PALAEOGENOMICS OF PATHOGENS

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QUIZ

1. What is necrobiome and where do we find it?

Group of organisms associated with decay of other organisms‘ remains.

It‘s present in all our samples from remains (both skeletal and mummified)

2. What ways of parchment sampling are used?

Eraser rubbings

Fragments of the parchment

3. What are museomics?

Omics used for the analyses of historical biomolecules from museum collections.

4. What is biocodicology? What can we learn from it?

> Biocodicology is an emerging field that studies the biological information stored in ancient manuscripts and is currently revolutionizing the field of codicology (Fiddyment *et al.*, 2019) by incorporating high-throughput molecular techniques such as proteomics (Fiddyment *et al.*, 2015), genomics and metagenomics (Teasdale *et al.*, 2015, 2017). These technologies make it possible to extract the biological information stored for centuries in ancient manuscripts, especially in parchment objects.

What was the parchment made from, species, sex and population affinity. Fragment relationship. Origin of stains. Pathogens. Preservation and organisms that could endanger the document. Parchment Quality Index. Treatment. Human handling. …

5. What are some of the steps for validation?

Authentication based on damage

Competitive mapping

Good reference, database choice!!

Unique markers

Does it make biological and historical sense?

6. Write at least 5 examples of sources for metagenomics of ancient samples.

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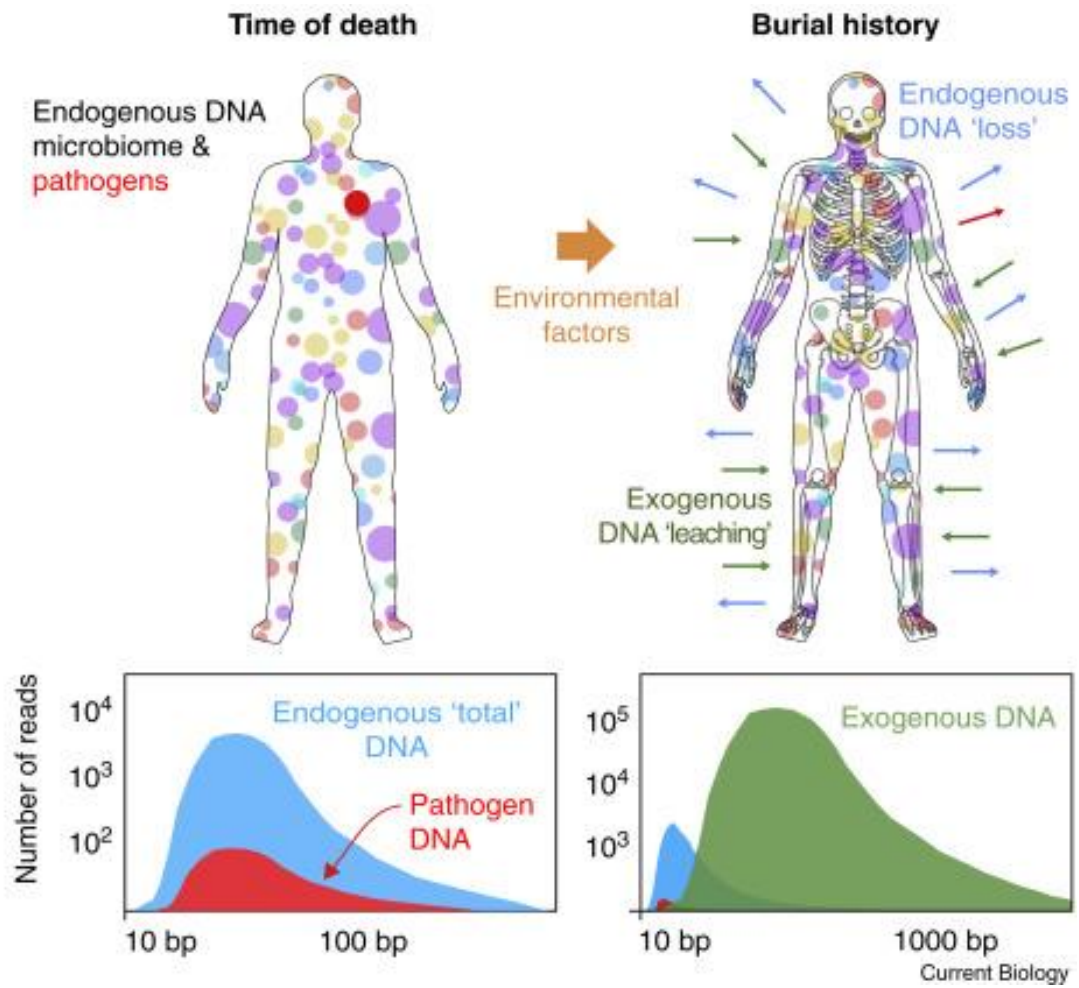

Degradation and preservation of host DNA (including the microbiome and circulating pathogens) occurs rapidly after death. DNA degrades in an environmentally informed manner, where water, temperature, pH, microbial soil content and other factors shorten the remaining endogenous DNA but most is lost. At the same time, environmental (exogenous) DNA swamps out the original signal, with fragment-length distributions that both overlap and extend beyond the ancient DNA in the sample. Medieval peoples were well acquainted with death as the 15th century manuscript illustration on the left suggests (image: © British Library Board: Add MS 37049). Here, a recently buried noblewoman (endogenous) sits atop the worms and other vermin (exogenous), who will soon set upon her corpse. The image accompanies a Middle English poem relating a discussion between the decaying woman and eager worms [138].

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PMCID: PMC7534838
PMID: 33022266

The Recovery, Interpretation and Use of Ancient Pathogen Genomes

Sebastián Duchêne,[1,*] Simon Y.W. Ho,[2] Ann G. Carmichael,[3] Edward C. Holmes,[4,**] and Hendrik Poinar[5,6,7,***]

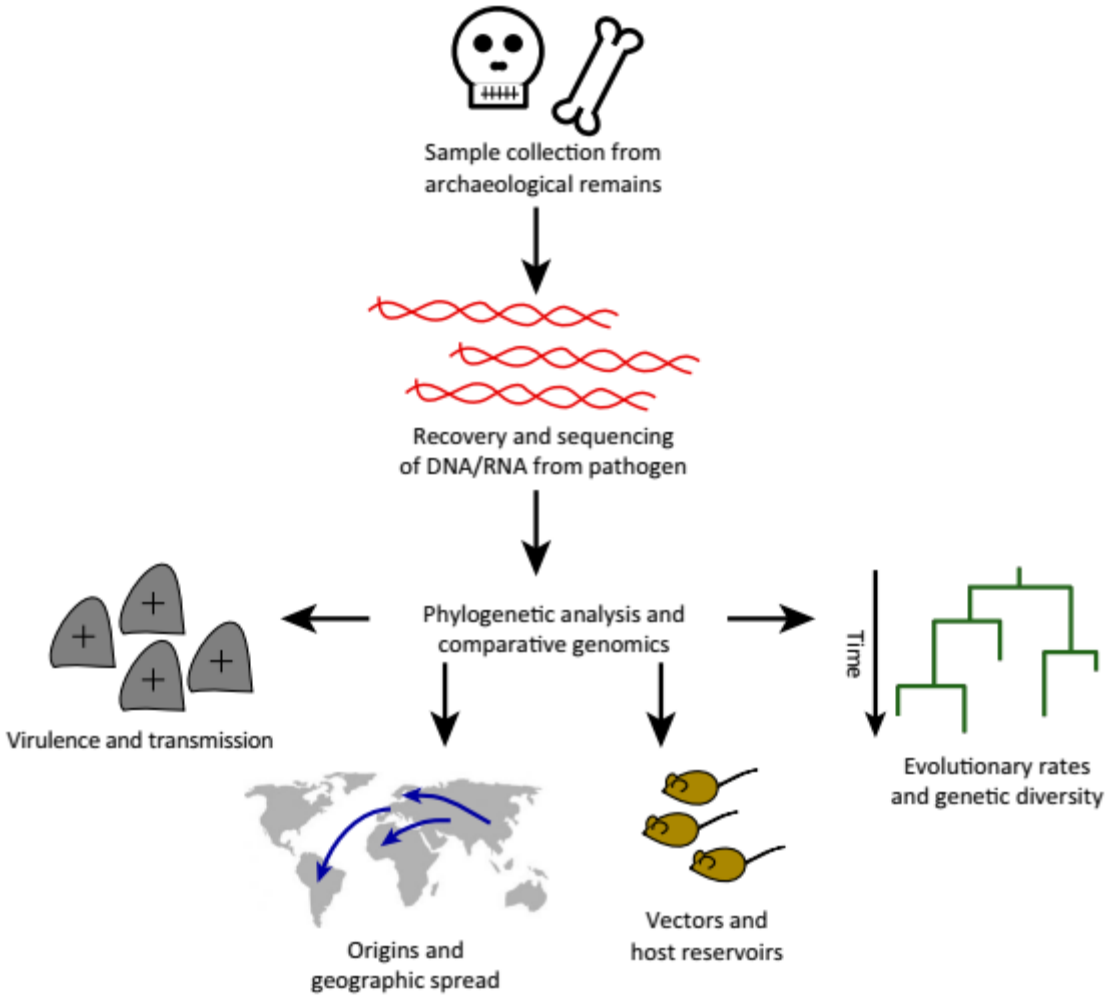
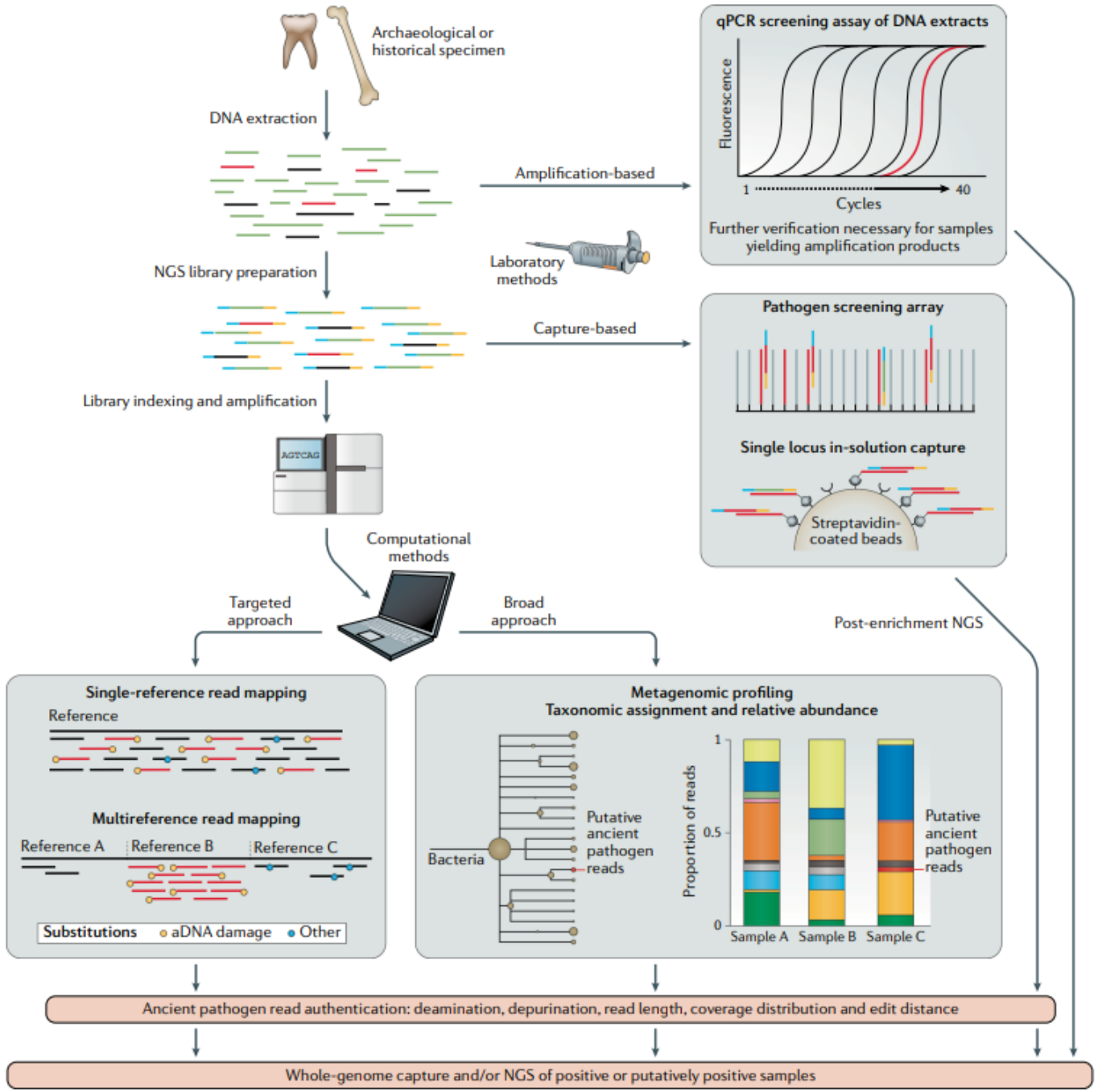


Figure 2. Overview of Microbial Genomics of Ancient Pathogens. Studying ancient pathogens can be a valuable tool in answering many historical and biological questions. These include what could have caused the high mortality of past diseases, how they spread across continents, how vectors and host reservoirs contributed to their virulence and transmission, and the origins and diversity of pathogens in the past. For a more detailed explanation of the methods used in ancient pathogen genomics we refer the reader to an excellent review by Drancourt and Raoult [79].

Andam et al., 2016 DOI: 10.1016/j.tim.2016.08.004

Fig. 2 | **Methods for the detection and isolation of pathogen DNA from ancient metagenomic specimens.** The diagram provides an overview of techniques used for pathogen DNA detection in ancient remains by distinguishing between laboratory and computational methods. In both cases, processing begins with the extraction of DNA from ancient specimens[183]. As part of the laboratory pipeline, direct screening of extracts can be performed by PCR (quantitative (qPCR) or conventional) against species-specific genes, as done previously[17,61,63,64]. PCR techniques alone, however, can suffer from frequent false-positive results and should therefore always be coupled with further verification methods such as downstream genome enrichment and/or next-generation sequencing (NGS) in order to ensure ancient DNA (aDNA) authentication of putatively positive samples. Alternatively, construction of NGS libraries[184,185] has enabled pathogen screening via fluorescence-based detection on microarrays[66] and via DNA enrichment approaches[17]. The latter has been achieved, through single locus in-solution capture[26,28] or through simultaneous screening for multiple pathogens using microarray-based enrichment of species-specific loci[65] and enables post-NGS aDNA authentication. In addition, data produced by direct (shotgun) sequencing of NGS libraries before enrichment can also be used for pathogen screening using computational tools. After pre-processing, reads can be directly mapped against a target reference genome (in cases for which contextual information is suggestive of a causative organism) or against a multigenome reference composed of closely related species to achieve increased mapping specificity of ancient reads. Alternatively, ancient pathogen DNA can also be detected using metagenomic profiling methods, as presented elsewhere[41,71,72], through taxonomic assignment of shotgun NGS reads. Both approaches allow for subsequent assessment of aDNA authenticity and can be followed by whole pathogen genome retrieval through targeted enrichment or direct sequencing of positive sample libraries.



Spyrou et al., 2019; DOI: 10.1038/s41576-019-0119-1

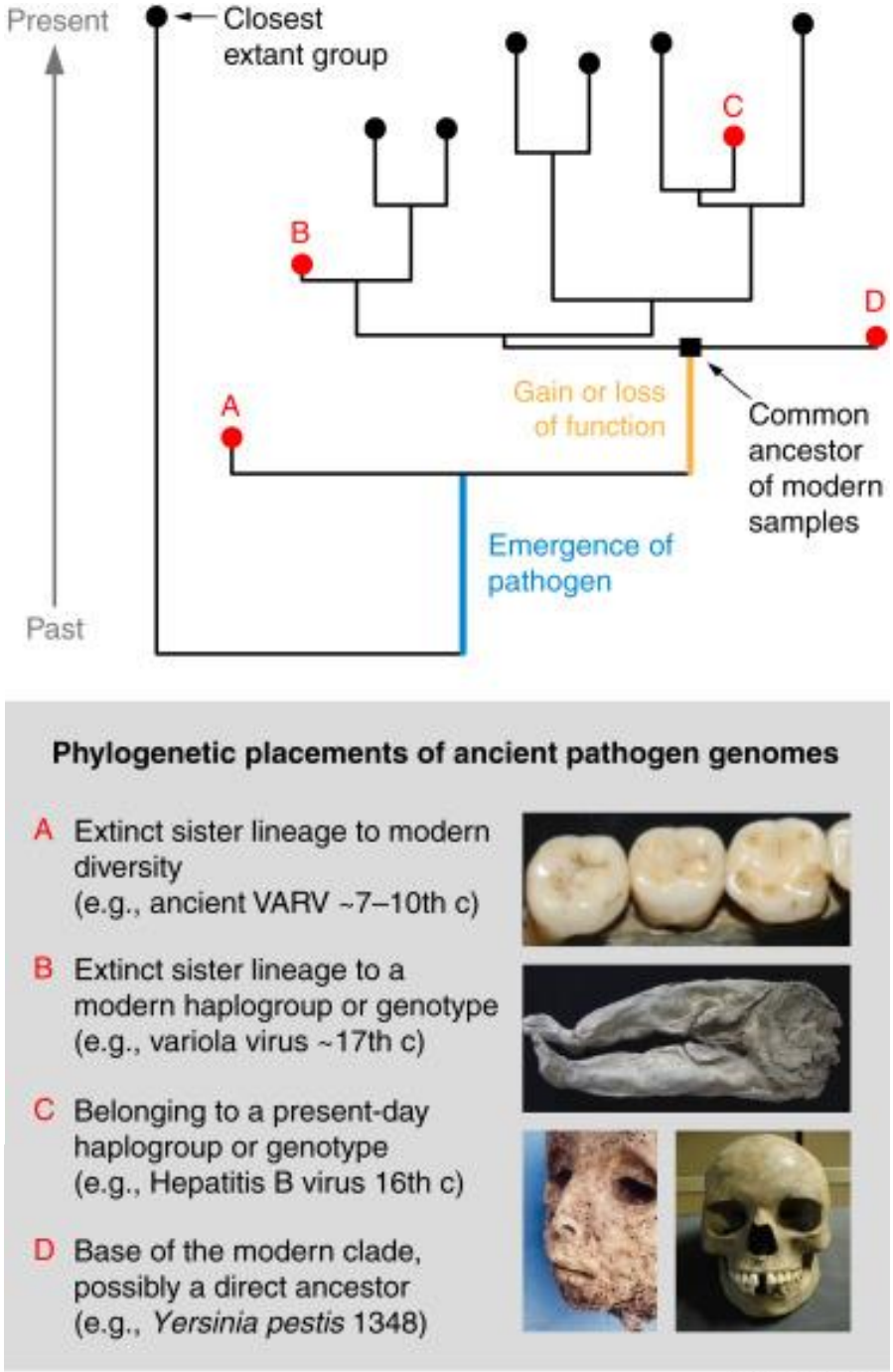
Table 1 | **Ancient pathogen genomic data recovered from archaeological or historical specimens**

