



UiO : University of Oslo

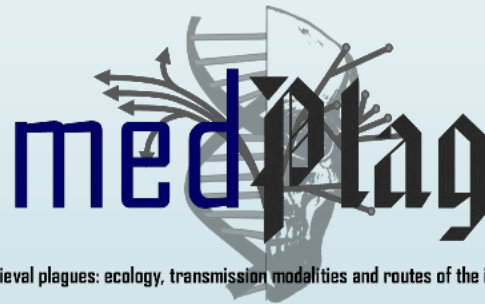
CEES

Centre for Ecological and
Evolutionary Synthesis

Fuori dalla “Terra delle Tenebre”: un approccio multidisciplinare per capire la diffusione della peste nel passato



European Research Council
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the European Commission



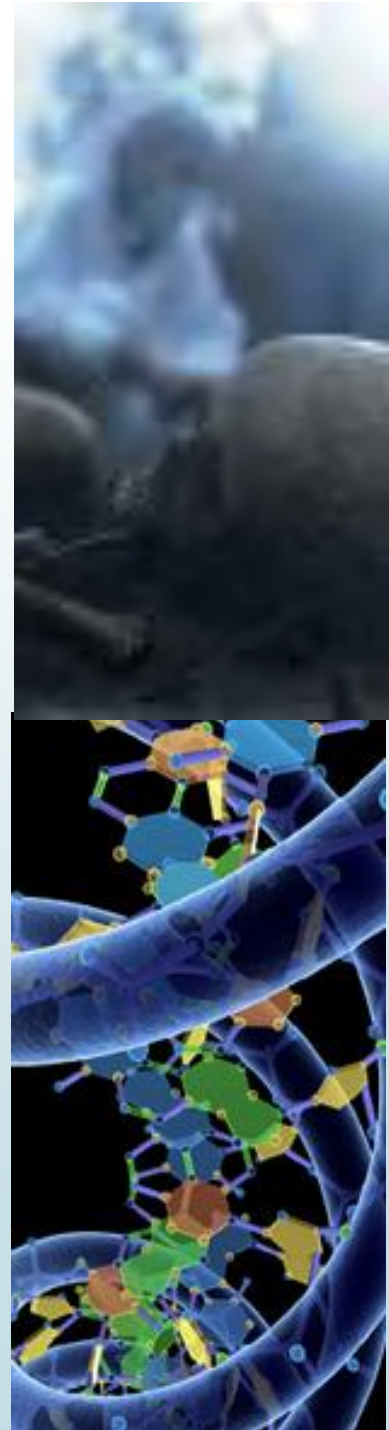
The medieval plagues: ecology, transmission modalities and routes of the infections.



Dipartimento di
Scienze
dell'Ambiente e della
Prevenzione

Barbara Bramanti,

PhD, Associate Professor, University of Ferrara





medplag

The medieval plagues: ecology, transmission modalities and routes of the infections.



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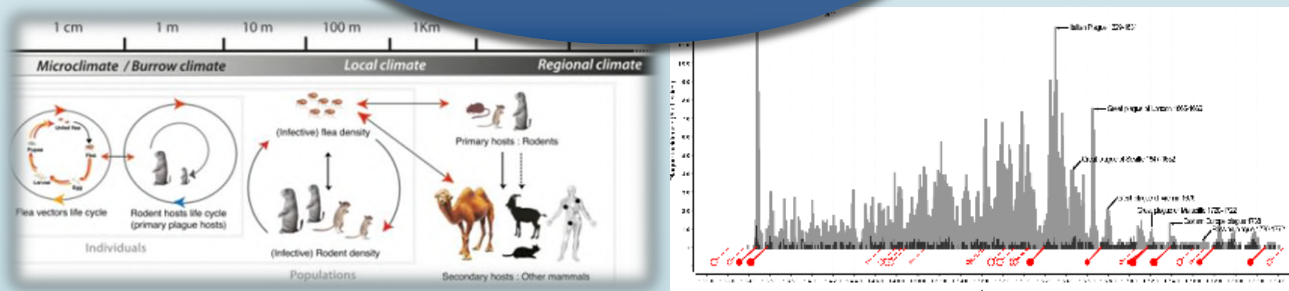


Storia

Archeo-
antropologia &
genomica
(aDNA)



Clima, ecologia,
Modelli matematici



La peste esiste in tre forme

<https://www.cdc.gov/plague/symptoms/index.html>



Bubonic plague

Febbre, mal di testa, brividi, debolezza, „bubbone“

Se non curata,

Tasso di letalità: ca. 40-60%



Septicemic plague

Febbre, brividi, debolezza estrema, dolori addominali, shock, possibili petecchie ed emorragie in organi interni

Tasso di letalità: 100%



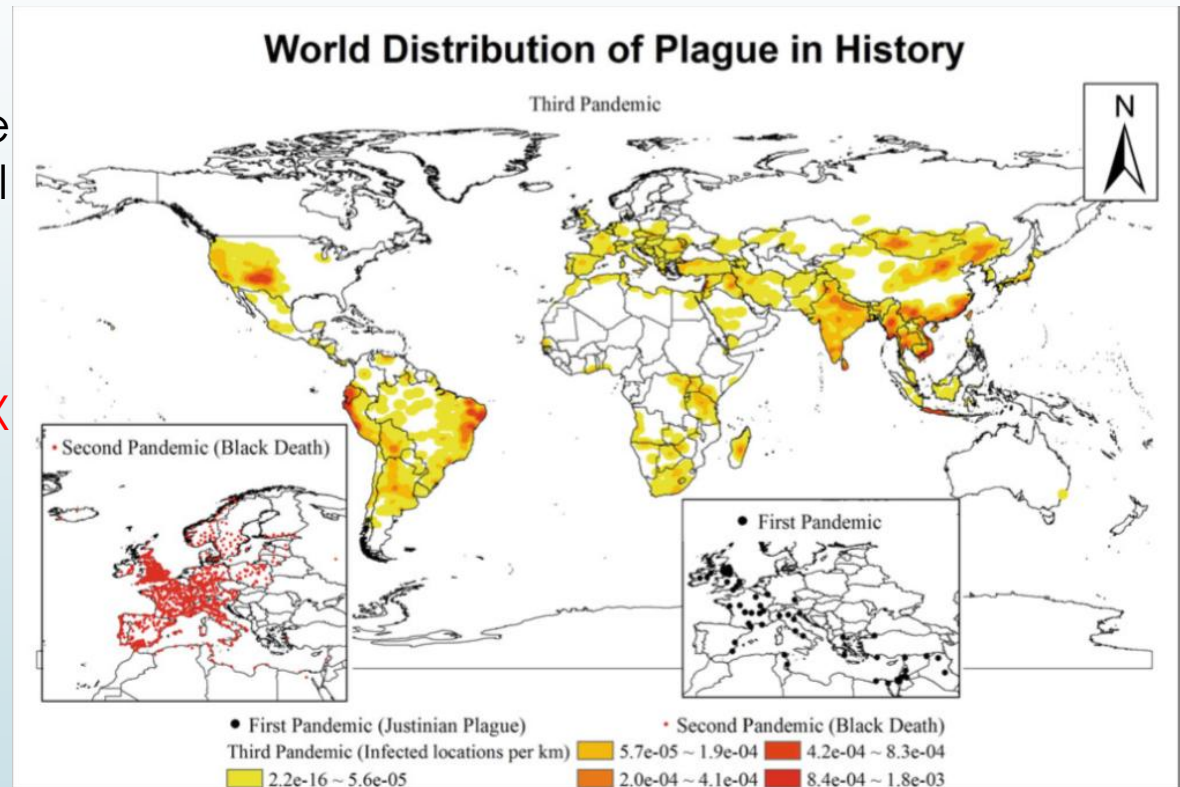
Pneumonic plague

Febbre, mal di testa, debolezza, polmonite con respiro accorciato, dolori al torace, tosse ed emottisi

Tasso di letalità: 99%

Tre pandemie storiche

- La Prima: 571-572 (Peste di Giustiniano) fino al VII secolo
- La Seconda: 1346-1353 (Black Death) fino al XIX secolo
- La Terza: 1894 (Hong Kong) – in corso

