A Tale of Two Maladies: The Burden of Helminth Infections in the Era of the Antonine Plague

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Abstract

The Antonine Plague was a disease of disputed identity that affected the Roman Empire from 165-180 CE. Written sources from authors such as Galen and Aelius Aristides offer some insight into the societal impacts of the Antonine Plague, but bioarchaeological evidence of the disease is limited and frequently debated. Consequently, there is also minimal understanding of how concurrent infections impacted disease outcomes, a weakness that this study aims to address. Parasitic infections have been shown to dampen the body's immune system and weaken the affected individual, impacting their ability to fight off disease. However, there is also evidence that some helminth infections can offer the host protection against viruses. To better understand the relationship between helminths and the agent of the Antonine Plague, this project will compare helminth presence between a plague mass grave and surrounding burial sites not associated with the epidemic. A mass grave in modern-day Gloucester, England (then known as Glevum), which holds at least 91 individuals buried during the window of the epidemic, is one of the foremost sites of evidence for the Antonine Plague. Other nearby cemeteries and burial sites from the same time period have been identified using the UK Archaeology Data Service and records from Cotswold Archaeology. This project will analyze soil samples from the mass grave at 120-122 London Road and from nearby cemeteries for the presence of parasites including roundworm (*Ascaris lumbricoides*) and whipworm (*Trichuris trichiura*) using genetic analysis. To supplement this analysis, soil samples will be collected from any newly discovered burials and from contemporary latrines, and microscopy and sequencing will be performed on these samples to evaluate the presence of helminths. Any differences in helminth presence between the individuals buried in the mass grave and those buried in surrounding areas could not only lend insight into how helminth infections might have affected the host in concurrent infections with the agent of the Antonine Plague but also provide further evidence of the identity of this pathogen based on known pathogen interactions with helminth infections. As the helminths of interest spread through the fecal-oral route, this study also has the potential to deepen the understanding of sanitary conditions and related health disparities in the Antonine Period.

Overview

This project aims to study the effects of helminth infection alongside the Antonine Plague (165-180 CE). The Antonine Plague in particular is a relevant target for this research because its causative agent remains unknown. Uncovering trends in helminth co-infections in an Antonine Plague mass grave compared with archaeological sites unassociated with the epidemic could lend insight into the interactions between helminths and the agent of disease. The proposed research will take place in modern-day England's Gloucestershire County, as the primary archaeological site believed to be evidence of the Antonine Plague is a mass grave located in the city of Gloucester. To contextualize samples from the mass grave, samples will also be taken from nearby archaeological sites dated to the same time period. Archaeological evidence of helminths can be found in pelvic soil samples collected from burial sites, preserved human feces, or soil samples collected from latrine and human waste disposal areas, so site selection has focused on availability of such samples.

Collected samples will be tested for helminth presence through both microscopy and sequencing. Although the small number of samples may limit the utility of differences in helminth prevalence between the plague mass grave and other sites, any findings of helminth presence would still mark a step forward in the study of archaeological helminth co-infection. Additionally, the spatial distribution of selected sites could allow for preliminary understandings of differences in helminth dynamics between rural and urban settings, lending further utility to the study.

Intellectual Merit

Currently, the causative agent of the Antonine Plague is not known. While many descriptions of the disease match the known symptoms and spread of smallpox, some records of the outbreaks do not fit this diagnosis. This research has the potential to generate more information on the nature of the causative pathogen by exploring its relationship with co-infective helminths. As helminth infections are known to interact differently depending on the co-infecting pathogen, any data about helminth infections in individuals contemporary to the Antonine Plague, particularly those infected, could lend further insight into the nature of the disease. Data collected from this study could help to clarify prevalent questions in the field about the identity of the pathogen and the societal impacts of the Antonine Plague epidemic.

