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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	no software was used in data collection
Data analysis	leeHom (v1.2.5); network-aware-bwa (v0.5.10-evan.10); biohazard (v1.0.2); samtools (v1.9); mapDamage (v2.0); GATK (v4.1.4.1); LCLAE (2016); TrimGalore (v0.2.7); STAR (v2.4.1d); SLiM (v3.7.1); RSEM (v1.2.21); cellranger (v3.0.2); souporcell (v2.0); singularity (v3.4.0); R (v4.1) with limma (v3.48.3), textTinyR (v1.1.3), ggplot2 (3.3.6), and seurat (v4.0.4) packages. Novel code for the analyses in this project can be found at github.com/TaurVil/VilgalysKlunk_yersinia_pestis/ and https://github.com/steinrue/diplo_locus/.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Hybridization capture data from the ancient individuals have been deposited in the NCBI Sequence Read Archive (SRA) under BioProject PRJNA798381. Expression data have been deposited to GEO under accession number GSE194118 (for macrophages) and the NCBI SRA under accession number PRJNA871128 (for PBMCs). Cytokine and CFU data are available in Table S8 and S9, respectively.

We also used previously published data from the following sources: DeCODE project recombination rates (https://doi.org/10.1038/ng917); human genome B values (https://doi.org/10.1371/journal.pgen.1000471); Ensembl annotations for hg19 (https://grch37.ensembl.org/Homo_sapiens/Info/Index); yersinia pestis reference genome from NCBI(https://www.ncbi.nlm.nih.gov/genome/?term=yersinia%20pestis); genetic variation from the 1000 Genomes Project (http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/).

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes for ancient genomics were based on the number of individuals who could be sampled and for whom remains were enriched for sufficient endogenous DNA to sequence. Power to detect selection was confirmed via simulation. Sample sizes for expression data were selected based upon previous analyses in Dr. Barreiro's lab demonstrating sufficient power to detect infection effects and some genetic effects in similarly designed studies.
Data exclusions	Ancient genomic data were excluded when they failed to meet DNA quality or coverage standards. No expression data were excluded. One sample was excluded from the CFU data analyses because the cell cultures were noticeably contaminated.
Replication	All attempts at replication were successful, including strong concordance in expression results between heat-killed and live yersinia pestis. Analysis of ancient DNA cannot be replicated due to sample availability; however sampling at two separate locations serves as pseudo-replication and increases confidence in the strongest signatures of selection.
Randomization	Ancient genomes represent a natural experiment and were therefore not capable of being randomized. For expression analyses, cells from each individual were split into two batches, one of which was exposed to yersinia pestis and the other mock-infection control.
Blinding	not applicable as all outcome measures were objectively measured.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☐	☒ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Mouse Anti-Human CD14 (BD Biosciences)
Validation	The purity of the isolated monocytes was verified using an antibody against CD14 (BD Biosciences) and only samples showing > 90% purity were used to differentiate into macrophages.

Palaeontology and Archaeology

Specimen provenance	The specifics of each sample location and date are provided in Table S1 of the current manuscript. Briefly, samples come from the UK, London specifically from three burial sites, East Smithfield and St. Mary Graces, St. Nicholas Shambles, St. Mary Spital. For those stemming from Denmark and a wider geographic spread, they come fromo Nordby, Ribe, Viborg, Haagerup and Horsens.
Specimen deposition	Samples from London have been provided to us by Museum of London Center for Human Bioarchaeology. Samples from Denmark

Specimen deposition	stem from the Horsens Museum, the Viborg Museum, the Moesgaard Museum, Museum Lolland-Faster, Øhavsmuseet, Faaborg, and ADBOU.
Dating methods	The London cemeteries are dated based on a combination of primary sources, Bayesian radiocarbon dating, and archaeological remains (primarily coins). We did the same for our Danish samples, as best we could from associated dates, which are less precise due to the lack of records associated with many of the cemeteries and the imprecision of the dating method based on arm position at burial used to date medieval burials in this region. We therefore group Danish samples into either an Early (~850-1350) or Late (1350-1800) period corresponding to before or after the Black Death period.

☒ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	No ethical approval was required given that none of the samples could be linked to living descendants. Usage of the samples was approved by the Museum of London's Collection Committee.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Human derived cell for infection experiments were obtained from healthy male donors aged 18 to 55 years old of European and African American descent. Each donor's blood was tested for Hepatitis B, Hepatitis C, Human Immunodeficiency Virus (HIV), and West Nile Virus, and only samples negative for all of the tested pathogens were used and we controlled for genetic ancestry (previously inferred from whole genome sequencing) in all analyses.
Recruitment	Depending on the experiments, samples were collected by the Indiana Blood Center (Indianapolis, IN, USA) or the "Etablissement Français du Sang" in Paris. Individuals consented their blood to be used for research purposes.
Ethics oversight	This study has been approved by the Institutional Review Board at the University of Chicago (protocol #: IRB19-0432).

Note that full information on the approval of the study protocol must also be provided in the manuscript.