Pathogen	Infectious disease	Method of retrieval	Number of genomes[a]	Biological insights	Refs
Bacterial pathogens					
Borrelia recurrentis	Relapsing fever	Shotgun sequencing	1	• Isolation from 15th-century CE human remains from Norway • Genome signatures of reductive evolution, associated with typical virulence profile, and recent ecological adaptation	40
Brucella melitensis	Brucellosis	Shotgun sequencing	1	• Isolation from a calcified nodule identified in an individual's pelvic girdle • Presence of *B. melitensis* in Sardinia during the 14th century CE	47
Gardnerella vaginalis	Bacterial vaginosis	Shotgun sequencing	1	• Identified in human remains from Troy dating to 13th century CE • Association with women's mortality during childbirth in the past • The identified strain clusters among modern *G. vaginalis* diversity	48
Helicobacter pylori	• Ulcers of the upper gastrointestinal tract • Increased risk of gastric carcinoma	In-solution capture followed by NGS	1	• Isolation from European Copper Age, 5,300-year-old mummy (Ötzi) • Unadmixed strain, contrary to modern European strains, which are hybrids of two ancestral populations	49
Mycobacterium leprae	Lepromatous leprosy	• Shotgun sequencing • Microarray-based capture followed by NGS	27	• First de novo assembled ancient pathogen genome • Estimated emergence >5,000 years ago • European origin of leprosy in the Americas • High *M. leprae* diversity in medieval Europe	27,28, 105,201
Mycobacterium tuberculosis	Tuberculosis	• Shotgun sequencing • Microarray-based capture followed by NGS	19	• Genomes from pre-Columbian human infections show phylogenetic clustering within animal-adapted lineage present today in seals • Molecular dating analysis suggests emergence of MTBC <6,000 years ago • Analysis of European genomes shows past occurrence of multiple infections and suggests origin of lineage 4 during the 4th to 5th century CE	26,52,123
Salmonella enterica subsp. *enterica* serovar Paratyphi C	Enteric (paratyphoid) fever	• Shotgun sequencing • Microarray-based capture followed by NGS • In-solution capture followed by NGS	11	• *S. enterica* subsp. *enterica* serovar Paratyphi C presence in 12th-century CE Norway • Paratyphi C serovar was also identified among 16th-century individuals from Mexico that were associated with the major post-contact 'cocoliztli' epidemic	41,109
Staphylococcus saprophyticus	• Urinary tract infections • Puerperal fever	Shotgun sequencing	1	• Identified in ~800-year-old human remains from Troy • Association with women's mortality during childbirth in the past • The identified lineage is not commonly associated with human disease today	48
Tannerella forsythia	Periodontal disease	Shotgun sequencing	1	• Isolation from medieval human remains (circa 950–1200 CE) • First pathogen genome reconstructed from ancient dental calculus	46
Treponema pallidum	• Syphilis (*Treponema pallidum* subsp. *pallidum*) • Yaws (*Treponema pallidum* subsp. *pertenue*) • Bejel (*Treponema pallidum* subsp. *endemicum*)	Microarray-based capture followed by NGS	3	• Isolated from individuals who lived in Mexico City between the 17th and 19th centuries CE • Different Treponema subspecies (*T. pallidum* subsp. *pallidum* and subsp. *pertenue*) caused similar skeletal lesions usually identifiable as skeletal syphilis in infants	29
Vibrio cholerae	Cholera	Microarray-based capture followed by NGS	1	• Isolation from 19th-century alcohol-preserved intestinal specimen from an individual affected during the second cholera pandemic • The identified strain shows highest similarity with the classic pathogenic biotype O1	55
Yersinia pestis	Bubonic, pneumonic and septicaemic plague	• Shotgun sequencing • Microarray-based capture followed by NGS • In-solution capture followed by NGS	38	• Bacterium affected humans as early as 5,000 years ago • Both flea-adapted and non-adapted variants were present in Eurasia during the Bronze Age • Causative agent of the Plague of Justinian (6th century CE) • Causative agent of Black Death and persistence in Europe during the second plague pandemic (14th to 18th century CE) • Possible European origin of third plague pandemic lineage	20,30–39
Viral pathogens					
HBV	Viral hepatitis	• Shotgun sequencing • In-solution capture followed by NGS • Whole-genome PCR[b]	17	• Identified in ancient human specimens as early as 7,000 years ago • Neolithic genome lineage related to contemporary strains identified in African non-human primates • Complex evolutionary history of HBV and identification of ancient recombination event giving rise to genotype A strains	43,44, 53,54
HIV	AIDS	Whole-genome PCR[b]	8	• Analysis of HIV RNA from archival specimens of seropositive individuals enrolled in HBV studies during the late 1970s • HIV was introduced into the Americas from the Caribbean in the early 1970s	57
B19V	• Erythema infectiosum (fifth disease) in children • Arthropathies in adults • Hydrops fetalis or fetal death in pregnant women • Pure red-cell aplasia	In-solution capture followed by NGS	10	• Genomic signatures of B19V identified in human remains dating as early as ~7,000 years ago • Contrary to previous estimates of a most recent common ancestor younger than 200 years, phylogenetic and molecular dating analysis of ancient genomes showed a much lengthier association of B19V with human populations	45
Influenza virus	Influenza	Whole-genome PCR[b]	1	• First reconstructed genome from historical RNA virus • Avian source of 1918 influenza pandemic (Spanish flu, 1918–1920) • Reconstructed virus particle displayed increased virulence under laboratory conditions	58,202
VARV	Smallpox	In-solution capture followed by NGS	1	• Genome reconstruction from a 17th-century mummy from Lithuania • Recent emergence of 20th century VARV lineages (divergence during the 18th century CE)	50
Eukaryotic pathogens					
Phytophthora infestans	Late blight (also known as potato blight)	Shotgun sequencing	18	• First sequenced ancient eukaryotic (plant) pathogen genomes • Isolated from historical herbarium specimens • A unique *Phytophthora infestans* genotype caused the Irish potato famine and during the 1900s became replaced by the US-1 lineage that dominated worldwide until the 1970s	59,60
Plasmodium falciparum and *Plasmodium vivax*	Malaria	In-solution capture followed by NGS	5	• Oldest *Plasmodium falciparum* detection from southern Italy (1st to 2nd century CE) • *Plasmodium falciparum* and *Plasmodium vivax* mitochondrial genome isolation from 20th century microscopy slides • Possible introduction of *Plasmodium vivax* in the Americas through European contact	42,56

B19V, human parvovirus B19; CE, current era; HBV, hepatitis B virus; MTBC, *Mycobacterium tuberculosis* complex; NGS, next-generation sequencing; VARV, variola virus. [a]The indicated numbers include whole pathogen genomes and specimens yielding genome-wide data. [b]Whole-genome PCR amplicons from the studies of influenza virus[58], HIV[57] and HBV[54] that were sequenced using capillary sequencing (Sanger method).

Spyrou et al. 2019; DOI: 10.1038/s41576-019-0119-1

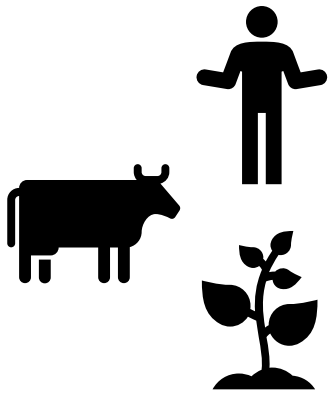
Schematic phylogenetic tree showing how ancient genomes can provide information on key various aspects of the evolutionary history of pathogens. An ancient pathogen genome can potentially be placed as (A) an extinct sister lineage to the modern diversity (e.g., ancient variola virus from 7th–10th century [103]; image: teeth from an East Smithfield individual used to indicate source from which ancient variola-like sequences have been isolated, courtesy of Sharon DeWitte, Museum of London); (B) an extinct sister lineage to a modern haplogroup or genotype, but still falling within the modern clade of the pathogen (e.g., variola virus from the 17th century; image: VD21 child mummy from Vilnius, Lithuania, from which smallpox was detected, from [10]); (C) belonging to a present-day haplogroup or genotype (e.g., hepatitis B virus from the 16th century [9,125]; image: child mummy from Naples, Italy, with HBV detected, © 2018 Patterson Ross *et al.* CC BY 4.0); or (D) at the base of the modern clade, possibly as a direct ancestor (e.g., *Y. pestis* from 1348 [5]; image: skull of an individual from East Smithfield that yielded a Black Death genome, courtesy of Jelena Bekvalac, Museum of London (MIN86)). The square symbol denotes the common ancestor of modern pathogen samples. Importantly, the emergence of a pathogen in its present host could have occurred *at any point along* the branch between the divergence from its closest extant or extinct relative and the most recent common ancestor of the sampled isolates (branch in blue). Ancient pathogen genomes can help narrow this window of emergence [90] while also shedding light on any gain or loss of function along the branches leading up to the modern clade (branch in orange).

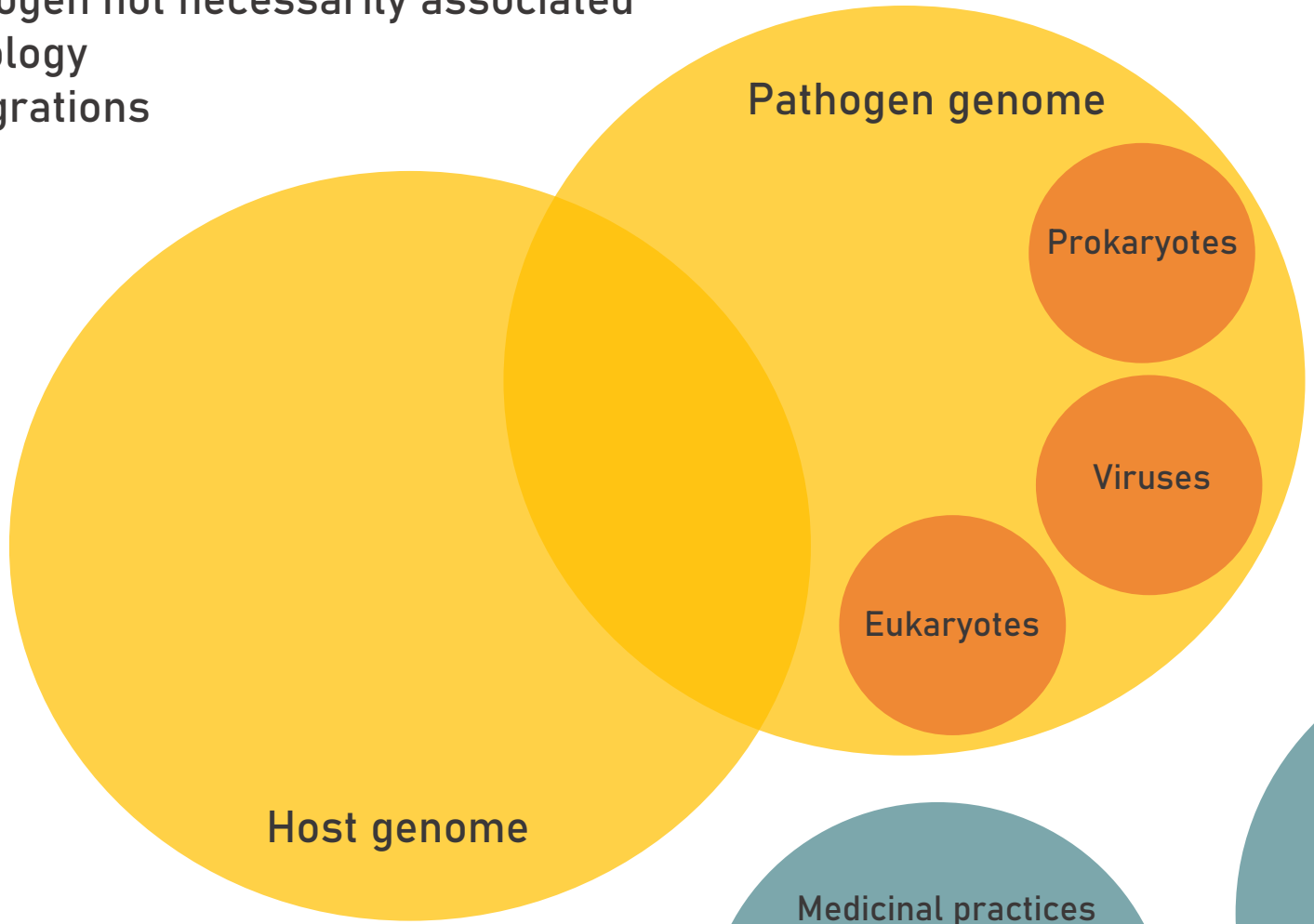


Duchêne et al., 2020 DOI: 10.1016/j.cub.2020.08.081

PALEOGENOMICS IN PATHOGEN RESEARCH

- Fast rate of evolution
- Pathogen morphology often inaccessible or insufficient
- Presence of pathogen not necessarily associated with visible pathology
- Tracking host migrations



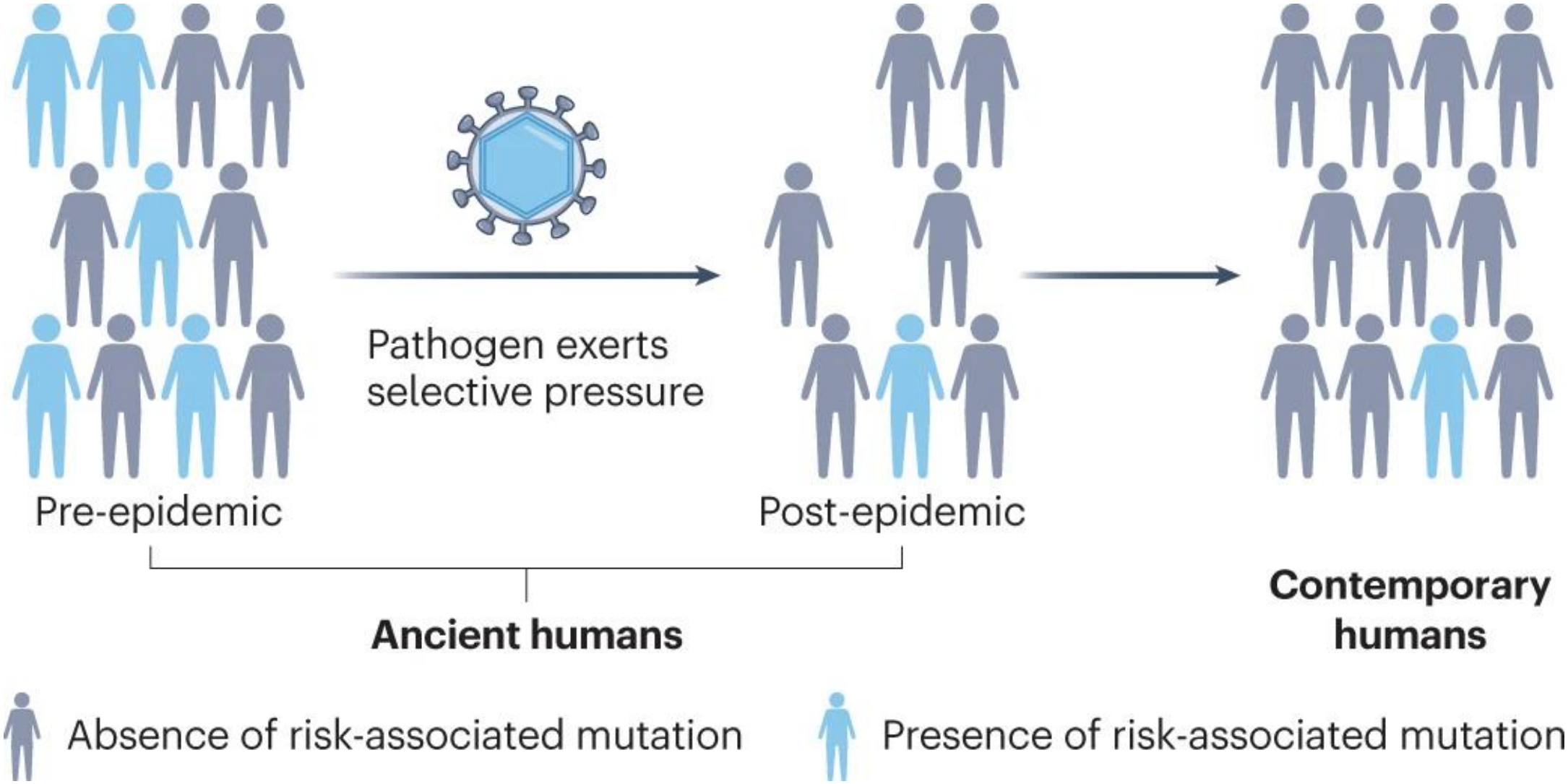


Palaeopathology

Historical records

Medicinal practices

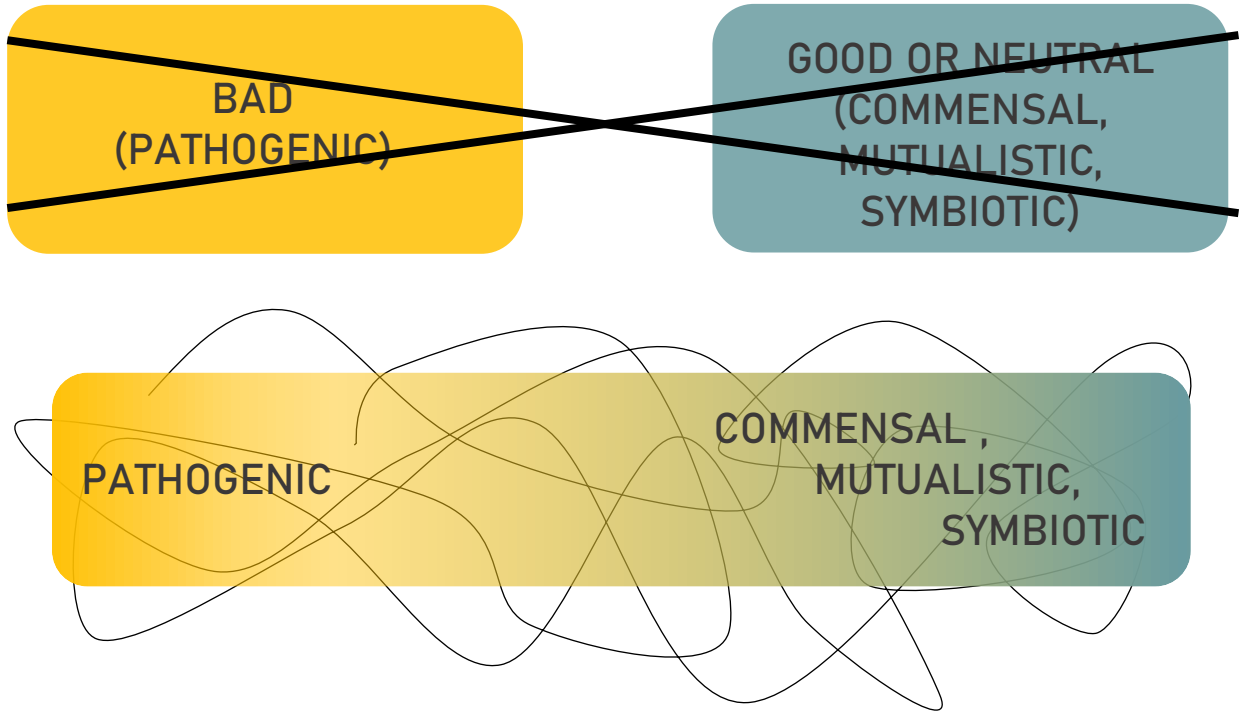
DISEASE-RELATED CHANGES



Protective variants in e.g. *TLR10–TLR1–TLR6* gene cluster, human leukocyte antigen-associated *PPT2* and *EGFL8*

Kerner et al., 2023; DOI: 10.1038/s41591-023-02244-4

PALEOGENOMICS IN PATHOGEN RESEARCH



ACTIVE? LATENT? NON-PATHOGENIC?

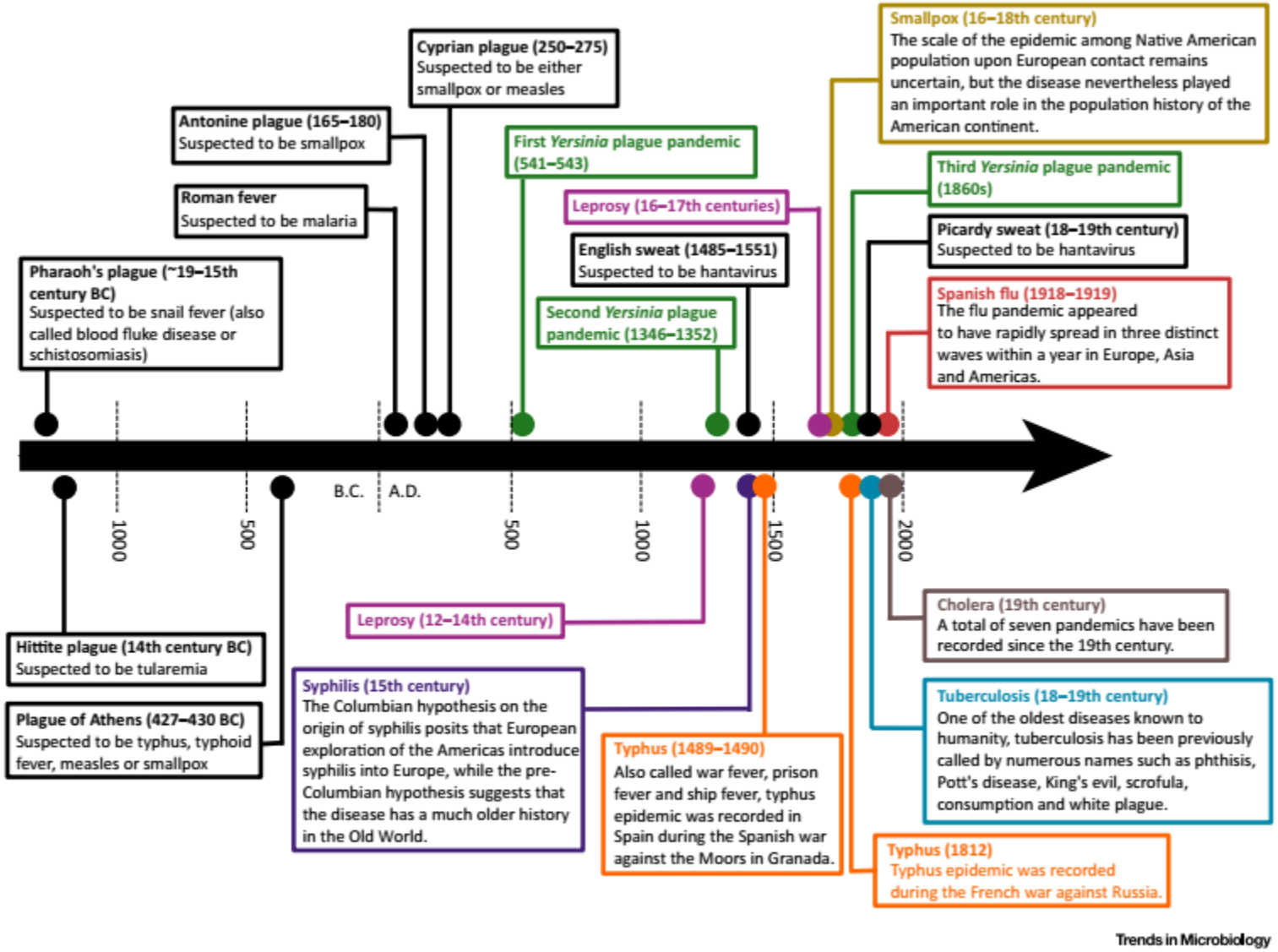


Figure 1. Overview and Timeline of Historically Notable Disease Outbreaks in Human History. Colored dots represent different outbreaks and epidemics. Black dots indicate disease outbreaks of unresolved origins [1,67–75]. The origin of syphilis remains contentious, with two hypotheses put forward to explain the epidemic in Europe in the 12th–14th centuries [1,76–78]. Not shown are seven Bronze Age (~3000 BC) *Yersinia* plague strains [46]. Location of dots represents approximate time and should not be taken as precise estimates of the time of occurrence of the disease.

