Plague dynamics in times of climate change and increasing pressure on ecosystems.

A literature review with a focus on the Democratic Republic of Congo, Madagascar, and One Health

Plague bacterium Yersinia pestis: 3D illustration (Image Credit: Kateryna Kon)

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Plague dynamics in times of climate change and increasing pressure on ecosystems.

A thesis submitted in partial fulfillment of the requirement for the degree of
Master of Science in International Health

by

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Acronyms and Abbreviations

AFROHUN	Africa One Health University Network
AMR	Antimicrobial Resistance
AR	Assessment Report
ATACH	Alliance for Transformative Action on Climate and Health
BMZ	German Federal Ministry for Economic Cooperation and Development
BP	Bubonic Plague
CASS	Social Sciences Analytics Cell
CC	Climate Change
CCKP	Climate Change Knowledge Portal
CHW	Community Health Workers
CMIP	Coupled Model Inter- comparison Project
COP	Conference of the Parties
COVID- 19	Corona-Virus Disease of 2019
DoD	U.S. Department of Defense
DRC	Democratic Republic of Congo
EID	Emerging and re- emerging Infectious Diseases
ENM	Ecological Niche Modeling
ENSO	El Niño Southern Oscillation
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GCSC	German Climate Service Center
GHI	Global Hunger Index
GHG	Greenhouse Gas
GHS	Global Health Security
HS	Health System
HZ	Health Zones
IDP	Internally Displaced People
IH	International Health
IHR	International Health Regulations
IOD	Indian Ocean Dipole
IOM	International Organization of Migration
IPC	Integrated Food Security Phase Classification
ITCZ	Intertropical Convergence Zone

IPCC	International Panel on Climate Change
JPA	Joint Plan of Action
KAP	Knowledge, Attitude, and Practice
LIC	Lower Income Countries
LSCP	Large- Scale Climate Phenomena
MoA	Ministry of Agriculture
MoH	Ministry of Health (DRC), Ministry of Public Health (Madagascar)
MSF	Médecins Sans Frontières
NA	North America
NASA	National Aeronautical and Space Administration
ND-GAIN	Notre Dame Global Adaptation Initiative
NTD	Neglected Tropical Diseases
OCHA	UN Office for the Coordination of Humanitarian Affairs
OH	One Health
OHCEA	One Health Central and Eastern Africa
OHHLEP	One Health High-Level Expert Panel
OP	Orientale Province (DRC)
PDO	Pacific Decadal Oscillation
PIK	Potsdam Institute for Climate Impact Research
POC	Point of Care
PP	Pneumonic Plague
PPP	Purchasing Power Parity
RCP	Representative Concentration Pathway
RDT	Rapid Diagnostic Test
SDG	Sustainable Development Goals
SP	Septicemic Plague
SSP	Shared Socioeconomic Pathway
TCM	Trophic Cascade Model
US	United States
USD	United States Dollars
UHC	Universal Health Coverage
UN	United Nations
UNDP	United Nations Development Programme
UNEP	United Nations Environment Programme

UNICEF	United Nations Children`s Fund
UNU	United Nations University
USAID	United States Agency for International Development
USDA	United States Department of Agriculture
WASH	Water, Sanitation and Hygiene
WHO	World Health Organization
WB	World Bank
WBG	World Bank Group
WFP	World Food Programme
WMO	World Meteorological Organization
WOAH	World Organization for Animal Health

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Definition of terms

Arthropod vectors "include mosquitoes, flies, biting midges, ticks, mites, fleas, bugs, lice, and other arthropods that carry and transmit disease-causing organisms, or pathogens, from one host to another (1)."

Biodiversity: "Variety of plant and animal life in the world or in a habitat or ecosystem (2)."

Climate "is the average weather conditions for a particular location over a long period of time, ranging from months to thousands or millions of years. The World Meteorological Organization (WMO) uses a 30-year period to determine the average climate (3)."

Climate change " is the term used to describe changes in the state of the climate that can be identified by changes in the average and/or the variability of its properties and that persists for an extended period, typically decades or longer. "Anthropogenic" or "human-induced climate change" results from human activities which are already affecting weather and climate extremes in every region across the globe. These can include: burning of fossil fuels, deforestation, land use and land use changes, livestock management (...)(3)."

Climate Projection: "The simulated response of the climate system to a scenario of future emission or concentration of greenhouse gases and aerosols, generally derived using climate models (2)."

Ecology: "Study of the relationships between organisms and their environment (4)."

Ectoparasite "are parasites that live on the external surface of hosts (...), for example, fleas and lice of various terrestrial vertebrates (5)."

El Niño-Southern Oscillation: "Recurring natural phenomenon characterized by fluctuating ocean temperatures in the equatorial Pacific, coupled with changes in the atmosphere, which have a major influence on climate patterns in various parts of the world (6)."

Emerging infectious disease: "A disease caused by a pathogen that has not been observed previously within a population or geographic location (7)."

Endemic: "A native species whose geographic range or distribution is confined to a single given area (8)."

Enzootic: "Low level of disease that is constantly present in an animal population (8)."

Epizootic: "A large and sudden outbreak of disease in animals (9)."

Evapotranspiration: "The process of transferring moisture from the earth into the atmosphere. The sum of evaporation and transpiration is evapotranspiration (2)."

Exposure: "The likelihood or frequency of contact and infection with a zoonotic agent (4)."

Global Warming: "The gradual increase, observed or projected, in global surface temperature, as one of the consequences of radiative forcing caused by anthropogenic emissions (2)."

Host: “An organism that can be infected by an infectious agent under natural conditions (4).”

One Health: “is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development (10).”

Range Shift: “Changes of the distribution limits of a species, generally along altitudinal or latitudinal gradients (11).”

Re- emerging infectious disease: “Diseases that reappear after they have been on a significant decline. Reemergence may happen because of a breakdown in public health measures for diseases that were once under control. They can also happen when new strains of known disease-causing organisms appear (12).”

Reservoir host: “A host in which an infectious agent can be maintained and from which infection is transmitted to a target population (4).”

Spillover: “Process in which an infectious agent is transmitted into a novel host species (4).”

Sylvatic: “Diseases or pathogens that only affect wild animals (9).”

Vector: “An organism, typically invertebrate, acting as intermediary in the transmission of an infectious agent from a reservoir to a target population (4).”

Vulnerability: “Possibility of a given exposure to hazard resulting in harm (e.g., zoonotic disease outbreak) to a human target population (4).”

Zoonosis: “A disease that is of animal origin and has caused infection (and/or disease) in humans (9).”

Zoonotic hazard: “Relative number of available zoonotic infectious agents at a given space and time acting as potential sources of harm (e.g., zoonotic disease outbreak) to a human target population (4).”

Zoonotic pathogen/parasite: “Pathogen or parasite (e.g., bacteria, virus, fungi, helminth, protozoan) that is maintained in a non-human animal reservoir and is capable of infecting and causing disease in humans (4).”

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Love and gratitude go to my parents Almuth and Gerhart
who are always there for me and deserve only the best.

This is thesis is dedicated to you.

TD

Abstract

Introduction: Plague is still a highly fatal disease if left untreated. The two countries with the highest global incidence, the Democratic Republic of Congo and Madagascar, are characterized by weak health care systems and high climate vulnerability. This thesis explores the consequences of climate change on plague dynamics in both countries, considering the growing pressure on ecosystems and people, and the importance of adopting a holistic approach towards human, animal, and ecosystem health.

Methodology: A literature review was done of English language data published between January 2003 and November 2023. The focus was on studies from African countries, and North America as deemed relevant. Peer- reviewed articles were included as well as grey literature. A One Health framework was applied to structure the findings, integrating the impact of climate and land use change on the zoonosis as well as on socioecological processes.

Results: Both countries will be confronted with warming temperatures, less predictable rainfall patterns, and more extreme weather events like floods and droughts. The impact on plague dynamics in DRC and Madagascar is uncertain due to multiple limitations including weak surveillance systems, lack of research and complex interdependencies of the plague cycle components. The expected range shift of plague together with shrinking natural habitats is associated with an increased risk for genetic variation of Y. pestis and unpredictable outbreak characteristics in terms of location, time, and controllability. At the same time, there are indicators for an increasing risk of exposure as well as vulnerability towards plague infection among the population, especially in eastern DRC and southern Madagascar.

Recommendations: The governments of DRC and Madagascar are encouraged to implement a national OH strategic plan and strengthen their surveillance, decentralized laboratory, and health care capacities. Communities should be supported in practicing plague prevention as well as sustainable land- use methods, and in achieving the SDG needed to combat EID. International health authorities are requested to recognize the risk potential associated with changing plague dynamics and engage in targeted interventions and research projects.

Key search terms: Plague, Yersinia pestis, Democratic Republic of Congo, DRC, Madagascar, climate change, land use change, ecosystem degradation, biodiversity, One Health.

Word count: 13184

"It was about the beginning of September, 1664, that I, among the rest of my neighbors, heard, in ordinary discourse that the plague was returned again in Holland…"
Daniel Defoe: "A Journal of the Plague Year", 1722

Introduction

"I didn't even know plague still exists!" That's the sentence I heard most when asked about the subject of my thesis. I had felt the same a few years back. In 2018, I was organizing a journey through Madagascar with my mother. The travel agent informed us about a recent outbreak of plague on the island but reassured us at the same time; it had been contained. We went and had the most wonderful time full of beautiful encounters with people and the unique wildlife. Since then, however, it stuck in the back of my mind that I wanted to know more about the plague, this medieval scourge, and how the "old time disease" evolved and spread out in our times. Interestingly, I had been close to another highly plague- endemic region before: as a surgeon with Médecins sans Frontières (MSF), I had been based in Bunia (Ituri Province) and Dungu (Haut- Uele) in the northeast of the Democratic Republic of Congo (DRC).

To be able to study modern day plague in more depth, I choose it as my thesis topic for the Master of Science in International Health (MScIH). During the process of reading literature and understanding more about the dynamics of the zoonosis, my interest in Conservation Medicine increased. Together with the MScIH, I had also embarked on the International Diploma in Expedition and Wilderness Medicine (IDWEM) which I completed in 2022. It had nourished my passion for remote medicine and wildlife conservation and brought me in contact with the One Health concept. This approach emphasizes the interconnectedness and interdependence of human, animal, and ecosystem health. The importance of climate change (CC) in this context struck me while visiting a rural health care center in Northern Kenya in 2022. Situated in the heart of a Wildlife Conservancy, the ongoing drought was representing a vital threat to the animal population as well as impacting the life of the villagers. This helped me refining my research question. I started wondering about the impact of climatic and environmental changes on plague dynamics, and on the interactions between humans, animals, and the zoonosis.

These days, the COP28 in Dubai brings together the International Community united in their endeavor to limit global warming to 1,5°C compared to pre-industrial levels by 2050. For the first time, a "Health Day" is on the agenda, co- hosted by the World Health Organization (WHO) and the Alliance for Transformative Action on Climate and Health (ATACH), catapulting the climate- health nexus into the mainstream (13,14). One of the main health threats associated with CC and the growing pressure on ecosystems is an increasing transmission of zoonotic infectious diseases. One recent example in this context was the devastating impact of the COVID- 19 pandemic (4,15,16). The need for universal action in line with the 2030 Agenda for Sustainable Development, adopted by all UN Member states in 2015, is bigger than ever. May this thesis contribute to the "new phase of accelerated progress towards the Sustainable Development Goals" (SDG), declared in September 2023 (17,18).

Chapter 1 Background

1.1 Geographic, Demographic and Socioeconomic Information

1.1.1 DRC

DRC is the largest country in Central Africa with a population recently exceeding 100 million. It ranks among the five poorest nations in the world with at least 62% living under the poverty line of 2,15 USD/day in 2017 purchasing power parity (PPP) (19). More than half of the Congolese live in rural areas (20). In the cities, around 80% live in slums (21). With a demographic growth of 3,2%, the country is projected to double its inhabitants mid-century (22,23). The population relies on small scale agriculture for their income and food, with farming, animal husbandry, hunting, fishing, and forestry providing the source of living for three quarters of the Congolese (24,25). Figure 1 illustrates the different provinces and borders with neighboring countries (26).

DRC combines a wide range of ecological and topographical features. The vast central Congo Basin is surrounded by plateaus rising in mountain ranges towards the east (Fig 2)(27). The hot and humid northwest is home to the worlds` second largest tropical rainforest, whereas the central, eastern and southern parts are cooler and drier (24,25,28). The climate is influenced by different trade winds, mainly the Intertropical Convergence Zone (ITCZ), but also southeastern winds dominating the mountain climate in the eastern highlands (8)(10). Distinct dry and rainy seasons characterize the regions north and south of the equator (29). The mean annual temperature recorded between 1991 and 2020 was 24,3°C (30).

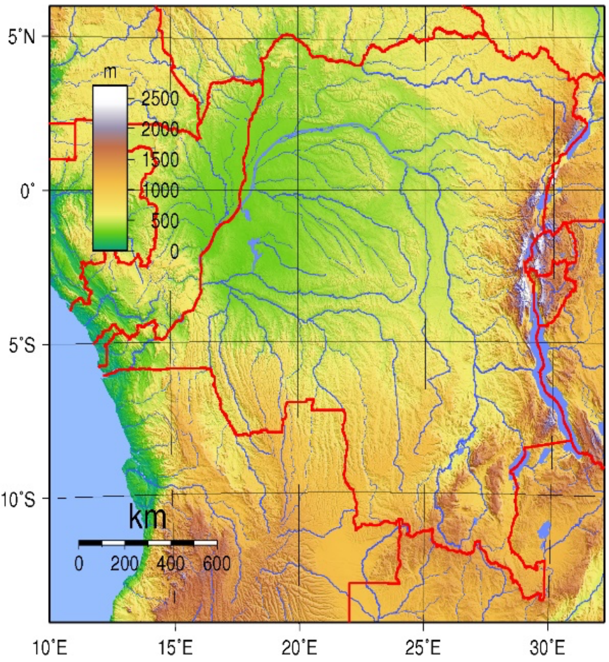


Figure 1: Political map of DRC (26)

Figure 2: Topographic map of DRC (27)

1.1.2 Madagascar

Madagascar is the world´s fourth largest island, situated southeast of Africa in the Indian Ocean (Fig 3) (31). It has a population of approximately 30 million people, 60% living in rural areas. Of the urban population, 70% live in slums (32). With over 80% of the Malagasy people having to manage on 2,15 USD/day or less, the country is one of the poorest in the world (33,34). The rapid population growth of 2,68% per year is expected to continue and surpass the 50 million by 2050 (35–38). Agriculture, animal husbandry, fishing, and forestry are the main sources of income and food for most Malagasy people. Slash- und burn- agriculture is widely practiced, a farming technique where forests are burned for planting (39,40).

The island combines a tropical coastline, plains, and different forest types with a spine of mountains running from north to south (Fig 4) (41): the central highlands with their characteristic rice- growing terrasses and a more temperate climate. Towards the south and southwest, the features change from subtropical into arid, semi- desert regions. The climate is strongly influenced by south-eastern trade winds and characterized by a dry and a rainy season, with regional variations (40,42,43). In the central highlands, the hot and humid rainy season lasts from October to April (44). Temperatures across the island range from 18°C to 26°C. The annual average recorded between 1991 and 2020 was 22,6°C (41,45,46).

