

A historico-medical perspective on ancient epidemics and their impact on past human societies

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Keywords

COVID-19 • Epidemics • History of medicine • Immunology • Plague • Prevention • Infectious diseases

Summary

The present article reviews the major historical plague epidemics that characterised human history by combining data derived from historical sources and biomedical evidence emerged in recent years thanks to advancements of palaeogenetics and palaeopathology.

Notes are offered on the Plague of Athens, the Antonine Plague, the Plague of Cyprian, the Justinian Plague, the Black Death down to more recent centuries and presenting key aspects that continued to be preserved over time and would also partly characterise the recent COVID-19 pandemic.

Introduction

The severe impact of the COVID-19 pandemic, amounting to more than 704,753, 890 cases worldwide and 7,010,681 deaths as of April 13, 2024 [1], on the world's population has led the international scientific community to reflect deeply on the history of epidemic-pandemic phenomena and the anthropic response, at medical as well as social and political levels. Indeed, those events have powerfully shaped the economic, political, and social aspects of human civilization [2-4]. Epidemic outbreaks have defined some of the basic tenets of modern medicine, pushing the scientific community to develop principles of epidemiology, prevention, immunization, and antimicrobial treatments [2-4].

The aim of this contribution is to retrace the main pestilential events that have disrupted human societies, starting from the mythical Achaean plague narrated in the Iliad to the plague of the 14th century AD, thus emphasising the interaction between scientific-epidemiological and socio-cultural components.

History of plague

Plague is an infectious disease of bacterial origin caused by the bacillus *Yersinia pestis*, a Gram-negative bacterium belonging to the enterobacteria family [5]. The disease is primarily a murine zoonosis, and its reservoir

is made up of various species of rodents including the common rat (*Rattus rattus*). Many types of animals, such as rock squirrels, wood rats, ground squirrels, prairie dogs, chipmunks, mice, voles, and rabbits can be affected by plague. Wild carnivores can become infected by eating other infected animals. The vector is the rat flea (*Xenopsylla cheopis*): when the latter bites an infected rat to feed on its blood, it receives the bacterium in the esophagus, where it multiplies [6]. The decimation of infected rat colonies forces fleas to seek alternative hosts, such as humans. In this case too, contagion occurs through the bite of the flea, which regurgitates the bacterium and carries it into the human blood. Added to these modes of transmission is, in the case of the pulmonary form, contagion from person to person through droplets, the respiratory droplets spread by coughing, and it can also be transmitted by animal scratches or by the inhalation of infected particles from animals having a respiratory infection; furthermore infection through the handling of infected animals is also documented or during the autopsy of infected animals [7-9].

Plague has occurred in people of all ages, though 50% of cases occur in people ages 12-45. It occurs in both men and women, though historically is slightly more common among men, probably because of increased outdoor activities that put them at higher risk. Modern antibiotics are effective in treating plague. Without prompt treatment, the disease can cause serious illness or death. Human plague infections continue to occur in

rural areas in the western United States, but significantly more cases occur in parts of Africa and Asia [10]. However, if the exact aetiology of the plague has only been clarified relatively recently, the disease has been well known since ancient times and has given rise to various pandemics throughout history, which is confirmed both in archaeological finds and in written sources. Regarding the latter, however, it should immediately be clarified that what the ancients would call *plague* did not necessarily refer specifically to infection by *Y. pestis*. The Latin word *pestis*, for example (as well as the corresponding terms that derive from it in many European languages) is in fact very often used to generally designate a misfortune, a calamity, a ruin, or a generic epidemic. Similarly, *plaga* (like the Greek *πληγή*), which gave rise to the corresponding Italian word *piaga* and the English *plague*, designates a serious damage, a scourge or a calamity; in the case of diseases, it does not specifically indicate what type of calamity [10]. Less vague, in the sense that it indicated a contagious infectious disease, is the term *pestilentia*, introduced in the late Roman Republican age and used for example by Julius Caesar (100-44 BC) to define the epidemic that broke out in Marseille, which forced the inhabitants to surrender. The use of *pestilentia* in these contexts is influenced by the miasmatic theory and is therefore frequently connected to the climatic and orographic conditions that accompany epidemics and endemics and is a sign of the progressive affirmation of the rationalistic interpretation of epidemics to the detriment of the long-standing tendency prevalent, to consider them – not knowing the pathogens – as catastrophic events to be attributed to supernatural intervention [11].

