however, to do a thorough search of gray literature for the entire Old World for this study. This summary, therefore, is not intended to be an exhaustive list of all reported evidence, but a synthesis of the strengths and weaknesses found in the literature and to illustrate trends concerning the reported distribution of treponemal disease.

6.3.1 | Europe

Synthesis of the data for Europe shows that most present-day countries have some reported evidence of treponemal disease across the longitudes and latitudes (Figure 2). Reports were evaluated to determine if evidence presented was reliable (i.e., contained thorough descriptions of lesions present and differential diagnoses), questionable (i.e., contained insufficient descriptions of lesions present or differential diagnoses), or may be useful but requires re-evaluation of the original skeletal remains (i.e., presents evidence that could potentially include treponematosis within a skeletal assemblage). Categories of questionable evidence and evidence that may be useful both require a re-evaluation of the skeletal remains to verify evidence of treponemal disease. Such reanalysis was beyond the scope of this review.

In Albania, Armenia, Bulgaria, Cyprus, the Czech Republic, Germany, Kosovo, Macedonia, Malta, Montenegro, Serbia, Slovakia, and Switzerland, no evidence, or only questionable or potentially useful evidence, was found. Surprisingly, little evidence exists from Austria, Denmark, France, Germany, the Netherlands, Poland, Russia, and Spain, countries that all have a long history of paleopathology research (Buikstra & Roberts, 2012). Most European evidence is from the late Medieval (12th–16th centuries A.D.) to post-Medieval (A.D. 1550–1850) periods, with some earlier evidence reported (e.g., Cole & Waldron, 2011, 2012, 2014; Henneberg & Henneberg, 1994; Henneberg, Henneberg, & Carter, 1992). Other evidence extends into the late 19th to early 20th centuries (e.g., Rodrigues Lopes, 2014). Most of the evidence is provided with a date range (as is common for archaeological cemetery excavations). Where dates are reported, sites and skeletons were most often dated using archaeological evidence, such as grave inclusions or the coffin wood. Radiocarbon dates are rarely reported and typically do not consider any potential reservoir effect or calibrate according to any offset that may be justified (see Section 4.1.2; see also Bayliss et al. [2003] and Philippsen [2013]), but there are occasional exceptions (e.g., Mays et al., 2003; Mays, Vincent, & Meadows, 2010; Lopez et al., 2017).

If any diagnosis more specific than treponemal disease was made, it was usually deemed to be syphilis, although it was sometimes unclear whether such attributions meant sexually acquired or endemic syphilis (bejel). Other than Henneberg & Henneberg (1994), however, there are no explicit suggestions that bejel or yaws were evident in European skeletal remains. Based on the published literature, CS is being diagnosed more frequently in recent years (e.g., Gaul, Grossschmidt, Gusenbauer, & Kanz, 2015; Ioannou, Henneberg, & Henneberg, 2017; Tomczyk, Mankowska-Pliska, Palczewski, & Olczak-Kowalczyk, 2015), perhaps because the diagnostic criteria are quite specific and have been described more recently in an accessible journal (Hillson et al., 1998). We note, however, that care needs to be taken in diagnosing CS using the presence of mulberry molars alone (e.g., Lauc et al., 2015) because of the low specificity of this lesion (see Section 6.1).

Most of the sites or samples reported had small numbers of individuals affected; frequently, only one individual was reported. A few studies describe individuals with treponemal disease within the context of large skeletal samples. Walker et al. (2015), for example, described 25 affected skeletons within a very large sample of 5,387 individuals from Medieval St. Mary Spital in London. Henneberg et al. (1992) and Henneberg & Henneberg (1994) studied a sample of 272 ancient Greek skeletons in which they found signs possibly indicating treponemal disease in 47 skeletons, including two with dental lesions of CS.

6.3.2 | Africa

In Africa (Figure 2), there is a dearth of secure evidence from antiquity (with only a few reports advanced), although many collections of human remains from Egypt and Sudan, particularly, have been investigated for paleopathological evidence (Baker and Judd, 2012; Buikstra, Baker, & Cook, 1993; Strouhal, 1994). Buikstra, Baker, & Cook (1993:24–25, 36–38) reviewed all published purported evidence of treponemal disease among ancient Egyptians and discussed the dismissal of early suggested evidence by Smith (1908) and Pales (1930). In fact, much negative evidence is presented (see Buikstra, Baker, & Cook, 1993:38). Strouhal (1994:152) reviewed much of the same literature and reiterated the "nonexistence of sound evidence for syphilis in ancient Egypt," including "the lack of any mention of syphilitic symptoms in Ancient Egyptian medical papyri."

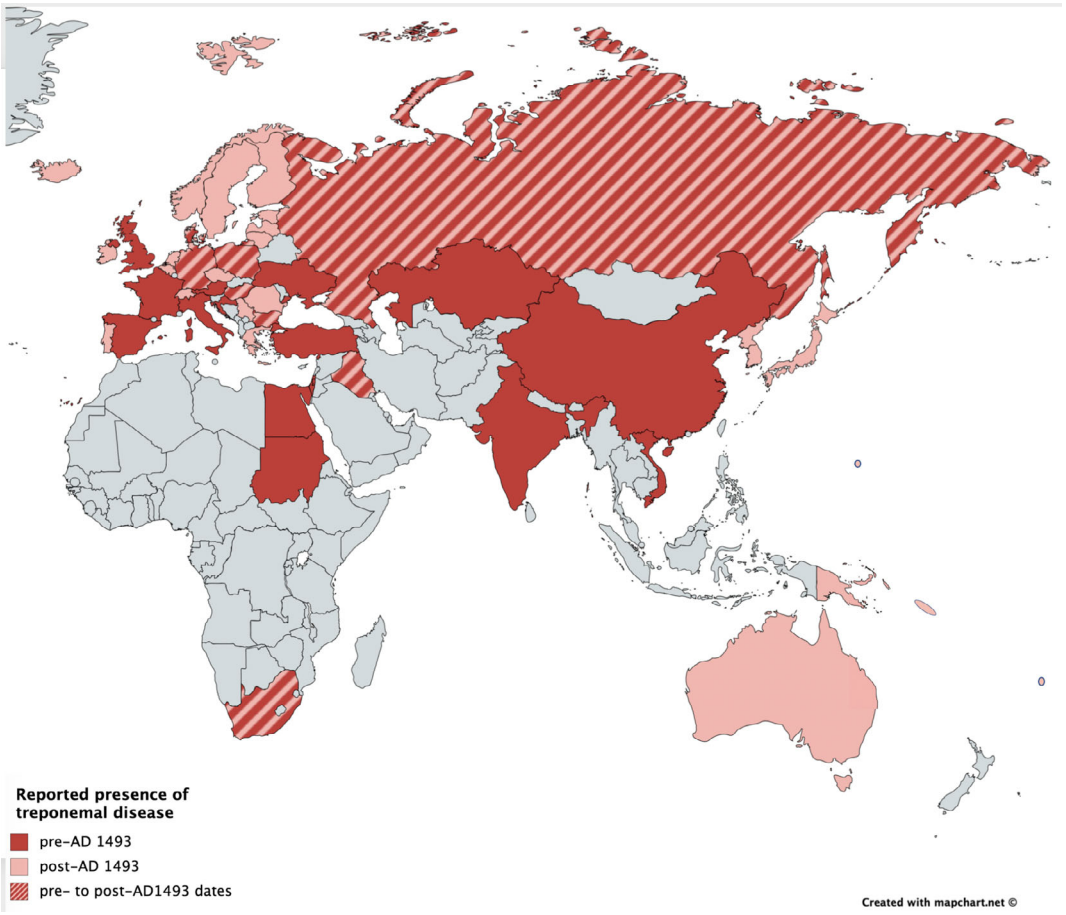

FIGURE 2 Presence of treponemal disease reported outside of the Americas in the surveyed paleopathology literature. For countries shown in gray, no reported evidence was discovered in this survey but may exist in material that was not accessed. Dates reported were derived from radiocarbon and/or standard archaeological methods

In regard to reported evidence published after the reviews conducted by Buikstra, Baker, and Cook (1993) and Strouhal (1994), Rothschild & Rothschild (1996:12) reported "[p]eriostitis compatible with Bejel," including bilateral tibial manifestations, in 24 Meroitic (19%) and 5 Ballana (24%) period individuals from the Semna South remains housed at Arizona State University. The site is misidentified in the article as "Sema South." Rothschild & Rothschild (1996:12) also stated that "[s]abre shin deformity was common, affecting 12-40% of affected Nubians." This claim is remarkable considering that neither Chuck Merbs, original curator of this collection for several decades, nor the present curator of ASU's Nubian collections (BJB) has observed any such evidence. Of additional note, Ortner (2003:313-316) misidentified remains from George Reisner's early 20th-century excavations at El Kurru, Sudan, as coming from "El Kurrew, Egypt"—an error repeated in subsequent literature (e.g., Harper et al., 2011). Repetition of such mistakes reinforces the necessity of investigating excavation history and site/burial context prior to publishing.

Despite the unsupportable claims made by Rothschild & Rothschild (1996) concerning the presence of treponemal disease in Sudanese Nubians, it is especially notable that they reported no evidence in 61 individuals from West African sites in northern Mali and Mauritania. Skeletal remains of *H. erectus* from the Koobi Fora Formation, East Lake Turkana, in Kenya (1.6 ± 0.1 million years old) are claimed by Rothschild, Hershkovitz, & Rothschild (1995) as evidence that treponemal infection arose in Africa. This contention is based upon a very brief description of the periosteal reaction observed on the long bones of KNM-ER 1808, with no supporting images. On the basis of such nonspecific lesions, this claim cannot be upheld.

In southern Africa, evaluation of skeletal series from the 19th-early 20th centuries revealed clear evidence of treponemal disease (e.g., Botha & Steyn, 2014), while only one earlier skeleton (dating between A.D. 1000 and 1300) has been suggested to have treponemal disease (Steyn & Henneberg, 1995). Interestingly, skeletal remains from a large series of chimpanzees and gorillas collected in west-central Africa between 1906 and 1933 revealed macroscopic and radiological evidence of treponemal disease in many individuals, indicating that it was likely endemic in African ape populations at least a century ago (Lovell, Jurmain, & Kilgore, 2000). This skeletal evidence may have implications for understanding the exchange of *T. pallidum* between human and nonhuman primates historically, and any DNA samples that might be obtained in the future could provide

historical depth for genomic data concerning strains in Africa (see Section 3.3).

6.3.3 | Asia and the Pacific Islands

In a review of the Asian evidence for treponemal disease, Vasalu (1994:154) indicated that "about 70% of the skeletal remains were yet to be reported and the rest were not studied for paleopathological aspects." Since then, more evidence has been forthcoming, but it is still sparse. Within Asia (Figure 2), treponemal disease has been reported in archaeological skeletal collections from Turkey, Israel, Iraq, Russia, Kazakhstan, India, Vietnam, China, and Japan (Harper et al., 2011:Table 1). In the Pacific Islands, evidence is reported in Micronesia (especially Guam, see below), Tonga in Polynesia (Buckley, 2000; Pietrusewsky, 1969; Pietrusewsky Douglas, Ikehara-Quebral, & Lauer, 2019), and Papua New Guinea and other parts of Melanesia (see Buckley & Oxenham [2016] for a review of skeletal remains from the Pacific Islands).

In Turkey, one skeleton from the 7th century A.D. was identified as afflicted with syphilis (Alpaslan & Bekmez, 2015) and another from the 13th century showed lesions of CS (Erdal, 2006). Cranial lesions in one of 68 crania from Safed, Israel, were consistent with treponematosis and were originally AMS radiocarbon-dated to A.D. 1290–1420 (95.4% confidence; Mitchell, 2003:118). Due to a laboratory error, repeat testing yielded a revised calibrated date of A.D. 1424–1479 A.D. with 95.4% confidence (Mitchell, 2009). Lesions in two skeletons from the site of Tell Gubba in the Himran Basin of Iraq were suggested to show bejel by Wada, Ikedea, & Suzuki (1987). These two individuals were dated to the Islamic period, with no specific date range provided.

Human skeletal evidence from India (3000–2000 B.C., 1000–700 B.C.), the Mariana Islands (A.D. 704–1521), Papua New Guinea (A.D. 1000–1600), Solomon Islands (A.D. 1530–1700), and subtropical Japan (A.D. 1600–1870) was considered by several authors to represent yaws, which is still endemic in these regions (e.g., Buckley & Tayles, 2003; Heathcote et al., 1998; Hernandez & Hudson, 2015; Lukacs & Walimbe, 1984; Pietrusewksy, 1976; Pietrusewsky, Douglas, & Ikehara-Quebral, 1997; Stodder, 1997; Trembly, 1996; Vasulu, 1993, 1994). Another skull from Iron Age India (last two centuries B.C.) was diagnosed more generally with treponematosis (Rao, Vasulu, & Rector Babu, 1996), as was new evidence from India reported by Mushrif-Tripathy (2019), from China dating between 770 and 221 B.C. (Pechenkina, Chen, & Fan, 2017), and from the Neolithic site of Man Bac in Vietnam (Buckley, Vlok, Domett, Trinh, & Oxenham, 2019), yet to be published fully.

Large skeletal series were frequently examined in Asia and the Pacific Rim. Trembly (1996), for example, included 481 skeletons from Guam, with eight individuals showing treponemal lesions. Suzuki, Matsushita, & Han (2005) examined 293 commingled individuals from China (500 B.C.–A.D. 150) and discussed two individuals thought to demonstrate bejel/endemic syphilis. Lesions found in 89 of 923 adult crania examined from Japan (A.D. 1603–1868) and two individuals from China (200 B.C.–200 A.D. and A.D. 960–1279), were thought by the authors to represent syphilis (Suzuki, 1984; Zhang, 1994). Recent work demonstrating the spread of syphilis into Korea at the end of the 19th century (Shin et al., 2018; Woo, Kim, Lee, Cho, & Pak, 2019) is also of interest in evaluating treponemal disease dissemination throughout Asia.

6.3.4 | Australia

Hackett (1976) discussed the patterning of treponemal disease in skeletal remains of native Australians, indicating that some remains he examined likely predated European contact (i.e., before A.D. 1770). Like Hackett (1976), Webb (1995:135–160) suggested that endemic forms of treponemal infection (yaws and bejel, the latter known as treponarid in Australia) were present prior to European contact. Domett, Wallis, Kynuna, Kynuna, & Smith (2006) described an individual from an archaeological site in northwest Queensland with diagnostic long bone changes of treponemal disease that they suggested were most likely treponarid. AMS radiocarbon dating and archaeological evidence place the burial between 1660 and 1890, with first European contact in this area in 1860–1861 (Domett et al., 2006:33).

6.3.5 | Observed trends

Previous reviews by Roberts (1994:106–108) and Harper et al. (2011:126) have discussed the shortcomings of extant reports. We reiterate many of these same issues in highlighting some of the good and poorer practices that are apparent in the available data, particularly in more recent reports. Additionally, we go beyond these prior reviews to synthesize trends in the surveyed reports and potential patterns of distribution that warrant more attention in future research.

Overall, the majority of the skeletal evidence in all the reports surveyed was observed macroscopically. Some investigators use imaging techniques, including plain film radiographs (e.g., Tomczyk et al., 2015) and computed tomography (e.g., Lopez et al., 2017). Very few include histological (e.g., Von Hunnius, Roberts, Boylston, & Saunders, 2005) or biomolecular analyses (e.g., Schuenemann et al., 2018). Lesions observed were sometimes described thoroughly (e.g., Walker et al., 2015), although many reports do not contain enough detail for independent evaluation, and some provide very little information. Supporting images were very helpful in assessing diagnoses (e.g., Lauc et al., 2015), but images were not always included or there was an insufficient number (e.g., Šlaus and Novak, 2007). In many cases, images were often of poor quality (e.g., Buzhilova, 1999: Rao et al., 1996; Suzuki et al., 2005; Zhang, 1994).

Some articles, including more recent publications, did not include information on the methods used to diagnose the pathology, particularly the bone changes that the author(s) believed to represent treponemal disease. However, many authors did present differential diagnoses, but sometimes they clearly had a preconceived diagnosis of treponemal disease. Some authors were more hesitant than others in being definitive about a diagnosis; use

of the more general designation of treponematosis rather than a specific form of treponemal infection has become more common in the past several decades and is a welcomed trend. In many studies, nonspecific periosteal lesions on long bones contributed to a diagnosis despite more recent work that should have discouraged continued overdiagnosis of such lesions (e.g., Weston, 2008, 2009, 2012). Hackett (1976) was referred to in many papers; others referenced Ortner (2003), who it should be noted followed Hackett (1976), or Aufderheide and Rodríguez Martín (1998). As mentioned previously, clinical studies frequently were not referenced. For example, no work referred to the massive Oslo study of untreated syphilis (Gjestland, 1955; see also the review and summary of this work by Harrison [1956]) or reports (e.g., Rockwell, Roof Yobs, & Moore, 1964) from the notorious Tuskegee syphilis study (all records from this study are held at the U.S. National Archives, http://catalog.archives.gov/search?q=Tuskegee%20syphilis%20study; see also the Centers for Disease Control and Prevention for information on this study and its ethical violations at https://www.cdc.gov/tuskegee/index.html; also Berche & Lefrère, 2010; Gray, 1998; Jones, 1993; McCallum, Arekere, Green, Katz, & Rivers, 2006; Reverby, 2009). Secondary skeletal changes were rarely addressed in any reports. An example is aortic aneurysm, a feature that sometimes occurs in the tertiary stage of syphilis, and may cause pressure erosion of thoracic vertebrae due to blood pulsation through the weakened wall of the aorta (Castro et al., 2016; Kelley, 1979; Roberts & Buikstra, 2019:391).