Figure 3: Political map of Madagascar (31)

Figure 4: Topographic map of Madagascar (41)

1.2 Health system (HS) and health

1.2.1 DRC

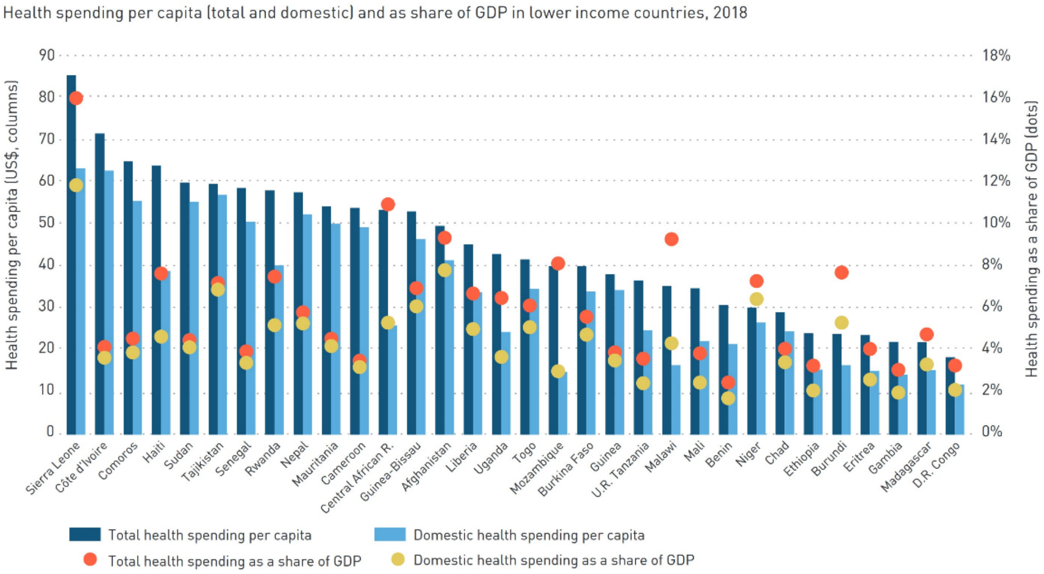
The HS of DRC is divided in three levels. The central administrative level, represented by the Ministry of Health (MoH) in the capital Kinshasa, intermediate level, divided in 26 provincial health divisions, and implementation level, consisting of 516 health zones (HZ). These are subdivided into approximately 8500 health areas, each operating a health center responsible for up to 10,000 people (47,48). Community health workers (CHW) help implementing health services and disease surveillance at community level (49,50). The leading causes of death are communicable diseases (malaria, tuberculosis, lower respiratory tract infections (LRTI), diarrheal diseases), although the proportion of non- communicable diseases is rising (51).

1.2.2 Madagascar

The HS of Madagascar is structured in a similar way. While the central unit, consisting of the Ministry of Public Health`s (MoH) directorates and services, defines the national policies, the regional level coordinates their implementation in the 22 regions of the country. The district level is divided in 114 health districts with over 2000 primary care health facilities, serving a population of 10,000 people each (52,53). Like in DRC, CHW play an important role in delivering preventive, promotive and curative services at community level (54–56). The main causes of mortality are diarrheal diseases and stroke, followed by LRTI. Further, tuberculosis, malaria, and malnutrition rank under the top 10 causes of death (57).

1.2.3 Health system funding

DRC and Madagascar are amongst the 32 lower income countries (LIC) with the most severe health- financing constraints on a global scale. They rank under the four least well-funded HS. In 2018, their total and domestic health spending per capita was at the bottom of the LIC according to the WHO (Fig 5) (58). Data from the World Bank (WB) in 2020 show DRC at fourth lowest (21,25 USD per capita) and Madagascar’s health expenditure at second lowest (17,95 USD) position in the world (59). Both countries are committed to achieve Universal Health Coverage (UHC); however, out-of-pocket payments still account for a large proportion of household health expenditures (53,60,61).



Health spending per capita (total and domestic) and as share of GDP in lower income countries, 2018

Figure 5: Health spending LIC (WHO)(58)

1.3 Plague

1.3.1 Generalities of the plague

Plague is a zoonotic disease caused by the bacterium Yersinia pestis (Y. pestis). It is characterized by its ability to persist silently in so-called enzootic (sylvatic) cycles in the wild (Fig 15). Here, the pathogen circulates between infected rodents or other small mammals (referred to as hosts) and fleas feeding on them (referred to as flea- or arthropod vectors) in the rodent burrows. During epizootics, the bacterium is transmitted from the primary wild host, generally resistant to Y. pestis, to amplifying secondary hosts (wild or semi- domestic) via infected flea bites. At this point, commensal rodents, domestic animals, and humans are at greatest risk of infection via contact with the intermediate hosts´ fleas (62–64). The potential host range of Y. pestis includes an estimated 350 mammals, out of these around 270 rodent species (12,65,66). The number of flea species listed in the context of plague is similarly impressive: almost 300 have been detected to carry Y. pestis, among these, between 30 and 80 species are considered plague vectors (62,65,67,68). The role of body lice and amoeba in plague transmission is still controversial (65,67).

Plague has the property to adapt to various ecological conditions (69,70). Frequently encountered characteristics of natural plague foci are rural areas, with a semi- arid or arid climate or low humidity type forest, at higher altitude compared to the rest of the country (67,71).

There are three main clinical presentations: bubonic (BP), septicemic (SP), and pneumonic plague (PP). Endemic regions are characterized by recurrent small BP outbreaks, often following a seasonal pattern. After an incubation period of 2-6 days, fever and malaise appear together with the characteristic painful lymph node swellings, the buboes. Left untreated, the mortality of BP ranges between 40-70%. The septicemic form is usually secondary to BP but can also occur without obvious buboes. PP develops either secondary from hematogenous spread to the lungs, or primary via droplet transmission from person to person. Both presentations have a high mortality, with PP representing the most lethal, fulminant form. If treatment is not initiated within 18-48 hours from the onset of symptoms, it is almost always fatal (72–75). Y. pestis can also be acquired via oral (consumption of raw or poorly cooked meat) and most likely via transcutaneous contamination (e.g. carcass skinning, post- mortem body contact during traditional funerals)(44,67,72,76).

A range of effective antibiotics are known today, however, the validation and modernization of current treatment protocols, especially for PP, is overdue (62,77). The gold standard for plague diagnostics is the bacterial culture from either bubo aspirates, blood cultures, or sputum. Rapid Diagnostic Tests (RDT) for Point of Care (POC) diagnostics have been developed in 2003 (78). Their sensitivity and specificity is currently subject to debate, suspecting a particularly low performance during PP outbreaks (79,80).

1.3.2 Plague on a global scale

Whilst Europe is free of plague today, natural plague foci persist in Asia, the Americas, and Africa (12,81). Plague has been classified as a re- emerging infectious disease due to an increase in human case numbers and geographical appearance during the 1990s (73,82). Over the last decades, a shift towards the African continent has been noted. Today, 97% of all declared human plague cases are reported from African countries. On the world map below, colors represent human plague cases reported to the WHO between 2000 and 2018 (Fig 6) (67). DRC and Madagascar clearly stand out as the most affected countries (67,71,83).

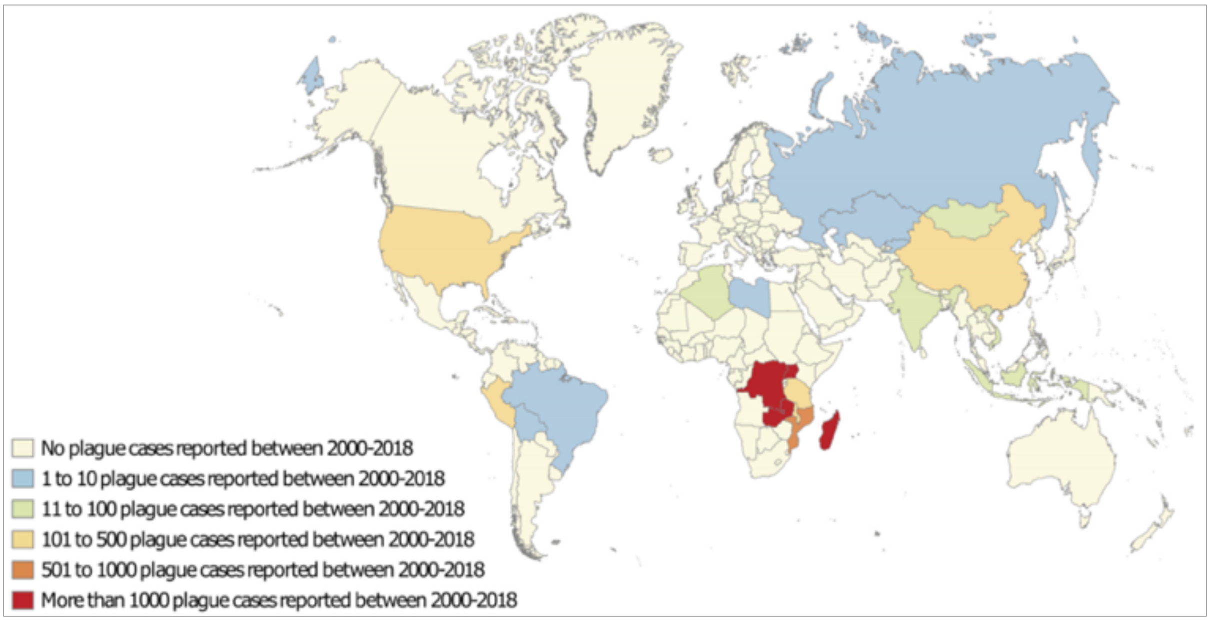
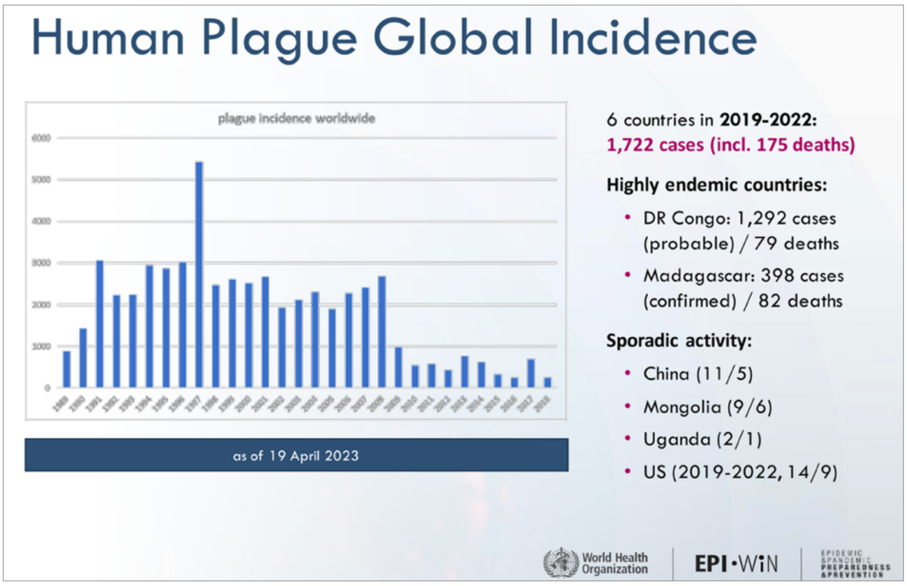


Figure 6: World map of plague cases reported to the WHO in the 21st century (67)

Figure 7 illustrates the global incidence over the last decades. Between 2019 and 2022, 1722 cases were counted (probable or confirmed), including 175 deaths. Sporadic activities have been reported from a few other countries. DRC and Madagascar however are considered highly endemic (84). Similar results have been published between 2010 and 2018 (85,86).


Human Plague Global Incidence

6 countries in **2019-2022:**
1,722 cases (incl. 175 deaths)

Highly endemic countries:

- DR Congo: 1,292 cases (probable) / 79 deaths
- Madagascar: 398 cases (confirmed) / 82 deaths

Sporadic activity:

- China (11/5)
- Mongolia (9/6)
- Uganda (2/1)
- US (2019-2022, 14/9)

Figure 7: Human plague global incidence 2019-2022 (WHO)(84)

Human plague cases occurring outside endemic areas, and suspected or confirmed cases of PP, are immediately notifiable under the WHO International Health Regulations (IHR)(2005) (67,73).

1.3.3 Plague in DRC

Plague was first reported in 1928 in the Ituri region, a high plateau situated in the northeast of the Orientale Province (OP). A second focus appeared shortly after in what is North Kivu today but has been silent since. In Ituri, sporadic cases happen throughout the year, making it one of the most active plague foci worldwide. Most cases are reported from the northeastern highlands, characterized by a cool mountain climate. Because of the vicinity to the equator, there is no strong seasonality. The area shares borders with the plague- endemic West Nile Region of Uganda, and South Sudan (71,87). In 2005 and 2006, PP outbreaks emerged in new locations of the OP, in mining camps in Bas- respective Haut- Uele (88). Different flea vectors (Xenopsylla cheopis= X. cheopis, and other species) and different hosts have been described for DRC: commensal rodents like Rattus rattus (R. rattus), Mastomys natalensis (M. natalensis), and Mus minutoides (M. minutoides), and the wild Nile rat (62,67,87). The role of the human flea (Pulex irritans) is not yet clarified (83,89). Systematic rodent and vector control programs collapsed progressively since the 1950s (83). Systematic epidemiological surveillance in the plague- endemic regions is impossible due to political instability and the extreme fragility of the HS (85). Health actors in the region report consistently that peripheral surveillance systems in eastern DRC are either dysfunctional or non- existent (90–93). Equally, testing for antimicrobial resistance of Y. pestis strains is not generally performed (85).

1.3.4 Plague in Madagascar

Plague arrived in the port city of Toamasina in 1898. From there, it spread to the central and northern highlands where it is now endemic above an altitude of 800 meters. Following a strong seasonality, the months with the highest incidence coincide with those with the highest temperatures and rainfall (October- March)(44,94). In 2017, a predominantly urban PP outbreak of unprecedented size grasped the attention of the International Health community.

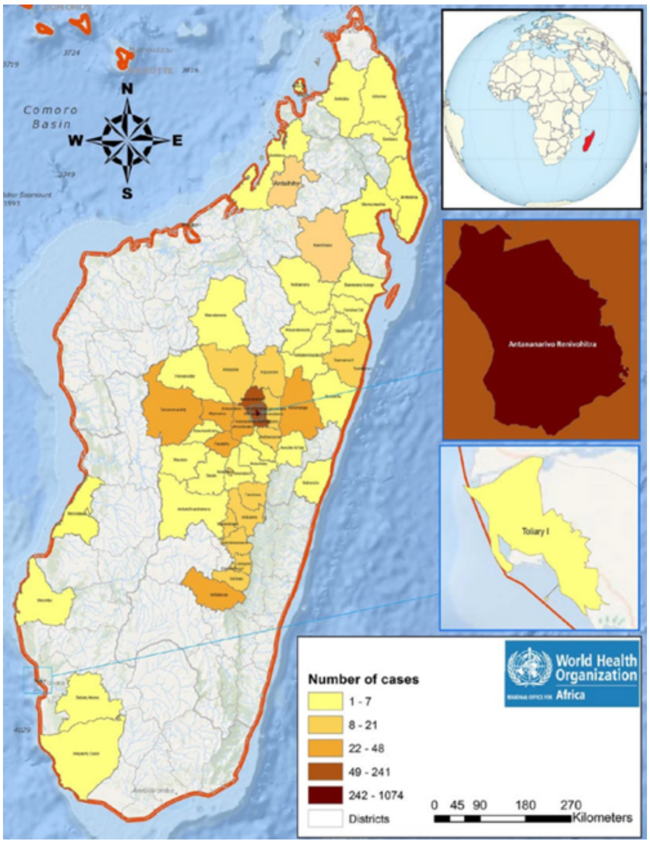
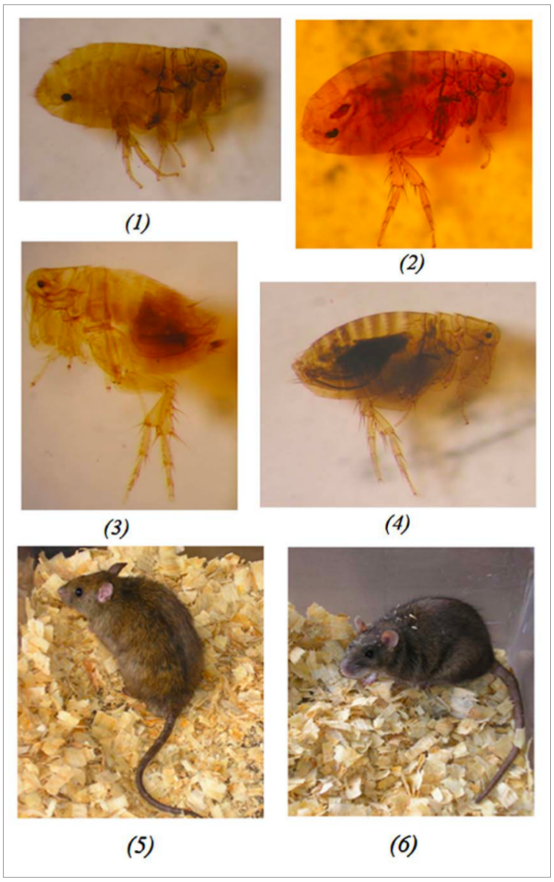


Figure 8: Geographical distribution of plague cases in 2017 (95)

It resulted in 2417 cases (498 confirmed, 793 probable and 1126 suspected) and 209 deaths (Fig 8)(95,96). One of its outstanding features was the early onset in August (97). Although in this case the index patient had been traveling from the central highlands, plague cases outside the endemic foci and at lower altitudes have been reported (98–100).