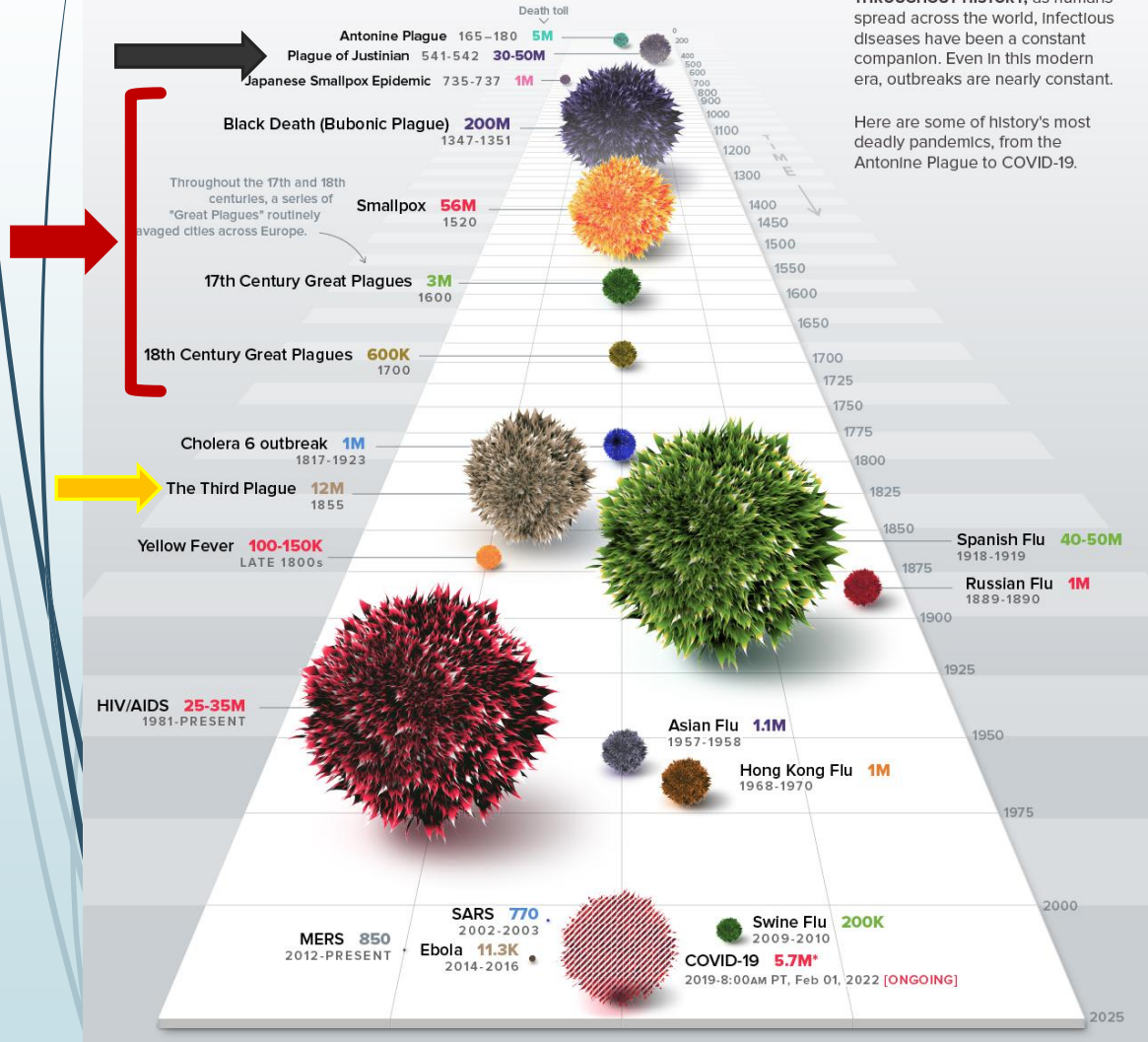


HISTORY OF PANDEMICS

PAN-DEM-IC (of a disease) prevalent over a whole country or the world.

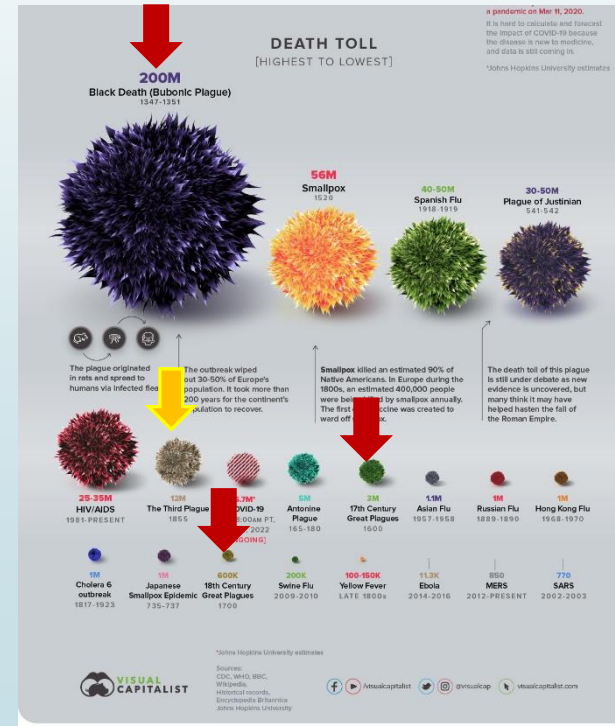
THROUGHOUT HISTORY, as humans spread across the world, Infectious diseases have been a constant companion. Even in this modern era, outbreaks are nearly constant.

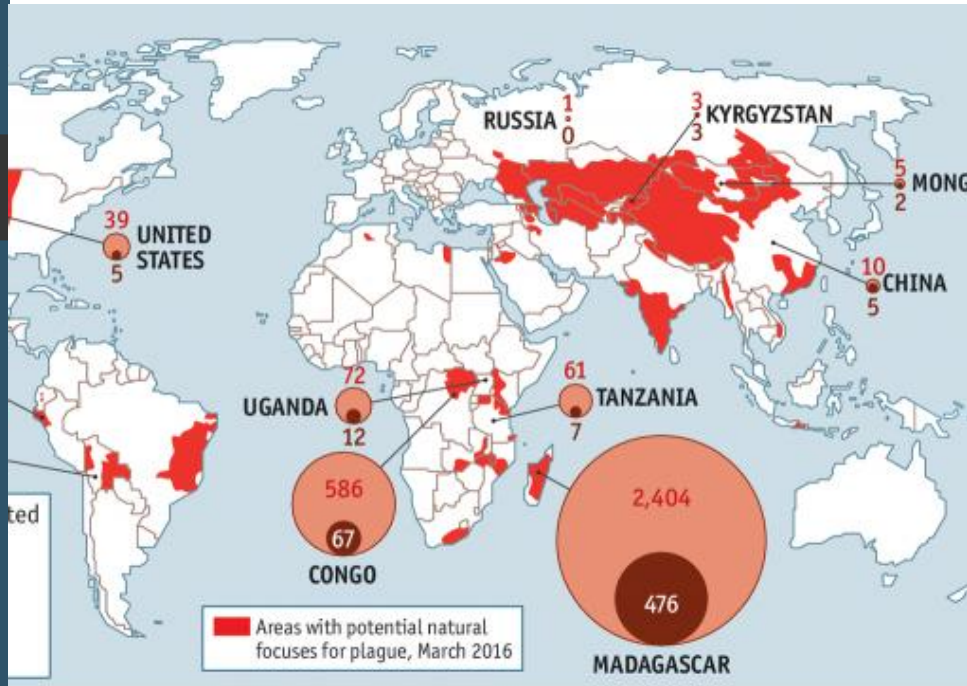
Here are some of history's most deadly pandemics, from the Antonine Plague to COVID-19.



[Immagine modificata da:](#)

Nicholas LePan,
VISUAL CAPITALIST
<https://www.visualcapitalist.com/history-of-pandemics-deadliest/>





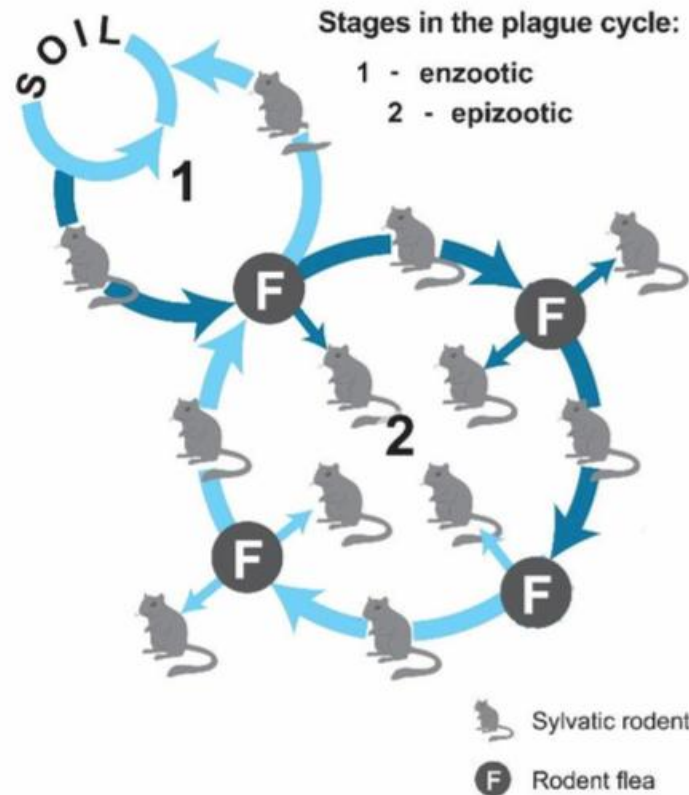
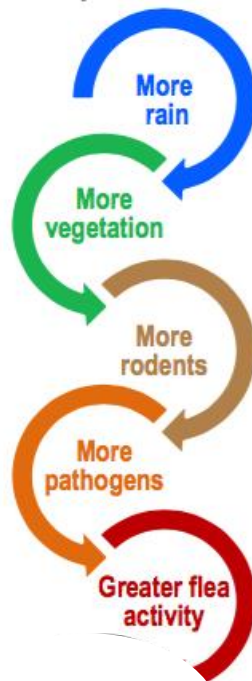
La peste è una **zoonosi**, preservata in **reservoirs**

(patogeno, ospite, e vettore – coesistono senza che la mortalità sia più elevata della norma)



Cosa accade nei reservoir in caso di precipitazioni oltre la norma?

