The role of louse-transmitted diseases in historical plague pandemics

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Plague pandemic among louse-transmitted diseases: a proposed epidemiological paradigm shift.

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Summary

The rodent-murine ectoparasite-human model of plague transmission does not fit for the Second Pandemic in Europe. Ancient genomes reveal that *Yersinia pestis* was unable to be transmitted by rat fleas until around 4,000 BP. Since prehistoric times, human lice have been reported and mentioned as probable source of plague during the second pandemic. Experimental models confirmed the efficiency of human lice as plague vectors through infected feces. These results suggest that *Y. pestis* could be a louse-borne disease, such as *Borrelia recurrentis, Rickettsia prowazekii* and *Bartonella quintana.* Recent studies have shown that louse-borne outbreaks often involve multiple pathogens, and several cases of co-transmission of *Y. pestis* and *B. quintana* have been reported. Furthermore, an exclusive louse-borne bacterium, namely *B. recurrentis*, was found to be circulating in northern Europe during the second pandemic. Current data make it possible to attribute large historical pandemics to multiple bacteria. All this evidence leads us to propose that human lice probably played a preponderant role in the interhuman transmission of plague and pathogen co-transmission during previous large epidemics, including historical plague pandemics.

Introduction

Recent insights concerning deadly historical plague pandemics profoundly change our views concerning the ecology and transmission of this causative agent, *Yersinia pestis*, and illustrates how the arising of cutting-edge technologies (e.g. whole genomes sequencing of ancient sample) have the potential to renew established paradigm. Indeed, the historical paradigm rats-rats' fleas-human, which was initially proposed in the frame of the third pandemics in Asia and focused most of the attention since then, has been somehow passively extended to the two earlier pandemics without systematical consideration of underpinning requirements (i.e the presence of rats and their fleas in sufficient abundance). In historical texts, the description of a fever associated with bubo has been pathognomonic of the plague since Justinian times, when it was very clearly described by Procopius (1). The *Y. pestis* lineage responsible for the Plague of Justinian (2–5) (541-750 AD) represented a (now extinct) clade which was distinct from the huge pandemic known as the "Black Death" that decimated Europe in the Middle Ages (1346-1353 for the so called "Black Death" and 1346 to the 19th century for the second pandemic (6–12). Despite the independency of these strains, the clinical symptoms were similar during both historical plague pandemics (5,8,11,13). Indeed, the "Black Death" was rather a word coined to refer to plague epidemics in the symbolic register (with a negative connotation) than a denomination used by contemporaries to describe the clinical manifestation of plague. Therefore, the "Black death" was later wrongly associated with purpuric fever or hemorrhagic fever (14) .

In 1894, at the beginning of the third pandemic, Alexandre Yersin's investigations carried out during the Hong-Kong plague led to the discovery of the *Y. pestis* bacteria, the causative agent of plague (15). In 1898, Paul-Louis Simond completed the epidemiological cycle proposed four years earlier by Yersin (16). He reported an indisputable mechanism by which infected fleas (*Xenopsylla cheopis*) could spread *Y. pestis* from one murid to another (17). The

discovery of late-stage biofilm-dependent transmission of *X. cheopis* (18,19) then made it possible to study 25 *Y. pestis* genes involved in the transmission of the plague by fleas (20). In particular, the *ymt* gene, which codes for a phospholipase D hydrolase and allows *Y. pestis* to survive inside the flea's digestive tract, is considered to be essential (21). All these studies demonstrated that *X. cheopis* is the vector transmitting plague from rats to rats, with a possible accidental transmission to humans. Later, new methods of whole genome sequencing of ancient DNA completely undermined this vision and molecular analysis traced the plague back to at least 5000 BP (22), detecting it not only on the arid shores of the Mediterranean but also in the northernmost part of Europe, hence in heterogeneous ecological environments (22–24). This finding provided an unexpected opportunity to question the classical epidemiological rats-rat flea-human transmission cycle. Our objective in this study was to systematically review data regarding *Y. pestis* transmission by human lice in the context of genomic evolution and co-transmission of other major epidemic deadly pathogens throughout human history, to broaden our view of plague transmission.

Ancient plague transmission enlightened by paleomicrobiology

Currently, paleomicrobiology studies make it possible to consider another model of plague diffusion which does not feature rats and rat fleas. Indeed, between 2011 and 2019, 80 ancient *Y. pestis* genomes were sequenced (3–5,8–12,22–26). These genomes were all recovered from Eurasian samples of teeth or bones and dated from 5000 BP (Sweden) (22) to 1722 (France) (10), thus covering the first two historical pandemics. Complete genome analysis confirmed the systematic presence of plasmid virulence-associated genes, such as the *pla* gene (pPCP1 plasmid) coding for a plasminogen activator or the *caf1* gene responsible for antiphagocytic activity (pMT1 plasmid), which are both associated with human mortality (27,28).

Furthermore, the archaeological identification of several individuals in the same grave, combined with the molecular presence of plague virulence-associated genes indicated that plague was already a deadly epidemic disease during the Bronze Age, as further described during historical pandemics (1,29). However, while 68/80 available ancient genomes do harbour the pMT1-encoded *ymt* gene, 12/80 ancient *Y. pestis* genomes dating from 5000 BP (Sweden) (22) to 1746-1626 cal BC (Russia) (24) lack this gene, (22–24) which is involved in the survival of *Y. pestis* in the flea's gut and is essential in effective plague flea transmission (30). Spyrou *et al.* indicate that the *ymt* gene probably appeared approximately 3,800 years ago during the Early Bronze Age and concluded that both *Y. pestis* flea-adapted and non-adapted variants circulated in Eurasia throughout the Bronze Age (26). These facts indicate that, for approximately 1,200 years, fatal plague did not necessarily require rat fleas (22–24,26). Regarding these results, *Y. pestis* appear to be a very old human pathogen present throughout Eurasia, even in its most northern part. Furthermore, the geographical location of the strains, combined with an absence of the *ymt* gene (Sweden, Germany, Estonia, Lithuania, Croatia, Russia, Norway, Austria and Poland (22–24)) does not seem to support a transmission mechanism mediated by rats and rat fleas (31–33). The presence of the *pla* gene in all ancient genomes is an unequivocal indicator that plague could be bubonic and therefore vectorised by arthropods (introduction of *Y. pestis* in human tissues following biting) (23). Genetic and archaeological studies (34–36) provide evidence that the only known competent plague vectors present during the Neolithic and Bronze ages in Eurasia were *Pulex irritans* (35,36) and the human louse (*Pediculus humanus* ssp.) (34,37,38). However, *P. irritans* is known to be a very poor plague vector (27,39) with a very low blocking capacity (40). Some authors have hypothesized that *P. irritans* could have been involved in the spread of plague during the second pandemic (39–41) but currently, the transmission rates obtained in the laboratory using early phase transmission [0.14 per cent] are too low to consider *P. irritans* as

an efficient vector (20,42,43) . Therefore, the most parsimonious hypothesis is that the human-human transmission of the plague at this time may have mostly involved human lice, given the absence of effective flea vector such *X. cheopis* and the presence of all associated virulence genes involved in the deadly bubonic plague.

The rat-and-flea model is not consistent with the historical demography of the second pandemic

Beyond Neolithic and Bronze age transmission, the epidemiological rat-rat fleas-human schema cannot explain the speed and magnitude of the second pandemic which spread much faster that the current third pandemic (32,39,44). In particular, this model is not compatible with the 1.5 to 6 km/day speed of dissemination of the Black Death as calculated using historical sources (45). Occasionally, this scheme cannot even be implemented given the absence of its protagonist (31). For example**,** in Northern Europe, there are very few archaeological records of *Rattus rattus* in the Middle Ages which appears to have been unevenly distributed in coastal towns (32,33). Current archaeozoological data does not appear to be compatible with the classical patterns of *Y. pestis*(31–33,46) given the low density of rat bones found from medieval archaeological sites in Nordic countries (32,33). Some authors argue, however, that the scarcity of rats in medieval Europe (47) is compatible with the classical model of transmission (rats-rat ectoparasites) observed in India during the third pandemic (29,48,49). These conclusions are based on unsupported assertions (43) or on mathematical models in which the plague can persist in relatively small rodent populations (50). Nevertheless, the current parsimonious hypothesis is that is very unlikely that rats could have played a significant role in vectorization of the plague in Nordic countries (32,33,43). In an example from the 15th century, two waves of plague killed approximately 50% of