Box 1

1) Synopsyllus fonquerniei female
2) Xenopsylla cheopis female
3) Synopsyllus fonquerniei male
4) Xenopsylla cheopis male
5) Rattus rattus
6) Rattus norvegicus

Figure 9: Main vectors and rodent reservoirs in Madagascar (44)

The main hosts are the black rat (R. rattus) in rural areas (domestic and sylvatic cycle), and the brown rat (R. norvegicus) in urban areas. The Asian house shrew Suncus murinus was involved in plague re-emergence in a harbor city (44,100). Two main flea vectors are known, the endemic flea Synopsyllus fonquerniei (S. fonquerniei), encountered only at altitudes above 800 meters, and mainly on outdoor rodents, and the introduced flea species X. cheopis which is predominantly found on indoor rodents at lower altitudes (Fig 9, Box 1)(44,101).

Systematic vector and rodent control programs have been discontinued in the past due to financial shortages (44,98). Human surveillance however has a long tradition in the country (85). The system relies on the notification of clinically suspect cases (96,98). No other systematic surveillance program, e.g. animal- based, is currently in place (102–104). Madagascar is confronted with an increasing flea resistance towards multiple insecticides (102,105,106). Further, R. rattus is increasingly resistant towards plague which can add to its distribution (44,62). Observations of antimicrobial resistant (AMR) strains of Y. pestis have repeatedly been reported from the island, evidently transmittable during PP outbreaks (44,107).

1.4 Key risks from CC and ecosystem disruption

The interconnectedness of global warming, environmental degradation and biodiversity loss, and human health becomes more and more evident, as reflected by the declaration of a "triple planetary crisis" (108–110). A particular health impact is projected for climate- sensitive infectious diseases, namely zoonotic diseases (15,111–113). In 2022, a Fact Sheet Africa was published by the 6th Intergovernmental Panel on CC (IPCC) (114). As key risks of CC it points out the negative effects on ecosystems and biodiversity, crops and livestock, and morbidity and mortality from heat and infectious diseases. All risks are expected to complete the transition to "high risk" before reaching a global warming of 2°C (1,09°C were reached in 2020) (Fig 10).

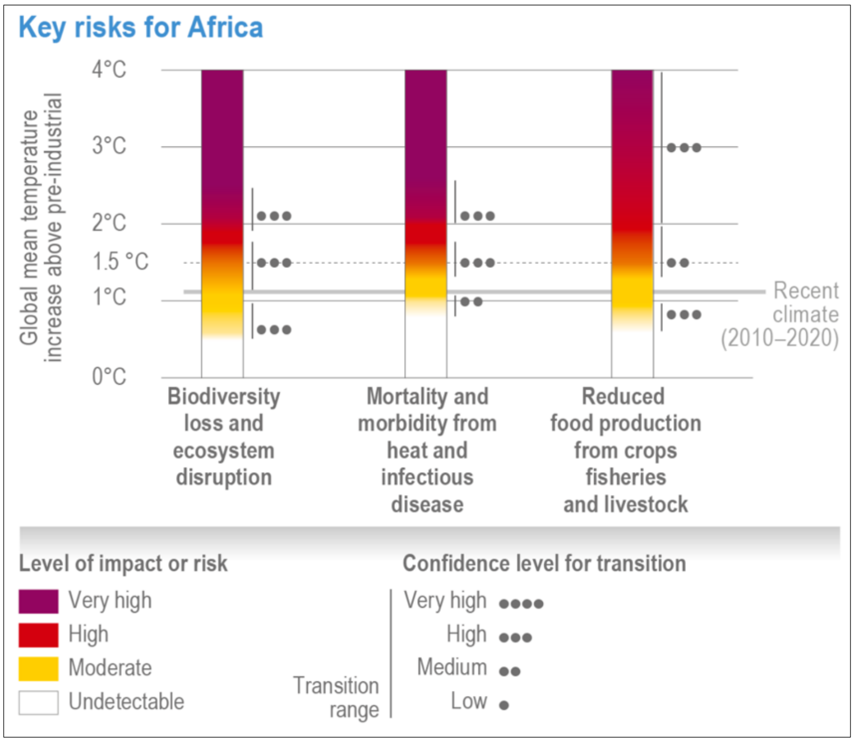


Figure 10: CC key risks in Africa in relation to global temperature increase (114)

DRC and Madagascar are particularly susceptible to these changes. Both range amongst the countries with the highest climate vulnerability, yet the lowest ability to cope with its negative effects (29). According to the Notre Dame Global Adaptation Initiative (ND-GAIN), ranking a country's susceptibility to climate- related hazards in relation to its capability to improve resilience, Madagascar positions under the last 15 countries out of 185, DRC under the last five (115,116). Deforestation and unsustainable agriculture represent an increasing problem for ecosystems and wildlife integrity (24,41,117–119). Weather extremes and environmental degradation are further expected to increase socio- economic adversities. The agricultural sector respective small- scale farming is highly susceptible to CC. Crop failure and negative impacts on livestock and infrastructure have devastating consequences for peoples´ livelihoods, exacerbating poverty conditions (29,120,121). In combination with factors like human population density and poor sanitation, climate and ecosystem changes increase the risk for malnutrition, vulnerability towards infectious diseases, and poor health (62,108,117).

1.5 One Health

Dating back several centuries in its origins, the understanding of the deep interconnectedness of human, animal, and environmental health lead to the foundation of the “One Health”(OH) initiative in 2004 (122–125). As a global strategy, it fosters a holistic, multidisciplinary, multisectoral approach integrating human and veterinary medicine and ecosystem health. Recognizing the complex interdependence between anthropogenic pressure on natural habitats, impoverishment, and the (re-) emergence of zoonotic diseases, advocates of the concept promote urgent OH strategy adaptation by politicians and governments including the strengthening of health systems, community participation, and disease surveillance (104,122,126–128).

In 2010, the Food and Agriculture Organization of the UN (FAO), the World Organization for Animal Health (WOAH), and the WHO launched a formal OH alliance, the tripartite collaboration, united by the vision to prevent, detect, and respond to “animal and public health risks attributable to zoonoses (…) with an impact on food security” (129,130). In 2021, the three organizations called on the UN Environment Programme (UNEP) to join in, acknowledging “the highest level of urgency and complexities surrounding OH” (131). By creating an interdisciplinary OH High-Level Expert Panel (OHHLEP), they now form the Quadripartite Alliance OH (FAO-WOAH-WHO-UNEP)(10,113,131). Their Joint Plan of Action (JPA) 2022-2026 aims to help achieve the SDGs in alignment with the 2030 Agenda (130). Figure 11 illustrates the interrelation between climate, environmental and biodiversity changes, and health security in line with OH. The “prevent”, “detect” and “respond” boxes indicate key points for interventions to reduce and mitigate the risk from infectious diseases (108).

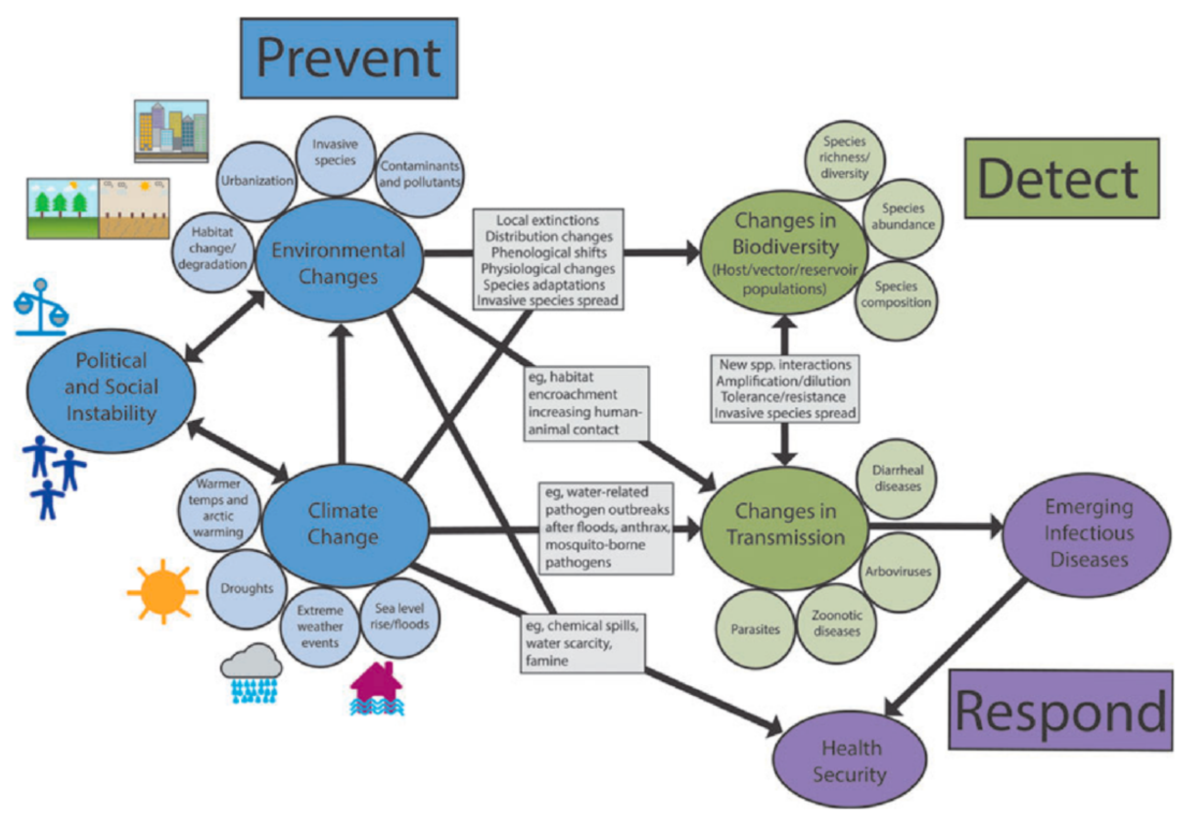


Figure 11: Interrelation of climate and environmental changes, biodiversity, and health (108)

1.6 (Re-) Emerging infectious diseases and the 2030 SDG- Agenda

Emerging and re- emerging infectious diseases (EID) and neglected tropical diseases (NTD) share essential health determining factors of underserved populations, e.g., limited access to health care, clean water, and hygiene. A wide range of SDG, running "through the heart of the problem of poverty, sanitation, education, hunger, health of the planet, (…) and health of the people", need to be addressed if EID are to be combated effectively (Fig 12) (126). Many scientists advocate for an OH approach in this context (126,127,132–135).

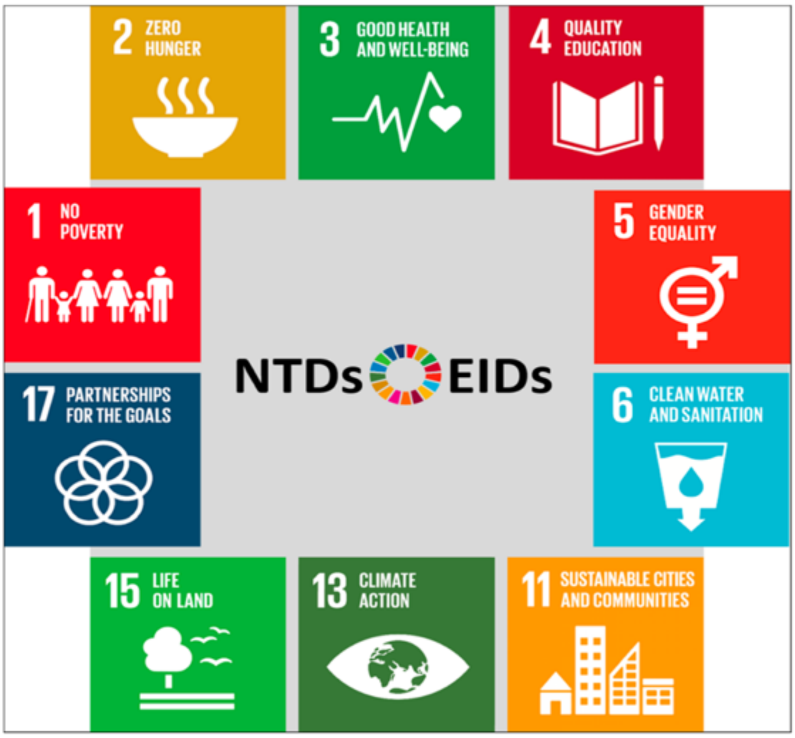


Fig 12: Key SDGs in combating EIDs (126)

Despite an increasing commitment across the globe, the implementation of OH in practice remains challenging (133). DRC and Madagascar are both part of the African Union OH Coordination Group (136). DRC is part of the Africa OH University Network, AFROHUN, formerly OH Central and Eastern Africa (OHCEA) (137,138). DRC has hosted a longitudinal U.S. Agency for International Development (USAID) Emerging Pandemic Threats Program PREDICT project ("One Health in action" 2009-2020) focusing on zoonosis associated with bushmeat consumption, bats, and viral diseases, and fostering innovative surveillance activities e.g., in North and South Kivu (139,140). According to the latest Global Health Security (GHS) Index Country Score Justification Summary, Madagascar is part of an OH network, however this is only accessible in French (141). Both countries lack a comprehensive OH strategic plan at national level, unlike many neighboring countries (142–148). A detailed analyses of each countries´ institutional preparedness regarding zoonotic diseases can be found here: (141,149).

Chapter 2 Problem Statement, Justification, Methods

2.1 Problem Statement

Plague was not a major global health threat for many years. The few annually reported cases were supposedly restricted to far off rural settings. During the urban PP outbreak in Madagascar in 2017 however, when the risk for a large, even international spread seemed real for some hectic weeks, the perception of the “old time disease” changed (85,96,97). The outstanding characteristics of this outbreak were, in addition to its early onset in August, its appearance in the capital city, home to an international airport, and the high numbers of PP cases. Thanks to the experts from the national Institut Pasteur and a broad international response, the outbreak was contained after two months, but not without having caused major panic and social disruption (96,150–152). Worryingly, it had taken more than two weeks to identify the first plague case. Until then, disease transmission from the index patient, deceased in a crowded bush taxi, and his fellow travelers had gone unnoticed by officials (97).

The progression from the bubonic to the pneumonic form is considered a reflection of the health care quality in a country (85,98,153). Remarkably, the two countries with the highest endemicity of plague worldwide are among the four countries with the lowest global health expenditure. Both countries remain with “major challenges” in achieving SDG 3 (“Good health and wellbeing”) according to the current Sustainable Development Report (154). Lack of access to healthcare facilities, weak logistics, and inadequate service provision often hinder an appropriate disease management (55,104,153,155). In both DRC and Madagascar, the only laboratory able to confirm the plague diagnosis is situated in the capital, while RDT are often lacking at the POC (55,156–158). True case numbers are likely to be underestimated under such circumstances (53,94,104,153). In eastern DRC, the situation is particularly bad. After decades of political instability, armed conflict, and displacement, millions of people face a humanitarian crisis (159,160). In Madagascar, human surveillance strategies are in place, but an increasing insecticide resistance and the detection of resistant Y. pestis strains are reason for concern (44,106,107). Both countries` epidemic preparedness at national level has been rated very low (161,162).

