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Article

# Zoonotic Barrier Disruption and the Rise of the Third Plague Pandemic: A One Health Analysis of 19th-Century Yunnan and the Emergence of *Yersinia Pestis* Strain 1.ORI

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## Simple Summary

This research explains how a major global plague pandemic began in the 19th century in the Yunnan region of China. We used a “One Health” approach, which looks at the deep connections between the environment, animals, and human society, and how these connections change over time and space. The plague strain 1.ORI, formed in populations of the Indian gerbil (*Tatera indica*) and penetrated into the populations of commensal rats, differs from other strains in that it is more efficiently spread by the fleas living on particular rats. In Yunnan, human activities like widespread deforestation for mining and farming destroyed the natural habitats of the wild rats. Losing their homes and food sources, these wild rats moved into human settlements. A population complex of commensal *Rattus* (RrC) rats was formed, into which the plague pathogen penetrated and formed anthropogenic (synanthropic) foci of infection. The disease, now in rats living close to people, easily jumped into human populations. This process was worsened by factors like food shortages and opium use, which weakened the health of both animals and people. By showing how these human-driven changes created a “perfect storm” for this specific plague strain to emerge and go global, our study provides a framework for understanding how new pandemics can start and how to prevent them today.

## Abstract

The emergence of the Third Plague Pandemic in 19th-century Yunnan, linked to *Yersinia pestis* strain 1.ORI, remains incompletely understood. Applying a One Health framework, this study investigates how human-driven ecological and societal disruptions during the 19th century compromised zoonotic barriers, facilitating initial spillover and a bottleneck event that enabled global spread. Our interdisciplinary methodology analyzes Qing dynasty gazetteers, historical medical records, and environmental data, integrated with biological evidence on transmission dynamics involving commensal rats and the flea vector *Xenopsylla cheopis*. Results indicate that convergent factors—including widespread deforestation, intensified mining/agriculture, population growth, high synanthropic rat densities, and the disruptions of the Panthay Rebellion—collectively created a high-risk interface for zoonotic transfer. Critically, comorbidities such as malnutrition, heavy metal exposure, and opium use likely eroded host immune resilience in both rodent and human populations, amplifying transmission. Yunnan's rapid socio-ecological transformation was thus a critical catalyst for pandemic emergence. This analysis underscores how historical land-use,

demographic shifts, and public health conditions shaped zoonotic risk. Crucially, a One Health assessment must analyze interactions across time and space, recognizing that environmental, biological, and socioeconomic changes occur on non-uniform temporal scales. This spatiotemporal perspective provides a framework that offers deeper insight into past pandemic origins and for anticipating contemporary vulnerabilities.

**Keywords:** *Yersinia pestis*; Panthay rebellion; Yunnan; one health; zoonotic spillover; 1.ORI; third plague pandemic

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## 1. Introduction

### *Understanding the Risk of Zoonotic Diseases Through Analysing Their Biological, Environmental, & Societal Context*

At the start of the 21st century, global health faces new threats driven by rapid socio-economic change, environmental disruption, and intensifying human-pathogenic microorganism contacts. Over thirty novel or reemerging infectious diseases—such as SARS, avian influenza, and Ebola—have appeared in recent decades, many fuelled by the erosion of ecological barriers that once limited zoonotic spillover. Central to gaining in resilience to zoonotic outbreaks (in zoonosis control) is a deeper understanding of how pathogens emerge, evolve, and adapt—particularly in relation to the erosion of the natural barriers that historically have limited zoonotic spillover. At the same time the pathogen evolution, dynamics of its virulence, and host-vector interactions must be studied not in isolation, but as part of an interconnected ecosystem—an approach championed by the One Health paradigm.

When conceiving of how microbes are affected by natural interconnected systems, it is helpful to see this connection in terms of microbes overcoming environmental and human barriers that have been eroded in the biosphere and more specifically in the wildlife, as well as pre-domestic, humans, and livestock in the domestic landscape. Microbes that develop into disease causing agents, termed pathogens, must overcome many barriers for a human zoonotic epidemic or pandemic to take place [1] (p. 2). As these barriers operate across different spaces and populations within the biosphere, human activities alter these natural processes and elevate the risk of zoonotic outbreaks. It is in these settings that human activity plays a role in these processes and the potential risk of a human zoonotic disease outbreak (Appendix 1).

Accordingly, large-scale environment altering activities can lead to a lack of environmental services that provide sufficient energy to the diverse plant and animal species in these geographic regions. This imbalance allows certain pathogens, along with their hosts and vectors, to gain a competitive advantage, leading to rapid population growth and a higher probability of spillover events and cross-species transmission. This process, termed allostatic overload (Appendix 2), not only disrupts ecological niches but also impairs immune function in wildlife, compounding the risk of zoonotic infections. As Plowright et al. (2024) emphasize, large-scale environmental changes (e.g., deforestation, urbanization) degrade zoonotic barriers by altering host-vector-pathogen interactions [2]. These disruptions create pathogen bottlenecks that select for strains with enhanced spillover potential.

The movement of zoonotic pathogens between wildlife, domestic animals, and humans—a process exemplified by *Yersinia pestis*, the plague bacterium—reveals how ecological disruption drives zoonotic spillover. The Third Plague Pandemic (mid-19th to early 20th century), caused by *Y. pestis* strain 1.ORI (biovar Orientalis), exemplifies this dynamic. Plague's historical prominence and well-documented evolution make it a critical case study in how environmental degradation, economic transformation, and demographic shifts converge to disrupt zoonotic barriers.

This article examines the natural factors that led to the emergence of the plague pathogen as a species of *Y. pestis* and the formation of its primary natural range in Asia, as well as socio-economic

and demographic factors that ensured its spread to Yunnan Province and the beginning of the 3rd plague pandemic in the world. Our hypothesis was that weakened zoonotic barriers created the conditions that allowed the Third Plague Pandemic to emerge, while the development of the *Yersinia pestis* strain 1.ORI, maintained by *Rattus* species and transmitted largely through the *Xenopsylla cheopis* flea, substantially heightened the likelihood of pandemic spread. Accordingly, this study first investigated the early emergence of *Y. pestis* strain 1.ORI, which moved from the India–Tibet borderlands through the Indian gerbil (*Tatera indica*) and then *Rattus* species to Yunnan and then continue through the *Rattus* species host to Hong Kong during the Third Plague Pandemic. Using a One Health framework, we analyzed how 19th-century ecological disruption and social change eroded zoonotic barriers, enabling the pathogen spillover. Our approach integrated the Qing dynasty gazetteers and historical medical records from Yunnan (principally around Dali in western Yunnan and Kunming in eastern Yunnan), environmental data from the late 18th to the 19th century, and biological evidence on the transmission efficiency of commensal rat hosts and *X. cheopis* fleas. The findings suggest that Yunnan’s rapid and destabilizing land-use changes in conjunction with the 1.ORI *Y. pestis* strain with its primary *Rattus* species host and *X. cheopis* flea vector produced a “perfect storm” for zoonotic emergence.

This study’s uniqueness lies in its systematic assessment of how the co-evolution of the *Yersinia pestis* 1.ORI strain and the erosion of zoonotic barriers in 19th-century Yunnan created the essential conditions for the Third Pandemic. We employ a novel analytical framework that integrates a bio-environmental tracing of the strain’s spatio-temporal adaptation with a One Health analysis of the factors compromising zoonotic barrier integrity.

This integrated approach addresses a critical gap in the existing scholarship. Previous research has yielded invaluable but fragmented insights, focusing on discrete aspects such as:

- Socio-economic factors, including the opium trade [3,4], the Panthay Rebellion [5–7]; demographic change [8], and currency devaluation [9,10].
- Environmental drivers, as 19th-century environmental and climate change in Yunnan [11–14]
- Biological components, including the 1.ORI strain itself [15], the flea vector *X. cheopis* [16], and *Rattus* host populations [17].

A pivotal intellectual consequence of the pandemic itself was the cultural and scientific fixation on hygiene [18] and the rat as the primary vector [19], a paradigm cemented by Simond’s discovery of the rat-flea transmission cycle in 1898 [20]. This narrow focus exemplifies a broader historical shift in tropical medicine, where research moved away from complex environmental contexts and toward a laboratory-based study of pathogens—a trend influenced by the political and funding priorities of colonial powers. The longstanding practice of funding pathogen-specific research while neglecting its environmental setting, exemplified by the British Colonial Office [21,22], created a disciplinary divide that interdisciplinary and transdisciplinary work, as the One Health Approach exemplifies, seeks to overcome.

However, no study has yet synthesized these disparate threads to demonstrate how the biological evolution of the 1.ORI strain and the socio-ecological disintegration of zoonotic barriers *jointly* precipitated the pandemic. Furthermore, our One Health approach explicitly emphasizes the dynamic spatio-temporal nature of zoonoses. We contend that zoonotic processes cannot be fully understood through static “snapshots in time.” Pathogens spread through space and evolve over time, shaped by ongoing biological and environmental changes. Recognizing this dynamism is essential to understanding how local spillovers escalate into pandemics.

This paper is structured to trace the sequence of events that led to the Third Plague Pandemic. Following a description of our integrated methodological framework, which combines biological, environmental, and historical analysis, the Results section is divided into two primary parts.

First, we establish the evolutionary pathway of the *Y. pestis* 1.ORI strain, detailing its origins in the *Tatera indica* - *Xenopsylla astia* system and its subsequent host dynamics upon entering Yunnan.

Second, we analyze the interrelated processes in 19th-century Yunnan that drove pandemic emergence. This analysis begins with the socio-economic shifts—including real wage decline,

population growth, and deforestation—that triggered widespread ecological change. We then demonstrate how these changes precipitated a biological breakdown of zoonotic barriers, exploring the roles of heavy metal contamination and opium-driven food insecurity in suppressing immune function and facilitating infection.

Finally, we synthesize these threads to show how displaced *Rattus* populations, concentrated in human settlements, created a demographic bottleneck for *Y. pestis*, setting the stage for the Panthay Rebellion to act as the final trigger that unleashed the pandemic. Accordingly, by systematically integrating the strain's evolution with the socio-ecological disintegration of Yunnan's zoonotic barriers, this study provides a comprehensive One Health explanation for the rise of the Third Plague Pandemic.

## 2. Methods and Materials

### *Research Framework Through an Integrated Approach*

This study employs a One Health framework to investigate the disruption of zoonotic barriers and the emergence of the Third Plague Pandemic in 19th-century Yunnan. We test the hypothesis that the convergence of a novel *Y.pestis* strain (1.ORI), specific environmental pressures, and profound socioeconomic changes created a synergistic “perfect storm,” enabling a local epizootic to escalate into a global pandemic. Our methodology integrates three analytical streams: 1) a biological analysis of the 1.ORI strain; 2) an environmental and demographic analysis of Yunnan; and 3) a regional contextual analysis of broader disruptions. Data from historical gazetteers, medical records, and paleoecological evidence—including core samples for pollen and sediment analysis—are synthesized to construct a dynamic, causal model of pandemic emergence.

#### **1) Biological analysis of *Yersinia pestis*, 1.ORI strain**

Conventional molecular phylogenetics is designed to trace quantitative genetic divergence in deep-time taxa, whose ancestral environments and adaptive pressures are largely unknown. The recent emergence of *Y.pestis*, however, provides a unique opportunity to move beyond establishing *what* happened to explaining *why* it happened. This study leverages that recency to interrogate the specific environmental pressures that shaped its evolution. Our methodology integrates foundational molecular phylogenies of *Y. pestis* [23–25], with an ecological-adaptationist analysis. We treat specific genetic changes—such as the ability to ferment glycerol (gly+/gly–) phenotype—not merely as phylogenetic markers but as functional adaptations to a new niche. By contextualizing these changes within the specific zoonotic system of the Mongolian marmot and a potential wound-based transmission route, as detailed in regional biogeographical studies [26], we construct a causal model. This model directly links the evolutionary mechanisms that created the 1.ORI strain to the historical-ecological drivers that facilitated its global spread via its *Rattus* hosts and *X. cheopis* vectors.

#### **2) Environmental and Demographic Analysis of 19th-Century Yunnan**

To assess pressures on zoonotic barriers in 19th-century Yunnan, we conducted a systematic analysis of valley regions as epicenters of environmental and demographic change. This analysis is structured around three interconnected themes:

**a. Landscape and Ecological Change:** We reconstructed anthropogenic landscape alteration by synthesizing:

**-Palaeoecological Data:** Pollen and sediment cores from Yunnan lakes of previous studies were analyzed for indicators of deforestation, agricultural intensification, and heavy metal contamination (e.g., lead, copper) from mining. This was supplemented by environmental modelling of deforestation based on palaeoecological archives and historical documentation.

