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TECHNICAL REPORT

PLAGUE IN A CHANGING ENVIRONMENT

A LITERATURE REVIEW FOR MADAGASCAR



September 2019

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Cover Photo: USAID/Madagascar (2009). A young child receives mid-upper arm circumference (MUAC) measurement.

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United States Agency for International Development

Adaptation Thought Leadership and Assessments (ATLAS)

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ACRONYMS

ENSO	El Nino Southern Oscillation
FEWS-NET	Famine Early Warning Systems Network
IOD	Indian Ocean Dipole
NDVI	normalized difference vegetation index

GLOSSARY

<i>Epidemic</i>	A sudden increase in the number of cases of a disease within a human population to levels above a normal expectation in that population or area.
<i>Pandemic</i>	An epidemic that has spread over several countries or continents, usually affecting a large number of people.
<i>Outbreak</i>	A sudden increase in the number of cases of a disease, usually in a small geographic area.
<i>Anthropophilic</i>	Something that prefers humans, e.g., a flea that prefers feeding on humans.
<i>Reservoir host</i>	An organism that is cycling or maintaining a disease-causing pathogen; this can be a maintenance host, which is not always affected by the disease, or an occasional reservoir host, which is also not always affected by the disease.
<i>Mortality rate</i>	The rate at which individuals in a population die, expressed as the probability of dying in a period of time. For a disease, this is 1/the average survival time of an infected individual.
<i>Purpura</i>	A purple spotted rash from bleeding under the skin due to the bursting of small blood vessels.
<i>Septicemia</i>	Infection of the bloodstream itself, usually by poisoning from bacterial toxins flooding the system; also called blood poisoning or toxemia.
<i>Gangrene</i>	The death and localized decomposition of bodily tissue due to a lack of blood flow or severe bacterial infection.
<i>Anthroponotic</i>	Disease spread from humans to animals.
<i>Zoonotic</i>	A disease that is of animal origin and has caused infection (and/or disease) in humans.
<i>Sylvatic</i>	Diseases or pathogens that only affect wild animals.
<i>Spillover events</i>	When a disease moves from its expected host to a new one; e.g., when humans are infected with viruses from eating bushmeat, or when great apes catch the flu from tourists. Usually used for animal-to-human transmission.

<i>Sentinel</i>	In epidemiological surveillance, an animal or other organism that signals disease events ahead of time, either by becoming visibly diseased or by seroconverting (becoming positive on a blood test).
<i>Mechanistic</i>	Determined by physical processes; explaining phenomena in deterministic terms.
<i>Seroprevalence</i>	The rate (proportion of the population) that is considered positive by a blood assay (test) for infection. This can be evidence of infection of a pathogen itself, or evidence of an immune response on the human host.
<i>Enzootic</i>	Endemic in an animal or nonhuman population.
<i>Epizootic</i>	A large and sudden outbreak of disease in animals.
<i>Ribotype</i>	Ribotyping is a molecular method in clinical diagnostics for bacteria. It uses rRNA typing (ribosomal RNA, in bacteria) to describe the similarities and differences between bacteria to determine relatedness (phylogenetics). It is sometimes referred to as the DNA fingerprint of bacteria.
<i>Sisal (hedges)</i>	Sisal is an agave that is cultivated worldwide for fiber production. Its fibers are used particularly for making ropes and matting.
<i>Seropositivity</i>	The status of testing positive on a clinical test (see also seroprevalence).

EXECUTIVE SUMMARY

This review identifies environmental factors that contribute to the emergence of plague and plague dynamics in Madagascar and aims to identify the potential implications for decision-making and intervention, particularly in a changing environment.

OVERALL FINDINGS

- **The dynamics of plague in Madagascar, or what causes plague to emerge and spread, are different in highland and lowland areas.** The ecology of the disease in urban areas in the highlands is different from that of urban areas in the lowlands. In the lowlands, near the port of Mahajanga, the Asian shrew (*Suncus murinus*), is most likely involved in the transmission cycle, and outbreaks have occurred during the drier seasons (usually July–November). In the highlands near the capital of Antananarivo, the rats, the black rat (*Rattus rattus*), and the sewer rat (*R. norvegicus*) are believed to be responsible for plague transmission, and outbreaks occur primarily during the rainy season (October–April).
- **Urban overcrowding and poverty have long been associated with plague outbreaks.** For example, sewer structures are likely to make *R. norvegicus*, currently limited to the west, more widely spread in cities.
- **In rural areas, in addition to storing crops in houses, land clearing for agricultural activities such as cutting trees and setting bushfires promote the spread of rats and increase interactions with humans.**
- **There are persistent areas of disease outbreaks in the central and northern highlands.** These are characterized by specific elevation, topography (areas above 800 meters), and climate, which shape flea and rat distributions. For example, outbreaks of plague in Antananarivo city occur between October and April, corresponding to warm and rainy weather, and plague is transmitted by the sewer rat (*R. norvegicus*).
- **The primary rodent vector in Madagascar, *Rattus rattus* (black rat), is found everywhere—in houses, villages, fields, and forests.** It has a gestation period of 21 days and a mean litter size of 5.4, meaning it can undergo rapid population growth. As warm-blooded mammals, rats are far more capable of behaviorally regulating temperature than insect vectors, meaning that they are likely to seek out domiciliary or peri-domiciliary habitats, or take advantage of other human manipulations of the environment, such as sewers, hedges, dense field crops, and storage spaces for food or other uses. This rat's genetic structuring may correlate to landscape structuring (topography), and thus plague dispersal. Other less effective but still relevant vectors in Madagascar include the oriental rat flea (*Xenopsylla cheopis*), dogs, domestic cats, wild cats, chickens, guinea pigs, opossums, and wild rodents generally. It has additionally been found on pigs, skunks, badgers, deer, foxes, prairie dogs, ground squirrels, and burrowing owls.

FACTORS INFLUENCING PLAGUE TRANSMISSION

SOCIAL AND STRUCTURAL FACTORS

Human–landscape interactions play a role in the ecology of plague.

- **Agricultural areas are more at risk from plague transmission than natural areas.** A model assessing relative risk by estimating the number of plague rodents in Tanzania suggested that plague risk is almost twice as high in agricultural areas compared with natural areas.

ENVIRONMENTAL AND CLIMATOLOGICAL FACTORS

The many studies examining the associations between temperature, precipitation, and plague are largely in temperate regions rather than tropical regions. Nevertheless, some interesting insights are noted below:

- **For Madagascar, information is limited on the role of climate in plague dynamics.** Studies point to an elevational barrier to the transmission cycle, likely an environmental constraint on the endemic flea (*S. fonquerniei*). This gradient includes an increased risk of household-level plague above 1,300 meters in Uganda, as well as an increased risk in Vietnam at elevations above 500 meters.
- **Climate likely impacts plague ecology through changing resources available for crop planting and storage practices and the effect of these changing practices on rodents.** At a larger scale, there is evidence that the El Niño Southern Oscillation (ENSO) impacts the seasonality of suitable climates for persistence of the rodent–flea cycle, and evidence suggesting that a warmer/wetter future may lead to reduced suitability for the endemic sylvatic cycle flea.
- **At a larger scale, changes in rainfall may lead to changes in planting, or simply altered timing of availability of crop resources, leading to changes in rodent populations and behavior.** The linked human behavior risk of harvest and storage would simply shift with the timing.
- **Large scale climate factors appear to increase the incidence of plague.** These include ENSO, a well-documented worldwide phenomenon where rising temperatures in the Pacific Ocean can impact rainfall patterns across the globe, and the Indian Ocean Dipole (IOD), a similar dynamic that occurs with regularity in the Indian Ocean. In the late 1990s, ENSO events became both stronger and more frequent and, combined with the IOD events, created warmer and wetter conditions for Madagascar. In this study, 1997 is an exemplar year, as it had the strongest El Niño and warm phase IOD, which led to warm and wet conditions in Madagascar and one of the largest plague incidence anomalies on record.
- **Longer-term patterns of plague occurrence are related to larger climate patterns, for both temperature and precipitation.** Warmer/wetter shifts in climate, if they occur during a typical cold and dry season, are likely to increase flea survival, shorten development time, and lead to favorable conditions for plague transmission.
- **Although the effect of precipitation on plague is complicated to detect directly at both small and large scales, studies suggest that more intense rainfall is associated with a decrease in plague incidence.** In contrast, a study in Uganda found that lagged normal rains between the rainy seasons (0.2–10 mm) were associated with higher plague incidence.
- **Factors correlated with plague suitability in sub-Saharan Africa include elevation, potential evapotranspiration, mean diurnal temperature range, annual rainfall, and**

the normalized difference vegetation index (NDVI) in December. NDVI is an indicator of vegetative health.

- **The relationship between plague and lagged rainfall has two potential mechanistic underpinnings.** The first is through trophic cascades, where in arid and semiarid regions, sufficient dry season rainfall leads to plant growth and an increase in rodent populations. The second is that higher rainfall may increase flea survival, meaning rodents may simply have higher flea burdens in following months, which is associated with increased human plague transmission.

CHANGING DYNAMICS, SURVEILLANCE, AND TREATMENT

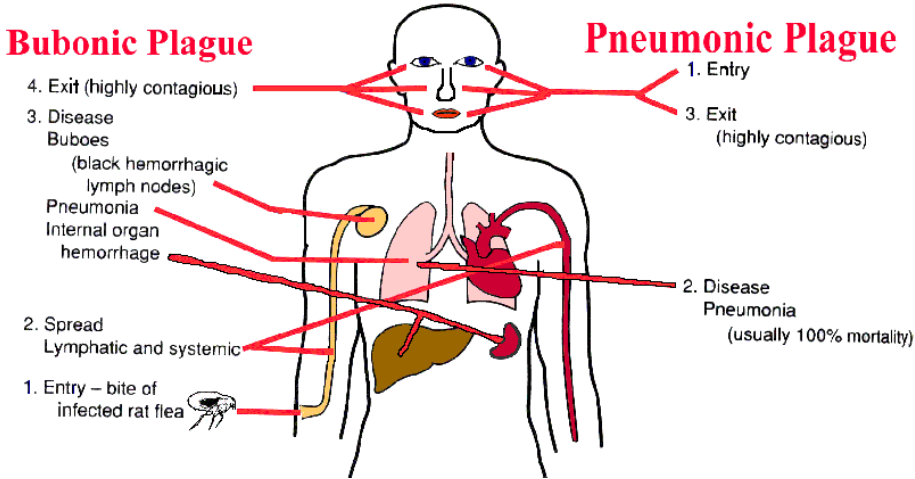
- **Rats are becoming more resistant to plague.** Dead rats are an indicator for plague; if rats are resistant this alters the possibility for using rats as early warnings of an epizootic. *R. norvegicus*, which live in urban areas, are less susceptible to plague than other species, and there is increasing evidence of resistance in *R. rattus*, the most common vector.
- **Fleas are gaining resistance to insecticides.** The cosmopolitan flea commonly found in rats caught in houses (*Xenopsylla cheopis*), the human flea (*Pulex irritans*), and a flea endemic to Madagascar (*S. fonquerniei*) are resistant to DDT, dieldrin, and malathion, and to some organochlorides reported in the early 1980s (Coulanges et al., 1982; Coulanges & Randrianantoanina, 1984b, 1984a). This makes it more difficult to eradicate plague vectors and human exposure.
- **Strains of the plague are becoming resistant to antibiotics.** The first antibiotic-resistant *Yersinia pestis* strains were isolated from Madagascar, with one strain found resistant to eight antibiotics (including those used specifically for plague prophylaxis and therapy). The evidence for antibiotic-resistant strains of *Y. pestis* from Madagascar came from a rat in the capital, Antananarivo.
- **While the black rat (*R. rattus*) is the most common vector, there are other rodents that could transmit the disease, posing challenges to early warning and surveillance.** Potential for more than just the black rat (*R. rattus*) to be a rodent reservoir, and for more than just the rat flea to be a vector, came under scrutiny in the late 1990s.
- **The appearance of plague in new areas in 2019 indicates the capacity for plague to establish new rodent–flea cycles in Madagascar and also warrants surveillance.** Surveillance efforts should target important geographic areas of the country, for example, looking at the oriental rat flea (*X. cheopis*) in the warm low-lying region foci defined herein, as well as the persistent foci in the highlands of the endemic flea (*S. fonquerniei*).
- **Warming under climate change may alter the suitability of Madagascar for plague in its endemic enzootic flea–rodent cycle.** The endemic flea (*S. fonquerniei*) is better adapted to the cool conditions of the highland regions, which supports the persistent enzootic foci (or hotspot) in the highlands, while the oriental rat flea (*X. cheopis*) is better adapted to the warm low-lying regions, common to other vector-borne diseases. The implication of these dynamics is that endemic flea transmissions may be reduced, while the rat flea transmission could increase in elevation as temperatures warm.

- **Modifying human behaviors could greatly reduce communities' exposure to plague.** In rural households, not storing grain inside the house would reduce rat and flea contact. Sleeping on elevated surfaces and not on floor mats would reduce flea bites. Rural households should be aware of the agricultural link to plague and flea exposures and closely monitor young field workers for any initial symptoms. Education efforts could support this awareness.

INTRODUCTION

Plague is caused by the bacterium *Yersinia pestis*, which naturally persists in transmission cycles between rodents and their fleas (Gage & Kosoy, 2005). This is the most lethal bacterium known to mankind, and plague is a WHO internationally notifiable disease (along with diseases such as cholera and yellow fever). This means that when a plague case is confirmed, WHO must be informed. As a bacterial infection in humans, plague is treated with readily available, widely marketed antibiotics such as tetracyclines and fluoroquinolones. While the disease has a long history with humankind, the eruption of plague outbreaks, epidemics, and pandemics is precipitated through contact between the natural cycle (rodent–fleas) and humans. The routes by which human infection occur can be primary or secondary. Primary exposure is a flea bite from a flea on a nondomestic vertebrate (e.g., see the mountain lion interaction in Yellowstone¹). In secondary exposure, peridomestic rodents (e.g., rats) create a bridge between a natural cycle of rodent–flea (or other vertebrate–flea) transmission, and fleas then bite humans, either as anthropophilic (human-preferring) fleas, or simply accidental bites. The primary reservoir host of plague is the black rat (*Rattus rattus*), an invader of new habitat, which has a nearly global distribution, primarily through transport on ships (Bonds et al., 2018).

Figure 1: Types of plague and their transmission/risks



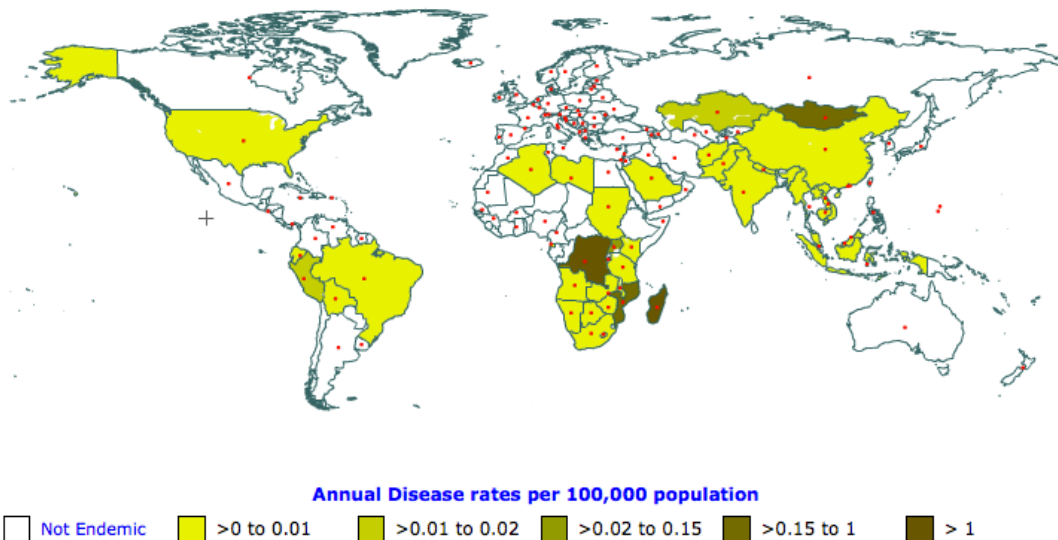
Source: <https://www.atsu.edu/faculty/chamberlain/website/lectures/lecture/plague.htm>

The primary form of human plague is bubonic plague (see Figure 1), typified by fever and lymphadenitis (swollen lymph nodes). The symptoms of bubonic plague mirror that of the flu and are often left untreated for days, which can increase mortality rates. Untreated bubonic plague has a 50%–60% mortality rate. Untreated infection can spread from lymph nodes to the lungs, resulting in secondary pneumonic plague, which then creates a new primary infection route to other people via respiratory droplets. Primary pneumonic plague has a short incubation period

¹ <https://www.npr.org/2019/02/05/691528804/colorado-runner-kills-mountain-lion-in-self-defense>

of 1–4 days (Mead, 2018) and is nearly 100% fatal without treatment. Plague can also manifest and become septicemic plague, or purpuric plague, wherein the tissue becomes poisoned and leads to purple and black external cues. This is thought to be where the Black Death derives its name. Subcutaneous bleeding leads to purpura, or blood spots, and this can progress to septicemia, or blood poisoning, and gangrene, particularly in the extremities. Septicemic plague can occur from direct contact with infected tissues and can be treated effectively if caught early enough. However, if untreated, mortality approaches 100%. An estimated 12% of cases of bubonic and primary septicemic plague develop into secondary pneumonic plague. This means that there is a roughly 1 in 10 chance that a purely anthroponotic outbreak (only transmitted from humans to animals) can occur from each zoonotic (transmitted from animal to human) transmission event. Figure 2 shows the global distribution of plague.

Figure 2: Global distribution of plague



Note: Disease is endemic to 38 countries. Source: <http://www.infectionlandscapes.org/2011/05/plague.html>

There have been three plague pandemics (Stenseth et al., 2008). Each pandemic is thought to have been caused by a different biovar of the *Y. pestis* bacterium—Antiqua, which can still be found in Africa and Central Asia; Medievalis, now limited to Central Asia; and Orientalis, which is currently global in distribution (Stenseth et al., 2008). The Justinian Plague of 542 is thought to have contributed to the collapse of the Roman Empire, the end of the golden age of antiquity, and the beginning of the Dark Ages (Rosen, 2007). In the wave of collapse due to the impact on society of missing family lines and heirs, a great deal of early property law emerged that is still in use. The second pandemic is perhaps the most well-known, the Black Death. Emerging in the 1300s, the pandemic recurred intermittently for around 300 years (Stenseth et al., 2008). The third pandemic does not have a proper name. In the late 1800s, Muslim persecution in parts of China led to a mass migration event, bringing plague to the ports, from which it spread to port cities across the globe: Alexandria, Bombay, Buenos Aires, San Francisco, Saigon, Sydney, and others. The steamship era led to outbreaks of plague in ports around the world in 1898, and

in November 1898, plague arrived in Madagascar (Mead, 2018). This third and ongoing pandemic has killed millions of people. While the pandemic eventually petered out in many regions, enzootic cycles were established in others, which persist to this day. Two regions are in the western United States and the central highlands of Madagascar.