Icelanders despite an attested absence of rats (31). However, this observation did not exclude the presence of other cold-resistant mammals that could have served as intermediate hosts. Finally, while it is acknowledged that the "eastern" rat flea (*X.cheopis*) has been the main vector of plague epidemics since the end of the 19th century, its role in spreading the Black Death is controversial as there are no fossil records of *X. cheopis* in Europe. However, remains of *P. irritans* have been discovered in these latitudes (51), which is consistent with the fact that the northern European climate may not be conducive to this tropical flea species, which were adapted to the warmer climate of southern Europe, as evidenced by their involvement in four's third pandemic plague outbreaks [Barcelona, Malta, Marseille, Ajaccio](52). Studies have demonstrated the incapacity and inefficiency of *Y. pestis* transmission by *X. cheopis* exposed to low temperatures (<10-12.5°C) (53–55). This finding questioned the etiology of the plague, suggesting that it has been caused by haemorrhagic fever viruses (56) without any scientifically identified causative agent. Accumulated evidence in favour of *Y. pestis* indicates that plague exhibited the very same clinical features, mortality and dissemination rates without rat and rat fleas, as illustrated by the northern epidemics (31,46). Furthermore, studies on plague and climate seem to indicate that plague introduction during the Black Death is correlated with hot Mediterranean summers in southern Europe, which are compatible with flea transmission (57). In contrast, in the southern Baltic states and Iceland, plague was driven by a cold climate (< 10°C) (57) or a climate consistent with the Little Ice Age (58). Such temperatures are completely incompatible with rat flea transmission but consistent with other vectors, such as human lice, that can live in the heat of clothes and could have be an effective *Y. pestis* vector following the 1.5/6km day speed of plague dissemination (45) which correspond to human travel through Eurasia to the most northern places in Europe (51). In summary, in the context of the plague epidemic, the two main methods of transmission are ectoparasites and aerosols. Considering that interhuman

transmission of plague through aerosols has proved to be ineffective unless particular conditions are met (59,60), the most plausible form for the ancient plagues is the bubonic form. Particularly during northern plague outbreaks, moreover, in particular during northern plague outbreaks, lice are the most plausible vector proposed (Figure 1).

History and role of lice in human infection

Lice are among the oldest human ectoparasites ever recorded. Lice are estimated to have appeared around 100 million years ago, and speciation between chimpanzee lice (*Pediculus schaeffi*) and human lice (*Pediculus humanus* ssp.) occurred approximately 5.6 million years ago (34). Ancient human lice have been recovered from all continents with the exception of Oceania. Lice dated as being 9,000 years old were retrieved from textiles in Israel (61). Lice have also been directly identified on mummified human bodies in Egypt and pre-Colombian America (62,63). Regarding European prehistory, ancient lice have been found in textiles in Austria (64). Based on these observations, one of the main candidates (with *P. irritans*) for a vector of plague in the Bronze Age is human lice. Furthermore, the same model is likely apply to the great medieval epidemics in northern Europe where the presence of lice has been confirmed (51). These outbreaks had a very high rate of mortality and led to the decline of northern populations (31,46). Louse-borne diseases are able to cause immense epidemics, as evidenced by contemporary observations. For example, in the Napoleonic wars, approximately 30% of Napoleon's soldiers died of typhus while they were infested with lice in the city of Vilnius during the Russian campaign (65). Lice also killed millions of people with louse-borne relapsing fever, typhus, and probably trench fever in Bolshevik Russia and later during World War II (66). The last extremely severe outbreak of louse-borne diseases was observed in Burundi in 1997, where they are likely to have killed

10,000 people and affected 100,000 others (67). The role of lice as a vector of *R. prowazekii* was first identified by Charles Nicolle, which earned him a Nobel Prize. Nicolle noted that patients whose clothes were removed and who were bathed prior to admission did not transmit typhus to others, including healthcare workers in the hospital (68). Searching patients' clothes revealed the only possible vector and source of transmission, the louse. Later, the louse was funded to be responsible for trench fever during World War I (69). Finally, the presence of *B. recurrentis* (the causative agent of relapsing fever) in lice was identified as early as the 19th century in Ireland (70). Among louse-borne outbreaks, therefore, it is generally difficult to determine which diseases are caused by different pathogens. Indeed, among Napoleon's soldiers, *R. prowazekii* and *B. quintana* were identified retrospectively as co-occurring during the same epidemic, but *B. recurrentis* was not tested for (65). In Burundi, the co-circulation of *R. prowazekii* and *B. quintana* during the same epidemic was highlighted, but *B. recurrentis* was not tested for (67). In historical studies in Douai performed by molecular testing dental pulp, the co-occurrence of *R. prowazekii* and *B. quintana* was highlighted (71). These studies represent the first evidence of *R. prowazekii* in Europe. The co-circulation of *Y. pestis* and *B. quintana* has also been observed in Venice and in Bondy (72,73), suggesting a coupled epidemic (Figure 2). Thus, given that many infectious diseases may be transmitted by the same mechanism, epidemic agents could be considered guilty by association (Figure 2).

The discovery of two microorganisms during the same pandemic is probably indicative of the fact that both pathogens have the same mechanism of transmission, allowing us to hypothesise that *Y. pestis* and *B. quintana* were co-transmitted by body lice in Venice and Bondy.

Supposed role of lice in ancient plague outbreaks

Observation of the natural infection of body lice (*Pediculus humanus humanus*) from plague-infected human began at the beginning of the 20th century when the spontaneous infection of head lice with plague (*Pediculus humanus capitis*) was found. With regard to body lice, in 1914 Swellengrebel and Otten recovered infected body lice from the clothes of a plague victim and from an inhabitant of a plagued house, and in 1935, the capacity of body lice to be infected by ingesting plague-contaminated blood was finally demonstrated (74). The first observation of human contamination by body lice was made among Andean Indians who developed pharyngeal plague after consumption of contaminated lice (75), although we do not know if the bacterial load present in infected body lice can cause this type of symptom, which was observed through the consumption of infected meat (76–78). The vectoral capacity of lice by contamination of their faeces was discovered by Blanc and Baltazard, but all these observations and experimentations were forgotten and then rediscovered (79). Indeed, in 2006, our laboratory unambiguously demonstrated the plague-vector potential of body lice by faecal contamination with viable *Y. pestis* bacteria using a rabbit experimental model (Figure 3) (80).

We also recently found *Y. pestis* in head and body lice during one of the last endemic outbreaks of the Democratic Republic of Congo (81,82). Experimental studies performed both in the 1950s and recently highlighted the vectoral capacity of lice for *Y. pestis* in rabbits (74,80,83). Interestingly, current models that integrate lice into plague transmission in the Middle Ages are able to explain the spread that could not be explained exclusively using the rat, human and rat flea model (84). All these studies could also shed light on the role played by clothing in the dispersal of *Y. pestis* in an epidemic context, as ancient populations were infested with lice until contemporary times (85) (Supplementary Figure 1).

Indeed, in the past, authors wrote on the danger posed by the clothing worn plague victims when it came to the spread of the plague, especially during the epidemics of Marseilles (1720-1722) (86) and Moscow (1771) (87). These observations could foreshadowed the role of lice and their infected faeces which was demonstrated in 1909 during an epidemic typhus outbreak by Nobel Prize winner Charles Nicolle (68). Further investigations may address whether such mode of transmission might apply to pneumonic plague contamination (Supplementary Figure 1).

Historical interhuman transmissions of *Y. pestis*

We re-analysed historical texts dealing with plague to consider the role of lice in the transmission of deadly infections, including plague. The very first mention of lice as putative vectors of plague was found in a treatise written by Nicolas Hartsoeker in 1722 (88). This text was written at the end of the Great Plague of Marseille (1720-1722) and refers directly to this outbreak (88). Hartsoeker argued that plague is not transmitted by the air but by the bite of microscopic insects, such as lice, which find refuge in rags, clothes and bedding. He described them as follows: “I conjecture that the plague is caused only by invisible insects which hide themselves willingly in these stuffs (tatters, goods or clothes) and make their nests inside; that these insects multiply extremely in a very short time…that these insects do not fly, or at least they do not fly very far, but that they do rather like lice that we win easily when those who are infected; that their bite is in proportion to their size, which is at least as dangerous as that of vipers; and that their numbers compensate for their smallness.” The hypothetical role of lice in the plague was also mentioned during the Moscow plague epidemic in 1771 by Russian scientists based on the role that clothing played in the contagion of the disease (86,87). It is interesting to note that the absence of reported cases of animal plague during some large

252 outbreaks such as Marseille (1720-1722) or Moscow (1771), revealed that there was probably
253 a mostly interhuman transmission that pneumonic plague cannot explain, given its low
254 transmission rate (87). Although more than 200 mammal species are susceptible to plague
255 (89), in some cases, no major epizootics were observed during plague pandemics. (86,87)
256 Finally, regarding ancient historical texts about second pandemic plague outbreaks, the great
257 majority of reported cases were bubonic (43). Bubo (meaning "swelling of lymph glands" in
258 Latin, coming from the ancient Greek word *boubṓn* which means "groin or swelling in the
259 groin") is an adenitis and was common during the 15th century (Supplementary figure 2).

