

Tuberculosis is an evolving disease: Paleoepidemiological and historical evidence

A thesis submitted by

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Abstract

Tuberculosis is a systemic infection responsible for approximately 20 to 25% of all deaths in Europe during the 18th century. The disease is spread by close contact with infected humans or animals (e.g. aerosol droplets generated through coughing, drinking infected milk).

Even when persons become infected with tuberculosis, they may not show signs or symptoms. In fact, only approximately 10% of infected individuals will develop active disease. This is related to the levels of immunity of the patient; only when immunity has been lowered sufficiently will signs and symptoms develop. Active disease rarely leads to skeletal lesions (3-5% of active cases) but can occur if the bacterium enters the bloodstream. These lesions usually affect vertebrae, but also the hip and knee.

At present, tuberculosis is re-emerging after a long decline and is developing resistance to drugs. The World Health Organization estimates that approximately one third of the world's population is infected. There have been reports of strains with resistance to multiple drugs (MDR-TB) as well as extensive drug resistance (XDR-TB).

This thesis seeks to show that tuberculosis is not just a disease, but a balance and co-evolution between host and pathogen. Previous literature has shown that when immunity is high enough, tuberculosis can have very low mortality rates. Pharmacotherapies (antibiotics plus isoniazid and PAS) are not necessary for this and conservative measures can be used instead. In order to accomplish this, this research involved several parts; each focussing on a separate time scale.

The first analysis was over a long time period (7250 BCE to 1899) and involved the meta-analysis of all reported paleopathological cases of tuberculosis in the literature

(N=531). Results showed frequency of skeletal lesions significantly decreased over time ($P<0.05$) and the distribution of skeletal lesions changed during this same period ($P<0.01$).

The second analysis involved a much shorter time period (1840-1935) of the second epidemiological transition in Switzerland. This research examined the effect of specific factors in the decline of tuberculosis during the 19th and 20th centuries. This showed the impact of improved living conditions and general health on tuberculosis mortality.

The third analysis further investigates the effects of good immunity on skeletal lesions. The Galler Collection contained skeletal remains and medical records of individuals with tuberculosis. This investigation showed how healthcare can result in “healing” of tuberculous skeletal lesions. This research also serves as a guide for paleopathological analyses.

Finally, logistic modelling of tuberculosis mortality in six countries showed reasons for the decline in certain areas. This investigation allowed the understanding of effectiveness of strategies in controlling tuberculosis. Public health measures and sanitation were found to be useful, but antibiotic use resulted in the fastest rate of decline. Milk quality control was important where bovine tuberculosis was at high levels.

The information gathered from these four investigations allows more efficient and cost effective treatment measures to be proposed for areas of the world where tuberculosis is re-emerging. These treatment strategies will also aid in the fight against strains of MDR and XDR tuberculosis.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Kara Holloway and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Kara Holloway

Date

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Dr Karl Link assisted considerably with the Galler skeletal Collection at the University of Zürich. He aided me in collecting and translating data, as well as editing of manuscripts.

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3. Holloway KL, Link K, Rühli F, and Henneberg M. 2012. Skeletal Lesions in Human Tuberculosis may sometimes heal: An aid to palaeopathological diagnoses (submitted to *PLOS ONE*, 26th February 2013).
4. Holloway KL, Staub K, Rühli F, and Henneberg M. 2012. Non-pharmacological treatment of tuberculosis may be successful as indicated by long-term epidemiological trends in the past (submitted to the *International Journal of Epidemiology*, 22nd February 2013).

Contributions for Manuscript 1: Evolution of human tuberculosis: A systematic review and meta-analysis of paleopathological evidence:

Kara Holloway wrote the first draft of the manuscript. Maciej Henneberg, Renata Henneberg and Miguel de Barros Lopes then helped to edit the draft into a final version.

Renata Henneberg provided the initial idea that was developed and conceptualised Maciej Henneberg and Kara Holloway.