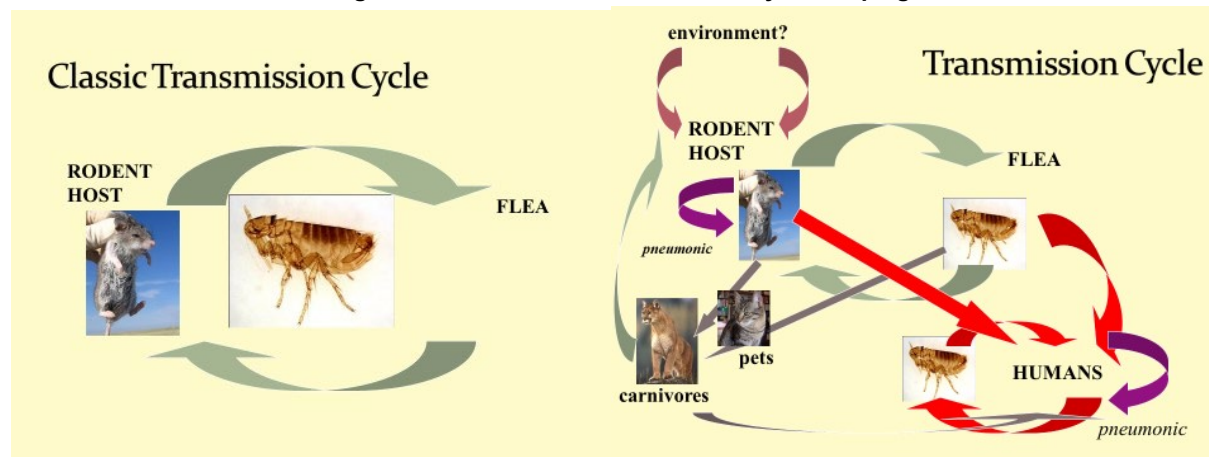
Understanding how and when new outbreaks are initiated is key to prevention and management. Interactions with persistent enzootic cycles of plague are the point of emergence for this potentially high-casualty, fast-moving disease. This review identifies environmental factors in the emergence of plague, describes plague in Madagascar, and recommends points of decision-making and intervention, particularly in a changing environment.

ENZOOTIC CYCLES OF PLAGUE

Plague is a flea-borne enzootic disease (only transmitted between nonhuman populations) in most forms of transmission, with the exception of the anthroponotic transmission chains (human to human only) that occur with primary pneumonic plague. However, every primary pneumonic plague outbreak starts in the enzootic realm, so this is likely the best place to address control and intervention.

Figure 3 describes the intersection of the sylvatic (wildlife–rodent) cycle of plague and the many potential contact points for it to become both urban cycling and directly transmitted to humans.

Figure 3: Human and wildlife–rodent cycles of plague



The flea transmission component of plague was discovered by Simond in 1898 (Gage & Kosoy, 2005). Thus, the knowledge that managing the environment around humans for the reduction of fleas is not new, but achieving it is still complicated. As there are multiple plausible routes of flea and small vertebrate reservoir transmission (via rodents such as rats and shrews, marsupials, prairie dogs, etc.), it is important to identify the most common culprits in the remaining pockets of enzootic plague. Fleas are insects in the Siphonaptera order. The primary plague flea vector in most large documented epidemics in Africa, Asia, and South America has been *Xenopsylla cheopis*, the oriental rat flea.

The method of transmission is interesting. In *X. cheopis*, the flea ingests infected blood, the bacteria multiply in the foregut (proventriculus), and the bacteria form a biofilm in the flea's midgut, which then starts to starve the flea, as it cannot digest the blood meal (Eisen et al., 2006; Sebbane et al. 2005). Thus, the flea starts repeated biting in attempts to feed successfully, and it regurgitates bacteria into the next host. While this "blocking" mechanism for transmission suggests that there is a delay of several days before fleas become infected (the bacteria require time to multiply), there is also evidence for early transmission (in days 1–3), suggesting that more rapid flea-spread plague is possible (Eisen et al., 2006).

While there is a tight relationship in the rat–flea cycle, and it is most commonly posited as the source of all plague spillover events into humans, plague can infect ALL rodents. In addition, plague can infect both cats and dogs, and while cats have been found to develop and transmit pneumonic plague (e.g., if a cat coughs on you, you can catch it), dogs appear to be more resistant to infection and rarely show symptoms. This means that domestic and peridomestic companion animals or pets (vertebrates) may be a rare transmission pathway and can be both a risk and an early indicator of outbreaks (sentinel).

In addition to *X. cheopis*, 80 species of flea are susceptible to *Y. pestis*. One key vector is *Pulex irritans*, the "human flea," which has a wide host spectrum, including dogs, domestic cats, wild cats, rats (both black and Norway), chickens, guinea pigs, opossums, and wild rodents generally. It has additionally been found on pigs, skunks, badgers, deer, foxes, prairie dogs, ground squirrels, and burrowing owls. Another flea is *Ctenocephalides felis*, the "cat flea," which regularly bites humans, dogs, rats, opossums, raccoons, foxes, and other vertebrates.

METHODOLOGY AND FINDINGS

We searched four databases and Google Scholar with the broad terms “Plague” and “Madagascar.” Web of Science returned 194 results, PubMed returned 164, WHO library database AFROLIB, 78 (no language restriction), and World Cat, 984 (all formats). Due to the style of web crawling by Google Scholar, >18,400 results were returned, so this set was reserved for further examination.

Papers or reports were excluded which did not have retrievable information beyond the title. The combined, nonduplicated results (227) were inspected for relevance. Titles and abstracts were scanned to assess relevance to this review; for example, purely diagnostic methods papers were excluded. The reduced set of 81 papers and reports was then reviewed; they are listed in the annotated bibliography, most with abstracts. The papers were used to generate a list of drivers of plague, presented in the Executive Summary, which, when combined with the information presented here, can help to elucidate the effect of climate and land use change on plague dynamics in Madagascar.

A second search was conducted on “Plague” and “Environmental*” in Web of Science (763 returned) and PubMed (1,344), to expand the scope of material to explore environmental drivers of plague dynamics that may be important in Madagascar. This combined list of 82 papers was inspected for relevance and further reduced by removing papers not relevant to Africa, with one exception describing a comparable highlands situation in Vietnam.

The results are presented in the following four sections. Section 1 examines the processes of plague transmission, Section 2 provides an overview of the history of plague in Madagascar, Section 3 describes insights linking climate and plague, and Section 4 offers insights on links between the environment and plague.

PLAGUE TRANSMISSION PROCESSES

In understanding how environmental drivers, broadly describing climate and landscape changes, may influence plague dynamics and emergence, it is important to have a conceptual model of the aspects that are likely to be impacted.

VECTOR

The flea is subject to environmental conditions, mainly temperature—which affects development, growth, and reproduction—and precipitation, which will mediate ambient humidity. The flea is also susceptible to infection and must have a ready blood meal. Kreppel et al. (2016) examined both the *Synopsyllus fonquerniei* flea, endemic to Madagascar, commonly found on outdoor rats, and *Xenopsylla cheopis*, which they refer to as a cosmopolitan flea, commonly found on rats caught in houses. They found that *S. fonquerniei* have greater transmission efficiency than *X. cheopis*, which may contribute to the persistence of enzootic plague in the

central highlands. They also conducted temperature and humidity experiments on the immature flea stages (larvae and pupae). They found that *S. fonquerniei* took longer to develop and had lower survival at high temperature and low humidity than *X. cheopis*. Their findings suggest that the endemic *S. fonquerniei* is better adapted to the cool conditions of the highland regions, which supports the persistent enzootic foci (or hotspot) in the highlands, while *X. cheopis* is better adapted to the warm low-lying regions, common to other vector-borne diseases. Future warming under climate change may therefore reduce the suitability of Madagascar to plague in its endemic enzootic flea–rodent cycle.

RODENT

The influence of climate on the maintenance reservoir of a disease must occur either directly, by subjecting the rodent to extremes, such as flooding, severe drought events, or even fire, or indirectly by affecting the distribution and availability of food and nesting resources. As warm-blooded mammals, rodents are far more capable of behaviorally regulating temperature than insect vectors, meaning that they are likely to seek out domiciliary (in the home) or peridomestic (around the home) habitats, or take advantage of other human manipulations of the environment, such as sewers, hedges, dense field crops, and storage spaces for food or other uses.

PEOPLE

Exposure to changing climates, in the form of shifting seasonal patterns of weather, may promote behavioral adaptations with ripple effects onto plague ecology. For example, the planting season for crops may be disrupted. Shorter seasons would lead to longer fallow periods or periods of scarcity. Longer seasons under a warmer/wetter scenario would promote rodent habitat for more of the year. The interaction between the human modified landscape and plague dynamics becomes apparent: People spending more time in the agricultural landscape creates greater exposure. Food scarcity has been correlated to changes in food storage practices, such as storing grain close to or in the house rather than away from the house. This may protect against robbery but bring rodents and their fleas closer to people.

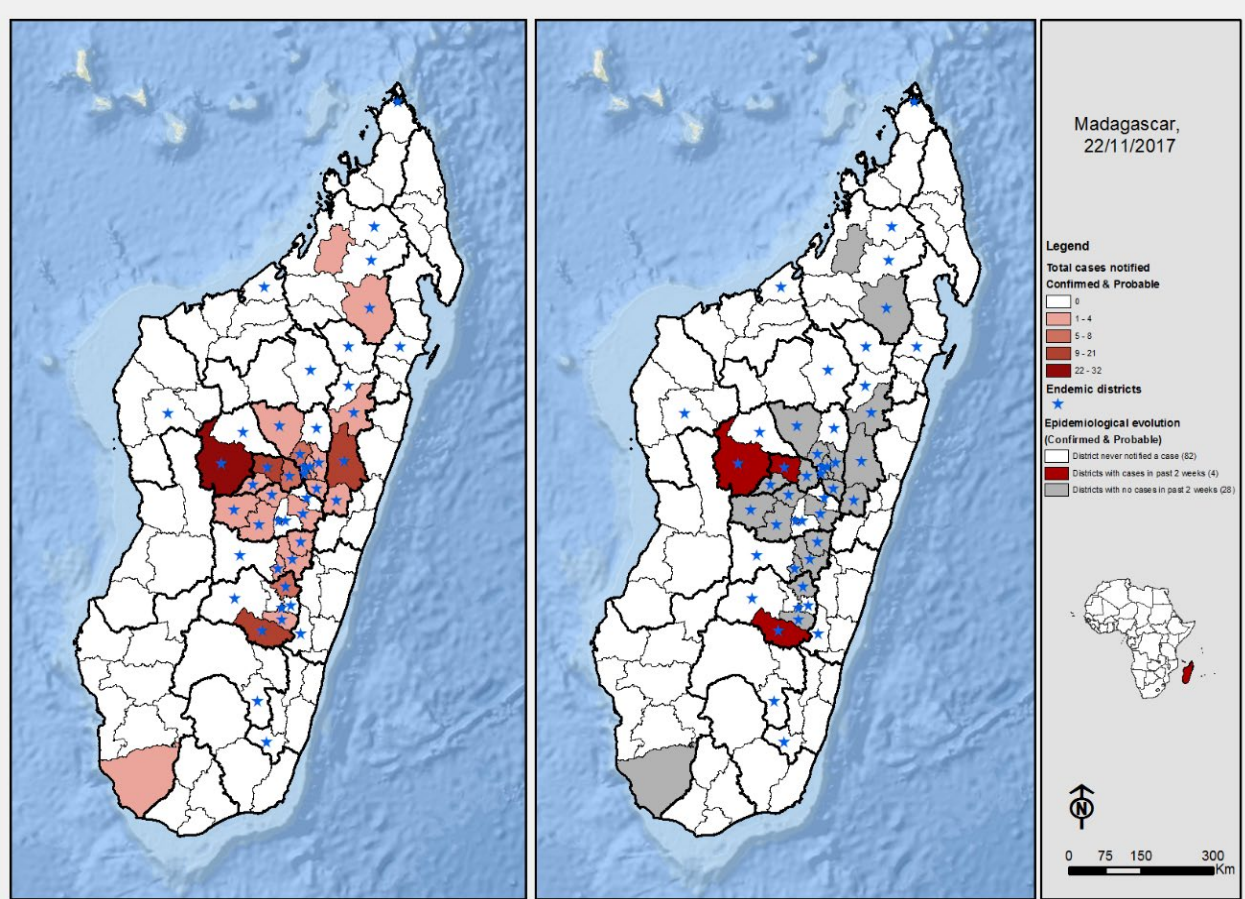
PLAGUE IN MADAGASCAR

From 2017 to the present, an ongoing epidemic has reignited fears about both the spread and management of plague. In late August 2017, a 31-year-old infected male traveled from the central highlands bound for Tamatave through Antananarivo. He died in transit, having made dozens of contacts, many of whom became ill. Additional cases of suspected plague were reported contemporaneously in many areas (see Figure 4): 2,417 cases from August 01 to November 22, 77% of which were bubonic plague (World Health Organization Regional Office for Africa, n.d.). This indicates that there are persistent enzootic foci of plague, which may result in ongoing spillover human cases, and which can also spark these much larger and far-reaching human transmission chains.

Plague arrived in Madagascar in 1898 at the port of Toamasina, and reached Antananarivo by 1921, following the construction of the railroads. It is considered endemic to the central and

northern highlands (above 800 m), with a main rodent reservoir, the black rat (*R. rattus*), and two flea species, *X. cheopis* and the endemic species, *S. fonquerniei*. In the 1950s, plague was brought under control in Madagascar by a combination of vaccination campaigns, improved housing and hygiene measures, and the discovery and use of streptomycin (antimicrobials) and insecticides to control fleas. During the following 30 years, 20–50 cases per year were reported for the entire country (Chanteau et al., 1998). However, in 1989 more cases were reported, and the number of suspected cases started to increase steadily.

Figure 4: Geographical distribution of confirmed and probable bubonic plague cases in Madagascar from 01 August through 22 November 2017



Source: <https://www.who.int/csr/don/27-november-2017-plague-madagascar/en/>

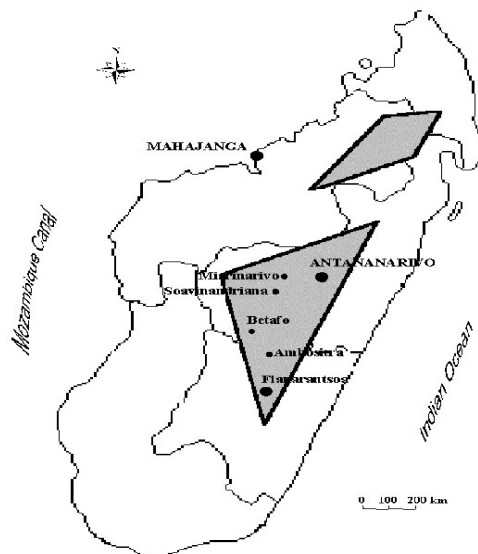
Two sets of plague dynamics emerged in Madagascar in 1991. Mahajanga is a west coast port with a plague season of July to November. In July 1991, 170 suspected cases were reported near the Marolaka marketplace, of which 41 were confirmed or presumptive. From 1995 to 1997, three July outbreaks occurred (corresponding to a drier season), and each outbreak was preceded by a high reported number of dead rats. In Mahajanga, the Asian shrew, *Suncus murinus*, is most likely involved in the transmission cycle (Duplantier et al., 2005). The shrew species, all carrying *X. cheopis* fleas, was implicated in these outbreaks due to being infected, caught in Mahajanga, and present both before and after the plague outbreaks. This plague cycled in local rodent and flea populations for several years and then disappeared. This was

probably an imported plague, transported to the port from the central highlands into the local rodent–flea cycle (Andrianaivoarimanana et al., 2019).

The other major plague dynamic is in the highlands, and also urban. In Antananarivo, no human cases were reported from 1953 to 1978, but in 1979 there was a confirmed case. Starting in the 1990s, 10–25 cases a year were confirmed or presumptive, and by 1996 confirmed cases were found in the capital. A 1995 study of rats trapped in a local market found that 10% were infected with *Y. pestis*, with 80% indicating plague exposure antibody responses and a high *X. cheopis* flea index (estimated monthly burden of fleas per rat) (Chanteau et al., 1998). Further rat testing in 1997 suggested that seroprevalence of *Y. pestis* in the rats was increasing. Interestingly, rodent surveillance initiated in the 1990s documented the replacement of *R. rattus* by *R. norvegicus* in the town, brought on by the construction of modern houses and sewage networks (Duplantier et al., 2005). It is thought that this modernization has a dual effect to reduce human plague cases: 1. People simply have less contact with rats and fleas because *R. norvegicus* prefer sewers and cannot occupy modern household materials; 2. *R. norvegicus* are less susceptible themselves to plague (Chanteau et al., 2003), so they stay alive while infected. Their fleas do not need to leave the host in search of another blood meal, and that reduces human bites. Conversely, rats that are no longer susceptible to plague will not exhibit epizootics with mass die-offs and may instead maintain plague within the city.

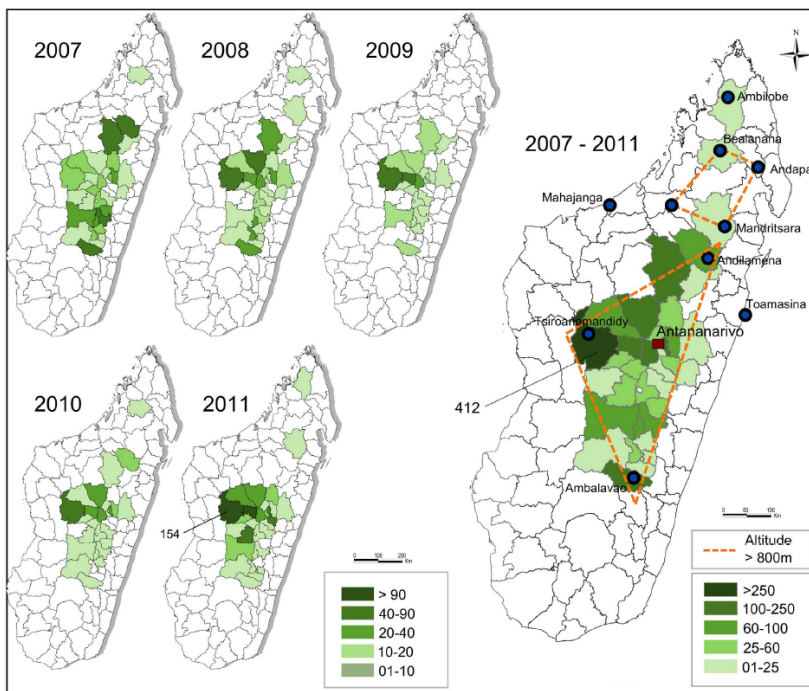
In 2013, researchers from the Unite Peste, Institut Pasteur de Madagascar, and other researchers described the persistent plague foci in Madagascar (Andrianaivoarimanana et al., 2013). Their findings were consistent with the 1998 reported endemic zones in Chanteau et al. (1998) (see Figures 5 and 6). A more recent study (Andrianaivoarimanana et al., 2019) examined the trends in human plague in Madagascar between 1998 and 2016, updating the geospatial view by examining the foci of the two types of cases, bubonic plague and pneumonic plague, and examining the locations of infection clusters (see Figure 7).

Figure 5: The two endemic plague foci in Madagascar, as described in 1998 by Chanteau et al.



