Article

Not peer-reviewed version

A Long View of Zoonotic Disease–Revelatory Parallels and Contrasts: An Ancient/Modern Comparative Analysis

Mark Orsag *, Giovanni Meledandri, Amanda McKinney, Melissa Clouse

Posted Date: 6 June 2025

doi: 10.20944/preprints202506.0485.v1

Keywords: interdisciplinary; holistic disease contexts; P. *falciparum*; roman empire; COVID-19 pandemic; ancient zoonotic pandemics; “spanish flu” pandemic; disease prevention; rising zoonotic threats; P. *knowlesi*

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 June 2025 doi:10.20944/preprints202506.0485.v1

Article

A Long View of Zoonotic Disease–Revelatory Parallels and Contrasts: An Ancient/Modern Comparative Analysis

Mark Orsag [1], Giovanni Meledandri [2], Amanda McKinney [3] and Melissa Clouse [4]

[1] History Department, Doane University, Crete, Nebraska, (USA)
[2] Humanities Department – Latin Language and Public Health, Guglielmo Marconi University, Rome (Italy)
[3] Health Science Freelance Faculty, Bellevue University, Omaha, Nebraska (USA)
[4] Bryan Health, Lincoln, Nebraska (USA)
* Correspondence: mark.orsag@doane.edu

Simple Summary: This article utilizes an interdisciplinary and comparative overlay of detailed and specific evidence, as well as broader examples and lessons from the ancient and modern histories of zoonotic disease outbreaks– drawn from both the zoonotic disease histories of the interconnected ancient Mediterranean World of the Roman Republic and Empire and our modern globalized planet. Our purpose is to reveal specific and broader informative analytical parallels and contrasts between ancient and modern zoonotic disease realities. Our consideration is unusually holistic in nature– aimed at elucidating a variety of factors that combine to shape the timeless interplay between zoonotic pathogens, environmental and climate factors and human societies.

Abstract: Our article presents an unusually broad and holistic analysis aimed at discerning specific and general patterns from ancient-modern comparative contexts of zoonotic disease. The article's interdisciplinary and consilient methodology is drawn from a range of disciplines: the humanities and social sciences (particularly historical analysis), medical knowledge (particularly epidemiology and pathology), molecular phylogenetics, demography, archaeology, numismatics, complex systems theory, etc. The article begins with the detailed exploration of a 463 BCE epidemic that likely marked the, ultimately transformative, debut of P. falciparum malaria for ancient Roman civilization. An interdisciplinary retrospective diagnosis methodology is then utilized to establish, with a very high degree of probability, a conclusion that constitutes the ancient side of the equation for our example. This conclusion is used, comparatively, to highlight threats emanating from the current spread of zoonotic P. knowlesi malaria. More broadly, the article, also employing the additional comparative lens of ancient and modern zoonotic pandemics, deduces six holistic concepts: (A) political, military and security contexts; (B) the effects of cultural perceptions; (C) the role of climate; (D) anthropogenic environmental factors; (E) perceptions, practices and capabilities of prevailing medical systems; and (F) holistic underlying states of the health of affected populations that perpetually help shape the parameters and outcomes of the complex relationship between zoonotic disease and human civilization. Such an interdisciplinarity-informed, holistic macro-level view is quite likely to be a necessary guide in the future to overcome past mistakes and better target existing resources given the rising threats from zoonotic diseases.

Keywords: interdisciplinary; holistic disease contexts; p. falciparum; roman empire; covid-19 pandemic; ancient zoonotic pandemics; "Spanish Flu" pandemic; disease prevention; rising zoonotic threats; P. knowlesi

---

Introduction: Lessons From a Transformative Ancient Outbreak

There was a significant epidemic in the city of Rome and surrounding areas beginning in the year 463 BCE. Two later ancient authors highlighted the event in their accounts because of its unusual and relevant severity. This epidemic, which both strongly reflected and yet also departed from predictable and annualized patterns of infectious disease, was embedded in a period of the early Roman Republic troubled by social crises and continuous wars among the various inhabitants of ancient central Italy. The early Romans were incessantly engaged militarily (whether as enemies or allies) with the people settled in the areas surrounding their *urbe*: such peoples as the Volsci, Aequi, Hernicians, Etruscans, Aurunces and others. At the same time, class conflict amongst Roman plebeians, aristocrats, and the Republic's Senate frequently resulted in secessions, betrayals, and outright warnings of civil war. Even in the context of such a fraught political and military situation, a seasonally/annually fully predictable (late summer early/fall) epidemic disease outbreak became unusually widespread and severe enough, with high mortality, that it merited significant historiographical coverage centuries later. Something about the event was clearly very different from the expected recurring seasonal infectious disease pattern. Two ancient authors, Dionysius of Halicarnassus and Livy (both from the later 1st Century CE Augustan early imperial period) produced (apparently relying on earlier sources now lost to time) accounts concerning the 463 BCE epidemic in annalistic format (Year of Rome 291, according to Cato; 293, according to Varro; 463 BCE, as noted above, according to the dating in use today). Thus, this outbreak deserves special modern scholarly consideration. Both the prevailing and contingent ancient sanitary fragility, cultural norms, expectations and the general familiarity with annualized patterns of (particularly malarial) disease would have restrained the mention of a less than extraordinary outbreak by authors such as Dionysius and Livy. This reality argues strongly in support of a relevance for the 463 BCE epidemic far above and beyond the ordinary. Indeed, we conclude that this event was not ordinary at all and likely represented the epidemic debut of the most severe form of malaria, caused by the parasite *plasmodium falciparum*, (or more inclusively its evolutionary lineage) in ancient Rome's history. *P. falciparum* is understood by modern medicine to be currently the cause of 90% of global malaria fatalities (which total, annually, around 600,000), with children under five years old accounting for "67% of global malaria deaths" [1]. This modern public health significance, effectively, was anticipated (over two millennia beforehand) by the history of ancient Rome. During the following centuries after 463 BCE, great malaria-related changes would result for the Romans. Excerpts of the two relevant ancient accounts are now indeed worth reviewing in greater detail.

Materials and Methods Ancient: The Accounts of Dionysius and Livy

Firstly, from Dionysius of Halicarnassus [2]: So, it [the disease] meandered among shepherds and settlers gradually throughout the region, ultimately invading Rome as well. It is not easy to recount how many servants, how many mercenaries, and how many of the indigent class perished. At first, their corpses were carried in heaps on chariots: but then those of the less respectable were thrown into the current of the [Tiber] river. Counting, a fourth of the senators perished, and with them two consuls, and most of the tribunes. That disease began around the early part of September. (According to the dating in use, the month of the beginning of the epidemic, indicated by Livy (see below), is August. And continued for a year backward, investing and consuming every month and age… [3,4].

Livy reports the same events, in the third book of his *Histories*, as recorded in the following passage **[3–13]**:

It was the sickly season and chanced to be a year of pestilence both in the city and in the country, for beasts as well as men; and the people increased the virulence of the disease, in their dread of pillage, by receiving flocks and country-folk into the city. This conflux of all kinds of living things distressed the citizens with its strange smells, while the country people, being packed into narrow quarters, suffered greatly from the heat and want of sleep; and the exchange of ministrations and mere contact spread the infection. The Romans could scarce endure the calamities which pressed hard upon them, when suddenly envoys from the Hernici [a people allied to Rome] appeared, announcing that the Aequi and the Volsci had joined forces and established a camp in their territory, from which base they were devastating their land with an enormous army. Not only did the reduced numbers of the senate {Dionysius also notes stricken senators too weak or lethargic to stand attempting to carry on the business of the Senate while "barely alive on litters"[4]} show their allies that the [Roman] nation was prostrated by the pestilence, but they also returned a melancholy answer to their suit, that the Hernici, namely, with the help of the[ir allies the…] Latins must defend their own possessions; for the City of Rome, in a sudden visitation of divine displeasure, was being ravaged by disease. If there should come any respite from their suffering, they [the Romans] would help their friends, as they had done the year before and on every other occasion ...From that time onward, little by little, both because of the peace obtained from the gods and the gradual exhaustion of the unhealthy season, the bodies in which the course of the disease had run its course began to return to health, while minds turned to the problems of the State."