2.2 Justification

The impact of climatic variables on plague has long been known and is even considered a relevant driver for the three major historical pandemics (64,163). Evidently, all plague cycle components (host, vector, and pathogen) are climate- dependent. Temperature, precipitation, and humidity levels play an essential role for flea and rodent survival and their population dynamics (63,101). However, much is still unknown about their multifactorial and complex interactions, especially given the changing weather in the 21st century. Together with increasing pressure on natural habitats through land use change, deforestation, and continuous population growth, zoonotic disease dynamics have become unpredictable. The alteration of natural ecosystems and biodiversity leads to new patterns of interaction between wildlife, domestic animals, and humans. Many researchers predict an increased risk for cross-species pathogen transmission with unforeseeable consequences (15,43,68,164,165). It is expected that “over the next century, the combined effect of climate change, land degradation and transformation, and increasing human- wildlife contact will bring about a massive increase in the spillover of pathogens that originate in wildlife and the burden of infections transmitted by arthropods”(166). In DRC and Madagascar, temperature and rainfall patterns have already started to shift, and extreme weather events are on the rise (29,43). However, despite the precarious health care situation in both countries, and multiple uncertainties regarding the force of future outbreak scenarios (e.g., questionable adequacy of surveillance and diagnostic measures, threatening antibiotic and insecticide resistance, genetic variations), publications about the impact of CC and ecosystem degradation on plague in DRC and Madagascar are scarce. “In the context of public health and wildlife conservation, we need an improved understanding of the mechanisms underlying the association between plague outbreaks and climate.” underscored some of the worlds´ leading plague experts back in 2011 (63). Arguably, we need it most for the world`s most affected countries.

2.3 Objectives

2.3.1 Main Objective

To explore the impact of CC and increasing pressure on ecosystems on plague dynamics, focusing on DRC and Madagascar. The findings shall help prioritizing interventions and research projects in line with OH in both countries.

2.3.2 Subobjectives

I: To explain how climate and land use change affect plague dynamics.
II: To investigate the interconnectedness with other potential drivers in this context, applying an OH approach.
III: To present future climate change projections for DRC and Madagascar.
IV: To discuss the resulting implications for the plague risk in both countries.
V: To provide recommendations to the governments of DRC and Madagascar for priority areas of interventions and research to tackle plague in the light of climate and land use change.

2.4 Methods and analytical framework

To address the objectives of this thesis, a literature review was conducted structuring the obtained information in a systematic way by using an analytical framework. First, the OH framework by Valles et al. was chosen, reflecting current research priorities in the field of plague as recently defined by an international expert panel (Fig 13)(62). It unfolds the complex interdependence of behavioral, socio-economic, ecological, and biological determinants of plague at micro- and macrolevel, pointing out public health and research priorities. It served as a base for a large proportion of the preliminary literature search. After realizing that its scope was too broad for this thesis, the focus was narrowed down to the subheadings “climatic changes” and “environmental”.

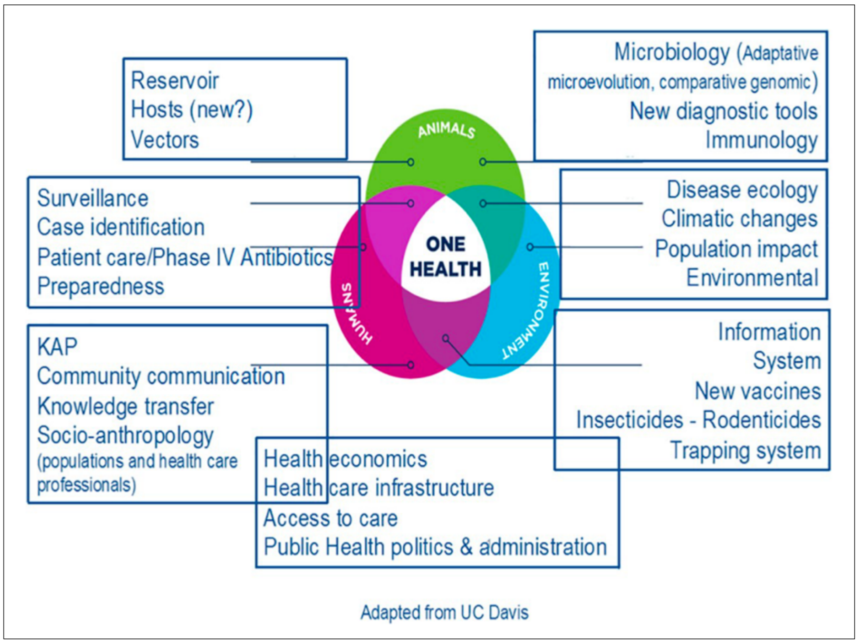


Figure 13: OH and plague framework (62)

Applying this focus, an enhanced analytical OH framework was identified, proposed by Gibb et al. It was published in the article "Ecosystem perspectives are needed to manage zoonotic risks in a changing climate" (2020), and was subsequently used to structure the results section (Fig 14)(4).

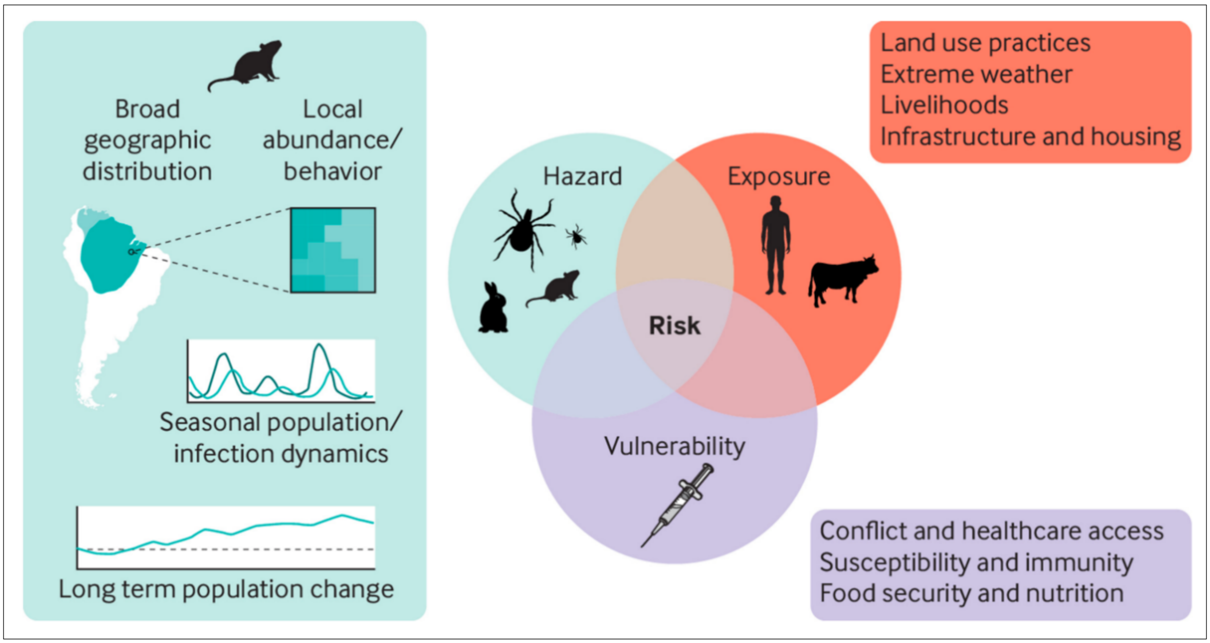


Figure 14: Framework illustrating the interconnectedness of zoonotic diseases and socioecological challenges (4)

The utility of this framework lies in its integration of climate and environmental changes, socioecological processes, and zoonotic infectious disease dynamics. It is based on the recognition that the individual disease risk depends on the level of exposure to the zoonotic hazard, and the vulnerability towards infection. Exposure and vulnerability are defined as the "determinants of risk" (167). Whether the hazard becomes a "realized risk" depends, according to the framework, on socioecological determinants. They themselves are subject to change.

The framework thus pays thus tribute to the impact of climate and ecosystem degradation on the zoonotic components, socioecological processes, and their interaction. It is based on the understanding that the described changes will often intersect with and aggravate each other, leading to an increased risk for spillover events (4).

The framework is divided into three domains, merging into the realized risk of infection. The first (green) domain represents the zoonotic hazard (associated with potential disease spillover). Its subdomains refer to the geographical distribution, local abundance, seasonal, and long- term dynamics of the reservoir hosts, vectors, and pathogen. The second (red) domain stands for the risk of exposure towards the disease, with subdomains listing land use practices, extreme weather, livelihoods, infrastructure, and housing. The third (purple) domain (vulnerability towards the disease) is represented by these subdomains: conflict and health care access, susceptibility and immunity, food security and nutrition. The overarching impact from climate and land use change is not visible but described in the article ("effects of global environmental change").

In the results section, the findings of the literature search have been structured along these three domains. "Vulnerability" was converted into "vulnerability hotspots". One subheading got excluded: "susceptibility and immunity". The inclusion of medical respective immunological aspects would have gone beyond the scope of this review. A subchapter on climate projections for DRC and Madagascar was added in accordance with the subobjectives of the thesis.

2.5 Selection and search strategy

Peer- reviewed articles and studies, documents, reports, and grey literature were used as sources of information about plague and its drivers in a changing world. Articles were selected based on their information content regarding the objectives of the thesis. The focus was on articles referring to DRC and Madagascar. However, data from other countries was included along the criteria described below. The websites of international organizations like WHO, WB, FAO, UN Office for the Coordination of Humanitarian Affairs (OCHA), the German Federal Ministry for Economic Cooperation and Development (BMZ) and others were accessed to review policies, factsheets, guidelines, etc. For the literature search, the online academic databases of the Vrije Universiteit (VU) Library were used including PubMed, as well as Google scholar as search engine. The snowballing technique was applied screening for relevant articles. Inclusion criteria: only documents published in English between 2003 and 2023 were included (with one exception: Parmenter et al. from 1999). The emphasis was on recent ones. The geographic scope was limited to studies from Africa and North America (NA) since climate-related plague studies from NA are available in large quantities. Including studies from other continents would have gone beyond the scope of feasibility (exception: mentioning of plague in history, chapter 3.1.1).
Key search terms: Plague, Yersinia pestis, Democratic Republic of Congo, DRC, Madagascar, climate change, land use change, ecosystem degradation, biodiversity, One Health.

2.6 Exclusion Criteria

Articles published in other languages than English were excluded. The literature search was limited to 20 years, so publications older than 20 years were excluded. Scientific studies from other countries or continents than Africa, Madagascar, or NA were excluded.

Chapter 3 Results

3.1 The hazard in the context of climate and land use change

3.1.1 Ambient temperature, humidity, and precipitation

Fleas are ectothermic (“cold-blooded”), and the survival especially of the early flea stages depends largely on temperature, humidity, soil moisture, and thus rainfall (166,168). The development of the immature stages happens “off- host” in rodent burrows. The conditions there, referred to as “microclimate”, are influenced by the outside temperature, soil characteristics, and precipitation, as illustrated in Figure 15 (63,101).

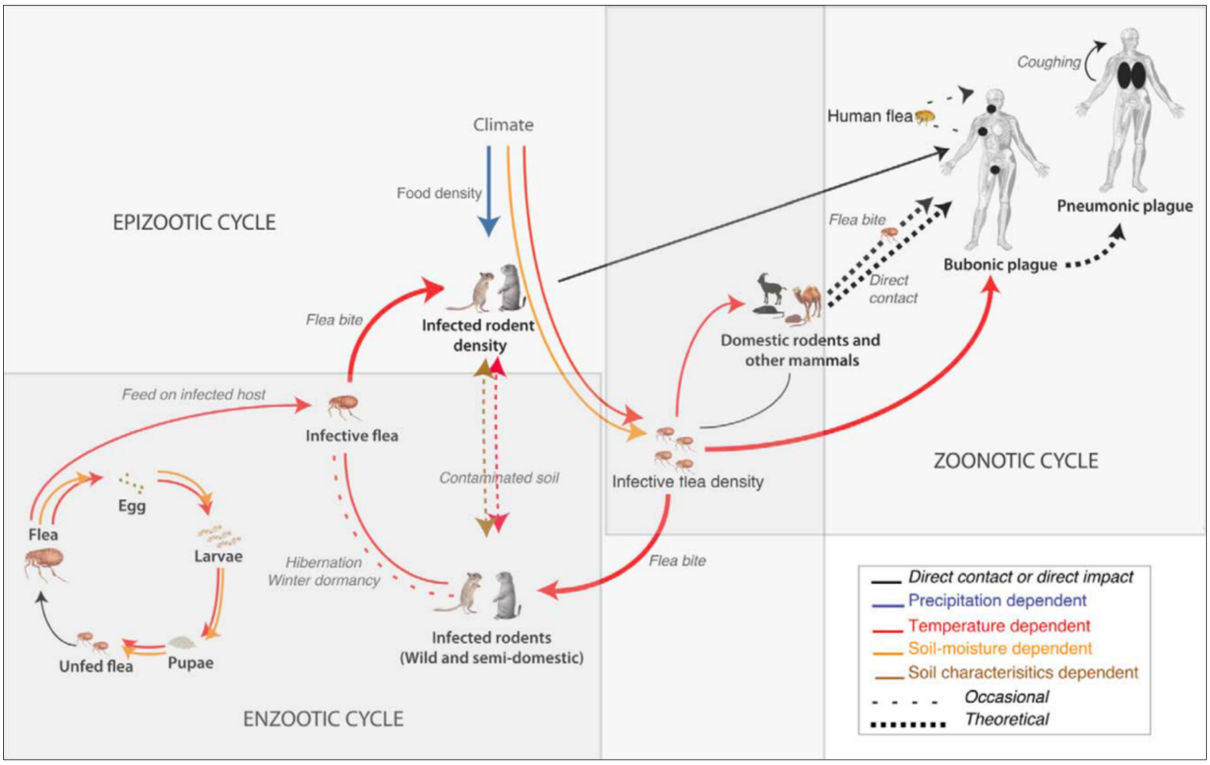


Figure 15: Different plague cycles and the impact of climate (63)

As a rule, “warmer is better“ for arthropod vectors. Flea development rates and abundance increase with warm-moist weather (68,169). Wetter- than- usual weather has been associated with historic plague spread in China (170). Even the Black Death period (1280- 1350) and the mid- nineteenth` century Third Pandemic, both believed to have originated from Central Asia, could be linked with unusually wet and warm climatic conditions (163,168). However, temperatures above (or below) a certain threshold hinder flea survival as well as disease transmission (63,168). Corresponding observations have been made for plague dynamics, often with a seasonal pattern. Historical data from different continents have shown a clear correlation of temperature and rainfall with plague outbreaks. Notably, case numbers were found to increase with rising temperatures, with a favorable temperature of 24- 27°C reported during plague outbreaks. At temperatures of 29 - 32°C, epidemics came to an end (63,168). An additional explanation is found in the foregut of adult fleas. After being ingested by the flea, Y. pestis forms a biofilm that increases blood regurgitation from the midgut and consequently disease transmission through the bite site (171–173). However, this biofilm seems to break down when temperatures rise above 27-28°C (168,174).

Kreppel and her team (2016) examined the susceptibility of immature stages of Madagascar's two main flea vectors to temperature and humidity (101). At an altitude above 800 m, both flea vectors are encountered on the island. However, the presence of the endemic flea species, S. fonquerniei, is seemingly restricted to these elevations. This study was the first to investigate the endemic flea under experimental conditions. The temperatures during the experiments ranged from 18°- 32°C, mimicking those recorded in rat burrows.

Their main findings:

- significant differences between the species were found for development time and time to death: S. fonquerniei succumbed faster under adverse conditions (higher temperatures and lower humidity).
- S. fonquerniei expressed a lower thermal developmental threshold (9°C versus 12,5°C for X. cheopis).
- a higher relative humidity had a protective effect for both species.