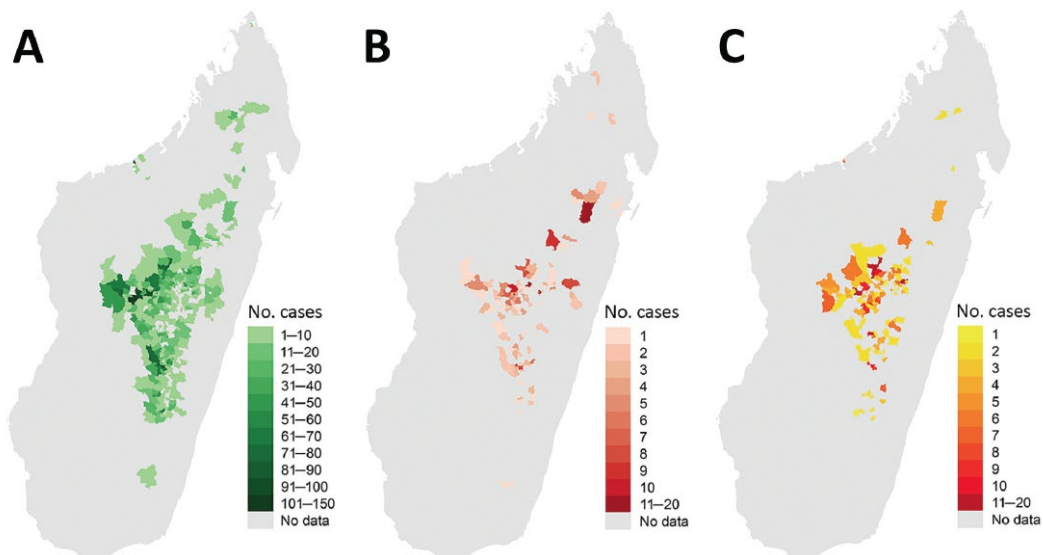
Source: (Chanteau et al., 1998)

Figure 6: The foci of plague cases in Madagascar from 2007 to 2011



Source: Andrianaivoarimanana et al., 2013 (Note the central triangle and the northern quadrilateral shapes of the two foci, demarcating areas above 800 m, thought to be a cut off for enzootic persistence. Figure adapted from Figure 1 in Andrianaivoarimanana et al., 2013)

Figure 7: Distribution of reported cases of plague from 1998 to 2016, for A. bubonic, B. pneumonic, and C. infection clusters



Source: Andrianaivoarimanana et al., 2019 . Note the similarity of the central cluster location, but with the added southern and northwestern locations of bubonic cases (A); note also the correspondence between pneumonic (B) and infection clusters (C).

In Madagascar, all *Y. pestis* strains belong to the Orientalis biovar, and there are four ribotypes (B, Q, R, and T); the most common is B, which was the original invading strain, and the other three are unique to Madagascar (Guiyoule et al., 1997). Madagascar is also where the first antibiotic-resistant *Y. pestis* strains were isolated, with one strain found resistant to eight antibiotics, including those used specifically for plague prophylaxis and therapy (Galimand et al., 2006). This points to both ongoing selection pressures for antibiotic resistance as well as high rates of circulation and divergence in the strains.

Madagascar is home to 13 genera of the Siphonaptera (fleas); four are endemic, of which two are implicated in plague transmission: *Xenopsylla* and *Synopsyllus*. There are five species of *Synopsyllus* in Madagascar, of which *S. fonquerniei* is the most prevalent (Andrianaivoarimanana et al., 2013). *S. fonquerniei* is found in the fur or burrows of black rats outside houses, but also in rice fields, savannas, and forests. It has been found on endemic hedgehogs, rodents, and even a lemur. It is therefore obviously a key part of the sylvatic cycle of plague in Madagascar. *R. rattus* is the main plague reservoir, and its arrival is linked to the colonization of Madagascar by humans; it is found everywhere, in houses, villages, fields, and forests (Brygoo, 1966). It has a gestation period of 21 days and can produce up to five litters of 6–12 young per year. In Madagascar it has a mean litter size of 5.4 (Andrianaivoarimanana et al., 2013), meaning it can undergo rapid population expansion.

While it is unlikely that soil persistence of *Y. pestis* plays a role in the transmission of plague in Madagascar under natural conditions, other human interactions with the environment likely do. The Ministry of Health has established a seven-year recommended period wait time in the traditional funerary behavior of exhumation (Famadihana) to prevent previously documented rapid spread of pneumonic plague from burial practices. However, the survival time of *Y. pestis* in corpses has not been assessed (Andrianaivoarimanana et al., 2013).

Urban overcrowding and poverty have long been associated with plague outbreaks, and as noted above, efforts to raise standards of living and modernize housing have been associated with rodent host switching in Madagascar. In rural areas, the storage of crops in houses, and agricultural activities such as deforestation and bushfires, promote the spread of rats and increased interactions with humans, leading to human plague cases. During the rice harvest, an increase in reproductive rate and migration of rats from households to sisal hedges was associated with low plague transmission in humans (Rahelinirina et al., 2010). Interpreting this into a management strategy is complicated, as there is not a clear directive about the configuration of houses, sisal hedges, and rice fields, but the implication that rats are in households prior to the rice harvest season may serve as an indicator for surveillance timing.

Table 1, from Andrianaivoarimanana et al. (2013), lists factors related to human plague from their review of the evidence in Madagascar to 2013. They establish a dichotomy of rural settings and high/low human plague, and urban settings, featuring the two key urban centers of plague in Madagascar, Antananarivo in the highlands and the port of Mahajanga.

Table 1: Factors related to human plague in Madagascar

Rural Settings	High Human Plague Season	Low Human Plague Season
Period of the Year	October to April	May to September
Weather	Warm and rainy	Dry and cold
Food Availability	Absence of crops in the fields	Rice harvest in the fields
Weather	Warm and rainy	Dry and cold
Rat Population (<i>R. rattus</i>)	Low abundance (low reproduction/outbreaks due to plague)	High rat reproduction (inside houses)
Flea Abundance	<i>X. cheopis</i> in the houses/ <i>S. fonquerniei</i> outside	No information available
Urban Settings	Antananarivo City	Mahajanga Coastal City
Average Altitude	1,200 meters	125 meters
Period of the Year	October to April	July to November
Weather	Warm and rainy	Dry and cool
Major Small Mammal Population	<i>R. norvegicus</i> (the sewer rat)	<i>Suncus murinus</i> (the Asian Shrew)
Flea Abundance	<i>X. cheopis</i>	<i>X. cheopis</i>

Source: Andrianaivoarimanana et al. 2013

LARGE-SCALE CLIMATE DRIVERS

A recent study (Kreppel et al., 2014) explored the roles that climate patterns that have worldwide or regional impacts on temperature and precipitation such as ENSO (El Niño Southern Oscillation) and the IOD (Indian Ocean Dipole)—whose western pole is located near Madagascar—may play in multiyear patterns of plague anomalies in Madagascar. The Japan Meteorological Agency’s (JMA) signal, indicating the components of ENSO leading to El Niño and La Niña patterns, was clearest and significant. The times when plague was less prevalent tended to occur during periods of decreasing JMA (strengthening La Niña, which translates, on average, into excess rainfall over the dry season and at the beginning of the rainy season but a deficit at the end of the rainy season), and increases in plague incidence during increasing JMA (strengthening El Niño); there were no similar associations with changes in IOD, precipitation, or temperature. However, longer-term patterns occurred with the larger climate patterns. From the 1960s to the mid-1970s, plague occurrence peaked 9 months prior to ENSO. This then switched in the 1980s to a 3–5-year occurrence, and then flipped again in the mid-1990s to a 1–2-year occurrence. In the 1980s, IOD and plague had a 3–5-year occurrence, and in 1995, a 1.5–4.5-year occurrence. In the 1990s–2000, IOD led plague by 9 months, and from 2003 to 2005, IOD lagged plague around 3 months with a 1–2-year occurrence. Occurrences appear for both temperature and precipitation with similar appearances of “flips” in the 1990s, indicating a broad change in changes and reoccurrences.

This study shows a strong association between ENSO and plague in Madagascar, with larger plague outbreaks associated with increasing rainfall from El Niño conditions. The study further shows that ENSO and IOD affect temperature cycles in Madagascar, and that these temperature cycles affect plague cycles. In the late 1990s, ENSO events became both stronger and more frequent and, combined with the IOD events, this created warmer and wetter

conditions for Madagascar. The year 1997 is an exemplar in this study, as it had the strongest El Niño positive IOD and one of the largest plague incidence anomalies on record. The authors suggest that the lags in this analysis, in which plague appears to lead climate anomalies, may indicate a lag that is an entire cycle behind (e.g., 1–2 years). Given that the ecology of the climate shift creates conditions to increase rodent and flea populations that may take at least a year or so to reach thresholds for spillover, this is plausible. As the authors point out, the warmer/wetter shifts, if they occur during a cold dry season, are likely to increase flea survival, shorten development time, and lead to favorable conditions for plague transmission.

ENVIRONMENTAL DRIVERS OF PLAGUE

In the extended literature search for drivers of plague that may be relevant to the Madagascar situation, several relevant studies of sub-Saharan Africa and Vietnam arose.

LARGE-SCALE PLAGUE MODELING

An ecological niche model (ENM) of plague in sub-Saharan Africa was constructed by Neerinckx et al. (2008) using a large suite of potential environmental and physical variables. In the models presented, as the authors note, a broad distribution is predicted, rather than the focal occurrences that typify human case reporting, and all environmental variables appear to contribute positively to predictions. Even at this large and perhaps overly generalized broad scale, the most important factors were elevation, potential evapotranspiration, mean diurnal temperature range, annual rainfall, and NDVI (which measures vegetation cover) in December. These clearly drive the cycle of transmission as described in Section 1 above and speak to the frequently mentioned elevation component for plague persistence, in addition to the role of temperature and moisture constraints. As observed by the authors, niche models provide an idea of suitability in multidimensional environmental and physical space, and particularly for a pathogen such as *Y. pestis*, suitability only manifests as disease occurrence if there are flea vectors, host vertebrates, human contacts, case reporting, and an initial introduction for establishment.

TANZANIA

A 2011 study in northern Tanzania (McCauley et al., 2015) sought to assess the impact of land use on plague activity in rodents by surveying rodents in conserved protected landscapes and in agricultural habitats. Land conversion to cultivation is one of the biggest ongoing land use changes in the world, and is prevalent in East Africa. The region sampled in the study is endemic for plague and had been recently active (based on rodent seroprevalence) at five of the six study sites in question.

The study found differences in abundances and plague seroprevalence in the rodents between the conserved and agricultural sites. The highly human-associated (commensal) *Mastomys natalensis* made up 75% of the seropositivity in rodents and had consistently higher abundance in agricultural sites than in conserved sites. A model of predicted plague seropositive rodents,

an estimate of relative risk, suggests that plague risk is almost twice as high in agricultural versus the conserved natural sites.

UGANDA

A study of the relationships between climate and plague cases was conducted for epidemiological data in the West Nile region of Uganda (Moore et al., 2012). The authors noted that the sparse availability of meteorological datasets where the majority of plague cases occur (East Africa and Madagascar) makes the examination of larger-scale ensemble products important. The authors constructed a set of models using Famine Early Warning Systems-Network (FEWS-NET), Tropical Rainfall Measuring Mission (TRMM), Climate Prediction Center morphing method (CMORPH), Global Precipitation Climatology Project (GPCP), and two reanalysis datasets European Centre for Medium-Range Weather Forecasts Product (ERA-Interim), and the National Center for Environmental Prediction (NCEP/DOE), which they compared with meteorological data from stations within a 500 km radius of the study site. They found that FEWS-NET rainfall data performed the best for the criteria in question. The authors pointed out that while there are many studies examining the associations between temperature and precipitation and plague occurrence, these are largely in temperate regions rather than tropical regions. The region in question, in northwestern Uganda, comprised considerable elevation and climatic gradients. The higher elevations in Okoro and Vurra counties experience lower temperatures and more rainfall than in the Nile Valley, but they have no publicly available meteorological data; hence the need to create meteorological data ensembles for the study.

The authors found that there was a negative association of plague case numbers with the number of days of rainfall >10 mm in the prior dry season, and a positive association with days between 0.2 and 10 mm of rain during the time between rainy seasons prior to the start of the plague season. The findings did not include a relationship with temperature; the temperature varies little, ranging from 21.8°C in August to 25.4°C in February, which the authors deemed “relatively minor,” and thus subsumed temperature into descriptions of rainy seasons instead.

The relationship between plague and lagged rainfall has two potentially mutual driving mechanisms. The first is a trophic cascade hypothesis, wherein, in arid and semiarid regions, sufficient dry season rainfall leads to plant growth and an increase in rodent populations. In the West Nile region of Uganda, *R. rattus* is the most commonly found rodent in and around human dwellings, and the endemic Nile rat, *Arvicanthus niloticus*, is the most abundant sylvatic rodent. Both species can breed year-round, given good conditions, and are prolific—as noted above, *R. rattus* can produce up to five litters of 6–12 young per year (mean 5.4 in Madagascar), while *A. niloticus* can produce 4–12 young every 23 days.

The second mechanism suggests a vector survival component, wherein the flea’s relationship with rainfall conditions is key. Higher rainfall may increase flea survival (Parmenter et al., 1999), meaning rodents may simply have higher flea burdens in following months, which is associated with increased human plague transmission.

In this region of Uganda, hut-level risk of plague has been positively associated with proximity to annual crops such as maize (MacMillan et al., 2011), and also with bare ground during the January fallow season (Eisen et al., 2010), indicating a large role for human–landscape interactions in the plague ecology of the region. Eisen et al. suggest that there may be a human behavioral element in the timing in the Ugandan system, wherein crops are harvested and then stored in houses, bringing the rodents and their fleas into close contact risk with humans. At a larger scale, changes in rainfall may lead to changes in planting, or simply altered timing of availability of crop resources, leading to changes in abundance and behavior of rodents. The linked human behavior plague risk of harvest and storage would simply shift with the altered timing.

It is thought that in the Ugandan West Nile system, there is a maintenance of *Y. pestis* in the sylvatic rodent host population (*A. niloticus*), which sometimes spills over to the *R. rattus* population. This leads to an epizootic in *R. rattus*, which lead to die-offs followed by increases in human plague cases. The fact that *R. rattus* epizootics result in die-offs is an indicator that these are not plague-resistant rats, that epizootics are the (infrequent) result of system changes leading to spillovers from the sylvatic reservoir, and—as Moore et al. (2012) also point out—that it is important to understand what leads to the contacts between the two rodent hosts, if contacts are driven by climate change or variability.

VIETNAM

Plague is present in Vietnam in the Central Highlands—a region commonly known as Tay Nguyen in the southwest. There are travel warnings for plague to this day (<https://www.iamat.org/country/vietnam/risk/plague>). Given the similar occurrence of plague largely concentrated in an agricultural highland region, it is pertinent to this review. There is remarkably little research about the environment and plague in Vietnam, beyond passing references to it being largely in agricultural areas. Pham et al. (2009) explored the ecology and environmental conditions that likely promoted plague cases from 1997 to 2002. The Central Highlands region is a plateau around 500 m above sea level, home to about 4 million people in 510 communes. The authors obtained data on the domestic fleas and rodents (per WHO surveillance protocols) and used temperature records, duration of sunshine, rainfall, and humidity as monthly averages from local meteorological stations. Using a Poisson regression model, they model incidence of plague as a function of rodent, flea, and climate variables. Plague peaked in the dry season (February–April had 63% of the cases), and plague occurrence was positively associated with increased rodent density and increased flea index (estimated burden of fleas per rodent). The risk of plague increased in the dry season when rainfall was less than 10 mm. The flea index increased with the lower dry season rainfall, suggesting a mechanistic link between the climate and flea burdens. The primary rodent host in the study is *Rattus exulans* (83%), with *Suncus murinus* (14%) the next most abundant, and low numbers of other *Rattus sp.* The primary flea species was *X. cheopis* (97%) followed by *P. irritans* (1.5%) and some cat flea species. The flea infection rate was quite low, varying between 1.7% and 2.7%, which suggests a low but persistent level of plague cycling in the rodent population. It is interesting to note that this is another study in which the Asian shrew *S. murinus* is implicated in the human plague ecology, in addition to the primary *Rattus sp* rodent host. This

speaks to the complications of managing the rodent host for plague elimination. Table 2 lists factors influencing the risk of plague.

Table 2: Factors associated with biophysical/climatic variables in plague studies

Factor	Study Location	Finding	Citation
Elevation	Uganda (West Nile)	Increased risk of household level plague cases >1300 m	Eisen et al., 2010
	Vietnam (Highlands)	Increased risk >500 m above sea level	Pham et al., 2009
Rainfall	Uganda (West Nile)	Negative association with the number of days of >10 mm rainfall in the prior dry season, and a positive association with days between 0.2–10 mm of rain during the time between rainy seasons prior to the start of the plague season.	Moore et al., 2012
	Uganda (West Nile)	Plague risk higher in wetter areas	Eisen et al., 2010
	Vietnam (Highlands)	Plague increased in dry season with rainfall <10 mm	Pham et al., 2009
Land Cover	Tanzania	Cultivated land has almost twice the plague sero-prevalence in rodents compared with conserved landscapes	McCauley et al., 2015
Temperature	Madagascar	<i>S. fonquerniei</i> development rate increases with temperatures below 30°C and decreases above 30°C	Andrianaivoarimanana et al., 2013; Kreppel et al., 2016
		Temperatures below 9.3°C decrease survival of larvae and pupae High temperatures and low humidity decrease survival of immature <i>S. fonquerniei</i>	

CONCLUSIONS

SUMMARY

While much is known about the biology of plague, its host rodents, and fleas in Madagascar, linking climate and environmental drivers to plague cases is complex. There are several connected but slightly different ecologies of plague. The highlands situation remains one of agricultural interactions with the landscape, and climate drivers of resources, rodents, and human interactions with rodents persist. The modernization of the urban setting in Antananarivo has improved plague risk reduction by removing the frequency of interactions, but may be leading to a rodent host switch, from the black rat *R. rattus* to the Norway rat, *R. norvegicus*. *R. norvegicus* is less susceptible to plague itself, thereby serving as a maintenance reservoir, and is not a useful sentinel of epizootics (no die-offs). This makes it a poor target for surveillance, as it may carry the disease but not transmit it. The port city of Marajanga presents another scenario, in which introduction of plague from the central highlands leads to establishment in local rodent populations, including the Asian shrew, sparking periodic outbreaks and raising concerns about potential export of plague from port cities.

The limited evidence linking large-scale climate change to the ecology of plague suggests that increasing El Niño events will make the dry season warmer and wetter, which will affect the highlands plague ecology by reducing suitability for the endemic flea vector (*S. fonquerniei*). Whether this will reduce plague risk or instead lead to an ecological switch to rodent dominance by *R. rattus* and *X. cheopis* cycles is worth monitoring. This climate-driven ecological niche is likely conflated with land conversion that creates cultivated habitat suitable for rodents and fleas. Teasing apart the roles of climate and human behavioral changes in habitat is complicated and will require more research.