**-Historical Documentation:** Qing dynasty gazetteers, travel logs, and scientific reports were systematically reviewed for evidence of deforestation for timber, mining, and charcoal production; agricultural expansion; and the development of mining operations.

**b. Socioeconomic Pressures and Human-Animal Interface:** We analyzed factors, as population density, evidence of forest rat populations to human settlements, that increased human exposure to

zoonotic reservoirs and compromised population resilience, through historical and palaeoecological sources.

**-Demographic and Labor Shifts:** Yunnan Historical primary and secondary sources were assessed to trace labor migration into valley regions to support mining and agricultural intensification, and to estimate rising human population density. These historical sources were analyzed in the context of the palaeoecological evidence that showed deforestation and increased cultivation in valleys where mining and agricultural labor migration was known to have been escalating.

**-Economic Destabilization:** We evaluated wage pressures and livelihood insecurity by analyzing historical data on the declining value of copper coins relative to silver under the Qing dual-currency system, which undermined purchasing power and inflated the cost of daily necessities as documented by: Li (2002) [27] and Hu (2014) [28].

**-Social Unrest:** The historic record of the prevalence of banditry and social unrest, such as the Panthay Rebellion, was documented as an indicator of systemic socioeconomic strain.

**c. Host Susceptibility and Barrier Permeability:** We investigated the hypothesis that documented immune stressors compromised zoonotic barriers in 19th-century Yunnan. The prevalence of malnutrition, heavy metal contamination, and opium abuse was first deduced from convincing direct and circumstantial historical and paleoecological evidence. Subsequently, we conducted a systematic review of biomedical literature to determine the specific mechanisms by which these factors impair immune function in mammals, thereby modeling their combined impact on facilitating *Y. pestis* spillover and spread.

**-Immunological Stressors:** Evidence for widespread opium use, heavy metal exposure (from sediment data and historical mining records), and malnutrition (inferred from economic data and historical reports on famine) was compiled to assess their potential synergistic impact on host susceptibility.

### 3) Regional Contextual Analysis: Indicators of Broader Zoonotic Barrier Disruption

To contextualize the Yunnan outbreak within wider regional dynamics, we noted preliminary historical and palaeoecological evidence of the same dynamics increasingly taking place in South and Southeast Asia in second half of the 19th century, prompting for a full-scale study of the 1.0RI region from Yunnan to Hong Kong. This preliminary assessment involved assessing historical and palaeoecological evidence on two major subject matter:

**a. The Spread of Conflict and Trade:** The trajectory of the Panthay Rebellion and other contemporaneous revolts, which disrupted landscapes and displaced populations, appear widespread during this period in China. Concurrently, the expansion of the opium economy and associated banditry networks may have help expand different factors, as demographic change, landscape change, and diminished immune system function that have been tied to the erosion of zoonotic barriers and disease dissemination.

**b. Regional Environmental Pressures:** Historical and environmental evidence for widespread deforestation and vegetation clearance beyond Yunnan was reviewed to assess the regional scale of habitat disruption favoring commensal rodents like *Rattus* spp.

*The historical reference points for the historical materials included:*

- **Digital gazetteer databases**, including the *Erudition Database of Local Gazetteers* (《方志数据库》) and *CNKI's Local Chronicles Collection*, were systematically consulted to extract primary references to plague outbreaks, rodent infestations, and ecological degradation across Yunnan during the Qing period. These digital platforms aggregate county-level and prefectural records from multiple editions, enabling comparative tracking of terminology evolution (e.g., 鼠疫) and spatial distribution patterns over time.
- **Printed historical compilations**, such as the *Guangxu-era Yunnan Tongzhi* (《云南通志》) and selected fascicles of the *Qing Veritable Records* (《清实录》), provided authoritative accounts of state responses to epidemic outbreaks, regional famines, and military–epidemic interactions. These sources were used to cross-reference local narratives and identify macro-level policy

changes (e.g., granary failures, mining decrees, population relocations) that shaped zoonotic conditions in 19th-century Southwest China.

- **Secondary literature** by Joseph Esherick, Edward Rhoads, and William Rowe, which proved helpful for triangulating demographic and political shifts.

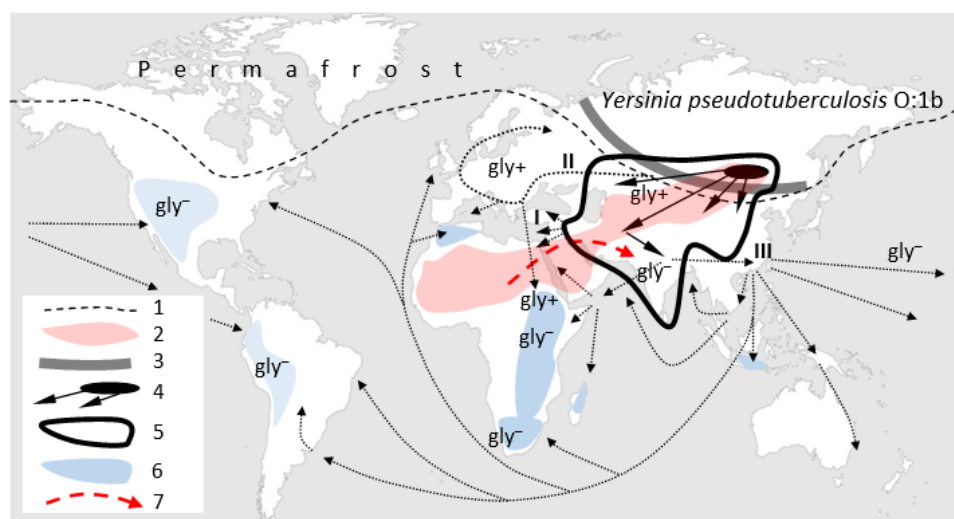
### 3. Results

#### I. *Y. pestis* Evolutionary Pathway of Adaption to Hosts, Vectors and Ecological Drivers Leading to the 3rd Plague Pandemic

##### A. Indicators of the Evolution of the 1.ORI Strain in the *Tatera indica* - *Xenopsylla astia* System

Understanding the biological evolution of *Y. pestis* requires examining how pathogens adapt to hosts, how environmental changes reshape disease dynamics, and how interactions between hosts, vectors, and pathogens can drive cross-species spillovers. Among zoonotic diseases, the plague stands out as one of the most studied due to its historical impact and well-documented evolutionary path.

A combination of modern molecular, genetic and environmental data has made it possible to reliably establish that 1) the direct ancestor of the plague pathogen is the pathogen of the Far Eastern scarlet fever *Yersinia pseudotuberculosis* O:1b [29], p.2. the transformation of the pseudotuberculosis population into the population of the plague pathogen took place in the recent historical past, no earlier than 30 thousand years ago, in the Late Pleistocene or Holocene [30,31] and 3) the speciation of *Y. pestis* occurred in natural conditions without any human influence in Central Asia in the parasitic system of the Mongolian marmot (*Marmota sibirica*) - marmot flea (*Oropsylla silantiewi*) [32]. From the settlements of the Mongolian marmot, the plague pathogen spread through parasitic contacts into populations of sympatric burrowing rodents (Rodentia) and pikas (*Ochotona*) and formed an area of primary natural foci in Asia and the far south-east of Europe (Figure 1). The plague existed exclusively in the form of natural foci until the development of human society violated the environmental barriers that restrain the pathogen within the boundaries of the wild. The socio-economic development of human society and demographic shifts have “released the Genie from the bottle”: through direct contact between hunters and wild rodents, the breeding of domestic animals that come into contact with wild animals in the territories of natural foci and ubiquitous synanthropization of rodents (rats, mice), primarily in the area of natural plague foci, humans have created conditions for the transfer of the introduction of the plague microbe into human society, the emergence of epidemics and pandemics. Thus, the development of human society at a certain stage led to the emergence of an important social problem – the health of society, the solution of which is currently being implemented within the framework of the One Health paradigm.



**Figure 1. Evolutionary spread of *Yersinia pestis* across three plague pandemics (I-III).** This map traces the origin and expansion of *Y. pestis* from its ancestor *Y. pseudotuberculosis* in Central Asia, within the range of the

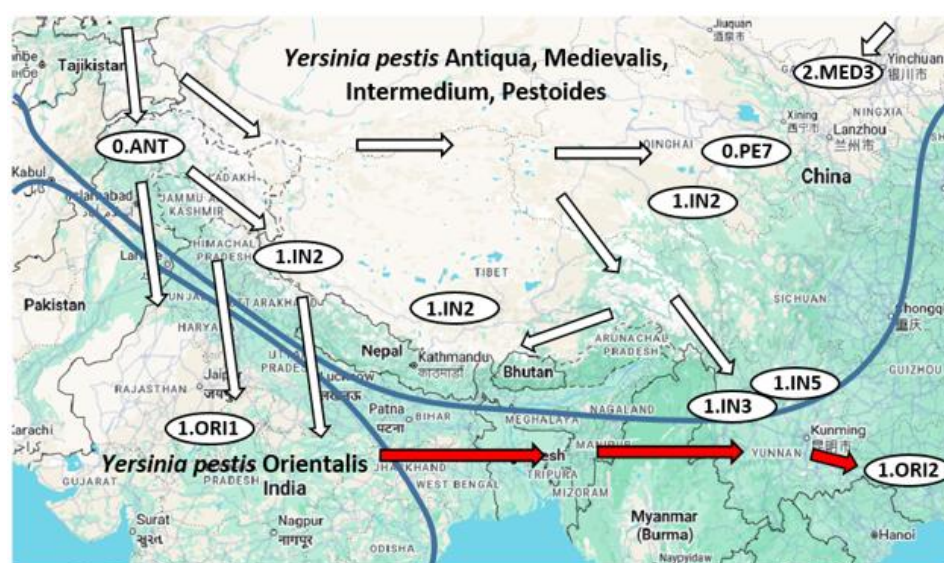
Tarbagan marmot (*Marmota sibirica*). Map Legend descriptions (1-7): (1) the southern boundary of the permafrost zone; thawing of which affects landscapes, vegetation, soil hydrology, greenhouse gases, & biodiversity; (2) the Sahara–Gobi arid zone, a natural barrier affecting disease spread; (3) the boundary of the dominant prevalence of *Y. pseudotuberculosis* O:1b, the progenitor strain of *Y. pestis*; (4) the geographic range of the Tarbagan marmot, the region of the origin of the plague microbe and direction of its natural expansion in Eurasia; (5) the geographic range of primary natural foci; (6) the geographic ranges of secondary natural foci; (7) the migration route of *Tatera* rodents from Africa to Asia during the Early Pleistocene. gly+ (gly-) is the strain ability (inability) to ferment glycerol, associated with human populations and trade routes originating in the Hindustan region. These movements helped launch global pandemics. This evolutionary and geographic perspective highlights how *Y. pestis* shifted from a regional zoonotic pathogen to a global threat through ecological changes, host shifts, and human activity [33].

Key elements include:

1. **Natural spread:** Formation of primary (wildlife-maintained) and secondary (adapted to new hosts and environments) plague foci across Eurasia.
2. **Geographic constraints:**
  - Permafrost boundary and Sahara–Gobi arid belt as ecological barriers.
  - Early Pleistocene migration of *Tatera* rodents (e.g., *T. indica*), which may have shaped host-vector dynamics.
3. **Human-driven expansion:** Global dispersal via trade routes, notably the gly- strain (1.ORI lineage) from South Asia.

Solid arrows indicate natural spread; dashed arrows show anthropogenic transmission.

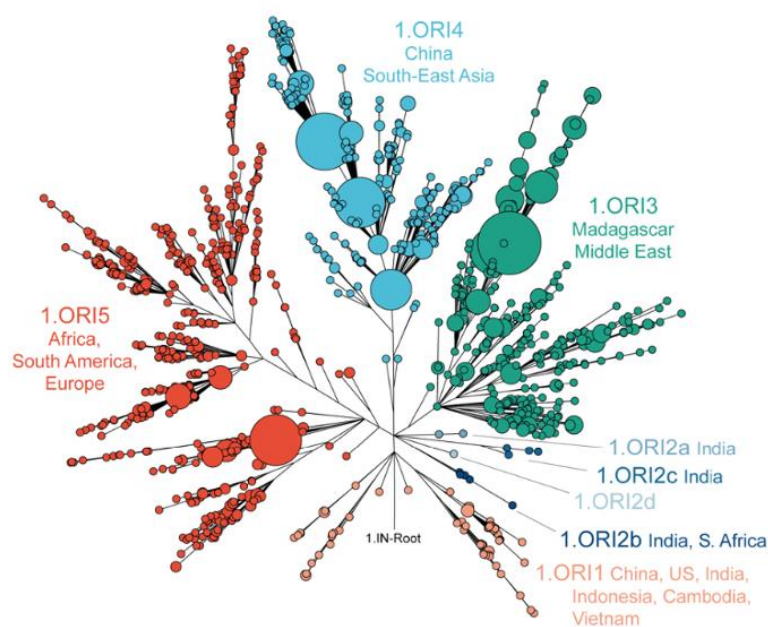
The map (Figure 1) also traces anthropogenic (human-driven) spread of plague, especially the movement of a non-glycerin-fermenting strain (gly-) associated with human populations and trade routes originating in the Hindustan region. This evolutionary and geographic perspective highlights how *Y. pestis* shifted from a localized zoonotic pathogen to a global threat through ecological changes, host shifts, and human activity [34]. This anthropogenic spread of *Y. pestis* and the plague is also illustrated in Figure 2, which focuses on the development of *Y. pestis* adaptations to different primary host populations that resulted in different gene variants, as 1ORI that spread from Yunnan to Hong Kong via *Rattus flavipectus* and the flea vector, *Xenopsylla cheopis*.