Alterations that may have resulted from mercury treatment have been increasingly recognized, particularly in the dentition (e.g., Iouannou & Henneberg, 2017; Ioannou, Henneberg, Henneberg, & Anson, 2015; Ioannou et al., 2015, 2017; Iouannou, Hunt, & Henneberg, 2017; Radu & Soficaru, 2016). Because mercury affects amelogenesis if ingested at significant repeated doses (around 650 mg), dental anomalies provide evidence for the use of mercurial treatments in infants and children (Ioannou, et al., 2015). Although arsenic and bismuth were also used to treat syphilis, neither arsenic (Konishi, et al., 1977; Sunny, Israt, Saha, Dithi, & Illius, 2013) nor bismuth (Dean, 1943; Ling, 1929; McCarthy & Dexter, 1935) cause serious enamel defects similar to those produced by mercury. The above-cited research on the alteration of permanent dentition from mercurial treatments has implications for identifying CS even in the absence of diagnostic skeletal and dental changes, although it must be cautioned that mercury was also used for treating some other conditions (see Section 4.2.3).

The extant data on treponemal paleopathology provide a base from which to work, revealing where gaps exist across certain regions or specific present-day countries, and where re-evaluation of specific sites/skeletons may be useful. Evidence from Europe is not as plentiful as anticipated in this survey. In Europe, evidence from the UK far exceeds that reported from other countries (e.g., see Roberts & Redfern, 2019), perhaps because it has a very good infrastructure for training; a national organization representing (mainly) bioarchaeologists (British Association of Biological Anthropology and Osteoarchaeology: https://www.babao.org.uk/); a strong commercial archaeology presence, including cemetery excavation; and thousands of skeletons curated in its many museums. Furthermore, there has been relatively little paleopathological work that has generated evidence for treponemal disease in Scandinavia and especially in the Balkans.

Lack of evidence in particular parts of the world may be due to persistent problems, including few paleopathologists working in these regions (in academia or commercial/contract archaeology), lack of available training, problems with accessing skeletal collections (e.g., Greece), or simply few skeletal remains in a country (e.g., Iceland). Publication in the country's language is often considered a barrier for Western scholars, biasing an understanding of the frequency and distribution of the disease. The apparent quantitative lack of data on treponemal disease in Old World contexts, as seen by English-language-constrained scientists, remains unlikely to reflect a real lack of evidence because there are "invisible" data in local journals specific to a country (e.g., Alpaslan & Bekmez, 2015; Novak and Krznar, 2010), in gray literature (e.g., Gebetsroither, 2005; Walth, 2016), in conference abstracts (e.g., Buckley et al., 2019; Henneberg, Henneberg, & Ciarallo, 2006; Mushrif-Tripathy, 2019; Novak, 2010; Stodder, Trembly, & Tucker, 1992), and in theses and dissertations (e.g., Novak, 2008; Rodrigues Lopes, 2014). In addition, skeletal collections may be curated in many countries where analysis has not yet taken place, where there may be barriers to access (e.g., researchers "protecting" their resource), or where even today there may be preferential recovery of skeletal elements (e.g., only skulls). In some areas, human skeletal assemblages represent limited time periods (e.g., relatively few prehistoric skeletons are available for study compared to later periods). Religious or cultural prohibitions on studying human remains may also exist. Additionally, taphonomic conditions may leave few preserved skeletal remains in a region (e.g., much of West and Central Africa, India, and southern China). Data on skeletons that have diagnoses of treponemal disease in commercial/contract archaeology contexts also may not be accessible due to restrictions on sharing data until the report comes to publication. In the UK, however, this "gray literature" may be online (e.g., Archaeology Data Service: http://www.archaeologydataservice.ac.uk/). A lack of an extensive contract/commercial archaeology business in a country might also mean that relatively few skeletons are excavated and analyzed. A final challenge for researchers who are interested in this subject matter is knowing where skeletal collections are curated (see Roberts & Mays [2010] for an example from the UK). Most curating institutions in the Old World do not have information to guide researchers to skeletal collections that might generate evidence for treponemal disease.

Some reported evidence from the Old World is clearly pre-Columbian in date based on standard archaeological methods and carefully conducted radiocarbon dating (see section 4.1). Much evidence, however, is post-Medieval (after the mid-16th century), and tertiary skeletal changes are found more commonly in later periods in Europe (e.g., Walker et al., 2015). Most of the reported evidence from the late Medieval and post-Medieval periods is from urban contexts, possibly because far fewer rural cemeteries have been excavated in

comparison to those necessitated by modern urban development. The proportion of the European population that lived in rural versus urban contexts in the Medieval and post-Medieval periods can be difficult to access, and information available varies by time and place due to circumstances including conflicts, epidemics, or natural disasters (Chris Gerrard, personal communication, October 6, 2019). Nonetheless, it is well-known that rural to urban migration for waged labor was common, gradually increasing the proportion of people living in urban areas, while those who remained in rural communities would have encountered urban populations through reciprocal trade (see, for example, Bairoch, Batou, & Chèvre, 1988; Cesaretti, Lobo, Bettencourt, Ortman, & Smith, 2016; Russell, 1972). In these contexts, the movement of people through immigration, trade, and social interactions provided ideal opportunities for infections to be transmitted. Of interest is that the UK sites where treponemal disease has been identified are often on the coast or close to the coast; this pattern also is noted in Latvia (Petersone-Gordina, 2016), Italy (Henneberg et al., 1992, Henneberg & Henneberg, 1994), Croatia (Novak, 2008), and Turkey (Alpaslan & Bekmez, 2015; Erdal, 2006). Further exploration of this pattern is warranted, along with investigating treponemal disease distribution relative to latitude and altitude.

6.4 | Recommendations for advancing recognition of treponemal disease in past populations

A uniform approach to investigating the evidence for treponemal disease and its distribution across time and space using rigorous diagnostic criteria will mitigate the ad hoc reporting of *potential* treponemal disease that has predominated in paleopathology to date. We advise investigators to consider Weston's (2008, 2009, 2012) caveats and the critiques of Rothschild & Rothschild (1995) regarding the use of nonspecific periosteal new bone formation as the sole means of diagnosing treponematosis. We encourage use of a weighted system of scoring (Table 1) and a recording form that explicitly lists observations to be made that are key to the diagnosis of treponemal disease (see Supporting Information). Documenting the presence, absence, and observability of lesions that are consistent with treponemal disease (e.g., periosteal reaction, mulberry molars, aortic aneurysm), strongly suggestive (e.g., saber shins, dactylitis), or diagnostic (e.g., advanced caries sicca, superficial cavitation/gummatous lesions on tubular bones, Hutchinson's incisors, Moon's molars) will ensure that future reports present accurate supporting evidence for the security of a diagnosis. This table and recording form undoubtedly can be improved as research on treponematosis proceeds. Integral to the use of this weighted scoring is the provision of specific diagnostic training for researchers, as conducted with the 2019 Paleopathology Association workshop on treponemal disease. Paleopathology training in academic environments has existed in some parts of the world for a long time (Buikstra & Roberts, 2012), and the late Don Ortner ran short 2- to 3-week courses intermittently from the 1970s to 2008 in the USA and the UK (Ortner et al., 2012) and general workshops on paleopathology with Bruce Ragsdale at the North American annual meetings of the Paleopathology Association. None of these courses or workshops, however, specifically focused on treponemal disease. Not all bioarcheologists have received adequate training in paleopathology, and there is frequently little emphasis placed on recognizing treponemal disease compared to other (more commonly archaeologically documented) diseases, particularly in the Old World. Training in paleopathology for students and colleagues in many countries is simply unavailable and must be improved through additional such workshops and short courses, and provision of support for participation of underrepresented colleagues (as for the first Summer School in Palaeopathology at Durham University, UK, in 2019). Hackett's (1976) volume, now available as an ebook, also should be consulted.

We encourage researchers to test Hackett's (1976) proposed diagnostic criteria "on trial" in an array of documented collections throughout the world and to look for lesions or patterns of lesions in individuals with known treponemal infection but with less advanced skeletal involvement that could add to the array of suggestive and diagnostic skeletal indicators. The previously described breakthroughs in identifying *Treponema* DNA in archaeological skeletons may also help paleopathologists identify lesions with diagnostic value, as will using methods of archaeological biogeochemistry to help identify and distinguish the effects of mercurial treatments on the skeleton and their impact on the expression of treponemal lesions (described in Section 4.2.3).

It is imperative that reports of any condition in paleopathology include a figure of the skeleton showing its bone preservation and the distribution of the lesions (preferably also the type of lesions), along with a detailed description and, where possible, high-resolution images of the bone changes that include a scale. Radiographic images, if obtainable, are also advisable. Notably, the surge in digital imagery (including both 2D and 3D) of human remains has led to increasing discussion of their ethical use (e.g., Smith et al., 2019). When the concerns of descendant communities prevent the publication of such images, it still may be possible to obtain consent to make them available to interested researchers in professional contexts. Contextual data must include accurate information on the site location and setting, site dating and all means used (e.g., artifact seriation, stratigraphy, radiocarbon dating), and a description of the disposition and general preservation of the remains (e.g., grave architecture, disturbance, body position and orientation, etc.). The original site report or primary publications must be referenced.

Researchers are encouraged to share information on skeletons with *possible* treponemal disease (images and descriptions) through secure social media/email lists/websites when it can be done without disrespecting descendants. Data sharing could particularly help people who have little training or knowledge in their assessment of pathological lesions. It would also spare journals from publishing studies for which a diagnosis of treponemal disease is suspect. Thus, media should be developed so researchers can share their findings, with ethical considerations in mind, if they are not sure about a diagnosis *before* they think about publishing. While such forums exist to an extent already (e.g., the closed Paleopathology group on Facebook, and newsletters sent by email to members of both the Paleopathology

Association and Paleopathology Club), expansion of such resources is desirable, providing that they are available only for appropriate use by professionals (not the general public) in a respectful manner.

Re-evaluation of skeletons with purported treponemal infection and the contexts from which they came is needed in light of inadequate documentation in the majority of surveyed publications. A wider search for the evidence, including the abstracts of poster and podium presentations, gray literature, theses, and journal papers and monographs in any language, must also be conducted. As Harper et al. (2011:126) also recognized, negative evidence in examined skeletal assemblages must also be reported to improve our understanding of where and when treponemal infection existed in the past, and where it did not.

7 | CONCLUSION

In this review, the current genetic evidence presented permits rejection of one of the four hypotheses delineated in Section 2—the Evolutionary Hypothesis—while the accumulating Old World skeletal evidence that is dated using the best practices recommended in Section 4.1 permits rejection of the Columbian hypothesis. Based upon clinical studies, genetic evidence, and research on diagnostic lesions in human skeletal remains, we conclude that syphilis, bejel (endemic syphilis), and yaws are the same disease from a pathophysiological viewpoint and are all caused by a single species, *Treponema pallidum*. All are treated today with antibiotics. We assert that their reported clinical "differences" are the result of the serendipity of transmission, age of acquisition, and variation in host response, rather than clear genetic differences in the etiological agents. Nonetheless, the epidemiological impact of treponemal disease in both present and past populations differs due to the mode (casual contact, sexual, or transplacental transmission) and route (e.g., skin or genitals) of infection, age of onset, and duration of the illness.

To advance our understanding of treponemal infection, a much broader and more extensive analysis of modern clinical and historical tissue samples is essential. For modern samples, as mentioned in Section 3, relevant metadata must be collected, including the source of infection, mode and route of transmission, and clinical manifestations. For historical and ancient DNA samples, geneticists and paleopathologists alike need a systematic approach to investigating evidence of skeletal pathology in extant collections or published reports, a recommendation that has been made repeatedly (e.g., Baker & Armelagos, 1988; Hackett, 1976; Harper et al., 2011; Powell & Cook, 2005b; Roberts, 1994; Williams, 1932). A systematic approach must include information on the site context and temporal attribution, as well as the demographic profile (age and sex information on the entire skeletal sample as well as those affected) in order to assess (a) changes in the patterns observed in skeletal manifestations (e.g., many or few bones affected, age distribution, etc.), (b) differences based on environmental conditions (e.g., coastal or inland, arid or humid, by altitude, etc.) within a region, and (c) variation across time or related to cultural differences (e.g., foraging versus farming; across political, religious, or social boundaries, etc.). Promotion of standardized investigation across geographic regions will contribute immensely to our understanding of the distribution of treponemal infection at various times over much of the Old World, vast expanses of which continue to be neglected.

Key to such work is the use of documentary sources and publications on treponemal infection in languages other than English or principal modern Western European languages (French, German, or Spanish). It is essential, therefore, for Western paleopathologists and bioarchaeologists to form liaisons with scholars publishing in other languages to obtain a more holistic view of the geographic distribution of the disease in the past. Collaboration with medical historians, as recommended by McGough (2005), is also necessary to interpret the enormous amount of material written about the origin of syphilis since the end of the 15th century. In some instances, translations are unreliable and misleading due to a poor understanding of the history and context in which the material was written (see Adorno [1993] for a review of one such example concerning Las Casas). Additionally, translators often have political agendas motivating their publication in a specific language at a particular time (Adorno, 1993). A rigorous reliance on primary sources or accurate translations of such works must be implemented, necessitating collaboration among anthropologists, physicians, historians, and linguists, particularly in regions of the world other than Europe or North America, and especially if they are to be used for any retrospective diagnosis (Arrizabalaga, 2002; Mitchell, 2011, 2016). Digital humanities initiatives are becoming increasingly common, and original sources are now available to scholars through online resources including the Internet Archive (http://archive.org/) and Project Gutenberg (http://www.gutenberg.org/). Collaborative translation efforts also are underway, including the Oviedo Project (http://pages.vassar.edu/oviedo/). The ability to access treatises in their original form and language will enable more complete and accurate translation of these works by qualified scholars. For example, several evaluations of historical documentation and literature shed light on the relationship between the 16th-century syphilis epidemic and increasing misogyny and persecution of women accused of witchcraft or perceived "moral failings," such as prostitution (e.g., Herero Ingelmo & Montero Cartelle, 2013; Juárez-Almendros, 2017; Losse, 2015; McGough, 2006, 2010; Ross, 1995).

Understanding individual lives and tracking co-morbidities and "lived experiences" is a growing focus in bioarchaeology (Baker & Agarwal, 2017; Byrnes & Muller 2017; Hosek, 2019; Stodder & Byrnes, 2019), including the care of diseased individuals (Roberts, 2017a; Tilley, 2015, 2016; Tilley & Cameron, 2014). While treponemal infection is frequently documented, few scholars explicitly address the impact of the condition on the affected individual or the community. Buckley and Tayles's (2003) article focusing on "the functional cost of tertiary yaws" is an exception. Secondary and tertiary stages of treponemal disease are often dismissed because they typically are not directly related to mortality, at least not during the reproductive years, yet the range of impacts people experienced from these infections in both the past and present includes morbidity rates of up to 50% (see Baker & Armelagos, 1988:719) and chronic disease, often

with facial disfigurement and neurological impairment. The prevalence of treponemal disease in some intensively studied precontact tropical villages was remarkably high (e.g., Schaffer & Carr, 2013; Stodder, 1997; Stodder, Trembly, & Tucker, 1992), and it is also being recorded increasingly in small and large skeletal assemblages from temperate environments (e.g., Smith, Betsinger, & Williams, 2010). Additional attention to the impact of treponemal morbidity on affected individuals and the groups within which they lived is, therefore, recommended.

There is much we still do not know about treponemal infection and its effects on humans through time. Reorienting investigations to move beyond the perennial debate about the origin of treponemal infection is essential to advance our understanding of its causative organism and the disease it produces in the bodies of humans and other primates. What is the extent of genetic diversity within *T. pallidum* and to what extent is it really substructured or organized into ecotypes? How has this diversity changed over time? How does *T. carateum* relate to *T. pallidum*? How do host physiological and immunological responses lead some but not others of those affected to develop serious sequelae, as has been shown for neurosyphilis and mutations of some toll-like receptor (TLR) genes (Marra et al., 2014)? How can understanding the host immune response inform our investigations in both bioarchaeology and in improving treatments for affected individuals today? Was there co-evolution of host and pathogen? If so, has it affected modern human biology? Was treponemal infection confined in the past to certain environments/climates? If so, how did it spread throughout the world, and how will current climate change affect its future distribution? This 2020 vision of treponemal infection is meant to encourage additional investigators working around the globe to conduct studies that will help build a more complete set of data on the frequency and patterning of this disease at different times and places and to seek answers to the many questions we have posed. We hope that research along these avenues of inquiry in the coming decade will generate a far more complete understanding of *T. pallidum* biology, its distribution in both the past and present, and its broader impact on the people and communities it affects.

ACKNOWLEDGMENTS

This work developed from a School for Advanced Research (SAR) Research Team seminar organized by Brenda Baker and Gillian Crane-Kramer that was held in Santa Fe, New Mexico, in April 2018. Funding from SAR permitted an international, interdisciplinary group to discuss this topic in depth. We are grateful to SAR for this opportunity, which led to involvement of additional scholars in a symposium on "The Evolution of Syphilis: A New Approach" organized by Baker for the 88th annual meeting of the American Association of Physical Anthropologists, and a workshop organized by Baker, Roberts, Henneberg, and Stodder, on "Diagnosing Treponemal Disease" for the annual meeting of the Paleopathology Association, in Cleveland, Ohio, in March 2019, for which the recording form was created.