The accounts themselves along with a supporting wealth of consilient interdisciplinary analyses strongly implicate *P. falciparum* in the 463 BCE outbreak. The disease clearly was part of, and in many ways fit well within, an established annualized pattern that was characteristic, then and later, of the late summer/early fall malarial "sickly" or "fever season". This was something that would have been well understood by both Livy and Dionysius centuries later. References to this phenomenon indeed constitute a common signifying trope that formed part of the broader cultural and literary heritage of the ancient Greco-Roman Mediterranean world with examples ranging from Homer's *Iliad* to Roman poetic traditions. [6,7]. The more prosaic words of the 1st Century CE Roman physician Celsus in his work *De Medicina* "lethal autumn" also reflect specific awareness of this disease phenomenon within Greco-Roman medicine [8].

Such annualized outbreaks of sickness in Rome had, however, centered, up to 463 BCE, around malarial fevers caused by the less deadly plasmodium parasites *P. vivax* and *P. malariae* [8]. Yet, the epidemic event of 463 BCE was different than the norm; both ancient accounts document large numbers of deaths not confined to children or the elderly but also including large numbers of presumably healthy adults. The high death rates indicate an at least partially epidemiologically naive population and a more virulent form of the disease. As noted, *P. falciparum* statistically causes 90% of human malaria fatalities [1] and fits the retrospective diagnostic parameters for 463 BCE, in a multifaceted sense, extremely precisely. Celsus (as well as other Greco-Roman physicians) accurately categorized malarial fever types (which we now know are caused by the plasmodium parasites *P.malariae*, *P.vivax* and *P.falciparum*) with a sound understanding of comparative pathologies, enabling environments and seasonality–peak August-October [9], pp. 55-62 and p. 71 if *not* of underlying (including vector/secondary host epidemiology) causation. 463 BCE thus seems to have marked a true watershed moment for ancient Rome in terms of increased disease impact from malaria.

While recitations of the elements of pathology in the accounts regarding the 463 BCE outbreak are limited, descriptions indicative of fatigue/lethargy or weakness (noted above) as a primary symptom and protracted illnesses from which numerous sufferers eventually recovered as well as the disease's seasonality are also strongly consistent with the *P. falciparum* pathology and epidemiology [1]. The described apparent rural to urban epidemiological progression of the outbreak is also consistent with malaria and, notably, inconsistent with other candidate pathogens such as tuberculosis, dysentery or other gastro-intestinal bacterial disorders. Additionally, the outbreak occurred during a time of Roman contact and conflict with the Volsci, whose coastal territories (then and later after their eventual incorporation into the expanding Roman state) constituted one of ancient Italy's primary malaria outbreak hotspots []9, p.179. The described unusual influx of animals and their herders (as a symptom of the prevailing (A) political, economic and security/military contexts that were characterized by an overall high level of disorder, uncertainty and insecurity, into the city) likely also greatly augmented and concentrated mosquito– including *Anopheles* vector/secondary host- presence in the city of Rome. This may well have been a key epidemiologically enabling factor that increased the scale of the outbreak and overcame the formerly countervailing

 doi:10.20944/preprints202506.0485.v1

epidemic malarial stochasticity that was linked to certain limitations on *Anopheles* presence [8]. A 2018 epidemiological study conducted in Indonesia, in fact, strongly "highlights the importance of livestock [presence] for amplified "malaria risk [by a factor of 2.8] rather than prophylaxis" in such proximity settings [10]. Another holistically exacerbating factor for the epidemic is that Romans would have been naive to *P. falciparum* pathology. Unlike Africans, they would not have long before developed variants such as the sickle cell trait "which is common in African populations and protects against fatal *P. falciparum* malaria." [11,12].

References in both ancient accounts to a preceding disease outbreak that devastated cattle and other animals in the 5th Century BCE also lend at least indirect (if unfortunately, also somewhat circular) support to the diagnosis of malaria through indirect possible implication of stagnant pools of contaminated water in that preceding outbreak. The now eradicated RNA single strand *paramyxoviridae* rinderpest virus is clearly a possible candidate pathogen in that instance, though the evidence in this regard is somewhat thinner and less compelling. Northern rinderpest strains had an extraordinary morbidity rate of nearly 100% [13], which is, however, consistent with both ancient accounts [2,5]. Rinderpest was "very fragile" in terms of aerosolization but that was not its primary path of transmission [14]. Stagnant pools (which could also have also been fertile environments for *Anopheles* mosquitoes that are the secondary host/primary vector of malaria) of contaminated water were. Ancient writers such as Livy seem to have erroneously conflated the epidemics [5]; modern science has additionally found no evidence of zoonotic transmission of rinderpest to humans [14]. and WGS analysis indicates a later to much later genetic (and zoonotic) emergence of measles from rinderpest; with these genetically linked viruses, however, continuing to co-exist in a temporal sense [15].

According to a relaxed clock Bayesian phylogenetics study with an HPD confidence level of 95%, the eleventh and twelfth centuries are the likely temporal window for measles emergence from rinderpest– the highly relevant early edge of that temporal window would be between 437 and 678 CE [16]. This would be far too late to be the cause of the 5th Century BCE epidemic or even of the much later (2nd-3rd Centuries CE) Antonine or Cyprian pandemics (see below). The described seasonality of the 463 BCE ancient outbreak also does not match that of measles [17], and therefore that alternative can be firmly ruled out. Though rinderpest itself was likely already present in the 5th Century BCE in ancient Italy. Rinderpest was certainly established in the Roman Empire sometime prior to the 4th Century CE. The detailed description contained in *De Mortibus Boum* (alternatively *Carmen bucolicum de virtute signi crucis domini*) written by the 4th century CE Roman poet Severus Sanctus Endeleichus strongly indicates regular and long-standing outbreaks of epizootic (and endemic) rinderpest disease in the European territories of the ancient Roman Empire [13,14].

More broadly, our proposed timeline and implicated pathogen, also (while not rising to the level of scientific conformation) fits seamlessly in terms of more holistically considered retrospective-diagnosis or deductive analysis, like a precisely shaped missing piece of a puzzle, into what we already know or can surmise about malaria and infectious disease history more broadly in ancient Italy. As to the far less likely possibility of more exotic/less common/unlikely pathogens that also *nonetheless fit the annualized seasonal pattern*, we reference the famous phrase of Dr. Theodore Woodward traditionally used to train medical students, "When you hear hoofbeats behind you, don't expect to see a zebra" [18]. Dates for the establishment and spread of malaria as an annualized/endemic (peak late summer early Fall seasonality) ancient disease in Europe do, however, vary somewhat in the established scholarship. Such timelines have been particularly disputed, and we hope that our conclusions here help clarify this question, for *P. falciparum*; though, it seems to have been well on the way to becoming endemic in nearby northern Greece by 500 BCE. General agreement also exists that *P. vivax* arrived earlier in Italy than *P. falciparum* [8]. Malaria outbreaks occurred from the 6th Century BCE onwards with the effects of endemic disease eventually becoming "considerable" in terms of killing or debilitating people [to the extent that malaria] altered the age structure of human populations" in the ancient Mediterranean World [8]. As noted above, we believe that our evidence, when considered holistically and consiliently, demonstrates that the epidemic of 463 BCE marked a key moment in this progression.

