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THE PLAGUE OF ATHENS: INVESTIGATING THE ENIGMATIC EPIDEMIC OF ANCIENT GREECE

ATENSKA KUGA: ISTRAŽIVANJE ZAGONETNE EPIDEMIJE ANTIČKE GRČKE

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SUMMARY

The ancient Greek historian Thucydides described in his book "History of the Peloponnesian War" one of the earliest epidemics in known human history, the "Plague of Athens". The plague, which lasted from 430–426 B.C., had a death toll estimated at around 75,000–100,000. The importance of the plague was immense. Pericles, the historical leader of Athens, was among its victims, and his death was just the beginning of the fall of the Golden Age of Athens. The enormous death toll from the plague weakened Athens, leading to its eventual defeat in the war against Sparta. So far, the cause of this plague is unknown, but its symptoms are well described. Thucydides himself suffered from the plague, but fortunately, he survived. Many assumptions have been made about the disease responsible. In this article, the possible explanations will be discussed, hoping to shed light on that historical mystery. A metric system was created to help estimate the possibility of each of the 17 pro-

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posed diseases being the actual reason behind the deadly plague. Out of all the presented diseases, typhoid fever seems to fit most of the criteria, thus being considered the most possible causative agent. Other scenarios are also discussed.

***Keywords**: plague of Athens, plague of Athens and cholera, measles, Scarlet fever, tuberculosis, Ebola, epidemic typhus, anthrax, typhoid fever, smallpox, malaria, ergotism, bubonic plague, meningococcal disease, dengue fever, Lassa fever, Yellow fever, Rift valley fever*

Introduction

According to Thucydides, the symptoms manifested abruptly, beginning with headache, high fever, ocular redness and inflammation, a haematoid appearance of the mouth, tongue, and pharynx, and halitosis, followed by sneezing, hoarseness, and coughing. The gastrointestinal symptoms started with nausea and bile vomiting, sometimes resulting in violent spasms. A rash – maculopapular or pustular with ulcers – was exhibited in the patient's erythematous skin. The affected individuals suffered from intense heat, prompting them to discard their clothing and seek relief in cold water, yet paradoxically, their skin was moist and normothermic to the touch. Polydipsia, insomnia, and stress were also prevalent among patients. After 7 to 9 days, most patients either succumbed to the disease or developed extensive abdominal ulcers accompanied by profuse diarrhea, ultimately leading to death. Gangrene of the extremities and eyes was a common occurrence among both survivors and victims of the plague. Interestingly, after being cured, some people suffered from amnesia, rendering them unable to recollect either their own identities or those of their loved ones.

Regarding immunity, Thucydides states that once an individual recovered from the disease, he was never fatally reinfected. This may be interpreted by the development of some form of immunity.

Thucydides further states that the disease was initially reported in sub-Saharan Africa, spreading to Egypt and Libya before reaching Athens through Piraeus, the city's port, since its inhabitants were the first to be infected. Remarkably, the Spartan troops besieging the city were not infected, while refugees entering the city fell ill soon after their arrival. The disease was spread to everyone regardless of age, health, or socioeconomic status.

Human-to-human transmission was likely the primary mode of spread, possibly via infected aerosols, as evidenced by the high attack rates occurring among physicians and people taking care of patients. It is also considered quite possible that it was a zoonotic disease, according to reports of animals succumbing to the illness after feeding on corpses. The plague made subsequent appearances in 429 BC and during the winter of 427/426 BC (Thucydides) (Littman, 2009).

Material and methods

The literature review utilized articles obtained from the PubMed database. A standardized data extraction form was employed to gather the relevant information. The search strategy involved using the Boolean query "plague of Athens" ([Title/Abstract]) AND ((ffrft[Filter]) AND (english[Filter])) in the PubMed database. The study adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. Initially, a total of 147 records were identified through a PubMed online database search, and an additional 7 were identified through a review of references. Therefore, the total number of records was 154. After removing duplicates, the remaining number of records was 149 (5 duplicates were removed). Out of these, 58 full-text articles were assessed for eligibility, and 91 records (including articles, titles, and abstracts) were excluded as they were deemed irrelevant. Consequently, this paper ultimately includes 58 selected papers.