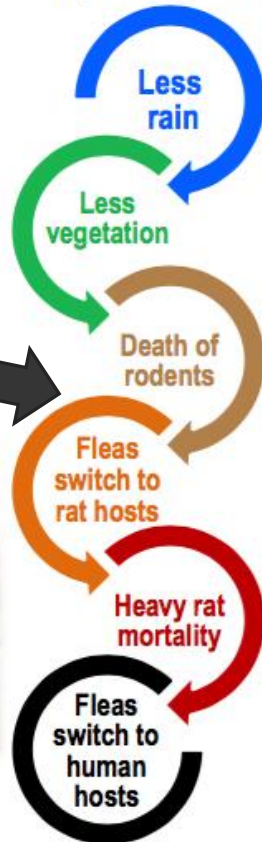
Trophic cascade



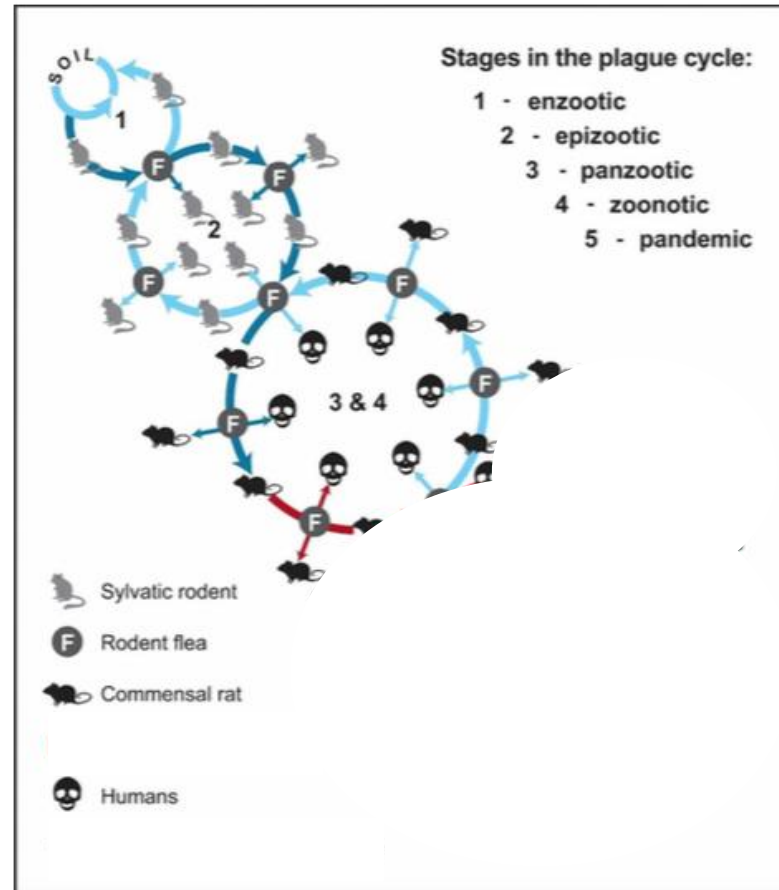
Courtesy Bruce Campbell (modified)

Sudden drought, or some other ecological shock, could then trigger the switch of plague from a rodent panzootic, via a human zoonotic, to a human pandemic:

Trophic cascade



Urban cycle



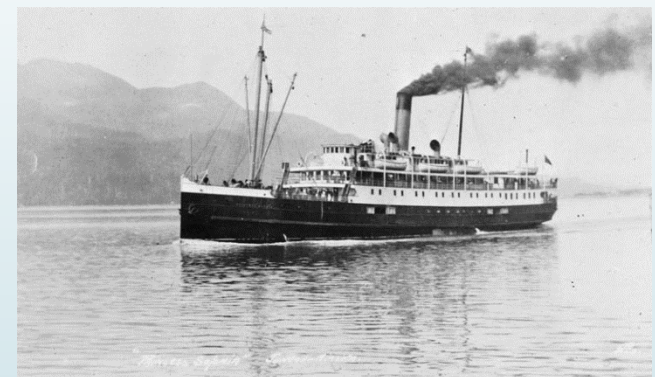
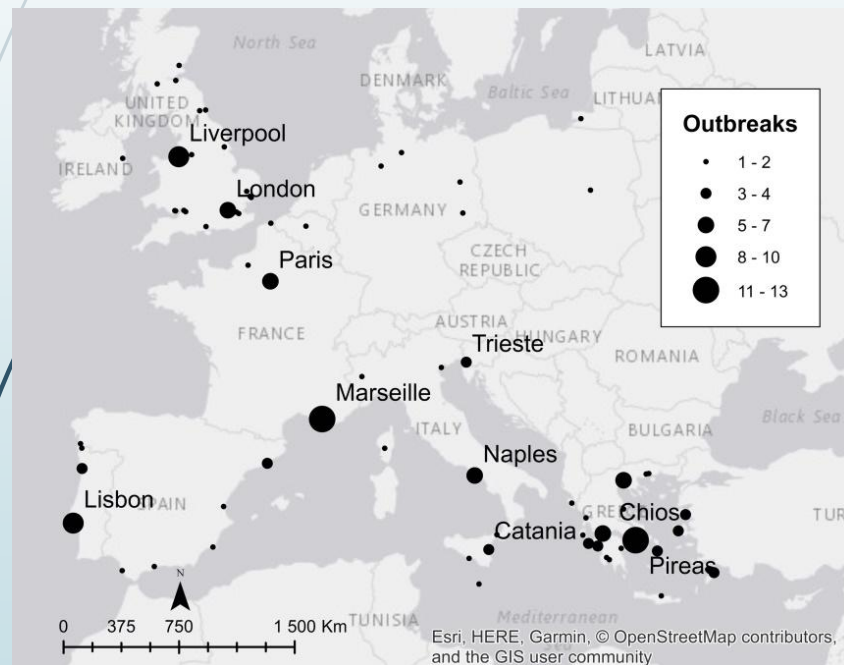
Courtesy Bruce Campbell (modified)

Questo modello si adatta perfettamente alla Terza Pandemia in Asia, USA...

La Terza pandemia in Europa 1899-1947

Bramanti et al. 2019-2

1,692 casi
457 morti



- **Quasi solo in città portuali**
- **Introdotta con le navi a vapore**

I ratti erano sottoposti ad attento esame



Avvisi pubblici cinesi, 1952



Liverpool Port Sanitary Authority rat-catchers dipping rats in buckets of petrol to kill fleas for plague control. Liverpool, England. Photograph, 1900/1920'. Image courtesy of Wellcome Collection. Credit: Wellcome Collection. CC BY 4.0.



Examining rats for bubonic plague in New Orleans, 1914 (courtesy N.L.M.)

