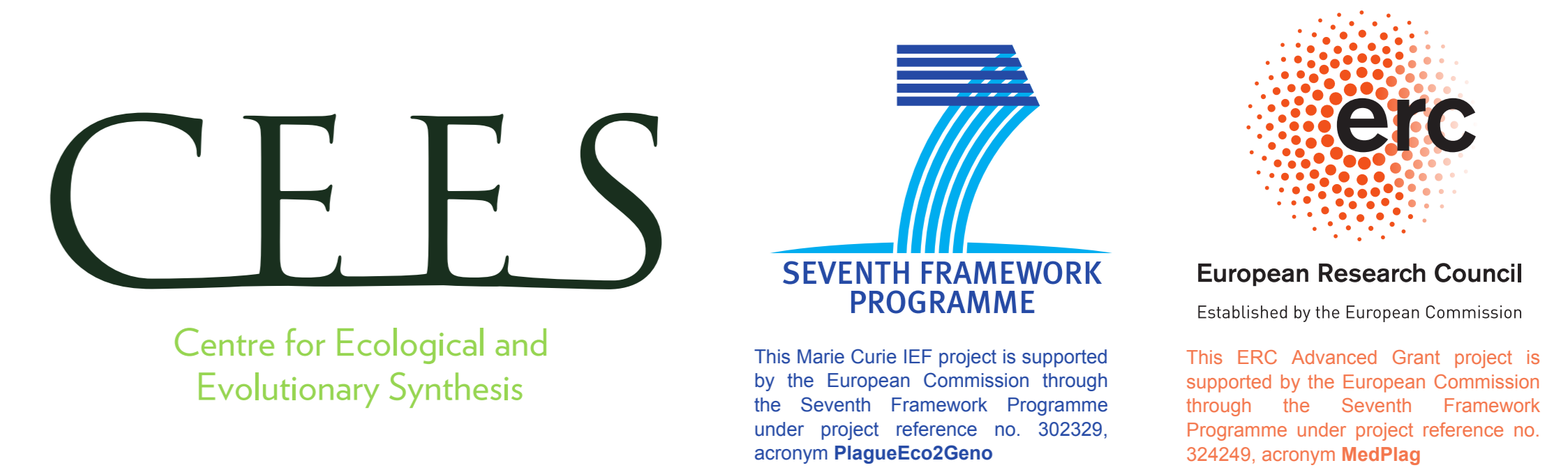


THE PULSE OF ASIA: THE BLACK DEATH AND SUCCESSIVE REINTRODUCTIONS OF PLAGUE INTO EUROPE

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Summary:

Historical records reveal that the *Black Death* traveled overland from Asia to Europe by the maritime traderoutes of the Black Sea and the Mediterranean Sea. After the *Black Death*, plague outbreaks continued to occur in mainland Europe for almost four centuries. The persistence of plague on the European continent has long fueled speculations that a European rodent reservoir for the bacterium must have existed, analogous to the wildlife rodents plague foci in Asia and Africa. However, no such reservoirs have ever been discovered.

Here we present compelling evidence that the introduction of the *Black Death* into Europe was not a singular event, but the first of a series of introductions of the bacterium, strongly tied to the climate in Asia. We analyzed the largest digitized dataset on medieval plague outbreaks in Europe against 14 annually resolved dendrochronologies from both Europe and Asia, and identified a climate pattern that can cause large-scale plague outbreaks amongst wildlife rodents. This pattern (a large decrease in annual precipitation over a short period of time) precedes the reintroduction of plague outbreaks into Europe by 9-12 years in Asian climate records, but is absent at biologically relevant delays in European climate records. The implications of these findings are that *Y. pestis* was potentially repeatedly introduced into Europe throughout the second plague pandemic, thus removing the necessity of a local wildlife reservoir to explain the persistence of plague on the European continent. The influx of plague from Asia at the start of the three known plague pandemics, and during the second pandemic provides the ecological context that is critical for interpreting the genetic history of *Y. pestis*.