260 During the Plague of Marseille (one of the most documented plague episodes),
261 lymphadenopathies were given different names according to their location on the body,
262 thereby lymphadenopathy of the glands around the ears was named "parotid".
263 Lymphadenopathies on inguinal and axillary parts of the body were known as "buboes", and a
264 lymphadenopathy located on other parts of the body was known as abscesses (90). In the
265 modern semiology of the plague, these three terms are grouped under the term "buboes".
266 During the second pandemic, buboes were primarily reported on the inguinal parts of the body
267 or on axillary parts of the body depending on the source (43,86); these locations are
268 compatible with human lice bites (Supplementary Figure 3, Figure 4). The most common
269 location of bubo, the groin, offers a refuge for body lice in the underwear (Supplementary
270 Figure 3, Figure 4) rather than popliteal adenitis, which may occur after fleabites to the legs.
271 At this time, underwear commonly covered the thighs. In the modern era, scratching lesions
272 following plague infection are usually found in the underwear area. After the second
273 pandemic, human body lice become rarer thanks to better hygiene among the populations,
274 however, on rare occasions, body lice may have been involved in plague transmission during
275 the third pandemic, as evidenced by the bubonic outbreaks in Glasgow (91) in 1900 and in the
276 Democratic Republic of Congo in 2010 (82).

The future of plague in the context of louse-borne diseases

The disappearance of massive *Y. pestis*, *B. recurrentis* and *R. prowazekii* outbreaks in countries with a high level of hygiene is most likely evidence of the dramatic disappearance of body lice and anthropophilic fleas (*P. irritans*), another potential vector for interhuman transmission of plague (40). Indeed, rats are still common in rich countries where body lice are scarce, and plague foci persist in poor countries reporting the largest number of plague cases, such as Congo and Madagascar (92,93). However, sporadic cases have been reported in the USA and northern Africa (94,95). The recent discovery and sequencing of *B. recurrentis* from the 15th century in northern Europe, at a time where plague was endemic (96) offers evidence of the circulation of both pathogens and body lice in the late medieval period. Indeed, *B. recurrentis* was circulating at the same time as *R. prowazekii* but in different locations (68). Moreover, *B. recurrentis* is transmitted by lice faeces, similar to *R. prowazekii* and *B. Quintana* (97). A zoonotic agent, such as the murine soft tick-transmitted *Borrelia duttonii* (98), may become an interhuman-transmitted pathogen, such as *B. recurrentis,* after a louse becomes contaminated when feeding on a patient with bacteraemia. Thus, *B. recurrentis* is probably a model organism for lice transmitted pathogens, and circulation of plague probably has more to do with human hygiene and the presence of body lice than to the transmission of the bacterium as a purely zoonotic pathogen. Moreover, the *pla* gene, which is considered a key factor in *Y. pestis* transmission, is unspecific and has been found in some strains of *Citrobacter koseri* isolated from rats or in *Escherichia coli* (99,100); this gene coding for a protease can partially explain human pandemics, but the success of *Y. pestis* as a zoonotic agent is rather due to the murine toxin, the *ymt* gene (89).

We can now construct a scenario for the passage of pathogens detected in wild animals, vectorized by arthropods which occasionally bite humans and are responsible for zoonosis (Figure 5). Among these pathogens, *B. quintana* can remain for years in human

organisms and populations (101). Similarly, typhus can relapse in the form of Brill-Zinsser disease as long as 40 years after the initial infection with *R. prowazekii*; indicating that humans can host the pathogen and transmit it through lice throughout their lifetimes (102,103). *B. recurrentis* is also an endemic relapsing fever pathogen persisting in the human body (104). However, because *Y. pestis* is not a persisting pathogen in the human organism and populations, plague is the only lice-borne transmitted disease that manifests itself in successive waves, resulting in multiple introductions in Europe due to the lack of a human reservoir (57).

Lice can considerably amplify the spread of the microbe, leading to the creation of a hypervirulent clone with a reduced genome size and massive interhuman transmission (105). Thus, *R. prowazekii*, which is well identified in flying squirrels in the United States, is likely to occasionally transmit infections to humans via its arthropods, resulting in a situation where a new typhus cycle can begin. Causative agents of recurrent tick-borne borreliosis, such as *B. duttonii* or *B. crocidurae*, have a very high genetic homogeneity. *B. recurrentis* clearly appears as an emerging clone of *B. duttonii* with a reduced genome (98). In some cases, *B. duttonii* is transmitted to humans (106), and human-to-human transmission could lead to the selection of a hypervirulent clone with a reduced genome size in epidemics of pediculosis. We have shown that *B. quintana* is also a zoonosis affecting cats (107). The transmission of *B. quintana* from cats to humans can be made through fleas, and its further spread by lice can occur on a considerable scale, for which we have an experimental model. However, *B. quintana* has been found in individuals who died approximately 2,000 years B.C. in Europe; at a time when cat fleas were probably not the main vector (64,108). In Poland, *B. quintana* was propagated on a large scale in volunteers to feed lice for typhus-producing lice colonies to produce the Weigl vaccine, as previously reviewed (109). The hyper-specialisation of *B. quintana* and its high level of transmission have been associated with a decrease in the size of

its genome compared to that of *B. henselae* (110). Finally, the same model can be suggested for plague which is a zoonotic agent that can affect several animals (murids, camels, sheep, and cats (89), and rat fleas are likely to bite humans during epizootics. Although the majority of plague cases result from the ectoparasite-borne transmission of *Y. pestis*, nevertheless the pathogen can also be efficiently transmitted by contaminated food (76–78). In situations of epidemics of pediculosis, such as those in eastern Congo (92), this sporadic form can be followed by a micro-outbreak. In special situations, body lice epidemics may occur. This type of epidemic occurred in the concentration camps during the Second World War. It was also observed during the civil war in Rwanda and Burundi as well as in eastern Congo where 100% of the refugee population was infested with lice and where two epidemics—epidemic typhus and trench fever—developed simultaneously (67). The nature and persistence of epidemics of pediculosis outside the contemporary era are very difficult to evaluate, as very few texts allow them to be analysed; however, it is likely that during these epidemics of pediculosis, several pathogens were transmitted. In addition to the cases that are authentically attributable to plague, with the presence of buboes, cases of severe fever sometimes associated with jaundice (such as cases infected with *B. recurrentis*) are likely to indicate one of several epidemics that are transmitted by lice.

Conclusion

In summary, current paleomicrobiological data provide an understanding of past pandemics transmitted by lice, which have probably been the vector, along with mosquitoes, of the most deadly and widespread pandemics in human history. The discovery of *B. recurrentis* from the 15th century in northern Europe highlights the vast circulation of human body lice during this period in this area and suggests that the louse was a competent vector, probably linked with

plague-related pandemics in the late Mediaeval era, as currently proposed by field studies, experimental studies and models. Moreover, the co-circulation of plague with other louse-borne diseases suggests that multiple pathogens may have been identified as plague. Furthermore, modelling of ancient plague epidemics shows that transmission by rats and rat fleas is not consistent with major outbreaks during the second pandemic. Finally, all these elements combined with the rediscovery and demonstration of the efficiency of lice as a plague vector provide substantial evidence on which to base a new theory around *Y. pestis* transmission in Medieval Europe. We currently have sufficient evidence demonstrating that lice played a major role in plague transmission and spread following the same schema as other louse-borne diseases. This proposed paradigm change allows for a better understanding of past and future epidemics.

Contributors

D.R and M.D contributed to the conception of the Review. R.B, M.D and D.R conducted the literature search, data extraction and data synthesis, R.B created figures, D.R provided photography, R.B, M.D and D.R wrote the manuscript. All authors contributed to the interpretation of the data and revision of the manuscript.

Conflicts of interests

We declare no conflict of interests.

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Figure legends:

Figure 1. Timescale of paleomicrobiological data related to louse-borne pathogens from 100.000 BP to the 19th century.

Figure 2. Map of detection of presumably co-transmitted ancient louse-borne bacteria in Europe from 11th to 19th century.

Figure 3. Schematic view of *Y. pestis* lice-to-human transmission mechanisms

Figure 4. Repartition of pediculosis on human body.

Pediculosis is caused by human lice biting, here we reconstructed pediculosis body repartition documented from more than 500 photography of modern pediculosis cases taken by medics of the Mediterranean infection institute.

Figure 5. **Schematic scenario showing how zoonotic agents might become agents transmitted among human population via body-lice**. Green: natural zoonotic sources of opportunist parasite. Blue: Secondary inter-human spreading via body lice ectoparasite, or primary lice-borne pathogens (*B. reccurentis*)

Reference List

1. Little LK, editor. Plague and the end of antiquity: the pandemic of 541-750. New York: Cambridge University Press; 2007. 360 p.

