A Decade of Plague in Madagascar: A Description of Two Hot Spot Districts

Sitraka Rakotosamimanana (raksitraka@pasteur.mg)
Institut Pasteur de Madagascar https://orcid.org/0000-0002-1028-0427

Daouda Kassie
Centre de Coopération Internationale en Recherche Agronomique pour le Développement: CIRAD

François Taglioni
Université de La Réunion

Josélyne Ramamonjisoa
Université d'Antananarivo

Fanjasoa Rakotomanana
Institut Pasteur de Madagascar

Minoarisoa Rajerison
Institut Pasteur de Madagascar

Research article

Keywords: plague, Madagascar, central highlands, epidemiology

Posted Date: December 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-132857/v1

Abstract

Background Human plague cases, mainly the bubonic form, occur annually in the endemic regions of the central highlands of Madagascar. The aim of the study is to compare the evolution of the epidemiological features of human plague in two districts of the central highlands.

Methods In Madagascar, all clinically suspected plague cases that meet clinical and epidemiological criteria specified in the World health organization standard case definition are reported to the national surveillance system. Data on plague cases reported between 2006 and 2015 in the districts of Ambositra and Tsiroanomandidy were analyzed. Statistical comparisons between the epidemiological characteristics of the two districts were conducted.

Results A total of 840 cases were reported over the period studied, including 563 (67%) probable and confirmed cases (C+P). Of these C+P cases, nearly 91% (488/536) were cases of bubonic plague. Reported clinical forms of plague were significant for both districts during 2006 to 2015 (*p=0.001*). Plague cases occurred annually in a period of 10 years in Tsiroanomandidy district. One year of absence of cases characterized Ambositra district during the same period.

Conclusion The differences in the epidemiological situation with respect to the plague from 2006 to 2015 in the two central highland districts may suggest that several factors other than biogeographical factors determine the expression of the plague and its evolution in this region. The need to take into account epidemiological situations according to the specific contexts of the districts could improve results in the fight against the plague in Madagascar.

Background

Plague is a zoonotic disease that can accidentally affect humans. They become infected after being bitten by fleas from rats infected with the disease and then develop bubonic plague, which can evolve into other forms of plague. Plague in humans can occur in three clinical forms: bubonic plague, pneumonic plague and septicemic plague. The disease can be treated with antibiotics, but delays in treatment can cause death or evolve to the pneumonic or septicemic form [1, 2].

Plague is a notifiable disease. Worldwide, since the 2000s, cases of human plague have occurred on three main continents, Asia, America and Africa [3, 4]. Africa is the most affected continent in the world between 2013 and 2018, accounting for 96.7% (2791 / 2886) of global cases. The majority of the notified global cases, i.e. 80.5% (2323 / 2886) of the cases during this period, were reported in Madagascar [3]. Plague is a public health problem in Madagascar [4]. Every year around 400 cases of human plague were reported in Madagascar (4). The predominant form of human plague in Madagascar is bubonic plague but cases of pneumonic plague can also be found there [5-8]. Epidemics of pneumonic plague may also occur in Madagascar, as recently in 2017, with 2417 cases and 209 deaths, representing a case-fatality rate of 8.6% [9, 10].

Since 1898, when the first cases of human plague appeared in Madagascar, most cases have appeared in the central highland regions located at an altitude of more than 800 meters where the plague is endemic [5, 6, 8], but can also appear in coastal areas [5, 6]. The plague season is generally between October and April in this region, where cases appear almost every year, with intra-regional heterogeneities, but cases may be reported outside this period [11]. Case reporting may be annual in the central highlands, but in some cases, periods of inactivity (absence of cases) may characterize the years.

The districts of Ambositra and Tsiroanomandidy (Map 1) are endemic foci of the plague in Madagascar. They form part of the geographical triangle of plague endemic districts in the central highlands or "plague triangle" [12, 13]. The district of Ambositra is located in the southern central highlands and counts 23 municipalities subdivised into 290 *fokontany* (the smallest administrative unit in Madagascar) and covers an area of 2943 km². The district of Tsiroanomandidy is located in the middle west of the central highlands; it has 18 municipalities subdivided into 212 *fokontany*. This district covers an area of 106,000 km².