Methods and Results:

The annual incidence of plague in cities in and nearby Europe (**top panel, grey lines**), was compared against the annual incidence in harbors of the Venetian maritime trade Network (VN) in the Mediteranean and Black Sea (**top panel, black lines**). We selected for potential years in which plague was reintroduced into Europe by identifying those years where plague had been absent for a number of years in all of these harbor towns (**second panel, blue squares**). The thus selected years almost exclusively were years in which the percentage of all plague outbreaks that occurred in these VN harbors peaked (**second panel, red line**), which supports assumption 2 of the hypothesis.

Visual inspection of the different climate records prior to these years suggested that a large number of sharp drops occurred at the same amount of time prior to each potential year of reintroduction (**second panel blue squares**) for the Western Central Asian, and Alpine Crescent climate records. In Asia (and presumably also in Europe) such drops reflect a rapidly decreasing primary production by the vegetation, which has the potential to collapse and synchronize the local rodent populations (**topright inset**), a scenario that would result in regional large-scale plague outbreaks (*Kausrud 2007*). We varied 5 relevant parameter to test the robustness of our observation, and tested its significance ($p_{val} < 0.001$) and effect size (expressed as the relative increased risk of a potential plague reintroduction occurring after a sharp climate drop N years earlier) with a chi-square goodness of fit between sharp climate drops and potential years of plague reintroduction. The parameters varied are the 14 **climate records**, the **delay N between climate drops and reintroductions** of plague in the VN, the **minimal size of the climate drop** in standard deviations, the **minimal duration of the absence of plague** in the VN (lower minimal duration means that we regard more years as a potential reintroductions of plague into Europe), and **how much variation was tolerated in the delay** between climate drops and potential reintroductions (to allow for some variation in the time it takes for plague to travel from Asia to Europe). The distribution of the results that were significant both in p-value and effect size is shown in the 3rd (**red lines**), and is compared against the expected frequency of significant results, based on 50 randomizations of the reintroduction years over the range 1320-1850, while keeping their number and minimal spacing intact (**blue lines**).

The two most frequently significant results are the climate records from Western Central Asia, with a dominant delay of 12 years, and from the European Alpine crescent, with a dominant delay of 9 years (**arrows, third panel**). The long delays between climate and plague outbreaks indicate that the plague reservoirs that respond to these climate records were unlikely to be located within Europe or on the north-African coast. The years where these two climate records experienced a sudden drop in precipitation and/or temperature are plotted as **circles in the first panel** (together with the plague incidence), marking the years in which plague potentially has been reintroduced into Europe, independent of whether these reintroductions were visible or obscured in panel 2 by plague outbreaks that were circulating in Europe at that time (*Elli 1984*).

Hypothesis:

1: *Plague was frequently reintroduced from Asia throughout the second pandemic.*