IMPLICATIONS FOR SURVEILLANCE AND TREATMENT FROM THE CHANGING DYNAMICS

- **Rats are becoming more resistant to plague.** Dead rats are an indicator for plague; if rats are resistant, this alters the possibility for using rats as early warnings of an epizootic. *R. norvegicus*, which live in urban areas, are less susceptible to plague than other species, and there is increasing evidence of resistance in *R. rattus*, the most common vector.
- **Fleas are gaining resistance to insecticides.** The cosmopolitan flea commonly found in rats caught in houses (*Xenopsylla cheopis*), the human flea (*Pulex irritans*), and a flea endemic to Madagascar (*S. fonquerniei*) are resistant to DDT, dieldrin, and malathion, and to some organochlorides reported in the early 1980s (Coulanges et al., 1982; Coulanges & Randrianantoanina, 1984b, 1984a). This makes it more difficult to eradicate plague vectors and human exposure.
- **Strains of the plague are becoming resistant to antibiotics.** The first antibiotic-resistant *Y. pestis* strains were isolated from Madagascar, with one strain found resistant

to eight antibiotics (including those used specifically for plague prophylaxis and therapy). The evidence for antibiotic-resistant strains of *Y. pestis* from Madagascar came from a rat in Antananarivo.

- **While the black rat (*R. rattus*) is the most common vector, there are other rodents that could transmit the disease, posing challenges to early warning and surveillance.** Potential for more than just the black rat (*R. rattus*) to be a rodent reservoir, and for more than just the rat flea to be a vector, came under scrutiny in the late 1990s.
- **The appearance of plague in new areas in 2019 indicates the capacity for plague to establish new rodent–flea cycles in Madagascar and also warrants surveillance.** Surveillance efforts should target important geographic areas of the country, for example, looking at the oriental rat flea (*X. cheopis*) in the warm low-lying region foci defined herein, as well as the persistent foci in the highlands of the endemic flea (*S. fonquerniei*).
- **Warming under climate change may alter the suitability of Madagascar for plague in its endemic enzootic flea–rodent cycle.** The endemic flea (*S. fonquerniei*) is better adapted to the cool conditions of the highland regions, which supports the persistent enzootic foci (or hotspot) in the highlands, while the oriental rat flea (*X. cheopis*) is better adapted to the warm low-lying regions, common to other vector-borne diseases. The implication of these dynamics is that endemic flea transmissions may be reduced while the rat flea transmission could increase in elevation as temperatures warm.
- **Modifying human behaviors could greatly reduce communities' exposure to plague.** In rural households, not storing grain inside the house would reduce rat and flea contact. Sleeping on elevated surfaces and not on floor mats would reduce flea bites. Rural households should be aware of the agricultural link to plague and flea exposures and closely monitor young field workers for any initial symptoms. Education efforts could support this awareness.

ANNOTATED BIBLIOGRAPHY

Andrianaivoarimanana, V., Kreppel, K., Elissa, N., Duplantier, J.-M., Carniel, E., Rajerison, M., & Jambou, R. (2013). Understanding the persistence of plague foci in Madagascar. *PLOS Neglected Tropical Diseases*, 7(11). Plague, a zoonosis caused by *Yersinia pestis*, is still found in Africa, Asia, and the Americas. Madagascar reports almost one third of the cases worldwide. *Y. pestis* can be encountered in three very different types of foci: urban, rural, and sylvatic. Flea vector and wild rodent host population dynamics are tightly correlated with modulation of climatic conditions, an association that could be crucial for both the maintenance of foci and human plague epidemics. The black rat *Rattus rattus*, the main host of *Y. pestis* in Madagascar, is found to exhibit high resistance to plague in endemic areas, opposing the concept of high mortality rates among rats exposed to the infection. Also, endemic fleas could play an essential role in maintenance of the foci. This review discusses recent advances in the understanding of the role of these factors as well as human behavior in the persistence of plague in Madagascar.

Andrianaivoarimanana, V., Piola, P., Wagner, D. M., Rakotomanana, F., Maheriniaina, V., Andrianalimanana, S. et al. (2019). Trends of human plague, Madagascar, 1998-2016. *Emerging Infectious Diseases*, 25(2), 220–228.

Madagascar is more seriously affected by plague, a zoonosis caused by *Yersinia pestis*, than any other country. The Plague National Control Program was established in 1993 and includes human surveillance. During 1998-2016, a total of 13,234 suspected cases were recorded, mainly from the central highlands; 27% were confirmed cases, and 17% were presumptive cases. Patients with bubonic plague (median age 13 years) represented 93% of confirmed and presumptive cases, and patients with pneumonic plague (median age 29 years) represented 7%. Deaths were associated with delay of consultation, pneumonic form, contact with other cases, occurrence after 2009, and not reporting dead rats. A seasonal pattern was observed with recrudescence during September-March. Annual cases peaked in 2004 and decreased to the lowest incidence in 2016. This overall reduction occurred primarily for suspected cases and might be caused by improved adherence to case criteria during widespread implementation of the F1 rapid diagnostic test in 2002.

Andrianaivoarimanana, V., Rajerison, M., & Jambou, R. (2018). Exposure to *Yersinia pestis* increases resistance to plague in black rats and modulates transmission in Madagascar. *BMC Research Notes*, 11(1), 898. OBJECTIVES: In Madagascar, plague (*Yersinia pestis* infection) is endemic in the central highlands, maintained by the couple *Rattus rattus*/flea. The rat is assumed to die shortly after infection inducing migration of the fleas. However, we previously reported that black rats from endemic areas can survive the infection whereas those from non-endemic areas remained susceptible. We investigate the hypothesis that lineages of rats can acquire resistance to plague and that previous contacts with the bacteria will affect their survival, allowing maintenance of infected fleas. For this purpose, laboratory-born rats were obtained from wild black rats originating either from plague-endemic or plague-free zones, and were challenged with *Y. pestis*. Survival rate and antibody immune responses were analyzed.

RESULTS: Inoculation of low doses of *Y. pestis* greatly increase survival of rats to subsequent challenge with a lethal dose. During challenge, cytokine profiles support activation of specific immune response associated with the bacteria control. In addition, F1 rats from endemic areas exhibited higher survival rates than those from non-endemic ones, suggesting a selection of a resistant lineage. In Madagascar, these results support the role of black rat as long term reservoir of infected fleas supporting maintenance of plague transmission.

Andrianaivoarimanana, V., Telfer, S., Rajerison, M., Ranjalahy, M. A., Andriamiarimanana, F., Rahaingosoamamitiana, et al. (2012). Immune responses to plague infection in wild *Rattus rattus*, in Madagascar: A role in foci persistence? *PLOS One*, 7(6).

Background: Plague is endemic within the central highlands of Madagascar, where its main reservoir is the black rat, *Rattus rattus*. Typically, this species is considered susceptible to plague, rapidly dying after infection inducing the spread of infected fleas and, therefore, dissemination of the disease to humans. However, persistence of transmission foci in the same area from year to year supposes mechanisms of maintenance among which rat immune responses could play a major role. Immunity against plague and subsequent rat survival could play an important role in the stabilization of the foci. In this study, we aimed to investigate serological responses to plague in wild black rats from endemic areas of Madagascar. In addition, we evaluate the use of a recently developed rapid serological diagnostic test to investigate the immune response of potential reservoir hosts in plague foci. **Methodology/Principal Findings:** We experimentally infected wild rats with *Yersinia pestis* to investigate short- and long-term antibody responses. Anti-F1 IgM and IgG were detected to evaluate this antibody response. High levels of anti-F1 IgM and IgG were found in rats one and three weeks respectively after challenge, with responses greatly differing between villages. Plateau in anti-F1 IgM and IgG responses were reached for as few as 500 and 1500 colony forming units (cfu) inoculated respectively. More than 10% of rats were able to maintain anti-F1 responses for more than one year. This anti-F1 response was conveniently followed using dipsticks. **Conclusion/Significance:** Inoculation of very few bacteria is sufficient to induce high immune response in wild rats, allowing their survival after infection. A great heterogeneity of rat immune responses was found within and between villages which could heavily impact on plague epidemiology. In addition, results indicate that, in the field, anti-F1 dipsticks are efficient to investigate plague outbreaks several months after transmission.

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The main public health issue in Madagascar at the beginning of the 21st century still involves transmissible infectious diseases including re-emerging diseases such as bubonic plague and emerging diseases such as HIV/AIDS, dengue fever and Chikungunya virus infection. Health and hygiene, especially access to clean water, is still poor especially in rural areas. No improvement in the public health situation with regard to malaria,

schistosomiasis or cysticercosis as well as non-infectious diseases such as protein-energy malnutrition is expected within the next decade.

Barmania, S. (2015). Madagascar's health challenges. *Lancet (London, England)*, 386(9995), 729–730.

Bertherat, E. G. (2015). Plague in Madagascar: overview of the 2014-2015 epidemic season. *Releve Epidemiologique Hebdomadaire*, 90(20), 250–252.

Blanchy, S. (1995). [A contribution to the history of understanding the epidemiology of plague in Madagascar]. *Histoire Des Sciences Medicales*, 29(4), 355–364. Plague appeared in Madagascar in 1898, the pandemic coinciding with the French conquest. Until 1921, harbor epidemics occurred in Tamatave, Majunga, Diégo-Suarez, Fort-Dauphin, Vatomandry. In 1921, probably favored by the building of roads and railways, plague takes root on the Highlands where it becomes endemic above 800 meters. The vaccine achievement by Girard and Robic with the EV strain, and its mass application from 1935 by Estrade, Milliau, Brault, Seyberlich and Jan Keguistel, allowed control of the disease. The discovery of D.D.T. and sulfamids led to the almost complete disappearance of the urban epidemics, allowing plague to subsist as only rural sporadic or familial cases with a low mortality. Mass vaccination stopped in 1959. Since 1988 the disease's incidence has been increasing, probably in relation to the quasi disappearance of insect control and antibiotics. Nevertheless, urban epidemics are still rare and limited, corresponding to the substitution, in the city, of *Rattus rattus*, the main reservoir and victim of the disease, by *Rattus norvegicus*, which is less sensitive to the infection.

Boisier, P., Rahalison, L., Rasolomaharo, M., Ratsitorahina, M., Mahafaly, M., Razafimahefa, M., et al. (2002). Epidemiologic features of four successive annual outbreaks of bubonic plague in Mahajanga, Madagascar. *Emerging Infectious Diseases*, 8(3), 311–316.

From 1995 to 1998, outbreaks of bubonic plague occurred annually in the coastal city of Mahajanga, Madagascar. A total of 1,702 clinically suspected cases of bubonic plague were reported, including 515 laboratory confirmed by *Yersinia pestis* isolation (297), enzyme-linked immunosorbent assay, or both. Incidence was higher in males and young persons. Most buboes were inguinal, but children had a higher frequency of cervical or axillary buboes. Among laboratory-confirmed hospitalized patients, the case-fatality rate was 7.9%, although all *Y. pestis* isolates were sensitive to streptomycin, the recommended antibiotic. In this tropical city, plague outbreaks occur during the dry and cool season. Most cases are concentrated in the same crowded and unsanitary districts, a result of close contact among humans, rats, and shrews. Plague remains an important public health problem in Madagascar, and the potential is substantial for spread to other coastal cities and abroad.

Boisier, P., Rasolomaharo, M., Ranaivoson, G., Rasoamanana, B., Rakoto, L., Andrianirina, Z., et al. (1997). Urban epidemic of bubonic plague in Majunga, Madagascar: Epidemiological aspects. *Tropical Medicine & International Health*, 2(5), 422–427.

After an absence of 62 years, an epidemic of plague occurred in the harbour city of Majunga (Madagascar) from July 1995 to March 1996, following sporadic cases in March and May 1995. By 15 March 1996, 617 clinically suspected cases of bubonic plague had been notified. Laboratory testing was carried out for 394 individuals: 60 (15.2%) were confirmed to have bubonic plague and 48 (12.2%) were considered as presumptive cases. The incidence was significantly higher in males in all age groups and in both sexes in the 5-19 age group. Twenty-four deaths were related to plague, but early treatment with streptomycin has confirmed its effectiveness insofar as the case-fatality ratio was only 8.7% among confirmed and presumptive cases admitted to hospital. The difficulty of clinically diagnosing bubonic plague was affirmed. The disease met favourable conditions through the poverty and low level of hygiene prevalent in most parts of Majunga.

Bonds, M. H., Ouenzar, M. A., Garchitorena, A., Cordier, L. F., McCarty, M. G., Rich, M. L., ... Farmer, P. E. (2018). Madagascar can build stronger health systems to fight plague and prevent the next epidemic. *PLoS Neglected Tropical Diseases*, 12(1), e0006131.

In August 2017, a 31-year-old man visiting Ankazobe District in the Central Highlands of Madagascar was bitten by a flea that presumably jumped from a cohabitating rat [1]. Within a week, he began to experience malaria-like symptoms as plague-causing bacteria invaded his lymph nodes and then moved to his lungs. En route to the eastern coast, he took a public taxi brousse through the nation's capital, Antananarivo, and died. The outbreak was officially detected a week later, preceding the infection of more than 2,200 confirmed, probable, and suspected cases as of November 2017, making it one of the world's worst plague epidemics in the past half century [2,3]. Though curable with antibiotics if detected early, more than 200 people have died...

Boyer, S., Miarinjara, A., & Elissa, N. (2014). *Xenopsylla cheopis* (Siphonaptera: Pulicidae) susceptibility to Deltamethrin in Madagascar. *PLOS One*, 9(11).

The incidence of bubonic plague in Madagascar is high. This study reports the susceptibility of 32 different populations of a vector, the flea *Xenopsylla cheopis* (Siphonaptera: Pulicidae), to the insecticide Deltamethrin. Despite the use of Deltamethrin against fleas, plague epidemics have re-emerged in Madagascar. The majority of the study sites were located in the Malagasy highlands where most plague cases have occurred over the last 10 years. *X. cheopis* fleas were tested for susceptibility to Deltamethrin (0.05%): only two populations were susceptible to Deltamethrin, four populations were tolerant and 26 populations were resistant. KD50 (50% Knock-Down) and KD90 (90% Knock-Down) times were determined, and differed substantially from 9.4 to 592.4 minutes for KD50 and 10.4 min to 854.3 minutes for KD90. Susceptibility was correlated with latitude, but not with longitude, history of insecticide use nor date of sampling. Combined with the number of bubonic plague cases, our results suggest that an immediate switch to an insecticide other than Deltamethrin is required for plague vector control in Madagascar.

Brouat, C., Rahelinirina, S., Loiseau, A., Rahalison, L., Rajerison, M., Laffly, D., et al. (2013). Plague circulation and population genetics of the reservoir *Rattus rattus*: the influence of

topographic relief on the distribution of the disease within the Madagascan focus. *PLOS Neglected Tropical Diseases*, 7(6).

Background: Landscape may affect the distribution of infectious diseases by influencing the population density and dispersal of hosts and vectors. Plague (*Yersinia pestis* infection) is a highly virulent, re-emerging disease, the ecology of which has been scarcely studied in Africa. Human seroprevalence data for the major plague focus of Madagascar suggest that plague spreads heterogeneously across the landscape as a function of the relief. Plague is primarily a disease of rodents. We therefore investigated the relationship between disease distribution and the population genetic structure of the black rat, *Rattus rattus*, the main reservoir of plague in Madagascar. Methodology/Principal Findings: We conducted a comparative study of plague seroprevalence and genetic structure (15 microsatellite markers) in rat populations from four geographic areas differing in topology, each covering about 150-200 km² within the Madagascan plague focus. The seroprevalence levels in the rat populations mimicked those previously reported for humans. As expected, rat populations clearly displayed a more marked genetic structure with increasing relief. However, the relationship between seroprevalence data and genetic structure differs between areas, suggesting that plague distribution is not related everywhere to the effective dispersal of rats. Conclusions/Significance: Genetic diversity estimates suggested that plague epizootics had only a weak impact on rat population sizes. In the highlands of Madagascar, plague dissemination cannot be accounted for solely by the effective dispersal of the reservoir. Human social activities may also be involved in spreading the disease in rat and human populations.

Brygoo ER (1966) Epidémiologie de la peste à Madagascar. *Archives de l'Institut Pasteur de Madagascar* 35, 9–147.

Bundschuh, M., & Groneberg, D. A. (2015). Outbreak of plague in Madagascar. *Zentralblatt für Arbeitsmedizin Arbeitsschutz und Ergonomie*, 65(1), 53–54. After 2011 and 2013 there was again an outbreak of *Yersinia pestis* in Madagascar in 2014. Until November 2014, the WHO reported 40 deaths and at least 119 infections since August 2014. Even in the capital, some cases have been reported. Due to the high population density, the increasing resistance of the fleas and the insufficient health system, there is a risk of further rapid spreading. This review summarizes information from the WHO and the RKI about the pathogen.

Burki, T. (2017). Plague in Madagascar. *Lancet Infectious Diseases*, 17(12), 1241.

Cabanel, N., Bouchier, C., Rajerison, M., & Carniel, E. (2018). Plasmid-mediated doxycycline resistance in a *Yersinia pestis* strain isolated from a rat. *International Journal of Antimicrobial Agents*, 51(2), 249–254.

The emergence of antibiotic-resistant *Yersinia pestis* strains represents a public health concern. Two antibiotic-resistant *Y. pestis* strains isolated from Madagascar have been previously identified and characterised. Both strains carried conjugative plasmids that conferred resistance to streptomycin or to multiple antibacterial drugs, respectively. Here we

characterised a novel *Y. pestis* strain (IP2180H) that exhibited resistance to doxycycline. This strain was isolated from a rat in Antananarivo (Madagascar) in 1998. Resistance was carried by a conjugative plasmid (pIP2180H) homologous to pB71 from *Salmonella enterica*. The plasmid of the previously identified streptomycin-resistant *Y. pestis* strain was also sequenced and it was found that the three antibiotic resistance *Y. pestis* plasmids sequenced until now are genetically unrelated and are also unrelated to multidrug resistance plasmids from the phylogenetically close bacterial species *Yersinia pseudotuberculosis*. The fact that the three antibiotic-resistant Malagasy *Y. pestis* strains were isolated from different hosts, at different times, from distant locations, and carried unrelated plasmids indicates independent horizontal acquisition of genetic material and further demonstrates the capacity of *Y. pestis* to acquire antibiotic resistance plasmids under natural conditions. Since these resistance plasmids can frequently carry or easily trap antibiotic resistance cassettes, the emergence of new multidrug-resistant *Y. pestis* strains may be expected and would represent a major health threat.

Chanteau, S., Rahalison, L., Duplantier, J. M., Rasoamanana, B., Ratsitorahina, M., Dromigny, J. A., et al. (1998). [Update on plague in Madagascar]. *Medecine Tropicale: Revue Du Corps De Sante Colonial*, 58(2 Suppl), 25–31.

After a thirty-year period of successful control, bubonic plague showed the first signs of return in Madagascar where a fatal outbreak occurred in Antananarivo in 1978. A second outbreak was observed in Mahajanga in 1991 after more than a half century. In 1997, 459 confirmed or presumptive cases were reported, as compared to 150 to 250 cases during the last years. However, the actual extent of this recrudescence must be placed in the perspective of a more efficient control program that has led to better reporting of suspected cases and availability of more accurate diagnostic techniques. Recent research has led to the development of highly effective immunological diagnostic tools (detection of antibodies and F1 antigen), allowing not only better surveillance of the disease in man and animals but also renewed study of the epidemiological cycle in the current environment. In this regard the capacity of several endemic fleas as vectors and the role of the rat *Rattus norvegicus* and the musk shrew *Suncus murinus* are currently under investigation. Genetic study of strains collected from 1936 to 1996 has demonstrated the appearance of 3 new ribotypes of *Yersinia pestis* since 1982 in the zones of strongest plague activity in Madagascar. A strain showing multiresistance to standard therapeutic antibiotic agents was isolated in 1995. Bubonic plague is a priority health problem in Madagascar but remains a major concern for the rest of the world.