These two districts were chosen because they belong to the central highlands region, but also because the Ambositra district was a very active endemic plague outbreak in the 2000s [8] and the Tsiroanomandidy district has been one of the main active plague outbreaks until now [13]. In 2017, we also conducted a study on Knowledge, Attitudes and Practices (KAP) in relation to the plague among the populations of these two districts. This study is a preliminary step in the implementation of the KAP study we conducted.

The aim of this study is to (1) describe the epidemiological characteristics and evolution of human plague in the two districts of the central highlands between 2006 and 2015 and(2) compare the epidemiological situations of human plague in the two districts during the same time period.

Methods

Study design

This is a study based on a retrospective and comparative descriptive analysis of data on reported plague cases between 2006 and 2015 in two districts in the central highlands of Madagascar.

The database

As plague is a notifiable disease, according to the National Plague Control Program (NPCP), all data relating to the reporting of plague cases in Madagascar are centralized in a database at the Central Plague Laboratory (CPL) which is managed by Institut Pasteur de Madagascar/Ministry of Public Health. Cases declared in health facilities between 1 January 2006 and 31 December 2015 for the two districts in the central highlands. The database contains various information: information on individuals such as address, age, sex, the reference health facility where the case was reported, date of onset of the disease (day/month/year), clinical forms of plague (bubonic, pulmonary, septicemic, etc.), status of the patient

(alive or deceased), travel made before the case was reported (yes/no), presence of dead rats observed in the vicinity of the reported case (yes/no), definition of cases according to the type of tests performed and other criteria (suspect, probable, confirmed).

A total of 840 cases of plague were reported for the two districts between 2006 and 2015.

Case definition

According to Madagascar's Ministry of Public Health and the WHO, cases are defined in three categories based on clinical and epidemiological criteria and the results of tests carried out on biological samples (10, 4):

Suspected cases (S): all persons presenting clinical signs suggestive of plague in a favorable epidemiological context.

Probable cases (P): any suspect person with a positive result on one of the following tests: F1 rapid diagnostic test (RDT), serological test or PCR and where isolation of *Yersinia pestis* by culture has not been performed or has been negative.

Confirmed cases (C): any suspect person for whom an isolation of *Y. pestis* by culture has been performed or a conversion observed or positive RDT and PCR.

Temporal evolution of plague incidence during the study period in the two districts

A time series analysis was performed based on the fluctuations in the incidence of plague cases during the study period. We first determined the seasonal variations in the incidence fluctuation by month for each district. We then determined whether over the ten years the incidence fluctuations or abnormalities followed the same pattern in both districts. Next, we compared the periodicity of the occurrence of cases between the two districts.

Based on demographic data from the RGPH 2018 (the last official census in Madagascar dates back to 1993), we have estimated the number of people in Madagascar between 2006 and 2015 (for an annual population growth rate of 2.9%). We calculated the incidence (number of cases per 100,000 inhabitants) of the monthly average of human cases (C+P) of plague between the period studied for each district. We then estimated the incidence per month for each year of the study period and broke down the study period into 120 months or 10 years. To determine the fluctuations in incidence or anomalies in incidence per month for each year, we subtracted the monthly incidence per year from the average incidence for the entire study period. According to the monthly incidence fluctuations, the months were categorized into three classes for both districts: months with positive incidence fluctuations (incidence fluctuation > 0.1 cases per 100,000 inhabitants), months with negative incidence fluctuations (incidence fluctuation < - 0.1 cases per 100,000 inhabitants) and months with no major fluctuation (incidence fluctuation between 0.1 cases per 100,000 inhabitants and -0.1 cases per 100,000 inhabitants).