Broader Impact

Any findings regarding the interaction between helminths and other human infections have the potential to inform both historical and modern perspectives of parasitic infections. While modern studies have established links between infectious diseases and contemporary helminth infections, the nature of such connections varies greatly between different pathogens, with helminth co-infection worsening outcomes in some diseases but offering protective effects in others. Gaining an understanding of historical patterns of helminth infections could help shed light on prevalent infectious diseases in selected geographical regions across time. Helminth co-infections can also be connected to social determinants of health such as diet and sanitation, which would help draw links between these social factors and historical outbreaks of disease such as the Antonine Plague. Scientists are still exploring the interactions between helminths and infectious diseases in modern human populations, so any research adding to the understanding of historical interactions between co-infective agents has the potential to inform ongoing research. Many modern helminth infections are more highly prevalent in socioeconomically disadvantaged countries and communities, indicating the importance of understanding helminth co-infections for modern health equity efforts.

Introduction

Between the years 165 and 180 CE, the Roman Empire experienced an outbreak of a disease known as the Antonine Plague, named for the contemporary reign of the emperor Marcus Aurelius Antoninus (Harper, 2017). He took power in 161 CE as a co-regent alongside Lucius Verus, both being adopted sons of the emperor Antoninus Pius (Birley, 2015). Soon after ascending to the throne, Lucius Verus embarked on a military campaign in Seleucia leading Roman forces in the Parthian War (Birley, 2015). Although Lucius Verus and his forces emerged victorious from the war, it is thought that the consequences of the siege of Seleucia extended beyond the military outcome (Birley, 2015). Archaeologists believe that the Antonine Plague was spread through this military engagement and was then spread west into Roman territory by the returning soldiers (Gilliam, 1961).

The Antonine Plague emerged at a time of heightened connections between the Roman Empire and entities outside its borders, most of which centered around the trade of both physical goods and people (Figure 1). It is very possible that increased contact between the Romans and outside societies contributed to the spread of the disease. Trade between the Roman Empire and eastern civilizations such as Han China may well have caused traders to travel through areas known to have harbored diseases (Duncan-Jones, 1996). Further supporting this hypothesis, records from China indicate the occurrence of a disease outbreak in the mid-to-late 100s CE (Duncan-Jones, 1996). So far, these records have not been definitively connected to the same causative agent of the Antonine plague, and such conclusions are made difficult by an absence of recorded symptoms and near-absence of recorded locations. Nonetheless, these contemporary outbreaks offer the possibility that the Antonine Plague could have constituted the first known pandemic.

Much of what is known about the Antonine Plague comes from primary written sources. Chief among these sources are the writings of Galen, a physician who lived through the epidemic (Littman & Littman, 1973). From Galen's writings, symptoms ranging from vomiting to coughing to the eruption of sores over the body can be identified, and this documentation has allowed for the tentative conclusion that the Antonine Plague was caused by smallpox (Littman & Littman, 1973). Other writers, including Aelius Aristides, have also contributed to the narrative of the Antonine Plague. Aelius Aristides himself was struck by the disease, and his documentation not just of living through the outbreak but of surviving infection provides valuable information on the experiences of the infected (Flemming, 2019). His writings contextualize the role of faith and religion in the time of the Antonine plague, exemplified in his mentions of visions of Asclepius and Athena leading him to a cure (Flemming, 2019). Between the works of these two authors, scholars have been able to piece together an understanding of the effects of the Antonine Plague on both biological and social levels.

Despite the intrigue of the Antonine Plague, there is relatively little definitive information on the epidemic and its impact on the Roman world. Figures such as mortality from the disease vary widely depending on the source, with estimates of population decrease ranging from as low as 1 or 2 percent to upwards of 20 percent (Gilliam, 1961; Harper, 2017). While most estimates of the Empire's population loss from the Antonine Plague fall in the moderate category around 10 percent, the sheer range of disagreement around this one figure exemplifies the general lack of consensus about the impacts of the Antonine Plague (Littman & Littman, 1973). Some, including historian Kyle Harper, argue that this outbreak contributed to the destabilization of the Roman Empire (Harper, 2017). Others remain more skeptical of the Antonine Plague's role in

Roman history, arguing that the catastrophic scenarios that some scholars have proposed are not necessarily accurate (Newfield et al., 2022).