Andam et al., 2016 DOI: 10.1016/j.tim.2016.08.004

DOMESTICATION, AGRICULTURE

- Increase in pathogens, including those affecting plants and animals
- Changes in human genome associated with pressure from pathogen spread
- Further changes with urbanisation

- Anthroponosis – human to human (rubella, smallpox, gonorrhea…)
- Zoonosis – between animal and human in any direction
    - Anthropozoonosis – animal to human (hemorrhagic fevers)
    - Zooanthroponosis – human to animal (influenza, tuberculosis)

    - Synanthropic – from animals with us (urban, domestic – urban rabies, cat scratch disease)
    - Exoanthropic – animals living in the wild (Lyme disease, wildlife rabies…)
- Sapronosis – abiotic environment (e.g., soil, decaying plant or animal remains) to living host (legionellosis, nontuberculous mycobacterioses, *Yersinia pseudotuberculosis)*

Hubálek, 2003; DOI: 10.3201/eid0903.020208

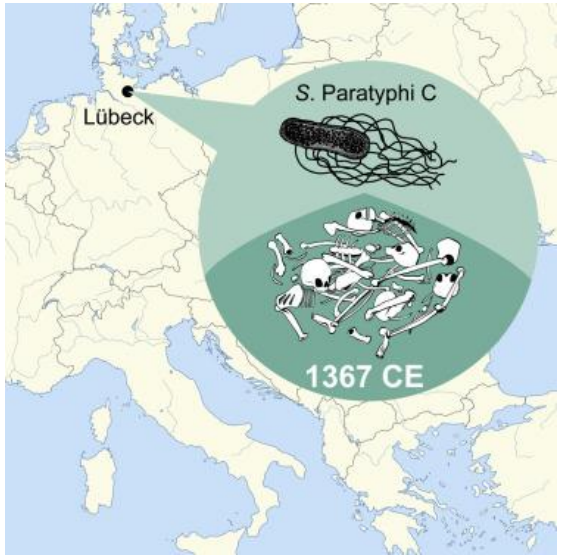
MASS GRAVES

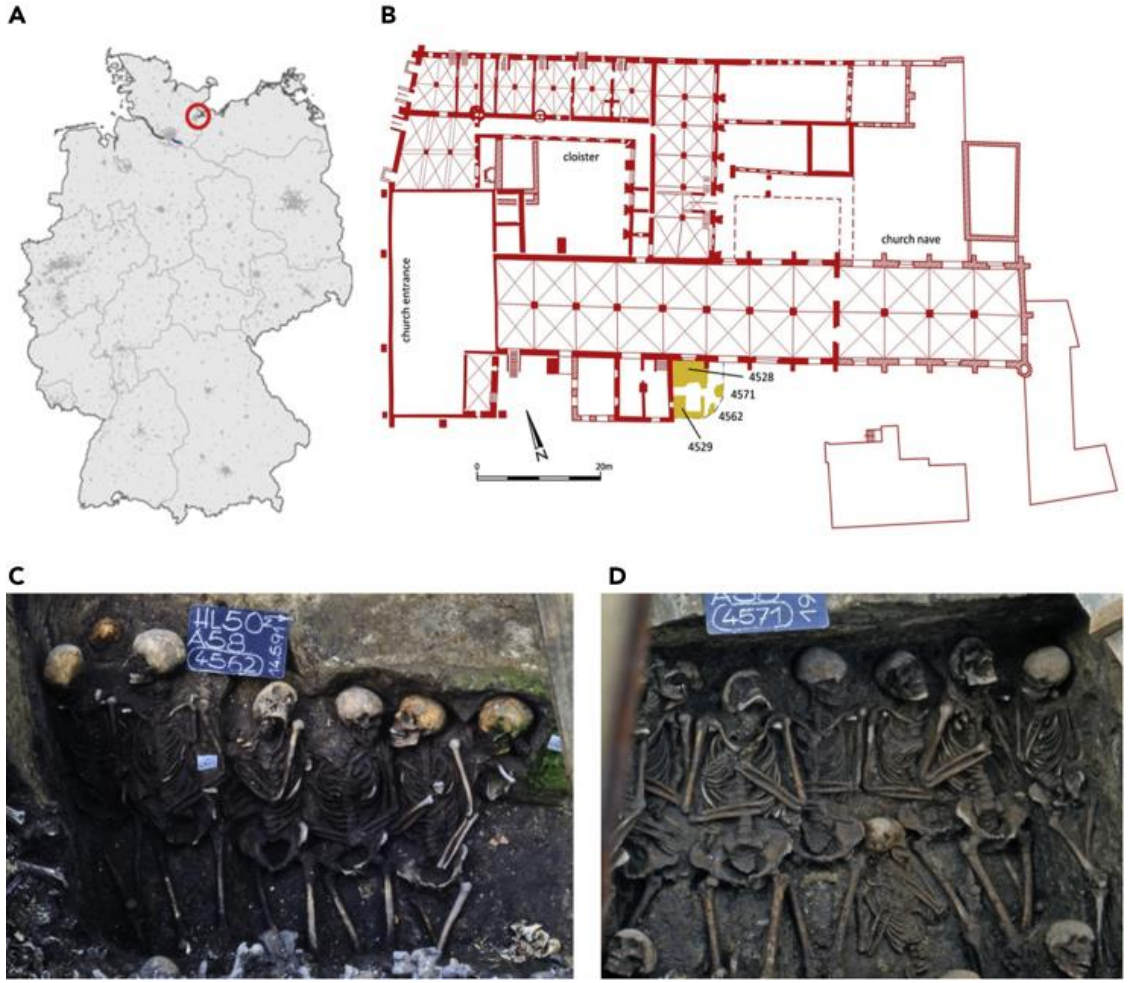
- INJURY FAMINE INFECTIOUS EPIDEMIC DISEASES
- Example:

iScience. 2021 May 21; 24(5): 102419.
Published online 2021 Apr 20. doi: 10.1016/j.isci.2021.102419
PMCID: PMC8100618
PMID: 33997698

Mass burial genomics reveals outbreak of enteric paratyphoid fever in the Late Medieval trade city Lübeck

Magdalena Haller,[1] Kimberly Callan,[1,2] Julian Susat,[1] Anna Lena Flux,[3] Alexander Immel,[1] Andre Franke,[1] Alexander Herbig,[4] Johannes Krause,[4] Anne Kupczok,[5,6] Gerhard Fouquet,[7] Susanne Hummel,[3] Dirk Rieger,[8] Almut Nebel,[1,9] and Ben Krause-Kyora[1,9,10,*]





WAYS TO STUDY CIVILIZATIONS DECLINE/COLLAPSE

- Possible epidemics
- Famine due to plant pathogens

Article | Published: 15 January 2018

Salmonella enterica genomes from victims of a major sixteenth-century epidemic in Mexico

Åshild J. Vågene, Alexander Herbig ✉, Michael G. Campana, Nelly M. Robles García, Christina Warinner, Susanna Sabin, Maria A. Spyrou, Aida Andrades Valtueña, Daniel Huson, Noreen Tuross, Kirsten I. Bos & Johannes Krause

Nature Ecology & Evolution **2**, 520–528 (2018) | Cite this article

9523 Accesses | **147** Citations | **1275** Altmetric | Metrics

Abstract

Indigenous populations of the Americas experienced high mortality rates during the early contact period as a result of infectious diseases, many of which were introduced by Europeans. Most of the pathogenic agents that caused these outbreaks remain unknown. Through the introduction of a new metagenomic analysis tool called MALT, applied here to search for traces of ancient pathogen DNA, we were able to identify *Salmonella enterica* in individuals buried in an early contact era epidemic cemetery at Teposcolula-Yucundaa, Oaxaca in southern Mexico. This cemetery is linked, based on historical and archaeological evidence, to the 1545–1550 CE epidemic that affected large parts of Mexico. Locally, this epidemic was known as '*cocoliztli*', the pathogenic cause of which has been debated for more than a century. Here, we present genome-wide data from ten individuals for *Salmonella enterica* subsp. *enterica* serovar Paratyphi C, a bacterial cause of enteric fever. We propose that *S.* Paratyphi C be considered a strong candidate for the epidemic population decline during the 1545 *cocoliztli* outbreak at Teposcolula-Yucundaa.

Article | Open access | Published: 06 February 2014

A complete ancient RNA genome: identification, reconstruction and evolutionary history of archaeological Barley Stripe Mosaic Virus

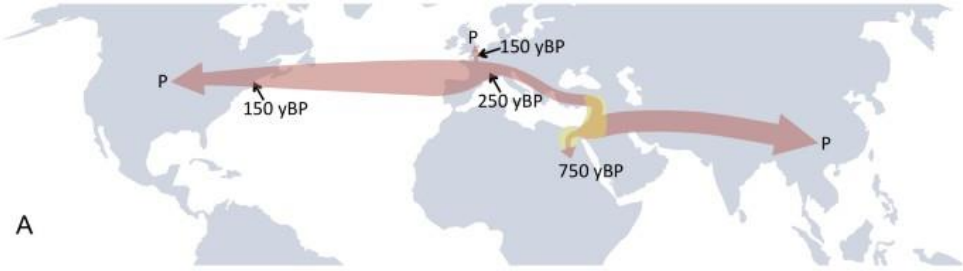
Oliver Smith, Alan Clapham, Pam Rose, Yuan Liu, Jun Wang & Robin G. Allaby

Scientific Reports **4**, Article number: 4003 (2014) | Cite this article

6439 Accesses | **66** Citations | **57** Altmetric | Metrics

Abstract

The origins of many plant diseases appear to be recent and associated with the rise of domestication, the spread of agriculture or recent global movements of crops. Distinguishing between these possibilities is problematic because of the difficulty of determining rates of molecular evolution over short time frames. Heterochronous approaches using recent and historical samples show that plant viruses exhibit highly variable and often rapid rates of molecular evolution. The accuracy of estimated evolution rates and age of origin can be greatly improved with the inclusion of older molecular data from archaeological material. Here we present the first reconstruction of an archaeological RNA genome, which is of Barley Stripe Mosaic Virus (BSMV) isolated from barley grain ~750 years of age. Phylogenetic analysis of BSMV that includes this genome indicates the divergence of BSMV and its closest relative prior to this time, most likely around 2000 years ago. However, exclusion of the archaeological data results in an apparently much more recent origin of the virus that postdates even the archaeological sample. We conclude that this viral lineage originated in the Near East or North Africa and spread to North America and East Asia with their hosts along historical trade routes.

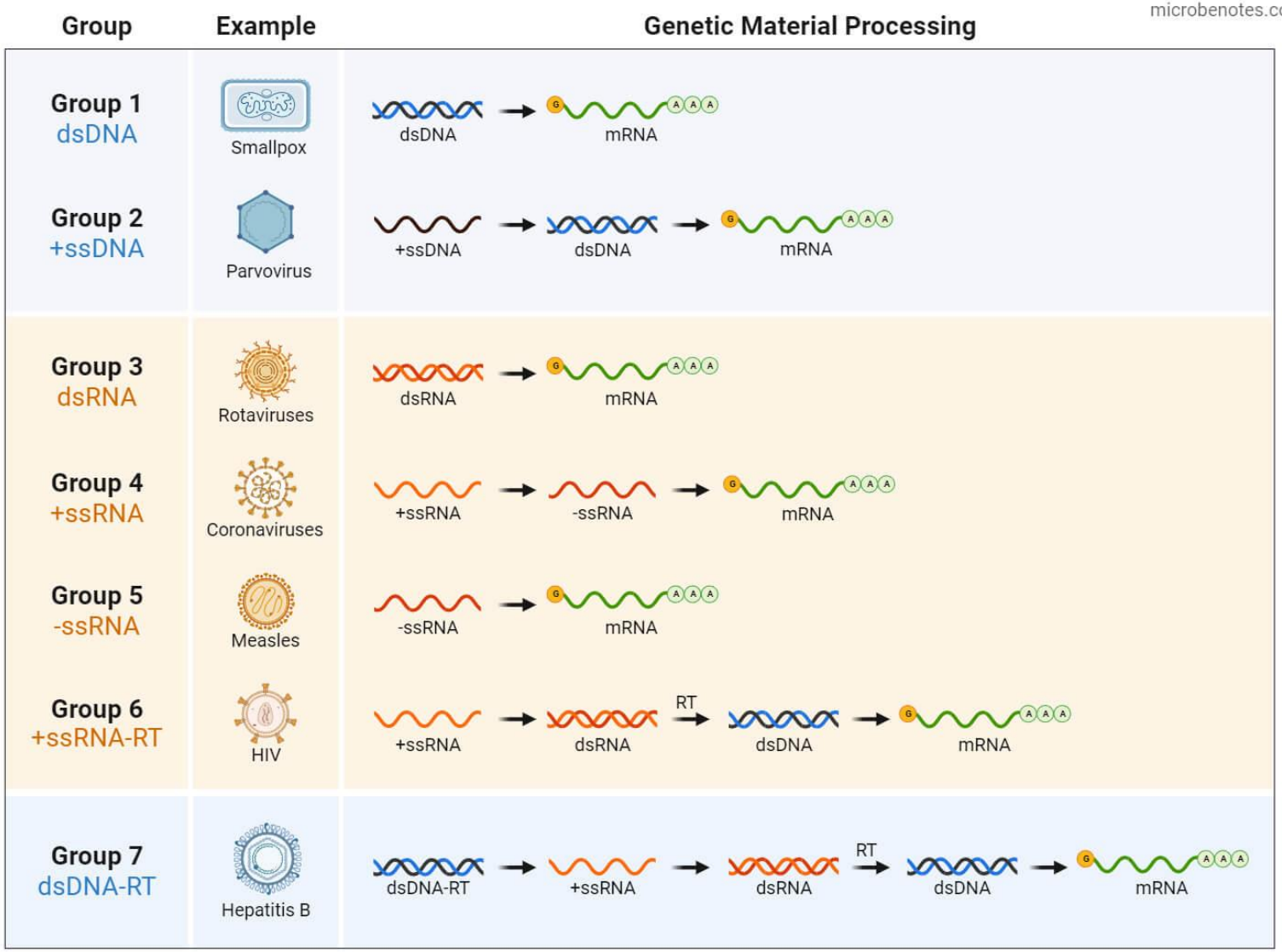


PALAEOVIROLOGY

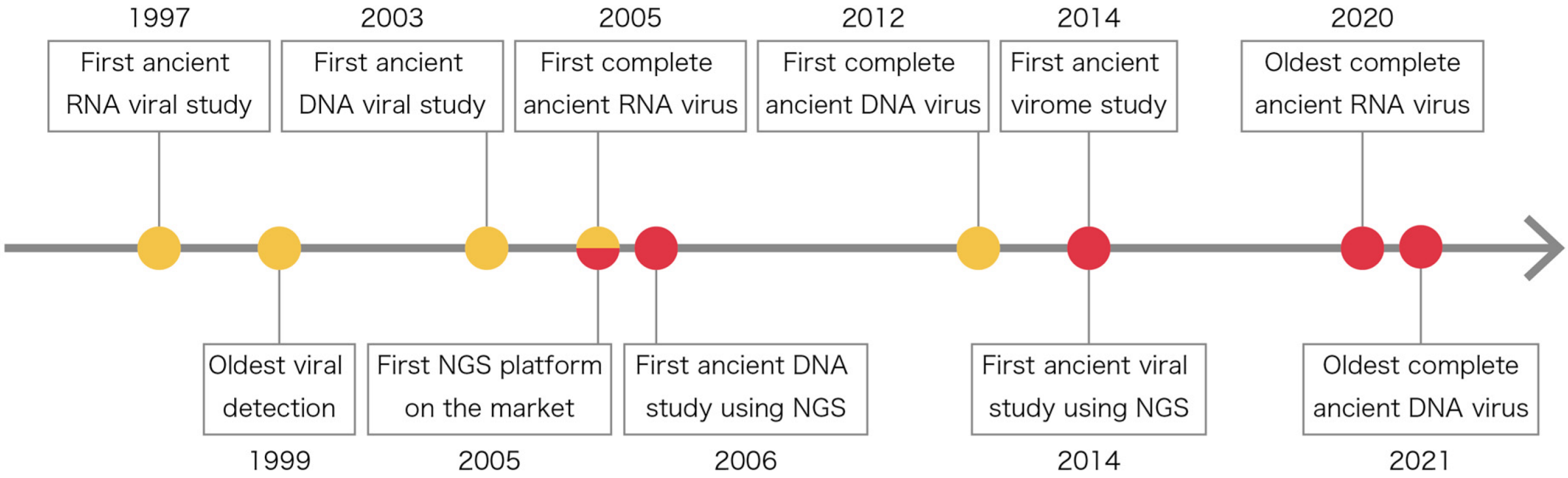
- Research of ancient viruses and their co-evolution with hosts
- Small genome, often tissue specific
- RNA and ssDNA challenging

- Ancient viruses, ancient host genomes
- Modern genomes of hosts
  - Endogenous viral element (EVE) – viral sequences integrated into genome through various mechanisms, including transposition
  - Endogenous retrovirus (ERV) – subset of EVEs, retroviruses in the genome of their hosts – evolutionary history

Baltimore Classification of Viruses



PALAEOVIROLOGY



Nishimura et al., 2022; DOI: 10.3390/v14061336

VARIOLA VIRUS

Research articles

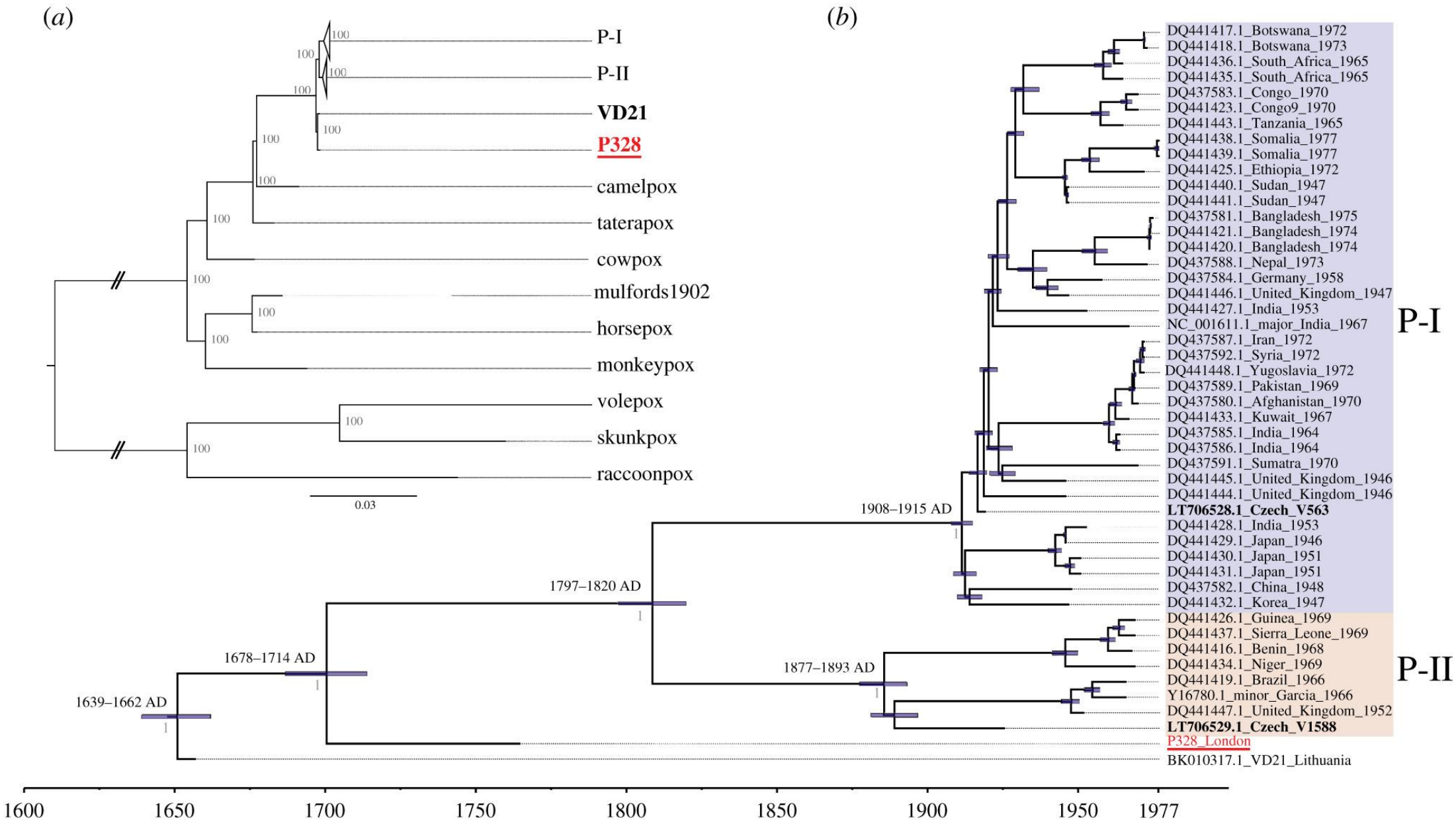
Variola virus genome sequenced from an eighteenth-century museum specimen supports the recent origin of smallpox

Giada Ferrari† ✉, Judith Neukamm† ✉, Helle T. Baalsrud, Abagail M. Breidenstein, Mark Ravinet, Carina Phillips, Frank Rühli, Abigail Bouwman‡ ✉ and Verena J. Schuenemann‡ ✉

Published: 05 October 2020 | https://doi.org/10.1098/rstb.2019.0572

- Was thought to originate around 3000–4000 years ago

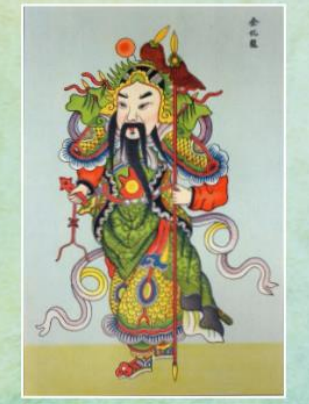
Ṣòpòna - James Gathany



Ferrari et al., 2020 DOI: 10.1098/rstb.2019.0572

THE SPREAD AND ERADICATION OF SMALLPOX

https://www.cdc.gov/smallpox/history/smallpox-origin.html

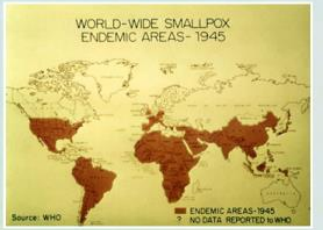


In China, people appealed to the god Yo Hoa Long for protection from smallpox.