From these monthly fluctuations in incidence per year, we calculated the trend in incidence fluctuations with a linear regression line for the period studied by district.

In order to detect seasonality in the monthly incidence fluctuations for each year, we decomposed the time series into quarters by calculating moving averages.

Data processing and analysis

Processing, database management and statistical analyses were carried out using Microsoft Excel © and Stata 13 © software. Qualitative variables were represented in frequency and/or proportion. For the comparisons between the two districts, we used the Chi squared test of comparison or the Fischer exact test if appropriate, for the qualitative variables. For the comparison of the quantitative variables between the two districts we used a Student's test for independent samples. The significance threshold was set at $p<0.05$.

Results

Characteristics of reported plague cases in the two districts

Of the total 840 cases reported in the two districts for the period under review, about 33% (277/840) of suspected cases (S), nearly 28% (239/840) of probable cases (P) and about 39% (324/840) of confirmed cases (C) were reported for this period (Figure 1).

Of the 563 probable and confirmed cases, about 4% (25/563) were cases of pulmonary plague (PP) and about 91% (512/563) were cases of bubonic plague (BP). Around 5% (26/563) of the reported C+P cases were cases with an unreported clinical form. In terms of demographic characteristics, about 41% (341/840) were female and about 59% (499/840) male. The age of the individuals was recorded in the database for about 99% (829/840) of them. The median age in years of reported cases was 12 years. The demographic characteristics of reported cases in the two districts according to the case definition were summarized in Table 1.

Table 1. Demographic and epidemiological characteristics of reported cases by district, by case definition, 2006-2015

	Ambositra		Tsiroanomandidy		p-value
Features	Suspected (n=52)	C+P (n=105)	Suspected (n=225)	C+P (n=458)	
Sex-ratio (Male/Female)	1.08(27/25)	1.14 (56/49)	1.56 (137/88)	1.58(279/179)	0.118
Age median (25-75 percentile)	15 (6-21)	18 (8-36)	12 (7-18)	12 (8-22)	-
BP / PP cases (unknown)	40/1(11)	85/10(10)	215/5(5)	427/11(20)	0.001

By district, for Ambositra the median age of reported cases is 14 years, for Tsiroanomandidy the median age is 12 years. The demographic characteristics of the reported cases according to the case definition as well as those of the patients reported by case categories by district have been summarized in table 1. A significant difference in mean ages in the two districts was found between Ambositra district (mean 19.5 95% CI, 16.98-21.97) and Tsiroanomandidy district (mean 16.1 95% CI, 15.11-17.7) (p=0.0026).

The clinical forms (BP and PP) were significantly different between the two districts (p=0.001) for the 794 cases reported with clinical forms filled in during the study period.

Of the 840 reported cases, 838 cases notified in the database had information on the presence or absence of dead rats in the vicinity of the dwellings of the reported cases. Reports of dead rats accounted for almost 18% (150/838) of the reported cases. Reporting of dead rats in Tsiroanomandidy district was significantly higher than in Ambositra district (19.9% vs. 9.5%; p=0.002).

For the district of Ambositra, a total of 157 cases were reported, of which nearly 33% (52/157) were suspected, around 28% (44/157) probable and around 39% (61/157) confirmed. Compared to the clinical forms among C+P cases in this district, out of the 105 probable and confirmed 0 cases notified, about 81% (85/105) were BP cases and around 9.5% (10/105) were PP cases. About 9.5 (10/105) were undocumented cases of clinical plague.

For Tsiroanomandidy districts, a total of 683 cases were reported, of which 33% (225/683) were suspected cases, about 28% (195/683) probable cases and about 38% (263/683) confirmed cases. Of the 458 C+P cases in this district, about 93.2% (427/458) were BP cases, about 2.4% (11/458) were PP cases and about 4.4% (20/458) were clinically uninformed cases of plague.

Cases reported by year and district

For both districts, the number of cases varies from year to year for the period studied.