Based on a highly detailed description of the pathology of semitertian fevers [19] from Celsus in the early 1st Century CE, one can safely conclude that the more pathogenic form of the disease *P. falciparum* had long been endemic in Italy before then [8]. Less detailed but telling references to annually be escaping, deadly "bad air", an allusion to the Greco-Roman humoral medical concept of disease-causing miasmas, in the late summer/early fall around the town of Tarquinia (with nearby apparently *Anopheles*-ridden malarial coastal marshes) indeed date as far back as the 2nd and even 3rd Centuries BCE. These are again indicative of the evolutionary lineage of *P. falciparum* causing endemic disease [8] by that, even earlier, period. As noted, Roman **(B) culture, more broadly, reflected and shaped perceptions and at times outcomes (**through inducing changes in behavior**)** the power of the annual late summer/early fall pestilential season's fear and menace. The First Century BCE famed poet Horace, in his *Odes* and *Epistles,* uses the phrase "fever season" not only to describe specific conditions in the late summer-early fall but also to represent periods of difficulty, illness, or even historical events that have caused suffering to humanity – a clear signifier of the trope's cultural recognition, power and relevance for ancient Romans [20].

Overall, one can conclude that the process of malaria becoming an endemic disease throughout non-alpine Italy was steady and significant but also slow and extended (hindered initially by the lack of consistent/sufficient presence of *Anopheles* mosquitoes) and took place between 700 and 100 BCE [8]. In fact, malaria reached the Italian north much later– only by around 1000 CE [19]; though the colder and drier prevailing climate there likely also inhibited the spread of the disease. The Pontine Marshes near Rome itself, however, were a suitable spot for the disease to become strongly established. By the First Century BCE, Julius Caesar was making the first of many historical attempts to drain the Pontine Marshes [9], pp.192-201. Horace, like many upper-class Romans, fled Rome during these unpleasant and dangerous months to avoid the muggy climate and the malarial disease that often spread through the city. This was common behavior among the well-to-do, who preferred to take refuge in villas and summer residences in the countryside in drier and cooler locations [20]. Besides the evidence from a multitude of literary sources, ancient Roman *P. falciparum* malaria infections and deaths, from corpses found at the Umbrian so-called "Infant Cemetery" from the 5th Century CE (occurring against the later backdrop of the Western Roman Empire's collapse) at the archaeological site of Lugnano, have been scientifically confirmed through PCR/DNA analysis [8]. That same 5th Century CE outbreak also highlighted the differences in terms of epidemiology and pathology for a naive population (in this case Attila's invading Huns whom the outbreak affected so severely as to likely drive them from Italy) and one that had been living with *P. falciparum* for nearly a millennium. The victims at Lugnano were (typically) children [21], p. 97. Lacking basic germ theory and modern blood tests to confirm and identify parasite species [22], a wide range of antimalarial drugs, ACT therapies used by modern medicine to treat uncomplicated forms of P.falciparum infection or the parenteral antimalarial therapies used to combat more severe cases [1], surviving adults at Lugnano desperately turned to magical remedies involving ravens' talons, "stones in the mouths of the small children's corpses" and pots of ash [21], p.97 The intensification of malaria with the onset of Italian *P.falciparum* infections that seems to have begun in 463 BCE indeed had significant and long term civilizational-level consequences for ancient Rome.

More broadly, **(C) changing climatic conditions** clearly also played a major role in the expanding epidemiological footprint of a variety of types of malaria in ancient Italy. A combination of written records and a range of consilient scientific data makes deducing relevant climate trends generally reliable from the 5th Century BCE onward. This was the early part of the era often characterized by historians as the Roman Warm Period (RWP), alternatively known as the Roman Climate Optimum (RCO). There are strong signs of warmer and wetter climate trends from around the 6th Century BCE onwards [23]. The Tiber River, for example, seems to have changed course by the 6th Century BCE due to, amongst other factors, steadily warmer temperatures. Wetter conditions also prevailed more generally, in a partially overlapping manner, between 800 to 400 BCE across the non-alpine regions of Italy [23]. The overall picture though is complex in more than one sense, often regionally varied and at times strongly interrupted. In 426 BCE, for example, an unknown stratospheric volcanic eruption took place that led to sharply cooler temperatures for the following three years. More consistent "warmer, wetter or more stable" climate conditions began to prevail around 200 BCE [23]. Malaria's arrival and expanding presence in ancient Italy was also enabled and exacerbated by additional **(D) anthropogenic environmental factors**: Increasing deforestation, interrelated practices of agriculture, increasing urbanization and other forms of human activity. The water table also rose in Italy by a meter between the 6th and 4th Centuries BCE [9], pp. 101-105. Over time, under these changed climate and environmental realities, malaria became more widespread and significant as an endemic disease in the emerging Roman Empire. Indeed, malaria (in all its three present types- *P. malariae, P.vivax and P.falciparum*), tuberculosis and many forms of dysentery were the most prominent diseases in ancient Rome. Chickenpox, diphtheria, mumps, and whooping cough also occurred in childhood, with less frequent attacks on adults [24].

Yet, it was malaria, augmented by the more deadly *P. falciparum* legacy that likely began in 463 BCE, that was the most consistently significant infectious disease threat for ancient Rome. Robert Sallares in *Malaria and Rome*: *A History of Malaria in Ancient Italy* (Oxford, 2002) noted that ancient Rome's holistic interaction with malaria (particularly *P. falciparum*) shows that "Malaria has an awesome power as a determinant of demographic patterns" [9, p.2]. These include population health, structure and life expectancy, and in Rome's case, malaria (again, particularly *P. falciparum*) was also a contributor to an extremely high rate of infant mortality. Especially if we agree with the complex systems theory-based analysis of the Club of Rome's Ugo Bardi that the Roman Empire of the 1st through 3rd Centuries was "larger, better organized and better managed than anything that had existed before" [25],p.13, malaria and its destructive demographic consequences (particularly those caused by *P. falciparum*) [9], p.2 constituted an annually-present key Bardian 'damping" [25], p.2 feedback and, largely unaddressed flaw in the holistic complex functioning of empire and a continuing quiet but damaging blow to Rome's civilizational resilience. The event of 463 BCE thus seems to have functioned as a key inflection point after which the threat to Roman civilization from malaria was afterwards amplified. Even more fundamentally, malarial disease impacts human populations at a deep biological level; "variants in the human genome that are associated with resistance to *Plasmodium* infection disease are estimated to be thousands of years old" in Africa [26], pp.283-304.

During the late 19th Century, however, the areas around Rome contributed to the foundational modern medical understanding of malaria (through the pioneering work of 19th-20th Century French physician Alphonse Laveran) and saw efforts in the use of engineering to eradicate malaria– through the successful draining of the Pontine Marshes [9], pp. 14-16. The influx of a new and deadlier form of malaria in 463 BCE also occurred against the developing **(E) perceptions, practices, knowledge and capabilities of the prevailing medical system and (F) the existing holistic underlying state of the health of the affected population.** Largely urban-based ancient Greco-Roman physicians associated the epidemiology/presence of malaria generally with marshes but not specifically with mosquito bites. Though, contrastingly, rurally based Roman agricultural experts such as Varro (2nd Century BCE) and Columella (1st Century CE) do seem to have been at least vaguely aware of the mosquito vector for the various malarial fevers [19]. The likely reason for this oversight by the physicians, along with the prevailing and distorting lens of Greco-Roman medicine's humoral theory (e.g., the famed second century CE physician Galen believed that severe quotidian fever was caused by an excess of phlegm [27]), is that the *Anopheles* secondary host/vector is complex and highly species dependent. Many of the relevant species are indistinguishable without the modern technology of a microscope [9], p.26. Thus, the prevalence of situations characterized by "lots of mosquitos but no malaria" likely explains why "ancient Greek and Roman physicians failed to notice the connection between the periodic intermittent fevers of malaria and mosquito bites" [9], p.45. The dangers of *P. falciparum*, a modern transdisciplinary combination of archaeology and medicine informs us, were also likely exacerbated "by [underlying] moderate degrees of malnutrition" amongst the Roman lower classes during both the Republican and Imperial periods [9], p.146.