**Figure 2.** This map illustrates Suntssov's research of the geographic spread 0.ANT1 or 1.IN2 gene variant into northern India in *Tatera indica* populations and formation of gene variant 1.ORI, which spread from India (red arrows to Yunnan).

History knows of three plague pandemics: the Plague of Justinian, which began in 541 in the city of Pelusium in the eastern Mediterranean, the “Black Death” (1346), which swept through medieval Europe, and the 3rd pandemic, which began in 1894 in Hong Kong and spanning many countries of the world. Information about the causes of the first pandemic is limited. The alleged source of the second pandemic is the marmots of Central Asia: hunting for marmots, their fur trade, and military operations in Central Asia, the Lower Volga region, and the northern Black Sea region led to human infection with the plague and its spread to Constantinople and Genoa, and further throughout Europe. More complete information is available about the 3rd pandemic. It was a pandemic of the “rat plague”: synanthropic rats received the pathogen from wild rodents in natural foci and “transferred” it to human society. In the 20th century, against the background of the third pandemic of the “rat plague” in 1910-1911 and 1947-1949, epidemics of the “marmot plague” broke out in Manchuria, which were associated with the hunting of marmots. But these epidemics had a regional scale and did not spread widely in the world.

The evolutionary pathway of the plague bacterium genovariant 1.ORI (biovar Orientalis), responsible for the 3rd Pandemic, can be traced to a parasitic system that through evidence of the pathogen’s adaption to its primary hosts and the geography tied to these hosts formed in the Indian subcontinent and spread into Yunnan, China [35]. The 1.ORI lineage likely emerged from a *Y. pestis* enzootic system adapted to the Indian gerbil (*Tatera indica*) and its flea vector *Xenopsylla astia* in hot climates (Figure 2). Unlike older *Y. pestis* strains (e.g., Antiqua, Medievalis), 1.ORI lost glycerin-metabolizing ability (*gly*-), a trait tied to its adaptation to *T. indica*’s physiology populating the Indian subcontinent. Unlike other Asian gerbils, which live in the more northern regions of Asia with a temperate climate and cold winters, *T. indica* is adapted to hot climates. This biological trait has important implications: rodents – hosts of plague microbe living in more cold countries that store fat metabolize it into glycerol, a substance that older strains of *Y. pestis* (such as *Antiqua* and *Medievalis*) could use, marked by the *gly*+ metabolic trait. However, the strain that drove the Third Pandemic – *Y. pestis* Orientalis (1.ORI lineages)—lacked this glycerin-metabolizing ability (*gly*-). This trait is found in strains emerging from natural plague reservoirs in northern India and possibly parts of the Middle East. Importantly, *T. indica* is the only primary host of *Y. pestis* known to carry the *X. astia* flea, which may have served as a bridge to marmot-associated plague of 1.IN gene variant typical for populations of the Himalayan marmot (*M. himalayana*) (Figure 3).



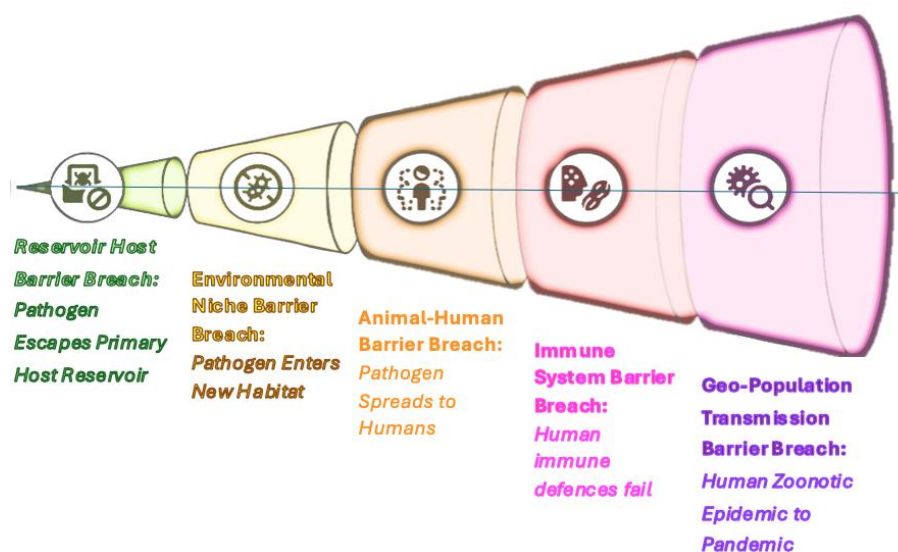
**Figure 3.** Mas Fiol et al. (2024) [36] illustrates the *Y. pestis* 1.IN root to the subsequent 1.ORI gene variants that spread around the world by commensal rats via its cosmopolitan vector *X. cheopis*.

### B. Host Dynamics of 1.ORI in Yunnan

The 1.ORI *Y.pestis* strain spread around the world [37]. But why this strain? It likely has to do with the efficiency of its transmission through its adaptable and quickly populating host *Rattus rattus* (RrC) and its flea vector, *X. cheopis* that has efficiently spread the pathogen. The spread of the 1.ORI lineage in Yunnan occurred through *Rattus flavipectus* (syn. *R. tanezumi*), which Aplin et al. (2011) argue belong to the same species complex as India's *R. rattus* (RrC) [38]. These closely related rodents show high ecological overlap as forest dwellers but maintain separate nesting sites when coexisting. Their ability to interbreed enhances the complex's adaptability and population growth, facilitating *Y. pestis* transmission. While no specialized fleas existed in their natural forest habitats, the introduction of *X. cheopis*, an African flea that was introduced to South/SouthEast Asia, adapted to human environments and created an efficient transmission system. This flea colonized both RrC members equally due to their ecological similarity. By the mid-19th century, *Y. pestis* had established in Yunnan's *R. flavipectus* populations, with Shi et al. (2018) documenting local evolution through unique CRISPR signatures [39]. Although 1.ORI originated in India's *R. rattus* populations, the ecological interchangeability within the RrC complex enabled seamless pathogen transfer to Yunnan's *R. flavipectus*. This host system's biological plasticity, combined with *X. cheopis* vector efficiency, created ideal conditions for the Third Pandemic's emergence. Yet the question remains: what triggered its pandemic emergence?

### C. Zoonotic Barrier Erosion in 19th-Century Yunnan

General ideas about the successive stages of erosion of zoonotic barriers leading to epidemics and pandemics of infections in human society are described in detail in the publication Plowright et al. (2024) (Figure 4).



**Figure 4.** Illustration of progressive barrier erosions leading to a human zoonotic pandemic based upon Plowright et al. (2024) [40], (p. 2). Image assisted by Napkin.ai.

Our interdisciplinary analysis reveals how Yunnan's mid-19th century socio-ecological crisis—marked by deforestation, mining booms, migration waves, opium epidemics, collapsing wages, and the Panthay Rebellion (a Muslim-led uprising in Yunnan from 1856–1873)—progressively dismantled protective zoonotic barriers through interconnected mechanisms. Rampant land-use changes forced wildlife displacement, creating unnatural ecological overlap between synanthropic rodents like *R. flavipectus* and human settlements. Concurrent demographic pressures from urbanization and population growth dramatically increased rat and flea densities in domestic spaces. Both human and rodent populations suffered parallel health crises: malnutrition, heavy metal contamination from mining, and widespread opium abuse compromised human immunity, while allostatic overload from resource scarcity (potentially exacerbated by environmental toxins) stressed rodent reservoirs,

impairing their immune function and driving nest establishment in human dwellings. These conditions converged with the exceptional vector efficiency of the *R. flavipectus*-*X. cheopis* system, whose superior plague-bearing capacity created an ideal transmission pathway. The resulting *Y. pestis* bottleneck favored the 1.ORI strain's dominance, whose gly- phenotype was pre-adapted for human transmission. This cascade of events—from initial marmot reservoir spillover to ecological breaches and immune suppression—mirrors modern spillover dynamics seen in SARS and Ebola outbreaks. The spread and expansion of human plague infections to the start of a pandemic after the Panthay Rebellion ultimately demonstrates how zoonotic barriers function as interdependent systems, with their collapse following predictable pathways that One Health approaches can potentially intercept.

## II. Three interrelated processes driving the emergence of the 3rd Plague Pandemic in Yunnan

The results of this study found three interrelated processes driving the emergence of the 3rd Plague Pandemic in Yunnan, China. These three interrelated processes were (1) the Socio-economic shifts leading to ecological changes, (2) the environmental and biological breakdown of zoonotic barriers and the synanthropic rat amplification, which led to (3) the pandemic “critical mass” that was triggered by the Panthay Rebellion. The Socio-economic shifts leading to ecological and biological changes entailed analysing how human activities eroded environmental and biological barriers that enabled plague spillover to proceed with increasing intensity while expanding in territory. These socio-economic shifts appear to mainly be instigated by:

### *Economic & Demographic changes:*

- real wage decline instigated by the fall of the copper peg to silver in late 18th-early 19th century (copper coins used by labourers for daily expenses); and from c.1870 Western countries adopt Gold Standard that led to dramatic selloff of silver;

- increased population density in valley regions due to mining and agricultural labour migration;

### *Human activities intensified, eroding environmental and biological barriers, exemplified by:*

- resource depletion through deforestation and mining, as well as vegetation clearance and agricultural intensification;

- immune barrier erosion through heavy metal contamination, opium abuse, famine and malnutrition;

- the erosion of forest habitat, instigating *Rattus flavipectus* migrating to human settlement areas & becoming more commensal to satisfy nutritional needs.

The impact that these socio-economic shifts that instigated human activity that changed the environment, leading to erosion of environmental zoonotic barriers fostering contexts for Reservoir Host Barrier Breach, where *Y. pestis* 1.ORI strain escaped the primary host reservoir, the Indian gerbil (*T. indica*) and with the Environmental Niche Barrier Breach entered the habitat of the opportunistic *Rattus* species (RrC - *Rattus.rattus* & *Rattus flavipectus*). RrC became increasingly commensal, focusing on food supplies in and around human settlement areas as their forest environment diminished from deforestation (to clear land for agriculture and mining, as well as developing needed charcoal for mining), which pushed these rodents to these valley settlement areas, thereby breaking down Animal-Human Barriers.

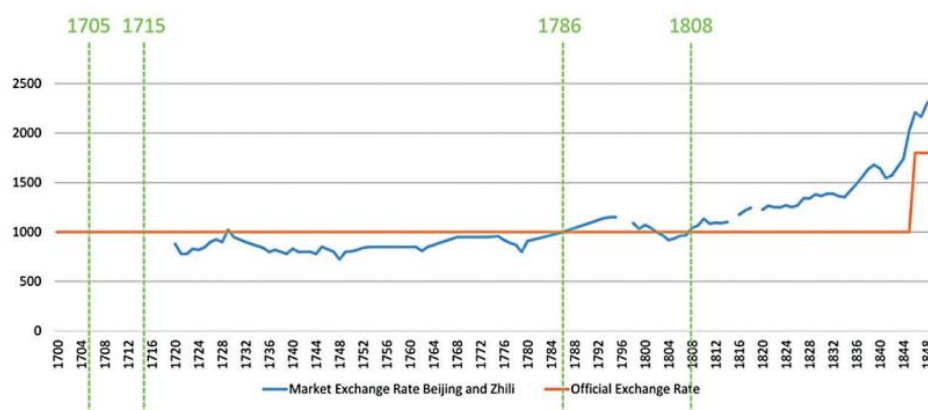
The Socio-economic shifts and the erosion of environmental barriers forced many animals to migrate to other environments that they could survive, one example of which is the synanthropic rat expansion. These rat populations left the forest habitat to human settlement and agricultural regions that led to the pandemic “critical mass”, which is when these environmental and health crises intensified, largely around the same time, to become acute, instigating the widespread transmission of the plague within Yunnan and beyond. This included the intensification of factors that eroded Immune System Barriers that negatively affect immune system function in host populations, including humans that can be instigated by: famine triggered by a lack of agricultural labour, increasing the threat of malnutrition, increasing physical wounds that diminished skin protection against pathogens entering bloodstream, diminished sanitary conditions during violent periods, and the expansion of the opium trade. The spread of *Y.pestis* and plague outbreaks was intensified

through war and displacement that instigated migration movements that led to Geo-population Transmission Barrier Breaches that included population mixing with other populations in other geographic regions, the expansion of bandits on trade routes, and environmental intensification expands eastward with instability in Yunnan & as real wages fall, creating a greater homogenisation effect on the landscape and diminished immune system function of potential hosts to fight infection—easing the adaption for the pathogen to spread through *R.flavipectus* and *X.cheopis*, & human populations.