For the Ambositra district, from 2006 to 2015, 18 out of 23 municipalities notified C+P cases of plague. A peak of probable and confirmed cases was reported for the year 2007 with 29 cases (28 cases of BP and 1 case of PP), i.e. about 28% of the C+P cases notified in this district from 2006 to 2015. The year 2010 is a period of silence in this district, as no cases of C+P plague have been reported there, however one suspect case has been notified.

For the district of Tsiroanomandidy, 16 out of 17 municipalities notified C+P cases during the period under review. The year 2011 is a year with a peak of probable and confirmed cases with 97 cases (89 PB cases, 3 PP cases and 5 cases not reported), i.e. about 21% of the C+P cases reported during the reporting period. The year 2007 is the year with the lowest number of C+P cases notified with 12 cases (about 3% of total C+P cases from 2006 to 2015 in this district) all of which are BP.

Temporal evolution of fluctuations in the incidence of plague cases in the two districts for the period studied

For the district of Ambositra, no cases of plague were reported during the months of July for the period under study. A period of silence marks the year 2010 before a resumption of plague activity during the last quarter of 2011. Non-significant changes in incidence were detected for the month of February (year 2013); the month of March (years 2014 and 2015); the month of July for the entire period studied; and the month of October (years 2007, 2008, 2013, and 2014 to 2015).

From 2006 to 2015, a downward trend in fluctuations in the incidence of plague cases was detected in Ambositra District (Figure 3). The trend in fluctuating incidence of plague cases decreased by $y = -0.0043x + 0.2871$ during the study period.

Decomposition into three-month seasons highlighted an irregularity in the fluctuations in incidence for the whole period studied in this district.

For Tsiroanomandidy district in relation to the period studied, each year the plague season generally begins between July and September before reaching a peak between October and December. No cases of plague were reported during the month of June during the period under study. In this district for the entire study period, fluctuations in incidences without major variations were detected during the month of April (for the years 2006 to 2009 and 2011), the month of June (for the entire study period) and the month of December (year 2012).

From 2006 to 2015, a slight upward trend of fluctuations in the incidence of plague cases was detected in the district of Tsiroanomandidy during the study period. The fluctuation in the incidence of plague cases in this district increased by $y = 0.0032x - 0.2062$ from January 2006 (M1) to December 2015 (M 120) (Figure 2).

Decomposition into three-month seasons showed no regularity in the fluctuations in incidence for the entire period under study in this district.

Age range and gender among C+P cases in both districts

For both districts, of the 563 C+P cases, the ages of 558 individuals were reported. Nearly 41% were female (227/558). The most represented age group is the 10-19 year olds, who account for nearly 36% (200/558) of the total C+P cases for the study period. Approximately 69% (387/558) of the C+P cases were < 19 years of age and just over 1% (7/558) were over 60 years of age.

There were no significant gender differences among C+Ps in the two districts during the study period.

Age and sex of C+P cases in Ambositra district, 2006 to 2015

For Ambositra district, age was reported for all 103 C+P cases, just over 47% (49/103) were female. Individuals under 9 years of age accounted for approximately 33% (34/103) of the total C+P cases in this district. Cases less than 19 years of age accounted for almost 61% (63/103) of the total C+P cases reported during the study period (Figure 4). About 1% (1/103) of probable and confirmed cases was at least 60 years of age.

Concerning the district of Tsiroanomandidy, out of the 458 C+P cases reported between 2006 and 2015, 455 cases had their age information. Almost 39% (178/455) were female. C+P cases under the age of 19 accounted for around 71% (324/455) of the total C+P cases during the study period. And 37% (171/455) of the total C+Ps were between 10 and 19 years old. Just over 1% of the C+Ps (6/455) were at least 60 years old (Figure 5).

No statistically significant difference was found between deaths by clinical form in the two districts.

Discussions

Although the first cases of human plague appeared in Madagascar in 1898, the plague still affects hundreds of people a year, particularly in the central highlands where it is endemic. We conducted a comparative descriptive study by analyzing epidemiological data on plague in two endemic districts in the central highlands of Madagascar for a period of 10 years. The results of the study showed differences in the epidemiological characteristics of the evolution of human plague in the two districts during the study period.