Maciej Henneberg is grateful to Dr. Renata J. Henneberg for her help and advice in preparation of his contributions to the SAR seminar and to this article. Gillian Crane-Kramer would like to thank Dr. Vincent Carey, Dr. Deborah Altimirano, Dr. Maciej Henneberg, and Dr. Jo Buckberry for their knowledge and support. Charlotte Roberts is very grateful to the following people for freely sharing data and papers, or pointing her in the right direction to data or other people: Tom Crist, Emily Glass, Ruzan Mkrtchyan (Albania); Maureen Marshall (Armenia); Michaela Binder (Austria); Marit Van Cant, Katrien Van de Vijver (Belgium); Amila Zukanovic (Bosnia and Herzegovina); Bisserka Gaydarska (Bulgaria); Mario Novak, Mario Šlaus, Marin Vodanović (Croatia); Tomáš Alušík (Czech Republic); Shirley Schermer, Martin Malve (Estonia); Kati Salo (Finland); Andrew Chamberlain, Eric Crubezy (France); Gisela Grupe, Christian Meyer, Natasha Powers, Michael Schultz (Germany); Anastasia Papathanasiou (Greece); György Pálfi (Hungary); Joe Walser III (Iceland); Eileen Murphy (Ireland); Gino Fornaciari (Italy); Elina Petersone-Gordina (Lativia); Rimantas Jankauskas (Lithuania); Sergiu Musteata, Angela Simalcsik (Moldova); Elena Rossoni-Notter (Monaco); Barbara Veselka (Netherlands); Per Holck, Berit Sellevold (Norway); Natasa Narsik (Poland); Ana Luisa Santos (Portugal); Ileana Buzic (Romania); Alexandra Buzhilova, Nick Marquez Grant, Tatyana Shvedchikoval (Russia); Marija Djuric (Serbia); Olalla Lopez Costas (Spain); Caroline Arcini (Sweden); Martin Haeusler, Frank Rühli (Switzerland); and Sue Anderson, Anwen Caffell, Malin Holst, Louise Loe, Lauren McIntyre (UK). Additional thanks go to Chris Gerrard (Durham University). Finally, Brenda Baker thanks Jane Buikstra and Lyle Konigsberg for extending the invitation to publish this work in *Yearbook of Physical Anthropology*, a private donor and the American Association of Physical Anthropologists for supporting nonmember participation at the 2019 symposium, and the private donor for funding figure reproduction in this article.

AUTHOR CONTRIBUTIONS

The authors are listed alphabetically. B.J.B. and G.C.K. organized the S.A.R. research team seminar, in which M.W.D., L.A.G., M.H., C.L., S.A.L., C.A.R., A.C.S., and A.L.W.S. participated, that stimulated conceptualization of this article. B.J.B. wrote the introduction, competing hypotheses, and New World evidence sections, all section introductions, and merged material contributed by all coauthors for the initial drafts, revised and final versions, and proof corrections. S.A.L., A.C.S., and S.W. wrote the section on epidemiological and genetic research with input from D.C.M. and B.J.B. on drafts. M.W.D. wrote the material on archaeological dating with input from B.J.B. on drafts. L.A.G. wrote the material on archaeological biogeochemistry. G.C.K. wrote the section on the use of historical and oral sources. B.J.B. and A.L.W.S. wrote the section on diagnosing treponemal disease in human skeletal remains with input from C.A.R. and M.H. C.A.R., B.J.B., M.H., and A.L.W.S. wrote the material on Old World skeletal remains and recommendations with input from C.L. on Asia. S.W. created Figure 1 with input from A.C.S. and S.A.L. M.H. created Figure 2 with input from B.J.B., C.A.R., and A.L.W.S. A.L.W.S. created Table 1 with input from B.J.B., M.H., and C.A.R. The recording form in supplementary information was created by A.L.W.S., B.J.B., C.A.R., and M.H. All authors contributed to the conclusions, critically reviewed the initial draft, and approved the revised manuscript. B.J.B., M.W.D., L.A.G.,

M.H., S.A.L., D.C.M., C.A.R., A.L.W.S., A.C.S, and S.W. reviewed the page proofs.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Brenda J. Baker https://orcid.org/0000-0002-9277-7815
Michael W. Dee https://orcid.org/0000-0002-3116-453X
Lesley A. Gregoricka https://orcid.org/0000-0001-6608-7709
Maciej Henneberg https://orcid.org/0000-0003-1941-2286
Sheila A. Lukehart https://orcid.org/0000-0001-9778-3301
David C. Mabey https://orcid.org/0000-0002-0031-8276
Charlotte A. Roberts https://orcid.org/0000-0002-2259-807X
Anne C. Stone https://orcid.org/0000-0001-8021-8314

REFERENCES

Achtman, M., & Wagner, M. (2008). Microbial diversity and the genetic nature of microbial species. *Nature Reviews Microbiology*, *6*(6), 431–440. https://doi.org/10.1038/nrmicro1872

Adorno, R. (1993). The politics of publication: Bartolomé de Las Casas's The Devastation of the Indies. *New West Indian Guide/Nieuwe West-Indische Gids*, *67*, 285–292. https://doi.org/10.1163/13822373-90002669

Akrawi, F. (1949). Is bejel syphilis? *The British Journal of Venereal Diseases*, *25*, 115–123. https://doi.org/10.1136/sti.25.3.115

Alpaslan, F. S., & Bekmez, M. S. (2015). Zeytinli ada (erdek-balikesir) topluluğundan erken bizans dönemi'ne ait bir sifilis (frengi) örneği. *Cumhuriyet Üniversitesi Sosyal Bilimler Dergisi*, *39*, 11–20.

Antal, G. M., Lukehart, S. A., & Meheus, A. Z. (2002). The endemic treponematoses. *Microbes and Infection*, *4*, 83–94. https://doi.org/10.1016/S1286-4579(01)01513-1

Anteric, I., Basic, Z., Vilovic, K., Kolic, K., & Andjelnovic, S. (2014). Which theory for the origin of syphilis is true? *The Journal of Sexual Medicine*, *11*, 3112–3118. https://doi.org/10.1111/jsm.12674

Arneborg, J., Heinemeier, J., Lynnerup, N., Nielsen, H. L., Rud, N., & Sveinbjornsdottir, A. E. (1999). Change of diet of the Greenland Vikings determined from stable isotope analysis and ^{14}C dating of their bones. *Radiocarbon*, *41*, 157–168. https://doi.org/10.1017/S0033822200019512

Arora, N., Schuenemann, V. J., Jäger, G., Peltzer, A., Seitz, A., Herbig, A., … Bagheri, H. C. (2016). Origin of modern syphilis and emergence of a pandemic *Treponema pallidum* cluster. *Nature Microbiology*, *2*, 16245. https://doi.org/10.1038/nmicrobiol.2016.245

Arriaza, B., Amarasiriwardena, D., Cornejo, L., Standen, V., Byrne, S., Bartkus, L., & Bandak, B. (2010). Exploring chronic arsenic poisoning in pre-Columbian Chilean mummies. *Journal of Archaeological Science*, *37*, 1274–1278. https://doi.org/10.1016/j.jas.2009.12.030

Arrizabalaga, J. (2002). Problematizing retrospective diagnosis in the history of disease. *Asclepio*, *54*, 51–70.

Aufderheide, A. C., & Rodríguez-Martín, C. (1998). *The Cambridge encyclopedia of human paleopathology*. Cambridge, UK: Cambridge University Press.

Ávila, A., Mansilla, J., Bosch, P., & Pijoan, C. (2014). Cinnabar in Mesoamerica: Poisoning or mortuary ritual? *Journal of Archaeological Science*, *49*, 48–56. https://doi.org/10.1016/j.jas.2014.04.024

Babcock, B. A. (1978). *The reversible world: Symbolic inversion in art and society*. Ithaca, NY: Cornell University Press.

Bacchilega, C. (2012). Folklore and Literature. In R. F. Bendix & G. Hasan-Rokem (Eds.), *A companion to folklore* (pp. 447–463). Oxford, UK: Wiley-Blackwell.

Bairoch, P., Batou, J., & Chèvre, P. (1988). *La population des villes Européennes: Banque de données et analyse sommaire des réesultats, 800–1850*. Geneva, Switzerland: Librairie Droz.

Baker, B. J. (2005). Patterns of pre- and post-Columbian treponematosis in the northeastern United States. In M. L. Powell & D. C. Cook (Eds.), *The Myth of Syphilis* (pp. 63–76). Gainesville, FL: University Press of Florida.

Baker, B. J., & Agarwal, S. C. (2017). Stronger together: Advancing a global bioarchaeology. *Bioarchaeology International*, *1*, 1–18. https://doi.org/10.5744/bi.2017.1005

Baker, B. J., & Armelagos, G. J. (1988). The origin and antiquity of syphilis: Paleopathological diagnosis and interpretation. *Current Anthropology*, *29*, 703–738. https://doi.org/10.1086/203691

Baker, B. J., & Judd, M. A. (2012). Development of paleopathology in the Nile Valley. In J. E. Buikstra & C. A. Roberts (Eds.), *The Global history of paleopathology: Pioneers and prospects* (pp. 209–234). New York, NY, and Oxford, UK: Oxford University Press.

Barnes, I., & Thomas, M. G. (2005). Evaluating bacterial pathogen DNA preservation in museum osteological collections. *Proceedings of the Royal Society B*, *273*(1587), 645–653. https://doi.org/10.1098/rspb.2005.3339

Bayliss, A. (2009). Rolling out revolution: Using radiocarbon dating in archaeology. *Radiocarbon*, *51*(1), 123–147. https://doi.org/10.1017/S0033822200033750

Bayliss, A., Shepherd Popescu, E., Beavan-Athfield, N., Bronk Ramsey, C., Cook, G. T., & Locker, A. (2003). The potential significance of dietary offsets for the interpretation of radiocarbon dates: An archaeologically significant example from Medieval Norwich. *Journal of Archaeological Science*, *31*(2004), 563–575. https://doi.org/10.1016/j.jas.2003.10.004

Beale, M., Marks, M., Sahi, S. K., Tantalo, L. C., Nori, A., French, P., … Thomson, N. R. (2019). Genomic epidemiology of syphilis reveals independent emergence of macrolide resistance across multiple circulating lineages. *Nature Communications*, *10*(3255), 1–9. https://doi.org/10.1038/s41467-019-11216-7

Beaumont, J., & Montgomery, J. (2016). The Great Irish Famine: Identifying starvation in the tissues of victims using stable isotope analysis of bone and incremental dentine collagen. *PLoS ONE*, *11*, e0160065. https://doi.org/10.1371/journal.pone.0160065

Beiner, G. (2007). *Remembering the year of the French: Irish folk history and social memory*. Madison, WI: University of Wisconsin Press.

Bentley, R. A. (2006). Strontium isotopes from the earth to the archaeological skeleton: A review. *Journal of Archaeological Method and Theory*, *13*(3), 135–187. https://doi.org/10.1007/s10816-006-9009-x

Berche, P., & Lefrère, J. -J. (2010). L'enquête Tuskegee sur la syphilis. *La Presse Médicale*, *39*, 1324–1329. https://doi.org/10.1016/j.lpm.2010.03.030

Bergmann, C. L. 2018 *Elemental analyses of archaeological bone using PXRF, ICP-MS, and a newly developed calibration to assess Andean paleodiets*. (Unpublished M.A. thesis). University of South Florida, Tampa, FL.

Betsinger, T. K., & Smith, M. O. (2019). A singular case of advanced caries sicca in a pre-Columbian skull from East Tennessee. *International Journal of Paleopathology*, *24*, 245–251. https://doi.org/10.1016/j.ijpp.2019.01.003

Betsinger, T. K., Smith, M. O., Helms Thorson, L. J., & Williams, L. L. (2017). Endemic treponemal disease in late pre-Columbian prehistory: New parameters, new insights. *Journal of Archaeological Science: Reports*, *15*, 252–261. https://doi.org/10.1016/j.jasrep.2017.07.033

Bloch, I. (1901). *Der Ursprung der Syphilis. Eine medizinische und kulturgeschichtliche Untersuchung*. Jena, Germany: Verlag von Gustav Fischer.

Bloch, I. (1908). The history of syphilis. In D. Power & J. K. Murphy (Eds.), *A system of syphilis* (Vol. 1, pp. 1–39). London, UK: Oxford Medical Publications Henry Frowde and Hodder and Stoughton.

Boldsen, J. L. (2001). Epidemiological approach to the paleopathological diagnosis of leprosy. *American Journal of Physical Anthropology*, *115*, 380–387. https://doi.org/10.1002/ajpa.1094

Boldsen, J. L., & Milner, G. R. (2012). An epidemiological approach to paleopathology. In A. L. Grauer (Ed.), *A Companion to Paleopathology* (pp. 114–132). Malden, MA: Wiley-Blackwell.

Botha, D., & Steyn, M. (2014). A palaeopathological assessment of the late 19th and early 20th century Khoesan. *International Journal of Osteoarchaeology*, *26*(2016), 266–280. https://doi.org/10.1002/oa.2419

Bouwman, A. S., & Brown, T. A. (2005). The limits of biomolecular palaeopathology: Ancient DNA cannot be used to study venereal syphilis. *Journal of Archaeological Science*, *32*, 703–713. https://doi.org/10.1016/j.jas.2004.11.014

Brettell, R., Montgomery, J., & Evans, J. (2012). Brewing and stewing: The effect of culturally mediated behaviour on the oxygen isotope composition of ingested fluids and implications for human provenance studies. *Journal of Analytical Atomic Spectrometry*, *27*, 778–785. https://doi.org/10.1039/C2JA10335D

Brickley, M. B., & Ives, R. (2008). The Study of Metabolic Bone Disease in Bioarchaeology. In *The bioarchaeology of metabolic bone disease*. San Diego, CA: Academic Press.

Brion, L. P., Manuli, M., Rai, B., Kresch, M. J., Pavlov, H., & Glaser, J. (1991). Long-bone radiographic abnormalities as a sign of active congenital syphilis in asymptomatic newborns. *Pediatrics*, *88*(5), 1037–1040.

Bronk Ramsey, C. (1995). Radiocarbon calibration and analysis of stratigraphy: The OxCal program. *Radiocarbon*, *37*(2), 425–430. https://doi.org/10.1017/S0033822200030903

Bronk Ramsey, C. (2009). Bayesian analysis of radiocarbon dates. *Radiocarbon*, *51*(1), 337–360. https://doi.org/10.1017/S0033822200033865

Bronk Ramsey, C., Dee, M., Rowland, J., Higham, T., Harris, S., Brock, F., … Shortland, A. (2010). Radiocarbon-based chronology for dynastic Egypt. *Science*, *328*, 1554–1557. https://doi.org/10.1126/science.1189395

Brothwell, D. R. (2005). North American treponematosis against the bigger world picture. In M. L. Powell & D. C. Cook (Eds.), *The myth of syphilis: The natural history of treponematosis in North America* (pp. 480–496). Gainesville, FL: University Press of Florida.

Brown, W., Donohue, J., Axnick, N., Blount, J., Ewen, N., & Jones, O. (1970). *Syphilis and other venereal diseases*. Cambridge, MA: Harvard University Press.

Bruins, H. J., van der Plicht, J., & Mazar, A. (2003). ^{14}C Dates from Tel Rehov: Iron-Age chronology, pharaohs, and Hebrew kings. *Science*, *300*(5617), 315–318. https://doi.org/10.1126/science.1082776

Buck, C. E., Litton, C. D., & Smith, A. F. M. (1992). Calibration of radiocarbon results pertaining to related archaeological events. *Journal of Archaeological Science*, *19*, 497–512. https://doi.org/10.1016/0305-4403(92)90025-X

Buckley, H. R. (2000). Subadult health and disease in prehistoric Tonga, Polynesia. *American Journal of Physical Anthropology*, *113*, 481–505. https://doi.org/10.1002/1096-8644(200012)113:4<481::AID-AJPA4>3.0.CO;2-1

Buckley, H. R., & Oxenham, M. (2016). Bioarchaeology in the Pacific Islands. In M. Oxenham & H. R. Buckley (Eds.), *The Routledge handbook of bioarchaeology in Southeast Asia and the Pacific Islands* (pp. 363–388). London, UK, and New York, NY: Routledge.

Buckley, H. R., & Tayles, N. (2003). Skeletal pathology in a prehistoric Pacific Island sample: Issues in lesion recording, quantification, and interpretation. *American Journal of Physical Anthropology*, *122*, 303–324. https://doi.org/10.1002/ajpa.10259

Buckley, H. R., Vlok, M., Domett, K., Trinh, H. H., & Oxenham, M. (2019). The antiquity of treponemal disease in the Asia-Pacific regions: Implications for settlement history. *American Journal of Physical Anthropology*, *168*(S68), 31.

Budd, P., Millard, A., Chenery, C., Lucy, S., & Roberts, C. (2004). Investigating population movement by stable isotope analysis: A report from Britain. *Antiquity*, *78*(299), 127–141. https://doi.org/10.1017/S0003598X0009298X

Buikstra, J., & Ubelaker, D. (Eds.) (1994). Standards for data collection from human skeletal remains. Arkansas Archeological Survey Research Series 44. Fayetteville, AR: Arkansas Archaeological Survey.

Buikstra, J. E. (Ed.). (2018). *Ortner's identification of pathological conditions in human skeletal remains*. New York, NY: Elsevier.

Buikstra, J. E., Baker, B. J., & Cook, D. C. (1993). What diseases plagued ancient Egyptians? A century of controversy. In W. V. Davies & R. Walker (Eds.), *Biological anthropology and the study of ancient Egypt* (pp. 24–53). London, UK: British Museum.

Buikstra, J. E., & Roberts, C. A. (Eds.). (2012). *The global history of palaeopathology. Pioneers and prospects*. New York, NY, and Oxford, UK: Oxford University Press.

Burke, P. (2004). *What is cultural history?* Cambridge, UK: Polity Press.