To evaluate the likelihood that each disease was responsible for the plague of Athens, a metric system was created. It consists of 3 categories, each of which awards 4 points to the disease. A 12 out of 12 score is the perfect match for the plague. The first category refers to the 4 most characteristic symptoms described by Thucydides: high fever, rash, gastrointestinal symptoms (vomiting and diarrhea), and gangrene. Each of those symptoms is worth 1 point. The second category is associated with transmission and immunity. Human-to-human transmission earns 2 points, while zoonotic disease and immunity after survival each earn one point. The third category is based on historical evidence. Microbial genes discovered in bodies plague are worth 3 points, and historical references of the disease before 430 B.C. are worth 1 point.

Results

Cholera

Cholera has been a well-known disease since ancient times, described by Hippocrates (460–370 B.C.), so it can be considered as a causative pathogen of the plague of Athens. Transmission of cholera usually occurs through water or food contaminated with Vibrio cholerae, a bacterium present in the feces of infected individuals and released into the environment in densely populated areas lacking proper sewage purification practices.

Human-to-human transmission has not been recorded. In its epidemic form, cholera affects everyone regardless of age and presents with more severe symptoms in the lack of immunity – reinfection leads to milder disease (Clemens et al., 2017). Symptoms include watery diarrhea (up to 20 liters per day) and vomiting, leading to lethal dehydration if left untreated, and the emission of a distinct fishy odor from the patient (Frost, 1976). Notably, cholera's symptoms do not include fever, rash, or gangrene. Therefore, it is quite unlikely for it to have caused the Athenian plague.

Measles

While there is no historical data about measles in antiquity, epidemiological studies indicate the virus evolved from a canine, cattle, or buffalo virus 6,000 years ago. This aligns with the critical community size for transmission, estimated at 250,000 to 400,000, a population size close to that of Athens in 430 B.C. Measles may be a cause of the plague of Athens (Cunha, 2004). Symptoms include fever, coryza, conjunctivitis, cough, and Koplik spots. After 3–4 days, an erythematous, gradually spreading maculopapular rash appears. Encephalitis is rare (1 in 1,000 cases), and gangrene is extremely rare compared to the Athenian plague (Moss, 2017). Surviving measles grants lifelong immunity. Measles is transmitted through infectious droplets and is highly contagious. Unlike the plague, it has no animal reservoir (Paules, 2019). This explains easy human-to-human infection. Animal deaths during the plague contradict the lack of animal reservoirs for measles.

Scarlet Fever

Although Hippocrates described streptococcal diseases, the first specific description of scarlet fever did not occur until 1578 by Jean Cottyar of Poitiers, and the lack of relevant historical references limits the likelihood of it being the cause of the Athenian plague (Ferretti & Köhler, 2016).

Symptoms include sore throat, headache, fever, nausea, vomiting, and a red rash spreading from the trunk (Nursing Standard, 2016). Since scarlet fever is caused by Streptococcus pyogenes, various complications, such as bacteremia, streptococcal toxic shock syndrome, acute rheumatic fever, and acute glomerulonephritis, are not uncommon. Transmission occurs through respiratory droplets and contact with contaminated objects, food, and body parts. It is highly contagious (Brouwer et al., 2016), and this matches the extreme contagiousness of the plague of Athens. Nevertheless, Streptococcus pyogenes is a strictly human pathogen with no animal reservoir, something which contradicts the zoonotic infection of 430 B.C. Athens (Ferretti & Stevens, & Fischetti, 2022).

Tuberculosis

Archaeological research reveals human skeletons showing signs of tuberculosis dating back 8,000 to 10,000 years, with the first relevant written reports tracing back to 5,700 B.C. in Chinese medical texts (Barbier & Wirth, 2016). Hippocrates described tuberculosis as 'phthisis,' confirming its potential possibility to be the cause of the Athenian plague in 430 B.C. Mycobacterium tuberculosis, the cause of tuberculosis, likely evolved from Mycobacterium bovis, which infects cattle (Kanabalan et al., 2021). Transmission occurs mostly through infectious droplets and by contact with diseased animals or their products, which explains the high contagiousness during the plague (Suárez et al., 2019). There is no immunity against tuberculosis, and reinfection is possible. The most common form of tuberculosis is pulmonary, presenting with symptoms such as coughing up blood or mucus, chest pain, weight loss, fever, chills, and fatigue. Other tuberculosis manifestations include back pain, headache, confusion, hematuria, pyelonephritis, peritonitis, pericarditis, lymphadenitis, ulcers, and neurological deficits (Smith, 2003; Ketata et al., 2015). The loss of extremities and other body parts leading to recovery can be attributed to other Mycobacteria species, such as M. leprae. However, symptoms like rash, diarrhea, and neurological deficits are more common in immunocompromised population, which does not align with the epidemic described by Thucydides.