Most C+Ps reported in both districts are under 19 years of age, as in most countries in sub-Saharan Africa [14-16] where the human plague is rampant. This characteristic has also been observed in epidemiological studies of plague in Madagascar [17, 8] and worldwide [18]. This can be explained by the socio-cultural practices and behaviors of individuals in this age group. Indeed, several authors explain this fact by a difference in the exposure of these individuals to the risk of plague for different age categories and according to gender, especially in rural areas due to agricultural activities [18]. As the rural

areas of the central highlands are often areas with strong agricultural practices, individuals under 19 years of age are more likely to be required to work in the fields than individuals in other age groups [19, 20]. These facts have also been observed in areas of plague endemicity in sub-Saharan Africa [21, 22]. In the district of Tsiroanomandidy in the mid-western central highlands, from 2006 to 2015, cases of human plague occurred annually, with a peak in 2011. In the case of Ambositra district in the southern axis of the central highlands, the period studied was marked by a period of silence in 2010. Significant differences in the clinical forms of plague observed in the two districts as well as in the status of registered individuals were also detected for the same period. These varied situations in the epidemiological expression of human plague for two districts in the central highlands with an average altitude of over 800 meters could be explained by the different biogeographical characteristics in these two districts. Indeed, although part of the same region known as the central highlands, these two regions are different both in terms of climate and the vegetation that covers them. As the plague is primarily a zoonosis, exposure to the plague risk in humans is dependent on environmental and climatic factors that brought the infected rats and their fleas into contact with humans [23-27]. Socio-political circumstances could also have contributed to the under-reporting of plague cases in Madagascar [28]. The absence of cases in Ambositra in 2009 can be explained by the explosion of a socio-political crisis on the large island in the same year, which had indirect repercussions on the health system in Madagascar. To this can be added the difficulties caused by the lack of logistics or materials and the geographical remoteness or isolation of certain areas, making it impossible to send biological samples to the Central plague laboratory [8].

Apart from this, the difference in the epidemiological context in relation to human plague in the two central highland districts could also be explained by the geographical characteristics of the two districts. Tsiroanomandidy district is larger in area than Ambositra district. This fact may have consequences for the management of human plague epidemics because the health space in the more densely populated and smaller Ambositra district is facilitated by the proximity of the health infrastructure to the population. Contrary to the district of Tsiroanomandidy where the surface area is larger and the population density less dense, the health structures are less close to the population. The control of space in campaigns to combat the hosts and vectors of the plague can also be a determining factor in the district of Ambositra because of its surface area.

Fluctuations in the incidence of plague cases do not vary in the same way in the two central highland districts between 2006 and 2015. Fluctuations in incidence in the Tsiroanomandidy district increased slightly while these fluctuations decreased slightly in the Ambositra district. The peak plague season usually begins in July and August in the Tsiroanomandidy district during the study period. In Ambositra district, the high plague season is not seasonal and varies from year to year. The fluctuations in incidence for both districts are irregular and vary from year to year. The fluctuations do not follow any seasonality. These differences in context and fluctuations in incidence can be explained by environmental-climatic factors (El Niño phenomenon). This fact is suggested by Kreppel and his team, who have highlighted relationships between climatic oscillations due to ENSO phenomena and the incidence of human plague in Madagascar [29]. Very few or no study on impact of other factors on plague incidence were carried out for Madagascar.

However, the limited knowledge of the population about the plague in the two districts may play a role in reporting cases of plague. Indeed, people living in areas endemic to human plague could easily recognize signs of the plague [30]. This could be helped by the existence of frequent awareness campaigns in endemic areas which may require more effort on case reporting in endemic areas.