Burke, P. (2016). *Popular culture in early modern Europe* (3rd ed.). London, UK: Routledge. https://doi.org/10.4324/9781315246420

Buzhilova, A. (1999). Medieval examples of syphilis from European Russia. *International Journal of Osteoarchaeology*, *9*, 271–276. https://doi.org/10.1002/(SICI)1099-1212(199909/10)9:5<271::AID-OA496>3.0.CO;2-E

Byrnes, J. F., & Bush, P. J. (2016). Practical considerations in trace element analysis of bone by portable x-ray fluorescence. *Journal of Forensic Sciences*, *61*, 1041–1045. https://doi.org/10.1111/1556-4029.13103

Byrnes, J. F., & Muller, J. L. (Eds.). (2017). *Bioarchaeology of impairment and disability: Theoretical, ethnohistorical, and methodological perspectives*. Cham, Switzerland: Springer. https://doi.org/10.1007/978-3-319-56949-9

Cappellini, E., Prohaska, A., Racimo, F., Welker, F., Pedersen, M. W., Allentoft, M. E., … Willerslev, E. (2018). Ancient biomolecules and evolutionary inference. *Annual Review of Biochemistry*, *87*, 1029–1060. https://doi.org/10.1146/annurev-biochem-062917-012002

Carroll, G. M. A., Inskip, S. A., & Waters-Rist, A. (2018). Pathophysiological stable isotope fractionation: Assessing the impact of anemia on enamel apatite δ^{18}O and δ^{13}C values and bone collagen δ^{15}N and δ^{13}C values. *Bioarchaeology International*, *2*(2), 117–146. https://doi.org/10.5744/bi.2018.1021

Castro, M. M., Benavente, M. A., Ortega, J., Acuña, R., Montero, C., Thomas, C., & Castro, N. (2016). Thoracic aortic aneurysm in a pre-Colulmbian (210 BC) inhabitant of Northern Chile: Implications for the origins of syphilis. *International Journal of Paleopathology*, *13*, 20–26. https://doi.org/10.1016/j.ijpp.2016.01.002

Čejková, D., Zobaníková, M., Chen, L., Pospíšilová, P., Strouhal, M., Qin, X., … Šmajs, D. (2012). Whole genome sequences of three *Treponema pallidum* ssp. *pertenue* strains: yaws and syphilis treponemes differ in less than 0.2% of the genome sequence. *PLoS Neglected Tropical Diseases*, *6*(1), e1471. https://doi.org/10.1371/journal.pntd.0001471

Centurion-Lara, A., Castro, C., Castillo, R., Shaffer, J. M., Van Voorhis, W. C., & Lukehart, S. A. (1998). The flanking region sequences of the 15-kDa lipoprotein gene differentiate pathogenic treponemes. *The Journal of Infectious Diseases*, *177*, 1036–1040. https://doi.org/10.1086/515247

Centurion-Lara, A., Giacani, L., Godornes, C., Molini, B. J., Brinck Reid, T., & Lukehart, S. A. (2013). Fine analysis of genetic diversity of the *tpr* gene family among treponemal species, subspecies and strains. *PLoS Neglected Tropical Diseases*, *7*(5), e2222. https://doi.org/10.1371/journal.pntd.0002222

Centurion-Lara, A., Molini, B. J., Godornes, C., Sun, E., Hevner, K., Van Voorhis, W. C., & Lukehart, S. A. (2006). Molecular differentiation of *Treponema pallidum* subspecies. *Journal of Clinical Microbiology*, *44*, 3377–3380. https://doi.org/10.1128/JCM.00784-06

Cesaretti, R., Lobo, J., Bettencourt, L. M. A., Ortman, S. G., & Smith, M. E. (2016). Population-area relationship for Medieval European cities. *PLoS ONE*, *11*(10), e0162678. https://doi.org/10.1371/journal.pone.0162678

Chuma, I., Roos, C., Atickem, A., Bohm, T., Collins, D., Grillová, L., … Knauf, S. (2019). Strain diversity of *Treponema pallidum* subsp. *pertenue* suggests rare interspecies transmission in African nonhuman primates. *Scientific Reports*, *9*, 14243. https://doi.org/10.1038/s41598-019-50779-9

Chuma, I. S., Batamuzi, E., Collins, D. A., Fyumagwa, R. D., Hallmaier-Wacker, L. K., Kazwala, R. R., … Knauf, S. (2018). Widespread *Treponema pallidum* infection in nonhuman primates, Tanzania. *Emerging Infectious Diseases*, *24*, 1002–1009. https://doi.org/10.3201/eid2406.180037

Cockburn, T. A. (1961). The origin of the treponematoses. *Bulletin of the World Health Organization*, *24*, 221–228.

Cohan, F. M., & Perry, E. B. (2007). A systematics for discovering the fundamental units of bacterial diversity. *Current Biology*, *17*(10), R373–R386. https://doi.org/10.1016/j.cub.2007.03.032

Cole, G., & Waldron, T. (2010). Apple Down 152: A putative case of syphilis from sixth century AD Anglo-Saxon England. *American Journal of Physical Anthropology*, *144*(2011), 72–79.

Cole, G., & Waldron, T. (2012). Letter to the editor: Syphilis revisited. *American Journal of Physical Anthropology*, *149*, 149–150.

Cole, G., & Waldron, T. (2014). Letter to the editor: Apple Down 152 putative syphilis: Pre-Columbian date confirmed. *American Journal of Physical Anthropology*, *156*(2015), 489.

Cook, D. C. (2005). Syphilis? Not quite. Paleoepidemiology in an evolutionary context in the Midwest. In M. L. Powell & D. C. Cook (Eds.), *The Myth of Syphilis* (pp. 177–199). Gainesville, FL: University Press of Florida.

Cook, D. C., & Powell, M. L. (2005). Piecing the puzzle together: North American treponematosis in overview. In M. L. Powell & D. C. Cook (Eds.), *The Myth of Syphilis* (pp. 442–479). Gainesville, FL: University Press of Florida.

Cook, D. C., & Powell, M. L. (2012). Treponematosis: Past, present, and future. In A. L. Grauer (Ed.), *A Companion to Paleopathology* (pp. 472–491). Malden, MA: Wiley-Blackwell.

Cook, G. T., Ascough, P. L., Bonsall, C., Hamilton, W. D., Russell, N., Sayle, K. L., … Bownes, J. M. (2015). Best practice methodology for ^{14}C calibration of marine and mixed terrestrial/marine samples. *Quaternary Geochronology*, *27*, 164–171. https://doi.org/10.1016/j.quageo.2015.02.024

Craig, N., Speakman, R. J., Popelka-Filcoff, R. S., Glascock, M. D., Robertson, J. D., Shackley, M. S., & Aldenderfer, M. S. (2007). Comparison of XRF and PXRF for analysis of archaeological obsidian from southern Peru. *Journal of Archaeological Science*, *34*, 2012–2024. https://doi.org/10.1016/j.jas.2007.01.015

Craig, O. E., Steele, V. J., Fischer, A., Hartz, S., Andersen, S. H., Donohoe, P., … Heron, C. P. (2011). Ancient lipids reveal continuity in culinary practices across the transition to agriculture in Northern Europe. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(44), 17910–17915. https://doi.org/10.1073/pnas.1107202108

Crane-Kramer, G. M. M. (2001). *The paleoepidemiological examination of treponemal infection and leprosy in Medieval populations from northern Europe*. (Unpublished doctoral dissertation). University of Calgary, Calgary, Canada.

Crissey, J. T., & Denenholz, D. A. (1984). Congenital syphilis. *Clinics in Dermatology*, *2*(1), 143–161. https://doi.org/10.1016/0738-081X(84)90018-X

Crosby, A. W., Jr. (1969). The early history of syphilis: A reappraisal. *American Anthropologist*, *71*(2), 218–227. https://doi.org/10.1525/aa.1969.71.2.02a00020

Crosby, A. W., Jr. (1972). *The Columbian exchange: Biological and cultural consequences of 1492*. Westport, CT: Greenwood Press.

Csonka, G., & Pace, J. (1985). Endemic nonvenereal treponematosis (bejel) in Saudi Arabia. *Reviews of Infectious Diseases*, *7*(Suppl. 2), S260–S265. https://doi.org/10.1093/clinids/7-Supplement_2.S260

Dabney, J., Knapp, M., Glocke, I., Gansauge, M.-T., Weihmann, A., Nickel, B., … Meyer, M. (2013). Complete mitochondrial genome sequence of a Middle Pleistocene cave bear reconstructed from ultrashort DNA fragments. *Proceedings of the National Academy of Sciences*, *110*(39), 15758–15763. https://doi.org/10.1073/pnas.1314445110

Dawson, M. H. (1987). The 1920s anti-yaws campaigns and colonial medical policy in Kenya. *The International Journal of African Historical Studies*, *20*, 417–435. https://doi.org/10.1002/ajhb.23021

de Melo, F. L., de Mello, J. C. M., Fraga, A. M., Nunes, K., & Eggers, S. (2010). Syphilis at the crossroad of phylogenetics and paleopathology. *PLoS Neglected Tropical Diseases*, *4*(1), e575. https://doi.org/10.1371/journal.pntd.0000575

De Niro, M. J., & Schoeniger, M. J. (1983). Stable carbon and nitrogen isotope ratios of bone collagen: variations within individuals, between sexes, and within populations raised on monotonous diets. *Journal of Archaeological Science*, *10*, 199–203. https://doi.org/10.1016/0305-4403(83)90002-X

Dean, M. R. (1943). Oral manifestations of bismuth therapy in the treatment of syphilis. *Journal of the American Dental Association*, *30*, 651–657. https://doi.org/10.14219/jada.archive.1943.0151

Dee, M. W., Rowland, J. M., Higham, T. F. G., Shortland, A. J., Brock, F., Harris, S. A., & Bronk Ramsey, C. (2012). Synchronising radiocarbon dating and the Egyptian historical chronology by improved sample selection. *Antiquity*, *86*, 868–883. https://doi.org/10.1017/S0003598X00047979

Demaitre, L. (2007). *Leprosy in premodern medicine: A malady of the whole body*. Baltimore, MD: Johns Hopkins University Press.

Dent, S. C. (2017). Interindividual differences in embodied marginalization: Osteological and stable isotope analyses of antebellum enslaved individuals. *American Journal of Human Biology*, *29*, e23021. https://doi.org/10.1002/ajhb.23021

Devièse, T., Massilani, D., Yi, S., Comeskey, D., Nagel, S., Nickel, B., … Higham, T. (2019). Compound-specific radiocarbon dating and mitochondrial DNA analysis of the Pleistocene hominin from Salkhit Mongolia. *Nature Communications*, *10*, 274. https://doi.org/10.1038/s41467-018-08018-8

Díaz de Ysla, R. (1539). Tractado có[n]tra el mal serpentino: Que vulgarmente en España es lammado bubas q[ue] fue ordenado en el ospital de todos los Santos d[e] Lisbona. Sevilla, Spain: Domenico de Robertis. Available from http://www.cervantesvirtual.com/obra/tractado-contra-el-mal-serpentino-que-vulgarmente-en-espana-es-llamado-bubas-que-fue-ordenado-en-el-ospital-de-todos-los-santos-de-lisbona/ and at https://reader.digitale-sammlungen.de/de/fs1/object/display/bsb10197838_00001.html.

Domett, K. M., Wallis, L. A., Kynuna, D., Kynuna, A., & Smith, H. (2006). Late Holocene human remains from northwest Queensland, Australia: Archaeology and palaeopahology. *Archaeology in Oceania*, *41*, 25–36. https://doi.org/10.1002/j.1834-4453.2006.tb00602.x

Doolittle, W. F., & Papke, R. T. (2006). Genomics and the bacterial species problem. *Genome Biology*, *7*(9), 116. https://doi.org/10.1186/gb-2006-7-9-116

Dundes, A. (2005). Folkloristics in the twenty-first century. *Journal of American Folklore*, *118*, 385–408. https://doi.org/10.1353/jaf.2005.0044

Dunne, J., Evershed, R. P., Salque, M., Cramp, L., Bruni, S., Ryan, K., … di Lernia, S. (2012). First dairying in green Saharan Africa in the fifth millennium BC. *Nature*, *486*(7403), 390–394. https://doi.org/10.1038/nature11186

Dutour, O., Pálfi, G., Bérato, J., & Brun, J. -P. (Eds.). (1994). *L'origine de la syphilis in Europe: avant ou après 1493?* Paris, France: Éditions Errance.

Edington, G. M. (1954). Cardiovascular disease as a cause of death in the Gold Coast African. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *48*, 419–425. https://doi.org/10.1016/0035-9203(54)90143-1

Edmondson, D. G., Hu, B., & Norris, S. J. (2018). Long-term *in vitro* culture of the syphilis spirochete *Treponema pallidum* subsp. *pallidum*. *MBio*, *9*(3), e01153. https://doi.org/10.1128/mBio.01153-18

Eerkens, J. W., & Bartelink, E. J. (2013). Sex-biased weaning and early childhood diet among Middle Holocene hunter-gatherers in central California. *American Journal of Physical Anthropology*, *152*, 471–483. https://doi.org/10.1002/ajpa.22384

Erdal, Y. S. (2006). A pre-Columbian case of congenital syphilis from Anatolia (Nicaea, 13th century AD). *International Journal of Osteoarchaeology*, *16*, 16–33. https://doi.org/10.1002/oa.802

Farnsworth, N., & Rosen, T. (2006). Endemic treponematosis: Review and update. *Clinics in Dermatology*, *24*, 181–190. https://doi.org/10.1016/j.clindermatol.2005.11.004

Fernández de Oviedo y Valdés, G. (1547). *Coronica de las Indias*: *Historia general y natural de las Indias*, *agora nueuamente impressa corregída y emendada*. Available from https://pages.vassar.edu/oviedo/spanish-original/, accessed July 2, 2019.

Fernández de Oviedo y Valdés, G. (1851-1855). *Historia general y natural de las Indias*, *islas y tierra-firme del mar océano*. J. Amador de los Rios (Ed.), 4 vols. Madrid, Spain: Real Academia de la Historia. Available from https://pages.vassar.edu/oviedo/spanish-original/, accessed on July 2, 2019.

Fernández de Oviedo y Valdés, G. (1959). Natural history of the West Indies. S. A. Stoudemire (Trans., Ed.). North Carolina Studies in the Romance Languages and Literatures, University of North Carolina at Chapel Hill, Department of Romance Studies no. 32. Chapel Hill, NC: University of North Carolina Press.

Finnegan, R. (2003). *Oral traditions and the verbal arts: A guide to research practices*. London and New York: Routledge. https://doi.org/10.4324/9780203393215

Fracostoro, G. (1911 [1530]). Hieronymous Fracastor's Syphilis: From the original Latin; A translation in prose of this immortal poem. St. Louis, MO: Philmar. Available from https://openlibrary.org/works/OL1149409W/Syphilis.

Frangos, C. C., Lavranos, G. M., & Frangos, C. C. (2011). Higoumenakis' sign in the diagnosis of congenital syphilis in anthropological specimens. *Medical Hypotheses*, *77*, 128–131. https://doi.org/10.1016/j.mehy.2011.03.044

Fraser, C. M., Norris, S. J., Weinstock, G. M., White, O., Sutton, G. G., Dodson, R., … Venter, J. C. (1998). Complete genome sequence of *Treponema pallidum*, the syphilis spirochete. *Science*, *281*(5375), 375–388. https://doi.org/10.1126/science.281.5375.375

Freedman, E., & Meschan, I. (1943). Syphilitic spondylitis. *American Journal of Roentgenology*, *49*, 756–765.

Fribourg-Blanc, A., & Mollaret, H. H. (1969). Natural treponematosis of the African primate. *Primates in Medicine*, *3*(0), 113–121.

Fuller, B. T., Fuller, J. L., Sage, N. E., Harris, D. A., O'Connell, T. C., & Hedges, R. E. M. (2005). Nitrogen balance and d15N: Why you're not what you eat during nutritional stress. *Rapid Communications in Mass Spectrometry*, *19*, 2497–2506. https://doi.org/10.1002/rcm.2090

Gann, T. (1901). Recent discoveries in Central America proving the Pre-Columbian existence of syphilis in the New World. *The Lancet*, *158*(4076), 968–970. https://doi.org/10.1016/S0140-6736(01)73254-0

Gaul, J. S., Grossschmidt, K., Gusenbauer, C., & Kanz, F. (2015). A probable case of congenital syphilis from pre-Columbian Austria. *Anthropologischer Anzeiger*, *72*, 451–472. https://doi.org/10.1127/anthranz/2015/0504

Gebetsroither, M. (2005). *Sensengasse – Anthropologische Auswertung*. Vienna, Austria: Unpublished report.

Gerstl, S., Kiwila, G., Dhorda, M., Lonlas, S., Myatt, M., Kebela Ilunga, B., … Ferradini, L. (2009). Prevalence study of yaws in the Democratic Republic of Congo using the Lot Quality Assurance Sampling method. *PLoS ONE*, *4*(7), e6338. https://doi.org/10.1371/journal.pone.0006338

Ghadouane, M., Benjelloun, B.-S., Elharim-Roudies, L., Jorio-Benkhraba, M., & El Malki-Tazi, A. (1995). Skeletal lesions in early congenital syphilis (a review of 86 cases). *Review du Rhumatisme (English ed.)*, *62*(6), 433–437.

Giacani, L., & Lukehart, S. A. (2014). The endemic treponematoses. *Clinical Microbiology Reviews*, *27*(1), 89–115. https://doi.org/10.1128/CMR.00070-13

Giuffra, V., & Fornaciari, G. (2018). *Combining paleopathography and paleopathology*: *The example of the Medici*, *Grand Dukes of Florence*. Paper presented at the 22nd European Meeting of the Paleopathology Association, Zagreb, Croatia.

