Old World tuberculosis: evidence from human remains with a review of current research and future prospects

Charlotte Roberts
Department of Archaeology
Durham University
South Road
England
DH1 3LE

(c.a.roberts@durham.ac.uk; Tel: +441913341154; Fax: +441913341100)

Abstract

The evidence for TB in archaeological human remains for the Old World is reviewed in published and some unpublished sources. The evidence of Pott's disease was considered specific for TB, with other bone changes, such as rib lesions, as non-specific. Limitations of the data are discussed. Most evidence for TB comes from skeletons from the northern hemisphere, particularly in Europe in the late Medieval period (12^{th}-16^{th} centuries AD), but there is early evidence in the Near/Middle East and Egypt. Many parts of Africa, Asia and Australasia have very little or no evidence. aDNA analysis has provided data on species and strains of the *M. tuberculosis* complex organisms affecting people in the past. The extant data suggest the first epidemiological transition (Neolithic agriculture and permanent settlements) led to an increase in TB, with later increases in urban environments of the late Medieval period. A number of causative factors were at play. Future research, particularly using biomolecular analysis, has the potential to further contribute to our understanding of the origin and evolution of TB, thus merging the disciplines of palaeopathology and evolutionary medicine.

Key words

Europe, diagnosis, limitations, aDNA analysis, diet, mobility, vitamin D, agriculture, urbanism

Introduction

It was only 25 years ago that Smith was seen to say that 'Tuberculosis is now a conquered disease in the British Isles and the rest of the industrialised world'[1], but it was not long before the World Health Organization had declared tuberculosis (TB) to be a global emergency **(**1993**)**. TB remains with the world today in both developed and developing countries, it infects a third of the world's population, and in 2012 around 8.6 million people developed TB and 1.3 million died[2]. In the UK, a recent report has highlighted that data there indicate that all sectors of society are affected, that it is an urban disease, and East London was TB capital Western world with a higher rate than India[3]. TB has affected the human population for thousands of years and yet it has not been possible to eradicate it today for a variety of reasons. These include the increasing resistance to antibiotics, susceptibility of human immunodeficiency virus compromised people, especially in Africa, increasing poverty, extensive human migration, and specific occupations that predispose people.

Studies of the palaeopathological evidence for TB in skeletons and mummies from archaeological sites have provided a deep time perspective on TB's origin evolution and history through research since the early 20th century[4]. This provides an extended view of the lived experiences of populations with TB which can be used to understand the problem today, and perhaps be used to plan for the future. Indeed, as a disease of the poor, it was apparently common among those living in poverty in the past and, logically, eliminating poverty in the world today could help to control this disease. A more recent development, especially as a result of the sequencing of the TB genome, is the analysis of ancient DNA of the TB bacteria. This is allowing a more nuanced view of TB to be developed, with data indicating the species and the genotypes (strains) of the bacteria that people suffered in the past. Comparing genotypes between past and present populations may in the future provide an opportunity to re-evaluate the reasons for antibiotic resistance, by helping to understand the factors that can lead to mutation of the subtypes and consequent resistance.

This paper aims to take a broad overview of the evidence for TB in archaeological human remains in the Old World by collating the data published to date. It will also review the diagnostic criteria used by palaeopathologists to identify TB, the

contributions of biomolecular analysis, the limitations of the data, and future prospects. In such a short review, it is important it is not possible to consider the evidence in great detail, and therefore the reader is referred to further information detailed in the reference section.

Materials and methods

Materials

The evidence for disease diagnosed in archaeological human remains is to be found both in published and unpublished outlets. However, much data from archaeological contexts are located in what is termed "the grey literature", or unpublished resources, thus making tracking down of evidence challenging. The data for TB in this paper is mainly based on published literature, although recognising the fact that some data may be invisible in unpublished sources. Indeed unpublished data abound in the discipline of archaeology due to many reasons (e.g. almost 40% of health data collated from over 300 cemetery sites in past Britain were unpublished)[5]. Most archaeological data, from pottery to buildings and human remains, are uncovered as a result of "developed-led funded" archaeology in advance of modern building projects; due to pressures of time and money, much data are simply not brought forward to publication. It is likely that this situation applies to most parts of the world. Scholars also do not necessarily publish in outlets that appear in database searches, such as PubMed or Medline, some data are simply never published, and not all scholars necessarily, for many reasons, access research that is written in languages other than english. However, there are now some facilities in archaeology where "grey literature" does appear and can be accessed (e.g. Archaeology Data Service: http://archaeologydataservice.ac.uk/; Archaeological Investigations Project: http://csweb.bournemouth.ac.uk/aip/aipintro.htm; OASIS or Online Access to the Index of Archaeolological Excavations; http://oasis.ac.uk/; accessed October 2013), assuming that scholars with relevant data actively seek to ensure they "engage" with these outlets. Therefore, the data that are used for this paper cannot be viewed as all encompassing, and of course the pattern may change as more data is collected and published, especially in parts of the world where palaeopathology as a discipline is developing or has yet to develop[6].