### A. Socio-Economic Shifts leading to Ecological Changes

#### 1. Real Wage Decline & the Devaluation of Coin Currencies

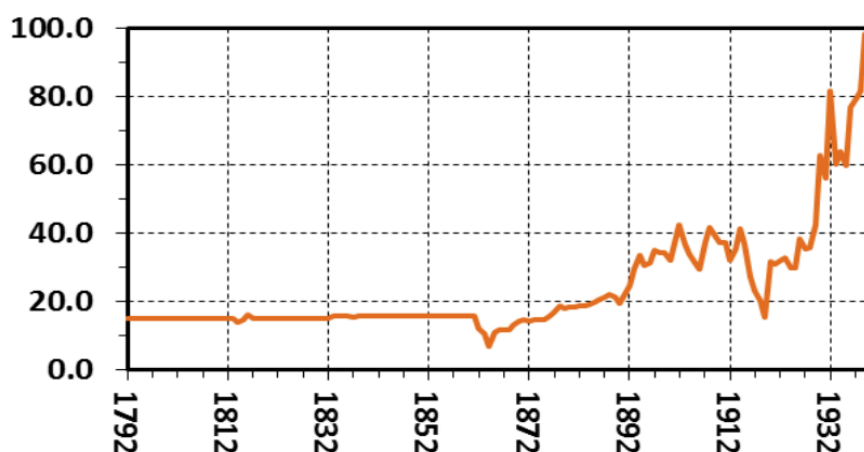
In Qing China, silver served large payments while copper cash (wen) mediated daily transactions. The often-cited equivalence of “one tael to one cash-string ( $\approx 1000$  wen)” was an accounting convention rather than a fixed legal peg. In practice, the liang–qian exchange ratio varied by time and region. From the late eighteenth century into the mid-nineteenth century, repeated attempts to stabilize the rate failed; after the “last copper century” (c. 1705–1808) [41] ended, shortages and quality deterioration of cash contributed to a persistent rise in the silver–copper ratio in many markets—from roughly  $\approx 1000$  to  $\approx 1500$ – $2000+$ , implying a  $\sim 25$ – $50\%$  depreciation of copper cash relative to silver [42–45]. Where wages for mining and rural labor were paid largely in copper cash, this relative depreciation—aggravated by food-price spikes in crisis years—eroded real income [46–50]. In Yunnan, the expansion of copper mining and associated charcoal demand and new clearings also reconfigured landscapes, exposing grain stores and settlements (see Table S1, entries under *barrier erosion: grain storage / human spaces / mines*), which increased human–rat contact and facilitated spillover [51–55].



**Figure 5. Copper Coin-Silver Exchange Rate.** Cao’s chart (2019) [56], p.137. illustrates the official copper-silver exchange rate (red line) compared with the Beijing and Zhili market exchange, from 1700 to 1850. Note that the market exchange rate broke through the copper-silver peg of 1,000 to 1, first in 1786 and then permanently in 1808, reaching around 2,250 to 1 in 1850.

By the mid-nineteenth century, the monetary system of the Qing Empire had gradually entered a structurally imbalanced state characterized by expensive silver and depreciating copper, a situation particularly acute in the southwestern frontier province of Yunnan. According to the statistical analysis of copper-silver exchange ratios by Hu Yuefeng (2021), the ratio in Yunnan during the mid-to-late 19th century remained at a persistently high level — almost never below 1:1000 and, in some years, rising to around 1:3000–4000 — significantly above the average levels observed in Jiangnan and other major market centres [58]. However, official mine production (based upon tax revenues) declined from the mid-19th century, which would have led to greater competition for fewer mining jobs. This presumably played part of the reason for diminished real wages for miners. However, while food stuffs and commodity price changes reflected fluctuations in silver price and taxes were paid in silver, the laborers were paid in copper coins that diminished in value (compared to silver)

from the late 18th/early 19th century, as the General Gazetteer of Yunnan observed, “Silver prices soared, copper coins were difficult to use; workers’ wages could purchase only half a *dou* of rice, and popular resentment surged.” [59]. Thus, conflict and tension between government officials and the people rose, leading to increased litigation [60]. This led to a growth in counterfeiting/ and possibly more illegal (untaxed) mines [61], (pp. 1-2), [62], (pp.19-20), agricultural cash cropping of opium and later tobacco [63], (p. 7), which led to greater agricultural intensity with less food production in valleys close to mining areas [64–66], as well the context that more banditry to develop within, along with the Panthay Rebellion. Additionally, silver diminished in value from 1870 (Figure 6) with the establishment of the gold standard in Western countries (instead of being based in gold & silver) that led to a selloff of silver. This led to a silver selloff resulting in losing half its value (relative to gold) when the pandemic hit Hong Kong in 1894.



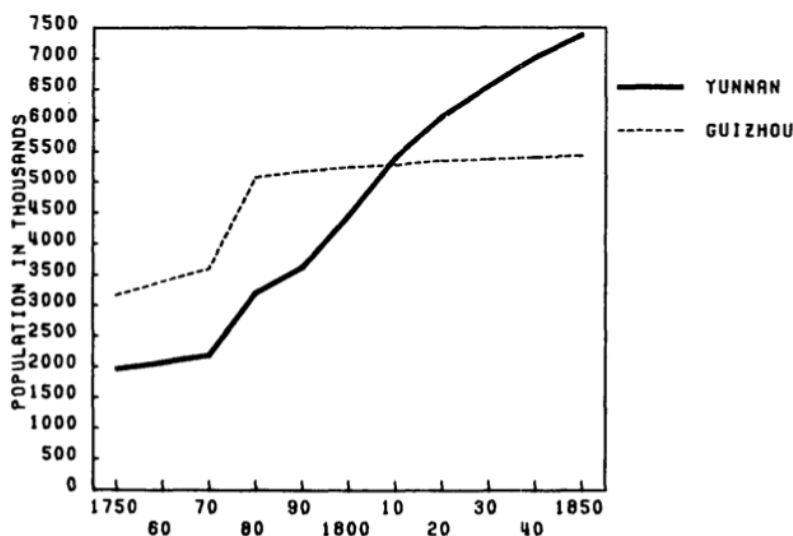
**Figure 6. Gold to Silver Ratio.** Flup’s gold to silver ratio chart (2016) [57] shows a consistent ratio, c. 16:1, until Western countries were increasingly committing to the gold standard (instead of silver and gold), especially from 1870.

## 2. Rapid Population Growth and Deforestation in late 18th and 19th century

The dramatic population increase in Yunnan of over 350% growth in a hundred years, from 1750 to 1850 (Figure 7) reflects the intensity the Qing government was putting into its copper and silver mining, which was centred in Yunnan. However, to do so entailed the difficulty of providing the food for these laborers in a mountainous region. Additionally, Yunnan was not just the mining centre of China, but also became the leading cultivator of opium poppies by the late 19th century for country’s opium market, which was the world’s largest [67,68] (pp.1111-1112). Yunnan moreover was the dominant consumer of the opium it produced [69] (p. 1114). It also became a major region for tobacco cultivation [70], (p. 741). Thus, limited agricultural lands were being used for these cash crops that are known to have detrimental effects on soil fertility [71,72], which were also more profitable than food crops. Thus, these rapid demographic changes of higher population densities in rural mountainous regions of Yunnan incentivised rapid deforestation, vegetative clearance, and intensive and expansive agriculture to help meet the demand. Lee (1982) observed this Qing dynasty phenomenon of increased population density in areas of diminished land availability, which was especially the case in Yunnan:

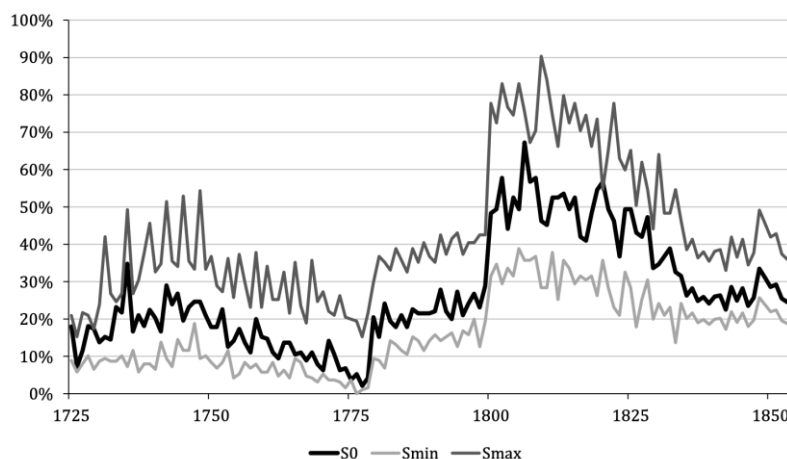
“In contrast to Ming population growth, the expansion of population during the Qing dynasty was inversely correlated to the availability of land. Indeed, in Yunnan population increased fastest where land was least available. In 1775 Kunming and Chengjiang, the two inner core prefectures, had 863,000 people and over 2 million registered *mu* of cultivated land, that is, approximately one-quarter of the population and one-quarter the provincial acreage. By 1825 their share of the provincial population had increased to well over 2 million, almost one-third of the registered population. Their proportion of the cultivated acreage, however, had shrunk to 1.6 million *mu*, less than one-sixth of

the provincial acreage. By the early nineteenth century, in other words, each acre of cultivated land in the core on the average supported twice as many people as an acre of cultivated land in the periphery" [73], (p. 40).



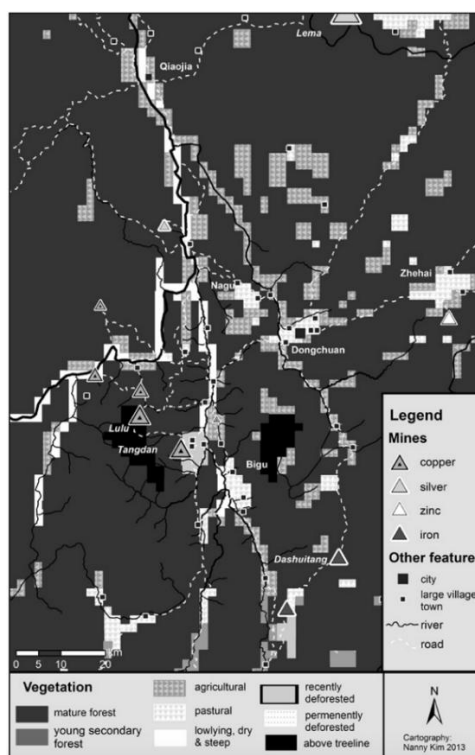
**Figure 7. Yunnan Population growth compared with Guizhou (1750-1850).** Lee (1982) [74], (pp. 722-723) illustrates the rapid population increase of over 350% in 100 years in Yunnan, where only about 6% of the land, typically in mountain valleys, is suitable for agriculture, compared to the substantial, but much less dramatic population increase of Guizhou, where the landscape is largely made up of agricultural lands.

The above population and deforestation graphs (Figure 7 and Figure 8) indicate a connection between a rapid increase in population growth and the intensification of deforestation from around 1775-1780 to meet increase mining and agricultural demand. The need for miners fostered most of the migration to Yunnan during this period, while this population influx led to agricultural intensification of these valley regions of mining zones. Yunnan, as characteristic of many mountainous regions, lacked a lot of agricultural lands. This with the intensity of cash crops opium and later tobacco led to insufficient food cultivation for the population, which led to more food being shipped to mining areas. Li et al. how these changes affected the landscape of the larger region, explaining "In the mountainous areas of China, the cropland cover expanded with the increase of people and immigration when the land use policy changed after the mid-18th century. According to agricultural historians, for example, the cropland area from 1724 to 1812 had increased by 32.6% in Sichuan (including Chongqing), by 250.6% in Guizhou, by 33.1% in Yunnan, by 63.8% in Hunan, and by 36.4% in Guangxi." [76]. More specifically with copper mining and production of the large region centered in Kunming, Yunnan and into bordering provinces of Guizhou and Sichuan, Braun et al. (2018, 50), reconstructed the impact of the mining and agriculture on deforestation (Figure 8), they found, "that the contribution of agriculture is about 80% at the beginning of the mining period, continually decreasing in the following years. In 1778 deforestation of primary forests was almost completely caused by mining, during the time of the height in copper production. Due to the following decrease in mining rates and the rising population, the share of agriculture for the destruction of the EBLF increased to a constant 100% since 1800. This indicates that agriculture is the main driving factor for deforestation in the 19th century" [77], (p. 50). However, they also found that the emergence of agricultural impact was closely related to dramatic increase in copper mining in the region, with the mines and smelters dominating in the early decades of the copper century during the Qing Dynasty, with "ecological succession turned out to have a massive impact by reducing overall deforestation by up to 75% and transiently increasing environmental diversity in mining areas." [78], (p. 50).