2. Harbeck M, Seifert L, Hänsch S, Wagner DM, Birdsell D, Parise KL, et al. Yersinia pestis DNA from Skeletal Remains from the 6th Century AD Reveals Insights into Justinianic Plague. PLoS Pathog [Internet]. 2013 May 2 [cited 2020 Mar 16];9(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3642051/

3. Wagner DM, Klunk J, Harbeck M, Devault A, Waglechner N, Sahl JW, et al. Yersinia pestis and the plague of Justinian 541-543 AD: a genomic analysis. Lancet Infect Dis. 2014 Apr;14(4):319–26.

4. Feldman M, Harbeck M, Keller M, Spyrou MA, Rott A, Trautmann B, et al. A High-Coverage Yersinia pestis Genome from a Sixth-Century Justinianic Plague Victim. Mol Biol Evol. 2016;33(11):2911–23.

5. Keller M, Spyrou MA, Scheib CL, Neumann GU, Kröpelin A, Haas-Gebhard B, et al. Ancient Yersinia pestis genomes from across Western Europe reveal early diversification during the First Pandemic (541-750). Proc Natl Acad Sci U S A. 2019 Jun 18;116(25):12363–72.

6. Haensch S, Bianucci R, Signoli M, Rajerison M, Schultz M, Kacki S, et al. Distinct clones of Yersinia pestis caused the black death. PLoS Pathog. 2010 Oct 7;6(10):e1001134.

7. Schuenemann VJ, Bos K, DeWitte S, Schmedes S, Jamieson J, Mittnik A, et al. Targeted enrichment of ancient pathogens yielding the pPCP1 plasmid of Yersinia pestis from victims of the Black Death. Proc Natl Acad Sci U S A. 2011 Sep 20;108(38):E746-752.

8. Bos KI, Schuenemann VJ, Golding GB, Burbano HA, Waglechner N, Coombes BK, et al. A draft genome of Yersinia pestis from victims of the Black Death. Nature. 2011 Oct 12;478(7370):506–10.

9. Spyrou MA, Tukhbatova RI, Feldman M, Drath J, Kacki S, Beltrán de Heredia J, et al. Historical Y. pestis Genomes Reveal the European Black Death as the Source of Ancient and Modern Plague Pandemics. Cell Host Microbe. 2016 Jun 8;19(6):874–81.

10. Bos KI, Herbig A, Sahl J, Waglechner N, Fourment M, Forrest SA, et al. Eighteenth century Yersinia pestis genomes reveal the long-term persistence of an historical plague focus. eLife. 2016 Jan 21;5:e12994.

11. Namouchi A, Guellil M, Kersten O, Hänsch S, Ottoni C, Schmid BV, et al. Integrative approach using Yersinia pestis genomes to revisit the historical landscape of plague during the Medieval Period. Proc Natl Acad Sci U S A. 2018 11;115(50):E11790–7.

12. Spyrou MA, Keller M, Tukhbatova RI, Scheib CL, Nelson EA, Valtueña AA, et al. Phylogeography of the second plague pandemic revealed through analysis of historical Yersinia pestis genomes. Nat Commun. 2019;10(1):1–13.

13. Mordechai L, Eisenberg M, Newfield TP, Izdebski A, Kay JE, Poinar H. The Justinianic Plague: An inconsequential pandemic? Proc Natl Acad Sci. 2019;116(51):25546–54.

14. Brossolet J, Mollaret HH. Pourquoi la peste?: le rat, la puce et le bubon. Gallimard; 1994.

15. Yersin A. Bubonic plague in Hong Kong. 1894. 1994.

16. Simond P-L. La propagation de la peste. In Annales de l'Institut Pasteur; 1898.

17. Simond M, Godley ML, Mouriquand PD. Paul-Louis Simond and his discovery of plague transmission by rat fleas: a centenary. J R Soc Med. 1998;91(2):101–4.

18. Bacot AW, Martin CJ. LXVII. Observations on the mechanism of the transmission of plague by fleas. J Hyg (Lond). 1914;13(Suppl):423.

19. Bacot AW. LXXXI. Further notes on the mechanism of the transmission of plague by fleas. J Hyg (Lond). 1915;14(Suppl):774.

20. Hinnebusch BJ, Jarrett CO, Bland DM. 'Fleaing' the Plague: Adaptations of Yersinia pestis to Its Insect Vector That Lead to Transmission. Annu Rev Microbiol. 2017 08;71:215–32.

21. Hinnebusch BJ, Chouikha I, Sun Y-C. Ecological opportunity, evolution, and the emergence of flea-borne plague. Infect Immun. 2016;84(7):1932–40.

22. Rascovan N, Sjögren K-G, Kristiansen K, Nielsen R, Willerslev E, Desnues C, et al. Emergence and Spread of Basal Lineages of Yersinia pestis during the Neolithic Decline. Cell. 2019 Jan 10;176(1–2):295-305.e10.

23. Andrades Valtueña A, Mittnik A, Key FM, Haak W, Allmäe R, Belinskij A, et al. The Stone Age Plague and Its Persistence in Eurasia. Curr Biol CB. 2017 Dec 4;27(23):3683-3691.e8.

24. Rasmussen S, Allentoft ME, Nielsen K, Orlando L, Sikora M, Sjögren K-G, et al. Early divergent strains of Yersinia pestis in Eurasia 5,000 years ago. Cell. 2015 Oct 22;163(3):571–82.

25. Damgaard P de B, Marchi N, Rasmussen S, Peyrot M, Renaud G, Korneliussen T, et al. 137 ancient human genomes from across the Eurasian steppes. Nature. 2018;557(7705):369–74.

26. Spyrou MA, Tukhbatova RI, Wang C-C, Valtueña AA, Lankapalli AK, Kondrashin VV, et al. Analysis of 3800-year-old Yersinia pestis genomes suggests Bronze Age origin for bubonic plague. Nat Commun. 2018 08;9(1):2234.

27. Perry RD, Fetherston JD. Yersinia pestis--etiologic agent of plague. Clin Microbiol Rev. 1997 Jan;10(1):35–66.

28. Sebbane F, Jarrett CO, Gardner D, Long D, Hinnebusch BJ. Role of the Yersinia pestis plasminogen activator in the incidence of distinct septicemic and bubonic forms of flea-borne plague. Proc Natl Acad Sci. 2006;103(14):5526–30.

29. Benedictow OJ, Benedictow OL. The Black Death, 1346-1353: the complete history. Boydell & Brewer; 2004.

30. Hinnebusch BJ, Rudolph AE, Cherepanov P, Dixon JE, Schwan TG, Forsberg A. Role of Yersinia murine toxin in survival of Yersinia pestis in the midgut of the flea vector. Science. 2002 Apr 26;296(5568):733–5.

31. Karlsson G. Plague without rats: The case of fifteenth-century Iceland. J Mediev Hist. 1996 Sep 1;22(3):263–84.

32. Hufthammer AK, Walløe L. Rats cannot have been intermediate hosts for Yersinia pestis during medieval plague epidemics in Northern Europe. J Archaeol Sci. 2013;40(4):1752–9.

33. Audoin-Rouzeau F, Vigne J-D. La colonisation de l'Europe par le rat noir (Rattus rattus). Rev Paléobiol. 1994;13(1):125–45.

34. Drali R, Mumcuoglu KY, Raoult D. Human Lice in paleoentomology and paleomicrobiology. Paleomicrobiology Hum. 2016;181–90.

35. Remicourt M, Andrieu-Ponel V, Audibert C, Baradat A, Battentier J, Belkacem D, et al. Les occupations pré et protohistoriques du Clos de Roque, a Saint-Maximin-la-Sainte-Baume (Var). 2012;

36. Panagiotakopulu E, Buckland PC. A thousand bites–Insect introductions and late Holocene environments. Quat Sci Rev. 2017;156:23–35.

37. Ashfaq M, Prosser S, Nasir S, Masood M, Ratnasingham S, Hebert PD. High diversity and rapid diversification in the head louse, Pediculus humanus (Pediculidae: Phthiraptera). Sci Rep. 2015;5(1):1–13.

38. Mumcuoglu KY. Control of human lice (Anoplura: Pediculidae) infestations: past and present. Am Entomol. 1996;42(3):175–8.

39. Cohn SK. 4 Epidemiology of the Black Death and Successive Waves of Plague. Med Hist. 2008;52(S27):74–100.

40. Eisen RJ, Bearden SW, Wilder AP, Montenieri JA, Antolin MF, Gage KL. Early-phase transmission of Yersinia pestis by unblocked fleas as a mechanism explaining rapidly spreading plague epizootics. Proc Natl Acad Sci. 2006;103(42):15380–5.