Data from skeletal remains and preserved mummies were considered for inclusion in this study from all periods of time and all regions of the Old World. This collation of data builds on those published in Roberts and Buikstra[7]. It should be noted that most data derive from skeletal remains because they are the most common type of human remains discovered in archaeology, and bodies are preserved only in special environmental circumstances, such as very cold and dry, or hot arid, conditions.

Methods

Selection of data for TB to include in this paper required specific criteria to be met. It should be noted that he majority of scholars who study ancient disease in human remains use macroscopic analysis to diagnose TB[8]. This is because this method is the most cost effective, with other methods (histological, radiographic and biomolecular) being out of the reach of most because of lack of availability of expertise and finance, and access to analytical facilities. Thus, it is argued by some that a lack of a biomolecular diagnosis for TB means that there is no "proof" that a person suffered TB. However, the process of diagnosis in human remains is rigorous. Bone formation and destruction, and plotting the distribution pattern of lesions in the skeleton are the first steps towards a differential diagnosis. Following this process, a list of possible differential diagnoses is formulated, and a most likely diagnosis is suggested. While there are challenges to inferring health from the skeleton[9], including the inability to produce absolute frequency rates in the past, other methods also have their limitations. For example, on the face of it, ancient DNA analysis, presents a method that can potentially provide real frequency rates for TB in the past, diagnose TB in people whose remains do not show any evidence, and give nuanced data about the species and strain of TB a person suffered, but the method depends on the preservation of aDNA in human remains, and the data produced being accurate[10].

The bone changes of TB may be specific, or pathognomonic to, TB, or could be non-specific, meaning they could be related to TB but could also be caused by a number of other diseases; only 3-5% of untreated people develop bone damage in their skeleton. This is via haematogenous and lymphatic spread from a primary focus (lungs or gastrointestinal tract), but more often than not it is the spine that is involved. Of course, evidence for TB in antiquity can also be located in documents and art[7]. These

data sources are not considered here. The pathognomonic changes are to be found in destructive lesions, with little or no new bone formation; these changes are especially seen in the lower thoracic and lumbar spine. The hip and knee joints can also be affected, but any bone of the body may be involved. The non-specific bone changes may include bone formation on the visceral surfaces of ribs, calcified pleura or granulomatous lung modules, destructive lesions of the bone underlying the skin lesions of lupus vulgaris, bone formation particularly on long bones, as seen in hypertrophic pulmonary osteoarthropathy, tuberculous dactylitis of the short bones of the hands and feet, and bone changes possibly as a result of tuberculous induced meningitis on the endocranium or gastrointestinal tuberculous involvement of the pelvic bones[7]. These non-pathognomonic bone changes can be caused by many other diseases, and should never be used alone to diagnose TB, and neither can they be "proved" to be caused by TB based on biomolecular analysis. When collecting data on tuberculosis from human remains it is important to accurately and consistently use the diagnostic criteria outlined, and when the biological data is interpreted it is vital that available archaeological and historical data are used to understand the patterns seen.

The data to be presented were collected mainly from published sources, and initially assessed for diagnostic accuracy before being used for final interpretations.

Results (Figure 1)

The data presented here provide an overview of the general distribution pattern of TB in the Old World both from a geographical and temporal viewpoint. Data for the New World tends to be later in date but are not discussed here, and can be found elsewhere [7,11]. Most of the data considered were from diagnoses of lesions in skeletons from a macroscopic point of view. However, there has been an increase in diagnoses using other methods over time, such as radiography, histology and ancient pathogen DNA analysis, the latter seeing increasing use in the last 20 years. Evidence for tuberculosis in skeletal remains from the Old world is plentiful in Europe but less so for the rest of the area. Apart from North and South America (New World), there is definite evidence in three other continents (of five) of the world (Europe, Africa and Asia); there is possible evidence in Australasia[7], but no evidence in the Antarctic.