Greco-Roman medicine also lacked a consistently applied or effective remedy for severe malaria that extended beyond basic palliative care. The resulting intermixing of mystical elements within (noticeable in the accounts of the 463 BCE outbreak) Greco-Roman medicine– conceptualization of malaria as a demon, magic, cults of *Dea Febris* (Goddess of Fevers) and amulets also didn't help matters. Regarding pathology, Greco-Roman physicians such as Celsus and Galen were on somewhat firmer ground. They correctly classified, for example, the intermittent (at times recurring over months or even years and associated with gastro-intestinal disorders and miscarriages) but generally non-fatal milder "quartan" fevers (those which we know today are caused by *P. malariae*) as different from the more dangerous semitertian or "quotidian" fevers associated, we know now, with *P. falciparum.* [9], pp.125-135. Malaria seems to have depressed Roman life expectancy overall in a way at least somewhat, if not exactly, analogous to *Yersinia pestis* infection during the later Middle Ages [9], pp.272-273. The physician Asclepiades of Bithynia described more severe forms associated with *P. falciparum* (semitertian or quotidian) and *P. vivax* (tertian) as "common" in ancient Italy by the 3rd to 2nd Centuries BCE [9], pp.219-220. One of the main symptoms of the more severe fevers was lethargy. The brilliant Galen, in the 2nd century CE, also inferred the concept of acquired immunity, noting the vulnerability of children and newcomers to these fevers [9], pp.219-220. He thus indirectly anticipated the modern medical conclusion that, "In low transmission areas, all ages are at risk due to low immunity" [1]. The Romans also had enough engineering capability and understanding of the importance of the threat from malaria to build, at the empire's height in the 2nd Century CE, mitigating drainage systems in the Campagna around Rome that helped limit the threat of malaria to the city itself for centuries. These complex mitigation/control systems, however, collapsed completely along with the Western Roman Empire during the 5th Century CE [19].

However, "during the 20th Century, malaria was eradicated from many temperate areas including the whole of Europe" [28]. Sophisticated detection and eradication methods have proved effective, and in today's Europe, malaria is largely a disease of travelers. Though some autochthonous cases of human-to-human transmission do occur [28]. While, as in ancient times, climate change (now more exclusively anthropogenic as opposed to naturally cyclic *and* anthropogenic) may mean that vector-borne malaria may once again become endemic to southern Europe [29], modern medical understanding and continued diligent use of a wide variety of eradication and control measures are likely to mitigate against renewed expansion of non-zoonotic malaria in the southern European lands that it once haunted in ancient times. Such expansion of mosquito vector-borne disease threats in Europe during an era of anthropogenic climate change and environmental disturbance is also, however, not limited to *Anopheles*-vector malaria. Invasive *aedes albopictus* mosquitoes, linked to the spread of tropical diseases such as dengue fever, chikungunya and the Zika virus have now been found in no less than 18 European countries. *Aedes aegypti* mosquitoes, linked to the spread of yellow fever, have recently become established in Cyprus [30].

Materials and Methods Modern: The Spread of Zoonotic Malaria

On our 21st century globalized planet, the non-zoonotic and zoonotic malaria goal for many countries is to meet the WHO's standard of "zero indigenous malaria cases for three years and a program for prevention of reestablishment of transmission" [31]. Globally, there are four main human non-zoonotic malaria-causing parasites: *P. falciparum* (with its more severe pathology), *P. vivax, P. ovale and P. malariae.* Five main types infect humans–*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, *P. knowlesi* (zoonotic and hosted by macaques) and *P. cynomolgi* (basically zoonotic and hosted primarily by chimps). Malaria's classification status as a zoonotic disease is deeply "ancient", even in terms of biological as opposed to humancentric timescales and is very complex. Current types of non-zoonotic malaria-causing parasites resulted from ancient zoonoses, with future zoonoses "possible." Other malaria-causing plasmodium parasites from simians [could] be transmitted to humans in the future" [32]. Particularly notable in this context is *P. cynomolgi,* which is an African type of

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 June 2025 doi:10.20944/preprints202506.0485.v1

plasmodium parasite that is hosted by chimpanzees but has also infected humans [32]. Indeed, in Africa today, patterns of spillover potentially blur lines between zoonotic and non-zoonotic forms of malaria, as the human forms (*P. vivax* and *P. falciparum*), which seem to have been the products of "ancient zoonoses" from African apes have now been genetically documented to spill over into wildlife populations from humans and then spill back over into humans [31]. Two-way spillovers of African *P. ovale* between humans and chimpanzees have also occurred [32]. *P. knowlesi* is a sixth specifically zoonotic form of malaria that spills over from macaques in Southeast Asia. Such complex epidemiological realities are also revelatory of, more broadly, malaria's deep biological history as simultaneously a zoonotic as well as human to human transmitted disease [31]. Highly pathological *P. falciparum,* according to WGS analysis, seems to have diverged from the primate-based *P. reichenowi* around 50,000 years ago while *P. vivax* is far older– having emerged around 2 million years ago [32].

The problem of emerging *P. knowlesi*-caused zoonotic malaria, often still misdiagnosed, is becoming quite widespread in Malaysia and Malaysian Borneo [33]. Both **climate change and anthropogenic environmental factors** have, as in ancient Italy, been contributors to the spread– with cases now detected quite far apart, with a western boundary of India's Andaman Islands and an eastern boundary of the Philippines [33]. Though an evolution toward naturally occurring human to human transmission has not been documented for *P. knowlesi*, that certainly seems a distinct possibility. With testing clearly now showing a growing problem "more prevalent than [had been] suspected. Appropriate strategies need to be developed for the prevention, diagnosis and treatment of zoonotic malaria" [33]. The case of 5th Century BCE Rome thus serves as a highly cautionary tale. Indeed, on an even "deeper time" biological history scale, PCR and high throughput DNA sequencing also now confirm that what we consider non-zoonotic human malaria is, in fact, a zoonotic disease– indications regarding (*P. vivax*) from Sub-Saharan Africa are especially clear in that regard. Indeed… "Presently available data are… compatible with a hypothesis that human *P. malariae* and *P. ovale,* like *P. falciparum* and *P. vivax,* also originated by cross-species transfer from African apes and then spread worldwide" [33].

Macaque-hosted zoonotic *P. knowlesi* is now a clear and growing "challenge" for malaria elimination and has now spread to seven countries. It has become "the major cause of malaria in Malaysia" [32]. *P. knowlesi*, while somewhat less severe (similar in manifestations of pathology but *sans* coma) than *P. falciparum*, still causes severe malaria in up to 10% of adult cases [34]. The *Anopheles* secondary host/vector is identical. The asexual stage of infection in humans is like that of *P. falciparum* but with a 24 hr. erythrocytic cycle. Unlike *P. ovale*, *P. cynomolgi* and *P. vivax,* relapses are not characteristic of knowlesi's pathology [34]. 90% of cases occur in adults "mostly living in forest edge areas undergoing intensive land use change [**anthropogenic human disturbance**]." High risk groups include farmers and plantation workers [34]. *P. knowlesi* is "unique among zoonotic malaria in being able to cause severe and fatal disease and is now the most common cause of death from malaria in [the nation of] Malaysia" [34]. Future mutations could certainly create an inflection, or to use Bardi's terminology, "tipping point" [25], p.3 in the region, by both making the disease directly transmissible between humans and therefore effectively non-zoonotic and more widespread (this has already been demonstrated in a laboratory setting but not yet conclusively in nature) and make it potentially more dangerous to vulnerable populations– such as children that have not been exposed frequently so far due to environmental/epidemiological factors and among whom no *P. knowlesi* fatalities have yet been recorded. Indeed, *P. knowlesi* already demonstrates more genetic diversity than either *P. falciparum* or *P. vivax* [34]. The rapid spread of the disease has outrun **the perceptions and capabilities of regional and local medical systems**, and much about the true extent of *P. knowlesi's* spread in Southeast Asia is not totally clear with the "true burden of clinical disease outside Malaysia not well characterized" [34]. Yet, it is quite clear that while the human-hosted plasmodium species continue their decline in these regions, "the burden of clinical disease from *P. knowlesi* will likely increase" [34]. As in ancient Rome in 463 BCE, the threat from a new form of malaria in modern Southeast Asia is clearly evolving, spreading and deepening in a way that highlights the key role played by certain

 doi:10.20944/preprints202506.0485.v1

shared contexts. Combating a similar negative outcome will require the targeted and effective application of the modern medical knowledge and resources available to us.