Chanteau, S., Rahalison, L., Ralafiarisoa, L., Foulon, J., Ratsitorahina, M., Ratsifasoamanana, L., ... Nato, A. (2003). Development and testing of a rapid diagnostic test for bubonic and pneumonic plague. *LANCET*, 361(9353), 211–216. [https://doi.org/10.1016/S0140-6736\(03\)12270-2](https://doi.org/10.1016/S0140-6736(03)12270-2)

Background: Plague is often fatal without prompt and appropriate treatment. It affects mainly poor and remote populations. Late diagnosis is one of the major causes of human death and spread of the disease, since it limits the effectiveness of control measures. We aimed to

develop and assess a rapid diagnostic test (RDT) for plague. **Methods** We developed a test that used monoclonal antibodies to the F1 antigen of *Yersinia pestis*. Sensitivity and specificity were assessed with a range of bacterial cultures and clinical samples, and compared with findings from available ELISA and bacteriological tests for plague. Samples from patients thought to have plague were tested with the RDT in the laboratory and by health workers in 26 pilot sites in Madagascar. **Findings:** The RDT detected concentrations of F1 antigen as low as 0.5 ng/mL in up to 15 min, and had a shelf life of 21 days at 60degreesC. Its sensitivity and specificity were both 100%. RDT detected 41.6% and 31% more positive clinical specimens than did bacteriological methods and ELISA, respectively. The agreement rate between tests done at remote centres and in the laboratory was 89.8%. With the combination of bacteriological methods and F1 ELISA as reference standard, the positive and negative predictive values of the ROT were 90.6% and 86.7%, respectively. **Interpretation** Our RDT is a specific, sensitive, and reliable test that can easily be done by health workers at the patient's bedside, for the rapid diagnosis of pneumonic and bubonic plague. This test will be of key importance for the control of plague in endemic countries.

Coulanges, P., Clerc, Y., & Randrianantoanina, E. (1982). [X. cheopis and S. fonquerniei, plague-carrying Malagasian fleas--demonstration of their resistance to DDT, dieldrin and malathion]. *Archives De l'Institut Pasteur De Madagascar*, 49(1), 171–191.

Coulanges, P., & Randrianantoanina, E. (1984a). [Exceptional resistance of Malagasy plague-transmitting fleas to insecticides]. *Bulletin de la Societe de Pathologie Exotique et de Ses Filiales*, 77(5), 705–711.

Two plague transmitting malagasy fleas *S. fonquerniei* and *X. cheopis*, caught in the cities of Tananarive, Antsirabe-Betafo and Ampefy were tested in conformity with WHO standards. These two fleas were resistant to DDT, dieldrin and malathion. Moreover, *X. cheopis* from the cities of Tananarive and Antsirabe-Betafo were resistant to fenitrothion and propoxur. This seems to be the first report of simultaneous resistance to organochlorinated, organophosphorylated and carbamylated products. The authors discuss the causes of this exceptional phenomenon and make some suggestions in order to obtain better knowledge and understanding of this phenomenon.

Coulanges, P., & Randrianantoanina, E. (1984b). [Resistance of Madagascan plague fleas to organochlorine, organophosphorus insecticides and carbamates]. *Archives de l'Institut Pasteur de Madagascar*, 51(1), 253–260.

Davis, D. H. (1953). Plague in Africa from 1935 to 1949; a survey of wild rodents in African territories. *Bulletin of the World Health Organization*, 9(5), 665–700.

The history of plague in Africa during the period 1935-49 is reviewed. Much of the information derives from a questionnaire sent to all African territories in 1950. The annual incidence of plague in Africa declined, particularly from 1946 onwards. In 1949, under 400 cases were reported, as compared with over 6,000 in 1935. By the end of 1949, plague was still active in the Belgian Congo, Kenya and Tanganyika, Madagascar, and southern Africa.

No cases were reported from Egypt, Tunisia, Algeria, Morocco, Senegal, or Uganda during 1949. A comparison of the seasonal incidence of plague with prevailing atmospheric conditions (temperature and rainfall) in African territories shows that human plague is more frequent in warm moist weather—60 degrees–80 degrees F (15 degrees–27 degrees C)—than in hot dry, or cold weather—over 80 degrees F (27 degrees C) or under 60 degrees F (15 degrees C). The highlands of equatorial Africa and of Madagascar appear to provide the optimum environment for the persistence of plague on the domestic (murine) plane and the high-veld and Kalahari of southern Africa on the sylvatic plane. The rat (*Rattus rattus*) and the multimammate mouse (*R. (Mastomys) natalensis*) and their fleas *Xenopsylla brasiliensis* and *X. cheopis* appear to be mainly responsible for the persistence of the reservoir in the East African highlands; *R. rattus* and *X. cheopis* play this role in Madagascar. The gerbils (Tatera and Desmodillus) and their burrow fleas *X. philoxera* and *X. piriei* are the main reservoirs of plague in southern Africa. Within these areas, *Pasteurella pestis* finds an environment suitable for its continued survival; the conditions seem to be comparable to those defined as obtaining in endemic centres in India. Elsewhere in Africa such endemic centres do not appear to exist.

WHO, Africa Regional Office (2008). 15ème Réunion annuelle du Groupe de travail sur la vaccination (TFI) en Afrique et 14ème Réunion annuelle du Comité de coordination interagences pour la Région africaine (ARICC) Antananarivo, Madagascar 11-14 décembre 2007. Final Report. Brazzaville.

D'Ortenzio, E., Lemaitre, N., Brouat, C., Loubet, P., Sebbane, F., Rajerison, M., et al. (2018). Plague: Bridging gaps towards better disease control. *Medecine et Maladies Infectieuses*, 48(5), 307–317.

After centuries of epidemics and more than a hundred years since the identification of the causative bacterium, very little is known about the plague dynamics in animal reservoirs, vectors and the changing vulnerabilities for humans. The recent plague epidemic in Madagascar in 2017 highlights these gaps existing within the knowledge of the disease dynamics, the factors influencing it, the performance of diagnostic tests and the best recommended treatment. As the eradication of plague will not be possible due to the widespread existence of the bacterium in wildlife, a One Health approach, drawing on animal, human and environmental health disciplines is needed to better control this poverty-related disease. This article focused on the various aspects of the disease for which more tools and better understanding are required to better control the disease in endemic countries.

Drancourt, M, Houhamdi, L., & Raoult, D. (2006). *Yersinia pestis* as a telluric, human ectoparasite-borne organism. *Lancet Infectious Diseases*, 6(4), 234–241.

The classic epidemiological model of plague is an infection of rodents that is transmitted to human beings by rodent ectoparasites. This model fits with observations of sporadic and limited outbreaks, but hardly explains the persistence of plague foci for millennia or the epidemiological features drawn from the descriptions of historical pandemics. A

comprehensive review of the published data, including scientific papers published in France between 1920 and 1940, allows the completion of the epidemiological chain by introducing soil as a reservoir, burrowing rodents as a first link, and human ectoparasites as the main driving force for pandemics. Modern studies are needed to confirm the validity of this controversial model and to assess the relative contribution of each link in the various epidemiological presentations of plague. If confirmed, these data should be taken into account to update public-health policies and bioterrorism risk management, particularly among ectoparasite-infested people.

Drancourt, M., & Raoult, D. (2018). Investigation of pneumonic plague, Madagascar. *Emerging Infectious Diseases*, 24(1), 183.

Duplantier, J., Catalan, J., Orth, A., Grolleau, B., & Britton-Davidian, J. (2003). Systematics of the black rat in Madagascar: consequences for the transmission and distribution of plague. *Biological Journal of the Linnean Society*, 78(3), 335–341. The plague has been present for a century in Madagascar; the only known reservoir is the black rat, which is also the main victim of this disease. Whereas the two plague foci are restricted to an altitude above 800 m, the black rat is distributed over the whole island, the only morphological variation being a within-site variability in belly colour. To resolve these apparent contradictions, an analysis of the different belly colour morphs and of populations living in different habitats and altitudes was undertaken. An allozymic study demonstrated that sympatric white- and grey-bellied rats (N = 26) living within the plague foci all belonged to the same species: *Rattus rattus*. This specific assignment was confirmed by a chromosomal analysis which showed that all 90 individuals studied presented the same diploid number, $2n = 38$, whatever the habitat and altitude. This study indicates that all specimens investigated in Madagascar could be referred to the same black rat species. Survival of rat populations, despite a century of coexistence with the plague, is most likely related to their high reproductive and recolonization potential, as well as selection of plague resistant genotypes. As the altitudinal limit of the plague foci does not seem to be related to characteristics of the rodent reservoir, investigations concerning the vectors are now essential.

Duplantier, J., Duchemin, J., Chanteau, S., & Carniel, E. (2005). From the recent lessons of the Malagasy foci towards a global understanding of the factors involved in plague reemergence. *Veterinary Research*, 36(3), 437–453.

Re-emergence of human cases of plague after decades of silence does not necessarily mean that plague foci are re-emerging. Most often, *Yersinia pestis* bacteria have been maintained and circulating at low levels in the rodent populations. It seems therefore more appropriate to speak in terms of expansion or regression phases for sylvatic rodent plague foci and to reserve the term re-emergence for human cases. From the analysis of well-documented human plague cases in Madagascar, we underline the causes of re-emergence that can be generalized to most world foci, and can help define environments at risk where the threat of new emergence lurks. In all recent plague outbreaks, usually more than one risk factor was at the origin of the re-emergence. The reduction or discontinuance of surveillance and control, as well as poverty and insalubrity, are the main factors in the re-

emergence of human cases, allowing increased contacts with infected rodents and fleas. Environment changes (i.e., climatic changes, deforestation, urbanization) induce changes in flea and rodent populations by (i) extension of rodent habitats (for example by replacing forests by steppes or farmlands); (ii) modifications in population dynamics (possible outbreaks due to an increase of available food resources); but also, (iii) emergence of new vectors, reservoirs and new *Y. pestis* genotypes. Numerous and spontaneous genomic rearrangements occur at high frequencies in *Y. pestis*, which may confer selective advantages, enhancing the ability of *Y. pestis* to survive, to be transmitted to new hosts, and to colonize new environments. Therefore, any environmental change should be taken as a warning signal and active surveillance programs should be initiated.

Duplantier, J., Duchemin, J., Ratsitorahina, M., Rahalison, L., & Chanteau, S. (2001). Emergence of plague in the Ikongo district of Madagascar, 1998. 2. Reservoir and fleas involved. *Bulletin de la Societe de Pathologie Exotique*, 94(2), 119–122.

Our survey of mammals and fleas arose as a result of an outbreak of bubonic plague at an usually low altitude in the Ikongo district (Madagascar), while a previous study had found anti-F1 antibodies in an endemic hedgehog. Animals were sampled with live traps in two hamlets (Antanambao-Vohidrotra, 540 m alt., and Ambalagoavy, 265 m alt.) and with pitfall traps in a neighbouring forest (750 m alt.). Rat fleas were collected by brushing the fur and free-living fleas by use of light traps. The introduced shrew *Suncus murinus* was found only in the village of Ambalagoavy, while the black rat (*Rattus rattus*) was found in all three sites, and the only seropositive rat was caught at Antanambao-Vohidrotra. In contrast, among the Tenrecidae (endemic shrews and hedgehogs) found in the forest near the first village, four animals were found seropositive for anti-F1 antibodies. One of them was carrying the endemic flea *Paractenopsyllus pauliani*, not yet reported as a vector of plague. The endemic vector of plague, *Synopsyllus fonquerniei*, was found only in the first village of Antanambao-Vohidrotra, and the cosmopolite flea *Xenopsylla cheopis* only in Ambalagoavy. Although no *Yersinia pestis* could be isolated and no F1-antigen could be detected in these animals, we found evidence of the recent transmission of plague in Antanambao-Vohidrotra and the nearby forest but not in Ambalagoavy. These data corroborate with the sylvatic plague cycle hypothesis in Madagascar and its involvement in the outcome of the bubonic plague outbreak in this district.

Duplantier, J., Laventure, S., Rasoamanana, B., & Chanteau, S. (1998). Rodents and plagues in Madagascar - History, current data and studies in progress. *Bulletin de la Societe de Pathologie Exotique*, 91(1), 76.

Eisen, R. J., Griffith, K. S., Borchert, J. N., MacMillan, K., Apangu, T., Owor, N., et al. (2010). Assessing human risk of exposure to plague bacteria in northwestern Uganda based on remotely sensed predictors. *American Journal of Tropical Medicine and Hygiene*, 82(5), 904–911.

Plague, a life-threatening flea-borne zoonosis caused by *Yersinia pestis*, has most commonly been reported from eastern Africa and Madagascar in recent decades. In these

regions and elsewhere, prevention and control efforts are typically targeted at fine spatial scales, yet risk maps for the disease are often presented at coarse spatial resolutions that are of limited value in allocating scarce prevention and control resources. In our study, we sought to identify sub-village level remotely sensed correlates of elevated risk of human exposure to plague bacteria and to project the model across the plague-endemic West Nile region of Uganda and into neighboring regions of the Democratic Republic of Congo. Our model yielded an overall accuracy of 81%, with sensitivities and specificities of 89% and 71%, respectively. Risk was higher above 1,300 meters than below, and the remotely sensed covariates that were included in the model implied that localities that are wetter, with less vegetative growth and more bare soil during the dry month of January (when agricultural plots are typically fallow) pose an increased risk of plague case occurrence. Our results suggest that environmental and landscape features play a large part in classifying an area as ecologically conducive to plague activity. However, it is clear that future studies aimed at identifying behavioral and fine-scale ecological risk factors in the West Nile region are required to fully assess the risk of human exposure to *Y. pestis*.

Gage, K. L., & Kosoy, M. Y. (2005). Natural History of Plague: Perspectives from More than a Century of Research. *Annual Review of Entomology*, 50(1), 505–528.

Abstract For more than a century, scientists have investigated the natural history of plague, a highly fatal disease caused by infection with the gram-negative bacterium *Yersinia pestis*. Among their most important discoveries were the zoonotic nature of the disease and that plague exists in natural cycles involving transmission between rodent hosts and flea vectors. Other significant findings include those on the evolution of *Y. pestis*; geographic variation among plague strains; the dynamics and maintenance of transmission cycles; mechanisms by which fleas transmit *Y. pestis*; resistance and susceptibility among plague hosts; the structure and typology of natural foci; and how landscape features influence the focality, maintenance, and spread of the disease. The knowledge gained from these studies is essential for the development of effective prevention and control strategies.

Galimand, M., Carniel, E., & Courvalin, P. (2006). Resistance of *Yersinia pestis* to antimicrobial agents. *Antimicrobial Agents and Chemotherapy*, 50(10), 3233-3236.

Gascuel, F., Choisy, M., Duplantier, J.-M., Debarre, F., & Brouat, C. (2013). Host resistance, population structure and the long-term persistence of bubonic plague: Contributions of a modelling approach in the Malagasy focus. *PLOS Computational Biology*, 9(5). Although bubonic plague is an endemic zoonosis in many countries around the world, the factors responsible for the persistence of this highly virulent disease remain poorly known. Classically, the endemic persistence of plague is suspected to be due to the coexistence of plague-resistant and plague-susceptible rodents in natural foci, and/or to a metapopulation structure of reservoirs. Here, we test separately the effect of each of these factors on the long-term persistence of plague. We analyse the dynamics and equilibria of a model of plague propagation, consistent with plague ecology in Madagascar, a major focus where this disease is endemic since the 1920s in the central highlands. By combining deterministic and stochastic analyses of this model, and including sensitivity analyses, we show that (i) endemicity is

favoured by intermediate host population sizes, (ii) in large host populations, the presence of resistant rats is sufficient to explain long-term persistence of plague, and (iii) the metapopulation structure of susceptible host populations alone can also account for plague endemicity, thanks to both subdivision and the subsequent reduction in the size of subpopulations, and extinction-recolonization dynamics of the disease. In the light of these results, we suggest scenarios to explain the localized presence of plague in Madagascar.

Gilabert, A., Loiseau, A., Duplantier, J.-M., Rahelinirina, S., Rahalison, L., Chanteau, S., & Brouat, C. (2007). Genetic structure of black rat populations in a rural plague focus in Madagascar. *Canadian Journal of Zoology-Revue Canadienne de Zoologie*, 85(9), 965–972.

The genetic structure of reservoir populations is a key characteristic in understanding the persistence of infectious diseases in natural systems. In the highlands of Madagascar, where plague has persisted since 1920, the black rat, *Rattus rattus* (L., 1758), is the sole species acting as a reservoir of the disease. Ecological surveys have shown a clear correlation between the locations of the plague-persistence area in Madagascar (above 800 m elevation) and the distribution area of one endemic plague vector, the flea *Synopsyllus fonquerniei*, which is found exclusively on rats living outdoors. This clear habitat segregation has led to the suggestion that *R. rattus* populations in the central highlands are divided into indoor- and outdoor-dwelling populations. Using eight microsatellite markers, we analysed the genetic structure of *R. rattus* populations living within a human plague focus in relation to habitat and geographic distance. We found that habitat by itself was not a structuring factor, unlike geographic distance. Nevertheless, the significant genotypic differentiation of *R. rattus* populations that was found at a fine spatial scale might relate to differences in population dynamics between rats in indoor and outdoor habitats.

Giorgi, E., Kreppel, K., Diggle, P. J., Caminade, C., Ratsitorahina, M., Rajerison, M., & Baylis, M. (2016). Modeling of spatio-temporal variation in plague incidence in Madagascar from 1980 to 2007. *Spatial and Spatio-Temporal Epidemiology*, 19, 125–135.

Plague is an infectious disease caused by the bacterium *Yersinia pestis*, which, during the fourteenth century, caused the deaths of an estimated 75-200 million people in Europe. Plague epidemics still occur in Africa, Asia and South America. Madagascar is today one of the most endemic countries, reporting nearly one-third of the human cases worldwide from 2004 to 2009. The persistence of plague in Madagascar is associated with environmental and climatic conditions. In this paper we present a case study of the spatio-temporal analysis of plague incidence in Madagascar from 1980 to 2007. We study the relationship of plague with temperature and precipitation anomalies, and with elevation. A joint spatio-temporal analysis of the data proves to be computationally intractable. We therefore develop a spatio-temporal log-Gaussian Cox process model, but then carry out marginal temporal and spatial analyses. We also introduce a spatially discrete approximation for Gaussian processes, whose parameters retain a spatially continuous interpretation. We find evidence of a cumulative effect, over time, of temperature anomalies on plague incidence, and of a very high relative risk of plague occurrence for locations above 800 m in elevation. Our approach provides a useful modeling framework to assess the relationship between

exposures and plague risk, irrespective of the spatial resolution at which the latter has been recorded.

Goodman, S. M., Andrianiaina, H. R. R., Soarimalala, V., & Beaucournu, J.-C. (2015). The fleas of endemic and introduced small mammals in central highland forests of Madagascar: Faunistics, species diversity, and absence of host specificity. *Journal of Medical Entomology*, 52(5), 1135–1143.