The majority of the evidence in the Old World is in Europe, with very few countries having no evidence (e.g. Belgium and Iceland) and some having much (e.g. the UK and Hungary). The definitive evidence in the Old World ranges in latitude from 20°-70°, and in longitude from 0°-120 °. All evidence is in the Northern Hemisphere. There are many parts of Africa, Asia and Australasia that have no evidence. The earliest dated evidence is from Israel (7250-6160 BC)[12], with early Egyptian (4500 BC)[13], German (5400–4800 BC)[14], Hungarian (5th millennium BC)[15], and Polish and Portuguese "Neolithic" data. However, most skeletal evidence comes from the Roman and later periods in Europe, and especially the early and late medieval eras (around 5th-15th centuries AD). Additional to the macroscopic data for tuberculosis, DNA of the *Mycobacterium. tuberculosis* complex has been amplified and analysed from a number of skeletons and mummies deriving from several countries. This has been to confirm a macroscopic diagnosis, to diagnose people who had TB but not bone damage, or to gain more nuanced information about the species and/or strain of the bacteria affecting the individual. Skeletons and mummies from Britain, the Czech Republic, France, Germany, Hungary, Lithuania, Spain, and Sweden in Europe, and Egypt, Israel, Japan and Siberia outside of Europe, have been successfully analysed for the presence of ancient tuberculous DNA, with Britain, Egypt, Hungary, Lithuania seeing the most work. This has provided data on the species of the *M. tuberculosis* complex to be established (e.g. *M. africanum* in Egypt in 2050-1650 BC[16]). These analyses have further highlighted modern strains of TB in archaeological remains (e.g. in 18th-19th century Hungary[17]), along with a strain of TB in 19th century human remains common in North America but not England[18].

Discussion

The evidence for tuberculosis presented in this paper is reliant on published sources of data that are readily accessible. There can be many limitations to undertaking such a broad based study, rather than a detailed analysis of a skeleton, or a group of skeletons, with TB from one archaeological site. However, to understand better the origin and evolution of TB, it is important to take a "big picture" approach so that the timing and location of the occurrence of TB in our ancestors' remains can be mapped.

The limitations of the data can be described as: it is limited to where excavations take place (often in urban situations in advance of modern development), there are problems of preservation of human remains available for analysis in different parts of the Old World, there is a lack of development of palaeopathology in certain regions, the fact that only a small percentage of people with untreated TB develop bone changes that can be recognisable, and that people in some periods of time and places cremated their dead, thus making the evidence generally invisible. It should also be noted that the absolute frequency of TB in the past cannot be known for many of the reasons discussed here. Even the presence or absence of TB in human remains can generate different scenarios[9]. For example, a skeleton with no bone changes of TB could have suffered the infection and died before they developed bone damage that is recognizable. Essentially, the evidence seen in skeletal remains is evidence of chronic infection, meaning that the person had had TB for some time before they died. However, the strength of a person's immune system i.e. whether they were resistant or not to the bacteria, and will also influence whether bone changes occur, and the diet a person eats is suggested to affect the development of tuberculous bone changes[19].

Bearing in mind the limitations of the data described above, along with some data probably lying in unpublished grey literature or in difficult to access published sources, what does the evidence for TB in human remains in the Old World represent and tell us about the experience of people with this infection in the past? The data comes mainly from remains of adults, with a mix of males and females being affected of different ages from young to old. Non-adults are not as affected as adults, but non-adult skeletons may not be preserved in the archaeological record, for various reasons. However, the data are such that it is not possible to reflect on the absolute frequencies of TB in males and females of different ages, in the past, unlike today.

Firstly, there is very early evidence in the Middle/Near East, including Africa, and a few parts of Europe. At the time these people suffered TB, there is evidence of the practice of agriculture with the domestication of plants and animals. It is well know that, with some exceptions, health declined with the (first) epidemiological transition (hunting and foraging to farming). This is explained as a result of living in settled communities (rather than being more mobile and hunting and gathering), eating a diet that lacked variety, quantity and quality and may be unreliable (harvest failure and

soil exhaustion), experiencing poorer levels of sanitation and hygiene, societies becoming more unequal, drinking contaminated water supplies, working in occupations that predispose to poorer health, and being exposed to zoonoses in domesticated animals. Living in crowded permanent settlements, as a result of population density increase that may be facilitated with agriculture, means that TB can spread more readily via droplet infection. People may also contract TB from infected meat and milk from their animals, or working with other of their products, such as skins. There have also been suggestions that adoption of agriculture led to lower vitamin D resources and a powerful selection on the immune response because of infectious disease and a rise in population density[20].

Notwithstanding the (rare) evidence outside of Europe, apart from the early data in the Near Middle/East and Africa, the evidence for TB increases in the Roman period of Europe (2nd-5th centuries AD) when people had started to live in towns. This was a time when population density increased again and there was much more mobility and trade and contact with people often from more distant places, thus enabling easier transmission of TB between people from different regions. This increased mobility has been corroborated more recently using stable isotope analysis, including on Roman populations[21]. Nevertheless, an increase again in TB appears in the early medieval period when people actually reverted to living in rural environments. The final increases come in the late medieval period (c.12th-16th centuries AD) and later, when urban living became much more the norm and living conditions were poor for many. For example, while many of the disadvantages of transitioning to agriculture apply for this period in Europe, added to these are increases in inequality leading to poverty, and a rise in mobility of people. Tuberculosis is classed as a disease of poverty today[22] and a poor diet can compromise immune system strength and make people more susceptible to contracting TB. Furthermore, a rise in poor air quality both indoors and outdoors occurred at this time, which can predispose the lungs to being more susceptible to attack by tuberculosis[23].