Ebola

Ebola Virus Disease (EVD) was first recorded in 1976 near the Ebola River in the Democratic Republic of Congo. African fruit bats are considered the animal reservoir of Ebola, which can also infect other animals, like antelopes and other Hominidae. Transmission occurs through human-to-human contact or contact with infected animals, their products, and bodily fluids (Wirsiy & Um Boock, & Tatah Kihla Akoachere, 2021). There is no immunity to Ebola, and surviving the disease does not protect against future infections. EVD onset is sudden, with symptoms including fever, headache, sore throat, myalgia, weakness, loss of appetite, skin rash, and cough. Gastrointestinal and neurological symptoms appear after 3 to 10 days, such as abdominal pain, nausea, vomiting, watery diarrhea, gum bleeding, confusion, seizures, hallucinations, agitation, and irritability. In later stages, patients become nonresponsive and comatose, experience bleeding from mucous membranes, and suffer from acute respiratory distress syndrome (Nicastri et al., 2019). The symptomatology of EVD does not fully align with Thucydides' descriptions, lacking peripheral gangrene and considering a rash as a determinant characteristic. Even though the disease of Thucydides was zoonotic, like EVD, its reservoir is African fruit bats and other animals not native to Greece. After all, it is quite unlikely for a disease to have vanished for 2,500 years and then suddenly reappear with no outbreaks in the span of all these centuries (Littman et al., 2001). In conclusion, the Ebola virus cannot be held responsible for the plague of Athens.

Epidemic Typhus

The first description of epidemic typhus was by Girolamo Cardano in 1536 in his book, Recentiorum Medicorum Usu Libellus, and the disease was first identified in Spain in 1083. It is suggested that epidemic typhus affected Athens in 430 B.C. (Raoult & Woodward, & Dumler, 2004). Epidemic typhus is caused by the bacterium Rickettsia prowazekii and transmitted by human lice, which deposit infected feces near bite sites, allowing the bacteria to enter the body through skin lesions, conjunctivae, or mucous membranes. Close contact with infected individuals or aerosols of fecal dust can also lead to infection (Bechah et al., 2008). Conditions like war, famine, and overcrowding facilitate the spread of typhus epidemics (Cowan, 2000). The plague of Athens occurred during the Peloponnesian War when the city was under siege. The reemergence of the disease with smaller epidemics in the following years, when the siege was over, can be attributed to various animal reservoirs, such as squirrels. Typhus symptoms include high fever, headache, pain, loss of appetite, thirst, and nausea. Maculopapular rash, central nervous system dysfunction, coughing, bacterial complications, gangrene, and multiple organ dysfunction syndrome can also manifest (Bechah et al., 2008).

While R. prowazekii does not cause gastrointestinal symptoms, it shares the specific characteristic of gangrene along with the plague, while other Rickettsial infections like Rocky Mountain Spotted Fever, caused by R. rickettsii, can have gastrointestinal symptoms and also various mammalian reservoir hosts, and could have been the causative agent of the plague (McDade & Newhouse, 1986). Dr. David Durack, Consulting Professor of Medicine at Duke University, stated after his research about the cause of the Plague: "Epidemic typhus fever is the best explanation. It hits hardest in times of war and privation, it has about 20 percent mortality, it kills the victim after about seven days, and it sometimes causes a striking complication: gangrene of the tips of the fingers and toes. The Plague of Athens had all these features." (Durack, 1999).