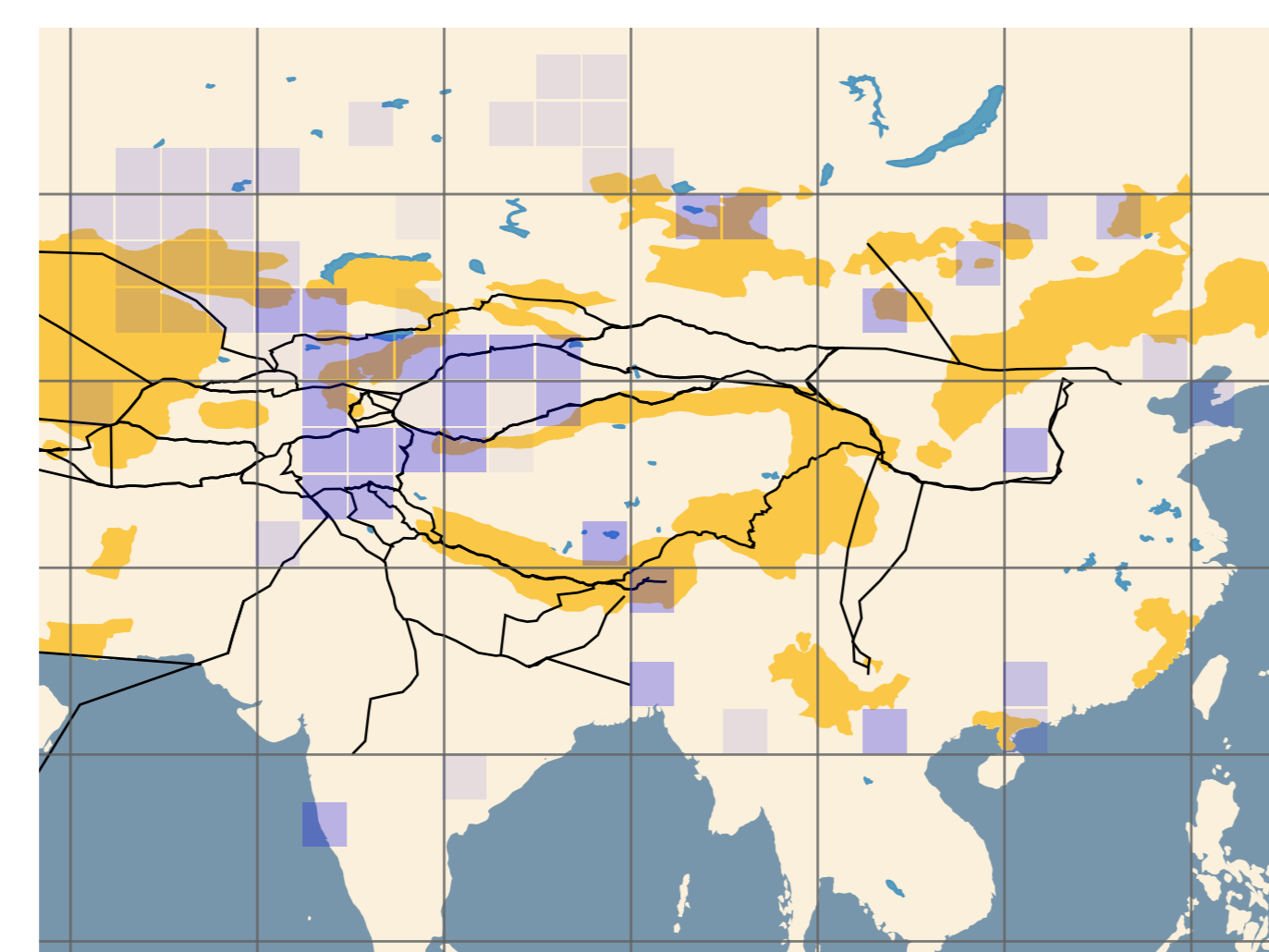
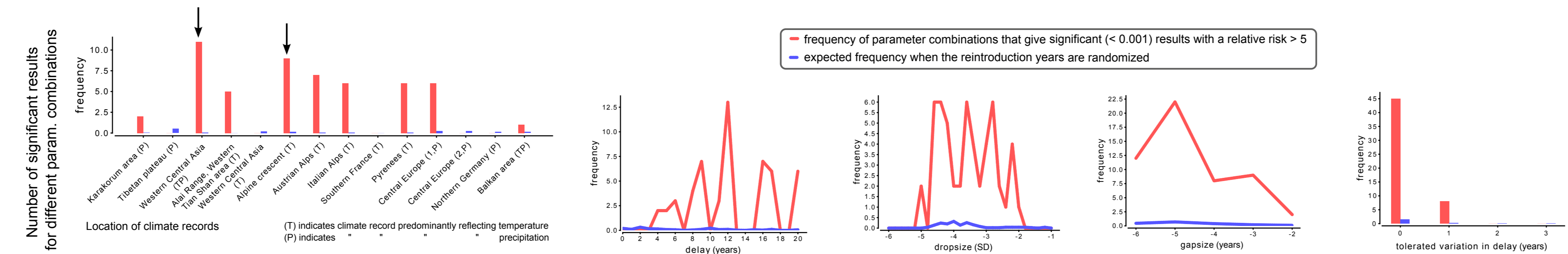
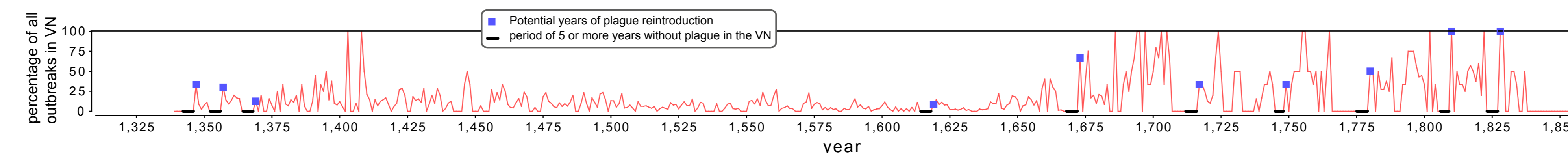