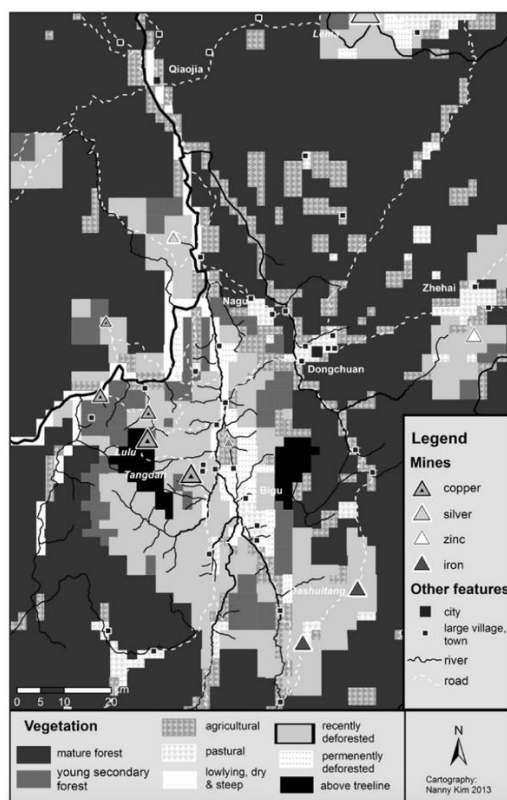
**Figure 8. Deforestation Rate Reconstruction in Southwest China During the Early-18th to Mid-19th Century.** Cumulative minimum (Smin), standard (SO) and maximum (Smax) percentage of both agriculture and copper mining causing forest decline in the mining area of southwest China (A. Braun adapted from Braun et al. (2015) [75], (p. 50).

Kim (2018) [79], (pp. 112, 118) found similar findings in their modelling vegetation change in a mining area around Dongchuan, about 160km north of Kunming (Figures 9 and 10), where they tied 18th century deforestation to mining whose increase in labour may have instigated a minor increase in agricultural lands, particularly south of Dashuitang. This reconstruction of deforestation (Figures 9 and 10) illustrates the expansion of deforestation is especially concentrated around known mines, not just a general intensification of deforestation in the region, and according to the model, the increase of migrant miners may have instigated a minor increase in agricultural lands, particularly south of Dashuitang.



**Figure 9. Model of Deforested Regions around Dongchuan, Yunnan (1700) (A) and Dongchuan, Yunnan (1800) (B).** (Kim 2018) [80], (pp. 112, 117) These are models of vegetation change in a mining area around Dongchuan, about 160km north of Kunming. These models were based upon historical records on copper mining outputs

and “existing research on outputs, smelting technologies and the organization of mining (esp. Yang Yuda’s research on fuel consumption and deforestation)” to estimate copper production. Then the study mapped population centres, land use, and transport networks using GIS to estimate relative impact of different players and activities based upon historical evidence to reconstruct the regional mine activity and the corresponding demands for charcoal, as well as that which was required for the laborers of the mines. [81] The model to the left (Figure 9) is at 1700, and the model to the right (Figure 10) is at 1800. Erosion implications.



**Figure 10.** Model of Deforested Regions around Dongchuan, Yunnan (1700) (A) and Dongchuan, Yunnan (1800) (B). (Kim 2018) [80], (pp. 112, 117) These are models of vegetation change in a mining area around Dongchuan, about 160km north of Kunming. These models were based upon historical records on copper mining outputs and “existing research on outputs, smelting technologies and the organization of mining (esp. Yang Yuda’s research on fuel consumption and deforestation)” to estimate copper production. Then the study mapped population centres, land use, and transport networks using GIS to estimate relative impact of different players and activities based upon historical evidence to reconstruct the regional mine activity and the corresponding demands for charcoal, as well as that which was required for the laborers of the mines. [81] The model to the left (Figure 9) is at 1700, and the model to the right (Figure 10) is at 1800. Erosion implications.



**Figure 11. Minimal Vegetation Landscape from the Xiaojiang Valley to the Huize Plateau.** (Kim 2018) [82], (p. 101) is a photo (2007) illustrating the lack of vegetation on the road from the Xiaojiang Valley to the Huize Plateau.

### *3. Erosion leading to Heavy Metal Contamination in Lake Water*

This influx of deforestation and vegetation clearance that resulted in more land lacking vegetation cover was not just a phenomenon of the larger Kunming region, but also seen around Dali, as Dearing et al. (2008, 24) found in investigating the Erhai Lake catchment area, though they found that the most severe phase of erosion and sedimentation began around 500 to 200 years ago that they thought was caused by agricultural expansion on more marginal slopes and a highly variable monsoon. However, the peak gully erosion, which supplied the majority of the sediment of the period, occurred substantially after this agricultural expansion. This increase in sediment load caused river channels to silt up, led to more frequent and severe flooding [83]. Li et al. (2017) found higher heavy metal contamination in Erhai Lake than expected in the mid-late 19th century, that may indicate illegal mines or unstated mine production to avoid taxes, which has been suspected by some researchers [84] (p. 67), or continued erosion over time leading to past heavy metal contamination to be exposed. Li et al. (2017) explain,

“Between the 1860s and 1890 CE, the EFs of Hg, Pb and Zn calculated based on the pre-anthropogenic background are above 1, and the Pb isotope ratios also showed higher values. This may be due to the influence of historical metal production in the late Qing Dynasty. Our analysis indicates that the use of pre-industrial sediment as a geochemical background in pollution studies underestimates the trace metal pollution in Erhai Lake. The EFs of Hg, Pb and Zn referenced to the pre-anthropogenic baseline are used in the pollution assessment in this work.” [85], (p.67).

The issue of heavy metal contamination in the region appears to have been increasing during the Ming Dynasty and in many regions appears to have peaked during the Qing Dynasty. An example of this lies just south of Kunming lies Yunnan’s largest lake, Dian Lake, which Lui et al. (2024) found the highest historical levels of sediment and heavy metals (Cu, Cr, Pb, Zn) on the Yunnan Plateau during the Ming-Qing period. They argue that the primary cause of the heavy metal contamination was the mining and metallurgy industry in the region, which the widespread deforestation increased soil erosion that transported the heavy metal waste into the lake sediments [86], (p. 8). Similarly, Hillman et al. (2014, 30) found the heavy metal contamination of P, Pb, and Hg

in Xing Yun Lake (south of Dian Lake and c. 100 km south of Kunming) reached their highest levels in c. 3500 years during the Qing Dynasty, which has been tied to human activity, namely, “the intensification of land use change and/or metal resource extraction” [87], (p. 30). Around Dali the same heavy metal contamination issues are found in Erhai Lake, where agricultural erosion that later led to gully erosion is believed to be particularly responsible for the increased sediment load during the Qing Dynasty.

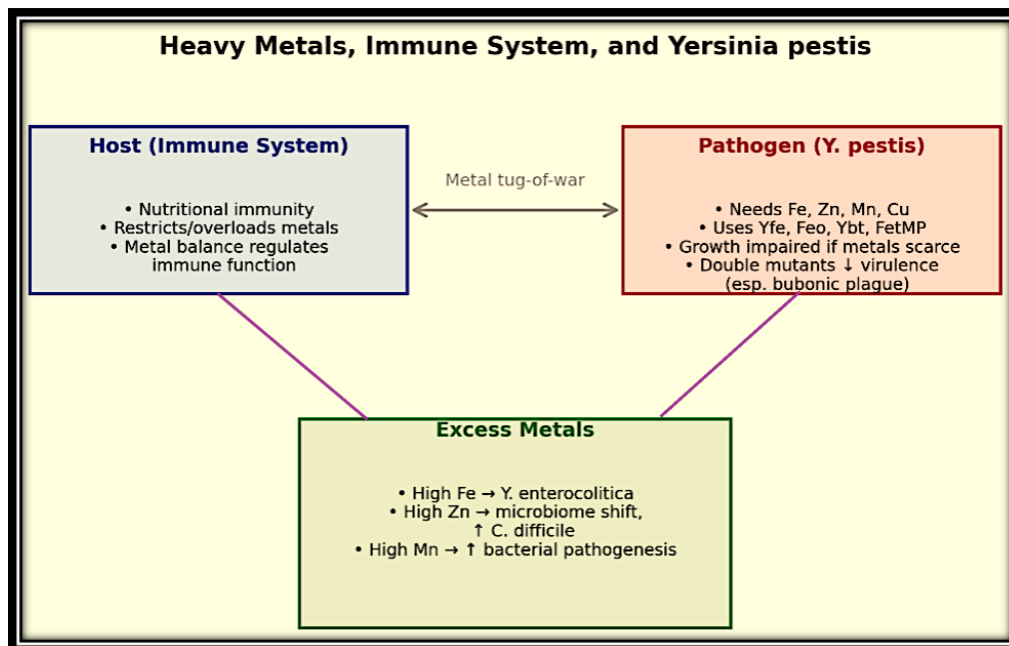
Interestingly, these regions are also known to be highly karst, which Zang et al. (2018, 401) found in their investigation in a karst region of southwest China that steeper and longer slopes, along with rainfall intensity impact the rate of erosion, with longer slopes increasing erosion almost linearly as the runoff accumulates, forming rills (micro-channels) that actively carry soil away [88], (p. 401). This hypothesis is also supported by research of recent heavy metal contamination, as Li et al. (2022) research of soil and ditch sediment in a long-term mine’s waste area observed, “The characteristics of soil heavy metal accumulation around mining areas [and nearby farmland] were influenced by topographic factors (elevation and slope), as well as natural factors (landscape, wind, rainfall and water flow),” [89], (p. 607). The lake sediment records appear to support Zang et al.’s findings, which would also mean that the level of heavy metal water contamination that people and potential rat hosts of *Y.pestis* were exposed to were especially high.

The impact of heavy metal contamination has been of increasing focus in recent decades in mining areas of Yunnan, which has seen high contamination rates in their soil, cultivated food, milk, and people and have been tied to health issues [90–92]. As explained by Yang et al. (2025), “the overall pollution levels of heavy metals in the soil of Yunnan Province and Jiangxi Province are particularly severe, and the effect made heavy metal pollution more pronounced in the forage samples of Yunnan Province” [93], (p. 6838). A more specific example of the impact of copper mining near Kunming, found a high level of heavy metal contamination that they hypothesized occurred during the mining process, “These findings suggest that after Cu was extracted from the primary ore via flotation, residual elements accumulated on the surface along with Cu tailings. During ore cracking, these elements are activated and released in ionic or molecular forms into the soil, leading to complex metal pollution. Cu is expected to be the dominant pollutant in Dongchuan, accompanied by Cd, Pb, and Zn contamination” [94], (p. 13). If this is indeed the case, then it would follow that the heavy metal contamination may have been even more pronounced during the first half of the 19th century, when copper production was at or near historical high, and other metals as silver, lead, and zinc were also extensively mined.

#### *B. Environmental and Biological Breakdown of Zoonotic Barriers and the Synanthropic Rat Amplification*

##### *1. Heavy Metals, Immune System Function and Yersinia pestis*

*Y. pestis* relies heavily on metal acquisition systems to establish infection, especially in bubonic plague, while dysregulated or excess heavy metals can weaken nutritional immunity, promote pathogen colonization, and impair immune defense [95], (p. 1367644). The host and the pathogen, *Y.pestis*, are essentially in a metal tug-of-war for essential metals, as the host (whether human or rodent) requires an ideal metal balance for optimum immune system function, while *Y.pestis* appears to need Fe, Zn, Mn, Cu to spread within the host and potentially to other hosts. *Y.pestis* depends upon the transport of metal tied to the sufficient presence of iron (Fe) [96], (p. 277), and when lacking requires multiple metal transport systems (Yfe, Feo, Ybt, FetMP) for growth [97], (p. 205), while excess host consumption of heavy metals can disrupt this balance, as high iron supports pathogenic *Yersinia enterocolitica* colonization, high zinc promotes gut microbiome shifts and *C. difficile* overgrowth, and increased manganese may also enhance bacterial pathogenesis [98].