Gjestland, T. (1955). *The Oslo study of untreated syphilis. Acta Dermato-Venereologica 55(S34)*. Oslo, Norway: Akademisk Forlag.

Grange, P. A., Allix-Beguec, C., Chanal, J., Benhaddou, N., Gerhardt, P., Morini, J.-P., … Dupin, N. (2013). Molecular subtyping of *Treponema pallidum* in Paris, France. *Sexually Transmitted Diseases*, *40*, 641–644. https://doi.org/10.1097/OLQ.0000000000000006

Gray, F. D. (1998). *The Tuskegee syphilis study*. *The real story and beyond*. Montgomery, AL: New South Books.

Gray, R. R., Mulligan, C. J., Molini, B. J., Sun, E. S., Giacani, L., Godornes, C., … Centurion-Lara, A. (2006). Molecular evolution of the *tprC*, *D*, *I*, *K*, *G*, *and J* genes in the pathogenic genus *Treponema*. *Molecular Biology and Evolution*, *23*(11), 2220–2233. https://doi.org/10.1093/molvev/msl092

Greenaway, C., & Castelli, F. (2018). Migration medicine. *Infectious Disease Clinics of North America*, *33*(1), 265–287. https://doi.org/10.1016/j.idc.2018.10.014

Greenberg, S. B., & Bernal, D. V. (1992). Are long bone radiographs necessary in neonates suspected of having congenital syphilis? *Radiology*, *182*(3), 637–639. https://doi.org/10.1148/radiology.182.3.1535873

Gregoricka, L. A., Sheridan, S. G., & Schirtzinger, M. (2016). Reconstructing life histories using multi-tissue stable isotope analysis of commingled remains from St. Stephen's monastery in Jerusalem: Limitations and potential. *Archaeometry*, *59*(2017), 148–163. https://doi.org/10.1111/arcm.12227

Grillová, L., Oppelt, J., Mikalová, L., Nováková, M., Giacani, L., Niesnerová, A., … Šmajs, D. (2019). Directly sequenced genomes of contemporary strains of syphilis reveal recombination-driven diversity in genes encoding predicted surface-exposed antigens. *Frontiers in Microbiology*, *10*(1691), 1–14. https://doi.org/10.3389/fmicb.2019.01691

Grin, E. I. (1952). Endemic syphilis in Bosnia: Clinical and epidemiological observations on a successful mass-treatment campaign. *Bulletin of the World Health Organization*, *7*, 1–74.

Grmek, M. (2018). In P.-O. Méthot (Ed.), Ed. & translator *Pathological realities*: *Essays on disease*, *experiments*, *and history*. New York, NY: Fordham University Press.

Grzegorczyk, W., Grzegorczyk, J., & Grzegorczyk, K. (2016). Alleged cases of syphilis immortalized in the Krakow altarpiece by Veit Stoss in the light of new research on the origins of the disease in Europe. *Medical Review*, *14*(3), 340–357. https://doi.org/10.15584/medrev.2016.3.9

Guedes, L., Dias, O., Neto, J., da Piedade Ribeiro da Silva, L., Mondonça de Souza, S. M. F., & Mayo Iñiguez, A. (2018). First paleogenetic evidence of probable syphilis and treponematoses cases in the Brazilian Colonial period. *BioMed Research International*, *2018*, 1–8. https://doi.org/10.1155/2018/8304129

Hackett, C. J. (1951). *Bone lesions of yaws in Uganda*. Oxford, UK: Blackwell.

Hackett, C. J. (1963). On the origin of the human treponematoses. *Bulletin of the World Health Organization*, *29*, 7–41.

Hackett, C. J. (1976). *Diagnostic criteria of syphilis, yaws and treponarid (treponematoses) and some other diseases in dry bones*. Berlin and Heidelberg, Germany, and New York, NY: Springer-Verlag.

Handt, O., Höss, M., Krings, M., & Pääbo, S. (1994). Ancient DNA: Methodological challenges. *Experientia*, *50*, 524–529. https://doi.org/10.1007/BF01921720

Harkins, K. M., & Stone, A. C. (2014). Ancient pathogen genomics: Insights into timing and adaptation. *Journal of Human Evolution*, *79*, 137–149. https://doi.org/10.1016/j.jhevol.2014.11.002

Harper, K. N., Fyumagwa, R. D., Hoare, R., Wambura, P. N., Coppenhaver, D. H., Sapolsky, R. M., … Knauf, S. (2012). *Treponema pallidum* infection in the wild baboons of East Africa: Distribution and genetic characterization of the strains responsible. *PLoS ONE*, *7*(12), e50882. https://doi.org/10.1371/journal.pone.0050882

Harper, K. N., Ocampo, P. S., Steiner, B. M., George, R. W., Silverman, M. S., Bolotin, S., … Armelagos, G. J. (2008). On the origin of the treponematoses: A phylogenetic approach. *PLoS Neglected Tropical Diseases*, *2*(1), e148. https://doi.org/10.1371/journal.pntd.0000148

Harper, K. N., Zuckerman, M. K., Harper, M. L., Kingston, J. D., & Armelagos, G. J. (2011). The origin and antiquity of syphilis revisited: An appraisal of Old World Pre-Columbian evidence of treponemal infections. *Yearbook of Physical Anthropology*, *54*, 99–133. https://doi.org/10.1002/ajpa.21613

Harrison, L. W. (1956). The Oslo study of untreated syphilis. Review and commentary. *The British Journal of Venereal Diseases*, *32*, 70–78. https://doi.org/10.1136/sti.32.2.70

Harrison, L. W. (1959). The origin of syphilis. *The British Journal of Venereal Diseases*, *35*(1), 1–7.

Heathcote, G. M., Stodder, A. L. W., Buckley, H. R., Hanson, D. B., Douglas, M. T., Underwood, J. H., … Diego, V. P. (1998). On treponemal disease in the Western Pacific: Corrections and critique. *Current Anthropology*, *39*, 359–368. https://doi.org/10.1086/204745

Hedges, R. E. M., Clement, J. G., Thomas, C. D. L., & O'Connell, T. C. (2007). Collagen turnover in the adult femoral mid-shaft: Modeled from anthropogenic radiocarbon tracer measurements. *American Journal of Physical Anthropology*, *133*, 808–816. https://doi.org/10.1002/ajpa.20598

Henneberg, M., & Henneberg, R. J. (1994). Treponematosis in an ancient Greek colony of Metaponto, southern Italy, 580-250 BCE. In O. Dutour, G. Pálfi, J. Bérato, & J. -P. Brun (Eds.), *L'origine de la syphilis in Europe: Avant ou après 1493?* (pp. 92–98). Paris, France: Éditions Errance.

Henneberg, M., Henneberg, R. J., & Carter, J. C. (1992). Health in colonial Metaponto. *National Geographic Research and Exploration*, *8*, 446–459.

Henneberg, R. J., Henneberg, M., & Ciarallo, A. (2006). *Twins with probable congenital syphilis from Oplontis near Pompeii, victims of 79 AD volcanic eruption*. Poster presented at the annual meeting of the Palaeopathology Association, Anchorage, AK.

Hernandez, M., & Hudson, M. J. (2015). Diagnosis and evaluation of causative factors for the presence of endemic treponemal disease in a Japanese sub-tropical island population from the Tokugawa period. *International Journal of Paleopathology*, *10*, 16–25. https://doi.org/10.1016/j.ijpp.2015.04.001

Herrero Ingelmo, M. C., & Montero Cartelle, E. (2013). El *Morbus Gallicus* o Mal Francés en *La Lozana Andaluza de Franciso Delicado*. *Asclepio*, *65* (2), 021. https://doi.org/10.3989/asclepio.2013.21

Hillson, S., Grigson, C., & Bond, S. (1998). Dental defects of congenital syphilis. *American Journal of Physical Anthropology*, *107*, 25–40. https://doi.org/10.1002/(SICI)1096-8644(199809)107:1%3C25::AID-AJPA3%3E3.0.CO;2-C

Ho, E. L., & Lukehart, S. A. (2011). Syphilis: Using modern approaches to understand an old disease. *The Journal of Clinical Investigation*, *121*, 4584–4592. https://doi.org/10.1172/JCI57173

Hobson, K. A., Alisauskas, R. T., & Clark, R. G. (1993). Stable-nitrogen isotope enrichment in avian tissues due to fasting and nutritional stress: Implications for isotopic analyses of diet. *The Condor*, *95*(2), 388–394. https://doi.org/10.2307/1369361

Holcomb, R. (1935). The antiquity of syphilis. *Medical Life*, *42*, 275–325.

Holcomb, R. C. (1934). Christopher Columbus, and the American origin of syphilis. *United States Naval Medical Bulletin*, *32*(4), 401–430.

Hosek, L. R. (2019). Osteobiography as microhistory: Writing from the bones up. *Bioarchaeology International*, *3*, 44–57. https://doi.org/10.5744/bi.2019.1007

Hudson, E. H. (1946). A unitarian view of treponematosis. *American Journal of Tropical Medicine and Hygiene*, *26*, 135–139. https://doi.org/10.4269/ajtmh.1946.s1-26.135

Hudson, E. H. (1958). The treponematoses—or treponematosis? *The British Journal of Venereal Diseases*, *34*, 22–23.

Hudson, E. H. (1961). Historical approach to the terminology of syphilis. *Archives of Dermatology*, *84*, 545–562.

Hudson, E. H. (1965). Treponematosis and man's social evolution. *American Anthropologist*, *67*(4), 885–901. https://doi.org/10.1525/aa.1965.67.4.02a00020

Hudson, E. H. (1968). Christopher Columbus and the history of syphilis. *Acta Tropica*, *25*, 1–16.

Hutchens, A. R. (1992). *A handbook of Native American herbs*. Boston, MA: Shambhala Publications.

Hutchinson, D. L., & Richman, R. (2005). Regional, social, and evolutionary perspectives on treponemal infection in the Southeastern United States. *American Journal of Physical Anthropology*, *129*, 544–558. https://doi.org/10.1002/ajpa.20301

Ioannou, S., & Henneberg, M. (2017). Dental signs attributed to congenital syphilis and its treatments in the Hamann-Todd skeletal collection. *Anthropological Review*, *80*, 449–465. https://doi.org/10.1515/anre-2017-0032

Ioannou, S., Henneberg, M., Henneberg, R. J., & Anson, T. (2015). Diagnosis of mercurial teeth in a possibe case of congenital syphilis and tuberculosis in a 19th century child skeleton. *Journal of Anthropology*, *2015*, 103842, 1–11. https://doi.org/10.1155/2015/103842

Ioannou, S., Henneberg, R. J., & Henneberg, M. (2017). Presence of dental signs of congenital syphilis in pre-modern specimens. *Archives of Oral Biology*, *85*(2018), 192–200. https://doi.org/10.1016/j.archoralbio.2017.10.017

Ioannou, S., Hunt, D., & Henneberg, M. (2017). Five cases of dental anomalies attributable to congenital syphilis from early 20th century American anatomical collections. *Dental Anthropology*, *30*, 25–37.

Ioannou, S., Sassani, S., Henneberg, M., & Henneberg, R. J. (2015). Diagnosing congenital syphilis using Hutchinson's method: Differentiating between syphilitic, mercurial, and syphilitic-mercurial dental defects. *American Journal of Physical Anthropology*, *159*(2016), 617–629. https://doi.org/10.1002/ajpa.22924

Iyengar, V., & Woittiez, J. (1988). Trace elements in human clinical specimens: Evaluation of literature data to identify reference values. *Clinical Chemistry*, *34*(3), 474–481.

Jolliffe, D. M. (1993). A history of the use of arsenicals in man. *Journal of the Royal Society of Medicine*, *86*, 287–289.

Jones, J. (1876). Explorations of the aboriginal remains of Tennessee. *Smithsonian Contributions to Knowledge*, *22*(259), 1–171 Washington, D.C.: Smithsonian Institution.

Jones, J. H. (1993). *Bad Blood. The Tuskegee syphilis experiment* (2nd ed.). New York, NY: The Free Press.

Juárez-Almendros, E. (2017). *Disabled bodies in Early Modern Spanish literature: Prostitutes, aging women and saints*. Liverpool, UK: Liverpool University Press. https://doi.org/10.2307/j.ctt1ps32vm

Karem, K. L., & Pillay, A. (2014). On the origin of syphilis and contemporary views of disease dynamics. *Journal of Ancient Diseases & Preventive Remedies*, *2*(3), 118. https://doi.org/10.4172/2329-8731.1000118

Katz, A., & Krenkel, P. A. (1972). Mercury pollution: The making of an environmental crisis. *CRC Critical Reviews in Environmental Control*, *2*, 517–534. https://doi.org/10.1080/10643387209381589

Katzenberg, M., & Lovell, N. (1999). Stable isotope variation in pathological bone. *International Journal of Osteoarchaeology*, *9*, 316–324. https://doi.org/10.1002/(SICI)10991212(199909/10)9:53.0.CO;2-D

Kawahata, T., Kojima, Y., Furubayashi, K., Shinohara, K., Shimizu, T., Komano, J., … Motomura, K. (2019). Bejel, an nonvenereal treponematosis, among Men Who Have Sex with Men, Japan. *Emerging Infectious Diseases*, *25*(8), 1581–1583. https://doi.org/10.3201/eid2508.181690

Kelley, M. A. (1979). Skeletal changes produced by aortic aneurysms. *American Journal of Physical Anthropology*, *51*, 35–38. https://doi.org/10.1002/ajpa.1330510104

Kępa, M., Kozłowski, T., Szostek, K., Drozd, A., Walas, S., Mrowiec, H., … Grupa, M. (2012). Analysis of mercury levels in historical bone material from syphilitic subjects – Pilot studies (short report). *Anthropologischer Anzeiger*, *69*, 367–377. https://doi.org/10.1127/0003-5548/2012/0163

Klegarth, A. R., Ezeonwu, C. A., Rompis, A., Lee, B. P.-Y., Aggimarangsee, N., Chalise, M., … Jones-Engel, L. (2017). Survey of treponemal Infections in free-ranging and captive macaques, 1999-2012. *Emerging Infectious Diseases*, *23*(5), 816–819. https://doi.org/10.3201/eid2305.161838

Knauf, S., Barnett, U., Maciej, P., Klapproth, M., Ndao, I., Frischmann, S., … Liu, H. (2015). High prevalence of antibodies against the bacterium *Treponema pallidum* in Senegalese Guinea baboons (*Papio papio*). *PLoS ONE*, *10*(11), e0143100. https://doi.org/10.1371/journal.pone.0143100

Knauf, S., Batamuzi, E. K., Mlengeya, T., Kilewo, M., Lejora, I. A. V., Nordhoff, M., … Mätz-Rensing, K. (2012). *Treponema* infection associated with genital ulceration in wild baboons. *Veterinary Pathology*, *49*(2), 292–303. https://doi.org/10.1177/0300985811402839

Knauf, S., Gogarten, J. F., Schuenemann, V. J., De Nys, H. M., Düx, A., Strouhal, M., … Calvignac-Spencer, S. (2018). Nonhuman primates across sub-Saharan Africa are infected with the yaws bacterium *Treponema pallidum* subsp. p*ertenue*. *Emerging Microbes & Infections*, *7*(1), 157–154. https://doi.org/10.1038/s41426-018-0156-4

Koff, A. B., & Rosen, T. (1993). Nonvenereal treponematosis: Yaws, endemic syphilis, and pinta. *Journal of the American Academy of Dertamology*, *29*, 519–535. https://doi.org/10.1016/0190-9622(93)70217-H

Kojima, N., & Klausner, J. D. (2018). An update on the global epidemiology of syphilis. *Current Epidemiology Reports*, *5*(1), 24–38. https://doi.org/10.1007/s40471-018-0138z

Kolman, C. J., Centurion-Lara, A., Lukehart, S. A., Owsley, D. W., & Tuross, N. (1999). Identification of *Treponema pallidum* subspecies *pallidum* in a 200-year-old skeletal specimen. *The Journal of Infectious Diseases*, *180*, 2060–2063. https://doi.org/10.1086/315151

Konishi, K., Hara, K., Kambara, M., Waki, T., Nihida, H., Kuzushita, Y., … Oyazato, Y. (1977). Epidemiological studies of dental diseases in the arsenic poisoning of Osaka children caused by Morinaga dry milk. *Journal of Dental Health*, *27*, 69–77. https://doi.org/10.5834/jdh.27.69

Konstantinidis, K. T., & Tiedje, J. M. (2004). Trends between gene content and genome size in prokaryotic species with larger genomes. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(9), 3160–3165. https://doi.org/10.1073/pnas.0308653100

Krause, D. J., & Whitaker, R. J. (2015). Inferring speciation processes from patterns of natural variation in microbial genomes. *Systematic Biology*, *64*(6), 926–935. https://doi.org/10.1093/sysbio/syv050

Lanting, J., & van der Plicht, J. (1998). Reservoir effects and apparent ^{14}C-ages. *The Journal of Irish Archaeology*, *9*, 151–165.

Las Casas, Bartolomé de (1552). *Brevíssima relacíon de la destruyción de las Indias*. Seville, Spain: Sebastian Tugillo. Available from https://archive.org/details/breuissimarelaci00casa/page/n6.

Las Casas, Bartolomé de (1875–1876). *Historia de las Indias*. J. Sancho Rayon (Ed.) 5 vols. Madrid, Spain: Miguel Ginesta. Available from https://archive.org/details/historiaindias01casarich; https://www.gutenberg.org/ebooks/author/9232.