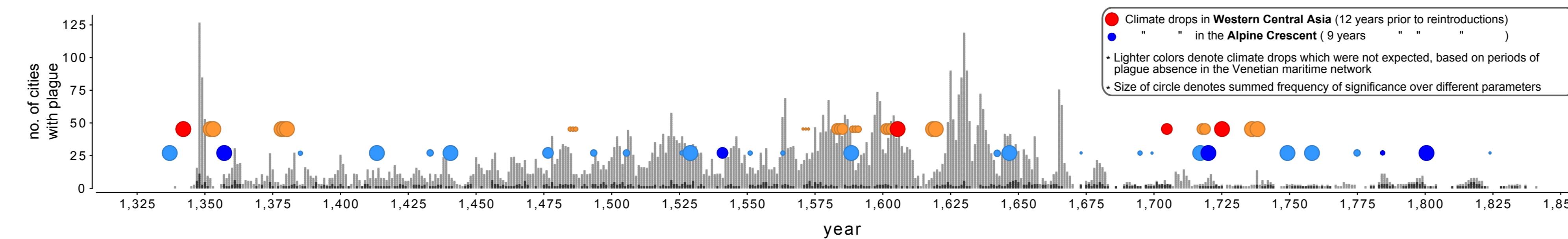
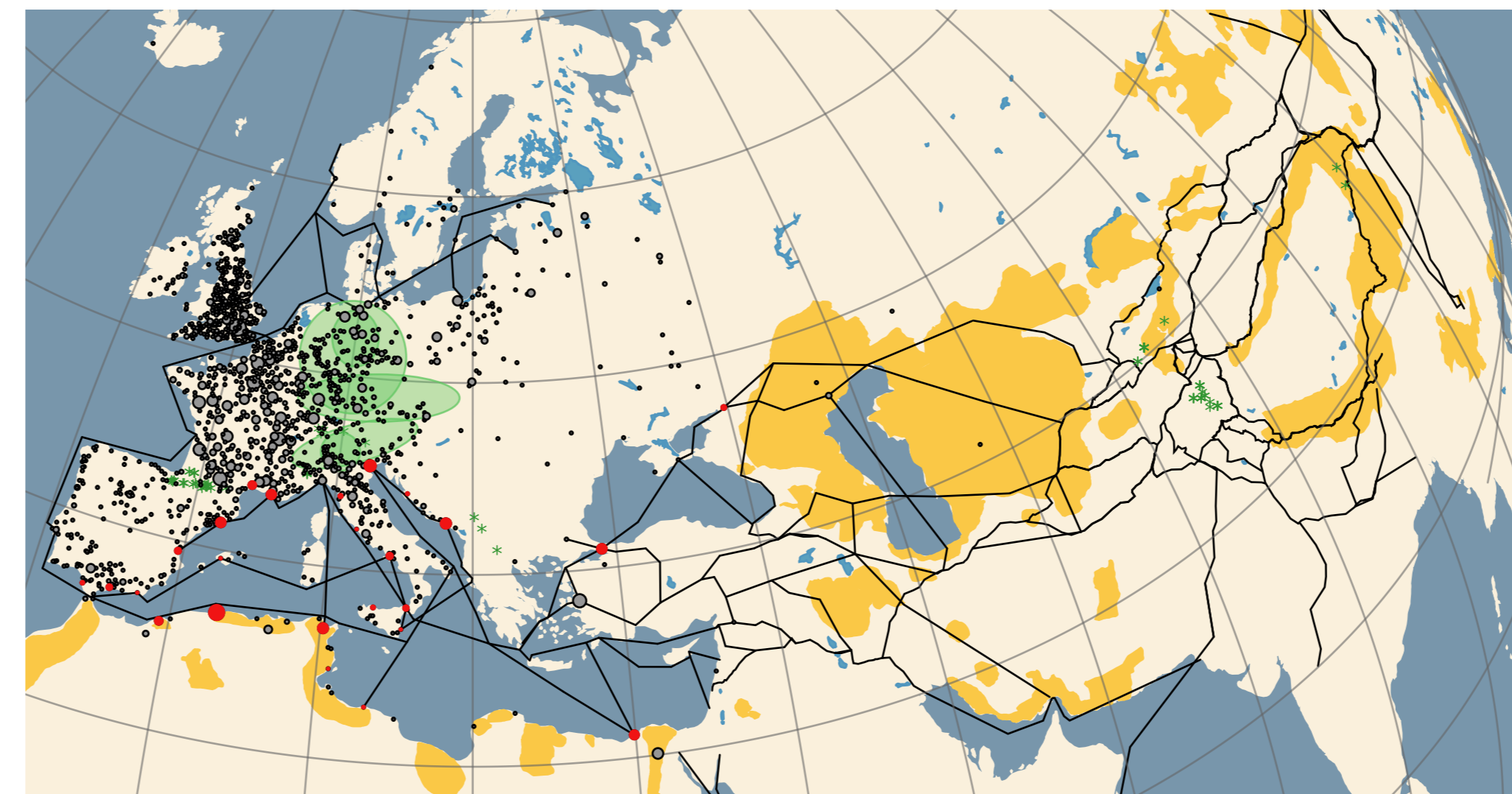
2: *Cities that are part of the Venetian maritime trade Network (VN) in the Mediterranean and Black Sea would likely be the first to be exposed to such new reintroductions.*