Data are presented on the flea species of the genera *Paractenopsyllus* (Ceratophyllidae, Leptopsyllinae) and *Synopsyllus* (Pulicidae, Xenopsyllinae) obtained from small mammals during two 2014 seasonal surveys at a montane humid forest site (Ambohitantely) in the Central Highlands of Madagascar. The mammal groups included the endemic family Tenrecidae (tenrecs) and subfamily Nesomyinae (rodents) and two introduced families Muridae (rodents) and Soricidae (shrews); no fleas were recovered from the latter family. The surveys were conducted at the end of the wet and dry seasons with 288 individual small mammals captured, including 12 endemic and four introduced species. These animals yielded 344 fleas, representing nine species endemic to Madagascar; no introduced species was collected. Some seasonal variation was found in the number of trapped small mammals, but no marked difference was found in species richness. For flea species represented by sufficient samples, no parasite-host specificity was found, and there is evidence for considerable lateral exchange in the local flea fauna between species of tenrecs and the two rodent families (endemic and introduced). The implications of these results are discussed with regards to small mammal species richness and community structure, as well as a possible mechanism for the maintenance of sylvatic cycles of bubonic plague in the montane forests of Madagascar.

Guiyoule, A., Rasoamanana, B., Buchrieser, C., Michel, P., Chanteau, S., & Carniel, E. (1997). Recent emergence of new variants of *Yersinia pestis* in Madagascar. *Journal of Clinical Microbiology*, 35(11), 2826-2833.

Harimalala, M., Telfer, S., Delatte, H., Watts, P. C., Miarinjara, A., Ramihangihajason, T. R., et al. (2017). Genetic structure and gene flow of the flea *Xenopsylla cheopis* in Madagascar and Mayotte. *Parasites & Vectors*, 10.

Background: The flea *Xenopsylla cheopis* (Siphonaptera: Pulicidae) is a vector of plague. Despite this insect's medical importance, especially in Madagascar where plague is endemic, little is known about the organization of its natural populations. We undertook population genetic analyses (i) to determine the spatial genetic structure of *X. cheopis* in Madagascar and (ii) to determine the potential risk of plague introduction in the neighboring island of Mayotte. Results: We genotyped 205 fleas from 12 sites using nine microsatellite markers. Madagascan populations of *X. cheopis* differed, with the mean number of alleles per locus per population ranging from 1.78 to 4.44 and with moderate to high levels of genetic differentiation between populations. Three distinct genetic clusters were identified, with different geographical distributions but with some apparent gene flow between both islands and within Malagasy regions. The approximate Bayesian computation (ABC) used to

test the predominant direction of flea dispersal implied a recent population introduction from Mayotte to Madagascar, which was estimated to have occurred between 1993 and 2012. The impact of this flea introduction in terms of plague transmission in Madagascar is unclear, but the low level of flea exchange between the two islands seems to keep Mayotte free of plague for now. Conclusion: This study highlights the occurrence of genetic structure among populations of the flea vector of plague, *X. cheopis*, in Madagascar and suggests that a flea population from Mayotte has been introduced to Madagascar recently. As plague has not been reported in Mayotte, this introduction is unlikely to present a major concern for plague transmission. Nonetheless, evidence of connectivity among flea populations in the two islands indicates a possibility for dispersal by fleas in the opposite direction and thus a risk of plague introduction to Mayotte.

Heitzinger, K., Impouma, B., Farham, B. L., Hamblion, E. L., Lukoya, C., Machingaidze, C., et al. (2019). Using evidence to inform response to the 2017 plague outbreak in Madagascar: a view from the WHO African Regional Office. *Epidemiology and Infection*, 147.

The 2017 plague outbreak in Madagascar was unprecedented in the African region, resulting in 2417 cases (498 confirmed, 793 probable and 1126 suspected) and 209 deaths by the end of the acute urban pneumonic phase of the outbreak. The Health Emergencies Programme of the WHO Regional Office for Africa together with the WHO Country Office and WHO Headquarters assisted the Ministry of Public Health of Madagascar in the rapid implementation of plague prevention and control measures while collecting and analysing quantitative and qualitative data to inform immediate interventions. We document the key findings of the evidence available to date and actions taken as a result. Based on the four goals of operational research—effective dissemination of results, peer-reviewed publication, changes to policy and practice and improvements in programme performance and health—we evaluate the use of evidence to inform response to the outbreak and describe lessons learned for future outbreak responses in the WHO African region.

Kmietowicz, Z. (2017). Pneumonic plague outbreak hits cities in Madagascar. *British Medical Journal*, 359.

Kreppel, K. S., Caminade, C., Telfer, S., Rajerison, M., Rahalison, L., Morse, A., & Baylis, M. (2014). A non-stationary relationship between global climate phenomena and human plague incidence in Madagascar. *PLOS Neglected Tropical Diseases*, 8(10).

Background: Plague, a zoonosis caused by *Yersinia pestis*, is found in Asia and the Americas, but predominantly in Africa, with the island of Madagascar reporting almost one-third of human cases worldwide. Plague's occurrence is affected by local climate factors which in turn are influenced by large-scale climate phenomena such as the El Niño Southern Oscillation (ENSO). The effects of ENSO on regional climate are often enhanced or reduced by a second large-scale climate phenomenon, the Indian Ocean Dipole (IOD). It is known that ENSO and the IOD interact as drivers of disease. Yet the impacts of these phenomena in driving plague dynamics via their effect on regional climate, and specifically contributing to the foci of transmission on Madagascar, are unknown. Here we present the

first analysis of the effects of ENSO and IOD on plague in Madagascar.

Methodology/Principal Findings: We use a forty-eight year monthly time-series of reported human plague cases from 1960 to 2008. Using wavelet analysis, we show that over the last fifty years there have been complex non-stationary associations between ENSO/IOD and the dynamics of plague in Madagascar. We demonstrate that ENSO and IOD influence temperature in Madagascar and that temperature and plague cycles are associated. The effects on plague appear to be mediated more by temperature, but precipitation also undoubtedly influences plague in Madagascar. Our results confirm a relationship between plague anomalies and an increase in the intensity of ENSO events and precipitation.

Conclusions/Significance: This work widens the understanding of how climate factors acting over different temporal scales can combine to drive local disease dynamics. Given the association of increasing ENSO strength and plague anomalies in Madagascar, it may in future be possible to forecast plague outbreaks in Madagascar. The study gives insight into the complex and changing relationship between climate factors and plague in Madagascar.

Kreppel, K. S., Telfer, S., Rajerison, M., Morse, A., & Baylis, M. (2016). Effect of temperature and relative humidity on the development times and survival of *Synopsyllus fonquerniei* and *Xenopsylla cheopis*, the flea vectors of plague in Madagascar. *Parasites & Vectors*, 9.

Background: Plague, a zoonosis caused by *Yersinia pestis*, is found in Asia, the Americas but mainly in Africa, with the island of Madagascar reporting almost one-third of human cases worldwide. In the highlands of Madagascar, plague is transmitted predominantly by two flea species which coexist on the island, but differ in their distribution. The endemic flea, *Synopsyllus fonquerniei*, dominates flea communities on rats caught outdoors, while the cosmopolitan flea, *Xenopsylla cheopis*, is found mostly on rats caught in houses.

Additionally *S. fonquerniei* seems restricted to areas above 800 m. Climatic constraints on the development of the two main vectors of plague could explain the differences in their distribution and the seasonal changes in their abundance. Here we present the first study on effects of temperature and relative humidity on the immature stages of both vector species.

Methods: We examined the two species' temperature and humidity requirements under experimental conditions at five different temperatures and two relative humidities. By employing multivariate and survival analysis, we established the impact of temperature and relative humidity on development times and survival for both species. Using degree-day analysis, we then predicted the average developmental threshold for larvae to reach pupation and for pupae to complete development under each treatment. This analysis was undertaken separately for the two relative humidities and for the two species. **Results:**

Development times and time to death differed significantly, with the endemic *S. fonquerniei* taking on average 1.79 times longer to complete development and having a shorter time to death than *X. cheopis* under adverse conditions with high temperature and low humidity.

Temperature had a significant effect on the development times of flea larvae and pupae. While humidity did not affect the development times of either species, it did influence the time of death of *S. fonquerniei*. Using degree-day analysis, we estimated an average developmental threshold of 9 degrees C for *S. fonquerniei*, and 12.5 degrees C for *X. cheopis*.

Conclusions: While many vector-borne diseases are limited to warm, low-lying regions, plague in Madagascar is unusual in being most prevalent in the cool, highland

regions of the country. Our results point towards the possibility that this is because the endemic flea vector, *S. fonquerniei*, is better adapted to cool temperatures than the exotic flea vector, *X. cheopis*. Future warming caused by climate change might reduce the area suitable for *S. fonquerniei* and may thus reduce the incidence of plague in Madagascar.

Laventure, S., Rasoamanana, B., Boisier, P., Rasolomaharo, M., Rahilison, L., Randriantsoa, J. et al. (1998). An epidemic of urban plague in Majunga, western coast of Madagascar. *Bulletin de la Societe de Pathologie Exotique*, 91(1), 85–86.

In August 1991, an epidemic of urban plague broke out in Majunga, a port on the western coast of Madagascar. As the first resurgence of the disease in this area in 70 years, the episode was a dramatic reminder of the ubiquity of the disease and laid low the falsely reassuring idea that plague was confined to well-known centers of high altitude. After the epidemic had claimed 12 victims, 21 patients suffering from bubonic plague and 7 cases of pneumonic plague, it was brought under control by treating exposed subjects and introducing antivectorial measures. Transmission to man continued in the shape of sporadic cases of bubonic plague until April 1992 and a total number of 41 probable or confirmed bacteriological cases (not counting those deceased) were recorded out of 202 suspected cases. The history of the disease related almost all these cases to the highly populated and unsanitary neighbourhood of Marolaka, situated on the edge of the Betsiboka estuary, and which has kept semi-rural characteristics. Its murine population had practically disappeared, decimated by an epizootic in early July. Out of the two captured sets of two *Rattus rattus* (41 fleas per animal) and two *R. norvegicus* each, three were carriers of the bacillus. Numerous shrew-mice (*Suncus murinus*) occupied the zone and three tested positive to the direct bacteriological test. For the insectivore, the mean *Xenopsylla cheopis* index was 4 (n=16) rising to 26 in positive animals. The discovery of a plague-infested rat carrying *X. cheopis* and the persistence of *P. irritans* after insecticide treatments, led us to doubt the efficiency of the antivectorial fight that had been undertaken. Risk of endemization was referred to. After a period of quiet of 3 years, isolated cases were detected in March and May 1995, followed by a new epidemic between July 1995 and March 1996 in which 617 clinical suspects of bubonic plague were notified. The confirmation by isolating the bacillus was obtained for 60 subjects, and 48 were considered to be probable cases. Twenty-four deaths were attributed to plague. Once again, the high density of cases came from Marolaka. Rats captured in June 1995 revealed the presence of *R. rattus* and *R. norvegicus* in small numbers and of *S. murinus* carrying *X. cheopis*. In early November the *Rattus* had practically disappeared. There remained numerous *S. murinus* (n=84) with an *X. cheopis* index of 5, despite the pulverization of insecticides. The bacillus was isolated from *R. norvegicus* as well as *S. murinus*. Plague is thus settling into the town of Majunga. The bacillus maintains itself in the estuary zone and in southern winters, for certain years, transmission among rodents is amplified, and then an epidemic breaks out. The epicenter of the disease is clearly Marolaka and its spread is limited to neighbouring areas. In such a biotype, the inter-epizootic cycle of the bacillus must be elucidated without delay. The actual role of shrew-mice as an efficient reservoir has not been established but quite obviously they allow the vectors to survive after the extinction of murine populations affected by plague. The operational efficiency of anti-vectorial measures should be evaluated in the field

while tests on the sensitivity of fleas to insecticides have highlighted the appearance of new forms of resistance.

Majumder, M. S., Cohn, E. L., Santillana, M., & Brownstein, J. S. (2018). Estimation of pneumonic plague transmission in Madagascar, August–November 2017. *PLoS Currents*, 10.

INTRODUCTION: Between August and November 2017, Madagascar reported nearly 2500 cases of plague; the vast majority of these cases were pneumonic, resulting in early exponential growth due to person-to-person transmission. Though plague is endemic in Madagascar, cases are usually bubonic and thus result in considerably smaller annual caseloads than those observed from August–November 2017. **METHODS:** In this study, we consider the transmission dynamics of pneumonic plague in Madagascar during this time period, as well as the role of control strategies that were deployed to curb the outbreak and their effectiveness. **RESULTS:** When using data from the beginning of the outbreak through late November 2017, our estimates for the basic reproduction number range from 1.6 to 3.6, with a mean of 2.4. We also find two distinctive periods of “control,” which coincide with critical on-the-ground interventions, including contact tracing and delivery of antibiotics, among others. **DISCUSSION:** Given these results, we conclude that existing interventions remain effective against plague in Madagascar, despite the atypical size and spread of this particular outbreak.

McCauley, D. J., Salkeld, D. J., Young, H. S., Makundi, R., Dirzo, R., Eckerlin, R. P., et al. (2015). Effects of land use on plague (*Yersinia pestis*) activity in rodents in Tanzania. *American Journal of Tropical Medicine and Hygiene*, 92(4), 776–783.

MacMillan, K., Ensore, R. E., Ogen-Odoi, A., Borchert, J. N., Babi, N., Amatre, G., et al. (2011). Landscape and residential variables associated with plague-endemic villages in the West Nile region of Uganda. *American Journal of Tropical Medicine and Hygiene*, 84(3), 435–442.

Mead, P. S. (2018). Plague in Madagascar—a tragic opportunity for improving public health. *New England Journal of Medicine* 378 (2): 106–8

Miarinjara, A., & Boyer, S. (2016). Current perspectives on plague vector control in Madagascar: Susceptibility status of *Xenopsylla cheopis* to 12 Insecticides. *PLOS Neglected Tropical Diseases*, 10(2). Plague is a rodent disease transmissible to humans by infected flea bites, and Madagascar is one of the countries with the highest plague incidence in the world. This study reports the susceptibility of the main plague vector *Xenopsylla cheopis* to 12 different insecticides belonging to 4 insecticide families (carbamates, organophosphates, pyrethroids and organochlorines). Eight populations from different geographical regions of Madagascar previously resistant to deltamethrin were tested with a World Health Organization standard bioassay. Insecticide susceptibility varied amongst populations, but all of them were resistant to six insecticides belonging to pyrethroid and carbamate insecticides (alphacypermethrin, lambda-cyhalothrin, etofenprox, deltamethrin, bendiocarb and propoxur). Only one insecticide (dieldrin) was an efficient pulicide for all flea populations. Cross resistances were suspected.

This study proposes at least three alternative insecticides (malathion, fenitrothion and cyfluthrin) to replace deltamethrin during plague epidemic responses, but the most efficient insecticide may be different for each population studied. We highlight the importance of continuous insecticide susceptibility surveillance in the areas of high plague risk in Madagascar.

Miarinjara, A., Rajohnson, D. M., Rahelinirina, S., & Boyer, S. (2017). Plague in Madagascar: Limiting the transmission by improving the control of *Xenopsylla cheopis*, the main flea vector of *Yersinia pestis*. *American Journal of Tropical Medicine and Hygiene*, 95(5, S), 408.

Miarinjara, A., Rogier, C., Harimalala, M., Ramihangihajason, T. R., & Boyer, S. (2016). *Xenopsylla brasiliensis* fleas in plague focus areas, Madagascar. *Emerging Infectious Diseases*, 22(12), 2207–2208.

Miarinjara, A., Vergain, J., Kavaruganda, J. M., Rajerison, M., & Boyer, S. (2017). Plague risk in vulnerable community: assessment of *Xenopsylla cheopis* susceptibility to insecticides in Malagasy prisons. *Infectious Diseases of Poverty*, 6.

Background: Prisons in Madagascar are at high risk of plague outbreak. Occurrence of plague epidemic in prisons can cause significant episodes of urban plague through the movement of potentially infected humans, rodents and fleas. Rodent and flea controls are essential in plague prevention to reduce human contact with plague reservoirs and vectors. Insecticide treatment is the key step available for the control of rat fleas which transmit the disease from infected rodents to human. The implementation of an adapted flea control strategy should rely on the insecticide susceptibility status of the targeted population. For the purpose of a plague prevention campaign in prisons, we conducted an insecticide resistance survey on *Xenopsylla cheopis*, the rat flea. Methods: Fleas were collected on rats caught in six prisons of Madagascar. They were exposed to insecticide treated filter papers and mortality was recorded following World Health Organization protocol. Results: The fleas collected in the prisons had different resistance patterns, while a high level of resistance to insecticides tested was described in the Antanimora prison located in the heart of Antananarivo, the capital of Madagascar. Conclusions: This finding is alarming in the context of public health, knowing that the effectiveness of flea control could be jeopardized by insecticide resistance. In order to establish more accurate rat fleas control in prisons, the main recommendations are based on continuous monitoring of the insecticide susceptibility of fleas, insecticide rotation, and the development of a new method for flea control.

Migliani, Rene, Chanteau, S., Rahalison, L., Ratsitorahina, M., Boutin, J. P., Ratsifasoamanana, L., & Roux, J. (2006). Epidemiological trends for human plague in Madagascar during the second half of the 20th century: a survey of 20,900 notified cases. *Tropical Medicine & International Health*, 11(8), 1228–1237. OBJECTIVES To describe the principal characteristics and epidemiological trends for human plague in modern times based on the largest reported series of cases from the highly active Malagasy focus. METHODS We used a file of 20 900 notified cases of suspected plague, 4473 of which were confirmed or probable, to carry out a statistical analysis of incidence and mortality rates and associated factors for 5-year periods from 1957 to 2001. RESULTS Our analysis of trends showed (1) an increase in the incidence

rate and the number of districts affected, (2) an increase in the proportion of bubonic forms (64.8%-96.8%) at the expense of the pneumonic forms (35.2%-3.2%) more frequent in elderly subjects and (3) a decrease in case fatality rate (CFR, 55.7%-20.9%) associated with five factors: clinical form, season, province, urban/rural and period considered. The median age of patients was 14 years, and more men than women were affected. CONCLUSIONS Since the end of the 1980s, the incidence of plague in Madagascar has increased in both rural and urban areas because of multiple socioeconomic and environmental factors. However, the plague mortality rate has tended to decrease, together with the frequency of pneumonic forms, because of the strengthening of control measures. Making dipstick tests for the rapid diagnosis of human cases and epizootics in rats available for health structures should make it possible to raise the alarm and to react rapidly, thereby further decreasing morbidity and CFR.

Minicucci, L., Rahantarisoa, H., Bracher, J., Andrianasolo, R., Randriamanantsoa, R., Rakotondrainibe, M., et al. (2005). A multi-village pneumonic plague outbreak - Ampanotokana, Madagascar, January 2005. *American Journal of Tropical Medicine and Hygiene*, 73(6, S), 343.

