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Commentary on Seersholm Et al.: *Yersinia pestis* Infection Is Not Synonymous With Deadly Plague in Neolithic Scandinavia

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ABSTRACT

Objectives: Emerging genomic evidence has identified ancestral strains of *Yersinia pestis* in ancient human populations, which has sparked debates about its pathogenic role in later Neolithic societies. Here, we review published evidence linking anthropological and biological data reflecting the past natural history of *Y. pestis* infection.

Materials and Methods: Review of reported ancient *Y. pestis* genomes, paleomicrobiological, archaeological, and ecological data related to ancient plague.

Results and Discussion: While some researchers attributed the Scandinavian Neolithic population decline to plague epidemics, we argue that early *Y. pestis* strains were more likely associated with outbreaks of food-borne enteritis rather than flea-borne plague. This hypothesis is supported by genetic, archaeological, and ecological analyses, which indicate that *Y. pestis* evolved key flea-borne transmission mechanisms only later in its history.

1 | Introduction

Yersinia pestis (*Y. pestis*) is a deadly bacterium causing primary digestive, pneumonic, and bubonic plague, and secondary septicemic plague occurring, respectively, after the ingestion of contaminated food, inhalation of contaminated aerosols, and the bite of an infected hematophagous insect (mainly fleas), with a fatality rate reaching almost 80% for untreated septicemia (Barbieri, Signoli, et al. 2020). Recent genomic analyses revealing *Y. pestis* ancient deoxyribonucleic acid (aDNA) in approximately 17% of Middle Neolithic farmers spanning six generations, in southern Scandinavia (Seersholm et al. 2024) led Seersholm et al. to conclude that fatal plague precipitated the decline of the same Neolithic farmers' populations. Here, commenting on Seersholm et al.'s study and reviewing paleogenetic and anthropological data, we propose a different view, suggesting that *Y. pestis*, together with closely related *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*, was, an enteropathogen in the Neolithic context, and still occasionally is. Following the consumption of contaminated food, *Y. pestis* would cause primarily enteritis, developing, at an unknown frequency, into deadly septicemia. Therefore, we suggest that the term "*Y. pestis* infection" is more accurate than "plague" to describe the natural history of *Y. pestis* in the late Neolithic farmers' communities, as reported by Seersholm et al.

2 | Materials and Methods

This work builds upon the recent study by Seersholm et al. (2024), which analyzed skeletal remains from 108 individuals recovered from eight megalithic graves and one stone cist across southern Scandinavia. Using population-scale ancient

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genomics to investigate ancestry, social structure, and pathogen presence, the authors reported evidence of Neolithic plague in at least 18/108 (17%) of the sampled individuals, spanning wide geographic areas (Table 1). By integrating anthropological, paleomicrobiological, and genomic data from *Y. pestis* reported in 28 previously published studies and from GenBank, we offer a complementary perspective to further explore the implications of *Y. pestis* infection in early European populations.

3 | Results and Discussion

3.1 | Insights Into Ancestral *Y. pestis* Strains

Genomic studies have conclusively demonstrated the presence of ancestral *Y. pestis* strains in prehistoric populations across Eurasia, specifically positioned within a pre-Late Neolithic Bronze Age (LNBA) phylogenetic branch (Seersholm et al. 2024) (Figure 1). The observation that 18 of 108 studied individuals yielded genomic evidence of *Y. pestis*, although inconclusive regarding the actual prevalence of plague in these populations, indeed indicates exposure to the pathogen at rates far above modern figures. Evolutionarily, Neolithic *Y. pestis* genomes are positioned intermediately between modern *Y. pestis*, *Y. pseudotuberculosis* and *Y. enterocolitica* genomes in terms of content and synteny. Both *Y. pseudotuberculosis* and the earliest *Y. pestis* strains shared the pCD1 plasmid, which is essential for virulence (Cornelis et al. 1998; Yang et al. 2023). The pre-LNBA ancestral branches of *Y. pestis* harbor the pPCP1 plasmid and presumably an ancestral version of the pMT1 plasmid, containing, respectively, the *pla* and *caf* loci, which are important for producing a high incidence of bubonic plague transmitted by fleas (Sebbane et al. 2006, 2009; Andrades Valtueña et al. 2022; Sodeinde et al. 1992). However, in the case of Neolithic pre-LNBA strains, which showed low coverage of the *caf* gene (25%–50%), the *pla* gene is an ancestral form, thought to be associated with transmission to a narrow mammalian host spectrum and/or low incidence of plague (at least in some rodents) (Andrades Valtueña et al. 2022; Sebbane et al. 2020). In addition, pre-LNBA strains lacked several genetic features important for high incidence of flea-borne plague, including the *ymt* and *ypmt1.66c* genes, located on the pMT1 plasmid of modern strains (Demeure et al. 2019; Andrades Valtueña et al. 2017; Sun et al. 2014). Moreover, the pre-LNBA branches preserved the toxic ancestral ureolytic activity, which kills over 40% of infected fleas within one day, as well as functional genes of *Y. pseudotuberculosis* that hinder the generation of a carbohydrate polymer essential for

TABLE 1 | *Yersinia pestis* whole genome sequences reported from 18 neolithic farmers in Scandinavia, sorted by sample type as retrieved in Seersholm et al. (2024).