Il ruolo dei ratti (Europa, III pandemia)

Bramanti et al. 2019-2

- Malta 1936-7: In 3 mesi, **più di 1500 ratti esaminati**; di questi **15 ratti erano infetti**.
- Barnett, S. A. 1948 Rat control in a plague outbreak in Malta. *Epidemiol. Infect.* **46**, 10–18: „**plague outbreaks always come to an end even if nothing is done to kill rats or their fleas**“.
- Il ruolo dei ratti **nel sostenere le epidemie** è moderato in Europa



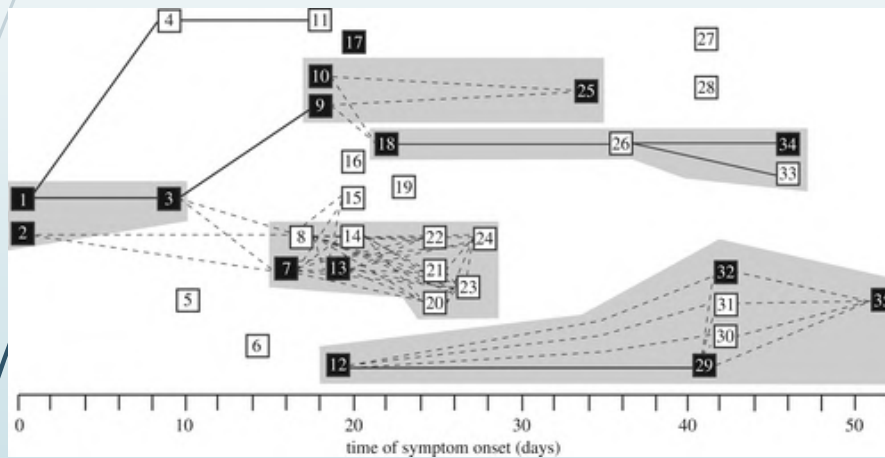
Albireo 2006



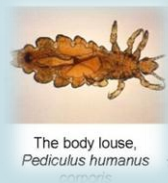
Un modello alternativo di trasmissione Glasgow 1900

DEAN ET AL. 2019

- NO EPIZOOSI
- TUTTI I CASI SONO STATI RICONDOTTI AD ALTRI CASI (UMANI)



Dean et al. Royal Society Open Science 2019



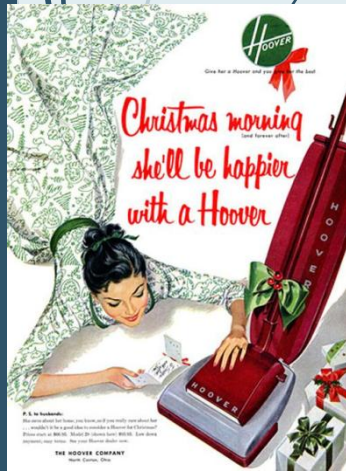
Glasgow, tenements 1900.

La peste scompare dall'Europa negli anni 50 del secolo scorso

Bramanti et al. 2019-2

Maggior pulizia, igiene e controllo degli insetti insieme a una
Politica di Prevenzione Internazionale

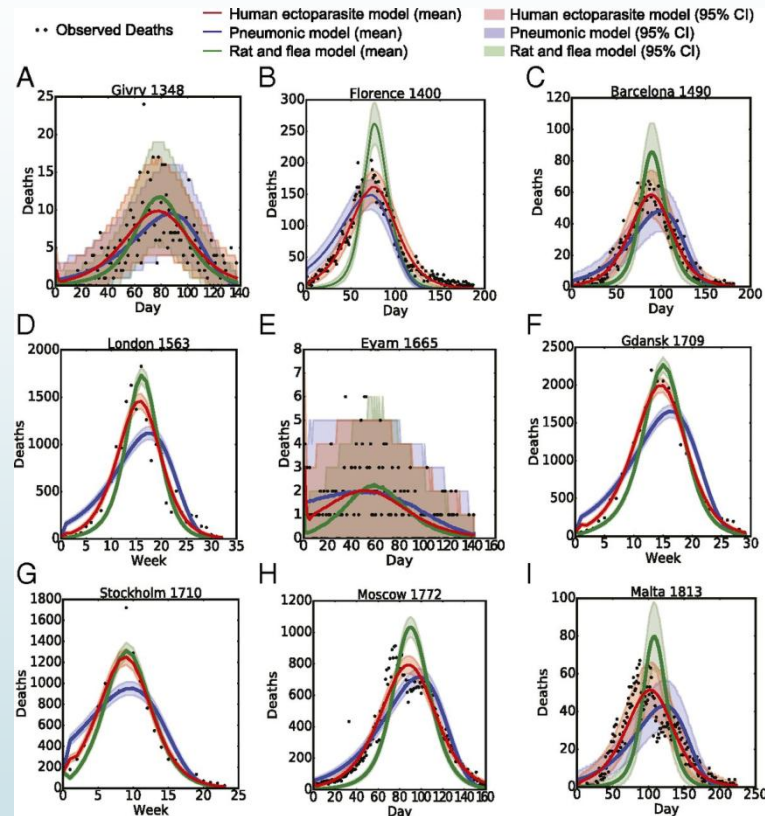
E la mancanza di reservoir in Europa...



E nei secoli precedenti?

Dean et al. PNAS 2018-1

Dean et al. PNAS 2018-2 (Reply)



► Persino per il passato il modello degli ectoparassiti è plausibile

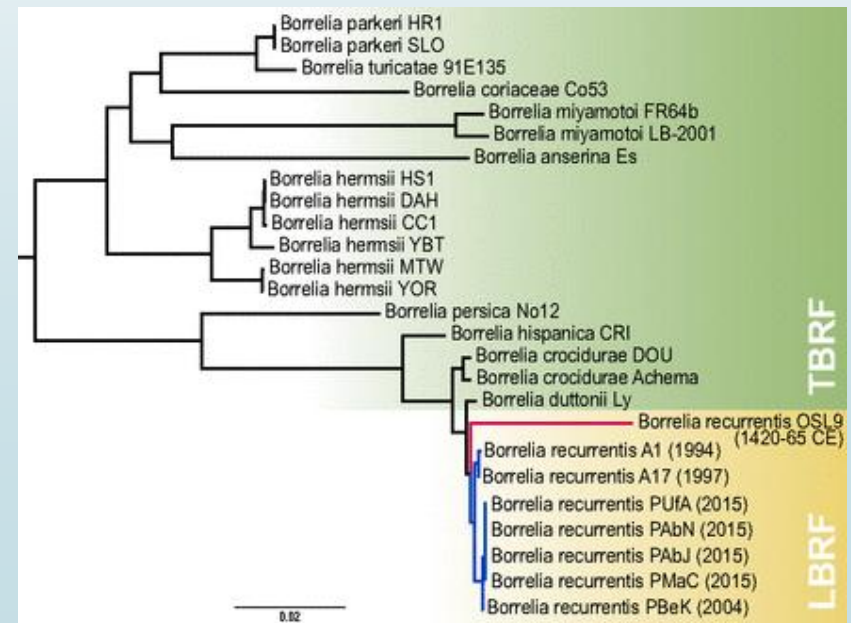
Altra infezione trasmessa dal pidocchio del corpo (Oslo XV secolo)

Guellil et al. 2018

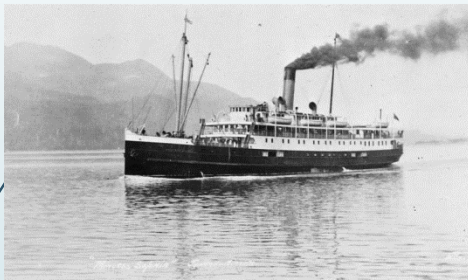


The body louse,
Pediculus humanus corporis

Borrelia recurrentis
Louse-borne relapsing fever (LBRF)



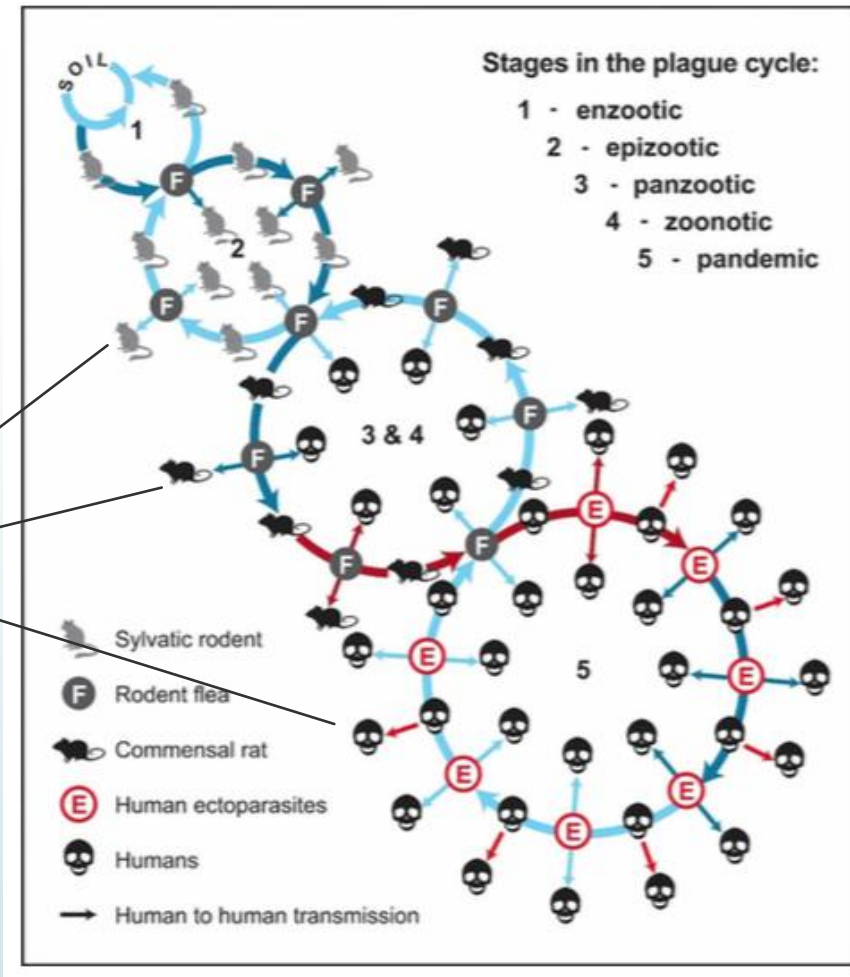
Meccanismo alternativo per epidemie (senza reservoir e ratti...)