Moore, S. M., Monaghan, A., Griffith, K. S., Apangu, T., Mead, P. S., & Eisen, R. J. (2012). Improvement of disease prediction and modeling through the use of meteorological ensembles: Human plague in Uganda. *PLOS One*, 7(9). Climate and weather influence the occurrence, distribution, and incidence of infectious diseases, particularly those caused by vector-borne or zoonotic pathogens. Thus, models based on meteorological data have helped predict when and where human cases are most likely to occur. Such knowledge aids in targeting limited prevention and control resources and may ultimately reduce the burden of diseases. Paradoxically, localities where such models could yield the greatest benefits, such as tropical regions where morbidity and mortality caused by vector-borne diseases is greatest, often lack high-quality in situ local meteorological data. Satellite- and model-based gridded climate datasets can be used to approximate local meteorological conditions in data-sparse regions, however, their accuracy varies. Here we investigate how the selection of a particular dataset can influence the outcomes of disease forecasting models. Our model system focuses on plague (*Yersinia pestis* infection) in the West Nile region of Uganda. The majority of recent human cases have been reported from East Africa and Madagascar, where meteorological observations are sparse and topography yields complex weather patterns. Using an ensemble of meteorological datasets and model-averaging techniques, we find that the number of suspected cases in the West Nile region was negatively associated with dry season rainfall (December-February) and positively with rainfall prior to the plague season. We demonstrate that ensembles of available meteorological datasets can be used to quantify climatic uncertainty and minimize its impacts on infectious disease models. These methods are particularly valuable in regions with sparse observational networks and high morbidity and mortality from vector-borne diseases.

Mouchet, J., Giacomini, T., & Julvez, J. (1995). [Human diffusion of arthropod disease vectors throughout the world]. *Sante (Montrouge, France)*, 5(5), 293–298.

The present distribution of animals and plants throughout the world is the result of an evolutionary process involving tectonic, climatic and biotic factors. Humans, since their

appearance, have contributed to the spreading of many species including disease vectors and pests. When humans left their native African home, they brought with them ectoparasites such as lice and acarids. During the neolithic era, humans were leading domesticated animals which carried their own parasites into new areas. Dwelling commensals, flea, bugs, triatomids, flies, and cockroaches followed human migrations. In the second millennium, sailboats transported mosquito species which were resistant and reproduced on board, including *Culex quinquefasciatus*, *Aedes aegypti*, and *Ae. albopictus*. Steamers further shortened the length of trips and allowed the transport of anophelines. The opening of the Tamatave-Port-Louis line was immediately followed by the transport of *An. gambiae* from Madagascar to Mauritius and Reunion, and epidemics of malaria occurred on the two islands which had been free of the disease. Also, *An. gambiae* was transported from Senegal to Brazil. Old tires destined for recycling carried *Ae. albopictus* to the USA, Brazil, and then Italy. The pandemic of the plague at the end of the nineteenth century was propagated from harbour to harbour by steamers carrying both infected rats and their fleas *Xenopsylla cheopis*. Aircraft have reduced the travel time so much that in less than two days, an insect could reach every point of the world. As soon as the airports had been built on the islands of French Polynesia, they were all colonized by *Ae. aegypti*. The same phenomenon occurred with midges (Fig. 2). Also, the construction of the airport on a Galapagos Island coincided with the importation of the blackfly *Simulium bipunctatum* from the continent. In addition, infected malaria mosquitos imported from tropical countries reached Europe and contaminated airport employees and local inhabitants. Six cases of malaria were recorded during the summer of 1994 around the Charles de Gaulle Airport, north of Paris, suggesting that the anophelines could have been imported from West and Central African countries which are served by this airport. The serious threat of vector importation is moderated by the vector's difficulty in adapting to new conditions. However any prediction is questionable.

Neerinckx, S. B., Peterson, A. T., Gulinck, H., Deckers, J., & Leirs, H. (2008). Geographic distribution and ecological niche of plague in sub-Saharan Africa. *International Journal of Health Geographics*, 7. Background: Plague is a rapidly progressing, serious illness in humans that is likely to be fatal if not treated. It remains a public health threat, especially in sub-Saharan Africa. In spite of plague's highly focal nature, a thorough ecological understanding of the general distribution pattern of plague across sub-Saharan Africa has not been established to date. In this study, we used human plague data from sub-Saharan Africa for 1970-2007 in an ecological niche modeling framework to explore the potential geographic distribution of plague and its ecological requirements across Africa. Results: We predict a broad potential distributional area of plague occurrences across sub-Saharan Africa. General tests of our model's transferability suggest that our model can anticipate the potential distribution of plague occurrences in Madagascar and northern Africa. However, generality and predictive ability tests using regional subsets of occurrence points demonstrate the models to be unable to accurately predict independent occurrence points outside the training region. Visualizations show plague to occur in diverse landscapes under wide ranges of environmental conditions. Conclusion: We conclude that the typical focality of plague, observed in sub-Saharan Africa, is not related to fragmented and insular environmental conditions manifested at a coarse continental scale. However, our

approach provides a foundation for testing hypotheses concerning focal distribution areas of plague and their links with historical and environmental factors.

Nguyen, V. K., Parra-Rojas, C., & Hernandez-Vargas, E. A. (2018). The 2017 plague outbreak in Madagascar: Data descriptions and epidemic modelling. *Epidemics*, 25, 20–25.

From August to November 2017, Madagascar endured an outbreak of plague. A total of 2417 cases of plague were confirmed, causing a death toll of 209. Public health intervention efforts were introduced and successfully stopped the epidemic at the end of November. Plague, however, is endemic in the region and occurs annually, posing the risk of future outbreaks. To understand the plague transmission, we collected real-time data from official reports, described the outbreaks characteristics, and estimated transmission parameters using statistical and mathematical models. The pneumonic plague epidemic curve exhibited multiple peaks, coinciding with sporadic introductions of new bubonic cases. Optimal climate conditions for rat flea to flourish were observed during the epidemic. Estimate of the plague basic reproduction number during the large wave of the epidemic was high, ranging from 5 to 7 depending on model assumptions. The incubation and infection periods for bubonic and pneumonic plague were 4.3 and 3.4 days and 3.8 and 2.9 days, respectively. Parameter estimation suggested that even with a small fraction of the population exposed to infected rat fleas (1/10,000) and a small probability of transition from a bubonic case to a secondary pneumonic case (3%), the high human-to-human transmission rate can still generate a large outbreak. Controlling rodent and fleas can prevent new index cases, but managing human-to-human transmission is key to prevent large-scale outbreaks.

Nyirenda, S. S., Hang'ombe, B. M., Kilonzo, B. S., Kangwa, H. L., Mulenga, E., & Moonga, L. (2017). Potential roles of pigs, small ruminants, rodents, and their flea vectors in plague epidemiology in Sinda District, Eastern Zambia. *Journal of Medical Entomology*, 54(3), 719–725.

A cross-sectional study was conducted in the Eastern part of Zambia that previously reported a plague outbreak. The aim of the study was to evaluate the potential role of pigs, goats, and sheep as sero-surveillance hosts for monitoring plague, and to investigate the flea vectors and potential reservoir hosts to establish the current status of plague endemicity in the district. Serum samples were collected from 96 rodents, 10 shrews, 245 domestic pigs, 232 goats, and 31 sheep, whereas 106 organs were eviscerated from rodents and shrews. As for fleas, 1,064 *Echidnophaga larina* Jordan & Rothschild, 7 *Xenopsylla cheopis* (Rothschild), and 382 *Echidnophaga gallinacea* (Westwood) were collected from these animals in 34 villages. Enzyme-Linked Immunosorbent Assay (ELISA) and Polymerase Chain Reaction (PCR) tests were performed on serum, and organs and fleas to determine IgG antibodies against Fraction 1 antigen and pla gene of *Yersinia pestis*, respectively. ELISA results showed that 2.83% (95% CI = 0.59-8.05) rodents, 9.0% (95% CI = 5.71-13.28) domestic pigs, 4.7% (95% CI = 2.39-8.33) goats, and 3.2% (95% CI = 0.08-16.70) sheep were positive for IgG antibodies against Fra1 antigen of *Y. pestis*. On PCR, 8.4% (95% CI = 3.96-15.51) of the rodents were detected with *Y. pestis* pla gene, whereas all fleas were found negative. The common fleas identified were *E. larina* from pigs, whereas *X.*

cheopis were the only fleas collected from rodents. The presence of sero-positive animals as well as the occurrence of *X. cheopis* on local rodents suggests that *Y. pestis* remains a risk in the district.

Pham, H. V., Dang, D. T., Minh, N. N. T., Nguyen, D., & Nguyen, T. V. (2009). Correlates of environmental factors and human plague: an ecological study in Vietnam. *International Journal of Epidemiology*, 38(6), 1634–1641.

Methods: The study included all 510 communes of the Central Highlands region (with a total population of about 4 million) where 95% of the incidence of plague cases in Vietnam had been reported from 1997 through 2002. Plague was clinically ascertained by using a standard protocol from WHO. Data on domestic fleas and rodents were obtained by using traps and periodic surveillance in accordance with the WHO guidelines. Temperature, duration of sunshine, rainfall and humidity were recorded as monthly averages by local meteorological stations. The association between these ecological factors and plague was assessed by using the Poisson regression model. Results: From 1997 through 2002, 472 cases of plague were reported, of whom 24 (5.1%) died. The incidence of plague peaked during the dry season, with about 63% of cases occurring from February through April. The risk of plague occurrence was associated with an increased monthly flea index (RR and 95% CI: 1.93; 1.61-2.33 for months with the flea index > 1) and increased rodent density (RR 1.23; 1.15-1.32 per each 3% increase in density). Moreover, the risk of plague increased during the dry season (RR 2.07; 1.64-2.62), when rainfall fell < 10 mm (RR 1.44; 1.17-1.77). Conclusions: These data suggest that the flea index, rodent density and rainfall could be used as ecological indicators of plague risk in Vietnam. The data also suggest that the occurrence of plague in Vietnam's Central Highlands likely resulted from multiple causes that remain to be delineated.

Rabaan, A. A., Al-Ahmed, S. H., Alsuliman, S. A., Aldrazi, F. A., Alfouzan, W. A., & Haque, S. (2019). The rise of pneumonic plague in Madagascar: current plague outbreak breaks usual seasonal mould. *Journal of Medical Microbiology*, 68, 292-302.

Madagascar has just emerged from the grip of an acute urban pneumonic plague outbreak, which began in August 2017, before the usual plague season of October-April and outside the traditional plague foci in the northern and central highlands. The World Health Organization reported a total of 2417 confirmed, probable and suspected cases, including 209 deaths between 1 August and 26 November 2017. The severity and scope of this outbreak, which has affected those in higher socioeconomic groups as well as those living in poverty, along with factors including the potential for use of multi-drug-resistant strains of plague in bioterrorism, highlights the ongoing threat posed by this ancient disease. Factors likely to have contributed to transmission include human behaviour, including burial practices and movement of people, poor urban planning leading to overcrowding and ready transmission by airborne droplets, climatic factors and genomic subtypes. The outbreak demonstrates the importance of identifying targeted pneumonic plague therapies and of developing vaccines that can be administered in planned programmes in developing countries such as Madagascar where plague is endemic. The dominance of pneumonic

plague in this outbreak suggests that we need to focus more urgently on the danger of person-to-person transmission, as well as the problem of transmission of plague from zoonotic sources.

Raharimanga, V., Ratsitorahina, M., Migliani, R., Rosso, M. L., Rahalison, L., & Chanteau, S. (2001). [The plague at the Tsenabe Isotry market in Antananarivo: a complex epidemiologic situation]. *Archives de l'Institut Pasteur de Madagascar*, 67(1–2), 19–20.

The transmission of *Yersinia pestis* is intense among rats in the wholesale market Tsenabe Isotry in the capital Antananarivo (anti-F1 sero-prevalence 80%, flea index 8.4 for a cut-off risk index of > 1). However, there have only been three plague-suspected (not laboratory confirmed) human cases in this district during a four-year period from 1995 to 1999. A seroepidemiological survey among the market vendors was undertaken in June 1999 to test the hypothesis that the low incidence of human plague is due to acquired immunity. In addition, surveillance of the rat and the flea populations in the market was carried out. Only 3 (3.2%) of 95 screened vendors were anti-F1 IgG positive, whereas the markers of plague transmission among rodents and fleas were still high. This result suggests that the low incidence of human plague was not due to acquired immunity but to other factors such as the limited contact between humans and the rat fleas because of the abundance of rats, the absence of epizootic due to the resistance of rats in the capital and a particular behaviour of the predominant rat *Rattus norvegicus*.

Rahelinirina, S., Duplantier, J. M., Ratovonjato, J., Ramilijaona, O., Ratsimba, M., & Rahalison, L. (2010). Study on the movement of *Rattus rattus* and evaluation of the plague dispersion in Madagascar. *Vector-Borne and Zoonotic Diseases*, 10(1, SI), 77–84.

Plague affects mainly the rural areas in the central highlands of Madagascar. *Rattus rattus* is the main rodent host of *Yersinia pestis* in these localities. Since the introduction of plague, endemic foci have continued to expand, and spatiotemporal variability in the distribution of human plague has been observed. To assess the movements of *R. rattus* and evaluate the risk of dispersion of the disease, a field study at the scale of the habitats (houses, hedges of sisals, and rice fields) in the plague villages was carried out during high and low seasons of plague transmission to humans. The systemic oral marker Rhodamine B was used to follow rats' movements. Baits were placed in different habitats, and trapping success was carried out once a month for 3 months after the bait distribution. Plague indicators (reservoirs' abundance, flea index, *Y. pestis* prevalence in fleas, and *Y. pestis* antibody prevalence in rats) were determined. The highest abundance of rats and marking efficiency were observed in the sisal hedges and the rice fields. Marked rats were captured most commonly near the points where baits were initially placed. The main movements of rats were observed between the houses and sisal hedges. Major differences were observed between the seasons of high and low plague transmission. During the season of low plague transmission, rats were more abundant in the sisal hedges and rice fields, with rats moving from the houses to the rice fields. During the high plague transmission season, rats moved from the hedges of sisal to the rice fields. Important indicators of vector abundance and plague transmission were higher during the high plague transmission season. The three

study habitats were the risk areas for plague transmission, but the risk appeared highest in the houses and sisals. Rats' movements according to the season were likely directed by the availability of food.

Rahelinirina, S., Harimalala, M., Margueron, T., Ramihangihajason, T., Mansotte, F., Rajerison, M., et al. (2018). Risk of maritime introduction of plague from Madagascar to Mayotte. *Acta Tropica*, 187, 140–143.

Plague is a rodent-borne disease caused by *Yersinia pestis*. Most human infections are bubonic plague, as a result of being bitten by infected rodent fleas. Madagascar, Democratic Republic of Congo and Peru are the three most affected countries. Plague was introduced into eastern Madagascar in 1898 by boat from India. It is estimated that the risk of introduction of plague from Madagascar to neighboring islands is very high due to the maritime links. We conducted a study of plague reservoirs and vectors in Longoni Port in Mayotte and Mahajanga Port in Madagascar during two seasons to highlight a non-negligible risk of introduction of *Y. pestis* to Mayotte. The results showed that two main reservoirs of plague in Madagascar, *Suncus murinus* and *Rattus rattus* and the main flea vector *Xenopsylla cheopis* exist in and surrounding the port of Longoni. *Y. pestis* was isolated from *Rattus norvegicus* captured close to the port of Mahajanga during this study. Plague bacteria circulate within populations of rodent without causing rodent die-off in Mahajanga. The risk of introduction of plague from Madagascar to Mayotte exists due to the regular exchanges. Continuous surveillance of rat, shrew and flea populations is therefore necessary in all the surrounding countries that have regular exchanges with Madagascar to prevent the spread of the plague.

Rahelinirina, S., Rajerison, M., Telfer, S., Savin, C., Carniel, E., & Duplantier, J.-M. (2017). The Asian house shrew *Suncus murinus* as a reservoir and source of human outbreaks of plague in Madagascar. *PLOS Neglected Tropical Diseases*, 11(11).

Identifying key reservoirs for zoonoses is crucial for understanding variation in incidence. Plague re-emerged in Mahajanga, Madagascar in the 1990s but there has been no confirmed case since 1999. Here we combine ecological and genetic data, from during and after the epidemics, with experimental infections to examine the role of the shrew *Suncus murinus* in the plague epidemiological cycle. The predominance of *S. murinus* captures during the epidemics, their carriage of the flea vector and their infection with *Yersinia pestis* suggest they played an important role in the maintenance and transmission of plague. *S. murinus* exhibit a high but variable resistance to experimental *Y. pestis* infections, providing evidence of its ability to act as a maintenance host. Genetic analyses of the strains isolated from various hosts were consistent with two partially linked transmission cycles, with plague persisting within the *S. murinus* population, occasionally spilling over into the rat and human populations. The recent isolation from a rat in Mahajanga of a *Y. pestis* strain genetically close to shrew strains obtained during the epidemics reinforces this hypothesis and suggests circulation of plague continues. The observed decline in *S. murinus* and *Xenopsylla cheopis* since the epidemics appears to have decreased the frequency of spillover events to the more susceptible rats, which act as a source of infection for humans.

Although this may explain the lack of confirmed human cases in recent years, the current circulation of plague within the city highlights the continuing health threat.

Rajonhson, D. M., Miarinjara, A., Rahelinirina, S., Rajerison, M., & Boyer, S. (2017). Effectiveness of fipronil as a systemic control agent against *Xenopsylla cheopis* (Siphonaptera: Pulicidae) in Madagascar. *Journal of Medical Entomology*, 54(2), 411–417.

Fipronil was evaluated as a systemic control agent for the rat flea *Xenopsylla cheopis* (Rothschild), the main vector of *Yersinia pestis* (Yersin), the causative agent of plague, in Madagascar. The effectiveness of fipronil as a systemic control agent against *X. cheopis* was assessed by determining the toxicity values of the “Lethal Dose 50” (LD50). Two techniques were used to evaluate the systemic action of the insecticide on the vector: 1) an artificial feeding device filled with blood-fipronil mixture from which *X. cheopis* was fed and 2) rodent hosts, *Rattus norvegicus* (Berkenhout) and *Rattus rattus* (L.), which fed on fipronil-treated bait. As a standardized control method, the susceptibility of *X. cheopis* to fipronil was evaluated by exposure to impregnated paper within World Health Organization (WHO) insecticide test protocol to compare its effect to the systemic activity of the studied insecticide. Results showed that when administered in a systemic way, fipronil appears to be more effective: the toxicity level was evaluated to be ninefold higher compared with the WHO test. Compared with other methods, which require indiscriminate dusting of rodent burrows and human dwellings, fipronil applied in a systemic way enables the direct targeting of the plague vector. Thus, this method appears to be a superior alternative to fipronil-dusting for the control of the main plague vector in Madagascar. However, subsequent tests in the field are necessary to confirm the suitability of fipronil administration in a systemic way on large scales.

Ratovonjato, J., Duchemin, J. B., Duplantier, J. M., & Chanteau, S. (2000). [*Xenopsylla cheopis* (Siphonaptera: Xenopsyllinae), fleas in rural plague areas of high altitude Madagascar: level of sensitivity to DDT, pyrethroids and carbamates after 50 years of chemical vector control]. *Archives de l'Institut Pasteur de Madagascar*, 66(1–2), 9–12.