While no single study can provide answers to the many questions that surround this outbreak, there is no doubt that further research into the Antonine Plague and its associated biosocial factors could offer clarity as to the causative agent and the societal impacts of the disease. This work aims to make progress in this area by exploring the role of helminth co-infection with the Antonine Plague. By examining the frequency and archaeological patterns of helminth infections, it may be possible to learn more about the Antonine Plague's clinical manifestations and social patterns.

Literature Review

The Antonine Plague was a disease that spread across much of the Roman Empire between 165 and 180 CE. From authors writing at the time of the outbreak, symptoms of Antonine Plague have been identified. The contemporary physician Galen provided much of the currently available clinical information on the disease, entering symptoms including sores, coughing, and vomiting into the historical record (Littman & Littman, 1973). His description of the course of the disease has led many historians and archaeologists to conclude that the Antonine Plague was an outbreak of smallpox, a disease caused by variola virus (Littman & Littman, 1973; Harper, 2017). However, there remain inconsistencies between the descriptions of the disease and modern knowledge of smallpox. Most notably, Aelius Aristides's claim that the livestock became sick alongside the humans is frequently cited as a reason for disagreement with the smallpox identification, as smallpox has not been observed to spread between species in this manner (Flemming, 2019). Some scholars have proposed alternative hypotheses including bubonic plague and measles, while others have simply disputed the identification of smallpox without offering alternatives (Silver, 2012; Flemming, 2019; Newfield et al., 2022). The temporal distance of the Antonine Plague from modern science complicates disease identification further, as infectious diseases (particularly viruses) are known to mutate and evolve rapidly (Figure 2). Consequently, it is difficult to confidently say that the Antonine Period's version of the variola virus would have produced symptoms and patterns of spread similar to smallpox studied in recent decades.

Given the complexities of attempts to identify the agent of the Antonine Plague, there is great utility to be found in research that examines disease-associated factors from this time period. The study of ancient parasites has been applied across archaeological fields in the interest of learning more about the social and biological context of past societies. Helminths of particular interest include the soil-transmitted helminths (STHs) roundworm (*Ascaris lumbricoides*) and whipworm (*Trichuris trichiura*) (Figure 3), both of which are spread by the fecal-oral route through human populations and have been identified across many Roman archaeological sites (CDC, n. d.; Ledger et al., 2020, Ryan et al., 2022). While many infections with these helminths cause no symptoms, more serious cases can result in abdominal pain, blood loss, and stunted cognitive and physical growth (CDC, n. d.). Previous studies of helminth infections have contributed to understandings of sanitation practices and the biological consequences of social stratification (Mitchell, 2013). They have also yielded insights into diet and malnutrition, findings which have been utilized in conjunction with historical accounts of siege and famine to unravel the contributions of helminth infections to broader social campaigns such as imperial expansion (Mitchell, 2013).

Modern studies have shown that helminth infections can significantly alter the course of human disease, making research into co-infections a meaningful next step to understanding the path of historical epidemics like the Antonine Plague (Schlosser-Brandenburg et al., 2023). Interestingly, helminths have vastly different effects across different diseases, offering protective effects against some pathogens and greatly worsening symptoms and mortality of others (Gazzinelli-Guimarães et al., 2017; McFarlane et al., 2017). Little is known about the interactions between helminths and smallpox, the most widely accepted candidate for the Antonine Plague, because smallpox was eradicated from human populations in 1980. However, studies in mice have suggested that helminth infection may cause greater pathogenicity of smallpox (Gazzinelli-Guimarães et al., 2017). If the Antonine Plague was in fact caused by smallpox, then the distribution of helminth infection could have been an important predictor of survival during this period.

Helminth infections in the Roman Empire are relatively well-researched, and there is significant literature documenting the presence of helminths in Roman society. These studies span large geographic areas of the Empire, with data on helminth presence stretching from the eastern reaches in Turkey and Serbia to northwestern territories such as Britannia (Ledger et al., 2020, Ryan et al., 2022). While most helminth sampling is done by evaluating soil samples from latrines and cesspools, many studies have also utilized soil samples from the pelvic region of osteological remains to determine helminth presence (Ryan et al., 2022). Sites for archeological helminth sampling are relatively common throughout Europe, but more difficult to find are sites connected to the Antonine Plague. One of the most accepted sites connected to this outbreak is a mass grave in modern-day Gloucester, England, which dates to the Antonine Period (Simmonds et al., 2008). This project aims to synthesize existing data on helminth infections and the Antonine Plague in Britain with new archaeological findings to begin to create a picture of co-infections and their impact on the societal experience of the Antonine Plague.