Lauc, T., Fornai, C., Premuzic, Z., Vodanovic, M., Weber, G. W., Masic, B., & Rajic Sikanjic, P. (2015). Dental stigmata and enamel thickness in a probable case of congenital syphilis from XIV century Croatia. *Archives of Oral Biology*, *60*, 1554–1564. https://doi.org/10.1016/j.archoralbio.2015.07.002

Lee, C.-K., Kim, H.-S., & Kwon, J. (2005). The removal of heavy metals using hydroxyapatite. *Environmental Engineering Research*, *10*(5), 205–212. https://doi.org/10.4491/eer.2005.10.5.205

Lee, W. R. (1968). The history of the statutory control of mercury poisoning in Great Britain. *British Journal of Industrial Medicine*, *25*, 52–62. https://doi.org/10.1136/oem.25.1.52

Ling, T. M. (1929). The use of bismuth in the treatment of congenital syphilis. *The Lancet*., *214*(5542), 1034–1035. https://doi.org/10.1016/S0140-6736(01)09843-9

Lipski, J., & Przylipiak, S. (1959). W sprawie patomorfologii uzebienia w kile wrodzonej. *Polski Tygodnik Lekarski*, *14*, 524–528.

Lopez, B., Lopez-Garcia, J. M., Costilla, S., Garcia-Vazquez, E., Dopico, E., & Pardiñas, A. F. (2017). Treponemal disease in the Old World? Integrated palaeopathological assessment of a 9th–11th century skeleton from north-central Spain. *Anthropological Science*, *125*, 101–114. https://doi.org/10.1537/ase.170515

Losse, D. N. (2015). *Syphilis: Medicine, metaphor, and religious conflict in early modern France*. Columbus, OH: The Ohio State University Press.

Lovell, N. C., Jurmain, R., & Kilgore, L. (2000). Skeletal evidence of probable treponemal infection in free-ranging African apes. *Primates*, *41*, 275–290. https://doi.org/10.1007/BF02557597

Luger, A. (1993). The origin of syphilis: Clinical and epidemiologic considerations on the Columbian Theory. *Sexually Transmitted Diseases*, *20*, 110–117.

Lukacs, J. R., & Walimbe, S. R. (1984). Paleodemography at Inamgaom: An early farming village in western India. In J. R. Lukacs (Ed.), *The people of South Asia: The biological anthropology of India, Pakistan, and Nepal* (pp. 105–132). New York, NY: Plenum Press.

Lukehart, S. A., & Giacani, L. (2014). When is syphilis not syphilis? Or is it? *Sexually Transmitted Diseases*, *41*(9), 554–555. https://doi.org/10.1097/OLQ.0000000000000179

Mafart, B. (2002). Goundou: A historical form of yaws. *The Lancet*, *360*(9340), 1168–1170. https://doi.org/10.1016/S0140-6736(02)11205-0

Manchester, K. (1994). Rhinomaxillary lesions in syphilis: Differential diagnosis. In O. Dutour, G. Pálfi, J. Bérato, & J. -P. Brun (Eds.), *L'origine de la syphilis in Europe: avant ou après 1493?* (pp. 79–80). Paris, France: Éditions Errance.

Manning, S. W., Bronk Ramsey, C., Kutschera, W., Higham, T. F. G., Kromer, B., Steier, P., & Wild, E. M. (2006). Chronology for the Aegean Late Bronze Age 1700–1400 B.C. *Science*, *312*, 565–569. https://doi.org/10.1126/science.1125682

Marks, M., Solomon, A. W., & Mabey, D. C. (2014). Endemic treponemal diseases. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *108*, 601–607. https://doi.org/10.1093/trstmh/tru128

Marom, A., McCullagh, J. S. O., Higham, T. F. G., Sinitsync, A. A., & Hedges, R. E. M. (2012). Single amino acid radiocarbon dating of Upper Paleolithic modern humans. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(18), 6878–6881. https://doi.org/10.1073/pnas.1116328109

Marra, C. M., Sahi, S. K., Tantalo, L. C., Godornes, C., Reid, T., Behets, F., … Lukehart, S. A. (2010). Enhanced molecular typing of *Treponema pallidum*: Geographic distribution of strain types and association with neurosyphilis. *The Journal of Infectious Diseases*, *202*(9), 1380–1388. https://doi.org/10.1086/656533

Marra, C. M., Sahi, S. K., Tantalo, L. C., Ho, E., Dunaway, S. B., Jones, T., & Hawn, T. R. (2014). Toll-like receptor polymorphisms are associated with increased neurosyphilis risk. *Sexually Transmitted Diseases*, *41*(7), 440–446. https://doi.org/10.1097/OLQ.0000000000000149

Mays, S., Crane-Kramer, G., & Bayliss, A. (2003). Two probable cases of treponemal disease of Medieval date from England. *American Journal of Physical Anthropology*, *120*, 133–143. https://doi.org/10.1002/ajpa.10132

Mays, S., Vincent, S., & Meadows, J. (2010). A possible case of treponemal disease from England dating to the 11th-12th century AD. *International Journal of Osteoarchaeology*, *22*(2012), 366–372. https://doi.org/10.1002/oa.1210

McCallum, J. M., Arekere, D. M., Green, B. L., Katz, R. V., & Rivers, B. M. (2006). Awareness and knowledge of the U.S. Public Health Service syphilis study at Tuskegee: Implications for biomedical research. *Journal of Health Care for the Poor and Underserved*, *17*, 716–733. https://doi.org/10.1353/hpu.2006.0130

McCarthy, F. P., & Dexter, S. O., Jr. (1935). Oral manifestations of bismuth. *The New England Journal of Medicine*, *213*, 345–353. https://doi.org/10.1056/NEJM193508222130802

McCullagh, J. S. O. (2010). Mixed-mode chromatography/isotope ratio mass spectrometry. *Rapid Commununications in Mass Spectrometry*, *24*, 483–494. https://doi.org/10.1002/rcm.4322

McGough, L. J. (2005). Syphilis in history: A response to 2 articles. *Clinical Infectious Diseases*, *41*(4), 573–575.

McGough, L. J. (2006). Demons, nature, or God? Witchcraft accusations and the French disease in Early Modern Venice. *Bulletin of the History of Medicine*, *8*(2), 219–246. https://doi.org/10.1353/bhm.2006.0069

McGough, L. J. (2010). *Gender, Sexuality, and Syphilis in Early Modern Venice*. New York, NY: Palgrave MacMillan.

McLean, S. (1931). The osseous lesions of congenital syphilis. *American Journal of Diseases of Children*, *41*, 130–152, 363–395, 607–675, 887–922, 1129–1171, 1411–1418. https://doi.org/10.1001/archpedi.1931.01940120148017

Meheus, A. (2005). Non-venereal treponematoses. *Medicine*, *33*, 82–84. https://doi.org/10.1383/medc.2005.33.10.82

Mekota, A.-M., Grupe, G., Ufer, S., & Cuntz, U. (2006). Serial analysis of stable nitrogen and carbon isotopes in hair: Monitoring starvation and recovery phases of patients suffering from anorexia nervosa. *Rapid Communications in Mass Spectrometry*, *20*, 1604–1610. https://doi.org/10.1002/rcm.2477

Meyer, C., Jung, C., Kohl, T., Poenicke, A., Poppe, A., & Alt, K. W. (2002). Syphilis 2001 – a palaeopathological reappraisal. *Homo*, *53*, 39–58. https://doi.org/10.1078/0018-442X-00037

Miao, R. M., & Fieldsteel, A. H. (1980). Genetic relationship between *Treponema pallidum* and *Treponema pertenue*, two noncultivable human pathogens. *Journal of Bacteriology*, *141*, 427–429.

Mikalová, L., Strouhal, M., Čejková, D., Zobaníková, M., Pospíšilová, P., Norris, S. J., … Šmajs, D. (2010). Genome analysis of *Treponema pallidum* subsp. *pallidum* and subsp. *pertenue* strains: Most of the genetic differences are localized in six regions. *PLoS ONE*, *5*, e15713. https://doi.org/10.1371/journal.pone.0015713

Mikalová, L., Strouhal, M., Oppelt, J., Grange, P. A., Janier, M., Benhaddou, N., … Šmajs, D. (2017). Human *Treponema pallidum* 11q/j isolate belongs to subsp. *endemicum* but contains two loci with a sequence in TP0548 and TP0488 similar to subsp. p*ertenue* and subsp. *pallidum*, respectively. *PLoS Neglected Tropical Diseases*, *11*(3), e0005434. https://doi.org/10.1371/journal.pntd.0005434

Milner, G. R., & Boldsen, J. L. (2017). Life not death: Epidemiology from skeletons. *International Journal of Paleopathology*, *17*, 26–39. https://doi.org/10.1016/j.ijpp.2017.03.007

Mitchell, P. D. (2003). Pre-Columbian treponemal disease from 14th century AD Safed, Israel, and implications for the Medieval Eastern Mediterranean. *American Journal of Physical Anthropology*, *121*, 117–124. https://doi.org/10.1002/ajpa.10205

Mitchell, P. D. (2009). Technical note: A revised radiocarbon date for a case of treponemal disease from Safed, Israel, from the 15th century AD. *American Journal of Physical Anthropology*, *139*, 274. https://doi.org/10.1002/ajpa.21034

Mitchell, P. D. (2011). Retrospective diagnosis and the use of historical texts for investigating disease in the past. *International Journal of Paleopathology*, *1*(2011), 81–88. https://doi.org/10.1016/j.ijpp.2011.04.002

Mitchell, P. D. (2016). Improving the use of historical written sources in paleopathology. *International Journal of Paleopathology*, *19*(20117, 88–95. https://doi.org/10.1016/j.ijpp.2016.02.005

Mitjà, O., Hays, R., Ipai, A., Penias, M., Paru, R., Fagaho, D., … Bassat, Q. (2012). Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: An open-label, non-inferiority, randomized trial. *The Lancet*, *379*, 342–347. https://doi.org/10.1016/S0140-6736(11)61624-3

Mitjà, O., Hays, R., Ipai, A., Wau, B., & Bassat, Q. (2011). Osteoperiostitis in early yaws: Case series and literature review. *Clinical Infectious Diseases*, *52*, 771–774. https://doi.org/10.1093/cid/ciq246

Mitjà, O., Hays, R., LeIngei, F., Laban, N., Ipai, A., Pakarui, S., & Bassat, Q. (2011). Challenges in recognition and diagnosis of yaws in children in Papua New Guinea. *American Journal of Tropical Medicine and Hygiene*, *85*, 113–116. https://doi.org/10.4269/ajtmh.2011.11-0062

Mitjà, O., Marks, M., Konan, D. J. P., Ayelo, G., Gonzalez-Beiras, C., Boua, B., … Asiedu, K. (2015). Global epidemiology of yaws: A systematic review. *The Lancet. Global Health*, *3*, e324–e331. https://doi.org/10.1016/52214-109X(15)00011-X

Montgomery, J. (2002). *Lead and strontium isotope compositions of human dental tissues as an indicator of ancient exposure and population dynamics*: *The application of isotope source-tracing methods to identify migrants among British archaeological burials and a consideration of ante-mortem uptake*, *tissue stability and post-mortem diagenesis*. (Unpublished doctoral dissertation). University of Bradford, Bradford, UK.

Montiel, R., Solórzano, E., Díaz, N., Álvarez-Sandoval, B. A., González-Ruiz, M., Cañada, M. P., … Malgosa, A. (2012). Neonate human remains: A window of opportunity to the molecular study of ancient syphilis. *PLoS ONE*, *7*(5), e36371. https://doi.org/10.1371/journal.pone.0036371

Moon, H. (1885). Dental surgery. In T. Bryant (Ed.), *A Manual for the Practice of Surgery*, *4th rev. ed* (pp. 453–483). Philadelphia, PA: Henry C. Lea's Son & Co.

Mooney, J. (1891). *The sacred formulas of the Cherokees*. Seventh annual report of the Bureau of Ethnology to the Secretary of the Smithsonian Institution, 1885–1886. Washington, D.C.: Government Printing Office.

Mosher, G. M., Smith, M. O., Albrecht, J. L., & Salaka, V. P. (2013). Treponemal disease, tuberculosis and subsistence-settlement pattern in the Late Woodland period West-central Illinois. *International Journal of Osteoarchaeology*, *25*, 776–787. https://doi.org/10.1002/oa.2344

Murray, J. F., Merriweather, A. M., Freedman, M. L., & de Villiers, D. J. (1956). Endemic syphilis in the Bakwena Reserve of the Bechuanaland Protectorate. *Bulletin of the World Health Organization*, *15*, 975–1039.

Mushrif-Tripathy, V. (2019). Evaluating the evidence of treponemal disease from India. *American Journal of Physical Anthropology*, *168* (S68), 172.

Nachvátal, L., Pětrošová, H., Grillová, A., Pospíšilová, P., Mikalová, L., Strnadel, R., … Smajs, D. (2014). Syphilis-causing strains belong to separate SS14-like or Nichols-like groups as defined by multilocus analysis of 19 *Treponema pallidum* strains. *International Journal of Medical Microbiology*, *304*(5–6), 645–653. https://doi.org/10.1016/j.ijmm.2014.04.007

Nazaroff, A. J., Prufer, K. M., & Drake, B. L. (2009). Assessing the applicability of portable X-ray fluorescence spectrometry for obsidian provenance research in the Maya lowlands. *Journal of Archaeological Science*, *37*, 885–895. https://doi.org/10.1016/j.jas.2009.11.019

Noda, A. A., Grillová, L., Lienhard, R., Blanco, O., Rodríguez, I., & Šmajs, D. (2018). Bejel in Cuba: Molecular identification of *Treponema pallidum* subsp. *endemicum* in patients diagnosed with venereal syphilis. *Clinical*

Microbiology and Infection, *24*(11), 1210.e1–1210.e5. https://doi.org/10.1016/j.cmi.2018.02.006

Norn, S., Permin, H., Kruse, E., & Kruse, P. R. (2008). Mercury–A major agent in the history of medicine and alchemy. *Dansk Medicinhistorisk Årbog*, *36*, 21–40.

Novak, M. (2008). *Antropološka analiza antičke nekropole Zadar-Relja u kontekstu antičkih nekropola Hrvatske*. (Unpubished doctoral dissertation). University of Zagreb, Zagreb, Croatia.

Novak, M. (2010). A possible case of treponematosis in a Roman period site (1st-6th century AD) skeletal series from Zadar, Croatia. Paper presented at the 18th European Meeting of the Paleopathology Association, Vienna, Austria. Abstract in Scientific Program and Abstracts booklet, p. 99.

Novak, M., & Krznar, S. (2010). Prilozi poznavanju uvjeta i kvalitete života u ranonovovjekovnom podravskom selu na primjeru Torčeca kraj Koprivnice. *Podravina: časopis za multidisciplinarna istraživanja*, *9*(18), 59–88.

O'Shea, J. G. (1990). 'Two minutes with Venus, two years with mercury' - Mercury as an antisyphilitic chemotherapeutic agent. *Journal of the Royal Society of Medicine*, *83*(6), 392–395.

Oakberg, K., Levy, T., & Smith, P. (2000). A method for skeletal arsenic analysis, applied to the Chalcolithic copper smelting site of Shiqmim, Israel. *Journal of Archaeological Science*, *27*, 895–901. https://doi.org/10.1006/jasc.1999.0505

Olsen, K. C., von Heyking, K., Grupe, G., White, C. D., & Longstaffe, F. J. (2018). Investigating diet and disease in a Medieval German poorhouse population using isotopic analysis of human and faunal tissues. *Bioarchaeology International*, *2*(2), 147–163. https://doi.org/10.5744/bi.2018.1022

Olsen, K. C., White, C. D., Longstaffe, F. J., von Heyking, K., McGlynn, G., & Grupe, G. (2010). The effects of pathology on inter- and intra-individual nitrogen isotope compositions of bone collagen from a Medieval poorhouse: A preliminary study. *Paleopathology Newsletter*, *152*, 23–28.

Olsen, K. C., White, C. D., Longstaffe, F. J., von Heyking, K., McGlynn, G., Grupe, G., & Rühli, F. J. (2014). Intraskeletal isotopic compositions ($\delta^{13}C$, $\delta^{15}N$) of bone collagen: Nonpathological and pathological variation. *American Journal of Physical Anthropology*, *153*, 598–604. https://doi.org/10.1002/ajpa.22459

Ortner, D. J. (2003). *Identification of pathological conditions in human skeletal remains* (2nd ed.). San Diego, CA: Academic Press.

Ortner, D. J., Knüsel, C., & Roberts, C. A. (2012). Special courses in human skeletal palaeopathology. In J. E. Buikstra & C. A. Roberts (Eds.), *A global history of paleopathology: Pioneers and prospects* (pp. 684–693). New York, NY, and Oxford, UK: Oxford University Press.

Pääbo, S. (1989). Ancient DNA: Extraction, characterization, molecular cloning, and enzymatic amplification. *Proceedings of the National Academy of Sciences*, *86*, 1939–1943. https://doi.org/10.1073/pnas.86.6.1939

Pales, L. (1930). *Paléopathologie et pathologie comparative*. Paris, France: Masson.

Parker, L. (1860). *The modern treatment of syphilitic diseases, both primary and secondary* (4th ed.). London, UK: John Churchill.

Parrot, M. J. (1879). The osseous lesions of hereditary syphilis. *The Lancet*, *113*(2907), 696–698. https://doi.org/10.1016/S0140-6736(02)35509-0

Pechenkina, K., Chen, S., & Fan, W. (2017). Treponemal disease in early China. *American Journal of Physical Anthropology*, *162*(S64), 312.