Introduzione/i



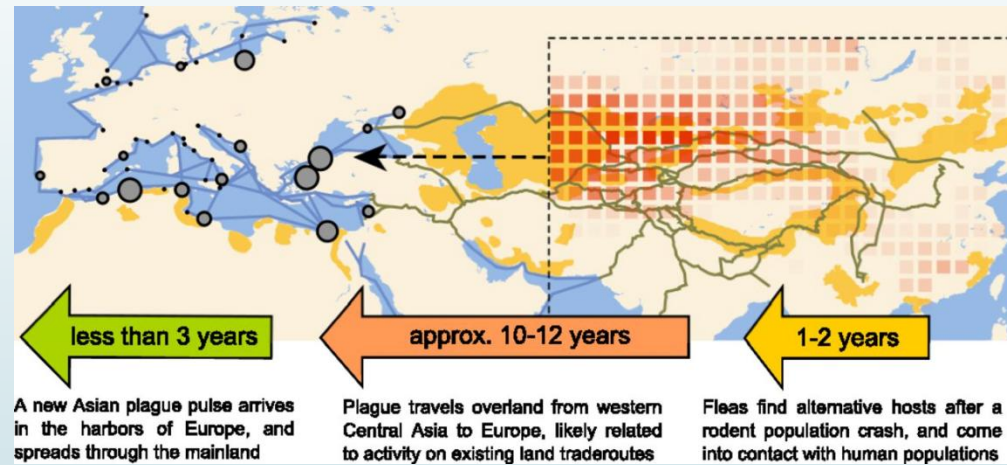
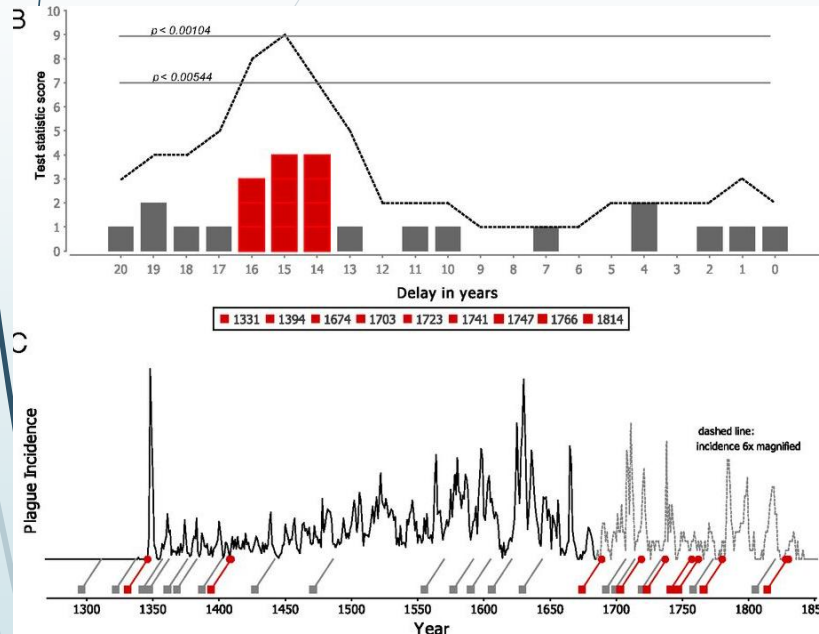
Circolazione in catene di trasmissione umana
(human ectoparasites or contact)



Courtesy Bruce Campbell

Climate-driven introduction of the Black Death and successive plague reintroductions into Europe

Schmid et al. 2015



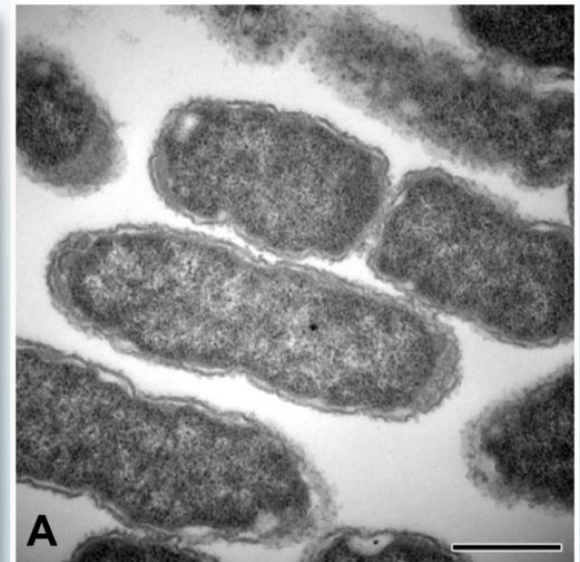
Prima Pandemia:

Harper The Fate of Rome (2017):

“Between AD 542 and AD 619, plague struck the capital [i.e. Constantinople] **on average every 15.4 years**”.

Patogeno: il batterio *Yersinia pestis*

- ❖ Fam. *Enterobacteriaceae*
- ❖ Coccobacillo
- ❖ gram-negativo
- ❖ Asporigeno
- ❖ Immobile
- ❖ Psicrofilo (0-20 °C)



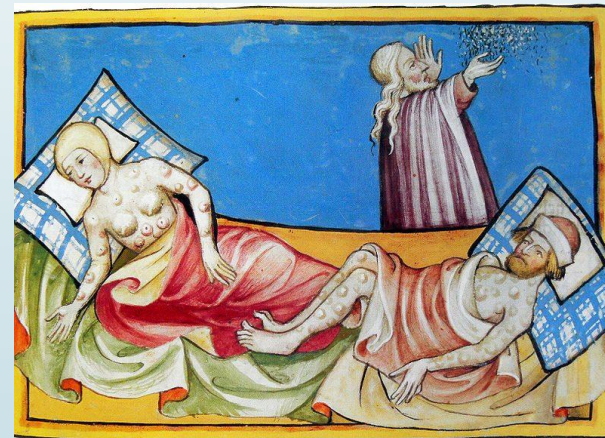
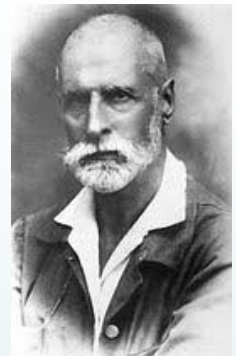
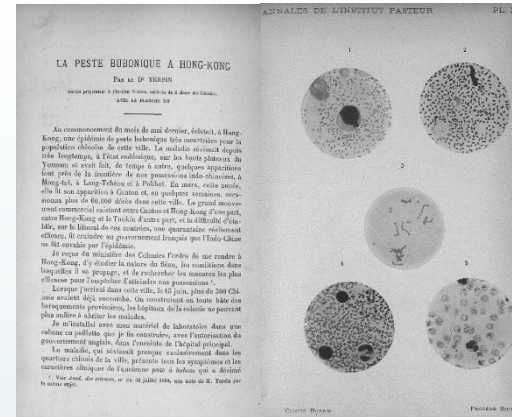
Attribution:

[Pawlowski DR, Metzger DJ, Raslawsky A, Howlett A, Siebert G, et al. \(2011\) Entry of *Yersinia pestis* into the Viable but Nonculturable State in a Low-Temperature Tap Water Microcosm. PLoS ONE 6\(3\): e17585. doi:10.1371/journal.pone.0017585 / CC BY](#)

La Scoperta: Alexander Yersin

„La maladie, qui sévissait presque exclusivement dans les quartiers chinois de la ville, présente tous les symptômes et les caractères cliniques **de l'ancienne peste à bubons qui a décimé maintes fois, dans les siècles passés**, les peuples de l'Europe occidentale comme ceux du Levant“.