The authors concluded that the endemic flea is better adapted to the cooler highlands, and sensitive to higher temperatures. Future warming could lead to reduced suitability for the endemic flea, thus decreasing plague prevalence in Madagascar. However, they also considered the possibility of warmer regions becoming more suitable for X. cheopis. This concern was shared by the authors of a recent USAID report: they consider a shift of the introduced species to higher altitudes (9). No comparable study has been identified for the DRC context.

3.1.2 Climate phenomena, weather patterns, geographical features

Because rodents are homeothermic, their immediate response to ambient temperature changes is less pronounced (175). Nevertheless, rodent population dynamics and subsequent disease transmission are also influenced by climate variables (Fig 15)(63). Parmenter et al. found a positive association between increased winter- spring precipitation and human plague cases in New Mexico. In 1999, they introduced the Trophic Cascade Model (TCM), hypothesizing a relation between precipitation patterns, increasing vegetation growth/food density, and time-lagged rodent abundance (176). Supporting evidence has been published since, mainly referring to the NA context (166,170,177–179).

Studies on plague dynamics at larger spatial scale originate predominantly from the US where plague circulates widely amongst local rodents, and extensive routine surveillance data exist (166,177,180–182). For the context of DRC and Madagascar, comparable studies are scarce. For DRC, no publication specifically addressing the relation between climate and plague dynamics has been identified. However, one Congolese study relating ecological features, including altitude and weather patterns, to plague outbreaks was found, as well as publications from neighboring countries and Africa as a whole (70,83,183–187). Two studies from Madagascar investigate the impact of large- scale climate phenomena (LSCP) (see below) respective temperature and precipitation on plague patterns on the island (94,188).

LSCP in the context of plague

Plague outbreaks have been associated with LSCP like the El Niño Southern Oscillation (ENSO), the Pacific Decadal Oscillation (PDO), and the Indian Ocean Dipole (IOD) (15,63,82,94,180,188–190). The ENSO is an ocean- atmospheric periodic variation in winds and sea surface temperatures in the equatorial Pacific Ocean that returns in irregular intervals of 2-5 (2-7) years and lasts for 9-24 months (94). As a global climate driver, ENSO is responsible for worldwide shifts in precipitation, temperature, and extreme weather events, like floods and droughts

(190). The PDO´s spatial pattern resembles those of the ENSO but has a decadal time- scale (periods of 20-30 years)(180,191). The IOD affects surface temperature on the Indian Ocean and thus the climate in Madagascar (94). LSCP are subject to continuous alterations themselves due to ongoing anthropogenic pressure, and will become less and less predictable (191,192).
In the following section, the above cited and a few more studies are presented in chronological order, focusing on the projected impact on plague dynamics (Table 1).

Study findings in the context of climate, weather, and geographical features

Nakazawa et al. (2007) analyzed national surveillance data for human plague cases in NA from 1965-1999 using a combination of geographic information system and ecological niche modeling (ENM)(181). Their results indicate a subtle future northward shift of human cases in accordance with the observed warming climate trends. (The exact temperature ranges are not made explicit in the text.)

Ari et al. (2008) analyzed a time series of human plague cases in the western US from 1950-2005 (177). Integrating LSCP, they concluded that increasing numbers of very hot days (defined as above 37°C) will have a strong negative impact on plague occurrence. Milder temperatures and above- normal precipitation stimulated plague outbreaks.

In 2008, Neerinckx and colleagues performed an ENM for Sub- Saharan Africa (70). The aim was to identify general distribution patterns and ecological requirements of plague, allowing the prediction of newly suitable biotopes. Looking at human plague data from 1970-2007, they found the potential for a broad geographic distribution in Africa under a large variety of conditions: “from dry lowlands to wet highlands”. The most relevant factors identified were elevation, evapotranspiration, temperature ranges, annual rainfall, and vegetation greenness at specific points in time. CC impacts were not specifically addressed in this study. The highest suitability was predicted for regions in the center and south of the continent, including areas where plague has never been reported, e.g., the Central African Republic and Nigeria. On the other hand, deserts, and very wet regions, like the Congo Basin in DRC, were predicted as unsuitable. The authors emphasized that an underestimation of the geographical distribution of plague reservoirs is likely with many foci still being unknown.

Using an elaborate, climate- driven simulation, Snäll et al. (2009) predicted lower levels of plague among black- tailed prairie dogs in NA (193). Notably, the plague probability in their model decreased in accordance with the projected increase in temperature. The explanation provided was the negative effect of heat on fleas (hot days defined as above 35°C). Again, precipitation was associated with a positive influence on rodent abundance and plague.

A study by Holt et al. (2009), modeling plague activity in ground squirrels under different future climate scenarios, projected a reduction of plague for the southern parts of California because of the negative effect of temperatures above 35°C on fleas (182). Since moderately warmer climates were found to be favorable, a subtle plague shift northwards along the coast by 2050, and to higher elevations, was predicted.

In 2010, an article about historical plague dynamics in Africa was published by Neerinckx et al. (183). Drawing their information from a large human plague database (1877- 2008), their main conclusion was the need for improved surveillance strategies. Examples for the negative impact of diminution of surveillance programs in the past were provided, for example a silent expansion of the plague focus in Ituri province, DRC. While the impact of climatic and ecological changes remained only speculative, the authors emphasized that global plague statistics would look very differently if plague occurrence was detected and reported more accurately.

Ari et al. (2010) investigated the association between ENSO, PDO, and human plague cases in the western US (180). They identified a positive correlation between plague occurrence and both LSCP. El Niño- events coinciding with positive PDO were associated with subsequent high plague counts. They also confirmed the positive correlation with precipitation in spring.

Eisen and her team (2010) presented a study located in the plague- endemic region in northwestern Uganda, neighboring the foci in OP, DRC (185). They aimed to identify fine- scale ecological features associated with disease occurrence in remote villages. Main findings were an increased plague risk at elevations above 1300 meters, and in wetter regions. A positive association was found with the reduced vegetation during the dry months, pointing towards a possible association with human behavior, e.g., agricultural practices, and rodent activities. In conclusion, the importance of ecological and environmental factors was confirmed.

Two years later, Moore et al. published results from the same region, based on local meteorological data (186). They found an increased plague risk when precipitation was increased in the months June/July just before the rainy (plague transmission) season in August, and vice versa (negative association with rainfall during the dry period in December- February). The authors assumed a mixed impact of weather patterns on flea abundance, rodent productivity, and farmers´ behavior, reflecting the complex disease dynamics.

This was partly in dissent with MacMillan et al. (2012) who sought to identify climatic factors with a predictive value for plague occurrence in the same region of Uganda (184). They found plague positively associated with rainfall during February (the driest month) and October/November when the rainy season normally ends, and with higher altitude (1300 m). A negative association was seen with precipitation in June (which is supposed to provide a short dry phase). In their analysis, an increase in rainfall was beneficial for vegetation growth and thus plague transmission, but permanent rain had a negative impact.

Kreppel et al. (2014) conducted the first study about the impact of LSCP on plague dynamics in Madagascar (94). The effects on the island weather are complex: El Niño- phases cause initially warmer and drier conditions after a time- lag of four to seven months, and cooler and wetter weather some more (8-12) months later. La Niña- phases induce opposing conditions. Positive IOD phases lead to warmer and wetter weather, with negative phases having the opposite effect. The authors analyzed data of human plague cases over a time span from 1960-2008. They were able to show a non- stationary, but strong association between ENSO events and disease dynamics, and a less pronounced association with IOD. Temperature and plague incidence could also be linked, precipitation to a lesser extent. A good example was found in the late 1990s, where the strongest El Niño- event in the time- series together with a positive IOD coincided with the largest recorded plague outbreak in Madagascar. Notably, they found evidence for time lags being an entire cycle behind (meaning plague outbreaks happening 1-2 years after an ENSO event). The coincidence of positive ENSO/IDO events with the cool dry season was found a potential risk constellation, resulting in higher numbers of plague cases.

Two years later, Giorgie et al. (2016) published a case- study looking at plague in Madagascar from 1980-2007, adding information on demographic distribution and elevation (188). They found confirmation for plague cases to occur predominantly above 800 m altitude, and again an association with temperature anomalies (not further specified).

Abedi et al. (2018) analyzed the relation between human plague cases and ecological features in northeastern DRC between 2004 and 2014 (83). They questioned data completeness and considered an under- as well as overestimation of human cases a likely limitation due to the difficult health care access and lack of laboratory confirmation. However, all plague cases could be ascribed to three distinct clusters in OP. Landscape features ranged from “equatorial forest lowlands” to “tropical mountain ecosystems”. The highest incidence was allocated in the latter, the Ituri highlands, characterized by higher elevation, lower mean temperature, and less precipitation (= cooler and drier) than other areas in OP, as well as lower vegetation growth/greenness levels. The authors concluded with a call for more proactive research in the region, e.g., investigations for genetic exchanges between rodent reservoirs in northeastern DRC and the adjacent plague focus in Uganda. Depending on security aspects, an active search in areas with plague- suitable characteristics and a history of plague was recommended, e.g., the old focus near Lake Edward, and the strengthening of local surveillance and testing facilities.

Rocke et al. (2019) conducted a plague risk study for the US Department of Defense (DoD)(194). Focusing on the western Great Planes and applying a combination of modeling techniques and field research, they examined the effects of CC on prairie dogs, ground squirrels, and their respective burrow microclimates. Taking a projected warming of up to 3,6°C into account, their models still predicted an increase in flea abundance between 450% and 540%, and a similarly high increase in burrow infestation. Their conclusion was an increasing risk for longer, and more severe, human plague outbreaks.

In 2019, Anyamba and colleagues presented the result of a collaboration of the National Aeronautical and Space Administration (NASA), the US Department of Agriculture (USDA), and the DoD (190). They had monitored diseases of public health concern during the strong ENSO 2015-2016, integrating global satellite data. Their analysis showed that above- normal rainfall was significantly associated with higher plague intensity in the southwest of the US (the region selected to investigate this possible association).

As part of a plague outbreak analysis (2021) in Ituri province addressed later in this chapter, unpublished data about epidemiological trends along the eastern border of DRC and western border of Uganda were shared (92). A northward extension of human plague incidence (red zones) between 1993 and 2020 is apparent in comparison to the historical focus (in pink, black dots indicate reported cases from Uganda)(Fig 16).

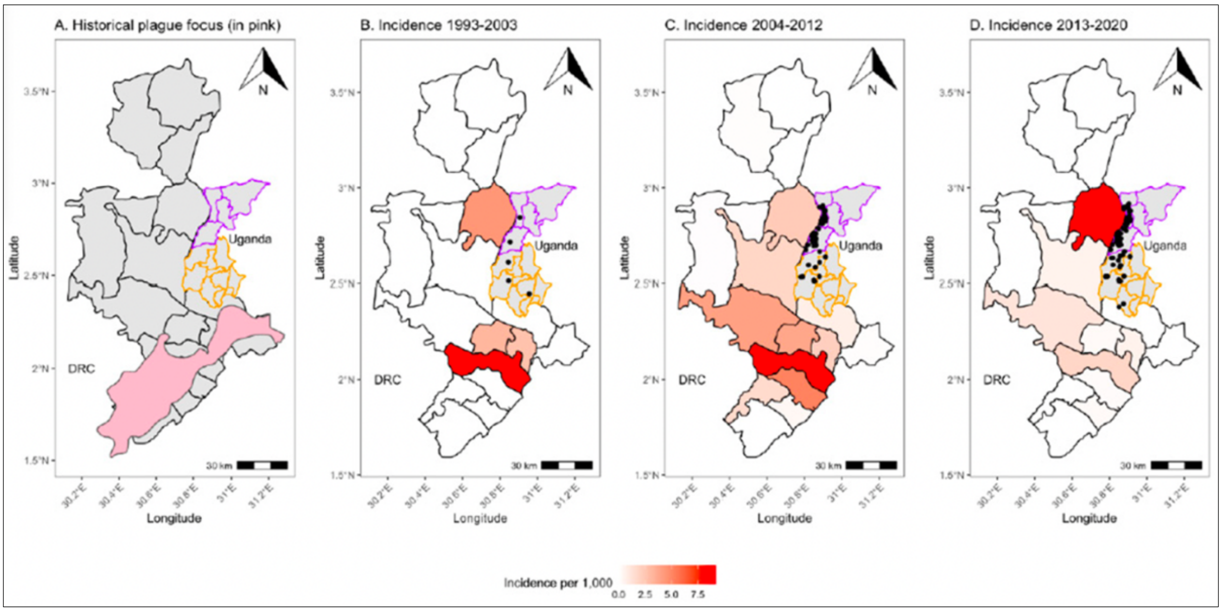


Figure 16: Extension of the Ituri plague focus over the last decades (92)

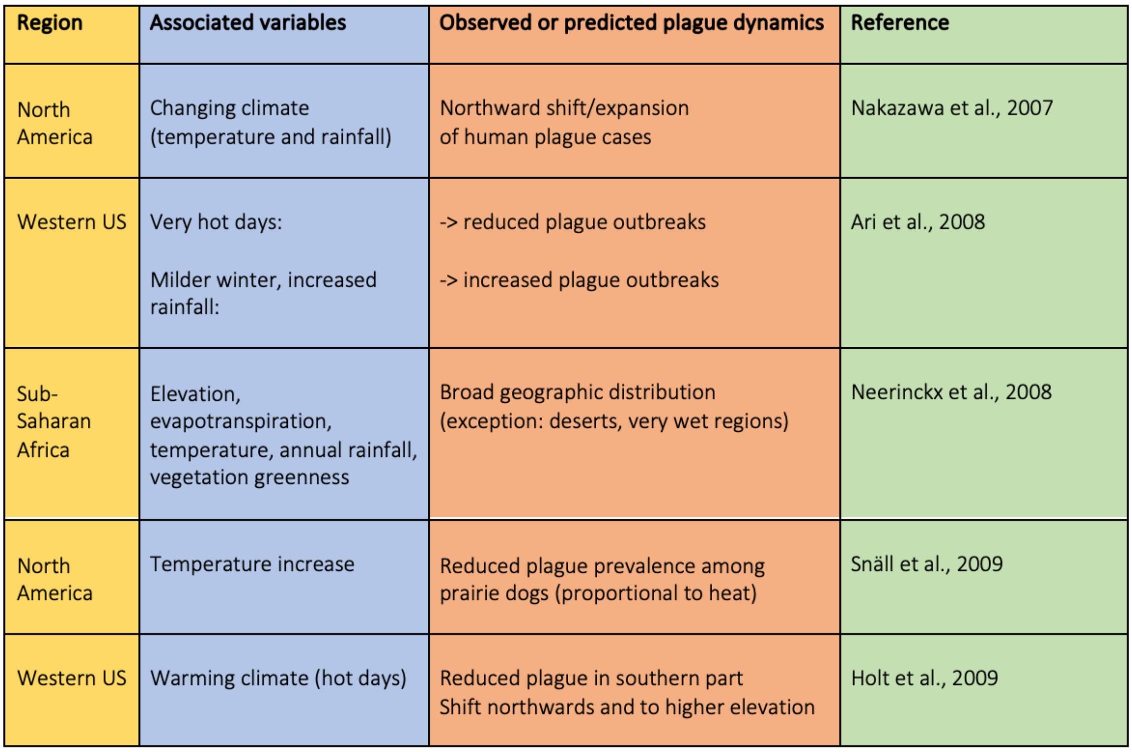
In 2021, Eisen et al. published the results of a long- term field study from western Uganda, looking at plague cases over 15 years (187). They confirmed a higher incidence at higher elevation sites, and rainfall patterns having an impact. Importantly, they emphasize the higher flea and rodent diversity at higher altitude having a positive impact on plague incidence.

These findings link together with a publication by Carlson et al. in 2022 (166). The team went back to the previously applied large data set of human plague cases from the western US. Adding wildlife and climate data to their scientific models, the time span was extended to 2017, providing information from seven decades.