Data for this research were collected by Kara Holloway. Maciej Henneberg assisted in providing contacts with additional data.

The analysis of data was completed by Kara Holloway with guidance from Maciej Henneberg, particularly in statistical tasks. The section titled: “Economic-cultural chronology” was devised by Maciej Henneberg.

Interpretations were carried out by Kara Holloway, Maciej Henneberg, Renata Henneberg and Miguel de Barros Lopes.

Contributions for Manuscript 2: Secular Trends in Tuberculosis

during the Second Epidemiological Transition: A Swiss Perspective:

The first drafts of the manuscript were prepared by Kara Holloway. Maciej Henneberg, Renata Henneberg, Miguel de Barros Lopes, Kaspar Staub, Karl Link and Frank Rühli all provided comments on the draft. Molly Zuckerman edited the drafts to create the final manuscript.

The original idea for this manuscript was devised by Maciej Henneberg and Kara Holloway, using the guidelines set up by Molly Zuckerman for the Postdoctoral Fellows Conference (South Carolina Institute of Archaeology and Anthropology).

Kaspar Staub provided information on Swiss history for this manuscript.

Data collection was completed by Kara Holloway. Kaspar Staub assisted with collection of data from historical records. Karl Link aided data collection from the Galler skeletal Collection by conducting database searches and providing translations for the medical texts written in German.

Analysis of the data was completed by Kara Holloway, with guidance from Maciej Henneberg.

Interpretations were devised by Kara Holloway and Maciej Henneberg.

Contributions for Manuscript 3: Skeletal Lesions in Human

Tuberculosis may sometimes heal: An aid to palaeopathological diagnoses:

Initial drafts of this manuscript were prepared by Kara Holloway. Karl Link and Frank Rühli provided comments and Maciej Henneberg made corrections.

The conceptualisation for this manuscript was completed by Kara Holloway. A trend in the data was noticed after a request from Karl Link for an abstract to send to the 9th International Congress of the German Society for Anthropology. Karl Link and Maciej Henneberg aided in the finalisation of this idea.

Data collection was completed by Kara Holloway. Karl Link provided translations and database searches, the same as for manuscript 2.

Analysis of data was performed by Kara Holloway. Maciej Henneberg provided some guidance and input into this process.

Kara Holloway provided interpretations for this data. Maciej Henneberg added comments.

Contributions for Manuscript 4: Non-pharmacological treatment of tuberculosis may be successful as indicated by long-term epidemiological trends in the past:

Preparation of the initial draft was completed by Kara Holloway. Maciej Henneberg wrote the paragraph titled: “Definition of a disease as a balance between infection and immunity” and made minor corrections. Kaspar Staub and Frank Rühli provided comments for the draft.

The concept for this work was devised by Maciej Henneberg and Kara Holloway.

Data collection were performed by Kara Holloway. Kaspar Staub assisted with data collection from historical records.

Data analysis was performed by both Kara Holloway and Maciej Henneberg. Graphs with historical dates and those for sanitation and milk quality control were prepared by Kara Holloway. Maciej Henneberg created the idea for preparing sanitation and milk quality control graphs. Maciej Henneberg also conducted the logistical modelling tasks. The original data for this was plotted by Kara Holloway.

Interpretations of the data were performed by both Kara Holloway and Maciej Henneberg.

Authorisation by all Coauthors:

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Karl Link

Kaspar Staub

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Holloway KL, Link K, Rühli F, and Henneberg M. 2012. Surviving tuberculosis: healing of skeletal lesions during the recovery from active disease. American Association of Physical Anthropologists. Portland, Oregon: American Journal of Physical Anthropology. Suppl 54, p 165.

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Holloway KL, Henneberg RJ, De Barros Lopes M, Staub K, Link K, Rühli F, and Henneberg M. 2011. Tuberculosis in the Second Epidemiological transition in Switzerland. Postdoctoral Fellows Conference, South Carolina Institute of Archaeology and Anthropology. Columbia, South Carolina, United States.

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