YERSIN, Alexandre. - La peste bubonique à Hong-Kong. In : Annales de l'Institut Pasteur, 1894, Vol. 8, pp. 662-7



2010: La prova viene dalla genetica (aDNA)

OPEN ACCESS Freely available online

PLOS PATHOGENS

Distinct Clones of *Yersinia pestis* Caused the Black Death

Stephanie Haensch¹, Raffaella Bianucci^{2,3}, Michel Signoli^{3,4}, Minoarisoa Rajerison⁵, Michael Schultz⁶, Sacha Kacki^{7,8}, Marco Vermunt⁹, Darlene A. Weston^{10,11,12}, Derek Hurst¹³, Mark Achtman¹⁴, Elisabeth Carniel¹⁵, Barbara Bramanti^{1*}

1 Institute for Anthropology, Johannes Gutenberg University, Mainz, Germany, **2** Laboratory of Criminalistic Sciences Department of Anatomy, Pharmacology and Legal Medicine, University of Turin, Turin, Italy, **3** Unité d'Anthropologie Bioculturelle, Faculté de Médecine, Université de Méditerranée-CNRS-EFS, Marseille, France, **4** Centre d'Etudes Préhistoriques, Antiquité, Moyen-Âge, UMR 6130 CNRS-250 University of Nice, Valbonne, France, **5** Center for Plague, Institute Pasteur de Madagascar, World Health Organization Collaborating, Antananarivo, Madagascar, **6** Department of Anatomy and Embryology Medical Faculty, Georg-August University, Göttingen, Germany, **7** Inrap, Villeneuve-d'Ascq, Archaeological Center, Villeneuve-d'Ascq, France, **8** Laboratoire d'Anthropologie des Populations du Passé, Université Bordeaux 1, Talence, France, **9** Department of Monuments and Archaeology, Municipality of Bergen op Zoom, Bergen op Zoom, The Netherlands, **10** Barge's Anthropologica, Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, The Netherlands, **11** Division of Archaeological Sciences, University of Bradford, Bradford, West Yorkshire, United Kingdom, **12** Department of Human Evolution, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany, **13** Worcestershire Historic Environment and Archaeology Service, Worcestershire County Council, Worcester, United Kingdom, **14** Environmental Research Institute, University College Cork, Cork, Ireland, **15** Yersinia Research Unit, Institut Pasteur, Paris, France

Abstract

From AD 1347 to AD 1353, the Black Death killed tens of millions of people in Europe, leaving misery and devastation in its wake, with successive epidemics ravaging the continent until the 18th century. The etiology of this disease has remained highly controversial, ranging from claims based on genetics and the historical descriptions of symptoms that it was caused by *Yersinia pestis* to conclusions that it must have been caused by other pathogens. It has also been disputed whether plague had the same etiology in northern and southern Europe. Here we identified DNA and protein signatures specific for *Y. pestis* in human skeletons from mass graves in northern, central and southern Europe that were associated archaeologically with the Black Death and subsequent resurgences. We confirm that *Y. pestis* caused the Black Death and later epidemics on the entire European continent over the course of four centuries. Furthermore, on the basis of 17 single nucleotide polymorphisms plus the absence of a deletion in *gipD* gene, our aDNA results identified two previously unknown but related clades of *Y. pestis* associated with distinct medieval mass graves. These findings suggest that plague was imported to Europe on two or more occasions, each following a distinct route. These two clades are ancestral to modern isolates of *Y. pestis* biovars Orientalis and Medievalis. Our results clarify the etiology of the Black Death and provide a paradigm for a detailed historical reconstruction of the infection routes followed by this disease.

Citation: Haensch S, Bianucci R, Signoli M, Rajerison M, Schultz M, et al. (2010) Distinct Clones of *Yersinia pestis* Caused the Black Death. PLoS Pathog 6(10): e1001134. doi:10.1371/journal.ppat.1001134

Editor: Nora J. Besansky, University of Notre Dame, United States of America

Received: May 28, 2010; **Accepted:** September 7, 2010; **Published:** October 7, 2010

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Funding: This research was supported by grants from the Deutsche Forschungsgemeinschaft (DFG Br 2965/1-1 and Br 2965/1-2), the University of Mainz (FP1-2007) and the Science Foundation of Ireland (05/F1/BB02). The RDT analysis was supported by Compagnia di San Paolo (2007.0171). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

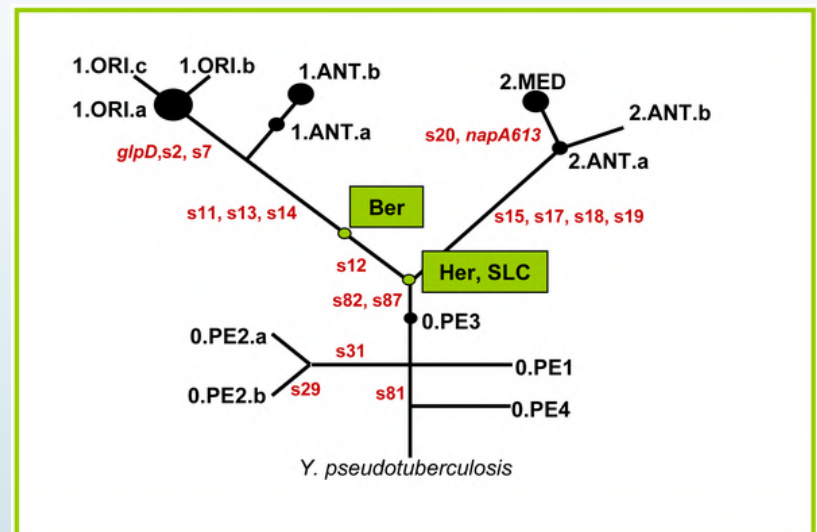
* E-mail: bramanti@uni-mainz.de

Introduction

Of the numerous epidemics in human history, three pandemics are generally accepted as having been caused by plague. Justinian's plague (AD 541–542) spread from Egypt to areas surrounding the Mediterranean [1]. In 1347, an epidemic known as the Black Death spread from the Caspian Sea to almost all European countries, causing the death of one third of the European population over the next few years [2]. This second pandemic persisted in Europe until 1750, causing successive and progressively declining epidemic waves. A third plague pandemic began in the Yunnan region of China in the mid-19th century, and spread globally via shipping from Hong Kong in 1894. During this last pandemic, the etiological cause of plague was identified as *Yersinia pestis*, a Gram-negative bacterium [3,4]. Most microbiologists and epidemiologists believe that *Y. pestis* was also the etiological agent of the first two pandemics. This belief is supported by ancient DNA (aDNA) analyses which identified

sequences specific for *Y. pestis* in the teeth of central European plague victims from the first and second pandemics [5–7]. Moreover, the *Y. pestis* F1 protein capsule antigen has been detected in ancient plague skeletons from Germany and France by immunochromatography [8,9].

Based on studies on modern strains, microbiologists have subdivided *Y. pestis* into three biovars: Antiqua, Medievalis, and Orientalis. These biovars can be distinguished depending on their abilities to ferment glycerol and reduce nitrate [10]. The Medievalis biovar is unable to reduce nitrates due to a G to T mutation that results in a stop codon in the *napA* gene [11], while the Orientalis biovar cannot ferment glycerol because of a 93 bp deletion in the *gipD* gene [11,12]. Conversely, the Antiqua biovar is capable of performing both reactions [10]. An apparent historical association of the routes of the three pandemics with the modern geographical sources of the three biovars led Devigant to propose that each plague pandemic was caused by a different biovar [10]. There is no doubt that the ongoing third pandemic

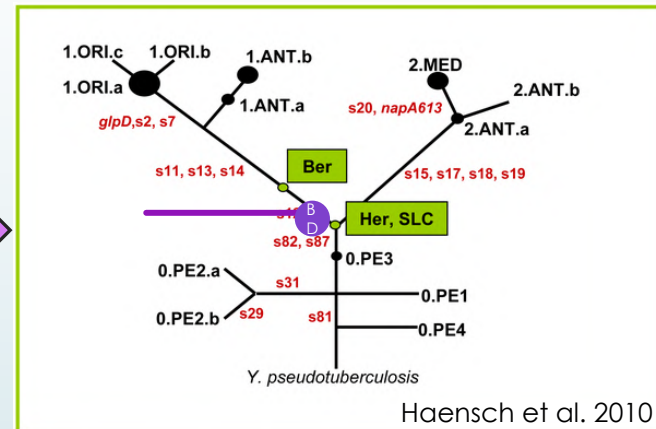


- E' la prima volta che delle linee di *Y. pestis* vengono piazzate su un albero filogenetico
- Si dimostra che sono estinte (no contaminazione!)