Their main findings:

- Plague foci have undergone a range shift to higher elevations due to favorable climatic conditions.
- The susceptibility of rodents to form reservoirs at higher altitudes has increased by up to 40%.
- Species diversity is a particular driver for spillover events between rodents.
- A subtle increase in spillover risk for humans at mid- elevations has been noted.
- Warmer- than- normal weather (on average around 0,8°C over the last decades) resulted in higher plague prevalence in the wildlife model.
- Spillover events towards humans were higher during wet and cold years. (One possible explanation: the search of flea vectors for new hosts when rodent numbers shrink.)
- The wildlife model suggested a plague reservoir extension towards Canada and Mexico.
- In summary: climatic factors together with host biodiversity in newly suitable locations are seen as the predominant drivers of transmission and spillover.

The authors concluded that "weather conditions have changed in a way that trends favorable for plague risk". They advocate for more research under an OH approach, and the reinforcement of multinational surveillance collaboration.



Region	**Associated variables**	**Observed or predicted plague dynamics**	**Reference**
North America	Changing climate (temperature and rainfall)	Northward shift/expansion of human plague cases	Nakazawa et al., 2007
Western US	Very hot days: Milder winter, increased rainfall:	-> reduced plague outbreaks -> increased plague outbreaks	Ari et al., 2008
Sub-Saharan Africa	Elevation, evapotranspiration, temperature, annual rainfall, vegetation greenness	Broad geographic distribution (exception: deserts, very wet regions)	Neerinckx et al., 2008
North America	Temperature increase	Reduced plague prevalence among prairie dogs (proportional to heat)	Snäll et al., 2009
Western US	Warming climate (hot days)	Reduced plague in southern part Shift northwards and to higher elevation	Holt et al., 2009

Western US	ENSO, PDO Increased rainfall in spring	Increased human plague cases	Ari et al., 2010
Western Uganda	Elevation Rainfall Vegetation	Increased plague >1300 m Increased plague in wetter regions and with less vegetation during dry months	Eisen et al., 2010
Western Uganda	Temperature Rainfall	Increased plague with rain prior to rainy (plague) season (June/July) Reduced plague with rain during dry season (Dec-February)	Moore et al., 2012
Western Uganda	Elevation Rainfall	Increased plague (at 1300 m) with rain in dry season and at end of rainy season (Oct/Nov) Reduced plague with rain during short dry season	MacMillan et al.,2012
Madagascar	ENSO, IOD	Strong, time- lagged association with plague outbreaks (ENSO>IOD), especially positive ENSO/IOD coinciding with cool, dry season.	Kreppel at al., 2014
Madagascar	Temperature, rainfall, elevation	Plague prevalence > 800 m Association with rainfall patterns	Giorgie et al., 2016
DRC (Oriental Province)	Elevation Temperature, rainfall Vegetation	Highest plague incidence at higher elevations, lower mean temperature, less annual rainfall, lower vegetation greenness (compared to neighboring areas)	Abedi et al., 2018
Western US	Temperature Rainfall	Increased flea abundance, burrow infestation-> human plague cases	Rocke et al., 2019
Western US	ENSO Rainfall	Increased plague with ENSO respective increased rainfall	Anyamba et al., 2019
DRC (Oriental Province)	Epidemiological trends	Northward extension of human plague cases	Unpublished data, 2021 (CASS)
Western Uganda	Elevation Rainfall	Increased plague at higher elevations Association with rainfall patterns	Eisen et al., 2021
Western US	Elevation Temperature Rainfall	Range shift to higher elevations Warmer weather-> higher prevalence Cold years-> spillover to humans increased. Extension of reservoirs towards north and south (Canada and Mexico)	Carlson et al., 2022

Table 1: Study results chapter 3.1.2 in chronological order

3.2 Exposure in the context of climate and land use change

3.2.1 Livelihoods, housing, and infrastructure

Publications addressing living conditions and infrastructure as drivers of human plague with a focus on the African context are presented in this chapter. They illustrate plague dynamics in rural as well as urban settings, and exemplary mitigation efforts. Most of the identified articles neither refer directly to climate nor land use change or ecosystem degradation. However, since these drivers are frequently intertwingled with, respective adding to, impoverishment and conflict, as demonstrated by the Ituri outbreak analysis, they have been included in this chapter (92,195).

One frequently cited risk factor for plague transmission is living in crowded dwellings, with poor sanitation and constructions inappropriate to exclude rats (76,82,83,98,195). A study from the plague- endemic West Nile Region in Uganda (2014) provided evidence for the predominant indoor- acquisition of human plague cases (196). Contributing factors were food storage inside huts (instead of using the traditional granaries outside), waste disposal nearby, and an infrequent renewal of the thatched roofs where rats often nest. Another association was found between sleeping on ground mats (mats being more likely to be flea- infested than other bedding material) and flea bites.

The cycle of CC, conflict, impoverished living conditions, and increased plague risk was analyzed in the Ituri Province in DRC in 2021. After a cluster of PP cases had been reported, the Social Sciences Analytics Cell (CASS) conducted an outbreak analysis together with the Provincial Health Division and United Nations Children`s Fund (UNICEF)(92). The results demonstrate the complex interplay between increasingly challenging living conditions, socio- behavioral aspects, and the risk of exposure to plague. The villagers reported a “considerable reduction in agricultural production” over the last years, explained by “seasonal unpredictability”, “warmer climate”, and “land- overexploitation”. The subsequent crop failure and loss of income motivated them to store their remaining crops and animals inside their houses to avoid theft (risk of stealing was likewise exacerbated because of lower agricultural yields and conflict). This in turn promoted flea infestation. Additionally, most people lacked the financial means to purchase beds, with the consequence that especially children slept on the floor exposing them more to flea bites. Poor sanitation, unsafe burial practices, and the absence of plague surveillance as well as reliable testing facilities were identified as further aggravating factors. Interestingly, the villagers had observed a behavior change amongst rats in recent years resulting in higher numbers indoors, especially during the progressively harsh rainy seasons. An increasing contact between domestic and food- searching wild rodents was further noted.

The impact of a changing urban infrastructure on plague dynamics was observed in Antananarivo, Madagascar’s capital. Rodent surveillance back in the 1990s revealed a vast replacement of R. rattus by R. norvegicus, also referred to as “sewer rat” (44). In contrast to the tree dweller R. rattus, the latter prefers living in large sewage networks. The observed decrease in human plague cases was seen as the result of two modifications: the construction of modern buildings with concrete roofs, and the extension of urban sewage systems.

For DRC, a publication from 2006 summarized the results of an inventory of small mammals and their fleas in Kinshasa (82). The completeness of the findings was however questioned because of the characteristics of the traps used. Mus musculus, the house mouse, was the predominant host, followed by R. rattus X. cheopis and X. brasiliensis were the identified flea vectors. With suitable hosts and vectors being present, the authors expressed their concern regarding a future urban plague outbreak, even more so in the light of expanding slums with poor infrastructure and hygiene. Disease spread from the plague- endemic eastern provinces via Kisangani and the Congo River was considered a realistic risk.

3.2.2 Extreme Weather

Weather extremes and natural disasters have recurrently been associated with plague outbreaks in the literature. The link can be obvious, e.g., when extreme floodings push "masses of infested rodents" out of their underground tunnels, or more hypothetical when outbreaks occur time- lagged after an earthquake (195). Some authors even suspect a causal relation with volcanic eruptions in the past (197). Heat waves and droughts can further directly impact rodent behavior, forcing them in closer contact to human settlements in search for food and water (15). On a longer term, the drought- induced aridification of landscapes can lead to reservoir shifts. An example has been reported from West Africa, where a gerbil population expanded over a distance of 200 kilometers towards an arid zone (195).

A PP outbreak analysis from northern Madagascar (2015) illustrates how extreme weather can impede outbreak containment efforts. In a remote rural area, previously free of plague, official health personnel arrived two weeks after the death of the index case, a young boy who had travelled back from his work in a copper mine. By that time, all contact persons, including his mother, one of her daughters, and a granddaughter had died with PP symptoms. Before the arrival of the medical team, treatment had been provided by a traditional healer. More fatalities happened in neighboring villages and after related funeral ceremonies before the chain was stopped. A proper field investigation however, essential for the identification of the plague focus, was delayed until two months later: access was hindered by thunderstorms (99). In chapter 3.3., more examples referring to the impact of extreme weather events on infrastructure can be found.

3.2.3 Land use practices

Back in 2005, Duplantier and colleagues already warned about the risks of human penetration into wildlife habitat, and the potential consequences for plague reemergence (195). The following findings are based on their own field- respective forest studies in Madagascar.

In the Ikongo district in the southeast, far off the plague- endemic highlands at an altitude well below 800 meters, human plague cases had been reported after decades of silence. Tracing back the sources in the forest- surrounded village, an endemic hedgehog was found to carry Y. pestis- antibodies, as well as a black rat and several shrews from the near woods (Fig 17). Off them, an endemic flea was collected that had not been described in the context of plague transmission before. Notably, a few years earlier the villagers had expanded the settlement through deforestation activities. In the Ambositra District in the central highlands, known for its wood industry and home to an active plague focus, sample activities in agricultural as well as forest land were initiated after the detection of new genetic variants of Y. pestis in this region. The different identified Y. pestis- strains all originated from small mammals (black rats and another endemic hedgehog species) trapped in the forest. Further, the hedgehog carried one of the new genetic variants. Four wild fleas were considered possible drivers of the new strain emergence. According to the authors, the ongoing conversion of wilderness into farmland, resulting in unnatural contact between wild species and commensal rats, might have led to a newly evolved sylvatic plague cycle, originating from human settlements.

Figure 17: Endemic hedgehog species in Madagascar (lowland streaked tenrec)(198)

The impact of "intense anthropogenic pressure from growing human populations, shifting land use patterns, increasing deforestation and a changing climate" on Madagascar's biodiversity was studied by Barrett et al. (2013), investigating lemur health (43). 107 species of these iconic primates are still present on the island, one third of them being critically endangered (Fig 18) (199). Geospatial and species distribution modelling was applied to predict future distribution patterns of lemur parasitism. These were deemed relevant beyond lemur health as ectoparasites have the potential to transmit diseases, including plague. Fleas were not part of the studied ectoparasites; however, those studied had the capacity to infect R. rattus and thus to cascade disease transmission to humans via this pathway. Because of constantly shrinking biohabitats, the authors projected significant changes in distribution patterns. The predicted overall- expansion of ectoparasites was 23%, for one helminths species even 60%. The scientists further pointed out that increasing interactions among novel hosts and ectoparasites could have unforeseen consequences (43).

Figure 18: Critically endangered lemur species (Verreaux's Sifaka) in Madagascar (Photo Chien C. Lee)

McCauley et al. (2015) conducted a field study in a plague- endemic region in Northern Tanzania (200). Rodents with their fleas were sampled from two types of habitats: “agricultural” and “conserved” (= a protected ecosystem). The collected animals were tested for Y. pestis-antibodies. Seropositivity was significantly higher amongst rodents from the agricultural site. This was explained by the predominance of a different rodent vector, M. natalensis, known for its high plague seroprevalence. Associated therewith, the composition of the collected flea vectors showed distinct patterns. Those known to be highly capable to transmit plague were predominantly found at the agricultural sites. For many of the other fleas their vector competence was unknown. The authors concluded that land- use change has a significant impact on rodent communities and increases the plague risk for humans.

In a study from southwestern Madagascar (2020), arthropod ectoparasites were analyzed for their disease transmission potential in the context of changing human- domestic animal- wildlife interaction (164). Ehlers and colleagues collected fleas, ticks, and lice from domestic and wild animals. The samples were examined for different pathogen- DNA, including Y. pestis. Screening for the plague bacillus was positive in two flea species: E. gallinacea and X. cheopis (and the village rat they were found on). The first one`s vector potential for human plague is unknown, the second one is well established. The authors emphasized the peculiarity of this finding far off the usual plague foci, and at sea level.

No scientific studies investigating the role of slash- and burn- agriculture in the context of plague in DRC, Madagascar, or the African continent have been identified. One USAID publication however saw a clear association between this farming technique and the disease on the island (151). “The root cause of Madagascar’s plague burden is thought to be widespread use of slash-and-burn agriculture.” The extensive, unsustainable forest firing would force rodents to escape from the bushes, resulting in more human plague cases in the villages. A drastic impact of this farming method on natural corridors, established to protect biodiversity hotspots in Madagascar, has further been observed. It adds to the deforestation activities associated with charcoal making and gemstone mining, the latter attracting migrant workers in large numbers (201). In northeastern DRC, slash- and burn- agriculture is commonly used by displaced people in lack of more sustainable alternatives (202).

3.3 Vulnerability hotspots in the context of climate and land use change

3.3.1 Eastern DRC

In July 2023, an infographic on the situation in North Kivu, South Kivu and Ituri provinces by OCHA drew the following picture: 7,8 million people are in need of humanitarian assistance, with only a small percentage reached (203). The humanitarian access to these provinces has even deteriorated lately. Some areas in Ituri and along the border with Uganda now constitute high access constraints (in dark blue, Fig 19)(204).

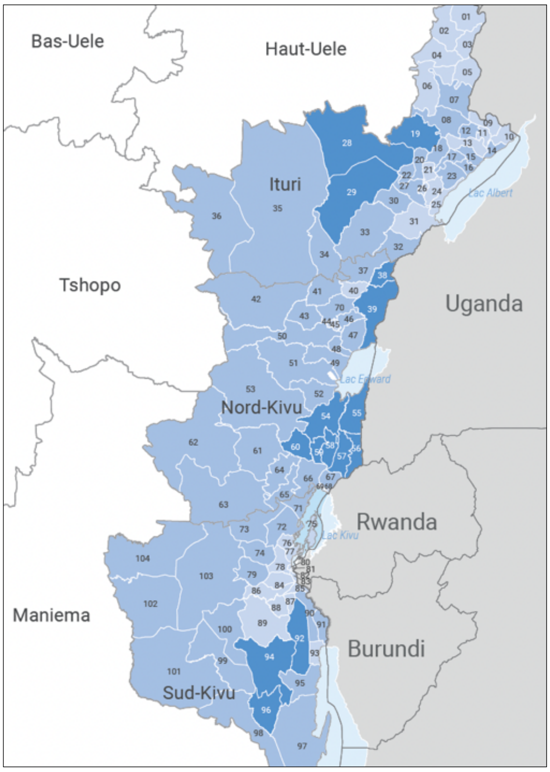


Figure 19: Map of HZ in the provinces Ituri, North and South Kivu, and respective access constraints (204)

According to the Integrated Food Security Phase Classification (IPC), large parts of the region face "crisis" and "emergency" levels of hunger (Fig 20) (203). A recent UN report warned: up to 26 million people could be threatened by acute food insecurity by the end of 2023, the highest number "anywhere in the world" (205).