41. Beaucournu J-C. A propos du vecteur de la peste en Europe occidentale au cours de la deuxième pandémie. Bull Société Fr Parasitol. 1995;13(2):233–52.

509 42. Benedictow OJ. Epidemiology of Plague: Problems with the Use of Mathematical
510 Epidemiological Models in Plague Research and the Question of Transmission by
511 Human Fleas and Lice. Can J Infect Dis Med Microbiol. 2019;2019.

512 43. Walløe L. 3 Medieval and Modern Bubonic Plague: Some Clinical Continuities. Med
513 Hist. 2008;52(S27):59–73.

514 44. Bramanti B, Stenseth NC, Walløe L, Lei X. Plague: A disease which changed the path
515 of human civilization. In: Yersinia pestis: retrospective and perspective. Springer;
516 2016. p. 1–26.

517 45. Christakos G, Olea RA, Yu H-L. Recent results on the spatiotemporal modelling and
518 comparative analysis of Black Death and bubonic plague epidemics. Public Health.
519 2007;121(9):700–20.

520 46. Brothen JA. Population decline and plague in late medieval Norway. In: Annales de
521 démographie historique. JSTOR; 1996. p. 137–49.

522 47. Davis DE. The scarcity of rats and the Black Death: an ecological history. J Interdiscip
523 Hist. 1986;16(3):455–70.

524 48. Liston WG. The Milroy Lectures, 1924, on the Plague. Br Med J. 1924;1(3310):997.

525 49. McCormick M. Rats, communications, and plague: toward an ecological history. J
526 Interdiscip Hist. 2003;34(1):1–25.

527 50. Keeling MJ, Gilligan CA. Metapopulation dynamics of bubonic plague. Nature.
528 2000;407(6806):903–6.

529 51. Sadler JP. Records of ectoparasites on humans and sheep from Viking-age deposits in
530 the former western settlement of Greenland. J Med Entomol. 1990;27(4):628–31.

531 52. Bramanti B, Dean KR, Walløe L, Chr. Stenseth N. The Third Plague Pandemic in
532 Europe. Proc R Soc B. 2019;286(1901):20182429.

533 53. Schotthoefer AM, Bearden SW, Vetter SM, Holmes J, Montenieri JA, Graham CB, et
534 al. Effects of temperature on early-phase transmission of Yersina pestis by the flea,
535 Xenopsylla cheopis. J Med Entomol. 2011;48(2):411–7.

536 54. Huchet J-B. L'animal-amphitryon: archéologie de l'ectoparasitisme.
537 Anthropozoologica. 2016;51(1):55–66.

538 55. Kreppel KS, Telfer S, Rajerison M, Morse A, Baylis M. Effect of temperature and
539 relative humidity on the development times and survival of Synopsyllus fonquerniei
540 and Xenopsylla cheopis, the flea vectors of plague in Madagascar. Parasit Vectors.
541 2016;9(1):82.

542 56. Drancourt M, Raoult D. Molecular history of plague. Clin Microbiol Infect.
543 2016;22(11):911–5.

57. Schmid BV, Büntgen U, Easterday WR, Ginzler C, Walløe L, Bramanti B, et al. Climate-driven introduction of the Black Death and successive plague reintroductions into Europe. Proc Natl Acad Sci. 2015;112(10):3020–5.

58. Streeter R, Dugmore AJ, Vesteinsson O. Plague and landscape resilience in premodern Iceland. Proc Natl Acad Sci. 2012;109(10):3664–9.

59. Raoult D, Mouffok N, Bitam I, Piarroux R, Drancourt M. Plague: history and contemporary analysis. J Infect. 2013;66(1):18–26.

60. Kool JL, Weinstein RA. Risk of person-to-person transmission of pneumonic plague. Clin Infect Dis. 2005;40(8):1166–72.

61. Zias J, Mumcuoglu KY. How the ancients de-loused themselves. Bibl Archaeol Rev. 1989;15:66–9.

62. Ewing HE. Lice from human mummies. Sci Wash. 1924;60(1556):389–90.

63. Raoult D, Reed DL, Dittmar K, Kirchman JJ, Rolain J-M, Guillen S, et al. Molecular identification of lice from pre-Columbian mummies. J Infect Dis. 2008;197(4):535–43.

64. Drancourt M, Tran-Hung L, Courtin J, Lumley H de, Raoult D. Bartonella quintana in a 4000-year-old human tooth. J Infect Dis. 2005;191(4):607–11.

65. Raoult D, Dutour O, Houhamdi L, Jankauskas R, Fournier P-E, Ardagna Y, et al. Evidence for louse-transmitted diseases in soldiers of Napoleon's Grand Army in Vilnius. J Infect Dis. 2006;193(1):112–20.

66. Raoult D, Roux V. The body louse as a vector of reemerging human diseases. Clin Infect Dis. 1999;29(4):888–911.

67. Raoult D, Ndihokubwayo JB, Tissot-Dupont H, Roux V, Faugere B, Abegbinni R, et al. Outbreak of epidemic typhus associated with trench fever in Burundi. The Lancet. 1998;352(9125):353–8.

68. Nicolle C. Recherches expérimentales sur le typhus exanthématique entreprises à l'Institut Pasteur de Tunis pendant l'année 1909. Masson; 1910.

69. Ruiz J. Bartonella quintana, past, present, and future of the scourge of World War I. Apmis. 2018;126(11):831–7.

70. Maurin M, Raoult D. Bartonella (Rochalimaea) quintana infections. Clin Microbiol Rev. 1996;9(3):273–92.

71. Nguyen-Hieu T, Aboudharam G, Signoli M, Rigeade C, Drancourt M, Raoult D. Evidence of a louse-borne outbreak involving typhus in Douai, 1710-1712 during the war of Spanish succession. PLoS One. 2010;5(10).

72. Tran T-N-N, Forestier CL, Drancourt M, Raoult D, Aboudharam G. Brief communication: co-detection of Bartonella quintana and Yersinia pestis in an 11th-15th burial site in Bondy, France. Am J Phys Anthropol. 2011 Jul;145(3):489–94.

580 73. Tran T-N-N, Signoli M, Fozzati L, Aboudharam G, Raoult D, Drancourt M. High
581 throughput, multiplexed pathogen detection authenticates plague waves in medieval
582 Venice, Italy. PloS One. 2011 Mar 10;6(3):e16735.

583 74. Blanc G, Baltazard M. Recherches expérimentales sur la peste. L'infection du pou de
584 l'homme, Pediculus corporis de Geer. CR Acad Sci. 1941;213(849):e51.

585 75. Chabaud A-G. Les arthropodes vecteurs de la peste bubonique (*suite et fin*). Ann
586 Parasitol Hum Comparée. 1947;22(5–6):357–79.

587 76. Arbaji A, Kharabsheh S, Al-Azab S, Al-Kayed M, Amr ZS, Abu Baker M, et al. A 12-
588 case outbreak of pharyngeal plague following the consumption of camel meat, in
589 north–eastern Jordan. Ann Trop Med Parasitol. 2005;99(8):789–93.

590 77. Christie AB, Chen TH, Elberg SS. Plague in camels and goats: their role in human
591 epidemics. J Infect Dis. 1980;141(6):724–6.

592 78. Saeed AAB, Al-Hamdan NA, Fontaine RE. Plague from Eating Raw Camel Liver.
593 Emerg Infect Dis. 2005 Sep;11(9):1456–7.

594 79. Blanc G, Baltazard M. Rôle des ectoparasites humains dans la transmission de la peste.
595 Bull Acad Natl Med. 1942;126:446.

596 80. Houhamdi L, Lepidi H, Drancourt M, Raoult D. Experimental model to evaluate the
597 human body louse as a vector of plague. J Infect Dis. 2006;194(11):1589–96.

598 81. Drali R, Shako J-C, Davoust B, Diatta G, Raoult D. A new clade of African body and
599 head lice infected by Bartonella quintana and Yersinia pestis—Democratic Republic of
600 the Congo. Am J Trop Med Hyg. 2015;93(5):990–3.

601 82. Piarroux R, Abedi AA, Shako J-C, Kebela B, Karhemere S, Diatta G, et al. Plague
602 epidemics and lice, Democratic Republic of the Congo. Emerg Infect Dis.
603 2013;19(3):505.

604 83. Ayyadurai S, Sebbane F, Raoult D, Drancourt M. Body lice, Yersinia pestis orientalis,
605 and black death. Emerg Infect Dis. 2010;16(5):892.

606 84. Dean KR, Krauer F, Walløe L, Lingjærde OC, Bramanti B, Stenseth NC, et al. Human
607 ectoparasites and the spread of plague in Europe during the Second Pandemic. Proc
608 Natl Acad Sci. 2018;115(6):1304–9.