Research Context and History of Work

There is evidence of helminth presence from archaeological sites across the Roman Empire, but little research has been done to explore the interactions between helminth infections and other infectious diseases that plagued the Roman Empire (Ledger et al., 2020, Ryan et al., 2022). The goal of this work is to address the current lack of knowledge surrounding archaeological helminth co-infections with epidemic diseases such as the Antonine Plague. Sites for this research were chosen from modern-day Gloucestershire, once part of Britannia, to develop a clear picture of the local burden of helminth infections. Britain boasts a long history of bioarchaeological research and significant quantities of archaeological data from the Roman period, making a more specific study into Antonine Period burials and sanitation feasible (Ryan et al., 2022). The choice to focus the study in Gloucestershire was largely based on the presence of the mass grave at 120-122 London Road in modern-day Gloucester, England (Simmonds et al., 2008). Since few sites related to the Antonine Plague have been identified, research into the epidemic is largely beholden to the few existing sites. In the interest of extending the utility of this research beyond the single hypothesized Antonine Plague site, the study also proposes the inclusion of multiple nearby sites, both burials and latrines, to develop a broader understanding of helminth presence in Roman Britannia. Basic details of the sites selected can be found below (Figure 4).

1. **120-122 London Road, Gloucester** is the primary archaeological site of interest for evidence of the Antonine Plague. While the site is part of the Wotton Roman cemetery, this area includes a mass grave containing 91 individuals that likely dates to the late second century CE, which matches the timeline of the Antonine Plague (Simmonds et al., 2022).

2. **97 London Road, Gloucester** sits nearby the primary hypothesized Antonine Plague site, also within the bounds of the Wotton cemetery. This specific site holds the remains of three individuals, two inhumation burials and one cremation. The remains are loosely dated between the mid first and late fourth centuries CE. However, these remains and many others nearby in the cemetery could be dated more precisely to identify individuals from the approximate period of the Antonine Plague (Thomson, 2017).
3. **Wadfield Villa, Wadfield, Gloucestershire** was a rural Roman settlement outside the Roman Glevum. In addition to the structural evidence discovered, shallow refuse pits and a single adult inhumation burial were found west of the villa. The findings are broadly dated between the late second and fourth centuries CE, which could put them within the timeframe of the Antonine Plague (Rawes, 1971).
4. **Trevor Road, Hucclecote, Gloucestershire** is a bathhouse site outside Roman Glevum that was active from the mid-second century through the mid-fourth century CE. Excavations have revealed the structure of the bathhouse, a drain, and a single inhumation burial of a young adult dated between 150 and 200 CE (Hunter, 1959).

Methods

Sites were identified and selected using the UK Archaeology Data Service and records from Cotswold Archaeology. This search was supplemented by use of *the Rural Settlement of Roman Britain*, an online database of rural Roman archaeological sites (Allen et al., 2015).

To obtain samples for the study, soil will be collected from the pelvic region of inhumations and from latrine or waste pit areas at sites where these are present. Helminth eggs are known to be preserved in soil over long periods of time, and they can be collected from places with remains of human waste. As helminths live in the human gastrointestinal tract, eggs can also be found in the pelvic region of human remains where the intestines were once located (Araújo et al., 2013). The most common method of detection for archaeological helminths is microscopy, which reveals helminth eggs that can persist in soil samples for millenia (Araújo et al., 2013). Initial sample analysis will focus on detection and quantification of helminth eggs through the microscopy technique outlined in a recent evaluation of helminth infections in British history, which includes rehydration and filtration, and visualization of the soil samples (Ryan et al., 2022). This analysis will allow for an initial understanding of the relative helminth burden and the helminth species present at each site. Osteological evidence is not observed from helminths, so potential impacts of helminth co-infection alongside the agent of the Antonine Plague will be explored by comparing differences between helminth species and abundance in plague-associated and unassociated sites and by using knowledge of modern helminth interactions to understand any patterns.