A striking example is given by the ‘plague’ (*νοῦσος*) narrated at the opening of the *Iliad* (I.10), caused by Apollo to punish the Achaeans and their supreme leader Agamemnon. The latter had refused to return the young Chryseis, his war prey, to her father Chryses, priest of the god, chasing him away in a bad way. Chryses, having set out towards the sea, then stopped to pray to Apollo, reminding him of the many opulent sacrifices made to him and imploring her revenge:

the old man prayed to the lord Apollo, whom fair-haired Leto bore: “Hear me, god of the silver bow, who stand over Chryse and holy Cilla, and rule mightily over Tenedos, Sminthian god, if ever I roofed over a temple to your pleasing, or if ever I burned to you fat thigh-pieces of bulls and goats, fulfill this prayer for me: let the Danaans pay for my tears by your arrows” So he spoke in prayer, and Phoebus Apollo heard him. Down from the peaks of Olympus he strode, angered at heart, bearing on his shoulders his bow and covered quiver. The arrows rattled on the shoulders of the angry god as he moved, and his coming was like the night. Then he sat down apart from the ships and let fly an arrow: terrible was the twang of the silver bow. The mules he assailed first and the swift dogs, but then on the men themselves he let fly his stinging shafts. [Iliad I. 35-52] [12]

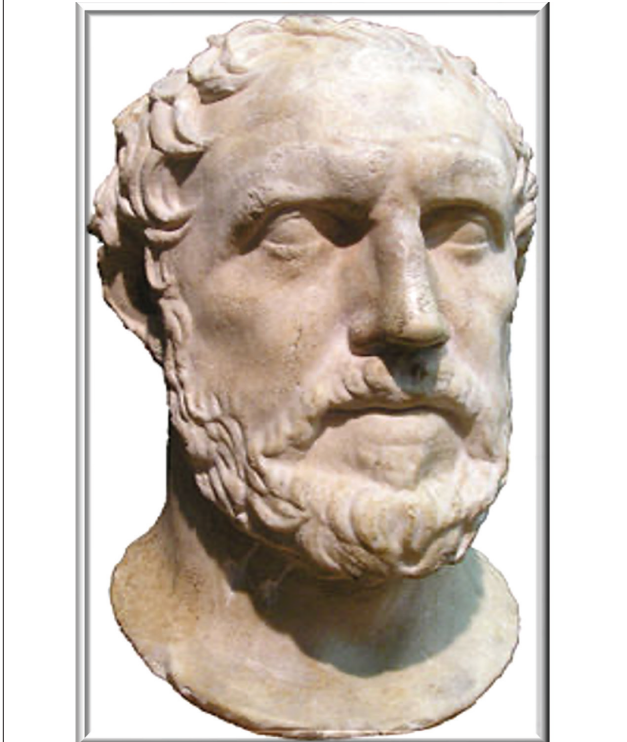
The plague that appears in the Greek camp therefore serves to punish the arrogance (*ὑβρις*) of Agamemnon, who had dared to challenge the gods by rejecting the request of one of their priests. The same equation plague = divine punishment is present other times in Greek literature, for example in Sophocles’ *Oedipus Rex* [vv. 25-30, 168-187] (around 430-420 BC). In the prologue it is narrated how the Thebans, devastated by the plague, beg the wise king Oedipus to intervene to stop the spread of the disease. In both the *Iliad* and *Oedipus Rex*, no description is made of the disease. What matters is only to underline how it is caused by the supernatural intervention of the gods, in the first case by Apollo, triggered by the wicked action of man. The symptoms of *νοῦσος* as well as its course are also ignored, making it impossible to exactly identify the type. The only useful detail provided by the poetic account of the *Iliad*, namely that it affects mules first, then dogs and finally men, corresponds to the ‘classic’ scheme of zoonoses, favored by promiscuity. No mention is made even of prophylaxis: the only precaution to contain the contagion seems to be the elimination of the corpses through cremation, while for the rest the Achaean camp remains totally exposed as well as its occupants, defenseless and submissive to the unraveling of the events.