Pedersen, D. D., Milner, G. R., Kolmos, H. J., & Boldsen, J. L. (2019). The association between skeletal lesions and tuberculosis diagnosis using a probabalistic approach. *International Journal of Paleopathology*, 27, 88–100. https://doi.org/10.1016/j-ijpp.2019.01.001

Pederzani, S., & Britton, K. (2018). Oxygen isotopes in bioarchaeology: Principles and applications, challenges and opportunities. *Earth-Science Reviews*, *188*(2019), 77–107. https://doi.org/10.1016/j.earscirev.2018.11.005

Petersone-Gordina, E., & Gerhards, G. (2016). *Evidence for venereal syphilis in post-Medieval Riga, Latvia*. Paper presented at the 22nd European Association of Archaeologists conference, Vilnius, Lithuania. Abstracted retrieved from http://eaavilnius2016.lt/abstract-book-2/

Pětrošová, H., Zobaniková, M., Čejková, D., Mikalová, L., Pospíšilová, P., Strouhal, M., … Šmajs, D. (2012). Whole genome sequence of *Treponema pallidum* ssp. *pallidum*, strain Mexico A, suggests recombination between yaws and syphilis strains. *PLoS Neglected Tropical Diseases*, *6*(9), e1832. https://doi.org/10.1371/journal.pntd.0001832

Pettitt, P. B., Davies, W., Gamble, C. S., & Richards, M. B. (2003). Palaeolithic radiocarbon chronology: Quantifying our confidence beyond two half-lives. *Journal of Archaeological Science*, *30*(12), 1685–1693. https://doi.org/10.1016/S0305-4403(03)00070-0

Philippsen, B. (2013). The freshwater reservoir effect in radiocarbon dating. *Heritage Science*, *1*(24), 1–19. https://doi.org/10.1186/2050-7445-1-24

Pietrusewsky, M. (1969). An osteological study of cranial and infracranial remains from Tonga. *Records of the Auckland Institute and Museum*, *6*, 287–402.

Pietrusewsky, M. (1976). Prehistoric human skeletal remains from Papua New Guinea and the Marquesas. Social Science & Linguistics Institute, University of Hawaii at Manoa, Asian and Pacific Archaeology Series no. 7. Manoa, HI: University Press of Hawaii.

Pietrusewsky, M., Douglas, M. T., & Ikehara-Quebral, R. M. (1997). An assessment of health and disease in the prehistoric inhabitants of the Mariana Islands. *American Journal of Physical Anthropology*, *104*, 315–342. https://doi.org/10.1002/(SICI)1096-8644(199711)104:3<315::AID-AJPA4>3.0.Co;2-U

Pietrusewsky, M., Douglas, M. T., Ikehara-Quebral, R. M., & Lauer, K. K. (2019). Skeletal and Dental Health of Early Tongans: The Bioarchaeology of the Human Skeletons from the To-At-36 Site, Ha'ateiho, Tongatapu, Tonga. *The Journal of Island and Coastal Archaeology*, *13*, 1–40. https://doi.org/10.1080/15564894.2018.1564711

Powell, M. L., & Cook, D. C. (2005b). Introduction. In M. L. Powell & D. C. Cook (Eds.), *The Myth of Syphilis* (pp. 1–8). Gainesville, FL: University Press of Florida.

Powell, M. L., & Cook, D. C. (Eds.). (2005b). *The myth of syphilis: The natural history of treponematosis in North America*. Gainesville, FL: University Press of Florida.

Powell, M. L., Jacobi, K., Danforth, M. E., & Eisenberg, L. E. (2005). "Syphilis in mound builders' bones." Treponematosis in the central Southern United States. In M. L. Powell & D. C. Cook (Eds.), *The Myth of Syphilis* (pp. 117–161). Gainesville, FL: University Press of Florida.

Powers, N., Ed. (2012). Human osteology method statement. Available from https://www.museumoflondon.org.uk/application/files/4814/5633/5269/osteology-method-statement-revised-2012.pdf.

Price, T., Burton, J., Sharer, R., Buikstra, J., Wright, L., Traxler, L., & Miller, K. (2009). Kings and commoners at Copan: Isotopic evidence for origins and movement in the Classic Maya period. *Journal of Anthropological Archaeology*, *29*(2010), 15–32. https://doi.org/10.1016/j.jaa.2009.10.001

Prümers, H., Trautmann, M., Trautmann, I., Lösch, S., & Pusch, C. (2012). Syphilis in South America: A closer look at pre-contact Bolivia. *RCC Perspectives*, *2012*, 41–61. https://doi.org/10.5282/rcc/5593

Quétel, C., Braddock, J., & Pike, B. (1990). *History of syphilis*. Baltimore, MD: The Johns Hopkins University Press.

Radu, C., & Soficaru, A. D. (2016). Dental developmental defects in a subadult from 16th-19th centuries Bucharest, Romania. *International Journal of Paleopathology*, *15*, 33–38. https://doi.org/10.1016/j.ijpp.2016.08.001

Rao, V. V., Vasulu, T. S., & Rector Babu, A. D. W. (1996). Possible paleopathological evidence of treponematosis from a megalithic site at Agripalle, India. *American Journal of Physical Anthropology*, *100*, 49–55.

https://doi.org/10.1002/(SICI)1096-8644(199605)100:1<49::AID-AJPA5>3.0CO;2-8

Rasmussen, K., Skytte, L., Jensen, A., & Boldsen, J. (2015). Comparison of mercury and lead levels in the bones of rural and urban populations in southern Denmark and northern Germany during the Middle Ages. *Journal of Archaeological Science: Reports*, *3*, 358–370. https://doi.org/10.1016/j.jasrep.2015.06.021

Rasmussen, K. L., Boldsen, J. L., Kristensen, H. K., Skytte, L., Hansen, K. L., Mølholm, L., … Eriksen, K. M. F. (2008). Mercury levels in Danish Medieval human bones. *Journal of Archaeological Science*, *35*, 2295–2306. https://doi.org/10.1016/j.jas.2008.03.003

Rasmussen, K. L., Skytte, L., Pilekaer, C., Lauritsen, A., Boldsen, J. L., Leth, P. M., & Thomsen, P. O. (2013). The distribution of mercury and other trace elements in the bones of two human individuals from Medieval Denmark – The chemical life history hypothesis. *Heritage Science*, *1*(10), 1–13.

Rasool, M. N., & Govender, S. (1989). The skeletal manifestations of congenital syphilis. *Journal of Bone and Joint Surgery*, *71B*, 752–755.

Reitsema, L. J. (2013). Beyond diet reconstruction: Stable isotope applications to human physiology, health, and nutrition. *American Journal of Human Biology*, *25*, 445–456. https://doi.org/10.1002/ajhb.22398

Resnick, D., & Niwayama, G. (1995). Osteomyelitis, septic arthritis, and soft tissue infection: Organisms. In D. Resnick (Ed.), *Diagnosis of bone and joint disorders* (pp. 2448–2559). London, UK: W. B. Saunders.

Reverby, S. M. (2009). *Examining Tuskegee: The infamous syphilis study and its legacy*. Chapel Hill, NC: University of North Carolina Press.

Richards, M. P., & Montgomery, J. (2012). Isotope analysis and paleopathology: A short review and future developments. In J. Buikstra & C. Roberts (Eds.), *The global history of paleopathology* (pp. 718–731). Oxford, UK: Oxford University Press.

Richens, J., Mayaud, P., & Mabey, D. C. W. (2014). Sexually transmitted infections (excluding HIV). In J. Farrar, P. J. Hotez, T. Junghanss, G. Kang, D. Lalloo, & N. J. White (Eds.), *Manson's Tropical Diseases* (23rd ed., pp. 292–318.e3). Philadelphia, PA: Saunders/Elsevier. https://doi.org/10.1016/B978-0-7020-5101-2.00024-8

Rissech, C., Roberts, C., Tomás-Batlle, X., Tomás-Gimeno, X., Fuller, B., Fernandez, P. L., & Botella, M. (2011). A Roman skeleton with possible treponematosis in the north-east of the Iberian Peninsula: A morphological and radiological study. *International Journal of Osteoarchaeology*, *23*(2013), 651–653. https://doi.org/10.1002/oa.1293

Roberts, C. A. (1994). Treponematosis in Gloucester, England: A theoretical and practical approach to the Pre-Columbian theory. In O. Dutour, G. Pálfi, J. Bérato, & J. -P. Brun (Eds.), *L'origine de la syphilis in Europe: avant ou après 1493?* (pp. 101–108). Paris, France: Éditions Errance.

Roberts, C. A. (2017a). Applying the "Index of care" to a person who experienced leprosy in late Medieval Chichester, England. In L. Tilley & A. A. Schrenk (Eds.), *New developments in the bioarchaeology of care* (pp. 101–124). Chaim, Switzerland: Springer.

Roberts, C. A. (2017b). Palaeopathology. In P. Mitchell & M. Brickley (Eds.), *Updated guidelines to the standards for recording human remains* (pp. 44–47). Reading, UK: Chartered Institute for Archaeologists and BABAO.

Roberts, C. A., & Buikstra, J. E. (2019). Bacterial infections. In J. E. Buikstra (Ed.), *Ortner's Identification of pathological conditions in human skeletal remains* (3rd ed., pp. 321–439). New York, NY: Academic Press.

Roberts, C. A., & Connell, B. (2004). Palaeopathology. In M. Brickley & J. I. McKinley (Eds.), *Recording guidelines for the standards for human remains* (pp. 34–39). Institute of Field Archaeologists Paper 7. Reading, UK: Institute of Field Archaeologists.

Roberts, C. A., & Cox, M. (2003). *Health and disease in Britain: From prehistory to the present day*. Stroud, UK: Sutton Publishing.

Roberts, C. A., & Mays, S. (2010). Study and restudy of curated skeletal collections in bioarchaeology: A perspective on the UK and its implications for future curation of human remains. *International Journal of Osteoarchaeology*, *21*, 626–630. https://doi.org/10.1002/oa.1175

Roberts, C. A., Millard, A. R., Nowell, G. M., Gröcke, D. R., Macpherson, C. G., Pearson, D. G., & Evans, D. H. (2012). Isotopic tracing of the impact of mobility on infectious disease: The origin of people with treponematosis buried in Hull, England, in the Late Medieval Period. *American Journal of Physical Anthropology*, *150*, 273–285. https://doi.org/10.1002/ajpa.22203

Roberts, C. A., & Redfern, R. (2019). 'The history of treponematosis continues to be one of the most contentious issues in science' (Ortner 2003:273) – some perspectives from bioarchaeology. In S. Sretzer (Ed.), *The Hidden Affliction: Sexually-transmitted infections in history and infertility* (pp. 93–123). Rochester, New York: Rochester University Press and Boydell & Brewer History of Medicine series.

Rockwell, D. H., Roof Yobs, A., & Moore, M. B., Jr. (1964). The Tuskegee study of untreated syphilis. The 30th year of observation. *Archives of Internal Medicine*, *114*, 792–798. https://doi.org/10.1001/archinte.1964.03860120104011

Rodrigues Lopes, C. C. (2014). *As mil caras de uma doença – sífilis na sociedade Coimbrã no início do século XX*. (Unpublished PhD dissertation). University of Coimbra, Coimbra, Portugal.

Román, G. C., & Román, L. N. (1986). Occurrence of congenital, cardiovascular, visceral, neurologic, and neuro-ophthalmologic complications in late yaws: A theme for future research. *Reviews of Infectious Diseases*, *8*, 760–770. https://doi.org/10.1093/clinids/8.5.760

Rosebury, T. (1971). *Microbes and morals*. New York, NY: Viking.

Rosebury, T. (1992). Columbus and the Indians. *Monthly Review (New York)*, *44*, 61–70.

Rosenberg, B. A. (1986). Reconstructed folktales as literary sources. In J. J. McGann (Ed.), *Historical studies and literary criticism* (pp. 76–89). Madison, WI: University of Wisconsin Press.

Ross, E. B. (1995). Syphilis, misogyny, and witchcraft in 16th-century Europe. *Current Anthropology*, *36*, 333–337. https://doi.org/10.1086/204365

Rothschild, B. M., Hershkovitz, I., & Rothschild, C. (1995). Origin of yaws in the Pleistocene. *Nature*, *378*, 343–344.

Rothschild, B. M., & Rothschild, C. (1995). Treponemal disease revisited: Skeletal discriminators for yaws, bejel, and venereal syphilis. *Clinical Infectious Diseases*, *20*, 1402–1408. https://doi.org/10.1093/clinids/20.5.1402

Rothschild, B. M., & Rothschild, C. (1996). Analysis of treponemal disease in North Africa: The case for Bejel in the Sudan, but absence in West North Africa. *Human Evolution*, *11*(1), 11–15.

Russell, J. C. (1972). *Medieval Regions and their Cities*. Bloomington, Indiana: Indiana University Press.

Salazar, J. C., & Bennett, N. J. (2014). Endemic treponematosis including yaws and other spirochaetes. In J. Farrar, P. J. Hotez, T. Junghanss, G. Kang, D. Lalloo, & N. J. White (Eds.), *Manson's Tropical Diseases* (23rd ed., pp. 421–432.e3). Philadelphia, PA: Saunders/Elsevier. https://doi.org/10.1016/B978-0-7020-5101-2.00037-6

Salesse, K., Kaupová, S., Brůžek, J., Kuželka, V., & Velemínský, P. (2019). An isotopic case study of individuals with syphilis from the pathological-anatomical reference collection of the National Museum in Prague (Czech Republic, 19th century A.D.). *International Journal of Paleopathology*, *25*, 46–55. https://doi.org/10.1016/j.ijpp.2019.04.001

Santos, A. L., Gardner, M. T., & Allsworth-Jones, P. (2012). Treponematosis in pre-Columbian Jamaica: A biocultural approach to the human cranium found in Bull Savannah. *Journal of Archaeological Science*, *40* (2013), 490–496. https://doi.org/10.1016/j.jas.2012.06.001

Sartin, J. S., & Perry, H. O. (1995). From mercury to malaria to penicillin: The history of the treatment of syphilis at the Mayo Clinic. *Journal of the American Academy of Dermatology*, *32*, 255–261. https://doi.org/10.1016/0190-9622(95)90136-1

Sawafuji, R., Cappellini, E., Nagaoka, T., Fotakis, A. K., Jersie-Christensen, R. R., Olsen, J. V., … Ueda, S. (2017). Proteomic profiling

of archaeological human bone. *Royal Society Open Science*, *4*(161004), 1–12. https://doi.org/10.1098/rsos.161004

Schaffer, W. C., & Carr, R. S. (2013). Temporal and spatial distribution of treponemal infection in South Florida: An epidemiological approach. *International Journal of Osteoarchaeology*, *25*(2015), 765–775. https://doi.org/10.1002/oa.2343

Schlecht, S. H. (2012). Understanding entheses: Bridging the gap between clinical and anthropological perspectives. *The Anatomical Record*, *295*, 1239–1251. https://doi.org/10.1002/ar.22516

Schrenk, A., Gregoricka, L. A., Martin, D. L., & Potts, D. T. (2016). Differential diagnosis of a progressive neuromuscular disorder using bioarchaeological and biogeochemical evidence from a Bronze Age skeleton in the UAE. *International Journal of Paleopathology*, *13*, 1–10. https://doi.org/10.1016/j.ijpp.2015.12.004

Schuenemann, V. J., Kumar Lankapalli, A., Barquera, R., Nelson, E. A., Iraíz Hernández, D., Acuña Alonzo, V., … Krause, J. (2018). Historic *Treponema pallidum* genomes from colonial Mexico retrieved from archaeological remains. *PLoS Neglected Tropical Diseases*, *12*(6), e0006447. https://doi.org/10.1371/journal.pntd.0006447

Schwarz, S., Skytte, L., & Rasmussen, K. L. (2013). Pre-Columbian treponemal infection in Denmark? A paleopathological and archaeometric approach. *Heritage Science*, *1*(19), 1–12. https://doi.org/10.1186/2050-7445-1-19

Scolnik, D., Aronason, L., Lovinksy, R., Toledano, K., Glazier, R., Eisenstadt, J., … Silverman, M. (2003). Efficacy of a targeted, oral penicillin-based yaws control program among children living in rural South America. *Clinical Infectious Diseases*, *36*, 1232–1238. https://doi.org/10.1086/374338

Sheehan, M. C., Burke, T. A., Navas-Acien, A., Breysse, P. N., McGready, J., & Fox, M. A. (2014). Global methylmercury exposure from seafood consumption and risk of developmental neurotoxicity: A systematic review. *Bulletin of the World Health Organization*, *92*, 254–269. https://doi.org/10.2471/BLT.12.116152

Shin, D. H., Lee, H. J., Hong, J. H., Woo, E. J., Shin, E., Kim, Y. -S., … Lee, E. (2018). A historical approach to syphilis infection in Korea. *Acta Medico-Historica Adriatica*, *16*, 185–202. https://doi.org/10.31952/amha.16.2.1

Shugar, A. N., & Mass, J. L. (2012). Introduction. In A. N. Shugar & J. L. Mass (Eds.), *Handheld XRF for art and archaeology* (pp. 17–36). Leuven, Belgium: Leuven University Press.

Sidell, J., Christopher, T., & Bayliss, A. (2007). Validating and improving archaeological phasing at St. Mary Spital, London. *Radiocarbon*, *49*, 593–610. https://doi.org/10.1017/S0033822200042491

Siena, K. (2001). The "foul disease" and privacy: The effects of venereal disease and patient demand on the medical marketplace in early modern London. *Bulletin of the History of Medicine*, *75*(2), 199–224. https://doi.org/10.1353/bhm.2001/0097

Siena, K. (2004). *Venereal disease, hospitals, and the urban poor: London's "foul wards," 1600–1800*. Rochester, NY: University of Rochester Press.