Smallpox goddess Shitala Mata, worshipped in northern India, was considered both the cause and cure of smallpox disease.

West African god of smallpox Shapona was thought to force the disease upon humans due to his "divine displeasure."

A container used to store the powdery variolation material in Ethiopia.



Worldwide distribution of smallpox and the countries in which it was endemic in 1945.

Smallpox is present in the Egyptian Empire.

Increased trade with China and Korea introduces smallpox into Japan.

Smallpox spreads to Asia Minor, the area of present-day Turkey.

Population expansion and more frequent travel renders smallpox endemic in previously unaffected Central and North Europe, with severe epidemics occurring as far as Iceland.

European colonization and the African slave trade import smallpox into the Caribbean and Central and South America.

Variolation—a process of grinding up dried smallpox scabs from a smallpox patient and inhaling them or scratching them into an arm of an uninfected person—is being used in China and India to control smallpox.

Variolation is introduced into England by Lady Mary Wortley Montagu, a wife of the British ambassador in Turkey.

In 1796, Edward Jenner, an English doctor, shows the effectiveness of previous cowpox infection in protecting people from smallpox, forming the basis for vaccination.

3RD CENTURY BCE	4TH CENTURY BCE	6TH CENTURY	7TH CENTURY	10TH CENTURY	11TH CENTURY	13TH CENTURY	15TH CENTURY	16TH CENTURY	17TH CENTURY	18TH CENTURY	20TH CENTURY

A written description of a disease that clearly resembles smallpox appears in China.

Smallpox is widespread in India. Arab expansion spreads smallpox into northern Africa, Spain, and Portugal.

Crusades further contribute to the spread of smallpox in Europe with the European Christians moving to and from the Middle East during the next two centuries.

Portuguese expeditions to African west coast and new trade routes with eastern parts of Africa introduce the disease into West Africa.

Variolation is a commonly used method for preventing smallpox in the Ottoman Empire (former Asia Minor, present-day Turkey) and North Africa.

European colonization imports smallpox into North America.

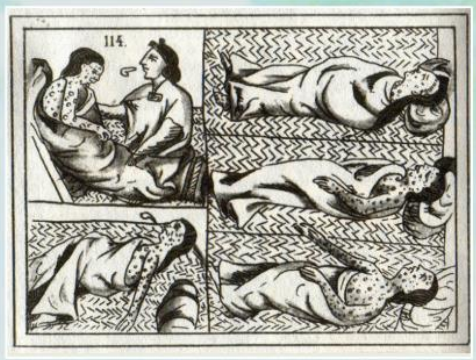
Smallpox is widespread in Africa, Asia, and South America in the early 1900s, while Europe and North America have smallpox largely under control through the use of mass vaccination.

After a global eradication campaign that lasted more than 20 years, the 33rd World Health Assembly officially declares the world free of smallpox in 1980.

Traces of smallpox pustules were found on the head of a 3,000-year-old mummy of the Pharaoh Ramses V.

Japanese woman defeats the "smallpox demon" by wearing red. In Japan, families who fell sick with smallpox set up shrines in their homes to appease the demon.

The Ottoman Empire in 1801 extended from Turkey (Anatolia) to Greece, Hungary, Bulgaria, Romania, northern Africa and parts of Middle East. Smallpox is thought to arrive here from Asia through major trade routes, like the Silk Road.

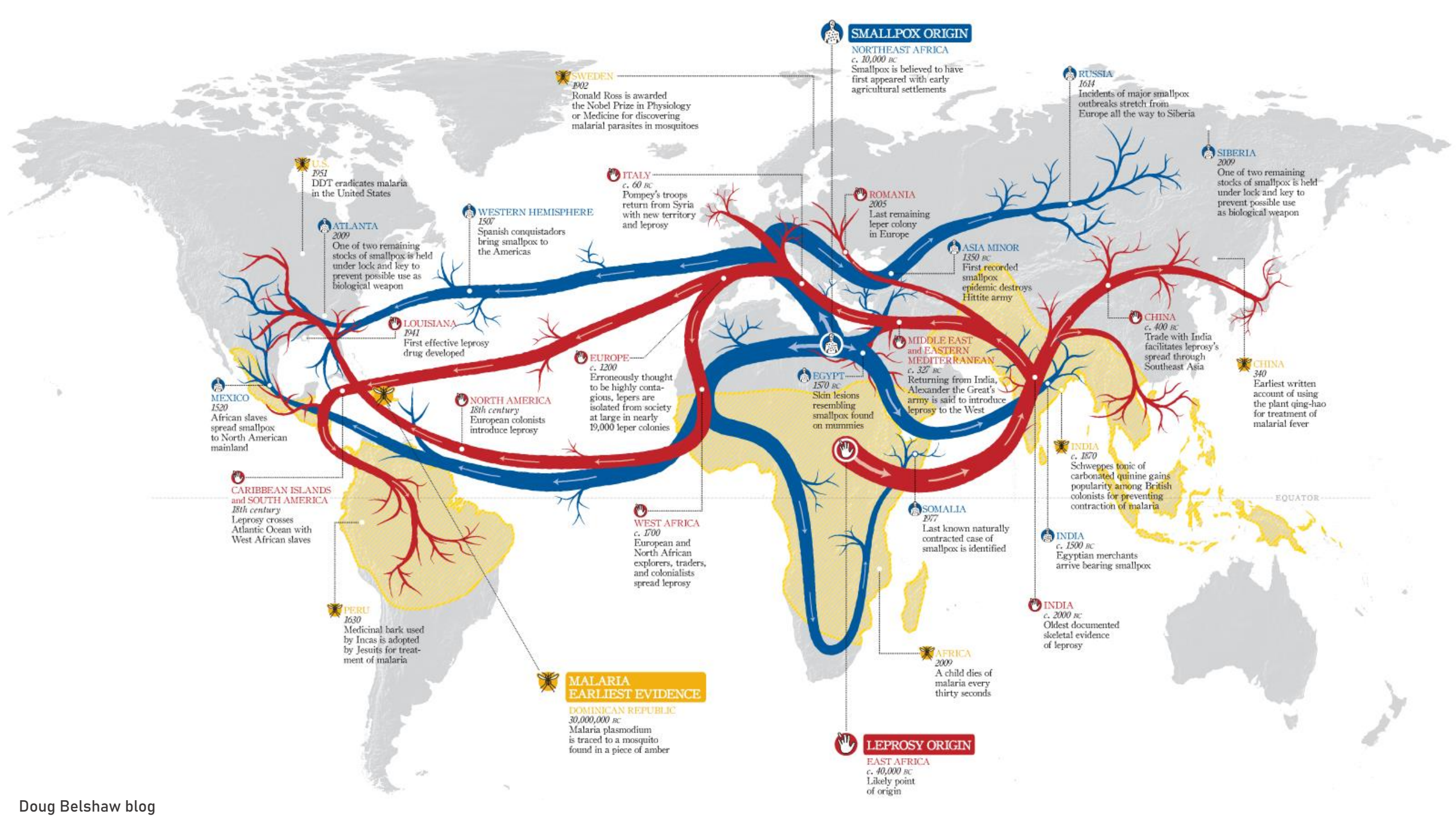


Introduction of smallpox into Mexico by the Spanish around 1520 was one of the factors that led to the demise of Aztec Empire. Franciscan missionary Bernardino de Sahagun, who lived there from 1545 until his death in 1590, illustrated this in his accounts of the Aztec history entitled "General History of the Things of New Spain."

Lady Mary Wortley Montagu, a survivor of smallpox herself, had both of her children variolated and was the foremost advocate of the technique in England.

Edward Jenner (1749-1823)

CS266551-A


SMALLPOX ORIGIN
NORTHEAST AFRICA
c. 10,000 BC
Smallpox is believed to have first appeared with early agricultural settlements
SWEDEN
1902
Ronald Ross is awarded the Nobel Prize in Physiology or Medicine for discovering malarial parasites in mosquitoes
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Incidents of major smallpox outbreaks stretch from Europe all the way to Siberia
SIBERIA
2009
One of two remaining stocks of smallpox is held under lock and key to prevent possible use as biological weapon
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DDT eradicates malaria in the United States
ITALY
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Pompey's troops return from Syria with new territory and leprosy
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2005
Last remaining leper colony in Europe
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1350 BC
First recorded smallpox epidemic destroys Hittite army
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1941
First effective leprosy drug developed
CHINA
c. 400 BC
Trade with India facilitates leprosy's spread through Southeast Asia
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c. 1200
Erroneously thought to be highly contagious, lepers are isolated from society at large in nearly 19,000 leper colonies
MIDDLE EAST and EASTERN MEDITERRANEAN
c. 327 BC
Returning from India, Alexander the Great's army is said to introduce leprosy to the West
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18th century
European colonists introduce leprosy
INDIA
c. 1870
Schweppes tonic of carbonated quinine gains popularity among British colonists for preventing contraction of malaria
EQUATOR
CARIBBEAN ISLANDS and SOUTH AMERICA
18th century
Leprosy crosses Atlantic Ocean with West African slaves
WEST AFRICA
c. 1700
European and North African explorers, traders, and colonialists spread leprosy
SOMALIA
1977
Last known naturally contracted case of smallpox is identified
INDIA
c. 1500 BC
Egyptian merchants arrive bearing smallpox
PERU
1630
Medicinal bark used by Incas is adopted by Jesuits for treatment of malaria
INDIA
c. 2000 BC
Oldest documented skeletal evidence of leprosy
AFRICA
2009
A child dies of malaria every thirty seconds
MALARIA EARLIEST EVIDENCE
DOMINICAN REPUBLIC
30,000,000 BC
Malaria plasmodium is traced to a mosquito found in a piece of amber
LEPROSY ORIGIN
EAST AFRICA
c. 40,000 BC
Likely point of origin

HEPATITIS B VIRUS

- Best studied virus in aDNA
- Global prevalence around 4 %
- Oldest ca 10000 BP

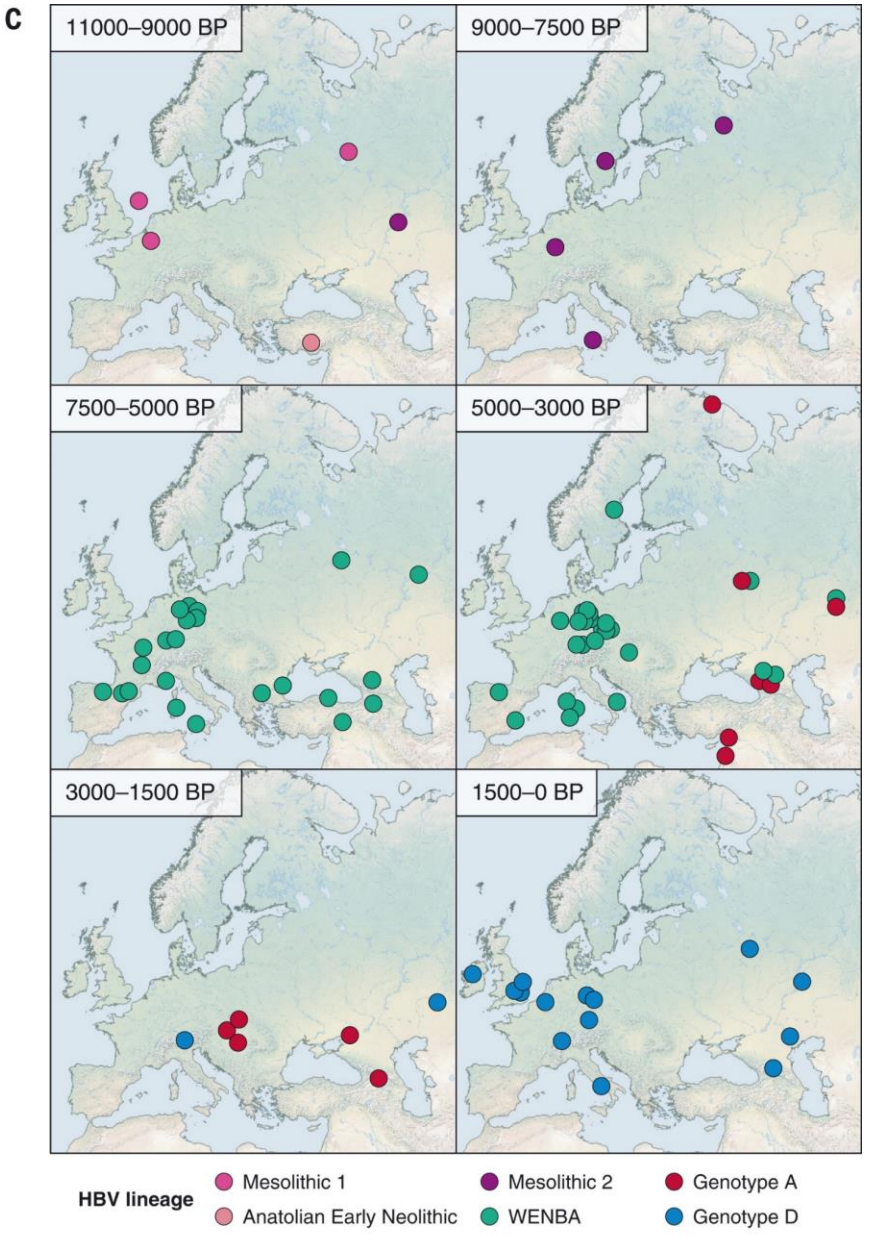
Ten millennia of hepatitis B virus evolution

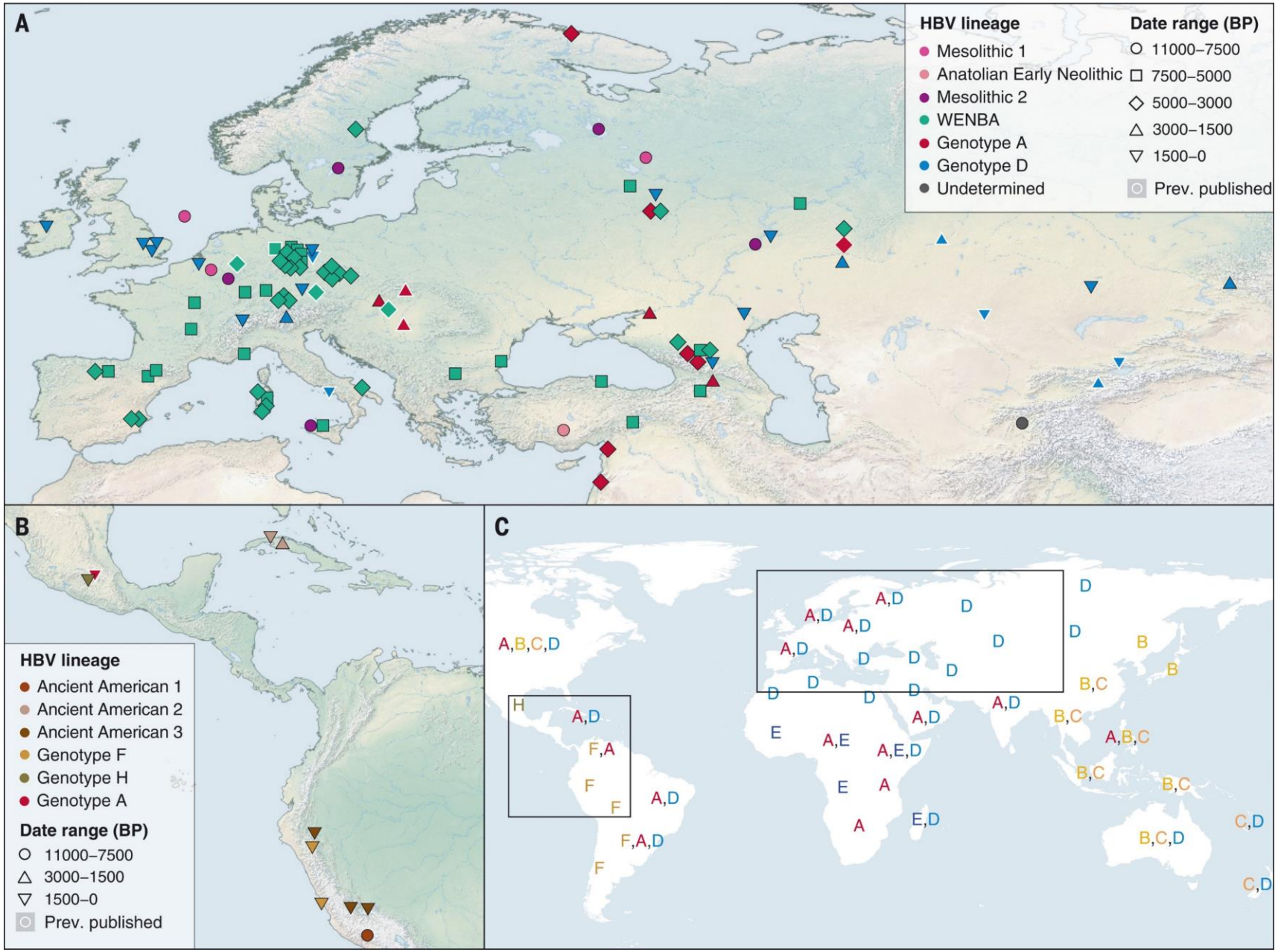
ARTHUR KOCHER, LUKA PAPAC, RODRIGO BARQUERA, FELIX M. KEY, MARIA A. SPYROU, RON HÜBLER, ADAM B. ROHRLACH, FRANZISKA ARON, RAPHAELA STAHL, [...], AND DENISE KÜHNERT +160 authors Authors Info & Affiliations

SCIENCE · 7 Oct 2021 · Vol 374, Issue 6564 · pp. 182-188 · DOI: 10.1126/science.abi5658