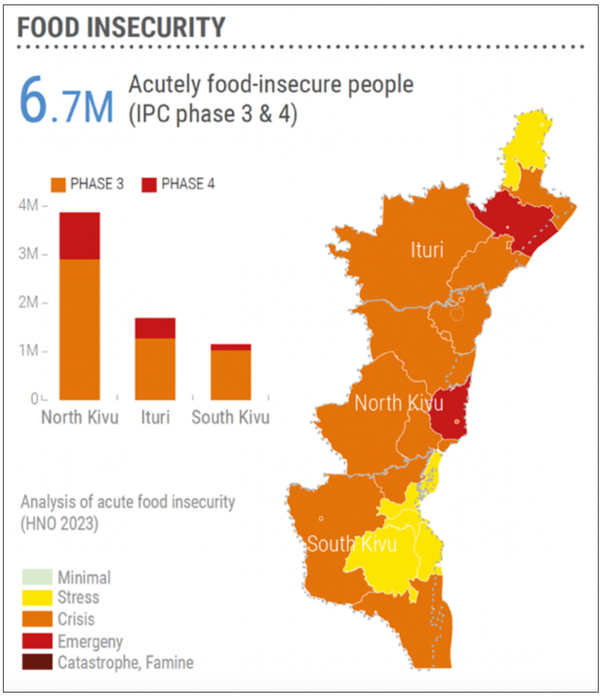


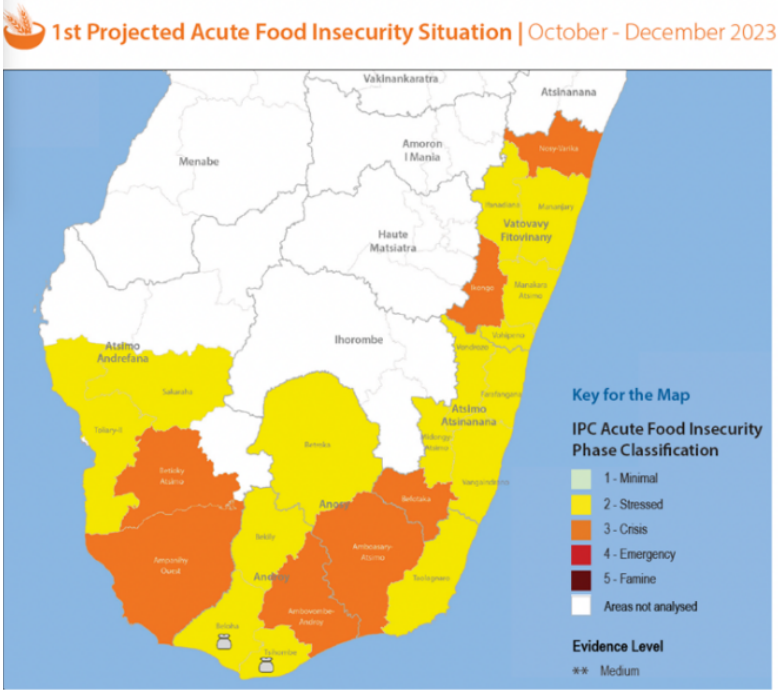
Figure 20: Analysis of acute food- insecurity eastern DRC (203)

MSF reported a surge of violence, displacement, hindered health care access, and hunger in Ituri Province In June 2023 (206). The World Food Programme (WFP) lanced an emergency funding appeal for the whole region in August 2023, mentioning the "extreme weather conditions" as one of the challenges (207). Torrential rains had caused massive floodings and mudslides in South- Kivu Province earlier in 2023, claiming hundreds of lives, destroying several health facilities, and rendering humanitarian access impossible in some regions (208,209).

CC acts as a driver of human insecurity and adds additional stress to conflict situations (210). Clashes have been reported between semi- nomadic herders and farmers in Ituri because of shrinking water resources (211). The USAID DRC Climate Risk Report 2023 forecasts an exacerbation of violence and conflict associated with the increasing weather variability, aridity, and resulting crop yield losses. They predict worsening health care access through damage to road- and sanitation infrastructure by heavy rainfalls (212). The negative impact on biodiversity, directly through changing weather patterns, indirectly through climate- adapted land use changes, aggravates the nutritional situation. It weakens the ability of ecosystems to regulate nutrient cycles, with negative dietary consequences for rural communities (213). The report further emphasizes the increasing risk for pests, vector- and waterborne diseases, as well as human- wildlife- pathogen transmission due to a range shift of species (212).

3.3.2 Madagascar

Together with DRC, Madagascar currently ranks under the top five countries with alarming levels of food insecurity according to the Global Hunger Index (GHI) (117,214). While this level is generally attributed to countries with armed conflict, Madagascar represents an exception: here, CC together with insufficient risk governance are considered the main drivers of humanitarian disaster (215). Especially the arid and semi- arid regions in the south are prone to recurrent droughts and famines. An association between undernutrition and the susceptibility towards infectious diseases including plague has been highlighted in a recent UN University (UNU) report (117). Over one million people are currently subject to high food insecurity in the south, and the situation is expected to worsen in 2024 (Fig 21)(216).



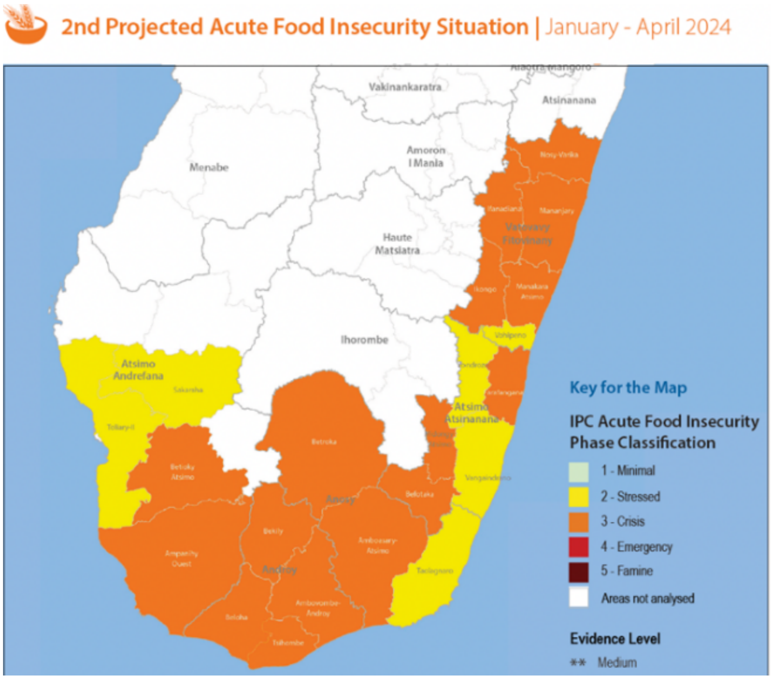


Figure 21: IPC Food Insecurity Snapshot 2023 and 2024 (216)

A Flash Appeal under UN coordination was launched in 2023 for the cyclone and drought-affected Grand Sud and Sud- Est. Only a limited number of people have been targeted so far (Fig 22)(217). Key drivers are CC- associated natural disasters: cyclones, floods, and droughts (216). Increasing sandstorms, pest infestations (e.g., locust outbreaks, triggered by "favorable breeding conditions" following cyclones in the north), and expanding cattle raiding violence aggravate the situation (218). The consequence is a large migratory trend towards northern urban centers. The UN International Organization of Migration (IOM) and the OCHA report rising numbers of Internally Displaced People (IDP) after tropical cyclones (120,219). Amongst the IDP, charcoal- making and illegal forest exploitation is a common "emergency coping strategy", further triggering ecosystem degradation and soil erosion in a vicious cycle (117).

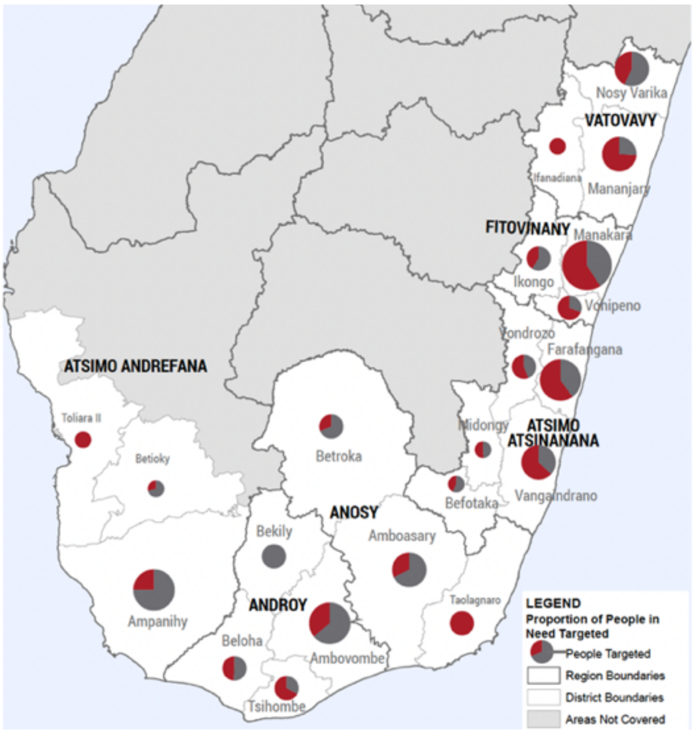


Figure 22: Proportion of people in need targeted (217)

The BMZ Climate Risk Profile Madagascar 2021 predicts a major impact of extreme weather events on infrastructure and thus health care access (41). The road network in Madagascar is amongst the least dense in the world. The existing mostly unpaved roads are in poor condition. Floods will make them increasingly impassable, while high temperatures add to their degradation. An additional aggravation of health care access is projected. The authors further point out the interrelation of CC, ecosystems, and human health in Madagascar. The multicausal decrease in biodiversity is associated with an increasing spread of invasive species. A widening geographic range of introduced vector- borne diseases, e.g., malaria, has already been observed, attributed to the favorable temperatures at higher altitudes.

3.4 CC projections for DRC and Madagascar

CC projections are generally divided in different scenarios. This is due to the uncertainties about future global emissions, depending on mitigation efforts. Representative Concentration Pathways (RCP) have been introduced as a measure of cumulative Greenhouse Gas (GHG) emissions by 2100. RCP 2.6 for example reflects a very strong mitigation scenario with low emissions, RCP 8.5 a high emission scenario (24)(220,221). (These model projections do not account for effects of future socioeconomic impacts. The recently introduced Shared Socioeconomic Pathway (SSP)- based scenarios aim to overcome this barrier (222–224)).

3.4.1 DRC

Current Climate Risk Fact Sheets and Climate Risk Country Profiles for DRC have been consulted. They have been published between 2013 and 2023 by different actors, including the WB Group (WBG) and the associated CC Knowledge Portal (CCKP), the German Climate Service Center (GCSC), and the USAID (24,29,30,212,225). Regional and global models are integrated, together with the Coupled Model Inter- comparison Project (CMIP) datasets that served as a basis for the 4th and 5th IPCC Assessment Report (IPCC-AR4 and -AR5)(29,213). Since today´s active plague foci are situated in northeastern DRC, the temperature projections for the northern and eastern climate zones have been prioritized where applicable.

Findings

Across most emission scenarios, models predict a continuous rise of temperatures (Fig 23)(24). Under a low emission scenario, the annual average surface air temperature is projected to increase by 1,5- 2,7° until the end of the century. Under a high emission scenario, temperatures could increase by 3,6- 5,1°C until the end of the century (212,213). The average number of hot days is projected to rise substantially (24).

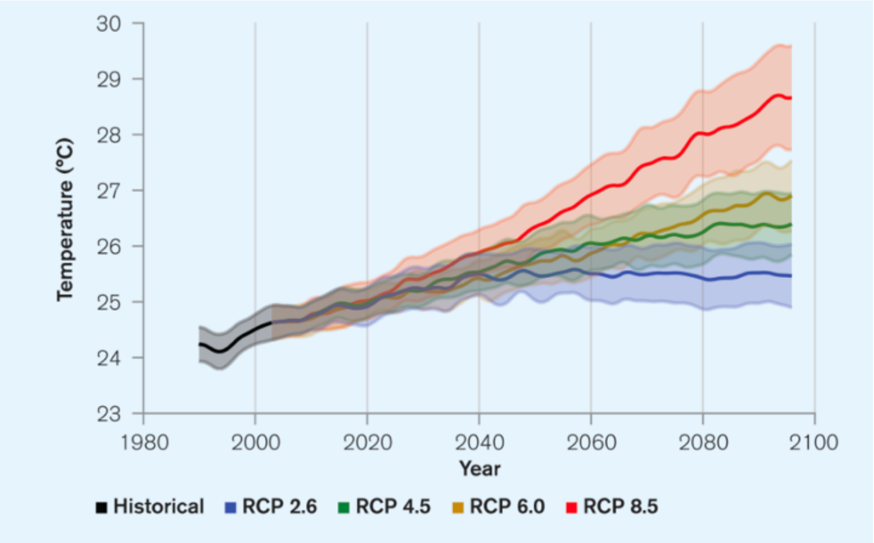


Figure 23: Historical and projected average temperature DRC (24)

The predicted changes in total precipitation across DRC are rather moderate, with a small tendency to increase (Fig 24). Rainfall characteristics however are expected to undergo substantial changes. There is consensus about more future variability in precipitation with an increased frequency of extremes, but also more sporadic rainfall. Dry spells during the rainy season are expected to occur more often as well as natural disasters like droughts and floods (24,212,213,220,225). The most drastic weather changes are projected for the northeast (29).

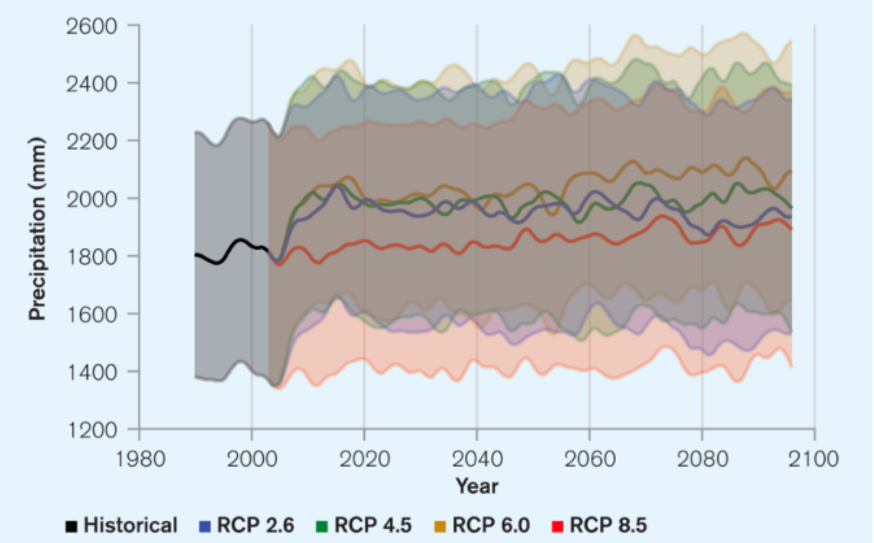


Figure 24: Projected changes in average annual precipitation DRC (24)

3.4.2 Madagascar

Climate risk projections published between 2011 and 2021 have served as a basis for this section. Authors include the WBG and the CCKP, the WHO, the USAID, and the BMZ in cooperation with the Potsdam Institute for Climate Impact Research (PIK) (40,41,46,226,227).

Findings

Across most emission scenarios, models predict a continuous rise of temperatures (Fig 25)(221).

Under a low emission scenario (RCP 2,6), the warming in Madagascar could be limited to 1,1°C by the end of the century compared to the historical reference period (221,227). Under a high emission scenario (RCP 8,5), temperatures are projected to rise by 4,1°C by 2100 (46,227). The annual number of very hot days is projected to rise substantially (41). The highest increases are projected for the southern part of the country (226).

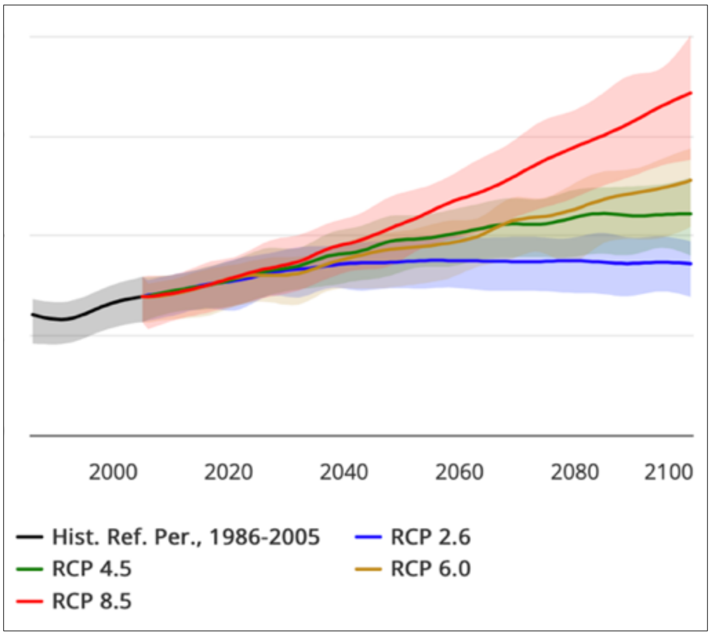


Figure 25: Projected mean temperature Madagascar (221)

The predicted changes in precipitation show some variability. Overall rainfall is expected to decrease, particularly during the dry season and inland. Some predictions suggest wetter conditions in the north (41,226). Under a high emission scenario, some models suggest a strong precipitation decline towards the end of the century (Fig 26)(41).