Just like the cause, the remedy is also, in both cases, linked solely to the supernatural sphere. In the *Iliad*, the soothsayer Calchas reveals what caused the plague, who will say that it broke out because of Apollo’s anger at the mistreatment of his priest; in Sophocles’ tragedy, however, the cause revealed by the oracle of Delphi is the killing, which went unpunished, of the previous sovereign Laius. Both human attitudes have caused the balance to be broken, and to remedy it will be necessary to restore it by returning, respectively, Chryseis to her father and identifying and punishing Laius’ murderer. The ‘didactic’ message conveyed by both episodes is therefore very clear: only respect for the will of the gods guarantees order and the *status quo*; on the contrary, the lack of respect towards the deities and the infringement of the rules triggers chaos and the epidemic, which is a symbolic manifestation of it.

Among the plagues mentioned in ancient sources, only very few can be attributed with certainty to *Y. pestis*. Biblical descriptions, for example, are very vague to allow for certain identification. The *Book of Samuel* [1 Sam 5] narrates the plague of the Philistines (ca. 11th century BC), sent by God as punishment for having stolen the ark of the covenant from the defeated Israelites. The disease manifests itself through ‘buboes’, and the people’ groans, ‘rose to heaven’.

Another alleged plague account relates to the siege of Jerusalem by Sennacherib’s Assyrian army (701 BC). The biblical source [2 Kings 19:3] limits itself to asserting that one morning the besieged awoke to discover that during the night an angel of the Lord had killed all their enemies; however Herodotus, who also cites the episode, adds that ‘when they arrived, the enemies suffered an invasion of field mice at night that gnawed at their quivers and bows and shield straps, so

Fig. 1. Tucicide (Θουκυδίδης) (Athens, 460 BC - Athens, after 404 or 399 BC) (Adapted by the authors) (Wikipedia Commons - public domain).



that the next day, left defenseless, they fled and fell in great numbers' [Herodotus II, 2.141] The only clue to a possible plague epidemic is the presence of rodents in large numbers, but the hint is too vague to be conclusive. As for the famous plague of Athens (430 BC), it was narrated in detail by Thucydides [*History of the Peloponnesian War* II.2, 47-54]. [13] Ever since the beginning of written evidence, it had always been supposed that a person who had recovered from a certain disease became immune to contracting it again. Indeed, some 2,500 years ago, Thucydides (460 BC-404 or 399 BC; Fig. 1), in his description of an epidemic that hit Athens, observed that "No one has ever been affected a second time, or at least fatally" [14, 15].

The plague arrived in Athens through the port at Piraeus shortly after the beginning of the Second Peloponnesian War (431-404 BC) fought between Athens and Sparta. The symptoms described have, over time, suggested its identification as typhus, Ebola or haemorrhagic fever; more likely, however, it was typhoid fever, given that its pathogen, *Salmonella enterica serovar Typhi*, was found in DNA extracted from the dental pulp of three teeth recovered from the Athenian cemetery of Kerameikos [16]. Thucydides reports the following symptoms of the disease: headache, red eyes, red throat, bad breath, sneezing, hoarseness, coughing, vomiting, convulsions, body blisters, fever, thirst, restlessness, sleeplessness, bowel ulcers, diarrhea, gangrene, memory loss.

Other plagues reported by sources also do not appear to be caused by *Y. pestis* but by other pathogens. Moreover,

Fig. 2. The angel of death striking a door during the plague of Rome: an engraving by Levasseur after Jules-Elie Delaunay (1894) (Wikipedia Commons -public domain).



it was not easy for the ancients to distinguish diseases only based on symptoms, so pathologies such as measles, chickenpox and smallpox were often confused with each other and with 'plague' itself [17].

This is the case, for example, of the Antonine Plague (165–180 AD) during the reign of *Marcus Aurelius* also known as the Plague of Galen (after Galen, the Greek physician who described it) (Figure 2).

Galen knew the plague and had direct experience because he was in Rome when the plague reached the city in AD 166 and also during an outbreak among troops stationed at Aquileia during the winter of AD 168-169.

His suggestions, notes and remarks to the plague are scattered and often brief but they are interesting and enough to identify and recognize the plague as smallpox [18]. His description of the exanthema is fairly typical of the smallpox rash; the symptoms described by Galen in the *Methodus medendi* while observing the troops stationed in Aquileia – fever, diarrhea, inflammation of the pharynx and eruptions on the skin, both dry or purulent, which manifested themselves around the ninth day of illness - rather indicate a smallpox pandemic with devastating consequences [17] (Fig. 3).