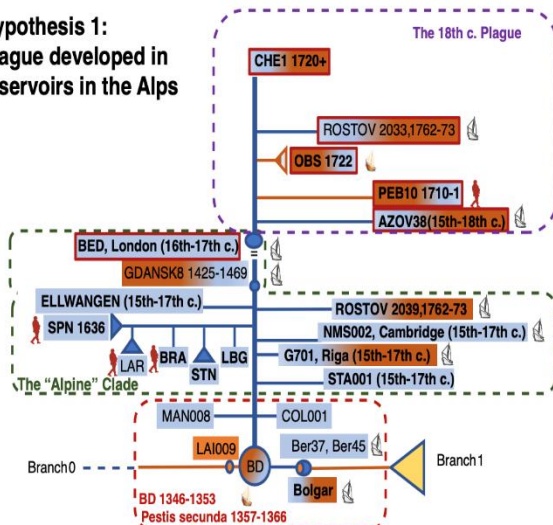
Questo modello si adatta anche alla Filogenesi attuale della peste antica? Il ramo post Black Death

Bramanti et al. PNAS 2021

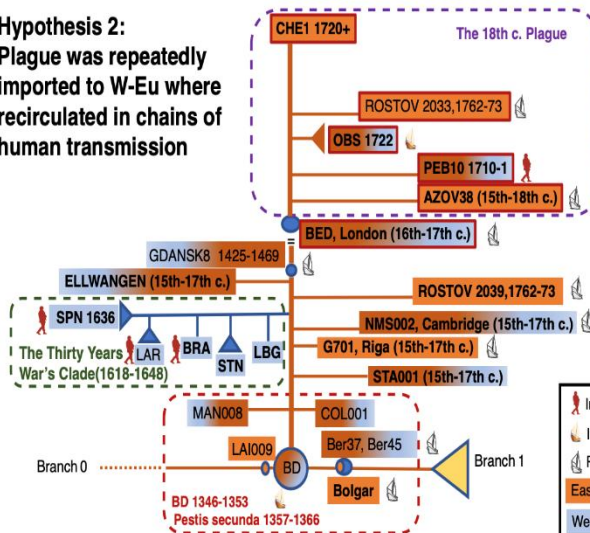
Nuovo reservoir, ma dove? →



Hypothesis 1:
Plague developed in
reservoirs in the Alps



Hypothesis 2:
Plague was repeatedly
imported to W-Eu where
recirculated in chains of
human transmission



DATI GENOMICI DA:

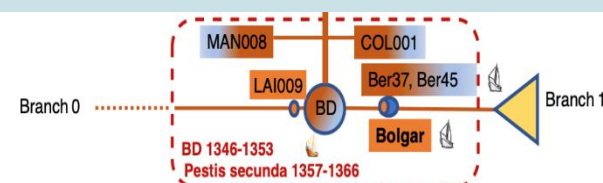
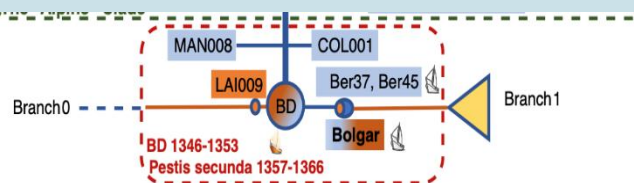
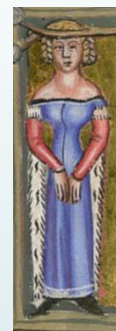
- BOS ET AL. 2016
- SPYROU ET AL. 2016 AND 2019
- NAMOUCHI ET AL. 2018
- GUELLIL ET AL. 2020
- MOROZOVA ET AL. 2020
- SUSAT ET AL. 2020
- SEGUIN-ORLANDO 2021

La peste del XIV secolo: Introduzioni multiple sulle vie delle pellicce?

NAMOUCI ET AL. 2018

BRAMANTI ET AL. 2019

MARTIN J (1978). Cah Monde Russe Sov 19:401–421

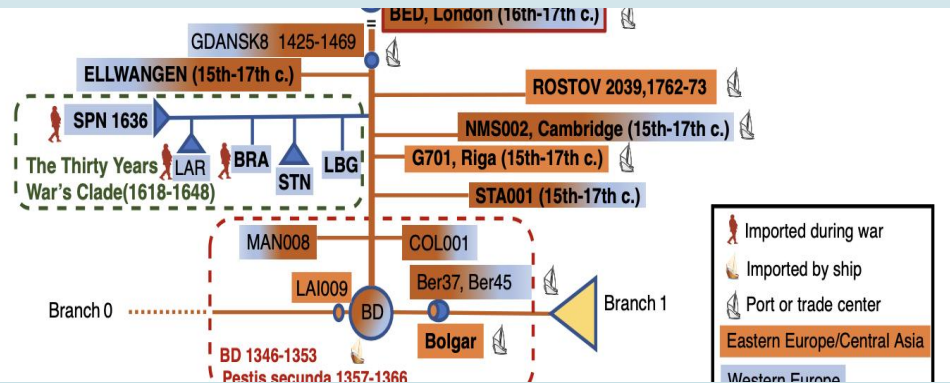
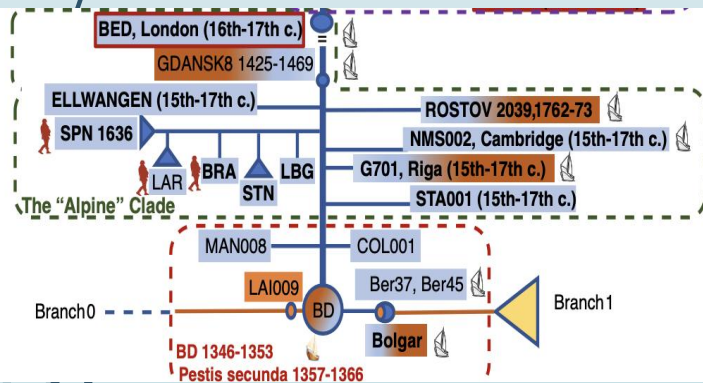


Imported during war
Imported by ship
Port or trade center
Eastern Europe/Central Asia
Western Europe

LAI009 from Russia

La Guerra dei Trent'Anni (1618-1648)

NAMOUCHI ET AL. 2018
 GUELLIL ET AL. 2020
 BRAMANTI ET AL. 2021

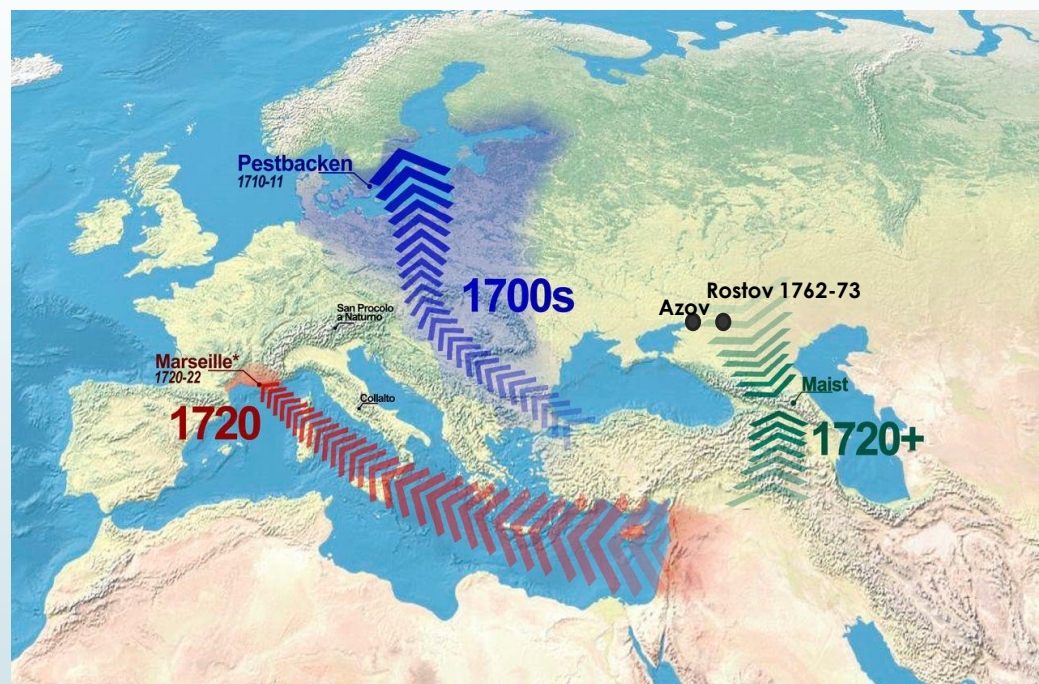


La Fine della Seconda Pandemia (XVIII s.): Il genoma più recente viene dal Caucaso...