Anthrax

Anthrax disease has been known since ancient times, first mentioned in the Book of Exodus. Some historians suggest that the fifth, sixth, and tenth plagues of Egypt could have been outbreaks of anthrax in cattle and humans, while the third, fourth, eighth, and ninth plagues may have contributed to its spread (Witkowski & Parish, 2002). Hippocrates was the one who named it "anthrax" due to the black skin lesions of its cutaneous form (Guichard & Nizet, & Bier, 2012). Anthrax manifests in three types: cutaneous, gastrointestinal, and inhalational. Cutaneous anthrax is characterized by a painless, itchy papule that turns into a vesicle and eventually forms a black eschar. It can lead to complications such as disseminated intravascular coagulation, renal failure, microangiopathic hemolytic anemia, and septic shock, and has a mortality rate of 0,2. Transmission occurs through contact between skin cuts and abrasions with infected animals or animal products (Kalamas, 2004). Gastrointestinal anthrax occurs when contaminated meat is consumed, causing symptoms such as abdominal pain, fever, diarrhea, and ulceration (Datta & Singh, 2002). Inhalational anthrax is rare and contracted by inhaling contaminated spores. Symptoms include fever, cough, malaise, and headache, and it can lead to shock and organ failure. None of these forms fully aligns with the symptoms and mode of transmission of the Athenian plague described by Thucydides (Wenner & Kenner, 2004). It is unlikely that anthrax, as we know it today, was responsible for the plague of Athens. Even if all the symptoms matched those described by Thucydides, the mode of transmission could not have caused such a widespread plague.

Ergotism

Ergotism, caused by the Claviceps purpurea fungus-infected products like bread and rye, likely existed during the Athenian plague. Ergot had various uses in Ancient Greece, from hallucinogenic purposes during the Eleusinian Mysteries to postpartum bleeding prevention, as suggested by Hippocrates. The plague of melanthion described by Hippocrates was probably ergotism (Grzybowski & Pawlikowska-Łagód & Polak, 2021). The disease involves blood vessel constriction leading to gangrene in the hands and legs, along with neurological symptoms like hallucinations and spasms. Initial systemic symptoms include fatigue, confusion, nausea, and severe pain. The affected area becomes inflamed, edematous, and painful, progressing to loss of sensation and gangrene. In some rare forms of the disease, high fever, vomiting, and diarrhea may also be present (Belser-Ehrlich et al., 2013). However, ergotism lacks key plague symptoms like rash, diarrhea, and common cold symptoms. Furthermore, a disease that spreads through human-to-human contact does not align with the food-borne nature of ergotism epidemics. Ergotism alone is unlikely to be the sole cause of the Athenian plague, but another disease may have contributed.

Lassa Fever

Since there is no recorded data on the existence of the disease before 1969, when 3 nurses in Nigeria presented with symptoms of a mysterious febrile disease, it cannot be safely assumed to be one of the causes of the plague of Athens (Happi & Happi, & Schoepp, 2019). The main route of transmission for Lassa fever is direct or indirect contact with infected rodents. Human-to-human transmission has also been reported among healthcare workers. However, airborne human-to-human transmission has not been reported, and most outbreaks seem to occur through reservoir-to-human transmission. Lassa fever symptoms include fever, headache, vomiting, diarrhea, cough, abdominal pain, and chest pain. Bleeding, especially from the conjunctivae, mouth, and gut, is a characteristic symptom. Severe cases may lead to shock, encephalopathy, hearing loss, and multiorgan failure. Gangrene and rash, the main symptoms of the mysterious disease in Athens, are not present in Lassa fever. The community mortality rate is only 0,01, whereas Thucydides stated one of 0,25. These discrepancies make it unlikely that Lassa fever was the cause of the plague of Athens (Asogun et al., 2019).

Yellow Fever

Studies on the phylogenetic origin of the Yellow fever virus (YFV) indicate that it emerged after 500 A.D. in Africa. Its spread in the American continent is the result of the slave trade between Europeans inhabiting the Americas, with African slaves acting as the hosts incubating the virus. The Yellow fever virus is transmitted to humans by the Aedes aegypti mosquito, with monkeys as the primary reservoir. Prior exposure to YFV leads to immunity. However, if the disease was transmitted through mosquito bites, it would also have affected the Spartan army surrounding Athens. The ancient texts state that the disease was transmitted human-to-human and report no cases among Spartan soldiers (Litvoc & Novaes, & Lopes, 2018). The first phase of the disease (viremia) begins with high fever, headache, nausea, vomiting, restlessness, pain in the back and extremities, and myalgia. The toxemic phase follows 3 days later, affecting approximately 0,15 of nonconvalescent patients experiencing high fever, chills, headache, jaundice, bleeding from the mouth, nose, eyes, stomach, oliguria due to renal failure, cardiovascular dysfunction, seizures, and multiorgan failure. The toxemic phase mortality rate ranges between 0,2 and 0,5 while the overall mortality rate is between 0,03 and 0,07 much lower than described by Thucydides (Rollins & Ramsey, & Parsh, 2017). While it shares symptoms with the Athenian, it lacks the presence of gangrene and rash, as well as the same mode of transmission. Nevertheless, it is suggested that typhus complicated by yellow fever could have been the actual cause of the plague.