Sample	Positive	Chi-2
Cementum	18–29/133 (13.5%–21.8%)	*p* value = 0.35–0.052
Petrous bones	3/38 (7.9%)	
Femur	0/3 (0%)	
Total	21–32/174 (12%–18.4%)	

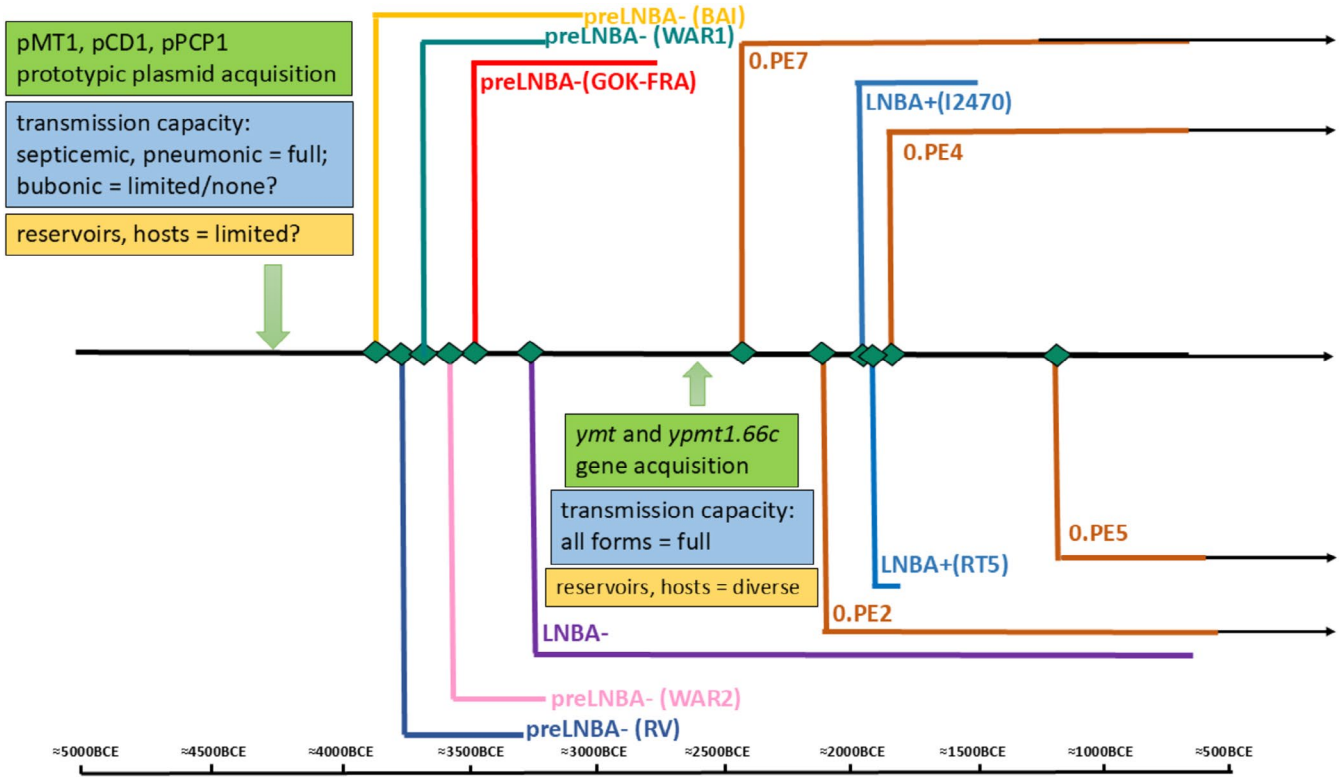

FIGURE 1 | The approximate time (with substantial uncertainty) of the divergence of each line and appearance of selected virulence factors in different *Yersinia pestis* evolutionary branches. Adapted from Slavin et al. (2024) and Macleod et al. (2024).