3: *By selecting years where plague re-entered the VN after a period of absence, we increase the chance that those years are related to new Asian reintroductions of plague, rather than the re-entrance of plague strains that were already circulating through Europe.*

4: *If plague outbreaks in Asia played a role in the outbreaks in Europe during the second pandemic, then the climate prior to the subset of years selected in (3) would be enriched for events that are associated with plague outbreaks in Asia. Such events should occur a more or less constant number of years prior to the reintroduction of plague into Europe.*

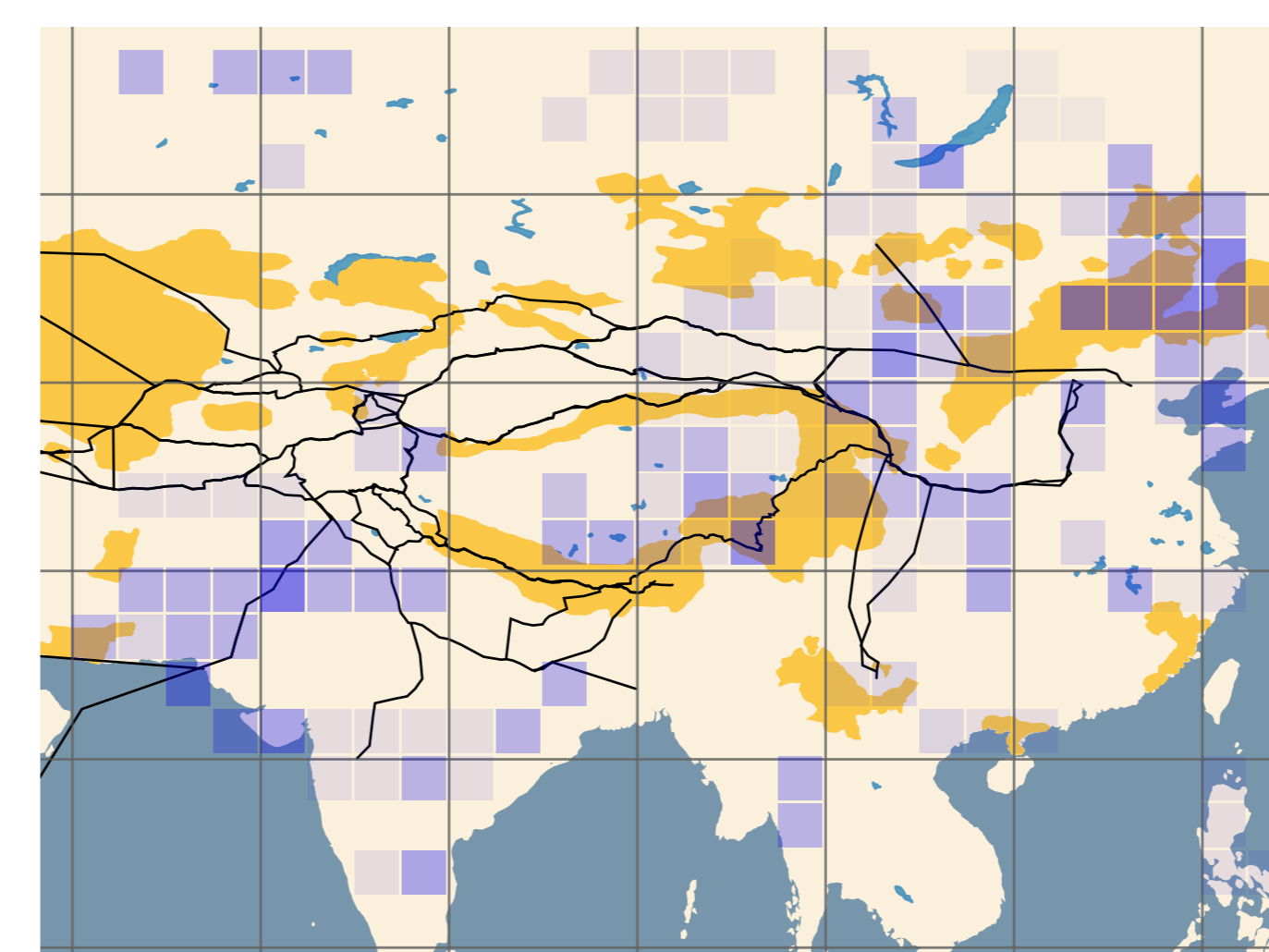
Datasets:

Tree-ring records from 14 locations (**green stars and regions**) were normalized and compared against a compilation of annually recorded medieval plague outbreaks in predominantly Europe (**grey circles**, size denotes frequency of outbreaks). Those harbors that belonged to the Venetian maritime trade network (which was the dominant maritime power during most of the second pandemic) in the Mediterranean and Black Sea, are colored **red**. Medieval Europe was connected to Asia through a network of traderoutes (**black lines**), passing through many of the current-day plague foci (**orange**).