The resistance of *Xenopsylla cheopis* from urban areas to pyrethroids and DDT, and their susceptibility to carbamate are known. We have evaluated the susceptibility of *X. cheopis* collected from three rural localities: Ambodisiarivo (district of Antananarivo Avaradrano), Mandoto (district of Betafo), Analaoa (district of Anjozorobe) in the province of Antananarivo and in Besoa (district of Ambalavao) in the province of Fianarantsoa. The standard WHO protocol was used and four insecticides were tested: deltamethrin 0.025%, cyfluthrin 0.15% (pyrethroids), DDT 4% (organochlorine), propoxur 1% and bendiocarb 0.1% (carbamate). *X. cheopis* was resistant to DDT 4% and deltamethrin 0.025% but was susceptible in the rural area around Antananarivo City. They were tolerant to deltamethrin 0.025% and cyfluthrin 0.15% but susceptible to propoxur 0.1% and bendiocarb 1% in the districts of Betafo and Anjozorobe. In Besoa, *X. cheopis* was resistant to DDT 4%, tolerant to deltamethrin 0.025% and cyfluthrin 0.15% but susceptible to propoxur 0.1% and bendiocarb 1%. These results indicate that DDT and pyrethroids cannot be recommended for vector control in the rural area around the capital. The use of pyrethroids in the other

districts of the central highland must be linked with a *X. cheopis* susceptibility control. In case of resistance to pyrethroids, carbamates would be proposed to control plague vector in the rural area. The high level of resistance to DDT and pyrethroid in the rural area around the capital confirms the importance of studying the flea population in different areas of Madagascar and the possibility of gene resistance propagation.

Ratovonjato, J., Rajerison, M., Rahelinirina, S., & Boyer, S. (2014). *Yersinia pestis* in *Pulex irritans* fleas during plague outbreak, Madagascar. *Emerging Infectious Diseases*, 20(8), 1414–1415.

Richaud, J. (1970). [Immunity of the tenrec to experimental plague: immunological aspect]. *Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales*, 164(4), 931–933.

Riehm, J. M., Projahn, M., Vogler, A. J., Rajerison, M., Andersen, G., Hall, C. M., et al. (2015). Diverse genotypes of *Yersinia pestis* caused plague in Madagascar in 2007. *PLOS Neglected Tropical Diseases*, 9(6).

Background: *Yersinia pestis* is the causative agent of human plague and is endemic in various African, Asian and American countries. In Madagascar, the disease represents a significant public health problem with hundreds of human cases a year. Unfortunately, poor infrastructure makes outbreak investigations challenging. **Methodology/Principal Findings:** DNA was extracted directly from 93 clinical samples from patients with a clinical diagnosis of plague in Madagascar in 2007. The extracted DNAs were then genotyped using three molecular genotyping methods, including single nucleotide polymorphism (SNP) typing, multi-locus variable-number tandem repeat analysis (MLVA), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) analysis. These methods provided increasing resolution, respectively. The results of these analyses revealed that, in 2007, ten molecular groups, two newly described here and eight previously identified, were responsible for causing human plague in geographically distinct areas of Madagascar. **Conclusions/Significance:** Plague in Madagascar is caused by numerous distinct types of *Y. pestis*. Genotyping method choice should be based upon the discriminatory power needed, expense, and available data for any desired comparisons. We conclude that genotyping should be a standard tool used in epidemiological investigations of plague outbreaks.

Roberts, L. (2017). Echoes of Ebola as plague hits Madagascar. *Science*, 358(6362), 430–431.

Rosen, W. (2007). *Justinian's Flea: The First Great Plague and the End of the Roman Empire*. Penguin.

It was the gold age of Emperor Justinian, who, from his glorious capital of Constantinople, united and reigned over an empire stretching from Italy to North Africa. It was the zenith of his achievements - and the last of them. In A.D. 542, the bubonic plague struck. In weeks the glorious classical world of Justinian was plunged into chaos, and the beginnings of a medieval Europe were born. It was the first pandemic the world had ever known and it left its indelible mark: when the plague finally ended, more than

25 million people lay dead. Weaving together history, microbiology, ecology, jurisprudence, theology, and epidemiology, Justinian's Flea is a unique and sweeping account of the little-known event that changed the course of an empire.

Roux, J., & Chanteau, S. (1998). Reflections on a plague epidemic in Madagascar. The place of applied research. *Bulletin de la Societe de Pathologie Exotique*, 91(1), 81–82.

Madagascar is one of the main areas of plague in the world, since it is reasonably estimated that there are over 1000 cases per year. The precise epidemiological data are presented in another paper. From an active and permanent focus in the highlands, plague can spread to border towns (for example, Majunga). In the capital, Antananarivo, the presence of murine plague is cause for worry. Why does such a situation persist when in theory we have all the necessary methods for fighting plague? In fact, the conditions maintaining the epidemic are complex; there are still many unknowns and numerous studies are still required. Those undertaken by the Pasteur Institute with other teams (DLMT Ministry, ORSTOM, US Army IP Paris...) are multidisciplinary. It would be interesting to present the studies in this paper, which will include results already reported: 1. In terms of the causal agent and the management of cases: The classic bacteriological diagnosis is delayed and of reduced sensitivity. Use of the *Yersinia* CIN agar-agar for isolating the *Y. pestis*. Direct field diagnosis test from pathological samples by highlighting the Ag F1. Effective serodiagnosis (Elisa-Ac F1). Tool of retrospective confirmation and seroepidemiology. Diagnosis by genetic techniques (hybridisation, PCR). Sensitivity of *Y. pestis* strains to antibiotics. Molecular study of *Y. pestis* strains. (Appearance of new variants and study of the multiresistance mechanism). 2. In terms of the reservoir of the virus: Classically the black rat (*Rattus rattus*) is the only reservoir in Madagascar. Population dynamics of the *R. rattus* in a rural center surveillance of endemic murine plague (bacteriology, seroepidemiology). Role of the *Suncus murinus* shrew-mouse and of *R. norvegicus* as a reservoir for the virus in urban areas. 3. In terms of vector fleas: Population and infection rate dynamics for the *Xenopsylla cheopis*, principal vector flea. Vector capacity of the *Synopsyllus fonquerniei*, Malagasy endemic rural flea. Sensitivity of fleas to insecticides. Present resistance. 4. In terms of man: Study of a therapeutic scheme better adapted to difficult field conditions. Seroepidemiological studies. Behavioural and environmental studies. Correlations with the periodicity of human cases.

Rubini, M., Gualdi-Russo, E., Manzon, V. S., Rinaldo, N., & Bianucci, R. (2016). Mortality risk factors show similar trends in modern and historic populations exposed to plague. *Journal of Infection in Developing Countries*, 10(5), 488–493.

Introduction: Plague has been responsible for two major historic pandemics (6th-8th century CE; 14th-19th century CE) and a modern one. The recent Malagasy plague outbreaks raised new concerns on the deadly potential of the plague-causing bacteria *Yersinia pestis*. Between September 2014 and April 2015, outbreaks of bubonic and pneumonic plague hit the Malagasy population. Two hundred and sixty-three cases, including 71 deaths, have been reported in 16 different districts with a case fatality rate of 27%. The scope of our study was to ascertain whether the risk factors for health in modern-day populations exposed to plague and in ancient populations that faced the two historic pandemics varied or remained

substantially unaltered. Methodology: The risk of mortality of the Malagasy population with those obtained from the reconstruction of three samples of European populations exposed to the historic pandemics was contrasted. Results: The evidence shows that the risks of death are not uniform across age neither in modern nor in historic populations exposed to plague and shows precise concentrations in specific age groups (children between five and nine years of age and young adults). Conclusions: Although in the post-antibiotic era, the fatality rates have drastically reduced, both modern and historic populations were exposed to the same risk factors that are essentially represented by a low standard of environmental hygiene, poor nutrition, and weak health systems.

Sebbane, F., Gardner, D., Long, D., Gowen, B.B., & Hinnebusch, B.J. (2005). Kinetics of disease progression and host response in a rat model of bubonic plague. *American Journal of Pathology*, 166(5), 1427–1439.

Stenseth, N.C., Atshabar, B.B., Begon, M., Belmain, S.R., Bertherat, E., Carniel, E., et al. (2008). Plague: Past, present, and future.” *PLoS Medicine* 5 (1): e3

Telfer, S., Brouat, C., Duplantier, J.-M., Rahelinirina, S., & Rahalison, L. (2010). Plague epidemiology and risk in the heterogeneous rural landscapes of Madagascar. *Vector-Borne and Zoonotic Diseases*, 10(1, SI), 98–99.

Tollenaere, C., Rahalison, L., Ranjalahy, M., Duplantier, J.-M., Rahelinirina, S., Telfer, S., & Brouat, C. (2010). Susceptibility to *Yersinia pestis* experimental infection in wild *Rattus rattus*, reservoir of plague in Madagascar. *Ecohealth*, 7(2), 242–247.

In Madagascar, the black rat, *Rattus rattus*, is the main reservoir of plague (*Yersinia pestis* infection), a disease still responsible for hundreds of cases each year in this country. This study used experimental plague challenge to assess susceptibility in wild-caught rats to better understand how *R. rattus* can act as a plague reservoir. An important difference in plague resistance between rat populations from the plague focus (central highlands) and those from the plague-free zone (low altitude area) was confirmed to be a widespread phenomenon. In rats from the plague focus, we observed that sex influenced plague susceptibility, with males slightly more resistant than females. Other individual factors investigated (weight and habitat of sampling) did not affect plague resistance. When infected at high bacterial dose (more than 10^5 bacteria injected), rats from the plague focus died mainly within 3-5 days and produced specific antibodies, whereas after low-dose infection (< 5,000 bacteria), delayed mortality was observed and surviving seronegative rats were not uncommon. These results concerning plague resistance level and the course of infection in the black rat would contribute to a better understanding of plague circulation in Madagascar.

Tollenaere, C., Rahalison, L., Ranjalahy, M., Rahelinirina, S., Duplantier, J.-M., & Brouat, C. (2008). CCR5 polymorphism and plague resistance in natural populations of the black rat in Madagascar. *Infection Genetics and Evolution*, 8(6), 891–897.

Madagascar remains one of the world's largest plague foci. The black rat, *Rattus rattus*, is the main reservoir of plague in rural areas. This species is highly susceptible to plague in plague-free areas (low-altitude regions), whereas rats from the plague focus areas (central highlands) have evolved a disease-resistance polymorphism. We used the candidate gene CCR5 to investigate the genetic basis of plague resistance in *R. rattus*. We found a unique non-synonymous substitution (H184R) in a functionally important region of the gene. We then compared (i) CCR5 genotypes of dying and surviving plague-challenged rats and (ii) CCR5 allelic frequencies in plague focus and plague-free populations. Our results suggested a higher prevalence of the substitution in resistant animals compared to susceptible individuals, and a tendency for higher frequencies in plague focus areas compared to plague-free areas. Therefore, the CCR5 polymorphism may be involved in Malagasy black rat plague resistance. CCR5 and other undetermined plague resistance markers may provide useful biological information about host evolution and disease dynamics.

Tollenaere, C., Ivanova, S., Duplantier, J.-M., Loiseau, A., Rahalison, L., Rahelinirina, S., & Brouat, C. (2012). Contrasted patterns of selection on MHC-linked microsatellites in natural populations of the Malagasy plague reservoir. *PLOS One*, 7(3).

Plague (*Yersinia pestis* infection) is a highly virulent rodent disease that persists in many natural ecosystems. The black rat (*Rattus rattus*) is the main host involved in the plague focus of the central highlands of Madagascar. Black rat populations from this area are highly resistant to plague, whereas those from areas in which the disease is absent (low altitude zones of Madagascar) are susceptible. Various lines of evidence suggest a role for the Major Histocompatibility Complex (MHC) in plague resistance. We therefore used the MHC region as a candidate for detecting signatures of plague-mediated selection in Malagasy black rats, by comparing population genetic structures for five MHC-linked microsatellites and neutral markers in two sampling designs. We first compared four pairs of populations, each pair including one population from the plague focus and one from the disease-free zone. Plague-mediated selection was expected to result in greater genetic differentiation between the two zones than expected under neutrality and this was observed for one MHC-class I-linked locus (D20Img2). For this marker as well as for four other MHC-linked loci, a geographic pattern of genetic structure was found at local scale within the plague focus. This pattern would be expected if plague selection pressures were spatially variable. Finally, another MHC-class I-linked locus (D20Rat21) showed evidences of balancing selection, but it seems more likely that this selection would be related to unknown pathogens more widely distributed in Madagascar than plague.

Tsuzuki, S., Lee, H., Miura, F., Chan, Y. H., Jung, S., Akhmetzhanov, A. R., & Nishiura, H. (2017). Dynamics of the pneumonic plague epidemic in Madagascar, August to October 2017. *Eurosurveillance*, 22(46), 2–7.

Transmission potential and severity of pneumonic plague in Madagascar were assessed. Accounting for reporting delay, the reproduction number was estimated at 1.73. The case fatality risk was estimated as 5.5%. Expected numbers of exported cases from Madagascar

were estimated across the world and all estimates were below 1 person from August to October, 2017.

Vogler, A. J., Andrianaivoarimanana, V., Telfer, S., Hall, C. M., Sahl, J. W., Hepp, C. M., et al. (2017). Temporal phylogeography of *Yersinia pestis* in Madagascar: Insights into the long-term maintenance of plague. *PLOS Neglected Tropical Diseases*, 11(9).

Background: *Yersinia pestis* appears to be maintained in multiple, geographically separate, and phylogenetically distinct subpopulations within the highlands of Madagascar. However, the dynamics of these locally differentiated subpopulations through time are mostly unknown. To address that gap and further inform our understanding of plague epidemiology, we investigated the phylogeography of *Y. pestis* in Madagascar over an 18 year period. **Methodology/Principal findings:** We generated whole genome sequences for 31 strains and discovered new SNPs that we used in conjunction with previously identified SNPs and variable-number tandem repeats (VNTRs) to genotype 773 Malagasy *Y. pestis* samples from 1995 to 2012. We mapped the locations where samples were obtained on a fine geographic scale to examine phylogeographic patterns through time. We identified 18 geographically separate and phylogenetically distinct subpopulations that display spatial and temporal stability, persisting in the same locations over a period of almost two decades. We found that geographic areas with higher levels of topographical relief are associated with greater levels of phylogenetic diversity and that sampling frequency can vary considerably among subpopulations and from year to year. We also found evidence of various *Y. pestis* dispersal events, including over long distances, but no evidence that any dispersal events resulted in successful establishment of a transferred genotype in a new location during the examined time period. **Conclusions/Significance:** Our analysis suggests that persistent endemic cycles of *Y. pestis* transmission within local areas are responsible for the long term maintenance of plague in Madagascar, rather than repeated episodes of widescale epidemic spread. Landscape likely plays a role in maintaining *Y. pestis* subpopulations in Madagascar, with increased topographical relief associated with increased levels of localized differentiation. Local ecological factors likely affect the dynamics of individual subpopulations and the associated likelihood of observing human plague cases in a given year in a particular location.

Vogler, A. J., Chan, F., Nottingham, R., Andersen, G., Drees, K., Beckstrom-Sternberg, S. M., et al. (2013). A decade of plague in Mahajanga, Madagascar: Insights into the global maritime spread of pandemic plague. *mBio*, 4(1).

A cluster of human plague cases occurred in the seaport city of Mahajanga, Madagascar, from 1991 to 1999 following 62 years with no evidence of plague, which offered insights into plague pathogen dynamics in an urban environment. We analyzed a set of 44 Mahajanga isolates from this 9-year outbreak, as well as an additional 218 Malagasy isolates from the highland foci. We sequenced the genomes of four Mahajanga strains, performed whole-genome sequence single-nucleotide polymorphism (SNP) discovery on those strains, screened the discovered SNPs, and performed a high-resolution 43-locus multilocus variable-number tandem-repeat analysis of the isolate panel. Twenty-two new SNPs were

identified and defined a new phylogenetic lineage among the Malagasy isolates. Phylogeographic analysis suggests that the Mahajanga lineage likely originated in the Ambositra district in the highlands, spread throughout the northern central highlands, and was then introduced into and became transiently established in Mahajanga. Although multiple transfers between the central highlands and Mahajanga occurred, there was a locally differentiating and dominant subpopulation that was primarily responsible for the 1991-to-1999 Mahajanga outbreaks. Phylotemporal analysis of this Mahajanga subpopulation revealed a cycling pattern of diversity generation and loss that occurred during and after each outbreak. This pattern is consistent with severe interseasonal genetic bottlenecks along with large seasonal population expansions. The ultimate extinction of plague pathogens in Mahajanga suggests that, in this environment, the plague pathogen niche is tenuous at best. However, the temporary large pathogen population expansion provides the means for plague pathogens to disperse and become ecologically established in more suitable nonurban environments. Importance: Maritime spread of plague led to the global dissemination of this disease and affected the course of human history. Multiple historical plague waves resulted in massive human mortalities in three classical plague pandemics: Justinian (6th and 7th centuries), Middle Ages (14th to 17th centuries), and third (mid-1800s to the present). Key to these events was the pathogen's entry into new lands by "plague ships" via seaport cities. Although initial disease outbreaks in ports were common, they were almost never sustained for long, and plague pathogens survived only if they could become established in ecologically suitable habitats. Although plague pathogens' ability to invade port cities has been essential for intercontinental spread, these regions have not proven to be a suitable long-term niche. The disease dynamics in port cities such as Mahajanga are thus critical to plague pathogen amplification and dispersal into new suitable ecological niches for the observed global long-term maintenance of plague pathogens.

Vogler, A. J., Chan, F., Wagner, D. M., Roumagnac, P., Lee, J., Nera, R., et al. (2011). Phylogeography and molecular epidemiology of *Yersinia pestis* in Madagascar. *PLOS Neglected Tropical Diseases*, 5(9).

Background: Plague was introduced to Madagascar in 1898 and continues to be a significant human health problem. It exists mainly in the central highlands, but in the 1990s was reintroduced to the port city of Mahajanga, where it caused extensive human outbreaks. Despite its prevalence, the phylogeography and molecular epidemiology of *Y. pestis* in Madagascar has been difficult to study due to the great genetic similarity among isolates. We examine island-wide geographic-genetic patterns based upon whole-genome discovery of SNPs, SNP genotyping and hypervariable variable-number tandem repeat (VNTR) loci to gain insight into the maintenance and spread of *Y. pestis* in Madagascar.

Methodology/Principal Findings: We analyzed a set of 262 Malagasy isolates using a set of 56 SNPs and a 43-locus multi-locus VNTR analysis (MLVA) system. We then analyzed the geographic distribution of the subclades and identified patterns related to the maintenance and spread of plague in Madagascar. We find relatively high levels of VNTR diversity in addition to several SNP differences. We identify two major groups, Groups I and II, which are subsequently divided into 11 and 4 subclades, respectively. *Y. pestis* appears to be maintained in several geographically separate subpopulations. There is also evidence for

multiple long-distance transfers of *Y. pestis*, likely human mediated. Such transfers have resulted in the reintroduction and establishment of plague in the port city of Mahajanga, where there is evidence for multiple transfers both from and to the central highlands.

Conclusions/Significance: The maintenance and spread of *Y. pestis* in Madagascar is a dynamic and highly active process that relies on the natural cycle between the primary host, the black rat, and its flea vectors as well as human activity.

WHO, Africa Regional Office (2008). 15ème Réunion annuelle du Groupe de travail sur la vaccination (TFI) en Afrique et 14ème Réunion annuelle du Comité de coordination interagences pour la Région Africaine (ARICC) Antananarivo, Madagascar 11-14 décembre 2007. Final Report. Brazzaville.

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