blocking fleas (i.e., long-term maintenance and transmission of *Y. pestis* by fleas) (Slavin and Sebbane 2022). These observations suggest that, unlike in later lineages, the transmission of Neolithic *Y. pestis* strains may not have been mediated by fleas. The spread of plague bacilli in humans by human lice remains a possibility, but the role and capacity of lice in plague epidemics remain controversial (Dean et al. 2018; Barbieri et al. 2019). Observations from two different models suggest that human lice transmission is biologically possible via contaminated bites and feces (Houhamdi et al. 2006; Bland et al. 2024). Accordingly, the detection of lice-transmitted *Borrelia recurrentis* in 5/108 individuals suggests the circulation of body lice in these Neolithic populations, making co-transmission of *B. recurrentis* and *Y. pestis* possible, as previously reported in 15th-century contexts (Barbieri et al. 2021). Moreover, Seersholm et al. detected *Y. pestis* DNA in fewer than 18% of the samples analyzed, with a higher detection rate in cementum compared to bone (Table 1). Since cementum is generally considered to be poorly vascularized (indeed, avascular) relative to bone (Yamamoto et al. 2016), this pattern suggests that *Y. pestis* might have been only marginally present in the bloodstream. Accordingly, the co-detection of *Y. enterocolitica* and *Y. pestis* in one individual (FRA013), as well as the detection of the enteric pathogen alone in three additional individuals that were reported by Seersholm et al., lends credence to the hypothesis that early *Yersinia* strains may have spread predominantly through food-borne transmission, causing enteritis in Neolithic (and early Bronze Age) Eurasia.

3.2 | The Case for Enteric *Yersinia* Infections

All three major *Yersinia* human pathogenic species—*Y. enterocolitica*, *Y. pseudotuberculosis*, *Y. pestis*—can potentially cause enteritis after the ingestion of contaminated food. Unlike *Y. enterocolitica*, *Y. pseudotuberculosis* causes enteric lymphadenitis, while *Y. pestis* can bypass the lymphatic system and cause septicemia and plague (Zhou and Yang 2009). Nonetheless, modern examples illustrate that *Y. pestis* can still cause enteritis. It is well documented that *Y. pestis*, like its recent ancestor *Y. pseudotuberculosis*, can cause enteritis in rodents and humans after consumption of contaminated food (Butler et al. 1982). In 2007, there was an outbreak of *Y. pestis* gastroenteritis in the Afghan province of Nimroz, following the consumption of undercooked meat from a clinically ill camel, with 382 suspected cases, including 83 probable cases and 17 deaths (Leslie et al. 2011). This illustrates that *Y. pestis* is less virulent following ingestion than via flea-borne transmission. Camels were certainly absent from Neolithic Scandinavia, but the archaeologically proven presence of pigs, goats, sheep, dogs, and cats may implicate these animals as sources of *Y. pestis* infection in human populations (Nyirenda et al. 2017; Li et al. 2008). In one recent publication, *Y. pestis* was detected in a dog from a Late Neolithic context in western Germany (c. 5100 BP), temporally overlapping with some of the earlier burials studied by Susat et al. (2024), while in another, the pathogen was detected in a South Urals sheep from around 3800 BP (Light-Maka et al. 2025). The role of environmental conditions, including soil texture and salinity, in *Y. pestis* persistence has been repeatedly highlighted (Barbieri, Texier, et al. 2020; Stenseth et al. 2022).

3.3 | Reassessing the Plague Hypothesis

Seersholm et al. considered the possibility that Neolithic *Y. pestis* strains followed a fecal-oral transmission route and exhibited attenuated pathogenicity, but ultimately favored an interpretation of virulence determined by genetic factors, largely based on detection of the *ypm* gene. In this section, we revisit this interpretation in light of additional genetic, ecological, and archaeological evidence, and argue that the infections observed may have been predominantly enteric, rather than vector-borne epidemic plague.

Although Seersholm et al. detected the bacterium in only 17% of the studied individuals, it is possible that it was present in more people, with most being mildly infected but some suffering a severe infection causing sepsis, as reported by Seersholm et *al*. This hypothesis is at odds with the idea that *Y. pestis* contributed to the decline of Neolithic populations. According to the proposed scenario, late Neolithic farmers of Scandinavia may not have experienced vector-borne epidemic plague outbreaks; rather, *Y. pestis* may have persisted there in cold soil, infecting locally grazing animals and spilling over zoonotically into humans in the form of bacterial enteritis. This aligns with the observation of *Y. pestis* aDNA in the 18 individuals reported by Seersholm et al. without definitive evidence of widespread mortality from plague. If this is true, then local Neolithic farmers may not have suffered deadly vector-borne plague, but rather an enteric *Y. pestis* infection following ingestion of contaminated food.

In conclusion, we propose that the Neolithic *Y. pestis* strains were predominantly enteropathogenic, causing deadly septicemia in an unknown proportion of individuals, evolving toward increased virulence and efficiency of flea-borne transmission in later lineages. This perspective offers a nuanced understanding of the pathogen's role in ancient populations, suggesting that the decline of Neolithic populations might have been less abrupt than in the proposed scenario of a rapid decline caused by bubonic plague. Rather, it was occurring over long periods and thus it may have been potentially more impactful on local populations in the long run.

Author Contributions

Hamadou Oumarou Hama: writing – original draft, project administration, conceptualization, methodology, validation, writing – review and editing. **Michel Drancourt:** writing – review and editing, project administration, validation, writing – original draft, formal analysis. **Philip Slavin:** writing – review and editing, validation, formal analysis. **Florent Sebbane:** writing – review and editing, formal analysis, validation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data reported in this manuscript are publicly available through the cited literature and GenBank. Relevant references and accession numbers are provided in the reference list.

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