Dengue Fever

Dengue fever virus, first recorded in 992 A.D. in a Chinese medical encyclopedia, is transmitted through the bite of infected female Aedes aegypti mosquitoes. As such, Dengue fever would have affected both the Athenians and the Spartans; however, its low contagiousness between humans diminishes the likelihood that it was the sole cause of the Athenian plague (Salles et al., 2018). The disease begins with symptoms such as high fever, headache, nausea, vomiting, weakness, sore throat, and body pain. Up to 0,5 of patients may develop a rash that spreads to the face and extremities. Respiratory and gastrointestinal symptoms, like diarrhea, can also affect some patients with severe disease. Bleeding from mucous membranes, such as the mouth, nose, uterus, and stomach, is a common manifestation of Dengue fever. Surviving the disease ensures immunity, and herd immunity can lead to virus eradication (Gubler, 1998).

Smallpox

The earliest precise description of smallpox can be found in Chinese writings from the 4th century A.D. However, there is older historical data that can be interpreted as smallpox, in Egypt, where 3 mummies have been discovered with a rash similar to smallpox. Moreover, some scientists suggest smallpox was the disease that plagued Alexander the Great's army in 327 BC on the Indus River. Transmission of variola virus, the causative agent of smallpox, primarily occurs through inhalation of aerosols, but contact with contaminated skin and bodily fluids can also result in transmission. Smallpox is a strictly human disease, and the corresponding zoonotic infections, cowpox and chickenpox, cause milder disease in humans.

Smallpox is among the most commonly proposed causes of the plague of Athens (Fenner et al., 1988), characterized by high fever, chills, headache, back pain, and a rash progressing to blisters and pustules. Gangrene of the extremities is possible. Severe cases can lead to bleeding and death within 24 hours. Survivors have permanent scars after the scabs fall off. One infection confers lifelong immunity (Meyer & Ehmann, & Smith, 2020). Smallpox shares symptoms with Thucydides' description, however, it lacks gastrointestinal involvement and zoonotic transmission, prerequisites for the Athenian plague.

Malaria

Malaria, mentioned in Chinese and Egyptian documents as early as 2700 B.C. and described by Homer and Hippocrates as characterized by malarial fevers and enlarged spleens, is transmitted by Anopheles mosquitoes via the Plasmodium parasite (Cox, 2010). Malaria symptoms include anemia, splenomegaly, and malarial paroxysm, featuring stages of cold, fever, and sweats. Severe cases can lead to complications like cerebral malaria, renal failure, and multiorgan failure (Garcia, 2010; Alkizim & Matheka, & Mwanda, 2011). Immunity developing after infection is gradually enhanced by recurring infections. Apart from the absence of a characteristic skin rash, malaria shares many symptoms with the Athenian plague and has similar immunity. However, it did not meet the criteria for direct human-to-human transmission, while the relevant transmission routes, such as blood transfusion, were unknown at that time. Furthermore, apart from the recently emerging Plasmodium knowlesii, all other Plasmodium species are not zoonotic.

Rift Valley Fever

Rift Valley fever virus (RVFV), discovered in 1930 near Lake Naivasha in Kenya's Rift Valley, infects a broad range of animals, including wild African species and domesticated livestock. Mosquitoes serve as the intermediate host, transmitting the virus between animals. Humans can contract RVFV through mosquito bites or direct contact with infected animals or their products. Person-to-person transmission has not been recorded. Thucydides described a disease transmitted through direct human contact (Wright et al., 2019). RVF symptoms encompass fever, sweating, headache, body aches, abdominal pain, and vomiting. Ocular issues, jaundice, gingival bleeding, purpuric hemorrhagic rash, and neurological symptoms may also arise (Hartman, 2017). RVF does not manifest gangrene, diarrhea, or maculopapular rash. Survivors develop long-lasting immunity, akin to the Athenian plague. While previous RVF outbreaks might have transpired, no documented historical evidence links it to the Athenian plague (Javelle et al., 2020).