**Figure 12.** Heavy Metal Tug-of-War shown between the host, in order to provide the nutrients needed for a healthy immune system, and the pathogen, *Y.pestis*, which needs the metal nutrients to grow and spread within the host and potentially spillover to other hosts. The excess metals lead to increase risks to host immune systems and pathogen growth. Image assisted by ChatGPT.

Ellwanger, Ziliotto and Chies (2025,2) has found the highest heavy metal contamination levels to be especially tied to mining, which appears to be exemplified by the exceptionally high heavy metal contamination in the samples taken in lakes in close proximity to Yunnan mining areas during the Qing Dynasty. Since these samples of metal contamination have been found to be at peak or near peak levels during the late Qing period, the risks affecting biological barriers to zoonotic infections are especially high [99], (p. 105). Copper and iron concentrations in water, in the northwest region, close to Dali, had an especially high peak around the early-mid 19th century (although the date is approximate), but it can be connected to copper mining in the region “highest MS (mean value of ~208 SI) and high concentrations of Cr, Cu, Ti and Fe [during the period 1450–1980 CE]” [100]. Similarly, an example just south of Kunming, Dian Lake with the highest historical levels of sediment and heavy metals (Cu, Cr, Pb, Zn) found on the Yunnan Plateau, which copper and zinc being needed by *Y.pestis* and its animal host, while lead has been cited in its capacity to diminish immune system function [101], (p. 110364).

#### 2. Opium, Food Security, Immune Systems & the Developing Plague Pandemic

Contemporary reports and gazetteers indicate that opium use was highly prevalent among laborers in late-Qing Yunnan, with a crowding-out effect on food expenditures. Physicians attached to the Kunming Customs in the 1880s noted that some railway and mining workers “spent about one-third of their daily income on opium,” a pattern that “undermined nutritional intake and basic livelihood security,” contributing to “physical decline and high mortality among the infirm” [102]. Consistent descriptions appear in local gazetteers: the Gazetteer of Gejiu Subprefecture records miners who that “a day’s labor could not match half a day’s smoke” (一日之工，不敌半日之烟，in Chinese) “(日吸夜眠，in Chinese)” and that “(一日之工，不敌半日之烟，in Chinese)”, implying that opium took precedence over food in household budgets [103], p.105. Beyond individual behavior, the Gazetteer of Guantong Department states that during outbreaks, “the poor had no access to medicine, while the rich relied on opium to resist illness... leading to countless deaths” (贫者无医，富者吸烟抵病...致死无数，in Chinese), highlighting maldistribution of medical care and the use of opium as a substitute for treatment among the poor [104], (p. 59). Together with currency distortions that compressed real purchasing power [105,106]. These practices likely increased nutritional vulnerability and, plausibly, reduced resistance to infection; we treat the latter as a mechanism-level

hypothesis to be evaluated against modern clinical evidence on opioid use and immune function. In our framework, these pathways intersect with barrier erosion (human-occupied spaces, mines) and spillover drivers (e.g., poverty-related overcrowding), as documented in Table S1.

*C. Rattus fleeing to Human Settlement Valley Habitat-The Setting for the Y.pestis bottleneck*

According to the historical documentation (See Figure 16) it appears the effect of deforestation and vegetation clearance for mining and agriculture led to the migration of rats to human settlement valleys in these regions, where human population densities were also increasing due to the need for more labor. The *Y.pestis* I.ORI strain followed its *Rattus rattus* (RrC) host that it was adapted to, which was efficiently transmitted by the flea vector, *X.cheopis*, that was also especially well adapted to. This is the first known incidence that *R. flavipectus* and *Rattus rattus* (RrC) more generally had been a primary host for *Yersinia pestis* in South/Southeast Asia. *R. flavipectus* [107], (p. 8200), the dominant rat in Yunnan, are burrow residing rats that typically live in forest, but are opportunistic and can migrate and adapt to human settlements. Contemporaneous historical documentation suggests was the case in Yunnan before deforestation and vegetation clearance for mining and agriculture forced the rodents migration to human settlement areas in the valleys, as the Gazetteer of Dongchuan Prefecture (c.1862-74) explained, “All the valleys were mined for copper; trees were long felled, grasses withered and earth cracked, water sources dried up, rats bred in abundance, and at night the sound of their rushing was like tides,” [108] which resulted in what the Imperial Maritime Customs Medical Report, Yunnan Station (June 1888) described as “vermin-infested valleys” [109]. The documentation of suspected plague outbreaks during the mid-19th century appears to be especially concentrated in these valley settlement regions in and around mining sites. These valleys became ideal locations for *R. flavipectus* migration from the deforested regions, where they survived on human food sources that were ideal places for *Y.pestis* to survive, propagate, and spread to increasingly dense human populations.

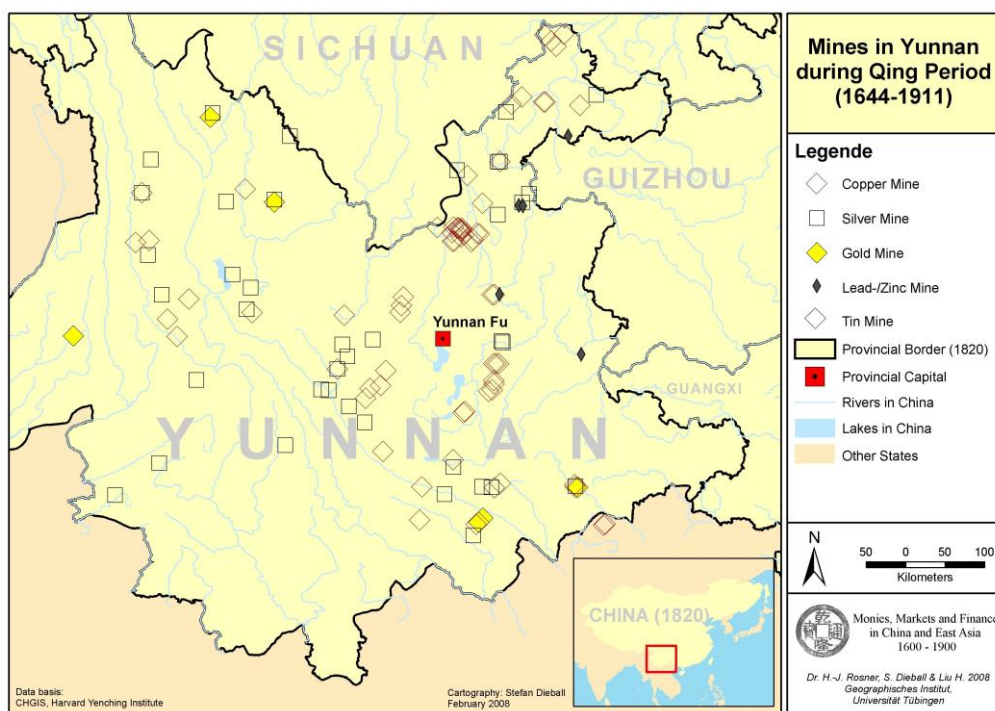
*R. flavipectus* presence did not equate the transmission of plague infections to human populations. This is exemplified by the red circled section in south-southwest Yunnan on the maps below, where *R. flavipectus* was known to live, but no human infections during the mid-late 19th century were documented. This area was of relatively lower altitude, consisting of green hills instead of Rocky Mountains, and was not an area where known mines existed during the Qing Dynasty.

The maps (Figures 13–15) suggest that recorded mid-19th-century outbreaks cluster (Figure 15) in mid-elevation basins and karst/red-plateau valleys, while extremely high elevations (where *Rattus flavipectus* is seldom present) and the lowest, densely vegetated tropical belts show fewer records. However, this evidence alone may just reflect a pattern in the available documentation—potentially shaped by settlement and reporting. Field evidence indicates that when *R. flavipectus* can feed outside of buildings, indoor trap success declines: Yin et al. report that vegetables around houses and maize grown within villages reduced captures of *R. flavipectus* by ~45% [113], (p. 463). In contrast, the karst and red-plateau regions hosted concentrated mining and agricultural expansion driven by labor migration. As Huang Fei describes for the Southwest, the *bazi* valley floors—about 6% of land area yet hubs of wet-rice agriculture and market life—became the focal points where groups competed for space and resources [114], (pp. 78-80). In Yunnan gazetteers, these valleys are repeatedly associated with intensive land-use change (deforestation for charcoal, vegetation clearance, expanded grain/opium cultivation) and surges of mobile labor [115].

A Kunming Prefecture gazetteer (Guangxu years) notes that “poppies were widely cultivated; consecutive droughts and floods hardened the soil; wild animals had no shelter, and rat hordes invaded villages” (光绪年间坝区多种罌粟，连年旱涝相继，土地板结，野物无所栖，鼠群入寨为患，in Chinese) [116] (卷四·物产志, p. 23). Taken together, these processes eroded habitat barriers (food available outdoors diminished; refuge altered) and concentrated *R. flavipectus* around human stores and dwellings, increasing opportunities for human–rat contact and potential spillover (see Supplementary Tables S1–S2 for coded instances). We therefore interpret Figure 16 as consistent with a barrier-erosion pathway operating in densely settled, mined, and farmed valleys, subject to the caveat of documentation bias.

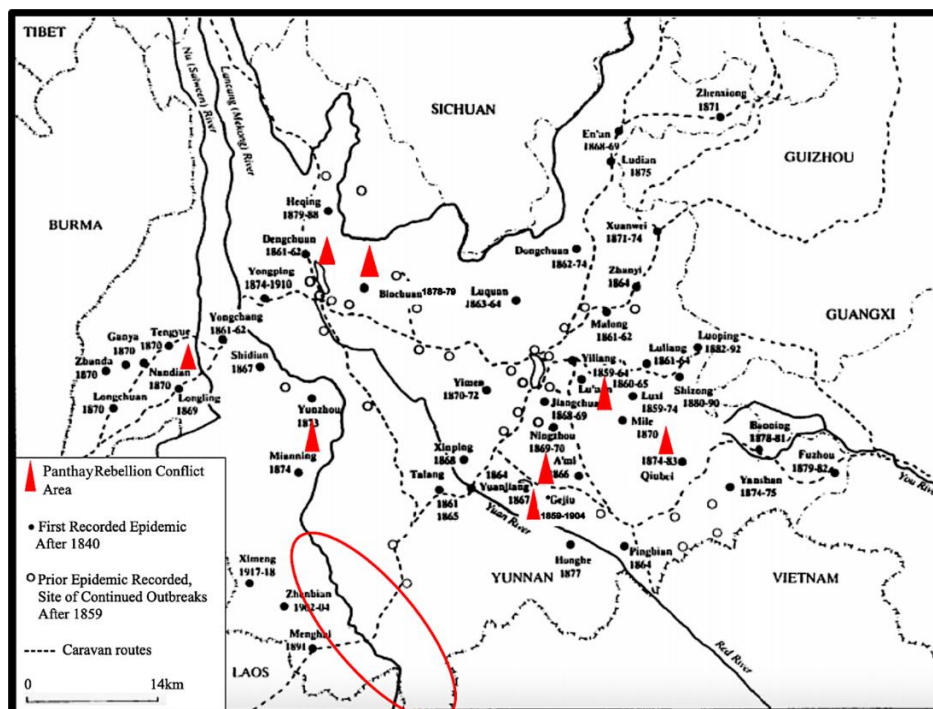


**Figure 13.** Google Map 1931 image of Yunnan, China. Note that the lowland greener region in the south-southwest of Yunnan (the red circled region) is an area without documented plague infections but is an area where *R.flavipectus* resides. However, Yin et al. (2008) findings make the case that *R.flavipectus* may have a significantly higher percentage living in the forest with greater habitat to provide food security, with diminished human density. Whereas the more mountainous region around Kunming, a centre for copper mining where the green forests were largely limited to valley regions, which the historical accounts indicate were a hotbed for plague infections (Figure 16).



**Figure 14.** Rosner, Dieball, and Liu (2008) [110], (p. 242) Map of known mines in Yunnan during the Qing dynasty. The mining regions are in the higher altitude mountainous areas, which is also where the documented

human plague infections appear to have largely occurred. Conversely, the red encircled region had no recorded outbreaks, despite a significant *R.flavipectus* population.