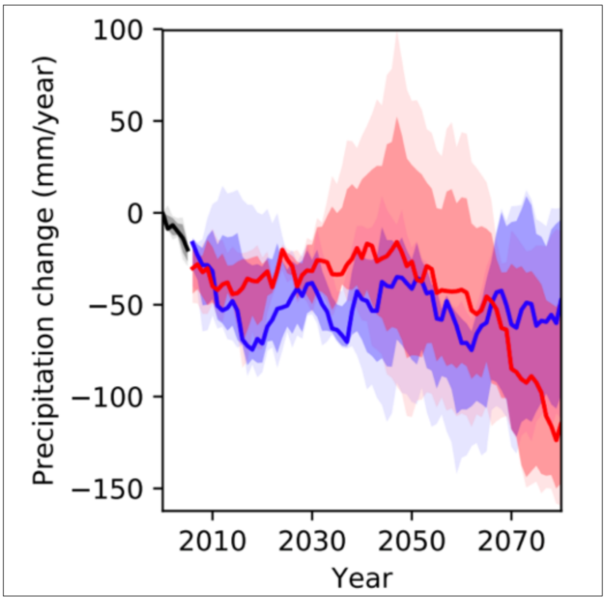


Figure 26: projected mean annual changes in rainfall Madagascar (41)

Seasonal rainfall patterns will become less predictable, extreme weather events increase in frequency or magnitude. This entails heavy rainfalls, cyclones, floods, and droughts (40,41,226).

Chapter 4 Discussion

Plague, if left alone, is predominantly a zoonosis that circulates quietly among fleas and rodents in their sylvatic habitat. With the growing pressure on ecosystems however, natural cycles become increasingly unstable. As summarized by one of the leading OH scientists Dr. W. Karesh: "The laws of biology haven't changed, but the playing field has changed dramatically"(228). While this observation affects most, if not all zoonotic infectious diseases on earth, plague is characterized by the extremely high fatality of its pneumonic form in absence of immediate treatment. Considering the weak health care systems in DRC and Madagascar, threatening antibiotic resistance of Y. pestis, and high- speed globalization, future disease dynamics are of Public as well as International Health relevance.

If this literature review revealed one thing to the author more than anything, it was the complexity of the involved dynamics, interdependences, and interactions of the plague cycle and its components at multiple levels and scales. To structure the scientific approach against this background, a framework (chapter 2.4, Figure 14) was identified that divided the determinants of disease in three domains: hazard, exposure, and vulnerability. The focus of this framework is on the impact of climate and land use change on the biological as well as socioeconomic drivers and subsequently disease dynamics, greatly matching the purpose of the thesis. However, while scientific publications on various plague- related aspects are available in large quantities, it turned out challenging to identify articles referring to the focus countries and climate respective land use change at the same time. To overcome the resulting gaps, studies from other countries (mainly Uganda and US) were consulted, as well as some publications referring to plague and one or more of the determinants but not necessarily climate or land use change.

Starting off with the climate susceptibility of the hazard, referring to the three plague cycle components, the following information was gathered. The average annual temperatures, depending on the applied emission scenario and rounded to whole numbers, are expected to range between 27-29°C for DRC respective 24-27°C for Madagascar by the end of this century. The optimum temperature for flea vectors and their disease transmission capacity ranges between 24-27°C, with a declining trend above 28°C. Looking exclusively at these numbers, the future ambient conditions could be considered suitable for plague in both countries, with some doubts regarding DRC under a high emission scenario towards the end of the century. However, these projections refer to average temperatures, whereas the absolute numbers of occasional very hot days are expected to increase as well. Since the microclimate in rodent burrows, and thus flea survival, depends on outside temperature as well as ambient humidity levels and soil moisture, hot spells and reduced rainfall could have a negative effect. Although meteorological data is scarce especially for DRC, there is consensus that precipitation patterns will become more erratic in both countries, with a tendency towards more extremes. Based on these projections, a possible trend towards less plague could be assumed for both countries- with a high level of uncertainty and predominantly reflecting the narrow ambient requirements of fleas. LSCP draw a slightly different picture, although their immediate impact is even less obvious. With time lags of up to several years, they can- as evidenced by several studies- increase human plague occurrence. This effect is mainly explained by the positive impact of rainfall on vegetation growth and thus food abundance for rodents. The respective literature originates predominantly from the US, and the transferability of the results to sub-Saharan flora and fauna remains uncertain. However, a strong association between ENSO and plague incidence was found by a study from Madagascar, too.

In Table 1 (chapter 3.1.2) the climatic, geographical, and ecological variables associated with plague dynamics have been summarized. The selected studies varied considerably in their geographical and research focus, the modeling techniques applied, and data sets included. The results are therefore difficult to compare, and their quality cannot be assessed without expert knowledge (e.g., meteorological, geographical, biological modelling). There is however consensus regarding the general susceptibility of plague to climatic and ecological variables. The factors consistently cited as the most relevant are temperature, rainfall, elevation, and vegetation. In line with the historically reported preference for "warm- moist weather", most of the NA studies describe very hot days as detrimental for plague, but additional rainfall to increase incidence. The African studies seem to differ slightly more in their conclusions: especially the impact of rainfall patterns on plague dynamics is judged quite controversially, frequently in a seasonal context.

Broad consensus however exists regarding the preference of plague reservoirs for higher altitudes. This seems particularly true for disease dynamics in times of CC. With warming temperatures, a range shift along altitudinal respective longitudinal gradients has been observed. This trend has been described for the highly active plague focus in Ituri (longitudinal), and the neighboring focus in Uganda (altitudinal). A shift towards new biotopes however bears unforeseeable risks. A large US based- study from 2022 (chapter 3.1.2) showed clearly that the rodent and flea biodiversity encountered at higher elevations lead to the formation of new plague reservoirs and an increased pathogen spillover. The remarkable capacity of fleas to adapt to certain climatic conditions can also be observed in the endemic species S. fonquerniei from Madagascar. An experimental study provided evidence that S. fonquerniei is indeed better adapted to cooler temperatures, but more susceptible to warmer temperatures and dryness than the introduced flea X. cheopis. Whether this fact will lead to less plague on the island under future warming trends, or simply induce a shifting towards X. cheopis as the predominant vector, is subject to debate. However, it underlines the huge uncertainties associated with the biology of arthropod vectors. According to an expert article, any flea species might- under suitable conditions- have the biological capacity to transmit plague, and a vast number of wild, still unknown flea species exists (68). In Tanzania, scientists compared rodents and fleas from agricultural land versus adjacent wilderness. Not only did they find a much higher plague seroprevalence amongst the rodent species from the cultivated land, but also several fleas with unknown vector competence. In Madagascar, investigations in forest- cleared land identified a new genetic variant of Y. pestis in an endemic hedgehog, together with several fleas previously not suspected as plague vectors. The impression was that a new sylvatic cycle had evolved due to the contact with humans and domestic rodents. The role of slash- and burn agriculture in this context is still understudied. However, the findings of this review point towards a vicious cycle between human interference with natural habitats, triggering of new vector- host capacities, and an increasing risk of exposure for certain population groups: migrant workers and displaced people, but also minors and farmers.

Likewise, an extension to previously plague- free areas, even at lower altitudes, must be taken into consideration. According to historical data from the African continent and elsewhere, plague has the property to form reservoirs under a large variety of conditions. In many countries, a preference for arid and semiarid landscapes has been observed. Under future climate scenarios, an increasing aridification of the south of Madagascar is expected. The expansion of reservoir rodents towards arid zones over long distances has been reported from the African continent. For Madagascar, a considerable expansion of distribution patterns of ectoparasites under the shifting environmental conditions was projected. Various outbreak reports from the island have documented a re- emergence at low altitudes during the last decades. All these aspects give rise to concern that- provided a suitable climatic “mix”- plague outbreaks might occur in other parts of the country, namely towards the south.

In the Grand Sud and Sud- Est, the populations´ vulnerability is high. After devastating extreme weather events, millions of people need humanitarian assistance. The situation can be considered a ticking time bomb. In previous years, plague outbreaks have occurred in the Ikongo district in the southeast, an area that has now been attested crisis levels of food insecurity. In the southwest, similarly confronted with a hunger crisis in 2024, an unexpected finding of Y. pestis in a rat was recently published (chapter 3.2.3). Considering the detection of Y. pestis- antibodies in areas where plague has never been reported from, future plague outbreaks must be expected in unexpected locations and during unusual months (229).

Regarding the association of plague outbreaks with socioecological determinants, namely under the influence of climatic and environmental changes, data availability is limited. Impoverished living conditions have frequently been associated with an increased plague risk in the literature. CC worsens precarious living conditions and adds to the risk of exposure and the vulnerability of people. In Madagascar, thousands of climate victims migrate northwards, living in provisional camps and depending on foraging for their survival. In eastern DRC, millions of people are displaced due to the conflict situation. The association between a negative impact of CC on agricultural productivity and prosperity, housing habits (e.g., food storage inside, sleeping on ground mats), rodent behavior (closer vicinity), and plague occurrence was illustrated by a recent PP outbreak analysis from eastern DRC (chapter 3.2.1). Apart from this report, no scientific evidence was identified investigating the association between CC, increasing poverty, and subsequent plague cases. The cascading pathway of climatic events amplified by social vulnerabilities resulting in population exposure and infectious disease outbreaks is however an established concept for other zoonotic diseases (169,230).

The negative impact of undernutrition on the resilience against infectious diseases is well established, too. While in Madagascar the plague- endemic foci are not (yet) congruent with the hotspots of humanitarian disaster, in DRC this is the case. Together with North and South Kivu, the Ituri province suffers a major humanitarian crisis. More people than anywhere else in the world are facing acute food insecurity. At the same time, the conflict situation makes humanitarian access increasingly difficult to impossible. It is somewhat disturbing that probably THE most active plague focus in the world is situated in a setting like this. Seemingly, no plague cases have been reported from North Kivu since the 1960ies, and none from South Kivu. However, in absence of functioning testing facilities, case numbers are probably underestimated. A re- emergence in North Kivu, or a newly emerging focus in other parts of the country, seems highly likely (as observed in the neighboring districts Bas- respective Haut- Uele). An eventual spread to urban centers- as seen in Madagascar- must also be considered. Remarkably, the most significant climate impact in DRC is predicted for the northeast. Extreme weather events are expected to further worsen health care access and infrastructure in both countries. In the light of these findings, illustrating the unpredictability of future plague dynamics, the necessity of an improved control system becomes evident. Many of the reviewed articles concluded with the call for increased surveillance activities and the adoption of an OH approach.

The analytical framework by Gibb et al. was useful in structuring the different determinants of disease and was covering most of the relevant aspects. What was missing? Certain behavioral aspects are suspected to increase exposure to plague, like rodent hunting and consumption, or body contact during traditional funerals (44,76,231–233). Those and other socio-cultural variables are not reflected by the framework despite potentially gaining in importance under the negative impact of CC and ecosystem disruption.

The lack of studies on plague and climate in the country context of DRC and to a lesser extent Madagascar is a limitation of this work since the comparability with data from the US is not necessarily given, rendering the transferability of results questionable. It underlines the need for more research in the country- and comparability context. Another possible limitation of this thesis is selection bias regarding the study selection. Further, information completeness must be questioned because i) the association between plague outbreaks and many socioecological drivers has not yet been studied, ii) publications in languages other than English (e.g., French) have not been included, iii) the detecting and reporting system for human plague cases is weak and thus data on plague incidence incomplete (especially in DRC).

The strength of this work is to have addressed an understudied topic with arguably high acuity. It has revealed a disease risk constellation with relevance to the International Health community. As to the best knowledge of the author, this study is the most complete conjunction of available information on this subject. Forthcoming studies can use this work as a base for further research on plague dynamics in DRC and Madagascar.

Chapter 5 Conclusion and Recommendations

5.1 Conclusion

Scientific opinions differ whether future climate scenarios will rather lead to an increase or decrease of plague cases, with little available evidence specifically for DRC or Madagascar. However, a range shift of plague towards more suitable geographic regions and altitudes is generally expected. Such shifts and the penetration of wild habitats are associated with a higher probability for the formation of new plague reservoirs, cross- species transmission, and genetic variation of Y. pestis. Findings from Madagascar underline this observation, namely the adaptation of the endemic flea vector to a cooler mountain climate, and the detection of new genetic variants in wild hosts. The real incidence of plague is unknown due to weak local and national surveillance systems, especially in DRC where a silent extension of the Ituri focus has already been noted. Changing weather patterns are expected to negatively impact the socioeconomic, health care, and security situation in DRC and Madagascar, and adaptive behavioral and agricultural practices to increase the risk of exposure. Outbreaks in unexpected locations with novel microbial characteristics must be anticipated. The population in eastern DRC and southern Madagascar, highly affected by humanitarian crisis, displacement, and acute food insecurity, represents the most vulnerable group in such a scenario. The review underlines the interconnectedness of human, animal, and ecosystem health. It demonstrates the need for a holistic, multidisciplinary, multisectoral approach. Priority interventions should embrace OH convictions, helping to prevent, detect, and respond to plague outbreaks in the future. More research is required for a better understanding of the complex dynamics involved.

5.2 Recommendations

The scope of this review did not allow for an in- depth analysis of the available institutional capacity and infrastructure in DRC and Madagascar needed to prevent, detect, and respond to plague outbreaks. It is therefore difficult to recommend specific measures without having done a proper field assessment. The findings and resulting eight recommendations shall rather be understood as a basis to discuss the possible implications of changing plague dynamics, assess necessities for the individual country context, propose measures, and create a road map for further action as appropriate.

1. Governments of DRC and Madagascar with their MoH and their Ministry of Agriculture, Livestock and Fisheries (MoA) are encouraged to assess their human and animal surveillance activities and decentralized laboratory capacities. An extension towards active human surveillance, diversified animal surveillance in plague- endemic and non-endemic regions, extended testing for antibiotic resistance should urgently be considered. In DRC, the reactivation of diagnostic paths established during the PREDICT project (139) could be evaluated.

2. Both governments with their MoA and their Ministries of Environment, Conservation of Nature, Water and Forests respective Sustainable Development are encouraged to assess their promotion of sustainable land use alternatives, reduction of deforestation activities, and strict protection of remaining ecosystems.

3. Both governments with their MoA and Ministry of Urban Planning and Housing are encouraged to assess the funding of community- based interventions to reduce the impact of CC and the risk of exposure to plague, e.g., training on agricultural resilience

and supply of climate- adapted seeds, local production of secure food storage containers and beds, rat- proof roof construction, and interventions adapted to the urban context.

4. Both governments with their MoH are encouraged to reinforce availability of RDT and plague- appropriate antibiotics in all HC, provide continuous training of health care personal to consider, recognize, and treat plague, training programs for CHW on plague prevention and management, and updated multimedia public awareness campaigns.

5. Both governments are encouraged to take the lead in adopting the OH approach and implementing a national OH strategic action plan, allowing for a strong collaboration across human, animal, and environmental health sectors. An OH- adapted model for the prevention and control of plague, introduced by Agrawal et al., can be found here: (104).

6. WHO is encouraged to publish the revised Plague Surveillance Guidelines as soon as possible (announced during the EpiWin Webinar “Managing plague in the field”)(84).

7. The International Health community should increase their engagement towards prevention and detection of plague and strengthen the capacity of WHO, ATACH, and other OH partners to be better prepared for future plague outbreaks. LIC should be supported in implementing key SDG needed to combat EID (chapter 1.6) in alignment with the UN 2030 Agenda for Sustainable Development.

8. Research priorities include the behavior and shifting of plague cycle components under changing environmental and climatic conditions, mapping of plague across Africa, comparability of plague studies from the US with African countries, the impact of socioeconomic drivers, impact of slash- and- burn agriculture, detection of genetic variations/cross- species transmission and AMR, utility of diversified animal surveillance for early plague detection, and validity of RDT, amongst others.

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