Ancient DNA traces the history of hepatitis B

Hepatitis B virus (HBV) infections represent a worldwide human health concern. To study the history of this pathogen, Kocher *et al*. identified 137 human remains with detectable levels of virus dating between 400 and 10,000 years ago. Sequencing and analyses of these ancient viruses suggested a common ancestor between 12,000 and 20,000 years ago. There is no evidence indicating that HBV was present in the earliest humans as they spread out of Africa; however, HBV was likely present in human populations before farming. Furthermore, the virus was present in the Americas by about 9000 years ago, representing a lineage sister to the viral strains found in Eurasia that diverged about 20,000 years ago. —LMZ





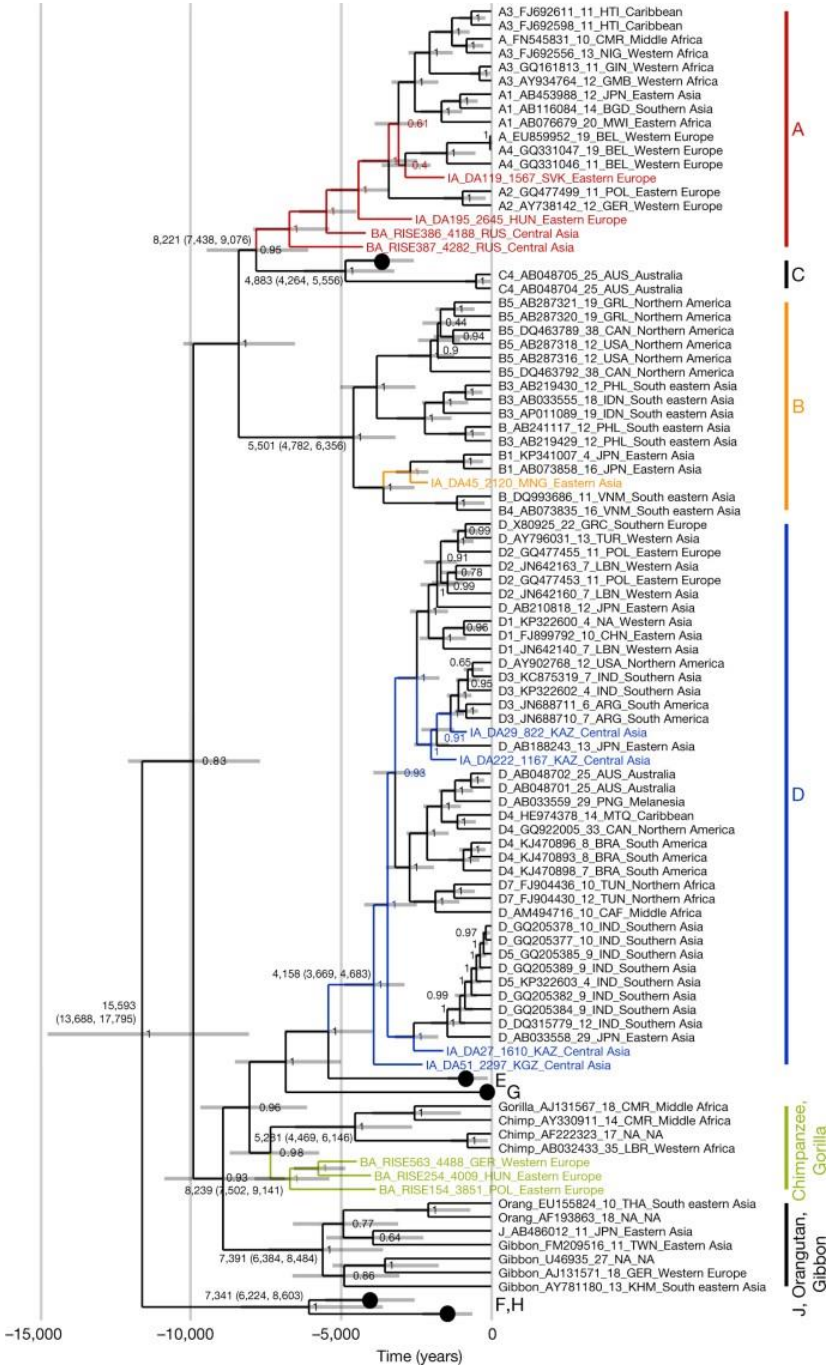
Kocher et al., 2021; DOI: 10.1126/science.abi5658

HEPATITIS B VIRUS

Letter | Published: 09 May 2018

Ancient hepatitis B viruses from the Bronze Age to the Medieval period

Barbara Mühlemann, Terry C. Jones, Peter de Barros Damgaard, Morten E. Allentoft, Irina Shevnina, Andrey Logvin, Emma Usmanova, Irina P. Panyushkina, Bazartseren Boldgiv, Tsevel Bazartseren, Kadicha Tashbaeva, Victor Merz, Nina Lau, Václav Smrčka, Dmitry Voyakin, Egor Kitov, Andrey Epimakhov, Dalia Pokutta, Magdolna Vicze, T. Douglas Price, Vyacheslav Moiseyev, Anders J. Hansen, Ludovic Orlando, Simon Rasmussen, Martin Sikora, Lasse Vinner, Albert D. M. E. Osterhaus, Derek J. Smith, Dieter Glebe, Ron A. M. Fouchier, Christian Drosten, Karl-Göran Sjögren, Kristian Kristiansen & Eske Willerslev



PLANT VIRUSES

- Barley stripe mosaic virus
- Herbarium specimens, seeds, dry leaves…

Article | Open access | Published: 20 July 2023

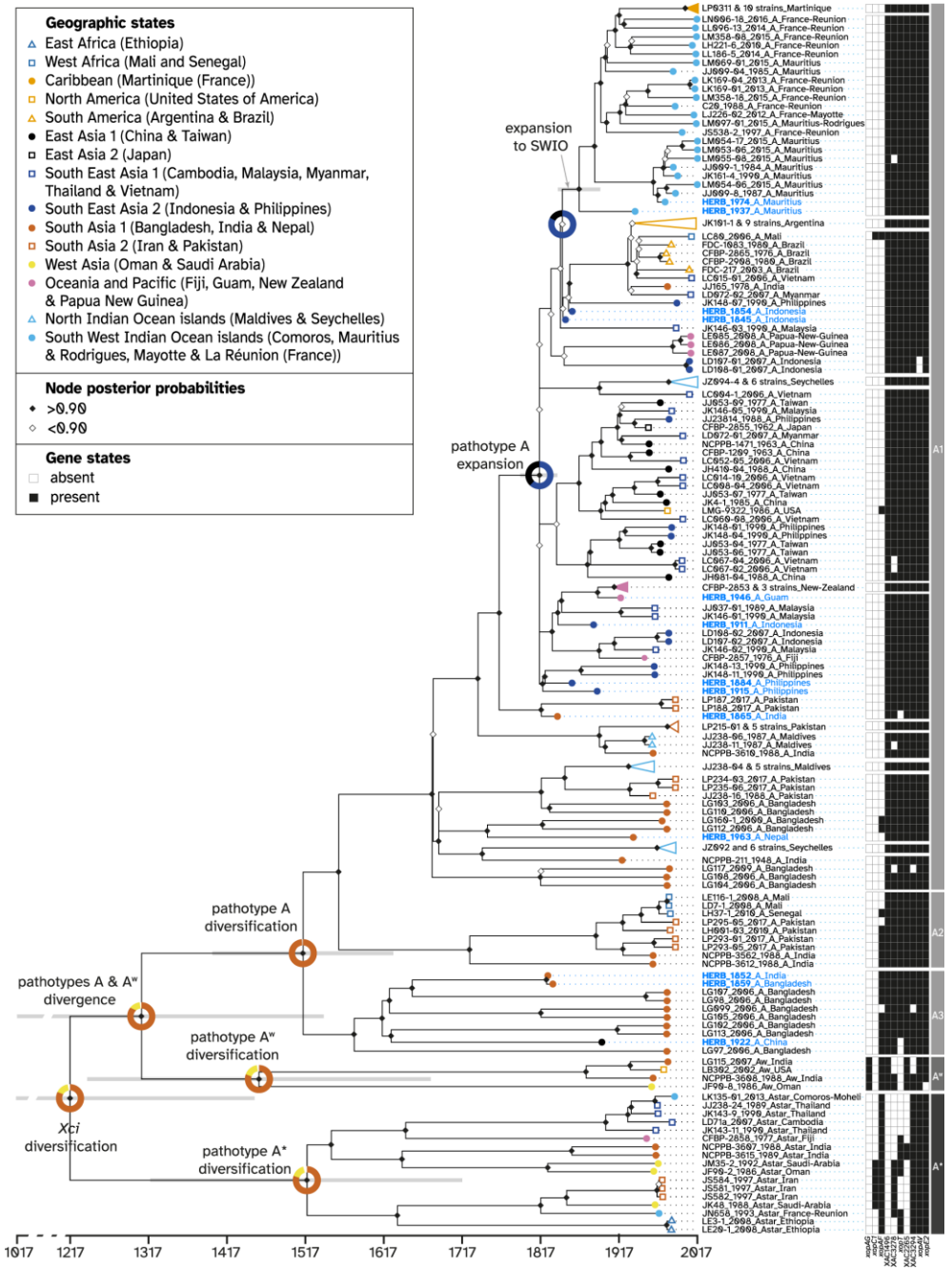
Herbarium specimen sequencing allows precise dating of *Xanthomonas citri* pv. *citri* diversification history

Paola E. Campos, Olivier Pruvost, Karine Boyer, Frederic Chiroleu, Thuy Trang Cao, Myriam Gaudeul, Cláudia Baider, Timothy M. A. Utteridge, Nathalie Becker, Adrien Rieux ✉ & Lionel Gagnevin ✉

Nature Communications **14**, Article number: 4306 (2023) | Cite this article

Abstract

Herbarium collections are an important source of dated, identified and preserved DNA, whose use in comparative genomics and phylogeography can shed light on the emergence and evolutionary history of plant pathogens. Here, we reconstruct 13 historical genomes of the bacterial crop pathogen *Xanthomonas citri* pv. *citri* (*Xci*) from infected *Citrus* herbarium specimens. Following authentication based on ancient DNA damage patterns, we compare them with a large set of modern genomes to estimate their phylogenetic relationships, pathogenicity-associated gene content and several evolutionary parameters. Our results indicate that *Xci* originated in Southern Asia ~11,500 years ago (perhaps in relation to Neolithic climate change and the development of agriculture) and diversified during the beginning of the 13th century, after *Citrus* diversification and before spreading to the rest of the world (probably via human-driven expansion of citriculture through early East-West trade and colonization).



BIOSAFETY

- Should such research take place?
- Should the methodology and genome be published? (Critique surrounding 1918 influenza virus)

- *Pithovirus sibericum* resurrection – infection of *Acanthamoeba*, >30,000-y-old

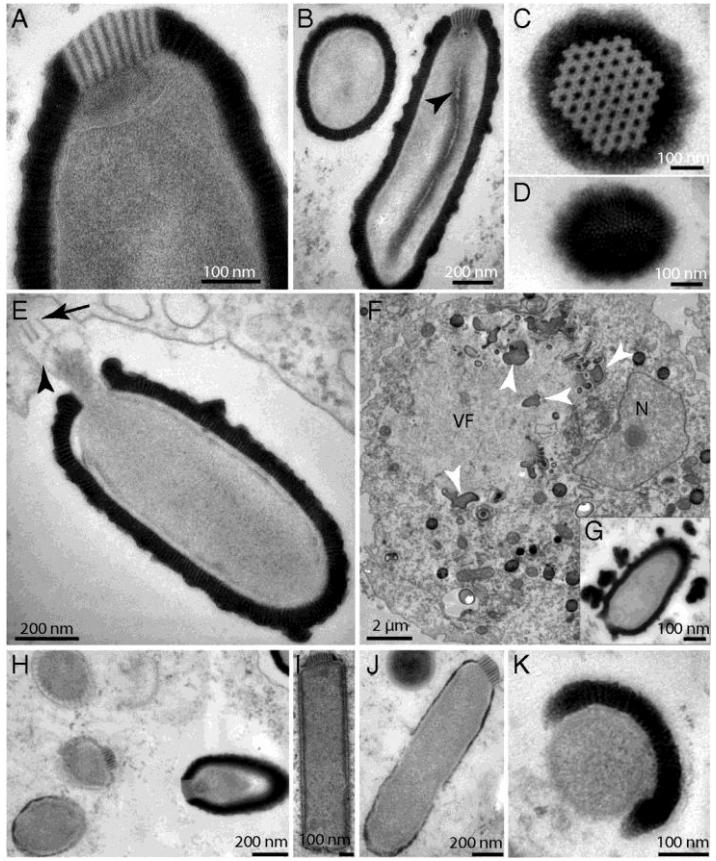
- Global warming, mining and drilling – potential threat from frozen viruses

Thirty-thousand-year-old distant relative of giant icosahedral DNA viruses with a pandoravirus morphology

Matthieu Legendre, Julia Bartoli, Lyubov Shmakova, +10, and Jean-Michel Claverie Authors Info & Affiliations

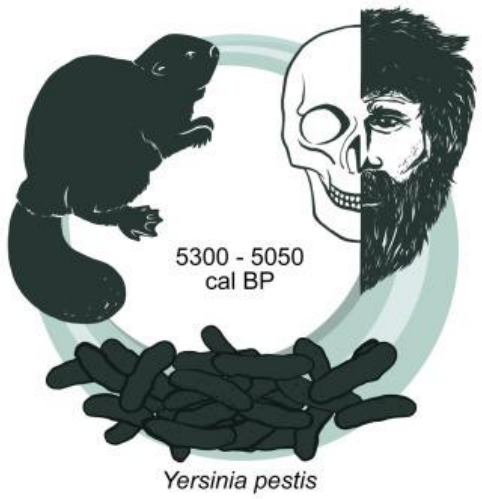
Edited by James L. Van Etten, University of Nebraska–Lincoln, Lincoln, NE, and approved January 30, 2014 (received for review November 7, 2013)

March 3, 2014 | 111 (11) 4274-4279 | https://doi.org/10.1073/pnas.1320670111



YERSINIA PESTIS

- Rodent reservoir, flea as a vector
- After infection
  - pathogen travels to lymph nodes causing bubonic plague (swelling – buboes)
  - lung infection – pneumonic
  - disseminated – septicemic
- Oldest case 5000 BP, probable emergence of this lineage 7000 BP during Neolithic

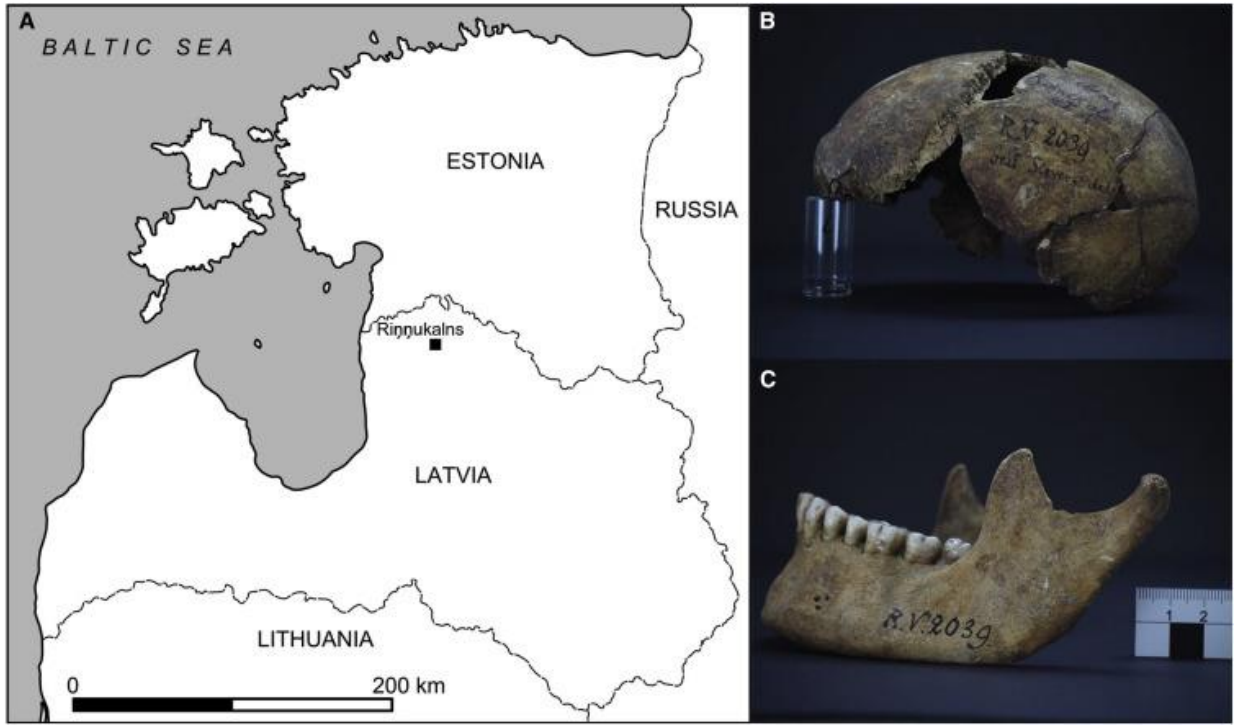


Volume 35, Issue 13, 29 June 2021, 109278

Report

A 5,000-year-old hunter-gatherer already plagued by *Yersinia pestis*

Julian Susat [1 11], Harald Lübke [2 11], Alexander Immel [1], Ute Brinker [2], Aija Macāne [3], John Meadows [2 4], Britta Steer [5], Andreas Tholey [5], Ilga Zagorska [6], Guntis Gerhards [6], Ulrich Schmölcke [2], Mārcis Kalniņš [6], Andre Franke [1], Elīna Pētersone-Gordina [6], Barbara Teßman [7], Mari Tõrv [8], Stefan Schreiber [1 9], Christian Andree [10], Valdis Bērziņš [6], Almut Nebel [1], Ben Krause-Kyora [1 12]



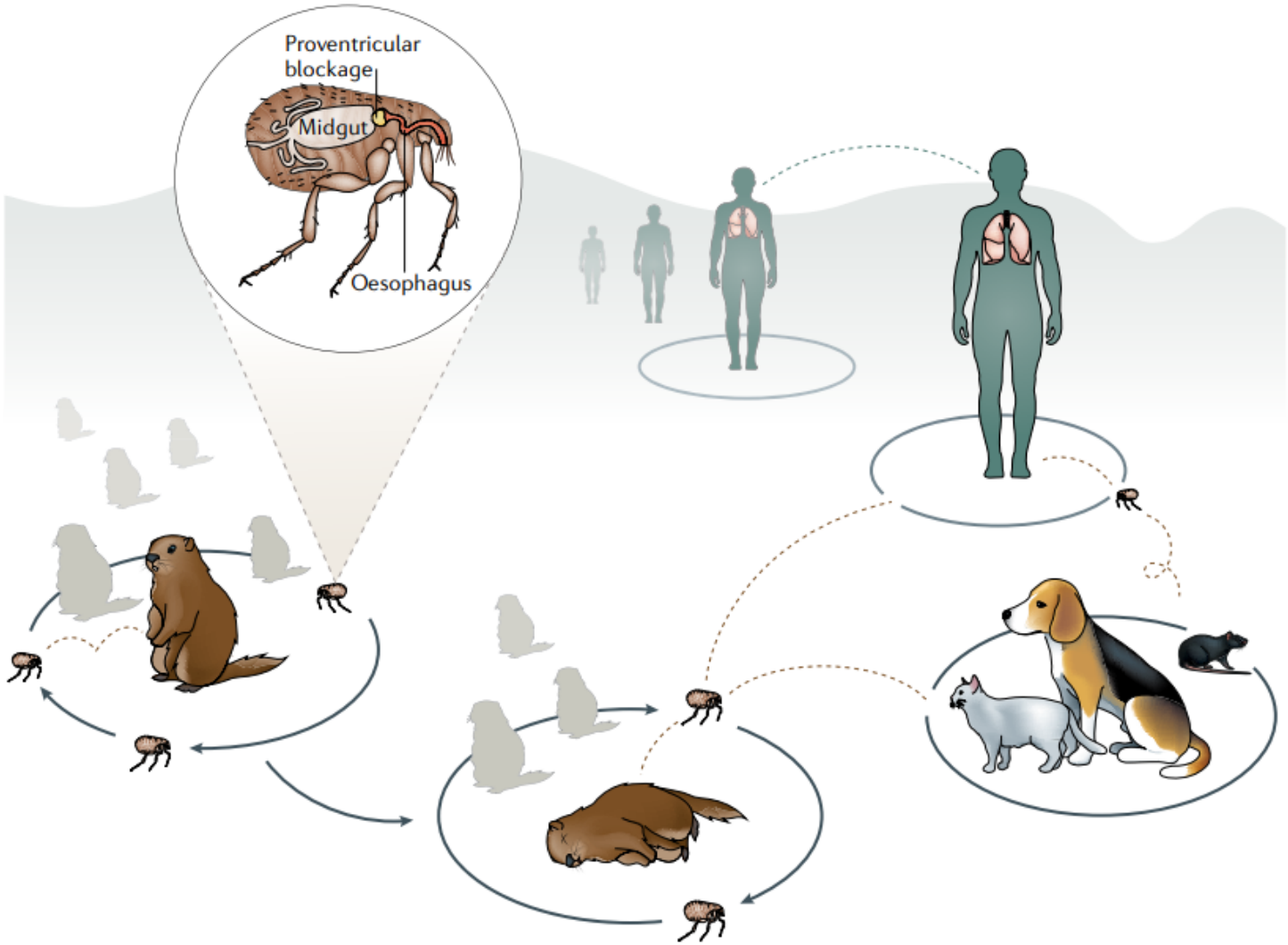


Fig. 5 | ***Yersinia pestis* ecology and transmission cycle.** A simplified version of the *Yersinia pestis* enzootic cycle, during which the bacterium is maintained among wild rodent populations through a flea-dependent transmission mechanism. Under poorly understood circumstances, plague epizootics, which are best explained as animal epidemics, can occur among susceptible rodent populations. During those periods, humans and other mammals are at highest risk of becoming infected with *Y. pestis*. Plague can manifest in humans in the bubonic, pneumonic and septicaemic forms. Pneumonic plague is the only form that can result in airborne transmission between humans.