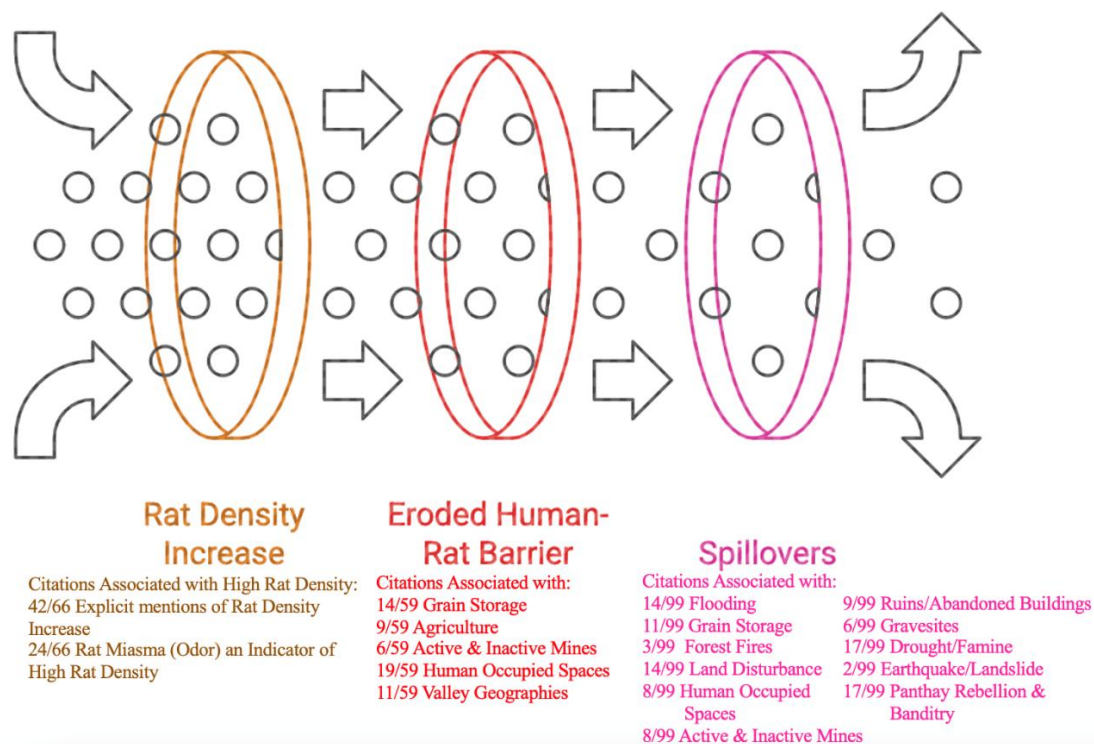


**Figure 15.** This Map is a reconstruction of C. Benedict’s map (1992) ‘The epidemics in Yunnan after 1859,’ [111], (p. 84) with the addition of Panthay Rebellion Conflict Areas based upon the Du Wenxiu Uprising (1856–1873) map by Liang et al. (2025) [112], (p.3). The centres of the Panthay Rebellion uprisings appear in the midst of documented human infections that are believed to be plague. These areas were largely around mining districts, where many laborers migrated in the valley settlement areas. Since much of the area around these valleys were deforested for the mines and agriculture, the contemporary reports suggest that the rats fled the forest to the settlements for food (See Figure.16). In contrast, the red encircled region is green hilly lowland, which is also inhabited by *Rattus rattus* (RrC) but has no documentation of infections believed to be plague during this time period.

A survey of the contemporary historical evidence (Figure 16) gives textual breakdowns of environmental overexploitation that fostered Environmental Niche Barrier Breach of the rat population, leading to the rodents to become increasingly commensal, leading to greater Animal-Human Barrier Breaches. Various causes of environmental erosion led to greater food insecurity in the forest and the spillover of the rats to human settlements, which may have led to malnourishment of both rat and human hosts, as well as an increased risk of co-infection, thereby potentially compromising immune system function.

An analysis of the contemporary 19th century Yunnan sources helps gain insight in the complex relationship between rat density and human plague outbreaks. Begon et al. (2019) observed that while low rat densities are a reliable predictor of a lack of plague outbreaks, high densities alone are not a clear predictor of an outbreak [119]. This historical evidence appears to support that observation, but interestingly people of the period also frequently made a connection with the rat health, or the threat to rat health being a predictor of human plague outbreaks, as a contemporary observer noted, “In the 17th year of Guangxu (1891), rats were seen fleeing the fields south of the city both morning and evening. Ten days later, a plague erupted. Elderly farmers said: ‘Rats are spiritual—they flee poison before it strikes’” [120]. This observation of the rats fleeing in large numbers being a signal of upcoming plague outbreaks is commonly seen in the historic record, but what led so many from their burrows? Rat Miasma (odor) has also frequently been cited as toxic in the historic record, even the

cause of plague deaths. Strong odor from rat excrement has often been cited as an indicator for high density burrows or nests [121,122]. However, Arakawa et al. (2010) observed particular odors from the excrement can signal to other rats that one or more of their cohabitants are suffering from a serious infection leading them to leave [123], or maybe a rat died and the odor from its decomposition instigated the migration. There appears to be an order of events that starts with a flood, storm, fire, drought and/or famine taking place that appears to affect the food security that leads people and rats going after the same food supply, as observed in Shiping during the 1880s, “During a famine, grain was scarce. At night, people competed with rats for food at the hearth. One child died after fighting a rat over a rice ball. The plague followed soon after” [124]. This chronology of food insecurity is often followed an erosion of the human-rat barrier, as well by rat miasma (which people must be in relatively close proximity to smell), and then plague outbreaks. This is demonstrated by this example from Zhaotong (1878) that illustrates an example of drought igniting a large-scale rat migration to people’s environs, rat miasma and then a plague outbreak, “In the summer of the 4th year of Guangxu (1878), prolonged drought cracked the fields. When the granaries were opened for famine relief, warehouse rats surged out, invading markets and shops. People fell ill, calling it ‘rat-poison miasma’ [125].



**Figure 16.** This inventory of historical Yunnan documentation is divided into three sections which illustrate the erosion of environmental barriers: A) rat population density (66 total citations), B) eroded human-rat barriers (59 total citations) and C) spillovers (99 total citations). Each of these are broken down into subcategories where the citations are displayed as fractions of the total of the category. The Rat (Population) Density Increase includes explicit mentions or indicates a high rat population density or mentions Rat Miasma (odor), which is an indicator of high rat population density [117,118]. Eroded Human-Rat Barrier only included that which explicitly mentioned evidence that illustrated contact or close proximity of people and rats. Note that the number of citations should just be taken as evidence of presence of Rat Density Increases, Eroded Human-Rat Barrier, and Spillovers, as well as the subcategories that make them up, but is not definitive evidence for comparison among them. Rather this data indicates strong evidence of these 3 categories being present, and the major subcategories within Eroded Human-Rat Barriers and Spillovers. Image assisted by Napkin.ai.

Accordingly, the critical factor for plague risk from animal reservoirs does not appear to be reservoir density alone, but health and immune status of the rat population also seems crucial. These

two factors may indeed be connected, but a time gap is often seen in the historical accounts that takes place between a population boom and the health/immune system consequences (that may be the result of the increased competition for food). Huise (1888) exemplified this phenomenon in observing, “In the 14th year of Guangxu (1888), great forest fires destroyed rodent nests, forcing them into rural settlements. Local people said, ‘When rats come in April, the dead cry in June.’ Three thousand perished in the outbreak” [126]. The historical record makes many references to an abundance of rats that overrun grain storage, agricultural, and home food storage areas, which may hold a sufficient supply in the beginning, but often are seen what appears to be migrating, searching, for new food sources.

The tie of rodent host health to the spread of *Y.pestis* and human plague infections is not restricted to the historical record, but also been observed by infectious disease ecologists and biologists, whose findings include:

- **Immune System Erosion:** As rat populations become overpopulated and their health declines (due to factors like overcrowded burrows), their immune systems become compromised. This makes them more susceptible to *Y. pestis* infection and less able to fight off the disease [127–129].
- **Dose and Immunity:** A healthy rat with a strong immune system can potentially inoculate itself against a low dose of the bacteria. Rats that survive infection and develop antibodies help decrease the spread of plague within the population [130].
- **Genetic Diversity:** Genetic diversity within the rat population is crucial for developing effective immune responses. Populations with high genetic variability are better at limiting large outbreaks, while genetically homogenous populations (due to bottlenecks) are at higher risk [131].
- **Spillover to Humans:** The outbreak spills over to humans when sick rats, seeking shelter (e.g., in houses), come into close contact with human living spaces. The provided historical accounts describe rats nesting in roofs and under stoves, leading to human cases [132,133].

In short, it would appear the risk of a human plague outbreak is highest when a high density of rats coincides with a decline in their overall health and immune function, facilitating the spread of the disease within the rat population and its subsequent transmission to humans. Thus, early in the increase in population may not be an indicator of increased risk of transmission to same species and different animal species, however, when the health effects of overpopulation of the rodent burrows take place over time. The ability for *Rattus rattus* (RrC) to have the ability to inoculate itself from *Y.pestis* infections tends to be more successful with lower doses [134] and would appear to require a healthy immune system. This ties different factors that can lead to the hosts immune systems eroding (See Plowright) and case studies [135]. *Rattus* that have exposed to *Y.pestis* and have the antibodies to the pathogen have been shown to decrease the spread of plague infections [136,137].

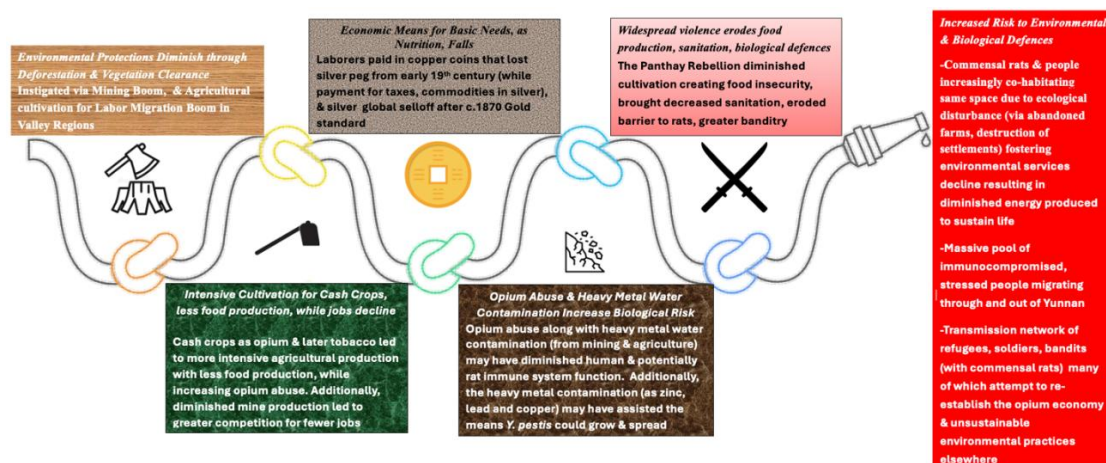
#### *D. The Pandemic “Critical Mass” (Panthay Rebellion Trigger)*

The mid-19th century Panthay Rebellion—a devastating conflict between the Hui Muslim community, other non-Han minorities, and the Qing state—appears to have served as a critical trigger for the Third Plague Pandemic. The rebellion did not just cause death through combat; it systematically collapsed the region’s socio-ecological defenses, creating ideal conditions for the plague bacillus (*Yersinia pestis*) to explode from a localized zoonosis into a widespread human pandemic. French diplomat Émile Rocher, traveling through Yunnan during the conflict, witnessed a terror that surpassed the fear of combatants. He reported villagers abandoning their homes to camp on high ground, fleeing “an adversary even more inhumane than the insurgents: the plague epidemics” [138]. From the late Qianlong into the Tongzhi/Guangxu reigns, plague activity intensified province-wide, with the Xianfeng–Tongzhi period (c. 1861–1874) marking a sharp spatial expansion of outbreaks driven by refugee flows and troop movements. Contemporary Chinese sources and later epidemiological surveys consistently attribute much of the excess mortality in these years to plague and famine rather than battle itself [139–142].

This collapse of “zoonotic barriers” followed a predictable cascade. Warfare devastated agricultural production, leading to famine and a desperate reliance on centralized granaries, as the

Gazetteer of Tengyue Subprefecture at the end of the Daoguang (道光) reign (c1850) illustrates, “During the Daoguang era, rebel troops entered the region; villages were destroyed, fields abandoned, vegetation vanished, and rats descended from the mountains into houses” [1403]. This intensified pressure on already eroded zoonotic barriers, as observed from Xuanwei in 1868 clearly describes this cascade: “In the 7th year of the Tongzhi reign (1868), after military chaos, the granaries within the city collapsed, and rat burrows spread beneath them. When the rainy season arrived, houses collapsed and flooded. An epidemic broke out beside the granaries, widely attributed to ‘rat miasma’” [144]. Food insecurity forced dependency upon the granaries that collapsed, fostering grave nutritional risks for both humans and commensal rats—which had long adapted to human settlements—competed for the same dwindling food stores within these granaries. Meanwhile, the broader economy collapsed, copper currency devalued, unemployment soared, the risk of injuries grew in often increasingly unsanitary conditions, while banditry and the opium economy spread, spurring large-scale migration of impoverished, malnourished, and often diseased populations.