Occurring against a similar background of both climate change and increased anthropogenic environmental disturbance, it is indeed the growing epidemiological footprint of zoonotic *P. knowlesi* that most strongly echoes ancient Roman malaria realities today. "Zoonotic malaria transmissions [more broadly, however,] are [also] widespread and growing, which poses a threat to public health" [32]. 368,000 cases were recorded in 87 malaria endemic countries in 2019 [32]. Rodent and avian based plasmodium parasites have no record of zoonoses, but non-human primates, as noted above, are another story. An additional, to *P. knowlesi* in Southeast Asia, current zoonotic malaria risk involves New World monkey-hosted forms *P. simium* (genetically similar to *P. vivax*) and *P. brasilianum* (indeed nearly "genetically identical" to *P. malariae*) [32]. The Atlantic Forest near Rio de Janeiro has been one hotspot for *P. simium* transmission. *Anopheles* mosquitoes remain the common secondary host/vector across all relevant malaria plasmodium parasite types. *P. brasilianum* and *P. simium* have both now caused malaria in humans [35 and 36].

Discussion: Broader Ancient-Modern Zoonotic Disease Parallels and Contrasts–Through the Revelatory Lens of Four Zoonotic Pandemics

In a more universal sense than the narrowly focused ancient-modern examples concerning the threatening spread of malaria, comparisons of four ancient and modern highly destructive zoonotic pandemics are also highly revealing. In a more rapid and immediate way than the process of differing plasmodium parasite lineages gradually becoming regionally-endemic pathogens, these massive "tipping point" outbreaks are examples , in our view, of "Black Swan" events that altered the paths of societies pushing them, to apply terminology from Ugo Bardi's complex systems analysis, toward a new civilizational "set of parameters" and/or ultimately collapse [25], pp. 2-3. The 2nd Century CE Antonine Plague and the 3rd Century CE Plague of Cyprian demonstrate interesting parallels and contrasts when compared with the 20th Century "Spanish Flu" and 21st Century COVID-19 pandemics. Both the ancient Roman Empire and the increasingly globalized modern world suffered through pandemics in consecutive centuries with all four events very likely (those occurring in ancient times) or, with scientific certainty (those occurring in modern times) linked to zoonotic pathogens. Chronologically and consecutively, these are the evolutionary lineage of smallpox [37], pp. 98-115, the viral hemorrhagic fever (VHF) evolutionary lineage of African filoviruses (Ebola and Marburg) [38], p.254, H1N1 influenza virus and SARS COV-2.

In terms of retrospective diagnosis/consensus, evidence for smallpox as the pathogen very likely to have caused the Antonine Plague was recently significantly strengthened even further by the 2024 discovery of a skeleton showing unmistakable signs of *osteomyelitis variolosa* (a known smallpox *sequela*) from the Western Cemetery at Cirencester (Corinium in Roman Britain) dating to the 3rd or 4th Century CE [39]. Significantly, the ancient zoonotic pandemics were thus very probably caused by weakly aerosolized or non-aerosolized pathogens with high CFRs. The modern pandemics were caused by more highly aerosolized, more contagious/ higher R_0 zoonotic pathogens with much lower CFRs. As noted above, the **perceptions, practices, knowledge and capabilities of the prevailing medical system and the existing holistic underlying state of the health of the affected population** consistently shaped the parameters and outcomes of ancient and modern pandemics in terms of epidemiology and pathology. While diseases in the ancient Roman world could have their pathologies augmented, as noted above, by amplifying (or in Bardi's terminology "positive" [25], p.2) feedback factors—such as naive populations and/or mild but chronic malnutrition amongst the lower classes, higher CFR ancient pandemic diseases such as the deadly Plague of Cyprian functioned more independently and reversed the annualized and generally-defining "sickly season" patterns of infectious disease and their culturally-acknowledged "ordinary seasonality of death in the Roman Empire" [38], p.140. The ancient Christian writer Eusebius indeed described the Plague of Cyprian as "the only thing that prevails over all hope" [40], p.139 [VII.22.6. Yet both the shortcomings of the widely prevalent Greco-Roman medical system and a variety of other features associated with

 doi:10.20944/preprints202506.0485.v1

Roman culture and urban life (such as the institution of the Roman baths and funerary practices common in the 3rd Century CE) would likely have also strongly and 'positively' amplified the generally rather low contagiousness suspected MARV lineage pathogen's R_0 [38], pp.161-225. Numismatic-based analysis indeed seemingly indicates a contemporary sense that the Greco-Roman medical system was also seen as having completely failed to contain the disease [38], p.36 during that fifteen-year (248-262 CE) pandemic. During the 21st Century COVID-19 pandemic, contrastingly, more than 40 vaccines were rapidly developed, approved by national regulatory authorities and generally effectively deployed. Along this nearly 2,000-year continuum, the "modern" Spanish Flu pandemic of 1918-1921, is revealed as actually something more of a transitional case than might reasonably be expected. The prevalence of the erroneous theory of the so-called "Pfeiffer bacillus", for instance, as the cause of influenza still proved a considerable impediment in terms of effective vaccine development and deployment [41,42]. Aspirin-based preventive regimens prescribed by physicians at the time may also actually have contributed, iatrogenically, to the unusually high rates of death amongst soldiers and other young healthy people during the pandemic [43].

More modern pandemics characterized by lower CFR pathogens, as in the cases of H1N1 and SARS-COV-2 are also, more collectively in these instances, different both due to the superior knowledge base and capabilities of modern medicine (strikingly revealed as far more fully modern in the early 21st Century as opposed to the early 20th) but also because of the more significant role, in terms of pathology, of amplifying interactions with the underlying burdens of chronic disease in modern populations. In 1918, "heart disease was quite different…damage to the four valves inside the heart from previous rheumatic fever, now rare…was common, difficult to diagnose and not correctable" [44]. In the 21st Century, a burden often caused by calorically sufficient but far less healthy sugar and fat-laden diets [45] was a major amplifying factor in the COVID-19 pandemic. Contrastingly, in 2025, the likely Antonine Plague smallpox pathogen has been eradicated, and most outbreaks of the VHF African filoviruses are now better understood and can be detected and contained even when they occur in unprecedented places such as the MARV outbreak that occurred in the West African nation of Ghana in 2022 [46]. While zoonotic diseases such as MARV (and even increasingly Ebola) should still be perceived as very serious threats (including in relation to possible bioterrorism), their disease ecology is better (if still for Ebola not completely) understood. Vaccines and effective containment/mitigation measures have also been developed against these deadly viruses.

Much of this progress has, however, been very recent. As noted above for the 1918-1921 "Spanish Flu" pandemic, etiologies were only partially accurate, and vaccination attempts imprecise and only tangentially effective [41]. But the pace of 21st Century understanding, treatment and containment are all truly impressive. When a pandemic threat emerged in terms of the SARS virus in the first decade of the 21st Century, effective treatments and containment strategies were rapidly and effectively deployed and the fundamental disease ecology revealed through the gold standard work of Chinese virologists who isolated the disease to its reservoir host– the Horseshoe Bat, publishing their results in 2005 [47].The low CFR, novel, respiratory and highly contagious SARS-COV-2, however, interacting with the underlying burden of chronic disease in modern populations, overwhelmed such modern mitigation measures as contact-tracing. Historian of disease Kyle Harper thus notes, considering this *longue durée* progression, that it was a "reasonable likelihood that the culprit [in such a 21st Century pandemic as opposed to an ancient one] world be a highly contagious RNA-virus of zoonotic origins spread via the respiratory route" [48], p.504. Such comparative holistic deductions could indeed better inform more efficient and cost-effective modern zoonotic pandemic preparedness solutions going forward into the near future.