Typhoid Fever

Although not distinguished from typhus until recently, typhoid fever, caused by the bacterium Salmonella typhi, has plagued humanity since antiquity. Ancient Greek and Roman writers described a deadly, febrile illness with symptoms similar to those of typhoid fever. Hippocrates himself documented 6 cases of typhoid fever in Book I and Book III of Epidemics. Consequently, it cannot be argued that this disease could have caused the plague of Athens (Cunha, 2004). Typhoid fever is transmitted primarily through feces- or urine-contaminated water or food. The main symptoms include fever, abdominal pain, fatigue, headache, hepatomegaly, splenomegaly, rash, and diarrhea, while peripheral gangrene is a rare complication of typhoid fever. Although the symptoms of typhoid fever align perfectly with the plague of Athens, gastrointestinal symptoms and gangrene, described by Thucydides as basic disease characteristics, do not frequently appear in typhoid fever, so they cannot be accounted for as a total match (Maskalyk, 2003; Anyanwu et al., 2018). Regarding immunity, it lasts no more than a year.

Nevertheless, in 1994, in the ancient cemetery located in Kerameikos, Athens, a mass grave containing over 150 dead bodies was discovered. Archaeologists linked that grave to the first year of the Peloponnesian War, around 430 B.C., when the plague of Athens struck. Molecular biology methods were used to recover genetic material causing bacteremia from the dental pulp of the bodies. The result highlighted the presence of Salmonella typhi DNA in the examined ancient DNA, a strong indication that typhoid fever was present during the plague, if not its cause (Papagrigorakis et al., 2006). Some scientists suggest that the plague was an act of ancient bioterrorism by the Spartans, as there was no other plausible explanation for such a massive typhoid fever epidemic among the Athenian population at the time (Papagrigorakis et al., 2013).

Bubonic Plague

Bubonic plague, caused by Yersinia pestis, whose DNA has been identified in Bronze Age skeletons from 3,800 years ago, may also be described in biblical texts. It is transmitted through fleas that infest rodents, acting as vectors, or through contaminated food. Human-to-human transmission can occur through contact or inhalation of infectious droplets. There is no immunity for survivors. The bubonic plague is characterized by fever, abdominal pain, headache, lymphadenopathy, and gastrointestinal symptoms (nausea, vomiting, diarrhea), the pneumonic subtype by flu-like symptoms and a purulent or bloody cough, while the septicemic subtype can lead to gangrene. Although the bubonic subtype alone may not encompass all symptoms, when all subtypes are considered together, the most significant symptoms of the Athenian plague are manifested. The rash observed during the plague of Athens could be interpreted as the bubonic plague's buboes, but that scenario is unlikely (Glatter & Finkelman, 2021).

Meningococcal Disease

Although Hippocrates described the symptoms of what would later be called meningococcal disease, the first epidemic was not recorded until 1805. Transmission occurs through infected aerosols and secretions, posing a higher risk in crowded, unsanitary conditions, as in besieged Athens. Furthermore, survivors acquire immunity (Rosenstein et al., 2001). Symptoms include fever, altered mental status, neurological deficits, seizures, neck stiffness, and coma. In meningococcal septicemia, patients present with flu-like symptoms. As the disease progresses, vomiting, diarrhea, chills, severe body aches, septic shock, peripheral vasoconstriction, disseminated intravascular coagulation, and gangrene can occur. Rare complications include septic arthritis, osteomyelitis, and pneumonia (Fitzgerald & Waterer, 2019). Therefore, meningococcal disease encompasses most of the symptoms described by Thucydides.

Discussion

Upon evaluating the symptomatology of the plague of Athens, it has been determined that high fever, rash, gastrointestinal symptoms, and gangrene are the most distinct features of the disease. Among the previously mentioned diseases, only measles, scarlet fever, typhoid fever, and meningococcal disease exhibit all 4 symptoms. However, the occurrence of gangrene in measles, scarlet fever, and typhoid fever is significantly lower than that provided by Thucydides. Moreover, typhoid fever is associated with a lower incidence of gastrointestinal symptoms. The nature of the rash described by Thucydides remains ambiguous, as it is unclear whether he refers to a pustular measles-like rash or a red spot rash akin to the aforementioned diseases (Table 1). Other diseases on the list exhibit symptomatology ranging from 3 to just 1 symptom (in the case of cholera), thereby aligning less closely with the symptoms described by Thucydides.