As a follow-up, genotyping of ancient DNA (aDNA) from helminths will be conducted using a protocol from Côté et al. that combines polymerase chain reaction (PCR) with next-generation sequencing (2016). To prepare samples for this experiment, aDNA extraction must be performed in a specialized facility with control over air pressure and sterility to protect the fragile aDNA. Primers will be developed to target unique genes from the helminths of interest and will be used for PCR identification of helminth aDNA. In accordance with the protocol, ion torrent adaptors will be annealed to the PCR products, and the ligated product will undergo sequencing to more confidently identify specific helminth species present in collected samples. The investigators who pioneered this protocol found that helminths could be successfully genotyped from samples where no intact helminth eggs were present, so this analysis will be conducted on all collected samples regardless of helminth findings in the microscopy stage (Côté et al., 2016).

Research Schedule

The proposed study will occur over a 12 month period. The first 6 months of that time will be on-site work in Gloucestershire at the sites detailed above. Work during this phase of the project will seek to obtain samples that can be used to test for helminth presence. As the sites being utilized have already undergone significant excavation, approximately the first month will be spent navigating the local archaeological archives to become familiar with any existing soil samples or documentation of helminth presence from the selected sites. Once existing data is evaluated, the study will perform further excavation at the sites to obtain soil samples from identified latrine areas and from pelvic areas of inhumations. Particularly in the Wotten cemetery, which encompasses two of the selected sites, it is possible that new archaeological work will yield further samples, which will be included in this first phase.

Following on-site sample collection, the second 6 months of the project will be dedicated to laboratory testing of the samples. In the first two months, this analysis will be focused on detection of helminth eggs through microscopy. The next two months will be used to genotype helminth DNA found in the samples using the approach outlined above. The final two months of the project will be used to analyze the data collected from these samples.

Intellectual Merit

This study has the potential to contribute meaningfully to bioarchaeological research by providing further insight into the identity of the pathogen that caused the Antonine Plague. The simple lack of archaeological sites connected to the Antonine Plague is a limiting factor in research that can be conducted into the outbreak, and this study proposes a new angle from which to examine the existing site. Modern research into helminth co-infections has elucidated interactions between helminths and various infectious pathogens, which allows hypotheses to be generated as to how the distribution of helminths might differ between affected and unaffected populations in times of disease. The finding that increased levels of helminth infection increases the disease burden from smallpox allows this study to evaluate the claim that smallpox was the causative agent of the Antonine Plague. If high levels of helminths are observed in samples from the plague site compared to unassociated sites, that could further support smallpox as the culprit of the epidemic. However, a higher helminth burden in unaffected sites would indicate that the pathogen might have instead been one against which helminths offer a protective effect. Regardless of the outcome, this study has the potential to advance the understanding of the Antonine Plague within the limitations of archaeological evidence.

Broader Impacts

Helminth infections and their impacts on other diseases are topics of interest in both archaeology and modern medicine. Many helminths, including those proposed for study in this project, are transmitted via the fecal-oral route, meaning that the burden of helminth infections within a community reveals trends in hygiene and sanitation. In an archaeological context, studying helminth co-infections can provide insight into the sanitary systems of past societies and can offer explanations as to how diseases impacted the people living there. As helminth infections can also cause malnutrition and stunted growth, the study of helminths also offers insight into the broader well-being of ancient populations. From a modern perspective, research into helminth co-infections of the past can strengthen current understanding of how such infections impact communities, particularly in lower-middle income countries, which are more likely to have endemic helminth infections. The low burden of helminth infections in high-income countries has resulted in a relative lack of attention to co-infections in scientific research, so any insights in this area can also contribute to the reduction of health inequities.

Preliminary Research and Training

The co-PI has laboratory-based training and experience inclusive of parasite identification from soil and biological samples. Their preparation includes significant coursework in biology as well as laboratory experience in molecular biology techniques. They have processed archaeological soil samples to identify parasite presence and have contributed to a peer-reviewed paper by performing DNA extraction to evaluate the presence of selected parasites in intermediate zoonotic hosts. These techniques will be directly utilized within the proposed project. While the co-PI does not have experience in archaeological fieldwork, necessary training and guidance will be provided by the PI, who has led extensive field-based research studies.