Changing climatic conditions and anthropogenic factors related to increased environmental disturbance also likely played a major role in all four major zoonotic pandemics. In the ancient cases, the Antonine Plague and the Plague of Cyprian both occurred during "pronounced cold phases" occurring between 160 to 180 CE and 245 to 275 CE as the RWP waned [49]. Regarding the "Spanish Flu", the period was denoted (in Europe) both by both colder temperatures and by a strong influx of marine air that constituted a "climate anomaly unmatched in 100 years" that exacerbated both WWI battlefield deaths and the interconnected pandemic in Europe [50]. In the case of SARS COV-2, the pandemic, conversely, occurred against the backdrop of anthropogenic global warming. Exact causal relationships in all these cases are, however, not certain or fully understood; they are all worthy of further exploration and research. Though the theme of pandemics occurring away from periods characterized by more average or steady state climate conditions seems to bridge the temporal divide between ancient and modern times. All four pandemics also took place against the backdrop of intensified periods of human movement and environmental disturbance. In ancient times, the 2nd and early 3rd Centuries CE largely marked the period of the Roman Empire's greatest territorial extent and the creation or intensification of multi-continental land and maritime trading networks that linked hitherto separate biogeographical zones. The Roman Empire in this period thus "threw open 'all the gates of the inhabited world'" [37], p.97. Rome's voracious consumption economy was also linked to environmental disturbance not only in Europe but also in Africa (including parts of Africa that lay beyond Rome's borders) [38], pp.123-131. Massive troop movements and the intensified demand for natural resources within the context of the world's first industrialized modern world war provided the backdrop for the "Spanish Flu." The mass troop movements [in particular] contributed to the global spread of pandemic influenza [51]. Unprecedented rapid and intensified patterns of intercontinental human movement, within the parameters of a now truly globalized 21st Century economy spread SARS-COV-2 around the world in well under a year– "Globalization and the geography of economic relations were the main drivers of the spatial structuring and speed of the international spread of COVID-19" [52].

Culture, more broadly, reflected and shaped perceptions and, at times, outcomes of zoonotic pandemic disease in both the modern and ancient worlds. The very consistent thread amongst both ancient and modern zoonotic pandemics was that the outbreaks notably sharpened existing cultural divides. Both ancient pandemics seem to have exacerbated differences and conflict between pagan traditionalists and Christians within the Roman Empire, leading to several major confrontations between the Roman state and Christian groups. Both sides saw destructive diseases as punishment for human defiance of divine authority but differed over whose divine authority was being defied [37], pp. 100-118 and 154-155. In modern times, during the Spanish Flu pandemic, groups such as the Anti-Mask League of San Francisco defied outbreak pandemic mitigation majors such as masking [53].This was a symptom of a broader cultural/political divide and sharpening conflict in the Western World between advocates of centralized government, including the deployment of sweeping governmental powers to fight contagion, and advocates of the sanctity of more unadulterated civil liberties– pandemics notwithstanding. Indeed, during the COVID-19 pandemic, conflicts over masking and other social distancing mitigation measures were even sharper and more widespread than during the earlier "Spanish Flu" [54]. In late 2021 for example, huge protests rocked both the Netherlands and Belgium. Similarly, in ancient times, the Plague of Cyprian seems to have witnessed even more intense cultural disputes between pagan traditionalists with unprecedentedly thoroughgoing campaigns (known to contemporary Christian groups as persecutions) undertaken by the emperors Trajan Decius (r. 249-251 CE) and (Valerian r. 253-260 CE) to suppress those unwilling to fully conform to the state cults of the emperor and the Roman pagan pantheon [38, pp.30-42 and 50-57]. In the United States during the COVID-19 pandemic, existing racial tensions and inequalities and overall political divides became more marked. Resulting mass protests, in turn, led to "significant and positive" infection rate growth in several US cities [55].

Political, economic and security/military contexts also display some striking parallels from ancient to modern times in terms of the destabilizing broader impacts of these four zoonotic pandemics. The zoonotic pandemics, in both ancient and modern times, arose during or helped trigger major conflicts. The Antonine Plague was linked, in the popular conception at the time, both with the Roman-Parthian war of the 160s CE and the attempted usurpation of Avidius Cassius against the Emperor Marcus Aurelius (r. 161-180 CE)– though modern historians have questioned whether the Romans were correct in these inferences [56]. The pandemic was almost certainly, however, a triggering factor for the ensuing and devastating Marcomannic Wars along the empire's Danubian frontier. The feedbacking combination of pandemic and war also had well-documented and extensive negative impacts on the empire's economy [57], pp. 374–375. The Plague of Cyprian functioned similarly as an important component of the Roman Empire's so-called 3rd Century Crisis–a period of political instability, rampant inflation, civil wars, political assassinations and enemy invasions across almost every imperial frontier [37], pp.129-158. The "Spanish Flu" pandemic, with its very name essentially being an indirect byproduct of wartime censorship, was similarly closely intertwined with World War I through troop movements and also intensive mobilization-related cultivation of chickens and pigs that may have spurred both key mutations in the H1N1 pathogen and the zoonotic leap to humans in Kansas. The virus's impact also likely speeded the attritional conflict's end [58]. The COVID-19 pandemic inflicted considerable economic damage and destabilized the politics of many nations around the world, helping to provoke waves of civil unrest [59]. In the pandemic's wake, major wars also broke out in Europe and the Middle East.

Conclusions

Ancient Greco-Roman culture's understanding of the threat posed by infectious disease and interrelated social disorder was perhaps best embodied by Thucydides' canonical account of the Plague of Athens (430 BCE) in his *The History of Peloponnesian War* [60]. While lacking modern scientific knowledge about zoonosis or microbial genesis, ancient Greeks and the Romans indeed developed concepts concerning public health. Such discourse was also of great socio-political importance; the 1st Century BCE Roman Republican dictator Lucius Cornelius Sulla Felix, for example, claimed the ability to master the epidemic fulgors with which the god Apollo Pythios could disseminate deadly plagues among humans [61]. Sulla thus used the widely feared threat of infectious disease to bolster his own political authority.

The 21st Century world faces increased threats from a wide range of zoonotic diseases. "Most of the new pathogens are zoonotic in origin" [62]. "Zoonotic outbreaks are also becoming more frequent" with some emerging pathogens displaying pandemic potential in terms of moving with an epidemiological speed (particularly in our globalized age) and feedbacking pathogenic impact that could overwhelm our defenses [62]. Such failures, despite the historically unprecedented recent advances in medical knowledge, indeed clearly occurred during the COVID-19 pandemic. In addition to the threats implicit in the operation of mass-production commercial CAFOs, zoonoses derived from spillover from wildlife have also "been emerging at an alarming rate due to deforestation and the change in ecosystems, such as land shifts, habitat alterations, global warming, and changes in the biological characteristics of pathogens and vectors…" [29]. Yet, resources are not unlimited; fine tuning and practicality of expense as well as in terms of planning and response are necessary. Against such a reality, a holistic awareness of the capabilities and limitations of our medical system, an understanding of the likely effects of epidemiological and pathology feedbacks from underlying population health, the effects of cultural perceptions, the influences of climate change and anthropogenic environmental disruption, as well as careful consideration of the possible political and military implications of zoonotic disease outbreaks are all factors that a comparative overlay of the zoonotic disease histories of the ancient and modern worlds demonstrates to be worthy of our consideration. Such interdisciplinary analysis, in our view, constitutes a key but overlooked component in attempting to analyze and predict the complex future parameters of the timeless human struggle with zoonotic disease [63, p.29]. History thus can, we assert, serve as a kind of informative prophecy… a macro-level symbiotic guide for a range of future scientific-medical adaptations and policy considerations to more holistically and effectively meet the increasing challenges likely arising from zoonotic disease for humanity in the future.