Šlaus, M., & Novak, M. (2007). A case of venereal syphilis in the Modern Age horizon of graves near the church of St Lawrence in Crkvari. *Contributions of the Institute of Archaeology in Zagreb*, *24*, 503–510.

Smith, G. E. (1908). The alleged discovery of syphilis in prehistoric Egyptians. *The Lancet*, *172*(4434), 521–524. https://doi.org/10.1016/S0140-6736(01)79018-6

Smith, J. L., David, N. J., Indgin, S., Israel, C. W., Levine, B. M., Justice, J., Jr., … Walter, E. K. (1971). Neuro-opthalmological study of late yaws and pinta II. The Caracas Project. *The British Journal of Venereal Diseases*, *47*, 226–251. https://doi.org/10.1136/sti.47.4.226

Smith, M. O. (2006). Treponemal disease in the Middle Archaic to Early Woodlands periods of the western Tennessee River valley. *American Journal of Physical Anthropology*, *131*, 205–217. https://doi.org/10.1002/ajpa.20427

Smith, M. O., & Betsinger, T. K. (2013). Subsistence and settlement correlates of treponemal disease: Temporal patterns in pre-Columbian East Tennessee. *International Journal of Osteoarchaeology*, *25*(2015), 855–865.

Smith, M. O., Betsinger, T. K., & Williams, L. L. (2010). Differential visibility of treponemal disease in pre-Columbian stratified societies: Does rank matter? *American Journal of Physical Anthropology*, *144*(2011), 185–195. https://doi.org/10.1002/ajpa.21381

Smith, S. E., Hirst, C. S., Ulguim, P. F., Henderson, C. Y., Biers, T., O'Mahoney, T., and Errickson, D. (2019). BABAO recommendations on the ethical issues surrounding 2D and 3D digital imaging of human remains. Available from https://www.babao.org.uk/assets/Uploads/BABAO-Digital-imaging-code-2019.pdf.

Snoddy, A. M. E., Buckley, H. R., Elliott, G. E., Standen, V. G., Arriaza, B. T., & Halcrow, S. E. (2018). Macroscopic features of scurvy in human skeletal remains: A literature synthesis and diagnostic guide. *American Journal of Physical Anthropology*, *167*, 876–895. https://doi.org/10.1002/ajpa.23699

Speakman, R. J., & Shackley, M. S. (2012). Silo science and portable XRF in archaeology: A response to Frahm. *Journal of Archaeological Science*, *40*(2013), 1435–1443. https://doi.org/10.1016/j.jas.2012.09.033

Ssegawa, P., & Kasenene, J. M. (2007). Medicinal plant diversity and uses in the Sango bay area, southern Uganda. *Journal of Ethnopharmacology*, *113*, 521–540. https://doi.org/10.1016/j.jep.2007.07.014

Stafford, I. A., Sánchez, P. J., & Stoll, B. J. (2019). Ending congenital syphilis. *Journal of the American Medical Association*, *322*, 2073. https://doi.org/10.10001/jama.2019.17031

Stamm, L. V. (2015). Pinta: Latin America's forgotten disease? *American Journal of Tropical Medicine and Hygiene*, *93*(5), 901–903. https://doi.org/10.4269/ajtmh.15-0329

Štaudová, B., Strouhal, M., Zobaníková, M., Čejková, D., Fulton, L. L., Chen, L., … Šmajs, D. (2014). Whole genome sequence of the *Treponema pallidum* subsp. *endemicum* strain Bosnia A: The genome is related to yaws treponemes but contains few loci similar to syphilis treponemes. *PLoS Neglected Tropical Diseases*, *8*(11), e3261. https://doi.org/10.1371/journal.pntd.0003261

Steckel, R. H., Larsen, C. S., Roberts, C. A., & Baten, J. (Eds.). (2018). *The backbone of Europe. Health, diet, work and violence over two millennia*. Cambridge, UK: Cambridge University Press.

Steinbock, R. T. (1976). *Paleopathological diagnosis and interpretation*. Springfield, IL: Charles C. Thomas.

Steyn, M., & Henneberg, M. (1995). Pre-Columbian presence of treponemal disease: A possible case from Iron Age Southern Africa. *Current Anthropology*, *36*, 869–873. https://doi.org/10.1086/204446

Stodder, A. L. W. (1997). Subadult stress, morbidity, and longevity in Latte Period populations on Guam, Mariana Islands. *American Journal of Physical Anthropology*, *104*, 363–380. https://doi.org/10.1002/(SICI)1096-8644(199711)104:3<363::AID-AJPA6>3.0.CO;2-W

Stodder, A. L. W. (2012). Data and data analysis issues in paleopathology. In A. L. Grauer (Ed.), *A Companion to Paleopathology* (pp. 339–356). Malden, MA: Blackwell.

Stodder, A. L. W., & Byrnes, J. F. (2019). (Re)Discovering paleopathology: Integrating individuals and populations in bioarchaeology. In C. M. Willermet & S. H. Lee (Eds.), *Evaluating evidence in biological anthropology: The strange and the familiar* (pp. 103–125). Cambridge, U.K: Cambridge University Press.

Stodder, A. L. W., Trembly, D., & Tucker, C. (1992). Paleoepidemiology and paleopathology of treponematosis in pre- and proto-historic villages in Western Micronesia. *American Journal of Physical Anthropology*, *35* (S14), 157.

Stokes, J. H., Beerman, H., & Ingraham, N. R., Jr. (1944). *Modern clinical syphilology* (3rd ed.). Philadelphia, PA: W. B. Saunders Company.

Stone, A. C., & Ozga, A. T. (2019). Ancient DNA in the study of ancient disease. In J. E. Buikstra (Ed.), *Ortner's identification of pathological*

conditions in human skeletal remains (3rd ed., pp. 183–210). London, UK & San Diego, CA: Academic Press, Elsevier.

Strouhal, E. (1994). Syphilis in ancient Egypt. In O. Dutour, G. Pálfi, J. Bérato, & J. -P. Brun (Eds.), *L'origine de la syphilis in Europe: avant ou après 1493?* (pp. 148–153). Paris, France: Éditions Errance.

Stuiver, M., Pearson, G. W., & Braziunas, T. (1986). Radiocarbon age calibration of marine samples back to 9000 cal yr BP. *Radiocarbon*, *28*(2B), 980–1021. https://doi.org/10.1017/S0033822200060264

Sunny, S. D., Israt, B., Saha, A. K., Dithi, A. B., & Illius, F. (2013). Oral health of the arsenic exposed and non-exposed children in Bangladesh. *City Dental College Journal*, *10*(1), 5–8. https://doi.org/10.3329/cdcj.v10i1.13834

Suzuki, T. (1984). *Paleopathological and palaeoepidemiological study of osseous syphilis in skulls of the Edo period*. The University of Tokyo Bulletin, No. 23. Tokyo, Japan: University Museum, University of Tokyo. Available from http://umdb.um.u-tokyo.ac.jp/DKankoub/Bulletin/no23/no23000.html.

Suzuki, T., Matsushita, T., & Han, K. (2005). On the possible case of treponematosis from the Bronze Age in China. *Anthropological Science*, *113*, 253–258. https://doi.org/10.1537/ase.040831

Švejda, J. (1952). Zmeny na zubech pri kongenitalni syfilis. *Ceskoslovenská Stomatologie*, *52*, 321–341.

Swiderski, R. M. (2008). *Quicksilver: A history of the use, lore and effects of mercury*. London: McFarland & Co.

Tampa, M., Sarbu, I., Matei, C., Benea, V., & Georgescu, S. R. (2014). Brief history of syphilis. *Journal of Medicine and Life*, *7*(1), 4–10.

Thomann, J. (2015). Early Persian medical works on antisyphilitic mercury medicines. *Asiatische Studien - Études Asiatiques*, *69*(4), 971–996. https://doi.org/10.1515/asia-2015-1047

Tilley, L. (2015). *Theory and practice in the bioarchaeology of care*. Cham, Switzerland: Springer. https://doi.org/10.1007/978-3-319-18860-7

Tilley, L. (2016). Showing that they cared: An introduction to thinking, theory and practice in the bioarchaeology of care. In L. Tilley & A. A. Schrenk (Eds.), *New developments in the bioarchaeology of care: Further case studies and expanded theory*. Cham, Switzerland: Springer. https://doi.org/10.1007/978-3-319-39901-0_2

Tilley, L., & Cameron, T. (2014). Introducing the Index of Care: A web-based application supporting archaeological research into health-related care. *International Journal of Paleopathology*, *6*, 5–9. https://doi.org/10.1016/j.ijpp.2014.01.003

Tomczyk, J., Mańkowska-Pliszka, H., Palczewski, P., & Olczak-Kowalczyk, D. (2015). Congenital syphilis in the skeleton of a child from Poland (Radom, 18th-19th century AD). *Anthropological Review*, *78*, 79–90. https://doi.org/10.1515/anre-2015-0006

Trembly, D. L. (1996). Treponematosis in pre-Spanish Western Micronesia. *International Journal of Osteoarchaeology*, *6*, 397–402. https://doi.org/10.1002/(SICI)1099-1212(199609)6:4<397::AID-OA289>3.0.CO;2-%23

Trouillot, M.-R. (1995). *Silencing the past: Power and the production of history*. Boston, MA: Beacon Press.

Tucker, F. (2007). Kill or cure? The osteological evidence of the mercury treatment of syphilis in 17th- to 19th-centry London. *London Archaeologist*, *11*(8), 220–224.

Turner, T. B., & Hollander, D. H. (1957). *Biology of the treponematoses. World Health Organization Monograph Series No. 35*. Geneva, Switzerland: World Health Organization.

Vasulu, T. S. (1993). The origin and antiquity of syphilis (treponematosis) in southeast Asia. *Human Evolution*, *8*, 229–233. https://doi.org/10.1007/BF02438113

Vasulu, T. S. (1994). On the origin and antiquity of treponematosis: An appraisal—Asia. In O. Dutour, G. Pálfi, J. Bérato, & J. -P. Brun (Eds.), *L'origine de la syphilis in Europe: Avant ou après 1493?* (pp. 154–156). Paris, France: Éditions Errance.

Von Hunnius, T. E., Roberts, C. A., Boylston, A., & Saunders, S. R. (2005). Histological identification of syphilis in pre-Columbian England. *American Journal of Physical Anthropology*, *129*, 559–566. https://doi.org/10.1002/ajpa.20335

Von Hunnius, T. E., Yang, D., Eng, B., Waye, J. S., & Saunders, S. R. (2007). Digging deeper into the limits of ancient DNA research on syphilis. *Journal of Archaeological Science*, *34*, 2091–2100. https://doi.org/10.1016/jas.2007.02.007

Von Hutten, U. (1533). *De Morbo Gallico*, Thomas Paynell, translator. Londini: Thomae Bertheleti. Available online at Early English Books Online Text Creation Partnership, http://name.umdl.umich.edu/A03916.0001.001, accessed November 11, 2019.

Wada, Y., Ikeda, J., & Suzuki, T. (1987). Probable treponematosis in human skeletons from the Himrin Basin of Iraq. *Journal of the Anthropological Society of Nippon*, *95*, 443–456.

Walker, D., Powers, N., Connell, B., & Redfern, R. (2015). Evidence of skeletal treponematosis from the Medieval burial ground of St. Mary Spital, London, and implications for the origins of the disease in Europe. *American Journal of Physical Anthropology*, *156*, 90–101. https://doi.org/10.1002/ajpa.22630

Walser, J. W., III, Kristjánsdóttir, S., Gowland, R., & Desnica, N. (2018). Volcanoes, medicine, and monasticism: Investigating mercury exposure in Medieval Iceland. *International Journal of Osteoarchaeology*, *29*, 48–61. https://doi.org/10.1002/oa.2712

Walth, Cherie K. (2016). *Archaeological investigations at the Naton Beach Site, Tumon, Guam. Volume II: The osteological analysis of the human remains*. SWCA Report No. 13–504. Albuquerque, NM: SWCA Environmental Consultants.

Warinner, C., Rodrigues, J. F. M., Vyas, R., Trachsel, C., Shved, N., Grossmann, J., … Cappellini, E. (2014). Pathogens and host immunity in the ancient human oral cavity. *Nature Genetics*, *46*(4), 336–344. https://doi.org/10.1038/ng.2906

Waterbolk, H. T. (1971). Working with radiocarbon dates. *Proceedings of the Prehistoric Society*, *37*, 15–33. https://doi.org/10.1017/S0079497X00012548

Webb, S. (1995). *Palaepathology of Aboriginal Australians*. Cambridge, UK, and New York, NY: Cambridge University Press.

Weston, D. A. (2008). Investigating the specificity of periosteal reactions in pathology museum specimens. *American Journal of Physical Anthropology*, *137*, 48–59. https://doi.org/10.1002/ajpa.20839

Weston, D. A. (2009). Brief communication: Paleohistopathological analysis of pathology museum specimens: Can periosteal reaction microstructure explain lesion etiology? *American J Physical Anthropology*, *140*, 186–193. https://doi.org/10.1002/ajpa.21081

Weston, D. A. (2012). Nonspecific infection in paleopathology: Interpreting periosteal reactions. In A. L. Grauer (Ed.), *A Companion to Paleopathology* (pp. 492–512). Malden, MA: Blackwell.

Wheeler, S. M., Williams, L., Beauchesne, P., & Dupras, T. (2013). Shattered lives and broken childhoods: Evidence of physical child abuse in ancient Egypt. *International Journal of Paleopathology*, *3*, 71–82. https://doi.org/10.1016/j.ijpp.2013.03.009

White, C. D., & Armelagos, G. J. (1997). Osteopenia and stable isotope ratios in bone collagen of Nubian female mummies. *American Journal of Physical Anthropology*, *103*, 185–199. https://doi.org/10.1002/1096-8644(199706)103:2<185::AID-AJPA11>3.0.CO;2-#

Willcox, R. R. (1951). Njovera: An endemic syphilis of Southern Rhodesia. *The Lancet*, *257*, 558–561.

Williams, H. (1932). The origin and antiquity of syphilis: The evidence from diseased bones, a review, with some new material from America. *Archives of Pathology*, *13*(779–814), 931–983.

Wilson, D. E. (2005). Treponematosis in the East Texas Gulf coastal plain. In M. L. Powell & D. C. Cook (Eds.), *The Myth of Syphilis* (pp. 162–176). Gainesville, FL: University Press of Florida.

Woo, E. J., Kim, J. -H., Lee, W. -J., Cho, H., & Pak, S. (2019). Syphilitic infection in a pre-modern population from South Korea (19th century AD). *Anthropological Science*, *127*, 55–63. https://doi.org/10.1537/ase.181122

Wood, J. W., Milner, G. R., Harpending, H. C., & Weiss, K. M. (1992). The osteological paradox: Problems of inferring prehistoric health from skeletal samples. *Current Anthropology*, *33*(4), 343–370. https://doi.org/10.1086/204084

World Health Organization. (2012). Eradication of yaws – the Morges strategy. *Weekly Epidemiological Record*, *87*, 189–200.

World Health Organization. (2018). *Report on the Health of Refugees and Migrants in the WHO European Region. No PUBLIC HEALTH without REFUGEE and MIGRANT HEALTH*. Copenhagen, Denmark: WHO. Available from. http://www.euro.who.int/en/health-topics/health-determinants/migration-and-health/publications/2018/report-on-the-health-of-refugees-and-migrants-in-the-who-european-region-no-public-health-without-refugee-and-migrant-health-2018

Yamada, M., Tohno, S., Tohno, Y., Minami, T., Ichii, M., & Okazaki, Y. (1995). Accumulation of mercury in excavated bones of two natives in Japan. *Science of the Total Environment*, *162*(2,3), 253–256. https://doi.org/10.1016/0048-9697(95)04435-4

Zhang, Z. (1994). The skeletal evidence of human leprosy and syphilis in ancient China. *Acta Anthropologica Sinica*, *13*, 294–299. English abstract available from. http://en.cnki.com.cn/Article_en/CJFDTOTAL-RLXB404.001.htm

Zobaníková, M., Strouhal, M., Mikalová, L., Čejková, D., Ambrožová, L., Pospíšilová, P., … Šmajs, D. (2013). Whole genome sequence of the *Treponema* Fribourg-Blanc: Unspecified simian isolate is highly similar to the yaws subspecies. *PLoS Neglected Tropical Diseases*, *7*(4), e2172. https://doi.org/10.1371/journal.pntd.0002172

Zuckerman, M. K. (2016). More harm than healing? Investigating the iatrogenic effects of mercury treatment on acquired syphilis in post-Medieval London. *Open Archaeology*, *2*, 42–55. https://doi.org/10.1515/opar-2016-0003

Zuckerman, M. K. (2017). Mercury in the midst of Mars and Venus: Reconstructing gender, sexuality, and socioeconomic status in relation to mercury treatment for syphilis in seventeenth- to nineteenth-century London. In S. C. Agarwal & J. K. Wesp (Eds.), *Exploring sex and gender in bioarchaeology* (pp. 223–261). Albuquerque, NM: University of New Mexico Press.

Zuckerman, M. K., Harper, K. N., & Armelagos, G. J. (2016). Adapt or die: Three case studies in which the failure to adopt advances from other fields has compromised paleopathology. *International Journal of Osteoarchaeology*, *26*, 375–383. https://doi.org/10.1002/oa.2426

SUPPORTING INFORMATION

Additional supporting information may be found at a link before the References in the online version of this article.

How to cite this article: Baker BJ, Crane-Kramer G, Dee MW, et al. Advancing the understanding of treponemal disease in the past and present. *Yearbook Phys Anthropol*. 2020;171 (Suppl. 70):5–41. https://doi.org/10.1002/ajpa.23988