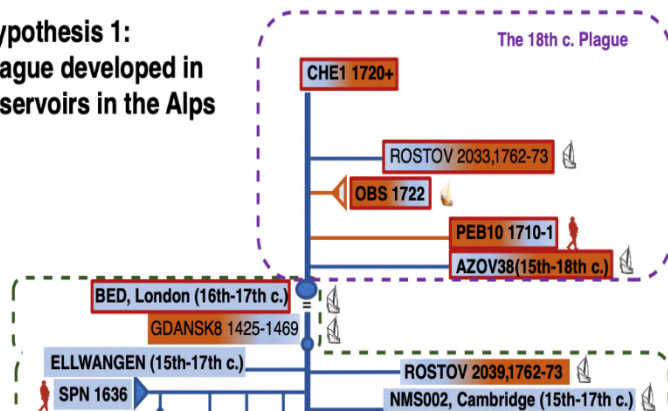
GUELLIL ET AL. 2020

MOROZOVA ET. AL. 2020

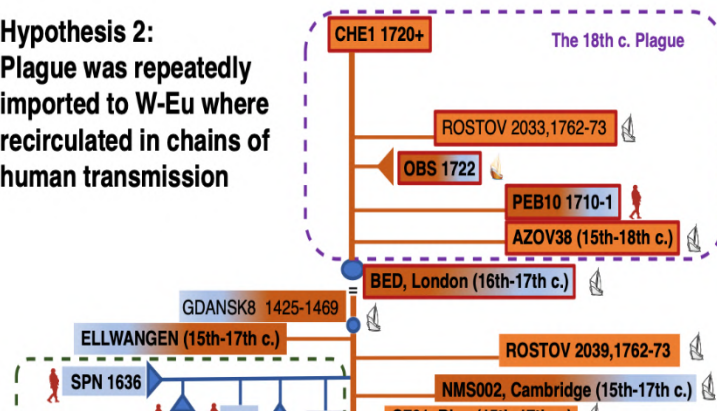
BRAMANTI ET AL. 2021



Hypothesis 1:
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Plague was repeatedly
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La fine delle pandemie di peste?

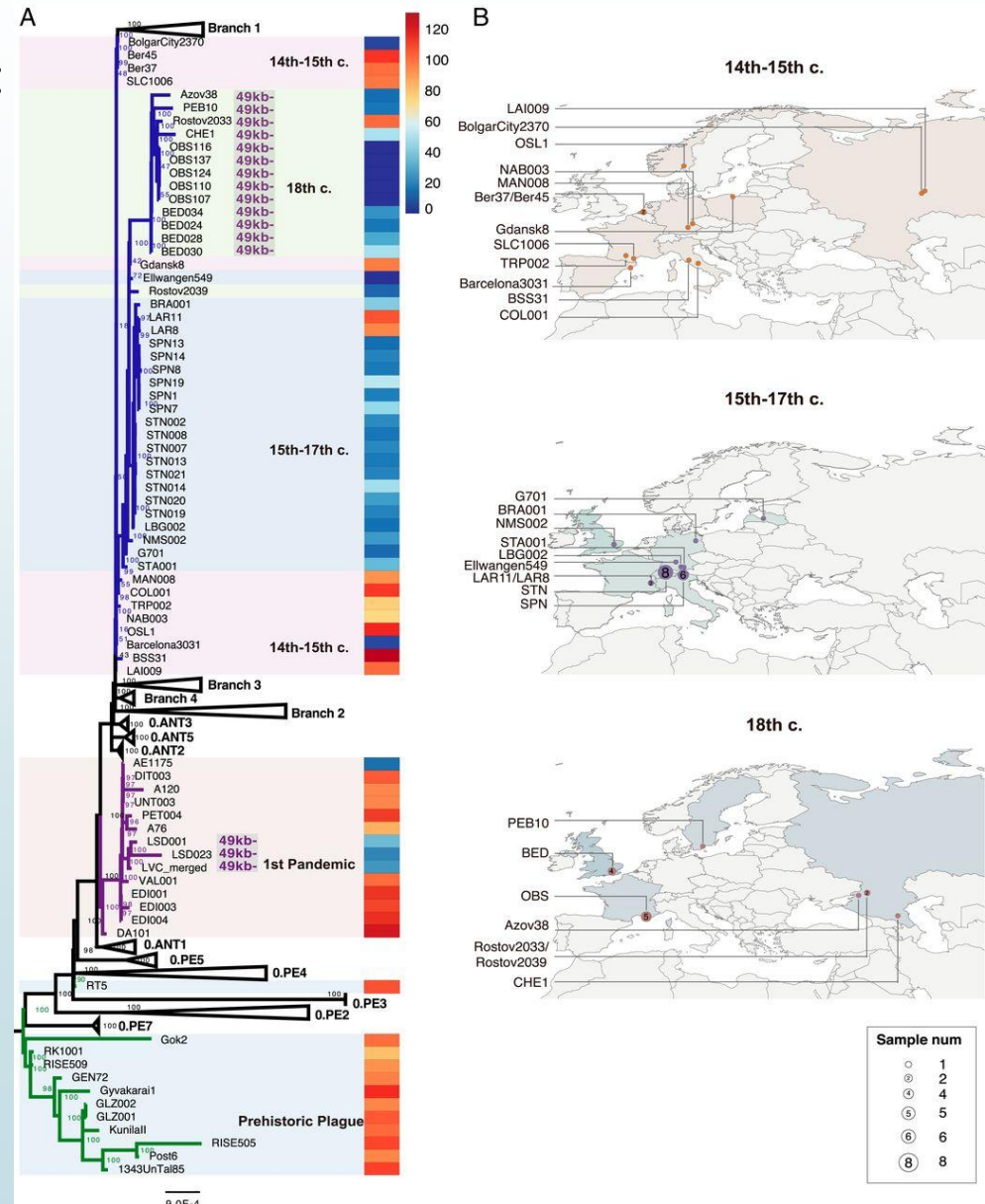
Due mutazioni convergenti:
49 Kb – delezione *
pla-deplezione **

* Spyrou et al. 2019;
 Guellil et al. 2020;
 Keller et al. 2019
 Bramanti et al. 2021

** Susat et al. 2020
 Bramanti et al. 2021

Spiegazione evolutiva:

Ridurre la virulenza
 può essere un
 vantaggio per il
 patogeno che
 aumenta il tempo di
 morte dell'ospite
 Adattamento
 all'Uomo?
 Bramanti et al. 2021





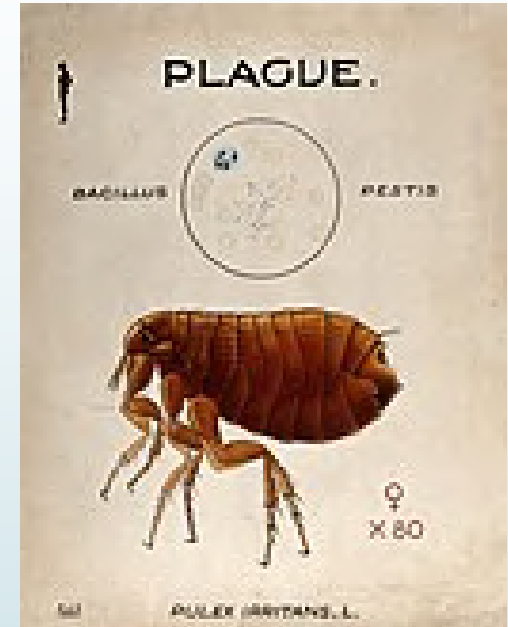
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Concludendo:

La genomica necessita di interpretazione

Il „modello dell'introduzione multipla“ si adatta bene alla Filogenesi attuale di *Y. pestis*'s della Seconda Pandemia

Plausibili teorie alternative sulla diffusione della peste nel passato possono aiutare ad impedire epidemie e pandemie nel futuro



Credit: Wellcome Collection

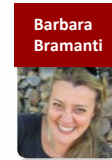
Grazie dell'Attenzione!



The medieval plagues: ecology, transmission modalities and routes of the infections.



The medieval plagues: ecology, transmission modalities and routes of the infections.



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aDNA - Work



Raffaella Bianucci



Stephanie Hänsch



Meriam Guellil



Oliver Kersten

Comparison among Yersinias



Claudio Ottoni

Bioinformatics



Mark Achtman



Amine Namouchi

Ecology – Epidemiology - Modeling



Ulf Büntgen



Nils Ch. Stenseth



Xu Lei



Fabienne Krauer



Boris Schmid



Katie Dean

Anthropology



Nicoletta Zedda



Natascia Rinaldo

History



Samuel Cohn



Lars Walloe

The fur- gene



Elisabeth Carniel



Javier Pizarro-Cerda



Ruifu Yang



Ryan Easterday



Anne Derbise



Pernille Nilsson



MedPlag-conclusive workshop. Ferrara, 2018

Partners (in alphabetic order): Aida Abdykanova, Caroline Arcini Ahlström, Egil Bauer, Chryssi Bourbou, Giulio Catalano, Elisabetta Cilli, Michael Derrik, Kenneth L. Gage, Christian Günzler, Giorgio Gruppioni, Elisabeth Iregren, Sacha Kacki, Anne Ø. Jensen, Herwig Leirs, Ole Christian Lingjærde, Qiyong Liu, Stefania Luciani, Isolina Marota, Marco Milanese, Simon Neerincx, Almaz Orozumbekov*, Elsa Pacciani, Mark J. Pallen, Ildikò Pap, Bodil Persson, Luisa Quaglia, Francois Ricaut, Mauro Rubini, Michel Signoli, Zhe Sun, Leif Chr. Stige, Kubat Tabaldiev, Hui Tang, Marco Vermunt, Ruifu Yang, Zhibin Zhang.