The Antonine Plague was a terrible, long, and destructive epidemic that had a terrible impact on the entire Roman Empire; it felled ten thousand people in first-century Rome; it began in Mesopotamia in late AD 165 or early AD 166 during Verus' Parthian campaign, and quickly spread to Rome. It was possibly contracted and spread by soldiers who were returning from the exhausting and challenging campaigns of war in the Near East.

It lasted at least until the death of Marcus Aurelius in AD 180. This pandemic then spread across the Empire to North Africa, Western Asia and other parts of Europe; it is believed to have caused five million deaths.

In the same way, the Plague of Cyprian (around 250-266 AD) (Fig. 4), which arrived in Rome after having devastated Africa and reached Britain, touching the *Vallum Hadriani*, favored by rapid emptying of cities. The disease

Fig. 3. Galen (Κλαύδιος Γαληνός). An 18th-century engraving by Georg P. Busch (Wikipedia Commons -public domain).



Fig. 4. 16th-century painting of Saint Cyprian, who documented the plague in his writings (Wikipedia commons - public domain).



takes its name from Archbishop Cyprian of Carthage, who described it in *De mortalitate* [Chapter 14]:

Now the fact that the belly, gripped by cramps, disperses the body's strength in an uncontrolled dysentery, that deep within the bones the infection flares up causing sores in the throat and to expand by boiling, that the intestines are shaken by continuous vomiting, that the eyes burn with bloodshot, that the feet or other limbs have to be amputated due to the contagion of the unhealthy gangrene, which due to this loss or damage to parts of the body, while weakness creeps in everywhere, the step becomes uncertain, the hearing fades, the sight becomes dark, all this is useful to show our true faith.

As we can see, however, these symptoms, recently rediscovered by Harper, would seem to point in the direction of a hemorrhagic fever like Ebola rather than the plague [19].

No doubt however for the well-known epidemic that raged in the Byzantine Empire, especially in Constantinople, between 541 and 542 during the reign of

Justinian I (527-565) and which we know well from the detailed account given by Procopius of Caesarea (490-565) [Bellum Persicum 2.22] and other authors such as Gregory of Tours and Paul the Deacon [20].

Considered the first plague pandemic in history [21], the Plague of Justinian caused a very high number of victims – almost 100 million according to Procopius – contributing to the decline of what remained of Roman Empire and the definitive transition between the Classical world and the Middle Ages. The *Y. pestis* bacillus responsible for the disease was found in some skeletons buried in Sens (France) and Aschheim, Bavaria (6th century); the analyzes conducted in 2014 by a team of scholars on the DNA extracted from the teeth of two individuals (A120 and A76) buried in the latter burial ground also demonstrated that the genomes belonged to a pathogen form a now extinct strain [22].

From the 6th century until around the year 1000, no major plagues or plagues occurred in Europe except for leprosy or scrofula [23]. However, around the turn of the millennium a milder climate (especially in the continental West), together with the recovery of trade

and the introduction of various technological innovations improved the quantity and quality of crops. The richer diet and the growth in individual living standards, combined with the sense of greater security conferred by the progressive stabilization of political structures, led to a progressive increase in the population which, however, in the long run led to the growth of urban development, with consequent overcrowding of the cities and deterioration of general hygienic conditions. Climatic conditions worsened again in the 14th century, when temperatures increased rains and the drop in temperature corresponded to a contraction in agricultural production which gave rise to various episodes of famine, leaving the population exhausted. The conditions were ideal for the outbreak of the second plague pandemic caused, once again by *Y. pestis*, the infamous Black Death which reached its peak in Europe from 1347 to 1351 causing about 15 to 25 million deaths.

The Black Death or bubonic plague

The bacillus appeared around the 1320s in Asia and reached the Crimea through the Russian steppes. Here the Tatar khan Ganī Bek occupied in the siege of Caffa (today's Fedosia, Crimea) ordered the corpses of the infected dead to be thrown inside the city walls as an *ante-litteram* 'bacteriological weapon'. From Caffa, a Genoese colony at the time, the plague was brought to Constantinople by Ligurian ships, finally landing in Europe from the ports of Genoa, Messina and Marseille to spread throughout the continent until reaching, in the space of three years, the extreme north and the Scandinavian peninsula.