Figure 1. Map of the Roman Empire under Marcus Aurelius. This map depicts both the territory of the Roman Empire at the time of the Antonine Plague and the directions of trade with areas outside of the Empire. Figure from ARCH1765 class.

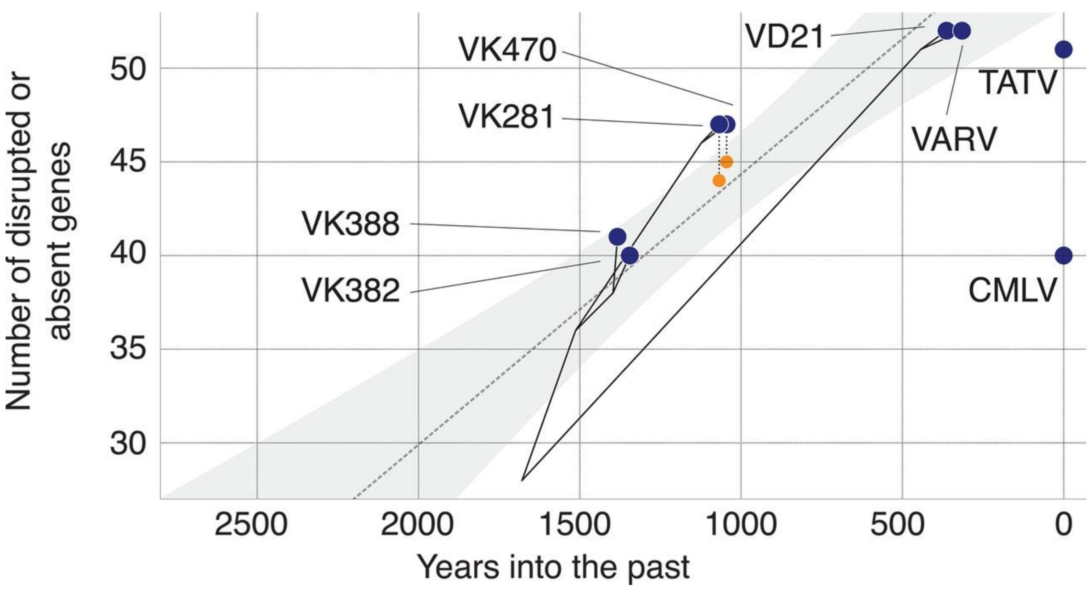

Figure 2. Analysis of historical variola virus strains shows increasing gene inactivation over time. This figure depicts the relationship between evolutionary time and the number of genes disrupted or absent from variola virus sequenced from Viking Age individuals in Northern Europe. Figure from Barbara Mühlemann et al., *Diverse variola virus (smallpox) strains were widespread in northern Europe in the Viking Age*, 2020 (published in *Science*).