Table 1: Symptoms of the disease

	High fever	Rash	Gastrointestinal	Gangrene	Total
Cholera	-	-	+	-	1
Measles	+	+	+	+	4
Scarlet fever	+	+	+	+	4
Tuberculosis	+	+	+	-	3
Ebola	+	+	+	-	3
Epidemic Typhus	+	+	-	+	3
Anthrax	+	+	+	-	3
Typhoid fever	+	+	+	+	4
Smallpox	+	+	-	+	3
Malaria	+	-	+	+	3
Ergotism	+	-	+	+	3
Bubonic plague	+	-	+	+	3
Meningococcal disease	+	+	+	+	4
Dengue fever	+	+	+	-	3
Lassa fever	+	-	+	-	2
Yellow fever	+	-	+	-	2
Rift valley fever	+	-	+	-	2

Among the diseases presented, epidemic typhus is the only one that meets all 3 conditions mentioned in the table above. If the possibility of zoonosis is excluded, the diseases that meet all the criteria are measles, scarlet fever, smallpox, meningococcal disease, and epidemic typhus. While Thucydides notes that animals consuming the corpses of plague victims died, it remains uncertain whether the disease itself caused these deaths. Nevertheless, human-to-human transmission and the presence of immunity are essential characteristics of the disease; without these, no disease can be definitively considered the cause of the plague (Table 2).

Table 2: Transmission of the disease and immunity

	Human to human	Zoonotic	Immunity	Total
Cholera	-	+	+	2
Measles	+	-	+	3
Scarlet fever	+	-	+	3
Tuberculosis	+	+	-	3
Ebola	+	+	-	3
Epidemic Typhus	+	+	+	4
Anthrax	-	+	-	1
Typhoid fever	-	-	+	1
Smallpox	+	-	+	3
Malaria	-	-	+	1
Ergotism	-	+	-	1
Bubonic plague	+	+	-	3
Meningococcal disease	+	-	+	3
Dengue fever	-	+	+	2
Lassa fever	+	+	-	3
Yellow fever	-	+	-	1
Rift valley fever	-	+	+	2

Finally, considering historical records, typhoid fever holds the advantage of the most substantial historical data. No other disease on the list has evidence of its causative agent's genetic material in bodies dating back to 430 B.C. in Athens. Additionally, several of the diseases mentioned lack historical data supporting their existence until recent times (Table 3).

Table 3: Historical evidence of the disease

	Gene	Historical Ref.	Total
Cholera	-	+	1
Measles	-	+	1
Scarlet fever	-	-	0
Tuberculosis	-	+	1
Ebola	-	-	0
Epidemic Typhus	-	-	0
Anthrax	-	+	1
Typhoid fever	+	+	4
Smallpox	-	-	0
Malaria	-	+	1
Ergotism	-	+	1
Bubonic plague	-	+	1
Meningococcal disease	-	+	1
Dengue fever	-	-	0
Lassa fever	-	-	0
Yellow fever	-	-	0
Rift valley fever	-	-	0

Overall, typhoid fever meets most of the criteria, scoring 9 out of 12 points. However, the absence of indications of human-to-human transmission poses a significant challenge that cannot be disregarded. It is noteworthy that the presence of S typhi DNA in bodies from an Athens graveyard dating back to 430 B.C. contributes to typhoid fever's high score. Measles and meningococcal disease, scoring 8 out of 12 points, are also strong contenders as the potential cause of the plague of Athens, especially given their manifestation of all the prerequisites, namely human-to-human transmission and immunity, as described by Thucydides. Epidemic typhus, tuberculosis, and scarlet fever each score 7 out of 12 points. Among these, scarlet fever is slightly more plausible as it encompasses all the symptoms of the Athenian plague. The remaining diseases score 6 or fewer out of 12 points—less than 0,5 of the requirements—which makes it considerably challenging for them alone to account for the occurrence of the plague of Athens.

The diverse range of symptoms and historical context indicate that multiple scenarios might account for the Athenian plague. One plausible scenario widely accepted among the scientific community suggests that the plague of Athens may have been the result of a combination of diseases. This implies that citizens of Athens may have suffered from two or even three different pathogens simultaneously. Some of the most commonly proposed disease combinations include typhus complicated by bubonic plague or dysentery, and yellow fever complicated by scurvy. Other intriguing disease duos involve simultaneous epidemics of measles, typhoid fever, or meningococcal disease with a Lassa fever epidemic, or perhaps an outbreak of smallpox coinciding with cholera. All of these combinations align remarkably well, scoring almost a perfectly with the disease described by Thucydides.