Accounts of the time show that, as in ancient times, the disease was considered a divine punishment which desperately attempted to be remedied through prayers, penances, processions and pilgrimages. The medicine of the time ignored the aetiology of the disease and proved completely powerless in containing the pandemic. A report compiled at the University of Paris, for example, attributed the blame for the plague to some unknown and inscrutable celestial event:

An astral conjunction, together with other conjunctions and eclipses, is the real cause of the gravely deadly corruption of the air around us, source of mortality and famine [...]. We believe that the present epidemic or plague comes directly from the air corrupted in its substance, and not only from the alteration of its qualities. This fact must be understood in this way: since the air is, in fact, by its nature pure and clear, it does not putrefy and does not become corrupt unless evil vapors are mixed with it, following any cause.

Many corrupt vapors, at the time of the said conjunctions and by their own virtue, rose from the land and the sea and spread into the air itself; many of those vapors, under the influence of the frequent blowing of hot and humid and violent southerly winds, owing to the damp and strange

vapors which those winds carried with them, have corrupted the air in its very substance. Consequently, this air, thus corrupted, necessarily penetrating the lungs, attracted by breathing, corrupts the gaseous substance that is found in it and, due to the humidity, causes everything that is close to it to putrefy. This is where the fevers arise from nature, which corrupt the principle of life [...]. We cannot hide the fact that, when the epidemic proceeds from divine will, we have no other advice to give than to humbly entrust ourselves to this will, without abandoning the doctor's prescriptions' – (translation of the quoted passage by the Authors) [24].

In the impossibility of identifying a certain cause, scapegoats were sought for, identified, as often happens in similar cases, in the 'weakest' and most marginal categories of society, especially women and Jews.

As for prophylaxis, it was almost non-existent: doctors examined patients wearing a sort of beak-shaped mask - the use of which was perfected in the seventeenth century, an experienced French physician named Charles de Lorme (1584–1678), (who practiced in various regions of Europe during the 17th century) and was court doctor of Louis XIII (1601-1643) [25].

In 1619, the bubonic plague erupted in Paris, and Delorme created the "plague preventive costume" (Fig. 5), which consisted of a long overclothing garment which went from the neck all the way down to the ankle; the gist was that the air could not penetrate. The outfit also contained gloves, boots, and a hat; the hat was made of waxed leather. The hat was not really part of the costume; it was more of a symbol of the physician's position as a medical practitioner. There was also a mask which had a nose half a foot long, shaped like a beak, filled with perfume with only two holes, one on each side near the nostrils; it could suffice to breathe and to carry along with the air one breathes the impression of the drugs enclosed further along in the beak. The mask is filled with aromatic herbs to help the wearer bear unpleasant smell. The eyes were also covered and protected with specs.

The doctor also has a stick to examine patients without touching them. With this complete set of equipment, Delorme and other physicians could assist patients who required their help [26].

During the 1619 French plague, Delorme was seen as a star, assisting numerous people struck by the plague. His clothing received many grants, and he was much appreciated; his name was associated with the term 'the beak doctor'.

Alternatively, those who could (like the Pope in Avignon) practiced fumigation with herbs and aromatic substances to purify the air [27].

The Black Death took around four years to make its way along the Silk Road from the Steppes of Central Asia, via Crimea, to the Western most parts of Europe, the Middle East and North Africa. The Black Death had epochal consequences on late medieval European society, triggering an economic recession that caused revolts by peasants in various parts of Europe, such as

Fig. 5. Copper engraving of a plague doctor of 17th-century Rome. (Wikipedia commons - public domain).



the jacquerie in France and England, and in Florence the riot of the Ciompi (wool workers), as well as the strengthening of the feudal system in Eastern Europe. In the long run, however, the demographic collapse imposed a redistribution of assets and incomes, creating new, better-paid jobs, while the shortage of labor led to the cultivation of only the most profitable and fertile land and stimulated new technological inventions. Those who survived therefore experienced a well-being that they had never achieved before. Even from a cultural point of view, the epochal tragedy represented a break with respect to values that had remained unchanged for centuries. Having called into question religious certainties, the man who escaped the scourge had to find a new role for himself within a universe in which everything was more precarious and he himself now appeared to be the direct architect of his own destiny. Despite its tremendous burden of mourning, the Black Death projected Europe into Humanism, closing the Middle Ages and starting a new era. A rough estimate is that 25 million people in Europe died from plague during the Black Death. By the end of the 1800s, developments in bacteriology and infection control meant that medical researchers were able to observe and investigate the disease in detail for the first time. Three types of vaccines [28, 29] namely killed whole-cell (KWC) vaccines, live attenuated vaccines (EV76), and recombinant subunit vaccines, have been developed against plague.