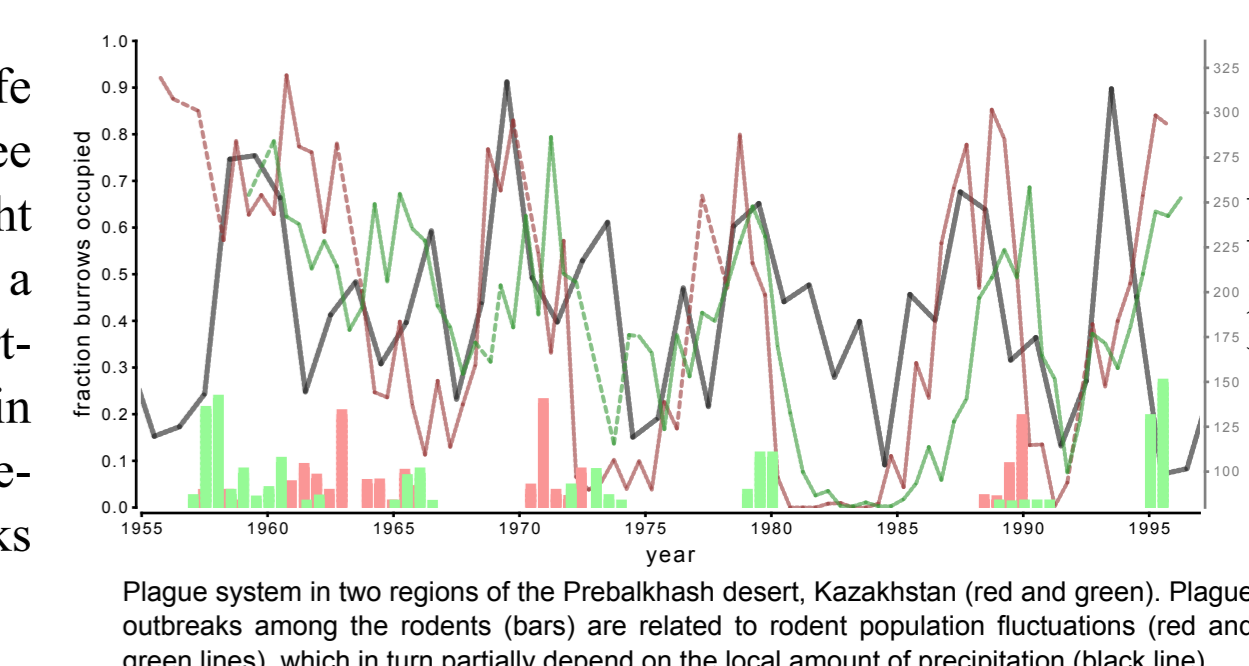
The **spatial distribution** of the sharp climate drops in Western Central Asia (**lefthand side**, mean size of climate drop of -4.1 SD), and the European Alpine Crescent (**righthand side**, -3.3 SD), were spatially plotted using the tree-ring derived PDSI drought index of Asia (*Cook 2010*).

The spatial distribution of sharp climate drops measured from treerings in **Western Central Asia** corresponds with sharp drops in climate in southern Kazakhstan, Kyrgyzstan, Tajikistan and northwest China, and overlaps with several plague systems and numerous trade routes. The spatial distribution in the Alpine Crescent corresponds to the Alps (not shown here), but also to a diagonal of climate drops crossing from south-west Pakistan to northeast China through multiple plague systems and trade routes.