Conclusion

The epidemiological characteristics of human plague in the two central highland districts suggest a new approach to plague control. Indeed, taking into account the particular bio-geographical, socio-cultural and behavioral contexts of the different districts where plague is endemic could improve results in the fight against plague in Madagascar. Establishing decentralized management of plague control in the allocation of material, human and financial resources according to the real needs of health administrations (depending on the real epidemiological, socio-demographic and socio-cultural contexts) would contribute to an improvement in the plague situation at different administrative levels in Madagascar.

Studies on the links between human behavior and the persistence of plague in Madagascar could also provide more insight into the dynamics of the disease on the island, but also on similar diseases in the world.

Abbreviations

BP : Bubonic plague **KAP**: Knowledges , Attitudes and Practices **OR**: Odds ratio **PP**: Pulmonary plague **SR**: Sex Ratio

Declarations

Ethical approval

The protocol of this study received approval from the Ethics Committee of Ministry of Public Health of the Madagascar Republic (notification N° 50-MSAN/EC April the 26th 2016).

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

MR, FR, SR conceived and designed the study.SR cured data. All authors participated in the analysis, discussion and interpretation of the results. MR and SR condensed the analysis and wrote the first draft of the manuscript and DK, FT, JR, critically reviewed the manuscript. All authors read, contributed to, and approved the final manuscript.

Acknowledgment

We would like to thank the Central Plague Laboratory for providing us the data.

References

1. Mead PS. Plague in Madagascar — A Tragic Opportunity for Improving Public Health. New England Journal of Medicine. 2017;378(2):106-8.
2. Rubini M. Emerging pathogens: The plague in Madagascar. Edorium J Infect Dis. 2015;2:1-3.
3. Bertherat E. Plague around the world. Weekly epidemiological record. 2019;94(25):289-92.
4. WHO. Weekly epidemiological record. 2016;8(91):89-104.
5. Boisier P, Rahalison L, Rasolomaharo M, Ratsitorahina M, Mahafaly M, Razafimahefa M, et al. Epidemiological features of 4 successive annual outbreaks of Bubonic Plague in Mahajanga, Madagascar. Emerging Infectiuous Diseases. 2002;8(3):311-5.
6. Boisier P, Rasolomaharo M, Ranaivoson G, Rasoamanana B, Rakoto L, Andrianirina Z, et al. Urban epidemic of bubonic plague in Mahajanga : epidemiological aspects. Tropical Medicine and International Health. 1997;2(5):422-5.
7. Brygoo E-R. Epidemiologie de la peste à Madagascar Archives de l'Institut Pasteur de Madagascar. 1966;35(39-11):9-149.
8. Chanteau S, Ratsitorahina M, Rahalison L, Rasoamanana B, Chan F, Boisier P, et al. Current epidemiology of human plague in Madagascar. Microbes and infection. 2000(2):25-31.
9. Nguyen VK, Parra-Rojas C, Hernandez-Vargas EA. The 2017 plague outbreak in Madagascar: Data description and epidemic modelling. Epidemics. 2018;25:20-5.
10. Randremanana R, Andrianaivoarimanana V, Nikolay B, Ramasindrazana B, Paireau J, Bosch QAt, et al. Epidemiological characteristics of an urban plague epidemic in Madagascar, August–November, 2017: an outbreak report. Lancet Infect Dis. 2019;19:537-45.