Spyrou et al., 2019; DOI: 10.1038/s41576-019-0119-1

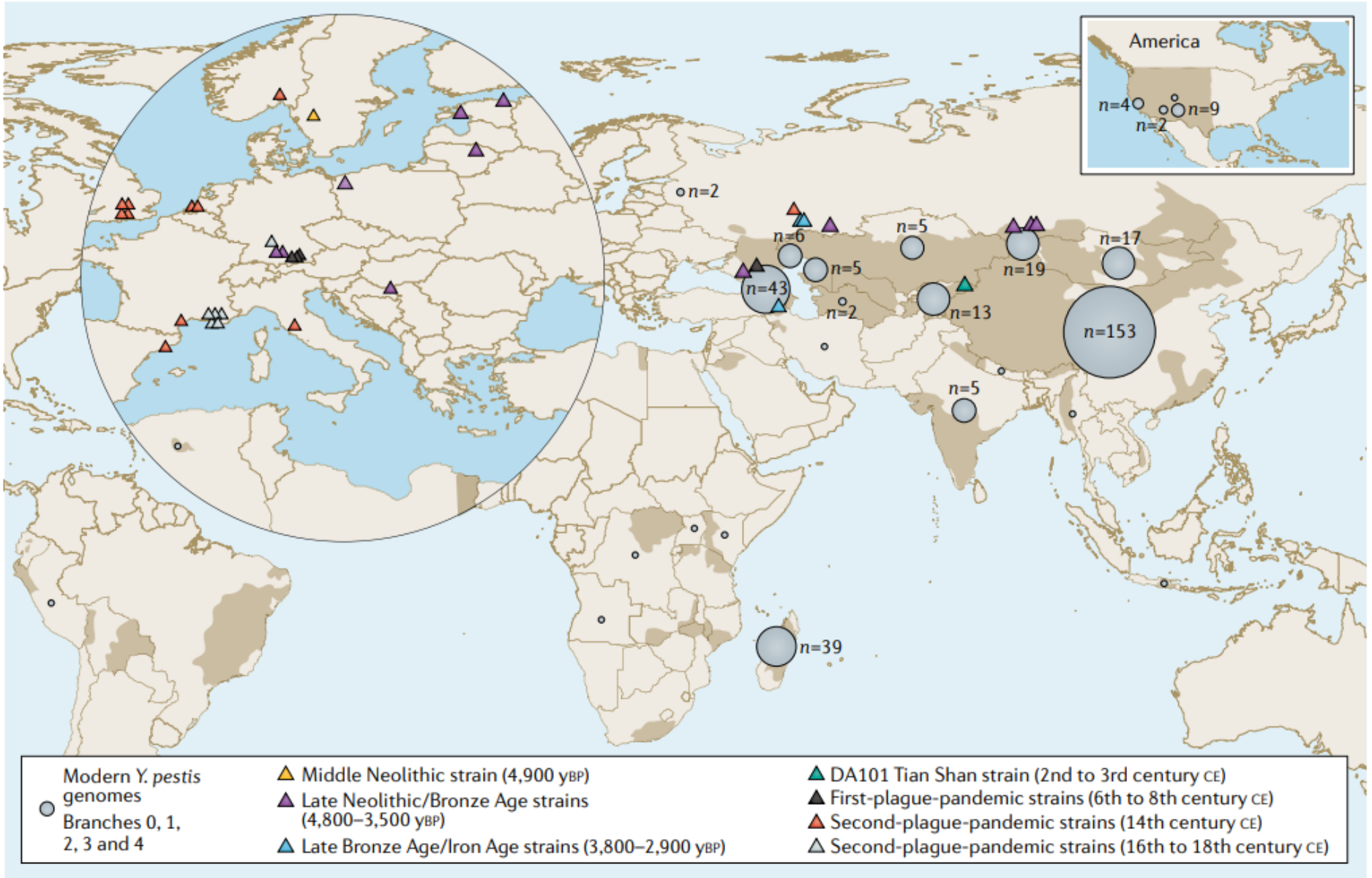


Fig. 4 | **Map of published modern and ancient *Yersinia pestis* genomes.** Published ancient specimens that have yielded whole *Yersinia pestis* genomes and genome-wide data are shown in triangles (n = 38), and their different colours indicate time period distinctions. A set of modern *Y. pestis* genomes (n = 336), from the following publications (released until 2018)[92,130,169–173,187–199,200], are shown as grey circles within their geographical country or region of isolation, and the size of each circle is proportional to the number of strains sequenced from each location (number indicated when more than one genome is shown). The areas highlighted in brown are regions that contain active plague foci as determined by contemporary or historical data. yBP, years before present. Adapted with permission from the 'Global distribution of natural plague foci as of March 2016' from https://www.who.int/csr/disease/plague/Plague-map-2016.pdf.

Spyrou et al., 2019; DOI: 10.1038/s41576-019-0119-1

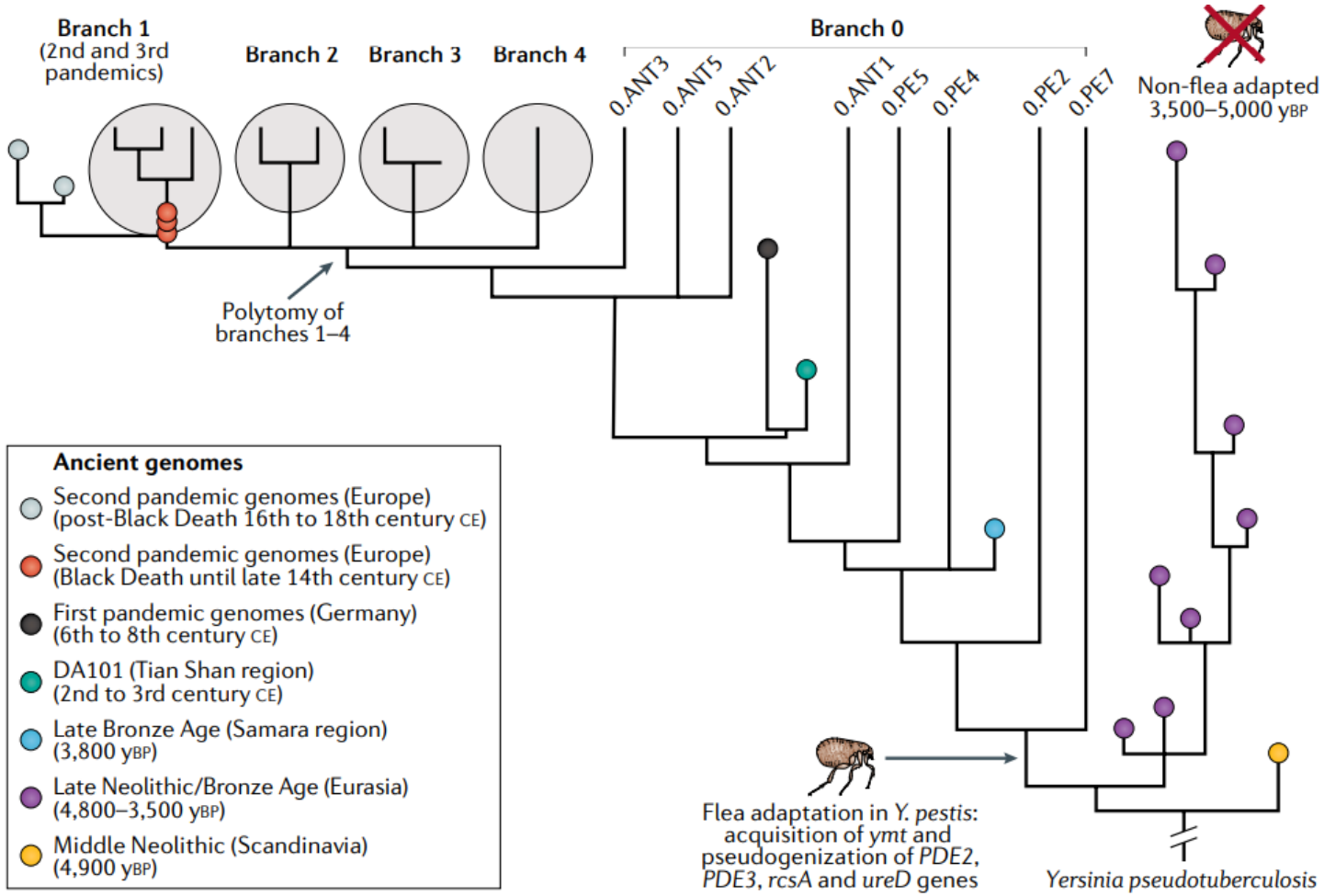


Fig. 6 | **Evolutionary history of *Yersinia pestis*.** A phylogenetic tree graphic depicting the evolutionary history of *Yersinia pestis* based on both ancient and modern genomes. Ancient strains that have been previously characterized by phylogenetic analysis are represented with coloured circles among the tree branches as follows: a Middle Neolithic genome is shown in yellow; Late Neolithic and Bronze Age (LNBA) genomes are shown in purple; a Late Bronze Age genome (RT5) encompassing signatures of flea adaptation is shown in blue; a pre-Justinian, 2nd century of the current era (CE), genome is shown in green; first-plague-pandemic genomes are shown in black; second plague pandemic, 14th-century genomes are shown in red; and post-Black Death (up until 18th century CE) genomes are shown in grey. Modern lineages are simplified and shown as branches of equal length in order to enhance the clarity of the graphic. The geographical distribution of modern strains is as follows (using universal country abbreviations): branch 1 (UGA, DRC, KEN, DZA, MDG, CHN, IND, IDN, MNM, USA and PER), branch 2 (RUS, AZE, KAZ, KGZ, UZB, TKM, CHN, IRN and NPL), branch 3 (CHN and MNG), branch 4 (RUS and MNG) and branch 0, including lineages 0.ANT3 (CHN and KGZ), 0.ANT5 (KGZ and KAZ), 0.ANT2 (CHN), 0.ANT1 (CHN), 0.PE5 (MNG), 0.PE4 (TJK, UZB, KGZ, RUS, CHN and MNG), 0.PE2 (GEO, ARM, AZE and RUS) and 0.PE7 (CHN). yBP, years before present.

Spyrou et al., 2019; DOI: 10.1038/s41576-019-0119-1

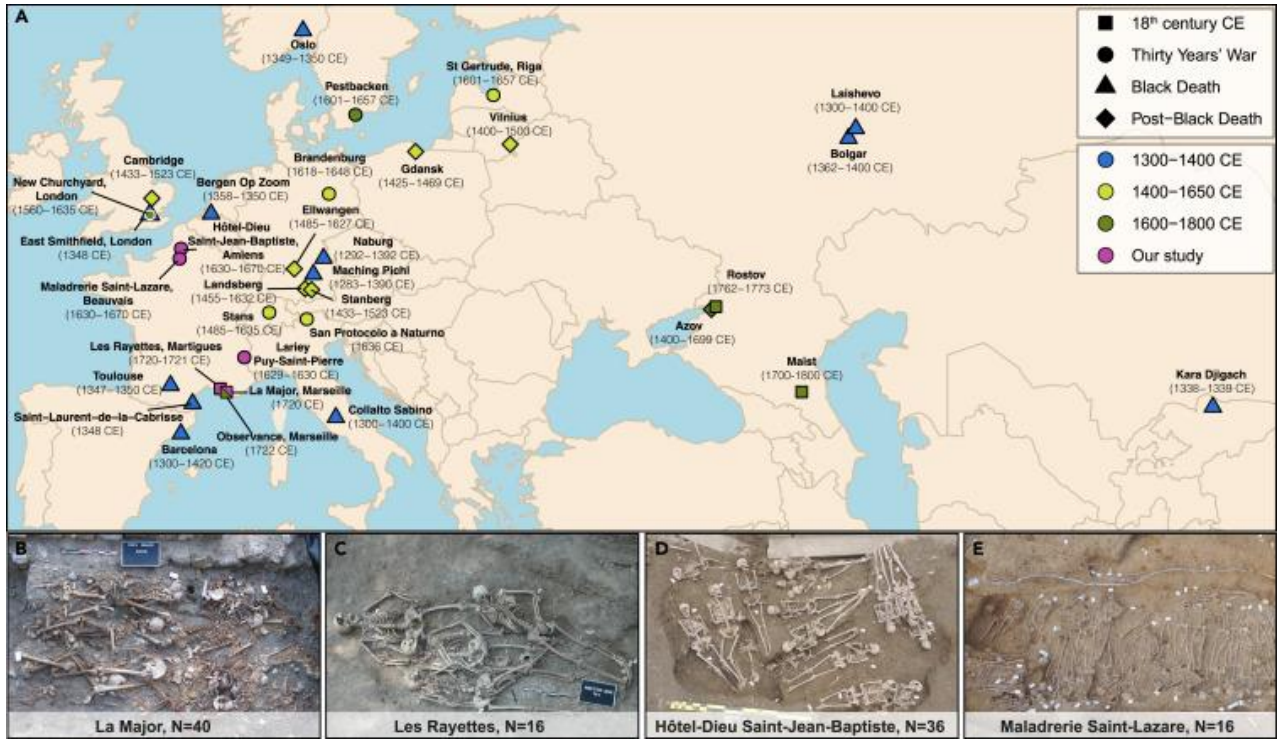
YERSINIA PESTIS

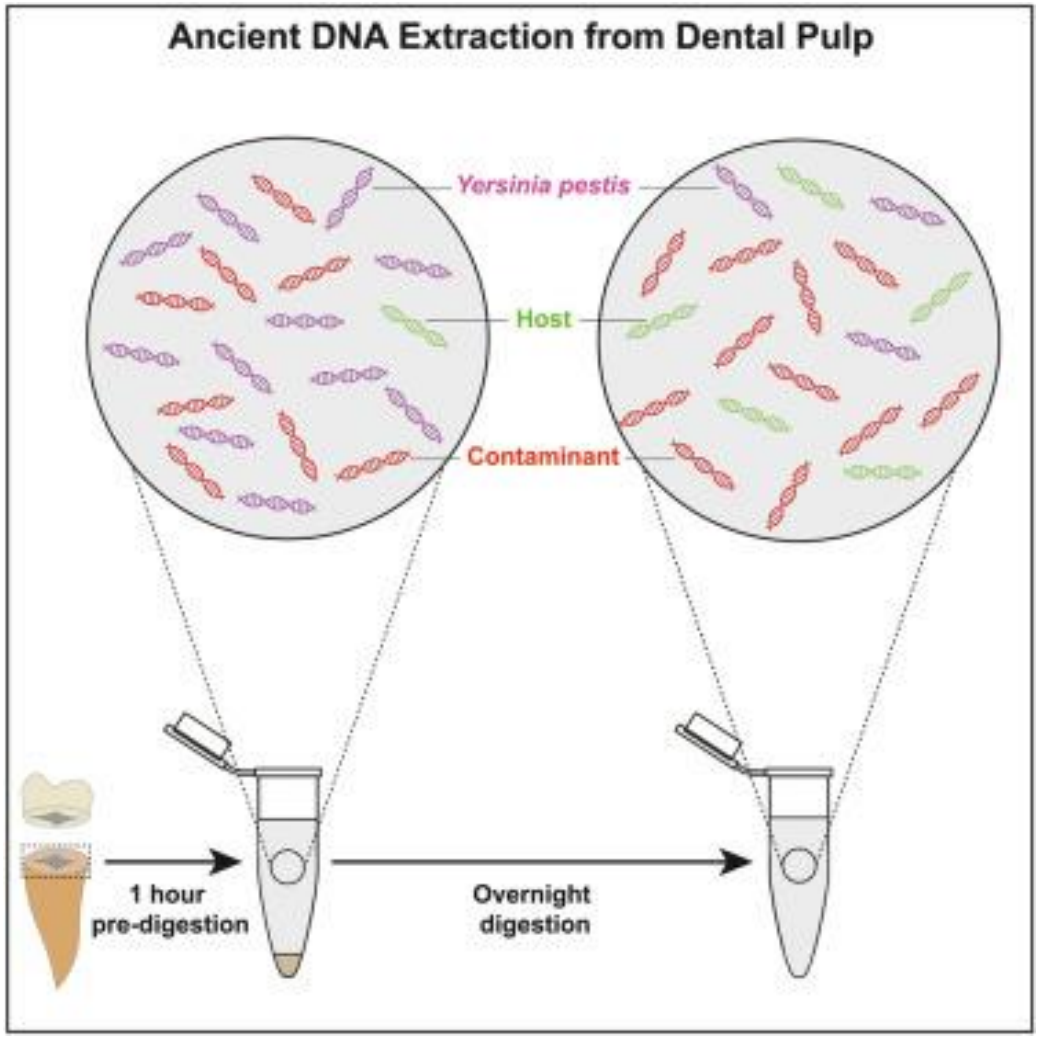
Volume 26, Issue 5, 19 May 2023, 106787

Article

Improving the extraction of ancient *Yersinia pestis* genomes from the dental pulp

Pierre Clavel [1], Lexane Louis [1], Clio Der Sarkissian [1], Catherine Thèves [1], Claudia Gillet [1], Lorelei Chauvey [1], Gaétan Tressières [1], Stéphanie Schiavinato [1], Laure Calvière-Tonasso [1], Norbert Telmon [1], Benoît Clavel [2], Richard Jonvel [3], Stéfan Tzortzis [4], Laetitia Bouniol [5], Jean-Marc Fémolant [5], Jennifer Klunk [6], Hendrik Poinar [7 8 9], Michel Signoli [10], Caroline Costedoat [10], Maria A. Spyrou [11], Andaine Seguin-Orlando [1], Ludovic Orlando [1 12]





MYCOBACTERIUM TUBERCULOSIS

Home > Genome Biology > Article

A seventeenth-century *Mycobacterium tuberculosis* genome supports a Neolithic emergence of the *Mycobacterium tuberculosis* complex

Research | Open access | Published: 10 August 2020
Volume 21, article number 201, (2020) Cite this article

Background

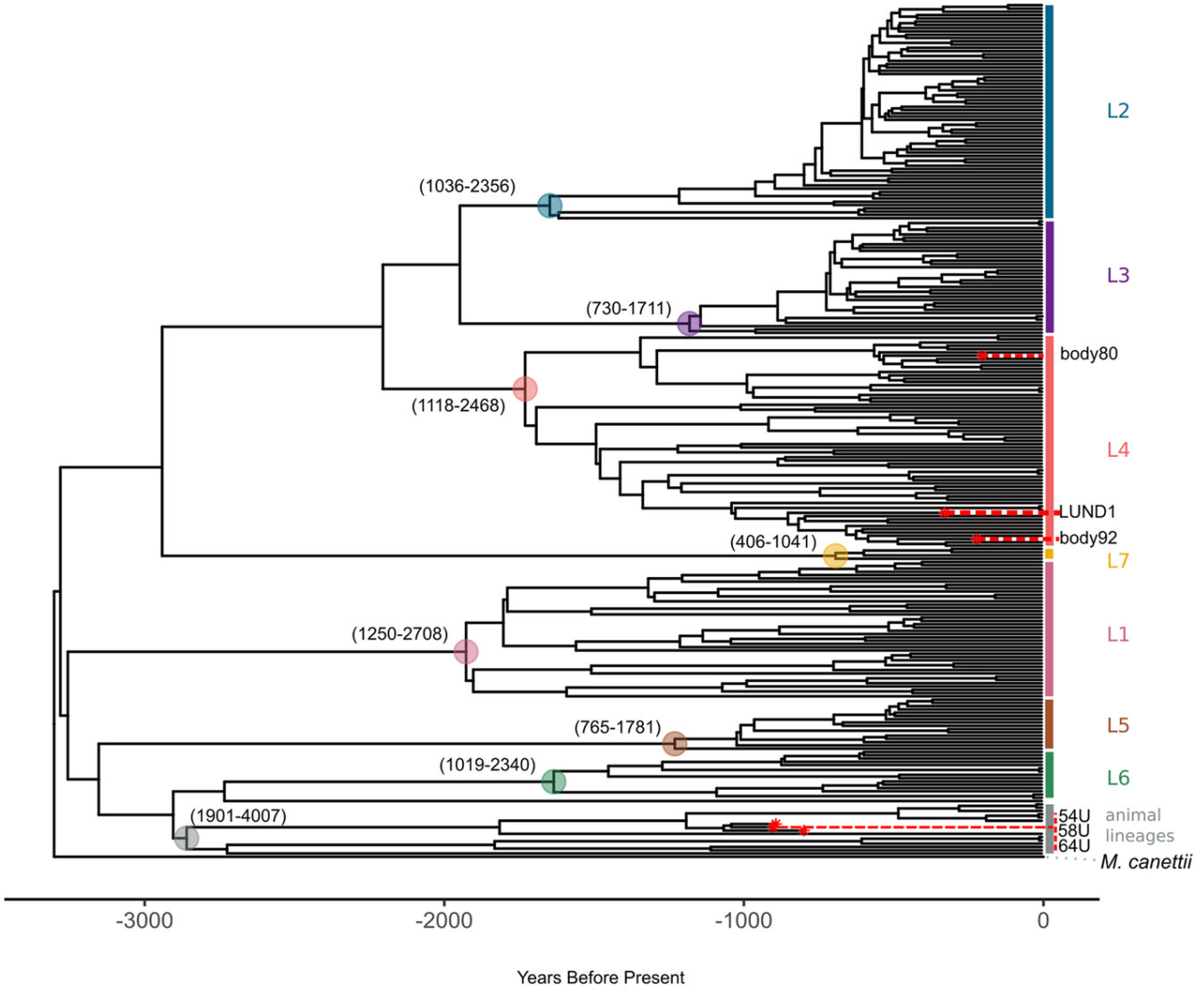
Although tuberculosis accounts for the highest mortality from a bacterial infection on a global scale, questions persist regarding its origin. One hypothesis based on modern *Mycobacterium tuberculosis* complex (MTBC) genomes suggests their most recent common ancestor followed human migrations out of Africa approximately 70,000 years before present. However, studies using ancient genomes as calibration points have yielded much younger dates of less than 6000 years. Here, we aim to address this discrepancy through the analysis of the highest-coverage and highest-quality ancient MTBC genome available to date, reconstructed from a calcified lung nodule of Bishop Peder Winstrup of Lund (b. 1605–d. 1679).