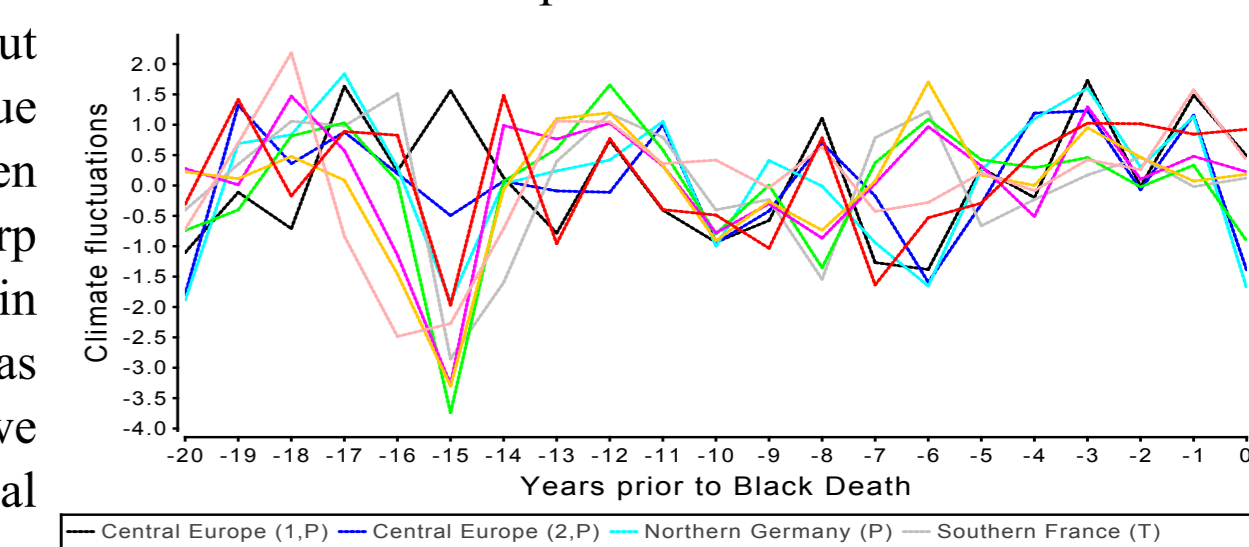
Role of climate in Asian plague systems

The second plague pandemic started in Europe with the *Black Death* in 1346, and continued to cause outbreaks in the centuries after. After 1675, recorded plague outbreaks became rare in continental Europe, but persisted along the North African and the eastern Mediterranean coastline. As per the *indian model of plague spread*, a wildlife rodent reservoir for plague was long suspected to have existed in Europe, but has never been discovered. Using our prior experience with wildlife plague systems in Asia (see inset figure), we sought whether we could detect a correlation between short-term climate fluctuations in Europe (derived from tree-rings) and plague outbreaks in Europe.



No evidence for wildlife plague reservoirs in Europe

We have extensively looked for correlations between European tree-ring based climate indicators and the timing of plague outbreaks in European cities, but found none whose (potentially false-positive) significant results also made sense on a spatial level. One climate pattern we can report is a unique decrease in precipitation and temperature throughout Europe approx. 15 years prior to the start of the *Black Death* epidemic (1346). However, its significance in the disease dynamics of plague is as of yet unknown. It should be noted that the alpine temperature climate records not only spatially correlated to the alps, but also to northern africa and parts of Asia, and through this latter correlation share some of the predictive value of the Asian climate records. We ruled out an European alpine plague reservoir, as the delay between climate patterns (such as sharp drops) and plague outbreaks in European cities was substantially longer than we would expect for a local rodent reservoir.



Conclusions:

It has recently been established that all three plague pandemics started from Asian strains (*Haensch 2010, Harbeck 2013*), but there is little information yet available on the dynamics of plague strains during a pandemic. For the second pandemic, we have analysed the potential role of plague foci outside of Europe, and find that regional climate patterns in Asia appear to have had a continuous role in reintroducing plague into Europe. Such an hypothesis is supported by the current phylogeography of plague (*Cui 2012*): the area affected by climate drops that corresponds to the spatial map of Western Central Asia climate records predominantly consists of rodents carrying Antiqua (0.ANT1-3) and Medievalis (2.MED1-2) plague strains. The diagonal covered by the spatial map of the Alpine Crescent climate records in Asia corresponds to the plague strains 2.ANT1-3, and 2.MED3 (*Cui 2012*). Future work on ancient DNA sequences from the period after the *Black Death* will test our prediction that strains from these regions have been introduced into Europe during the second pandemic.

The proposed mechanism by which regional climate can affect the plague dynamics on a continental scale is called the Moran effect (*Hudson 1999*), i.e. the ability of climate fluctuations to synchronize (rodent) populations over large spatial scales. Such a synchrony of population density would facilitate the percolation of plague (*Davis 2008*) through arid regions, resulting in large (but still regional) plague outbreaks amongst rodents (*Kausrud 2007*). If such outbreaks occur in areas frequently traversed by trade caravans, the chance of animals, humans, or trade goods in these caravans are exposed and become infected by the plague bacterium has suddenly and drastically increased. By this potential mechanism, regional climate effects in plague reservoirs in Asia can have consequences for the plague dynamics throughout the Eurasian continent.