Funding: This research received no external funding

Conflicts of Interest: The authors declare no conflict of interest.

 doi:10.20944/preprints202506.0485.v1

References

1. Zekar L, Sharman T., "Plasmodium falciparum Malaria" [Updated 2023 Aug 8]. *StatPearls;* 2025 https://www.ncbi.nlm.nih.gov/books/NBK555962/).
2. Dionysius Halicarnassus, *The Roman Antiquities Vulgarized by the Abbot Marco Mastrofini.* Tome III. Book IX, LXVII. Sonzogno, Milan, 1824 - Revised G. Meledandri, 2024. The Greek text excerpt, from Dionysius of Halicarnassus, The Roman Antiquities, IX, pp.67-69. https://www.perseus.tufts.edu/hopper//text?doc=Perseus:text:2008.01.0572:book=9:chapter=67&highlight=pe%2Fnhtos
3. Detienne, M., *L'invention de la mythologie (*Gallimard: Paris), 1992.
4. Pritchett, W.K., *Dionysius of Halicarnassus: On Thucydides* (English Translation based on the Greek text of Usener-Rademacher), Univ. of California Press, Berkeley, 2022.
5. Livy, *History of Rome - Ab Urbe condita libri, III, 67, 6-7.* Edited by Guido Reverdito. Garzanti. Milan, 2010. (Tr. & Rev. by Giovanni Meledandri, 2024).
6. Homer, *The Iliad of Homer.* Translated by A. Pope. [pt.2]." In the digital collection Eighteenth Century Collections Online. https://name.umdl.umich.edu/004836009.0001.002. University of Michigan Library Digital Collections, 2012. Accessed May 4, 2025. https://quod.lib.umich.edu/cgi/t/text/text-idx?cc=ecco;c=ecco;idno=004836009.0001.002;node=004836009.0001.002:3.3;seq=87;view=text;rgn=div2
7. Preston, K., "Aspects of Autumn in Roman Poetry", *Classical Philology*, 13(3), 1918, pp.272–282. http://www.jstor.org/stable/263258
8. Sallares R, Bouwman A, et al, "The spread of malaria to Southern Europe in antiquity: new approaches to old problems," *Med. Hist.*;48(3), 2004, pp.311-328. doi: 10.1017/s0025727300007651. PMID: 16021928; PMCID: PMC547919)
9. Sallares, R., Malaria and Rome: A History of Malaria in Ancient Italy, Oxford University Press, 2002.
10. Hasyim, H., Dhimal, M, *et al.* "Does livestock protect from malaria or facilitate malaria prevalence? A cross-sectional study in endemic rural areas of Indonesia." *Malar J* 17, 302, 2018. https://doi.org/10.1186/s12936-018-2447-6.
11. Loy DE, Liu W, et al, "Out of Africa: origins and evolution of the human malaria parasites Plasmodium falciparum and Plasmodium vivax" *Int J Parasitol* ;47(2-3) pp.87-97, 2017 doi: 10.1016/j.ijpara.2016.05.008. Epub 2016 PMID: 27381764; PMCID: PMC5205579.
12. Service, M, "Malaria Vectors" in, *Medical Entomology*, Cambridge Univ. Press, 1996.
13. Murcia, P. Donachie, W et al, "Viral Pathogens of Domestic Animals and Their Impact on Biology, Medicine and Agriculture," Editor(s): Moselio Schaechter, *Encyclopedia of Microbiology* (Third Edition), Academic Press, London, 2009, pp. 805-819.ISBN 9780123739445, https://doi.org/10.1016/B978-012373944-5.00368-0.(https://www.sciencedirect.com/science/article/pii/B9780123739445003680)
14. Pastoret, PP, Yamanouchi, K, et al, "5 - Rinderpest — an old and worldwide story: history to c. 1902, Editor(s): Thomas Barrett, et al in *Biology of Animal Infections, Rinderpest and Peste des Petits Ruminants*, Academic Press, London 2006, Pages 86-VI, https://doi.org/10.1016/B978-012088385-1/50035-6.(https://www.sciencedirect.com/science/article/pii/B9780120883851500356).
15. Bello, MB, Ruggah, AH, "Ecological distribution and phylogenetic diversity of measles virus genotypes in West Africa, 2001 to 2020", *Vacunas*, Volume 25, Issue 4, 2024, pp. 470-480 https://doi.org/10.1016/j.vacun.2024.09.002.
16. Furuse, Y, Suzuki, A, et al, "Origin of measles virus: divergence from rinderpest virus between the 11th and 12th centuries, *Virol J.* ,7:52, 2010 doi: 10.1186/1743-422X-7-52. PMID: 20202190; PMCID: PMC2838858.).
17. Yang, Q, Fu C, Dong Z, et al, "The effects of weather conditions on measles incidence in Guangzhou, Southern China" *Human Vaccine Immunotherapy.*10(4):1104-10, 2014 doi: 10.4161/hv.27826. Epub 2014 Feb 6. PMID: 24509358; PMCID: PMC4896574.),
18. Theodore Woodward" https://www.hda.org.uk Accessed on 15 May 2025.
19. Dagen, M, "History of malaria and its treatment,"Editor(s): Graham L. Patrick, *Antimalarial Agents*, Elsevier, Amsterdam, 2020, pp. 1-48 https://doi.org/10.1016/B978-0-08-101210-9.00001-9.(https://www.sciencedirect.com/science/article/pii/B9780081012109000019)
20. Horace *Odes*, 1.14-1.38 and *Epistles*, 1-11 https://www.thelatinlibrary.com Accessed on 10 May 2025.