There are three particularly relevant variables that operated alongside people who lived in late medieval Europe that may have contributed to the presence of TB that need further discussion; all three (specific diets, mobility and the vitamin D effect) are also being discussed in relation to the current challenge of TB, but they are variables

that need more exploration for the past. Its has been suggested that nutrition may influence the dissemination of tubercle bacilli to the skeleton and the process of the subsequent formation of lesions that are used by palaeopathologists to diagnose the infection[19]. Furthermore, clinical studies have found an association between iron intake and polymorphisms in the iron transporter gene SLC40A1 and an increased risk for TB[24]. Wilbur et al's study included hypothetical expectations of the immune response to TB and the skeletal changes expected, based on the amount of protein and iron a person consumes. This was then used to show how in some cases spinal disease would be expected while in other situations lesions on the ribs may be the only response to TB. Of note is that the number of individuals diagnosed with spinal TB in the archaeological record is much lower than the number of skeletons where new bone formation on the visceral surfaces of ribs is present. While not pathognomonic for TB, if their presence is correlated with the protein/iron status of the individual it may well be possible to argue for a tuberculosis cause. This work is only in its infancy in palaeopathology[14], but a lack of iron or protein consumption in the past would be highly likely for those living in poverty ridden urban situations. Furthermore, iron deficiency often goes hand in hand with infectious disease as the body withholds iron from pathogens that need it to survive and replicate.

The impact of rapid and extensive mobility on the spread of disease is also recognised increasingly today as a key risk factor for TB transmission. This might be from rural to urban environments for work purposes or it may be as a result of movement of people away from unfavourable areas[25]. It is well know that people were mobile very early on in the history of the human species, and that mobility increased as time passed. Once people started living in urban situations in late Medieval Europe, and markets and trade developed, the opportunity to spread disease, increased markedly. While we know that people suffered TB, as seen in their remains or through aDNA analysis, we have little scientific proof as yet of how far they travelled, and from where, to the destination where they died and were buried. Stable isotope analysis will rectify this situation in the future and allow us to nuance our understanding of the link between migration and TB occurrence. Finally, of specific interest is the link between vitamin D deficiency and TB, along with the different frequencies of the apolipoprotein E (apoE in populations today), according to latitude[26]. ApoE4 allele carriers are lower in frequency in Asian groups when compared to European

populations, but carriers are less likely to develop D deficiency. Vitamin D deficiency can compromise immunity and make people more susceptible to infectious disease, and especially TB[27], as seen in reduced UV exposure in Australia[28]. However, the palaeopathological evidence for TB in this overview study is mainly found in areas where UV light exposure is insufficient for most or part of the year. This suggest that people in the past may have adapted to a lack of UV light at those latitudes and become APoE carriers. Lack of UV light was also a problem in urban polluted situations in late Medieval Europe, and where workplaces and houses would have been dark),. As yet, there is no supporting evidence for this link in archaeological contexts.

Conclusions

The evidence of TB in Old World human remains is generally plentiful, but there are many gaps in our knowledge. Notwithstanding the limitations of the data, the evidence suggests that it became a challenge for humans at the advent of agriculture, but it was clearly and mainly a late medieval urban disease, likely of poverty affected populations. There is early evidence in a number of regions, including the Near and Middle East, but most data derive from urban late Medieval contexts in Europe. A number of factors likely played their part in TB's occurrence, including compromised immunity, poor diet, mobility, lack of UV light, exposure to infected animals, specific occupations, poor hygiene, and dense crowded living conditions. It was also a northern hemisphere problem at higher latitudes in the past.

aDNA analysis of the *M. tuberculosis* complex organisms is dealing providing nuanced data about the history of TB, including the strains affecting people and how they relate to TB strains today[29]. We also know much more about the genetic diversity of the *M. tuberculosis* complex. Further research in this field of study, including exploring resistance and susceptibility genes[30], and establishing ancient phylogeographic patterning around the world, will be a useful addition to understanding why people succumbed to this infection in past times. There is also much more research needed in palaeopathology to link the most common epidemiological factors for TB to the evidence of TB in human remains. To understand the data, it is necessary to place accurately diagnosed biological evidence

in archaeological and historical context (the “bioarchaeological approach”). Using the highest standards of data capture and analysis, using multiple methods and a multidisciplinary holistic approach, the prospects for learning more about TB in the past are promising. Palaeopathology clearly provides “deep time” evidence to study TB’s evolution, thus complementing the emerging discipline of evolutionary medicine.

3906 words

Figure caption

Figure 1: European countries with evidence of TB in human remains (shaded crosses), and with the earliest evidence (open crosses). Circled crosses = those countries where pathogen aDNA analysis has been performed

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