Results

A metagenomic approach for taxonomic classification of whole DNA content permitted the identification of abundant DNA belonging to the human host and the MTBC, with few non-TB bacterial taxa comprising the background. Genomic enrichment enabled the reconstruction of a 141-fold coverage *M. tuberculosis* genome. In utilizing this high-quality, high-coverage seventeenth-century genome as a calibration point for dating the MTBC, we employed multiple Bayesian tree models, including birth-death models, which allowed us to model pathogen population dynamics and data sampling strategies more realistically than those based on the coalescent.

Conclusions

The results of our metagenomic analysis demonstrate the unique preservation environment calcified nodules provide for DNA. Importantly, we estimate a most recent common ancestor date for the MTBC of between 2190 and 4501 before present and for Lineage 4 of between 929 and 2084 before present using multiple models, confirming a Neolithic emergence for the MTBC.

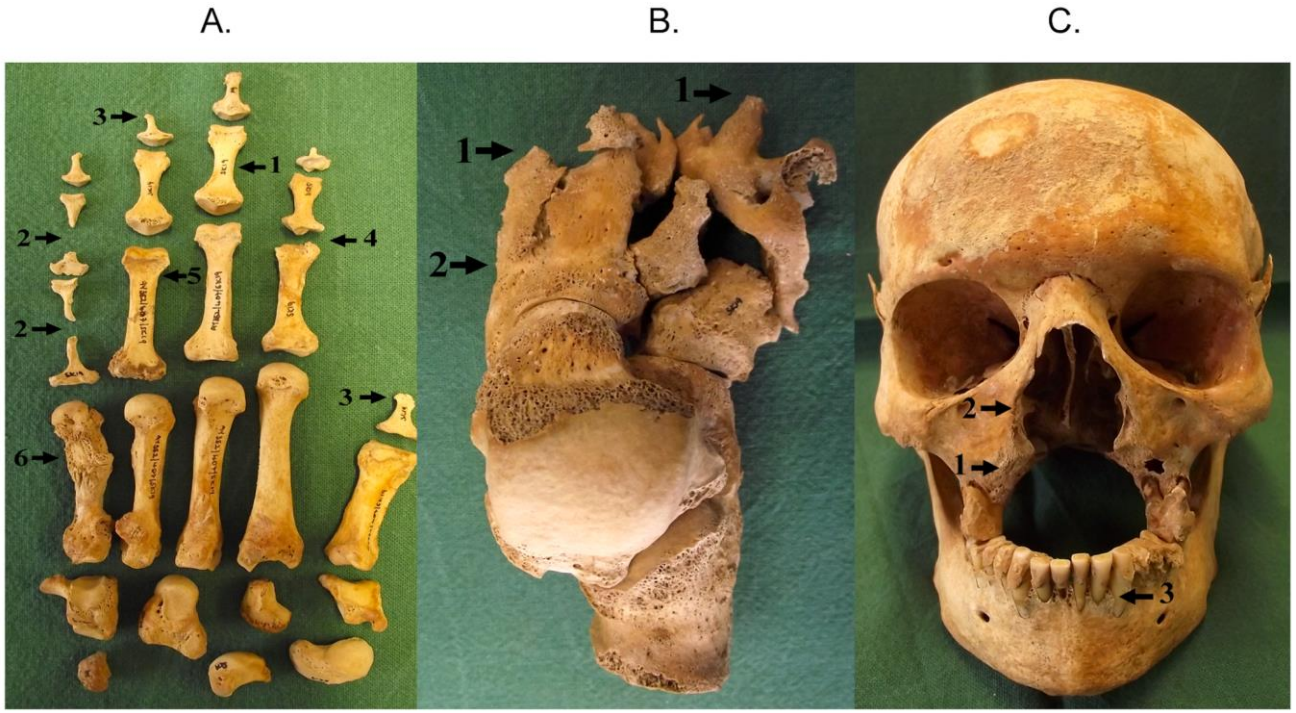


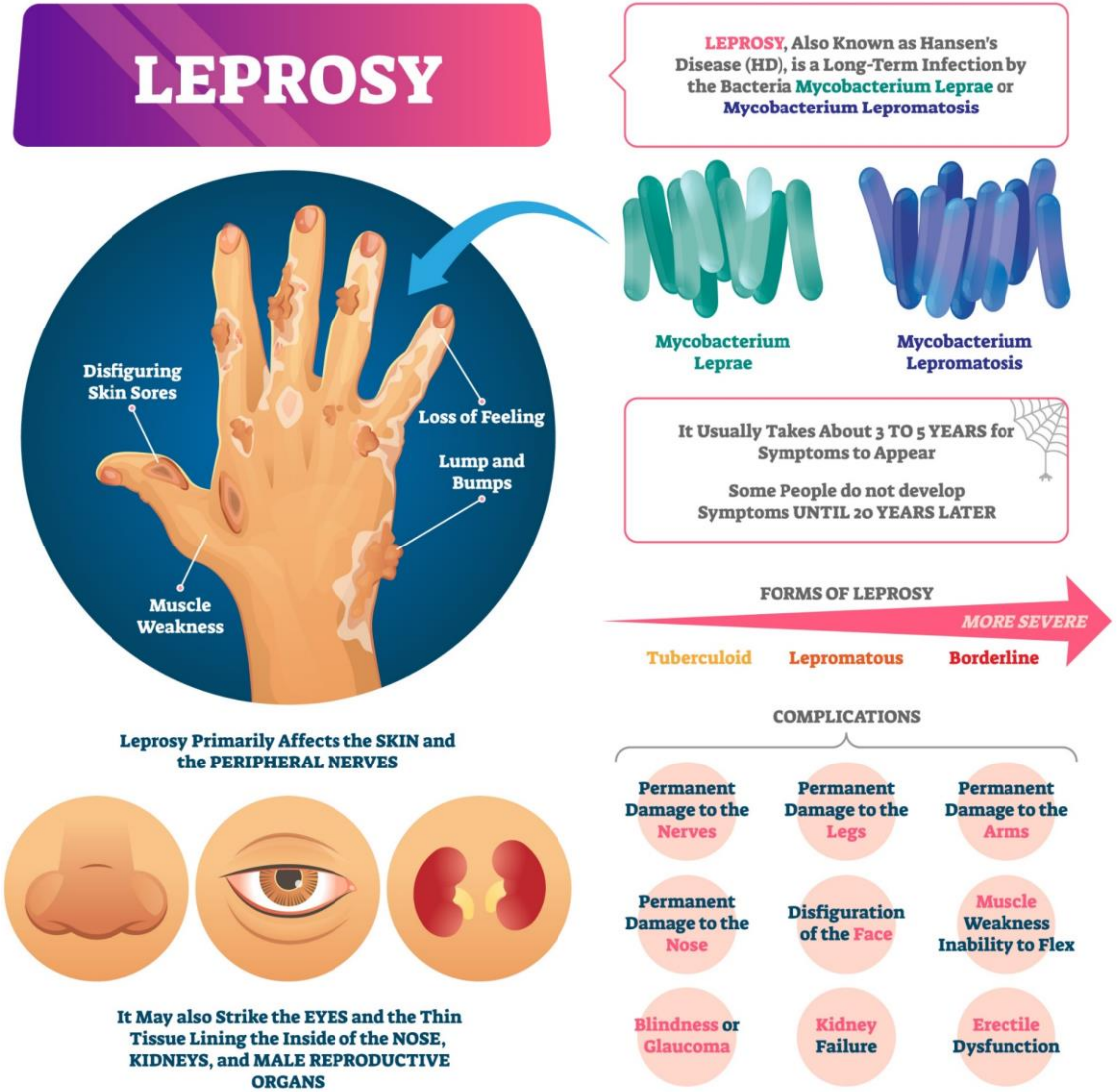
MYCOBACTERIUM LEPRAE

Detection and Strain Typing of Ancient *Mycobacterium leprae* from a Medieval Leprosy Hospital

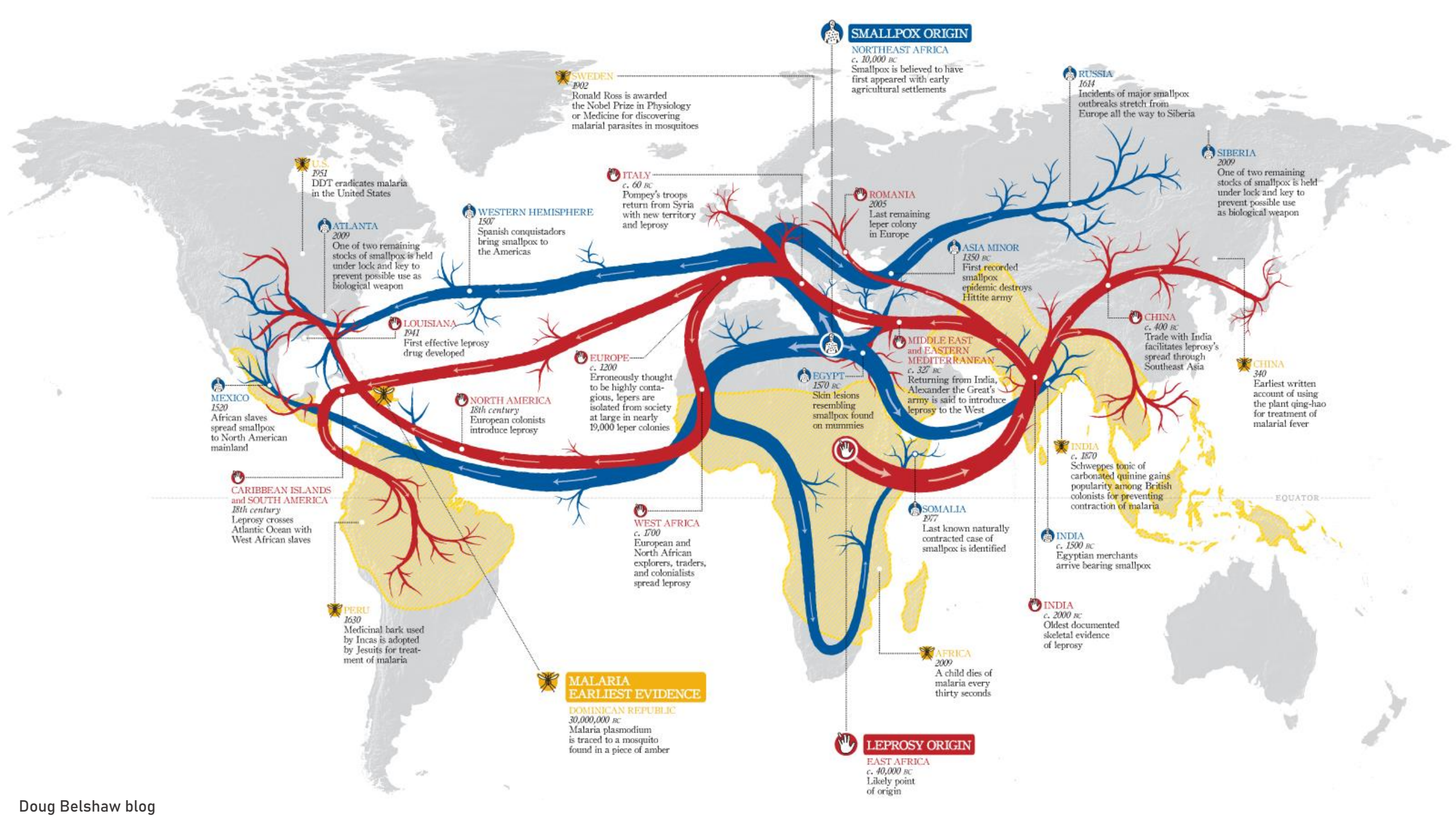
G. Michael Taylor, Katie Tucker, Rachel Butler, Alistair W. G. Pike, Jamie Lewis, Simon Roffey, Philip Marter, Oona Y-C Lee, Houdini H. T. Wu, David E. Minnikin, Gurdyal S. Besra, Pushpendra Singh, Stewart T. Cole, Graham R. Stewart

Published: April 30, 2013 • https://doi.org/10.1371/journal.pone.0062406





VectorMine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WEST AFRICA
c. 1700
European and North African explorers, traders, and colonialists spread leprosy
SOMALIA
1977
Last known naturally contracted case of smallpox is identified
INDIA
c. 1500 BC
Egyptian merchants arrive bearing smallpox
PERU
1630
Medicinal bark used by Incas is adopted by Jesuits for treatment of malaria
INDIA
c. 2000 BC
Oldest documented skeletal evidence of leprosy
AFRICA
2009
A child dies of malaria every thirty seconds
MALARIA EARLIEST EVIDENCE
DOMINICAN REPUBLIC
30,000,000 BC
Malaria plasmodium is traced to a mosquito found in a piece of amber
LEPROSY ORIGIN
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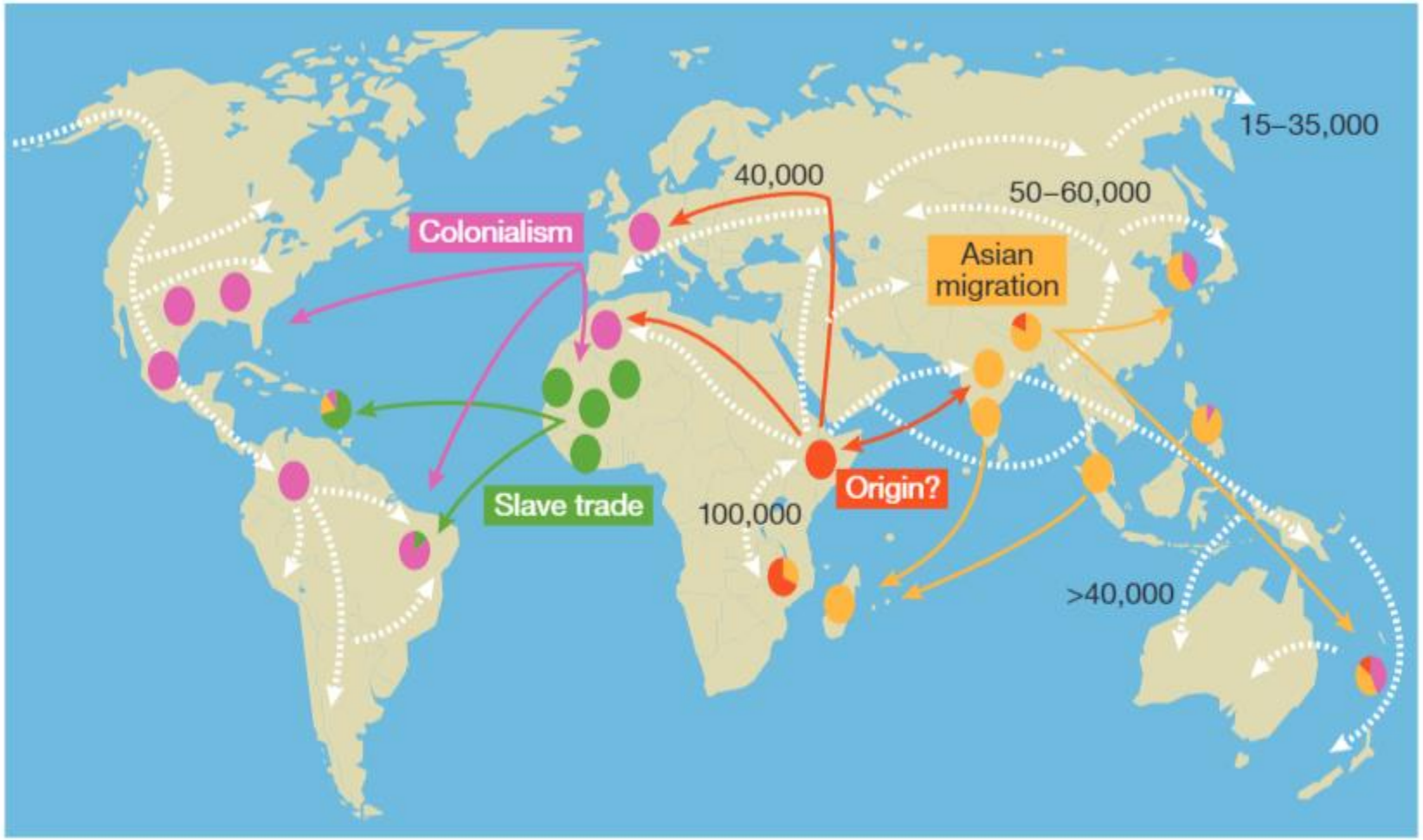


Fig 3 | Dissemination of leprosy in the world, based on the analysis of single-nucleotide polymorphisms. The ovals indicate the country of origin of the samples examined and their distribution into four SNP types: yellow, type 1; orange, type 2; pink, type 3; green, type 4. The coloured arrows indicate the direction of human migrations predicted by, or inferred from SNP analysis; white dotted arrows correspond to the migration routes of humans derived from genetic, archaeological and anthropological studies, with the estimated time of migration in years. From Monot *et al* (2005). Reproduced with permission from AAAS, Washington, DC, USA. SNP, single-nucleotide polymorphisms.

EMBO Reports, 2007; DOI: 10.1038/sj.embor.7400908

TREPONEMA PALLIDUM

- Syphilis (*Treponema pallidum* subsp. *pallidum)*
- Yaws *(Treponema pallidum* subsp. *pertenue)*
- Bejel *(Treponema pallidum* subsp. *endemicum)*

- Low pathogen load in tertiary stage

ELSEVIER

Journal of Archaeological Science
Volume 32, Issue 5, May 2005, Pages 703-713

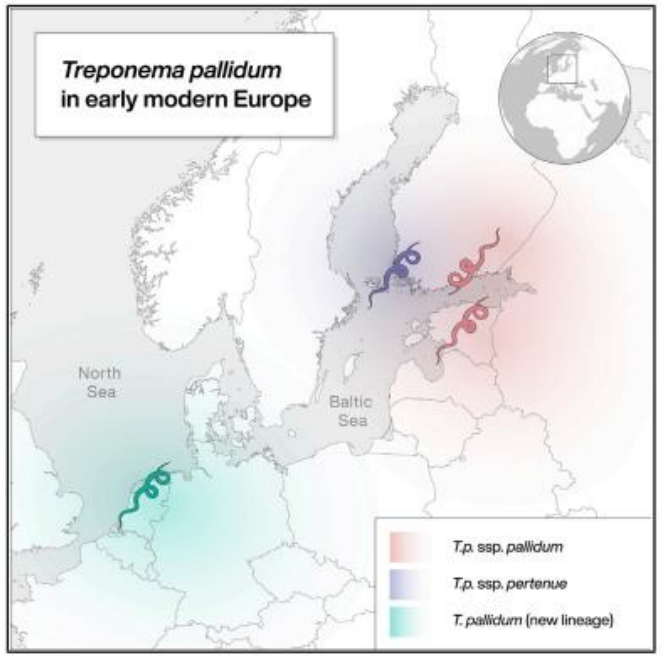
The limits of biomolecular palaeopathology: ancient DNA cannot be used to study venereal syphilis

Abigail S. Bouwman, Terence A. Brown

Example:

Ancient Bacterial Genomes Reveal a High Diversity of *Treponema pallidum* Strains in Early Modern Europe

Graphical Abstract



Authors

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In Brief

Majander et al. find a high diversity among the first ancient European treponemal genomes, including a newly discovered lineage. Dated around Columbus' contact with the Americas, these lineages and their overlapping spatial distributions suggest a possible Old-World origin of syphilis and the existence of endemic treponematoses in Europe.