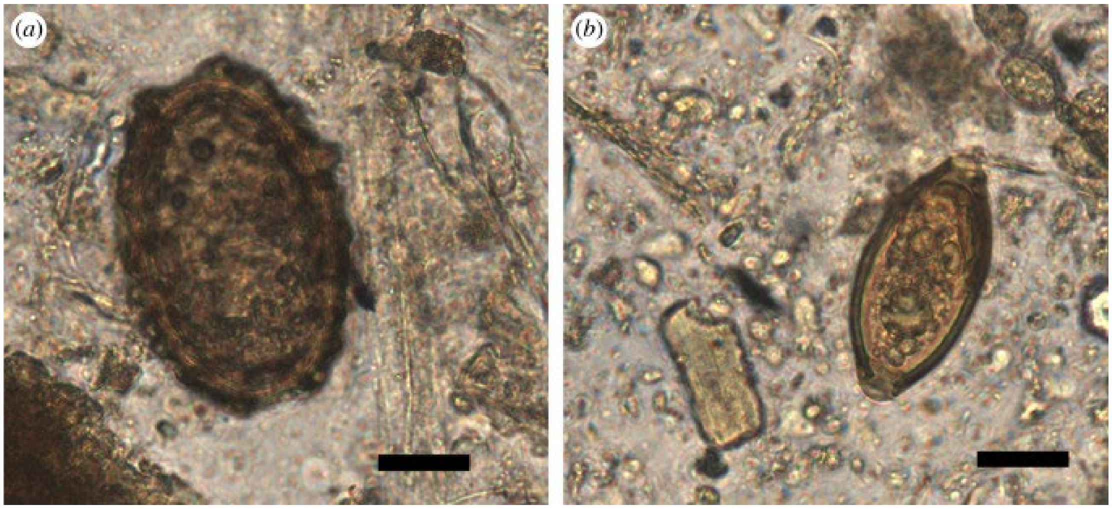

Figure 3. Microscopy images of eggs of the *Ascaris* (left) and *Trichuris* (right) species. Eggs from these prevalent human-infecting helminths can be successfully visualized and quantified from archaeological samples. Image from Flammer and *Smith Intestinal helminths as a biomolecular complex in archaeological research*, 2020 (published in *Philosophical Transactions of the Royal Society B: Biological Sciences*).

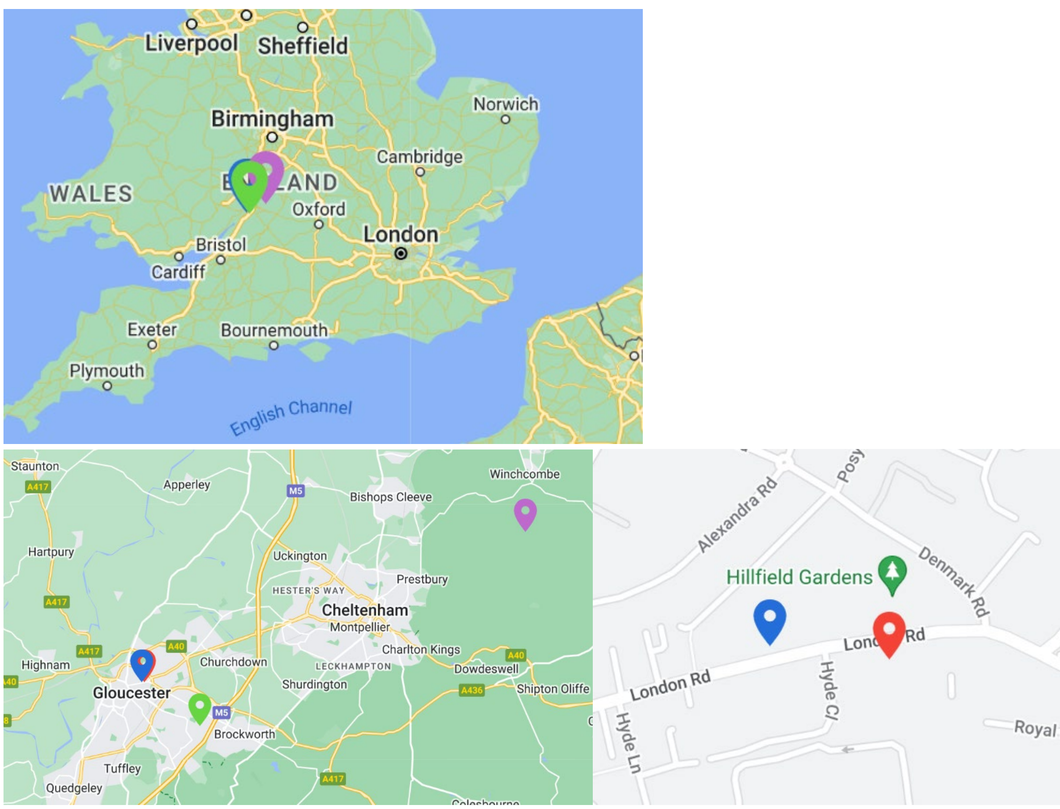

Figure 4. Selected sites for sample collection. 118-120 London Road (red), 97 London Road (blue), Wadfield Villa (purple), and Trevor Road (green) all fall within the British county of Gloucestershire. Map created from Google Maps

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