609 85. Buc'Hoz P-J. Histoire des insectes utiles et nuisibles à l'homme, aux bestiaux, à
610 l'agriculture et au jardinage. 1782. 440 p.

611 86. Chicoyneau F, Senac JB. Traite des causes, des accidens et de la cure de la peste, avec
612 un recueil d'observations, et un detail circonstancie des precautions qu'on a prises pour
613 subvenir aux besoins des peuples affliges de cette maladie, ou pour la prevenir dans les
614 lieux qui en sonst menances ... [Internet]. Pierre-Jean Mariette; 1744. Available from:
615 https://books.google.fr/books?id=Am9VAAAAcAAJ

616 87. Samojlovič DS. Opuscules sur la peste qui en 1771 ravage a Moscou. 1787.

88. Hartsoeker N. Recueil de plusieurs pièces de physique, où l'on fait principalement voir l'invalidité du Système de Mr Newton et où se trouve ... une dissertation sur la peste, etc. (Remarques de M. Leclerc, etc.). [Internet]. Chez la veuve de G. Broedelet & fils; 1722. Available from: https://books.google.fr/books?id=qpvv2cM3hrQC

89. Abbott RC, Rocke TE. Plague. U.S. Department of the Interior, U.S. Geological Survey; 2012. 79 p.

90. Astruc J. Dissertation sur la peste de Provence [Internet]. typis Bodmerianis; 1721. Available from: https://books.google.fr/books?id=qbQUAAAAQAAJ

91. Dean KR, Krauer F, Schmid BV. Epidemiology of a bubonic plague outbreak in Glasgow, Scotland in 1900. R Soc Open Sci. 2019;6(1):181695.

92. Abedi AA, Shako J-C, Gaudart J, Sudre B, Ilunga BK, Shamamba SKB, et al. Ecologic features of plague outbreak areas, Democratic Republic of the Congo, 2004–2014. Emerg Infect Dis. 2018;24(2):210.

93. Andrianaivoarimanana V, Kreppel K, Elissa N, Duplantier J-M, Carniel E, Rajerison M, et al. Understanding the persistence of plague foci in Madagascar. PLoS Negl Trop Dis. 2013;7(11):e2382.

94. Malek MA, Bitam I, Drancourt M. Plague in Arab Maghreb, 1940–2015: A Review. Front Public Health. 2016;4:112.

95. Kugeler KJ, Staples JE, Hinckley AF, Gage KL, Mead PS. Epidemiology of human plague in the United States, 1900-2012. Emerg Infect Dis. 2015 Jan;21(1):16–22.

96. Guellil M, Kersten O, Namouchi A, Bauer EL, Derrick M, Jensen AØ, et al. Genomic blueprint of a relapsing fever pathogen in 15th century Scandinavia. Proc Natl Acad Sci. 2018;115(41):10422–7.

97. Houhamdi L, Raoult D. Excretion of living Borrelia recurrentis in feces of infected human body lice. J Infect Dis. 2005;191(11):1898–906.

98. Lescot M, Audic S, Robert C, Nguyen TT, Blanc G, Cutler SJ, et al. The genome of Borrelia recurrentis, the agent of deadly louse-borne relapsing fever, is a degraded subset of tick-borne Borrelia duttonii. PLoS Genet. 2008;4(9).

99. Hänsch S, Cilli E, Catalano G, Gruppioni G, Bianucci R, Stenseth NC, et al. The pla gene, encoding plasminogen activator, is not specific to Yersinia pestis. BMC Res Notes. 2015;8(1):535.

100. Haiko J, Laakkonen L, Westerlund-Wikström B, Korhonen TK. Molecular adaptation of a plant-bacterium outer membrane protease towards plague virulence factor Pla. BMC Evol Biol. 2011;11(1):43.

101. Chomel BB, Kasten RW, Sykes JE, BOULOUIS H-J, Breitschwerdt EB. Clinical impact of persistent Bartonella bacteremia in humans and animals. Ann N Y Acad Sci. 2003;990(1):267–78.

102. Lutwick L. Brill-Zinsser disease. The Lancet. 2001;357(9263):1198–200.

655 103. Stein A, Purgus R, Olmer M, Raoult D. Brill-Zinsser disease in France. The Lancet.
656 1999;353(9168):1936.

657 104. Meri T, Cutler SJ, Blom AM, Meri S, Jokiranta TS. Relapsing fever spirochetes
658 Borrelia recurrentis and B. duttonii acquire complement regulators C4b-binding protein
659 and factor H. Infect Immun. 2006;74(7):4157–63.

660 105. Georgiades K, Raoult D. Defining pathogenic bacterial species in the genomic era.
661 Front Microbiol. 2011;1:151.

662 106. Raoult D, Birtles RJ, Montoya M, Perez E, Tissot-Dupont H, Roux V, et al. Survey of
663 three bacterial louse-associated diseases among rural Andean communities in Peru:
664 prevalence of epidemic typhus, trench fever, and relapsing fever. Clin Infect Dis.
665 1999;29(2):434–6.

666 107. La VD, Tran-Hung L, Aboudharam G, Raoult D, Drancourt M. Bartonella quintana in
667 domestic cat. Emerg Infect Dis. 2005;11(8):1287.

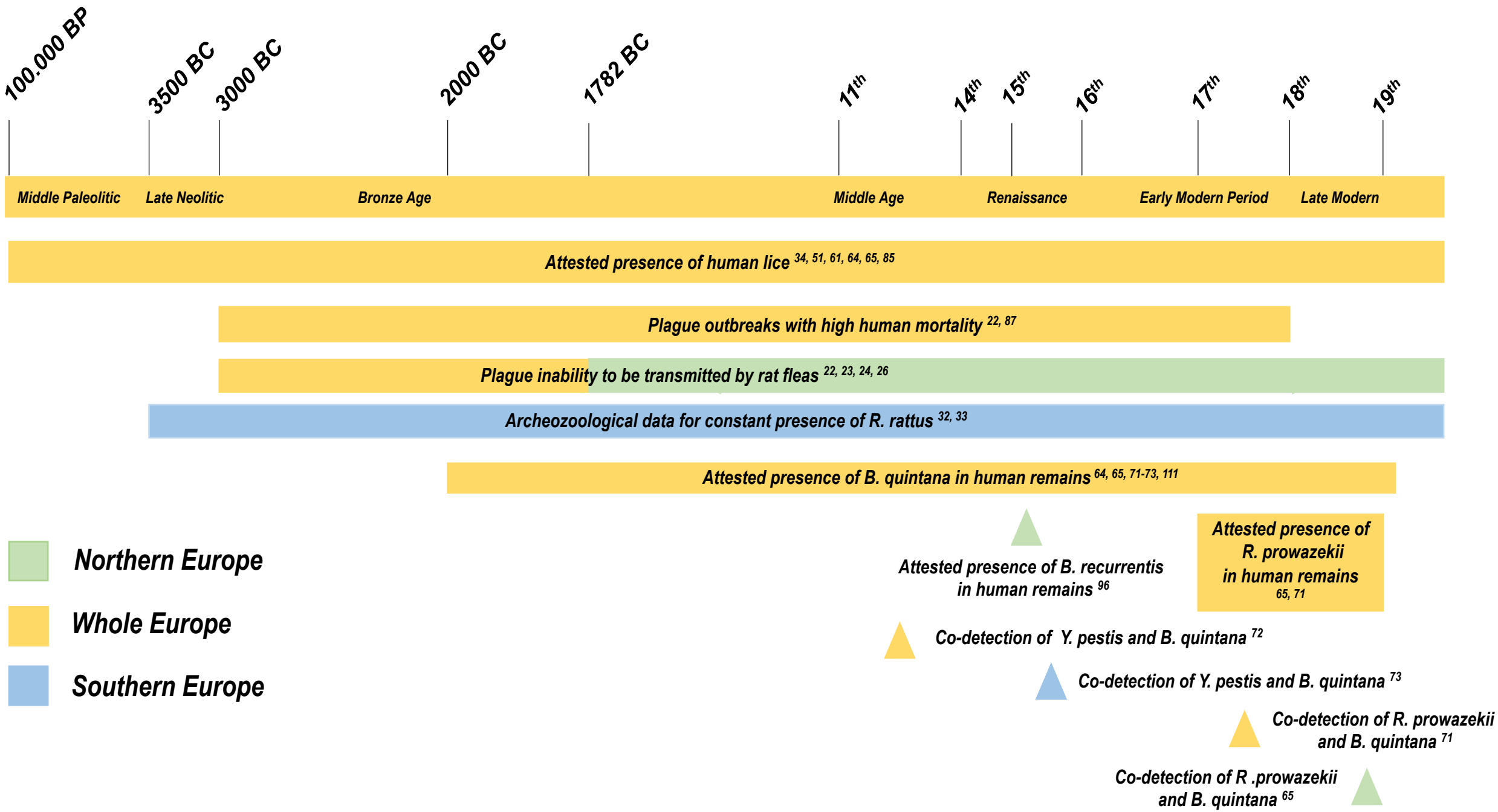
668 108. Ottoni C, Van Neer W, De Cupere B, Daligault J, Guimaraes S, Peters J, et al. The
669 palaeogenetics of cat dispersal in the ancient world. Nat Ecol Evol. 2017;1(7):1–7.