Highlights

- Four ancient *Treponema pallidum* genomes from early modern Europe were reconstructed
- The genomes are highly diverse and include syphilis, yaws, and an unknown lineage
- The new ancient *T. pallidum* lineage is a basal sister group to yaws and bejel
- Molecular clock dating would allow a pre-Columbian origin of *T. pallidum* in Europe

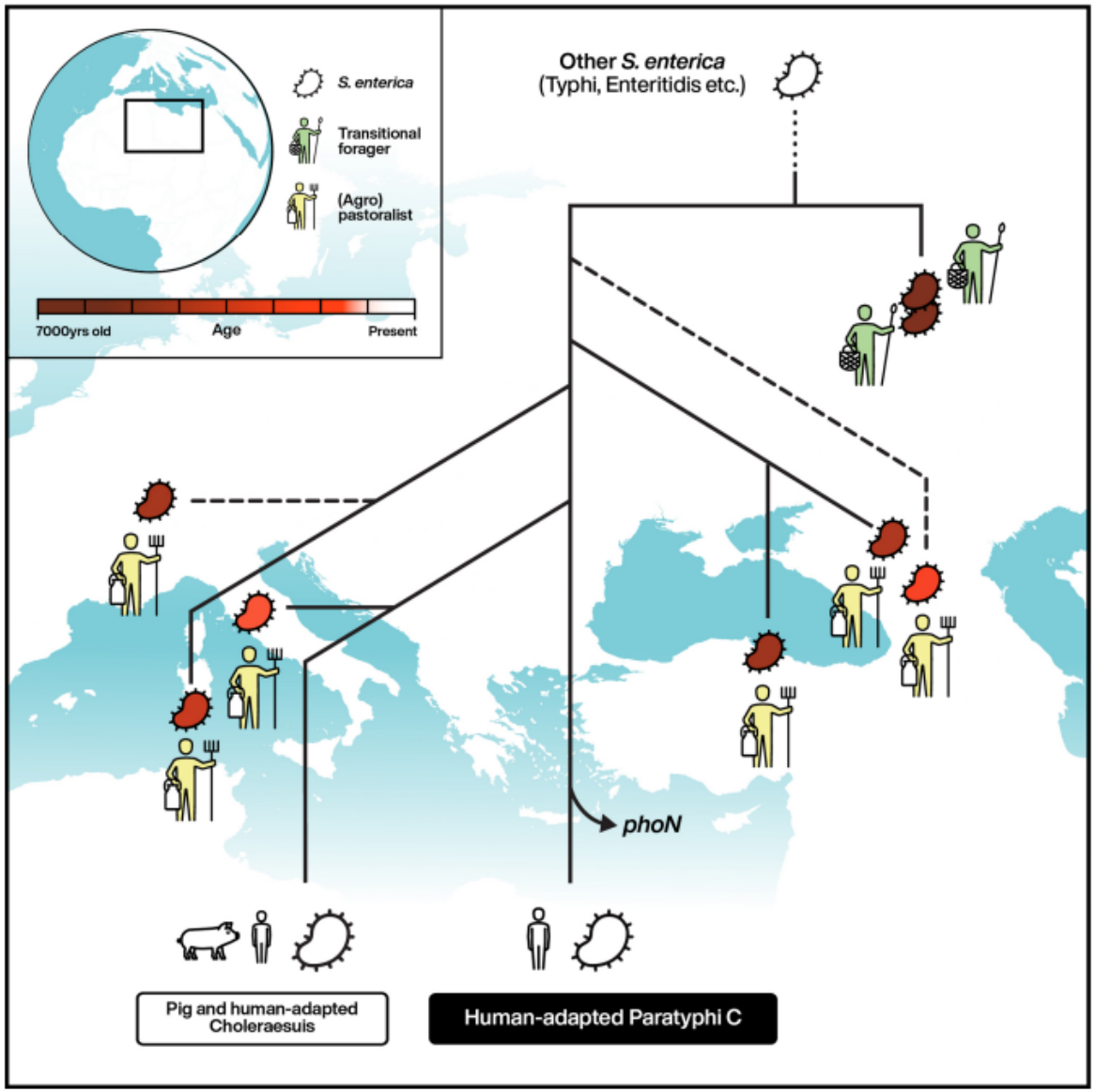
SALMONELLA ENTERICA

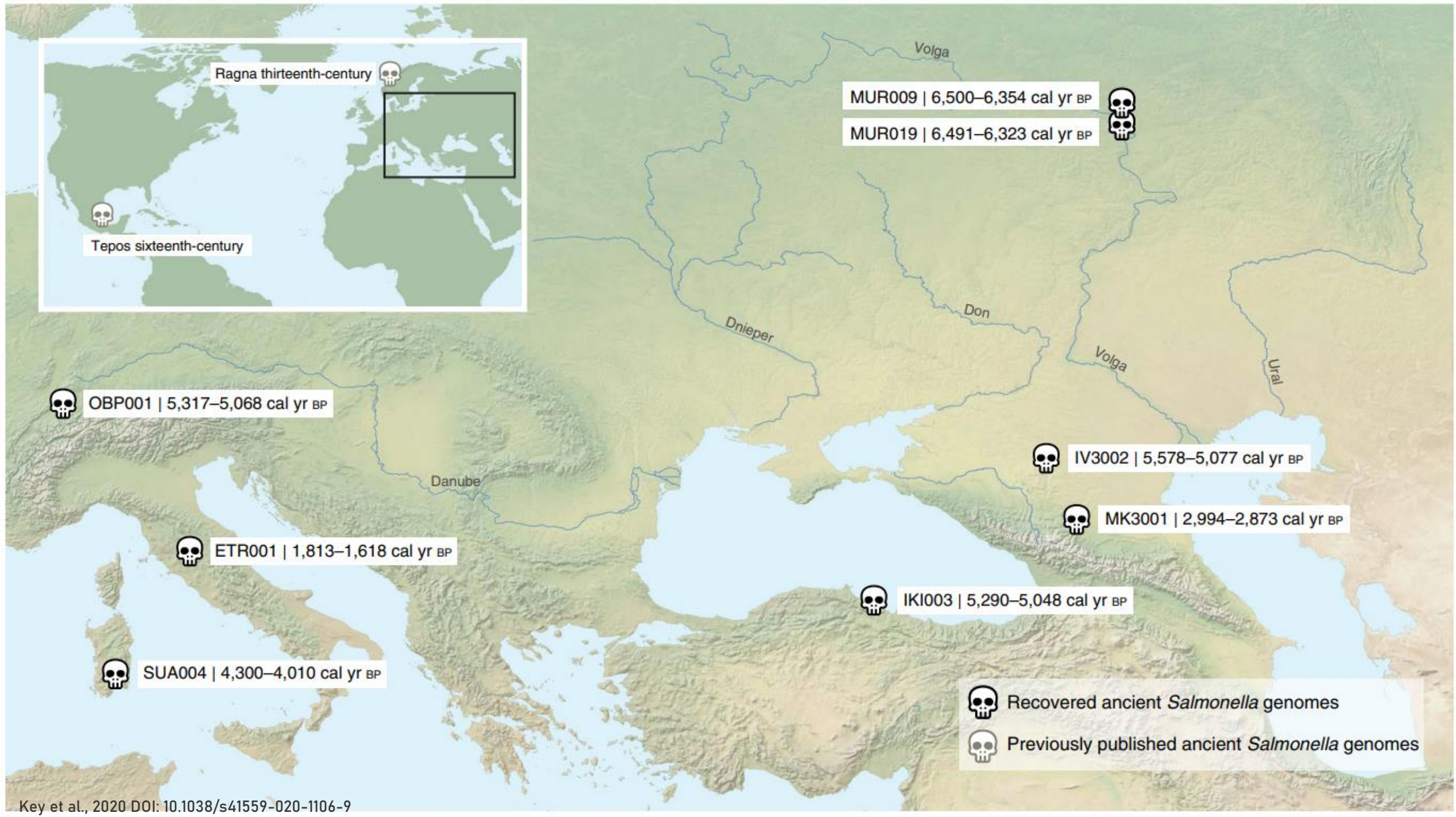
Article | Published: 24 February 2020

Emergence of human-adapted *Salmonella enterica* is linked to the Neolithization process

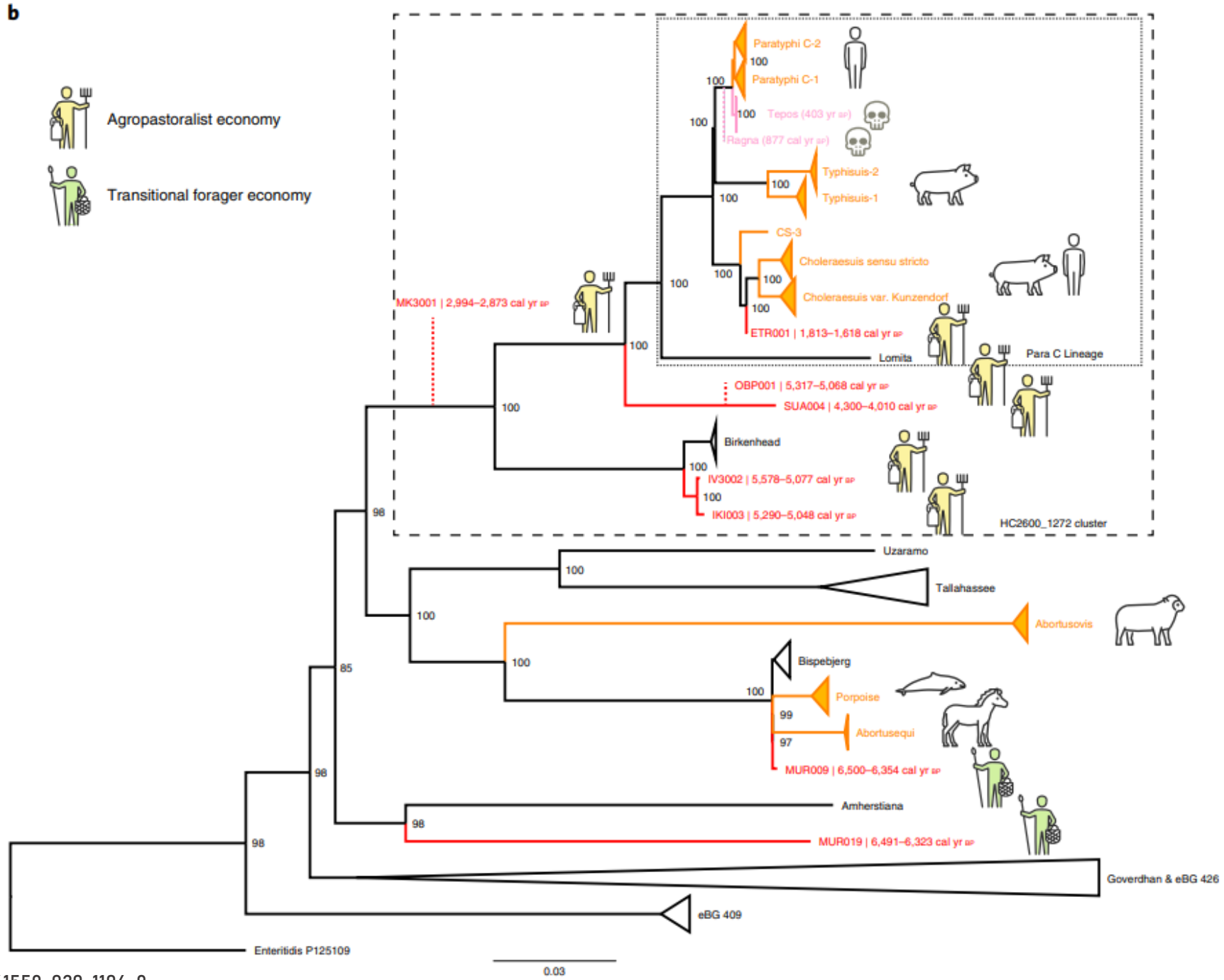
Felix M. Key, Cosimo Posth, Luis R. Esquivel-Gomez, Ron Hübler, Maria A. Spyrou, Gunnar U. Neumann, Anja Furtwängler, Susanna Sabin, Marta Burri, Antje Wissgott, Aditya Kumar Lankapalli, Åshild J. Vågene, Matthias Meyer, Sarah Nagel, Rezeda Tukhbatova, Aleksandr Khokhlov, Andrey Chizhevsky, Svend Hansen, Andrey B. Belinsky, Alexey Kalmykov, Anatoly R. Kantorovich, Vladimir E. Maslov, Philipp W. Stockhammer, Stefania Vai, Monica Zavattaro, Alessandro Riga, David Caramelli, Robin Skeates, Jessica Beckett, Maria Giuseppina Gradoli, Noah Steuri, Albert Hafner, Marianne Ramstein, Inga Siebke, Sandra Lösch, Yilmaz Selim Erdal, Nabil-Fareed Alikhan, Zhemin Zhou, Mark Achtman, Kirsten Bos, Sabine Reinhold, Wolfgang Haak, Denise Kühnert, Alexander Herbig & Johannes Krause — Show fewer authors

Nature Ecology & Evolution **4**, 324–333 (2020) | Cite this article





Key et al., 2020 DOI: 10.1038/s41559-020-1106-9



Key et al., 2020 DOI: 10.1038/s41559-020-1106-9

PLANT PATHOGENS

- *Phytophthora infestans* as one of the deadliest *oomycetes* – Irish potato famine caused death and emigration of >2 mil people

Article | Open access | Published: 18 July 2013

Reconstructing genome evolution in historic samples of the Irish potato famine pathogen

Michael D. Martin, Enrico Cappellini, Jose A. Samaniego, M. Lisandra Zepeda, Paula F. Campos, Andaine Seguin-Orlando, Nathan Wales, Ludovic Orlando, Simon Y. W. Ho, Fred S. Dietrich, Piotr A. Mieczkowski, Joseph Heitman, Eske Willerslev, Anders Krogh, Jean B. Ristaino & M. Thomas P. Gilbert

Nature Communications **4**, Article number: 2172 (2013) | Cite this article

6524 Accesses | **85** Citations | **74** Altmetric | Metrics

Abstract

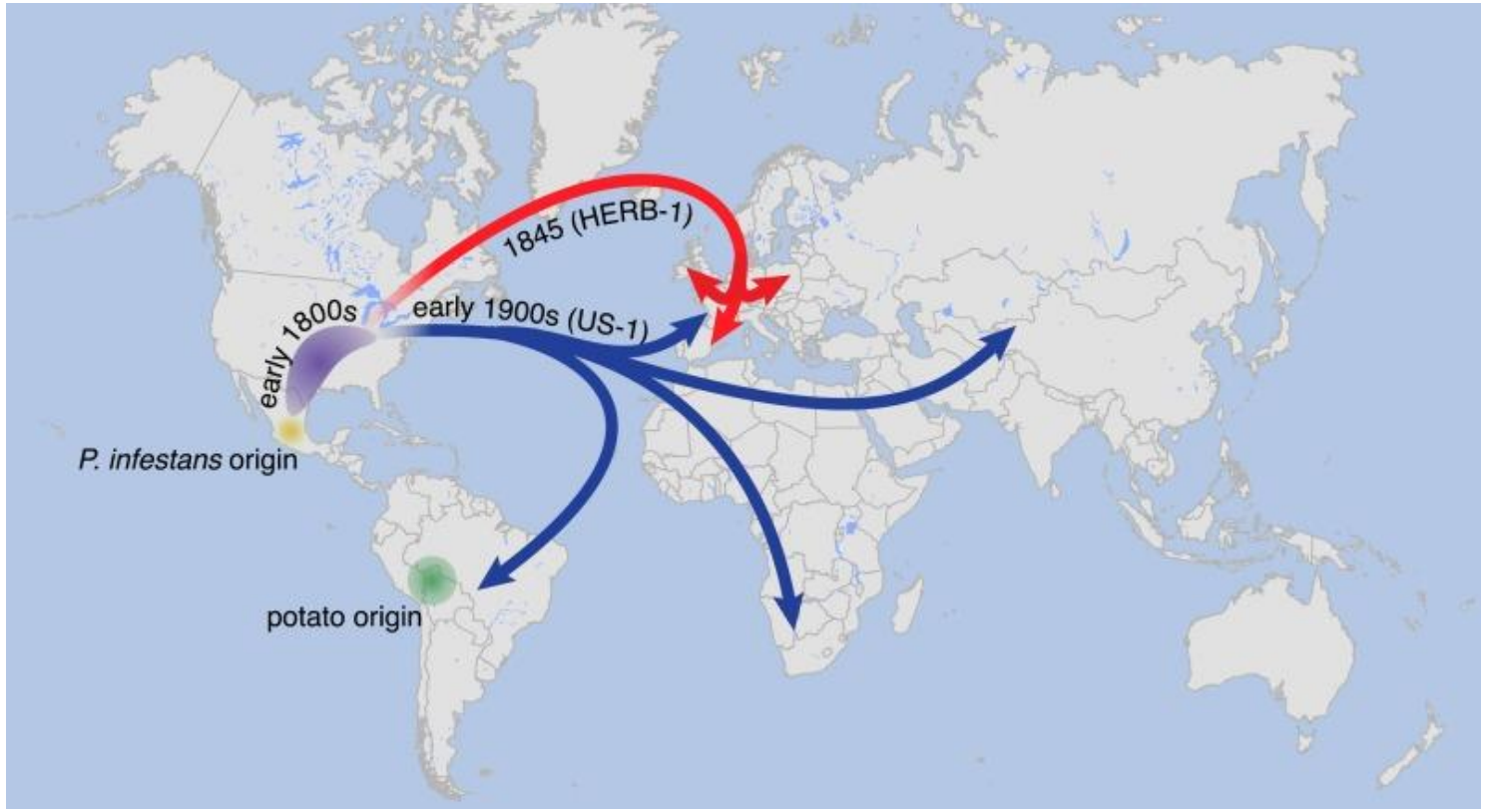
Responsible for the Irish potato famine of 1845–49, the oomycete pathogen *Phytophthora infestans* caused persistent, devastating outbreaks of potato late blight across Europe in the 19th century. Despite continued interest in the history and spread of the pathogen, the genome of the famine-era strain remains entirely unknown. Here we characterize temporal genomic changes in introduced *P. infestans*. We shotgun sequence five 19th-century European strains from archival herbarium samples—including the oldest known European specimen, collected in 1845 from the first reported source of introduction. We then compare their genomes to those of extant isolates. We report multiple distinct genotypes in historical Europe and a suite of infection-related genes different from modern strains. At virulence-related loci, several now-ubiquitous genotypes were absent from the historical gene pool. At least one of these genotypes encodes a virulent phenotype in modern strains, which helps explain the 20th century's episodic replacements of European *P. infestans* lineages.

PHYTOPHTHORA INFESTANS

eLife. 2013; 2: e00731.
Published online 2013 May 28. doi: 10.7554/eLife.00731
PMCID: PMC3667578
PMID: 23741619

The rise and fall of the *Phytophthora infestans* lineage that triggered the Irish potato famine

Kentaro Yoshida,[1,†] Verena J Schuenemann,[2,†] Liliana M Cano,[1] Marina Pais,[1] Bagdevi Mishra,[3,4,5] Rahul Sharma,[3,4,5] Chirsta Lanz,[6] Frank N Martin,[7] Sophien Kamoun,[1,‡] Johannes Krause,[2,‡] Marco Thines,[3,4,5,8,‡] Detlef Weigel,[9,‡] and Hernán A Burbano[9,*]



Genetic epidemiology of late blight in Australia using ancient DNA

Brittney M. Caruana[1,2] · Rudolf F de Boer[2] · Brendan Rodoni[1,2] · Noel O.I. Cogan[1,2] · Jacqueline Edwards[1,2]

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MORE TO LOOK INTO

- Bacteriophages (currently most studied in calculus and coprolites)
- *Borrelia recurrentis*
- *Plasmodium falciparum*

- *Mycobacterium tuberculosis*

- *Treponema pallidum*

Why should we study ancient pathogens?

- RNA and ssDNA viruses worst preservation
- Goddess of smallpox
- Domestication
- Spread of pathogens accross populations and continents and everything
- Phylogenetic trees
- Ways to study past diseases
- Ethical questions, biosafety
- Visible pathology and pathogens relationship, different load of pathogen in different stages