Thus, waves of vulnerable people, intimately exposed to plague-infected rat fleas in their homes and granaries, and often further weakened by opium, heavy metal contamination, and malnutrition, carried the disease with them as they fled [145]. This pattern repeated in areas like Yongshen in 1885, where post-war resettlement occurred amidst lingering rat colonies and little vegetation, leading to outbreaks illness from what physicians thought was caused by the ‘rat-burrow poisonous wind’ [146]. Accordingly, the Panthay Rebellion, as a large-scale human conflict, created a socio-economic crisis that triggered a domino effect through amplifying the erosion of zoonotic barriers during an already present zoonosis and lost containment with pandemic-scale consequences.



**Figure 17.** Suspected Major Forces Leading to Cutting off Barriers in Yunnan, China from the late 18th-early 19th century to the Panthay Rebellion Zoonotic. The development of zoonotic risk through the erosion of zoonotic barriers, thereby creating a bottleneck for *Yersinia pestis*. Image assisted by Napkin.ai.

The Panthay Rebellion was not an isolated event but part of a devastating wave of mid-19th century rebellions that crippled China. These included, most catastrophically, the Taiping Rebellion (Figure 18), which originated in Guangxi province bordering Yunnan and resulted in tens of millions of deaths [147]. These rebellions may be seen as regional networks of varying degrees of connection that were often tied to banditry and opium trade, which appears to often be the main funding source, while often attacking mines, a major funding source for the Qing Dynasty [148]. These opium trade networks largely worked in the mountain regions, which is also where the rebellions often would begin [149]. The extreme poverty most people found themselves in assisted rebellions level of support.

This period of unprecedented violence caused a massive decline in a population that had quadrupled over the previous 150 years, leading to the abandonment of farmland and a collapse in agricultural cultivation. It appears the subsequent population rebound triggered an increase in large-

scale deforestation and land clearance for agriculture [150]. If this is indeed the case, this would have two critical consequences: first, it significantly increased the frequency and severity of floods and droughts by removing natural vegetation that stabilized soils and watersheds. Scholars as Lee and Zhang (2013) have demonstrated a strong correlation between flooding and drought and epidemic outbreaks during the Qing Dynasty (See Appendix). Second, this habitat destruction forced animal reservoir hosts, like the plague-carrying rodent *Rattus flavipectus*, to migrate into human settlements in search of food and shelter, drastically increasing human-wildlife contact.

The Third Plague Pandemic emerged within an economic context that forced populations into human activity that helped create unsustainable environmental practices. According to Laybourn-Langton and Hill (2019), such “environmental breakdown” is a consequence of socioeconomic systems driven by unsustainable resource use [151], (p. 4). This pattern, which intensifies in the Anthropocene, erodes the barriers between humans and animal diseases, increasing the risk of zoonotic epidemics [152]. In mid-19th century China, this systemic unsustainability was starkly visible. Although China’s GDP represented the world’s largest at 33% of global output in 1820, a century of internal strife, including the Panthay and Taiping rebellions, cut its relative economic size to half that of Western Europe by 1870 [153,154]. This catastrophic decline shattered the state’s capacity to manage disasters and maintain public health. As historian Carol Benedict (1988) has argued, the resulting vacuum—filled by poverty, mass migration, and a destabilizing opium trade—created the perfect pathways for the plague to spread from its epicenter in the war-torn and environmentally degraded province of Yunnan [155].



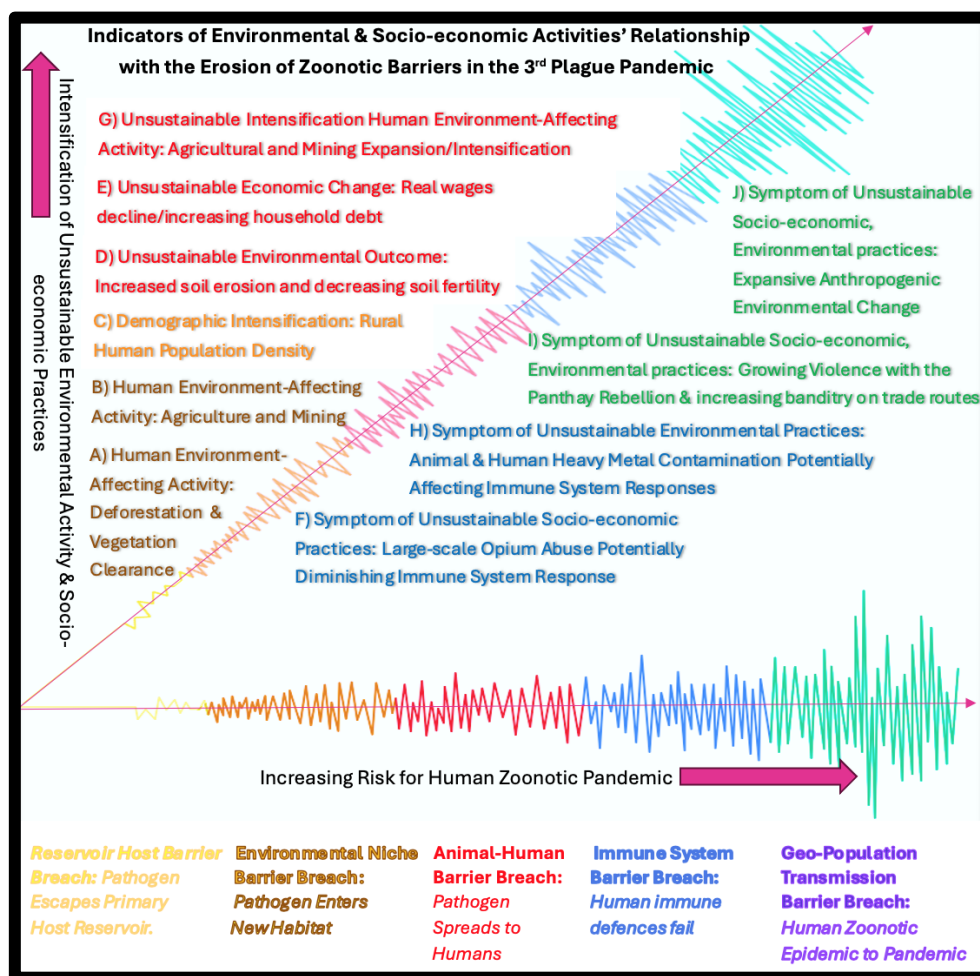
**Figure 18.** Map of Qing China and the Taiping Heavenly Kingdom captured territories (M. Bitton 2022) [156]. Tan shaded areas had various occurrences of the rebellion, which started in Guangxi, the orange areas indicate early lands of the rebellion and the brown areas are late territories of the rebellion. *Note.* This map, created by M. Bitton (2022), is a derivative work based on Peng (2021), Reilly ([Year of *The Taiping Heavenly Kingdom...*]), and the base map “China 1820 de.svg.” Reprinted from [or “Adapted from”] *Wikimedia Commons*, by M. Bitton, 2022 ([https://upload.wikimedia.org/wikipedia/commons/2/23/Taiping\\_Heavenly\\_Kingdom\\_map.svg](https://upload.wikimedia.org/wikipedia/commons/2/23/Taiping_Heavenly_Kingdom_map.svg)).

#### 4. Discussion and Conclusions

The development and spread of the *Yersinia pestis* 1.ORI strain, which ignited the Third Plague Pandemic, was a catastrophic convergence of a highly efficient pathogen-host-vector system and the widespread erosion of zoonotic barriers by human activity. The pandemic’s foundation was the 1.ORI strain itself, a lineage with a particular fitness for transmission. This pathogen formed in populations of the Indian gerbil on the Indian subcontinent found an ideal vehicle in a complex of closely related *Rattus* species, including *Rattus flavipectus* in Yunnan and *Rattus rattus* in India. Their high ecological overlap, ability to interbreed, and rapid population growth created a vast, interconnected reservoir

for the bacteria. Critically, the disease was delivered to humans by a supremely efficient vector, the *Xenopsylla cheopis* cosmopolitan flea having African roots.

However, this biological threat alone may have remained confined to wild rodent populations if not for profound human-induced changes that dismantled natural defenses. The erosion of zoonotic barriers began with economic and demographic shifts, such as labor migration fuelled by mining and agriculture, which crowded people into dense valley settlements. Simultaneously, environmental barriers were destroyed through rampant deforestation, mining, and agricultural intensification. These activities depleted resources and, most importantly, destroyed the forest habitats of rodents like *Rattus flavipectus*, forcing them to migrate into human settlements to survive, thus bridging the critical gap between the wild zoonotic cycle and human populations. Finally, the biological immune barriers of the human population itself were compromised. Heavy metal contamination from mining, widespread opium abuse, and famines leading to malnutrition created an immunocompromised populace far more susceptible to infection and death. In essence, the Third Plague Pandemic was not merely an outbreak of disease, but a man-made disaster, where economic ambition and environmental alteration created the perfect conditions for a deadly pathogen to leap from its natural reservoir and find a vulnerable, densely packed, immune-compromised human population.



**Figure 19.** The *Intensification of Unsustainable Environmental Activity & Socio-economic Practices* (indicated through letters: A-E, G), and the resulting symptoms because of these unsustainable practices (indicated through letters: F, H-J) are shown to increase the risk for human zoonotic pandemics (shown on x-axis) as such activities, practices, and symptoms increase in intensity and frequency. As environmental and demographic barriers that protect against a human zoonotic pandemic are broken, then some common symptoms are seen, which can affect the human and animal immune systems, as well as expanding to different geographic regions where other populations are affected by the spread of plague infections. Letters A-J are ordered by the sequence in which

these unsustainable actions are most frequently observed. As these practices increase, so does the risk of a human zoonotic pandemic.

This study of the Third Plague Pandemic's origins in Yunnan underscores that a comprehensive understanding of its expansion demands future research guided by a One Health approach. Such a framework is essential to holistically assess the erosion of zoonotic barriers across the pandemic's vast geography. Key investigative priorities should include environmental history to clarify land-use changes and contamination; bioarchaeological evidence to trace biological vulnerabilities in human and animal remains; analysis of the socioeconomic drivers behind unsustainable practices; and a critical examination of the knowledge systems that financed and justified them. Ultimately, siloed, discipline-specific research is insufficient, as factors in nature do not exist in isolation. The One Health framework is therefore necessary, as it acknowledges the interdependence of environmental, biological, and socioeconomic spheres. Furthermore, this approach must be applied dynamically across time and space, recognizing that the relevant temporal scales for biological, environmental, and socio-economic changes are not uniform. The biological evolution of a pathogen, the slow erosion of soils, and the rapid shifts in economic policy all operate on different clocks and across diverse geographies. A practical One Health approach should therefore embrace these multi-scalar timelines, tracing how the interconnected domains of health and environment co-evolve to shape pandemic risk across both space and time. Therefore, by integrating the study of past pandemics with present-day zoonoses, we can extract crucial lessons to better understand outbreak dynamics, address current risks, and forge a more sustainable, resilient path forward.

**Supplementary Materials:** The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1: Historical Quotes Inventory (Yunnan, 1849–1908)—a structured dataset linking each quotation to location clues, reign-year/Gregorian year, and thematic codes (rat density, erosion of human–*Rattus* barriers, spillover drivers). Table S2: Codebook for Categories and Subcategories—definitions for coding “barrier erosion” and “spillover” contexts (e.g., grain storage, flooding, fires, mines, ruins/gravesites, drought/famine, conflict). Table S3: Master List of Sources for MDPI Formatting—unique source entries extracted from gazetteer citations for final reference formatting.

**Author Contributions: Raymond Ruhaak (R.R.):** Served as the lead integrator and writer. Was responsible for the overall One Health conceptual framework, palaeoecological evidence, orchestrating the narrative, drafting the manuscript, corresponding with the journal, and managing the project. **Victor Suntsov (V.S.):** Provided the core evolutionary biology expertise. Developed the methodology and analysis for the *Y. pestis* 1.ORI strain's evolution and its interaction with its rat host and flea vector, specifically within the context of 19th-century anthropogenic change. **Li Yang (L.Y.):** Provided the core historical research. Was responsible for the methodology and investigation of primary and secondary historical sources, including translating evidence related to plague outbreaks and the integrity of zoonotic barriers during the Panthay Rebellion.

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**Data Availability Statement:** The dataset underlying the historical evidence is provided as Supplementary Materials (Tables S1–S3).

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