670 109. Gross L. How Charles Nicolle of the Pasteur Institute discovered that epidemic typhus
671 is transmitted by lice: reminiscences from my years at the Pasteur Institute in Paris.
672 Proc Natl Acad Sci U S A. 1996;93(20):10539.

673 110. Alsmark CM, Frank AC, Karlberg EO, Legault B-A, Ardell DH, Canbäck B, et al. The
674 louse-borne human pathogen Bartonella quintana is a genomic derivative of the
675 zoonotic agent Bartonella henselae. Proc Natl Acad Sci. 2004;101(26):9716–21.

676 111. Grumbkow P v, Zipp A, Seidenberg V, Fehren-Schmitz L, Kempf VA, Groß U, et al.
677 Brief communication: Evidence of Bartonella quintana infections in skeletons of a
678 historical mass grave in Kassel, Germany. Am J Phys Anthropol. 2011;146(1):134–7.

679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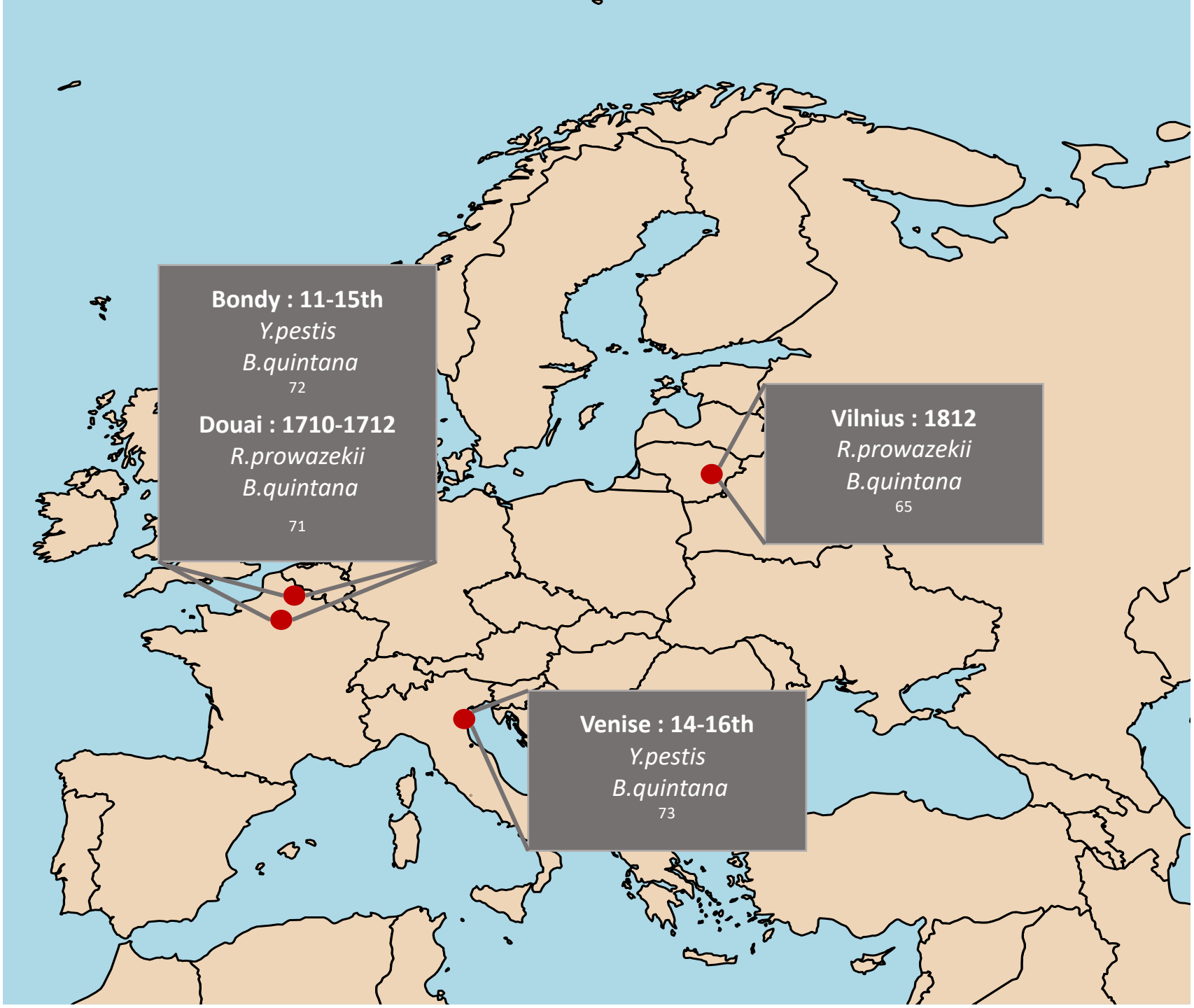
Late Neolitic
Bronze Age
Middle Age
Renaissance
Early Modern Period
Late Modern
Attested presence of human lice 34, 51, 61, 64, 65, 85
Plague outbreaks with high human mortality 22, 87
Plague inability to be transmitted by rat fleas 22, 23, 24, 26
Archeozoological data for constant presence of R. rattus 32, 33
Attested presence of B. quintana in human remains 64, 65, 71-73, 111
Northern Europe
Whole Europe
Southern Europe
Attested presence of B. recurrentis in human remains 96
Attested presence of R. prowazekii in human remains 65, 71
Co-detection of Y. pestis and B. quintana 72
Co-detection of Y. pestis and B. quintana 73
Co-detection of R. prowazekii and B. quintana 71
Co-detection of R .prowazekii and B. quintana 65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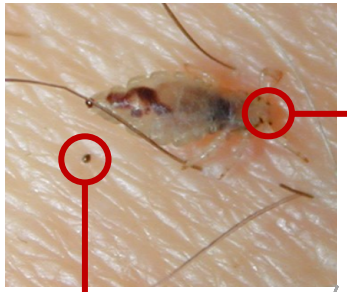
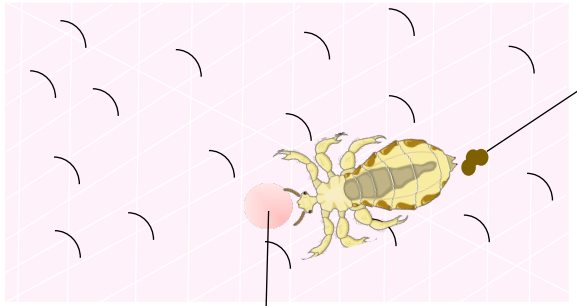
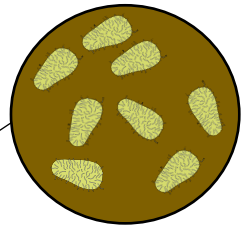


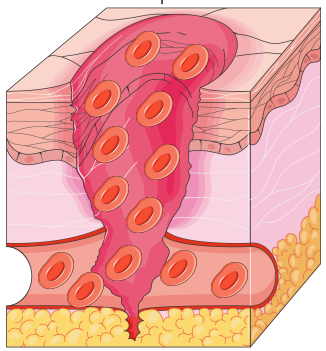
Bite point

Avoid infected feces

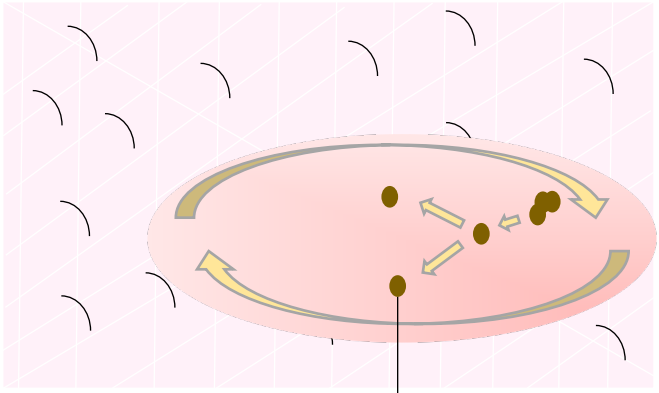




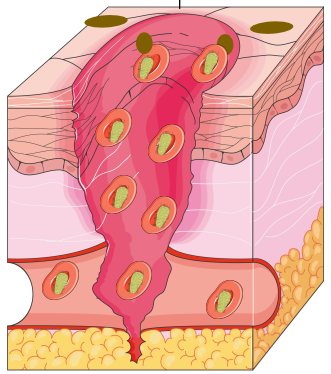
Lice feces are infected with viable Y. pestis bacteria