Another plausible scenario suggests that the plague could have been caused by an unknown disease that is now extinct. For instance, an arenavirus akin to Lassa Fever Virus, originating from Africa and afflicting the population of Athens for nearly four years before succumbing to herd immunity, could be the answer to this mystery. Such a virus would not only exhibit the full range of symptoms described by Thucydides but also possess the capability to be transmitted between humans and various animal species. Another line of argumentation, following a similar line of thought, suggests that the microorganism responsible for the plague may have been highly virulent at that time but subsequently became less lethal than its ancestor. In that case, the range of potential pathogens on the suspect list expands significantly. It is even possible that certain distinctive traits of the Athenian population made them susceptible to a disease that persists to this day. The research points to the need for understanding how infectious diseases evolve and how ancient diseases might have changed or disappeared. The study's findings suggest that some diseases, like those described by Thucydides, may have evolved or even vanished due to changes in human population dynamics, environmental conditions, or medical practices. This perspective encourages a broader examination of how infectious diseases adapt over time and how historical pandemics might have been influenced by such evolutionary processes.

Conclusions

The plague of Athens, which occurred around 2,500 years ago, presents challenges in identifying its causative agent due to several factors. The primary source of information on the disease is Thucydides' accounts, but his lack of medical expertise and the time gap of up to 20 years between the events and his documentation may introduce misinterpretations. Furthermore, the inability to isolate and culture the responsible microorganism poses a significant obstacle. Even if preserved bodies of plague victims were discovered, the microbes would have decayed over time. Molecular biology techniques such as Polymerase chain reaction

(PCR) could potentially be utilized to compare ancient genetic material with present-day bacteria and viruses, but only one cemetery from the plague era has been found. In this cemetery, DNA from S. typhi (the bacterium that causes typhoid fever) was detected. However, relying solely on this finding is insufficient, as it remains possible that individuals buried there were affected by both S. typhi and another pathogen, which might have been the actual cause of the plague.

The study highlights the importance of combining historical records with modern scientific techniques to unravel ancient medical mysteries. While historical accounts provide valuable clues, they are often incomplete or imprecise. Advances in genetic analysis, paleopathology, and other scientific disciplines offer new opportunities to verify or challenge historical accounts. Integrating these methods with historical research can yield a more accurate understanding of past pandemics and their impact on historical events. Continued interdisciplinary collaboration will be crucial for bridging the gap between ancient narratives and contemporary scientific evidence.

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SAŽETAK

Starogrčki povjesničar Tukidid u svojoj je knjizi "Povijest Peloponeskog rata" opisao jednu od najranijih epidemija u poznatoj ljudskoj povijesti, „atensku kugu". Kuga koja je trajala od 430. do 426. g. pr. Krista usmrtila je 75 000 – 100 000 ljudi. Važnost kuge bila je golema. Periklo, povijesni vođa Atene, bio je jedna od njezinih žrtava, a njegova je smrt bila tek početak pada zlatnog doba Atene. Velik broj smrtnih slučajeva od kuge oslabio je Atenu, što je dovelo do njezina konačnog poraza u ratu protiv Sparte. Uzrok ove kuge do sada nije poznat, ali su njezini simptomi dobro opisani. Sam Tukidid obolio je od kuge, ali je, srećom, preživio. U ovom će se članku raspravljati o mogućim objašnjenjima u nadi da će se taj povijesni misterij rasvijetliti. Stvoren je metrički sustav kako bi se pomoglo u procjeni mogućnosti da je svaka od 17 predloženih bolesti zapravo stvarni uzrok smrtonosne kuge. Od svih predstavljenih bolesti, tifus ispunjava većinu kriterija, stoga se smatra najvjerojatnijim uzročnikom. Razmatraju se i drugi scenariji.

Ključne riječi: *atenska kuga, atenska kuga i kolera, ospice, šarlah, tuberkuloza, ebola, epidemijski tifus, antraks, tifus, male boginje, malarija, ergotizam, bubonska kuga, meningokokna bolest, denga groznica, lasa groznica, žuta groznica, groznica Riftske doline*