21. Orsag, M., McKinney, A, “The Mother of All Collapses’: Complex Systems, Crises and Modern Analogues,” *Journal of Applied History* (Volume 6/Issue 1) July 2024, pp.66-105.
22. Cleveland Clinic, “Malaria” Malaria: Causes, Symptoms, Diagnosis, Treatment & Prevention), https://www.myclevelandclinic.com Accessed on 5 May 2025.
23. Paparella, C., Bernard, S., et al, “Historical archives from the Roman Monarchic and Republican periods show human perceptions of environment and climate change in Italy, 753–29 BCE” *The Holocene*, *35*(4), 2025 pp.397-408. https://doi.org/10.1177/09596836241307302 (Original work published 2025).
24. Kiple, Kenneth A. (ed.), The Cambridge World History of Human Disease (New York: Cambridge University Press) The Cambridge World History. Cambridge University Press; 2015. Pp. 54-75.
25. Bardi, U, The Seneca Effect; Why Growth is Slow, but Collapse is Rapid Springer, Switzerland, 2017.
26. Hedrick, P.W. “Population Genetics of Malaria in Humans,” *Heredity* Edinburgh, 107 2011, pp.283-304.
27. Wittern R. “Die Wechselfieber bei Galen [Galen's intermittent fever]. *Hist. Philos Life Sci.* 11(1), 1988, pp.3-22. PMID: 2682735.
28. European Centre for Disease Prevention and Control (ECDC), *Factsheet for health professionals about malaria* 2024 https://www.ecdc.europa.eu Aessed on 8 May 2025.
29. Editorial, “Twin threats: climate change and zoonoses,” *The Lancet Infectious Diseases*, Volume 23, Issue 1, 1, 2023 https://www.thelancet.com
30. Roxby, P. “Tiger mosquitoes behind dengue fever rise in Europe” *BBC: World News & Stories* June 11, 2024, https://www.bbc.com
31. Fornace, K.M., Drakeley, C.J., et al, “Zoonotic malaria requires new policy approaches to malaria elimination” *Nat Commun* 14, 5750, 2023. https://doi.org/10.1038/s41467-023-41546-6).
32. Su XZ, Wu, J. “Zoonotic Transmissions and Host Switches of Malaria Parasites,” *Zoonoses*. 1(1):11, 2021 doi: 10.15212/zoonoses-2021-0015. Epub 2021 Nov 2. PMID: 35282332; PMCID: PMC8909814.)).
33. Ramasamy, R., “Zoonotic malaria– global overview and research and policy needs”, *Front. Public Health* 17 Sec. Epidemiology Vol 2 2024 https://doi.org10.3389/fpubh.2014.00123).
34. Anstey NM, Grigg MJ, et al “Knowlesi malaria: Human risk factors, clinical spectrum, and pathophysiology” *Adv Parasitol*. 113:1-43, 2021. doi: 10.1016/bs.apar.2021.08.001. Epub 2021 Aug 28. PMID: 34620381; PMCID: PMC9299579.).
35. Lalremruata A, Magris M, et al, “Natural infection of Plasmodium brasilianum in humans: Man and monkey share quartan malaria parasites in the Venezuelan Amazon*” EBioMedicine*. 29;2(9):1186-92, 2015 doi: 10.1016/j.ebiom.2015.07.033. PMID: 26501116; PMCID: PMC4588399
36. Brasil, P, “Outbreak of human malaria caused by *Plasmodium simium* in the Atlantic Forest in Rio de Janeiro: a molecular epidemiological investigation,” *The Lancet Global Health*, Volume 5, Issue 10, 2017, pp. e1038 - e1046.
37. Harper, K The Fate of Rome: Climate, Disease & the End of an Empire Princeton University Press, 2017.
38. Orsag, M, McKinney, A, Reeder, DM, Interdisciplinary Insights from the Plague of Cyprian: Pathology, Epidemiology, Ecology and History Palgrave-Macmillan Switzerland: 2023.
39. Zhao, H, Wilson, A, “A case of *osteomyelitis variolosa* from Roman Britain, and the introduction of smallpox to the Roman world” *Journal of Roman Archaeology* (Published online) 2025, pp.1-32 doi:10.1017/S1047759424000357).
40. Pamphilus, Eusebius, *Ecclesiastical History* Trans. A.C. McGiffert Pantianos Classics, New York, 1890.
41. Eyler, JM, “The state of science, microbiology, and vaccines circa 1918,” *Public Health Reports* 2010 125 Suppl. 3, 2010, pp.27-36 PMID: 20568567; PMCID PMC2862332.
42. Najera,R., “The 1918-1919 Spanish Flu Pandemic and Vaccine Development “ *The College of Physicians of Philadelphia Mutter Museum and Historical Medical Library* The 1918-19 Spanish Influenza Pandemic and Vaccine Development | History of Vaccines, 2018 https://www.historyofvaccines.org Accessed 12 May 2025.
43. Starko, KM, “Salicylates and Pandemic Influenza Mortality, 1918-1919 Pharmacology, Pathology and Historic Evidence” *Clinical Infectious Diseases,* Volume 49 Issue 9 15, 2009 pp. 1405-1410. https://doi.org/10.1086/606060)

44. Holmes, F., “Heart Disease in the First World War” KU Medical Center, 2017 Heart Disease in the First World War) https://www.kumc.edu Accessed on 29 April 2025.
45. McKinney, A., “Pandemics, Ancient and Modern: Causes, Effects, Differences and Parallels” Amanda McKinney, Doane University – Pandemics, Ancient and Modern: Causes, Effects, Differences and Parallels - The Academic Minute, 2021 https://www.aacu.edu Accessed on 15 April 2025
46. BBC, 2022 “Ghana Confirms First Cases of Deadly Marburg Virus” 19 7 2022. https://www.bbc.com
47. Lau, SK, Woo, PC, et al, “Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats” Proc Natl Acad Sci, September 16, 2005 102 (39), 20005 pp.14040-14045 https://doi.org/10.1073/pnas.0506735102).
48. Harper, K., Plagues Upon the Earth; Disease and the Course of Human History Princeton University Press, 2021.
49. Zonneveld, K, Harper, K et al., “Climate change, society and pandemic disease in Roman Italy between 2000 BCE and 600 CE.” *Science Advances*, 10 (4), 2024.
50. More, A., Loveluck, C., et al, “The Impact of a Six-Year Climate Anomaly of the “Spanish Flu’ Pandemic and WWI” *Geo Health* Vol 4. Issue 9) 152020 https://.doi.org/10.1029/2020GH000277) Accessed on 17 May 2025.
51. CDC “1918 Flu Pandemic Commemoration,” 1918 Pandemic Influenza: Three Waves | Pandemic Influenza (Flu) | CDC), 1918 https://www.arcgive.cdc.gov Accessed on 5 May 2025.
52. Ernst, K.C., “Focus on COVID-19 and climate change,” In: *Fifth National Climate Assessment*. U.S. Global Change Research Program, Washington, DC, USA, 2023 https://doi.org/10.7930/NCA5.2023.F3. Accessed on 12 May 2025.
53. Dolan, B. “Unmasking History” Who Was Behind the Anti-Mask League Protests During the 1918 Influenza Epidemic in San Francisco” *Perspectives in Medical Humanities* May 19, 2020. Unmasking History: Who Was Behind the Anti-Mask League Protests During the 1918 Influenza Epidemic in San Francisco?) https://www.escholarship.org Accessed on 22 May 2025.
54. *BBC* “Covid: Huge protests across Europe over new restrictions” Covid: Huge protests across Europe over new restrictions, 21 11 2021. https://www.bbc.com
55. Valentine R. et al, “Relationship of George Floyd protests to increases in Covid-19 cases using event study methodology” *Public Health* (Oxf); 42 (4): 696-697, 2020 https://doi:10.1093/PubMed/fdaa127 PMID: 32756893 PMC: PMC7454741.)
56. Harper, K., “Germs and Empire.” in *Empire and Religion in the Roman World*, ed. H.I. Flower (Cambridge: Cambridge University Press, 2021.
57. MacDonald, B., “The Antonine Crisis: Climate Change as a Trigger for Epidemiological and Economic Turmoil.” in *Climate Change and Ancient Societies in Europe and the Near East: Diversity in Collapse and Resilience*, eds. P. Erdkamp et al. Palgrave-Macmillan, Switzerland, 2021, pp.373–410.
58. Holmes, F. “The Influenza Pandemic and the War” KU Medical Center The Influenza Pandemic and The War, 2017 https://www.kumc.edu Accessed on 16 May 2025.
59. Farzanegan, MR, “How has the pandemic affected civil conflict around the world?” *Economics Observatory* How has the pandemic affected civil conflict around the world? - Economics Observatory) April 2023 https//www.economics observatory.com Accessed on 25/May 2025
60. Thucydides, The History of the Peloponnesian War 2.48.1 https://www.gutenberg.org Accessed on 18 May 2025
61. Carcopino, J. *Silla* J. Rusconi ed., Milano, 1979.
62. The Independent Panel for Pandemic Preparedness and Response “What happened, what we've learned, and what needs to change | COVID-19: Make it the Last Pandemic”, 2020 https//www.recommendationstheindependentpanel.org Accessed on 9 May 2025.
63. Orsag, M., “History, Science and Prophecy?” included in “What is Scholarship Today: 12 Historians Share How They Do History” [Article features a dozen nationally selected historians whose research is contributing to a broadening of the definition of historical scholarship in line with the relevant January 2023 AHA resolution on the subject.] *Perspectives on History: The News Magazine of the American Historical Association*, 2025, pp.28-29).

doi:10.20944/preprints202506.0485.v1