The bite point is in contact with blood cells



Scracthing lesion leading to a dissemination of infected feces into the bite point or others micro-lesions

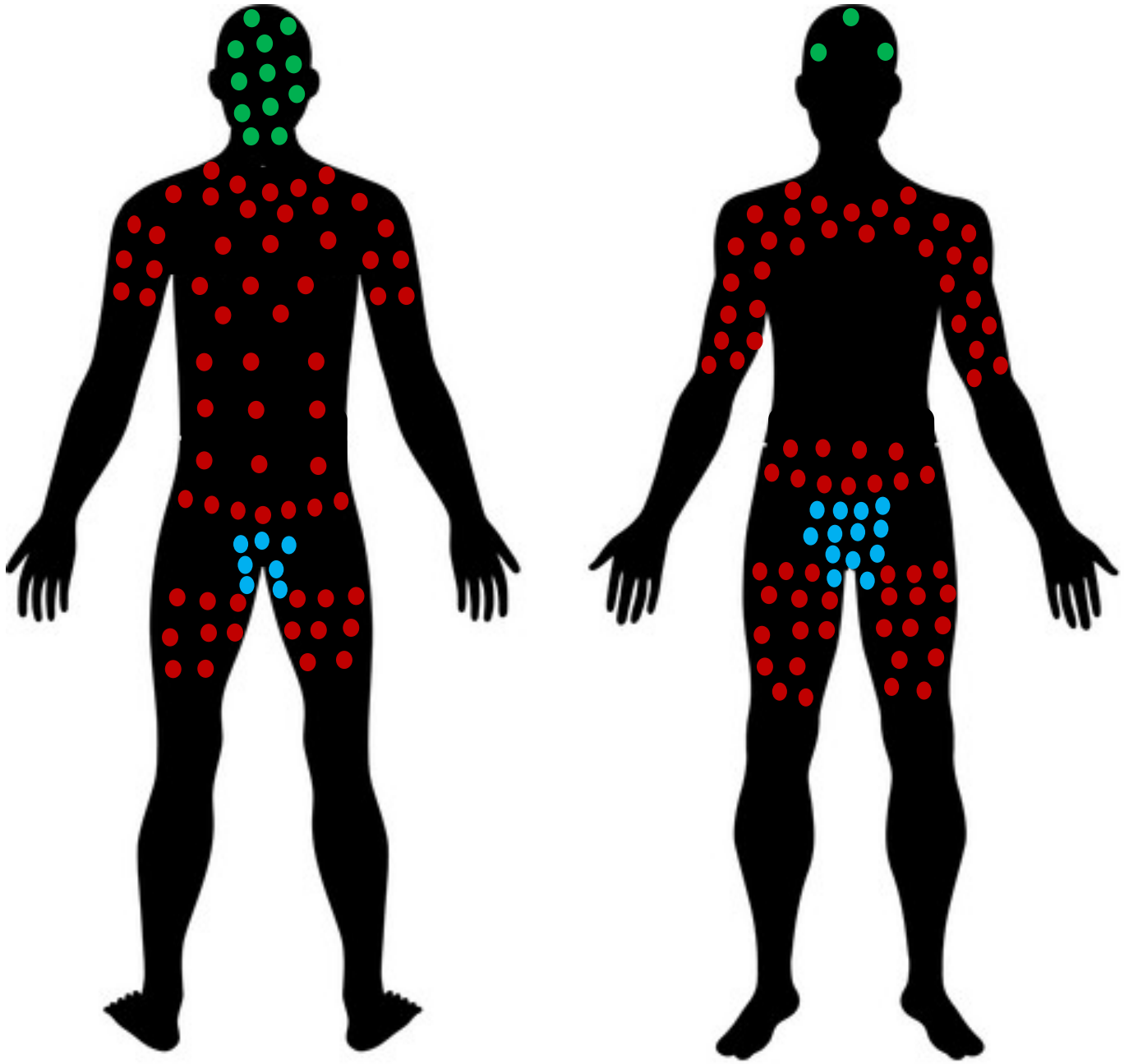


Introduction of viable Y. pestis bacteria with feces through micro-lesions or bite point of the skin and dissemination into the blood systems

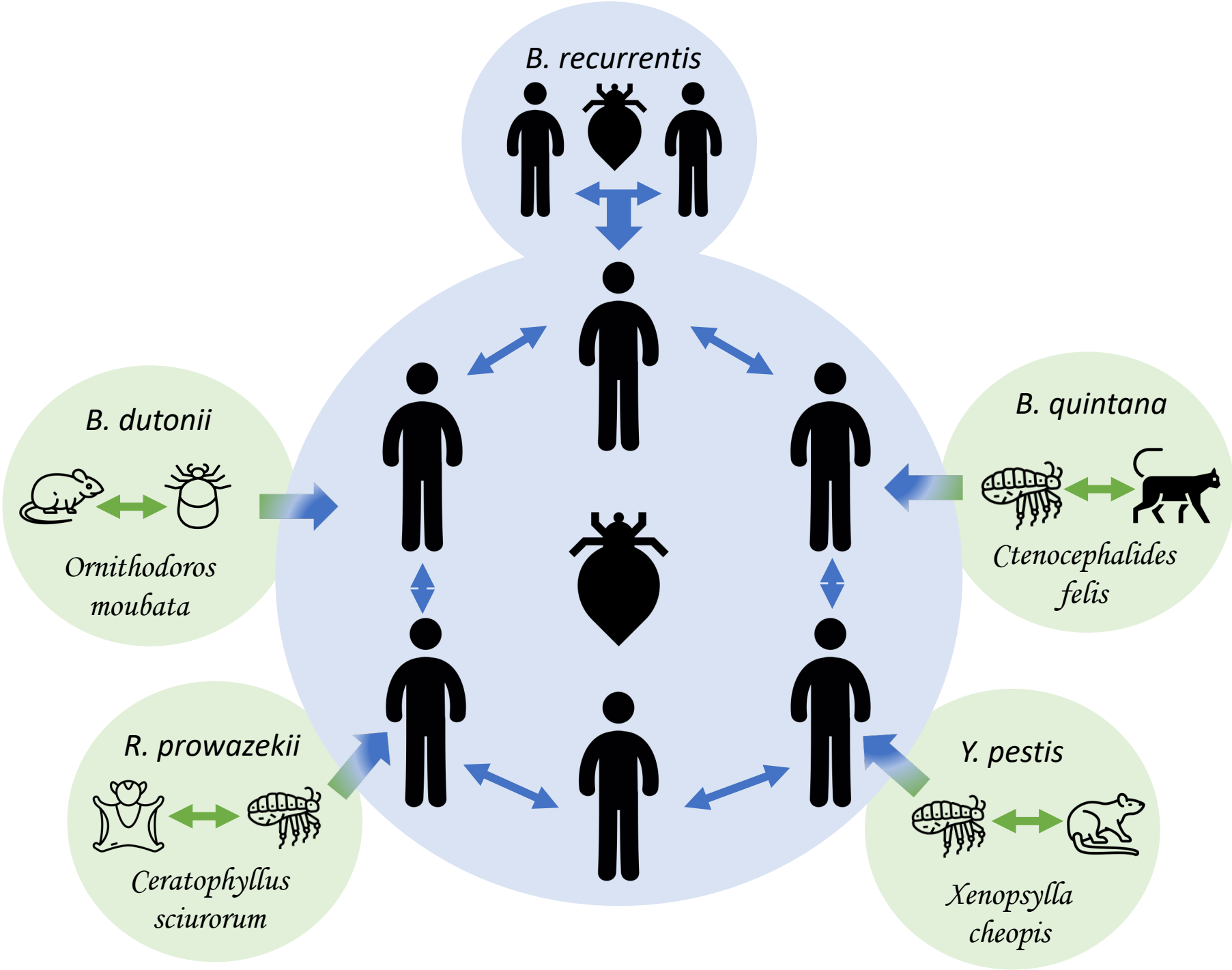
Pediculosis caused by Pediculus humanus capitis biting

Pediculosis caused by Pediculus humanus corporis biting

Pediculosis caused by Phtirius unguinalis biting



Back **Front**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B. dutonii
Ornithodoros moubata
B. quintana
Ctenocephalides felis
R. prowazekii
Ceratophyllus sciurorum
Y. pestis
Xenopsylla cheopis