Although KWC and EV76 vaccines provide protection against plague in animal models, both have side effects and need repeated immunizations for developing immunity in humans. Analysis of centuries-old DNA from both victims and survivors of the Black Death has

identified key genetic differences that helped people survive the plague. Evidence has been put forward that a gene variant that helped people survive the Black Death also significantly lessens the impact of COVID-19 [30]. The recent COVID-19 (2020) pandemic has brought the global population back to confront a world unprepared to deal with a health emergency of such magnitude, despite the fact that over time the cinema and media have helped shape the collective perception of pandemics, playing an educational role but also fueling myths and beliefs [31]. The contribution of health professionals, particularly WHO physicians [32], has been crucial, especially with the experience gained during the 2003 SARS outbreak that cost Dr. Carlo Urbani his life [33]. Early recognition of the disease and its systemic implications [34], in fact, coupled with the implementation of preventive measures, proved essential to improve treatments and limit damage. Historical containment measures such as quarantine and curfews have proven their relevance [35] in stemming the spread of infection as much as possible, while highlighting the need to prioritize preventive medicine during health crises rather than allowing it to be influenced by political considerations [36].

Pandemics are not only health emergencies, but also events with profound social, political, and systemic implications. Historical experience and preventive medicine remain central to managing and preventing future health crises, while international collaboration and science must guide global responses.

Concluding remarks

Our essential review of the major epidemics of the ancient world and the Middle Ages allows us to draw the following general conclusions: 1. Psychological mechanisms shared by world populations and ancestral nature have always characterized the way in which the human species has tried to 'rationalize' sudden epidemic phenomena and has tried to counter them. 2. The application of a historical-medical, archaeological and paleopathological approach to these problems not only allows scholars to reconstruct the origin and evolutionary path of infectious diseases, but also complements historical research in the strict sense, determining the global changes level of communities and societies shocked by the infectious phenomenon. 3. Epidemics have always represented a powerful catalyst in history. 4. A multidisciplinary approach to past epidemics can provide an interesting and useful key to understanding the pandemic events that characterize contemporary times. The next pandemic could be imminent, driven by factors such as urbanisation, climate change, global travel and zoonotic diseases; notwithstanding the enlightening insights gained from the recent outbreak, the medical community and the global population at large continue to exhibit deficiencies in their preparedness for future virus-based crises [37]. A review of the historical records of plague [38] and SARS [39] reveals that pandemics have a significant impact not only on public health but also on social and political dynamics [40]. It

is evident that innovation in health responses and global collaboration are vital to prevent and contain future epidemic threats [41]. The eradication of a pandemic is a complex process that necessitates a multidisciplinary approach, encompassing the eradication of infectious diseases and the utilisation of novel technologies [42, 43]. The effective management of infectious diseases requires a multidimensional approach that integrates innovation, global collaboration, and historical analysis [44-46].

Note

A preliminary version of this research was presented at the congress *Schemata, la città oltre la forma*. Università degli studi di Catania & Università degli studi della Campania “Luigi Vanvitelli”, Siracusa (Italy), 26-28 February, 2020. Moreover, apart from reference [8], for which a direct quotation was inserted, all other citations of classical sources were limited to reporting the relevant passage without giving a full bibliographic reference.

Acknowledgements

This research received no external funding.

Informed consent statement

Not applicable.

Data availability statement

Not applicable.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

FMG, EV, EP, LI, DR: designed the study; FMG, EV, EP, LI, DR: conceived the manuscript; FMG, EV, EP, LI, DR: drafted the manuscript; VV, LI, MV, MM, DR: revised the manuscript; LI, MM, MV, DR, EV: performed a search of the literature; DR, MV, EV, VV: critically revised the manuscript; FMG, EV, EP, LI, DR: conceptualization, and methodology; FMG, EV, EP, LI, DR, MM, MV: investigation and data curation; FMG, EV, EP: original draft preparation; MV, MM, VV: editing. All authors have read and approved the latest version of the paper for publication.

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Received on September 3, 2024. Accepted on September 25, 2024.

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How to cite this article: Galassi FM, Varotto E, Percivaldi E, Vittori V, Ingaliso L, Vaccarezza M, Martini M, Ribatti D. A historico-medical perspective on ancient epidemics and their impact on past human societies. *J Prev Med Hyg* 2024;65:E456-E463. <https://doi.org/10.15167/2421-4248/jpmh2024.65.3.3345>

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