11. Andrianaivoarimanana V, Kreppel K, Nohal E, Duplantier J-M, Carniel E, Rajerison M, et al. Understanding the persistence of plague foci in Madagascar. PLOS Neglected Tropical Diseases. 2013;7(11):1-8.
12. Chanteau S, Ratsifasoamanana L, Rasoamanana B, Rahalison L, Randriambelosoa J, Roux J, et al. Plague, a reemerging disease in Madagascar. Emerging Infectious Diseases. 1998;4(1):101-4.
13. Rakotoarisoa A, Ramihangihajason T, Ramarokoto C, Rahelinirina S, Halm A, Piola P, et al. Bubonic Plague Outbreak Investigation in the Endemic District of Tsiroanomandidy - Madagascar, October 2014. Case Rep Stud. 2016;5(1):103.
14. Forrester JD, Apangu T, Griffith K, Acayo S, Yockey B, Kaggwa J, et al. Patterns of Human Plague in Uganda, 2008–2016. Emerging Infectious Diseases. 2017;23(9):1517-21.
15. Neerinckx S, Bertherat E, Leirs H. Human plague occurrences in Africa: an overview from 1877 to 2008. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2010;104:97-103.
16. WHO. Global distribution of natural plague foci as of March 2016; 2016.
17. Andrianaivoarimanana V, Piola P, Wagner D, Rakotomanana F, Maheriniaina V, Andrianalimanana S, et al. Trends of Human Plague, Madagascar, 1998–2016. Emerg Infect Dis. 2019;25(2):220-8.
18. Pollitzer R. Plague. WHO, Monogr. 1954(Ser. No . 22).
19. Duplantier J-M, Duchemin J-B, Chanteau S, Carniel E. From the recent lessons of the Malagasy foci towards a global understanding of the factors involved in plague reemergence. Veterinary Research. 2005;36:437-53.
20. Duplantier J-M, Duchemin JB, Chanteau S, Carniel E. The rodent problem in Madagascar: agricultural pest and threat to human health. Ecologically Based Rodent Management Canberra, Australia: Australia Centre for International Agricultural Research. 1999:441- 59.
21. Eisen RJ, MacMillan K, Atiku LA, Mpanga JT, Zielinski-Gutierrez E, Graham CB, et al. Identification of Risk Factors for Plague in the West Nile Region of Uganda. Am J Trop Med Hyg. 2014;90(6):1047-58.
22. Kilonzo BS, Mvena ZSK, Machangu RS, Mbise TJ. Preliminary observations on factors responsible for long persistence and continued outbreaks of plague in Lushoto district, Tanzania. Acta Tropica. 1997;68:215-27.
23. Gage KL. Factors Affecting the Spread and Maintenance of Plague. Advances in Experimental Medicine and Biology. 2012;954:79-93.
24. Lucaccioni H, Granjon L, Dalecky A, Fossati O, Le Fur J, Duplantier J-M, et al. From human geography to biological invasions: the black rat distribution in the changing Southeastern of Senegal. PLoS ONE. 2016;11(9):1-16.
25. Mann JM, Martone WJ, Boyce JM, Kaufmann AF, Barnes AM, Weber NS. Endemic Human Plague in New Mexico: Risk Factors Associated with Infection. The Journal of Infectious Diseases. 1979;140(3):397-401.
26. Nyirenda SS, Hang'ombe BM, Machang'u R, Mwanza J, Kilonzo BS. Identification of Risk Factors Associated with Transmission of Plague Disease in Eastern Zambia. Am J Trop Med Hyg.

2017;97(3):826-30.

27. Rivière-Cinnamond A, Santandreu A, Luján A, Mertens F, Espinoza JO, Carpio Y, et al. Identifying the social and environmental determinants of plague endemicity in Peru: insights from a case study in Ascope, La Libertad. BMC Public Health. 2018;18:220.
28. Handschumacher P, Duplantier J-M, Chanteau S. La résurgence de la peste à Madagascar : une maladie centenaire à l'épreuve de l'histoire et de l'écologie. Espaces, Populations, Sociétés. 2000(2):195-208.
29. Kreppel K, Aminade C, Telfer S, Rajerison M, Rahalison L, Morse A, et al. A Non-Stationary Relationship between Global Climate Phenomena and Human Plague Incidence in Madagascar. Plos Negl Trop Dis. 2014;8(10):pp 13.
30. Kugeler JK, Apangub T, Forrestera JD, Griffitha KS, Candinib G, Abarub J, et al. Knowledge and practices related to plague in an endemic area of Uganda. International Journal of Infectious Diseases. 2017;64:80-4.

Figures

Figure 1

Studied districts localization and plague triangle Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

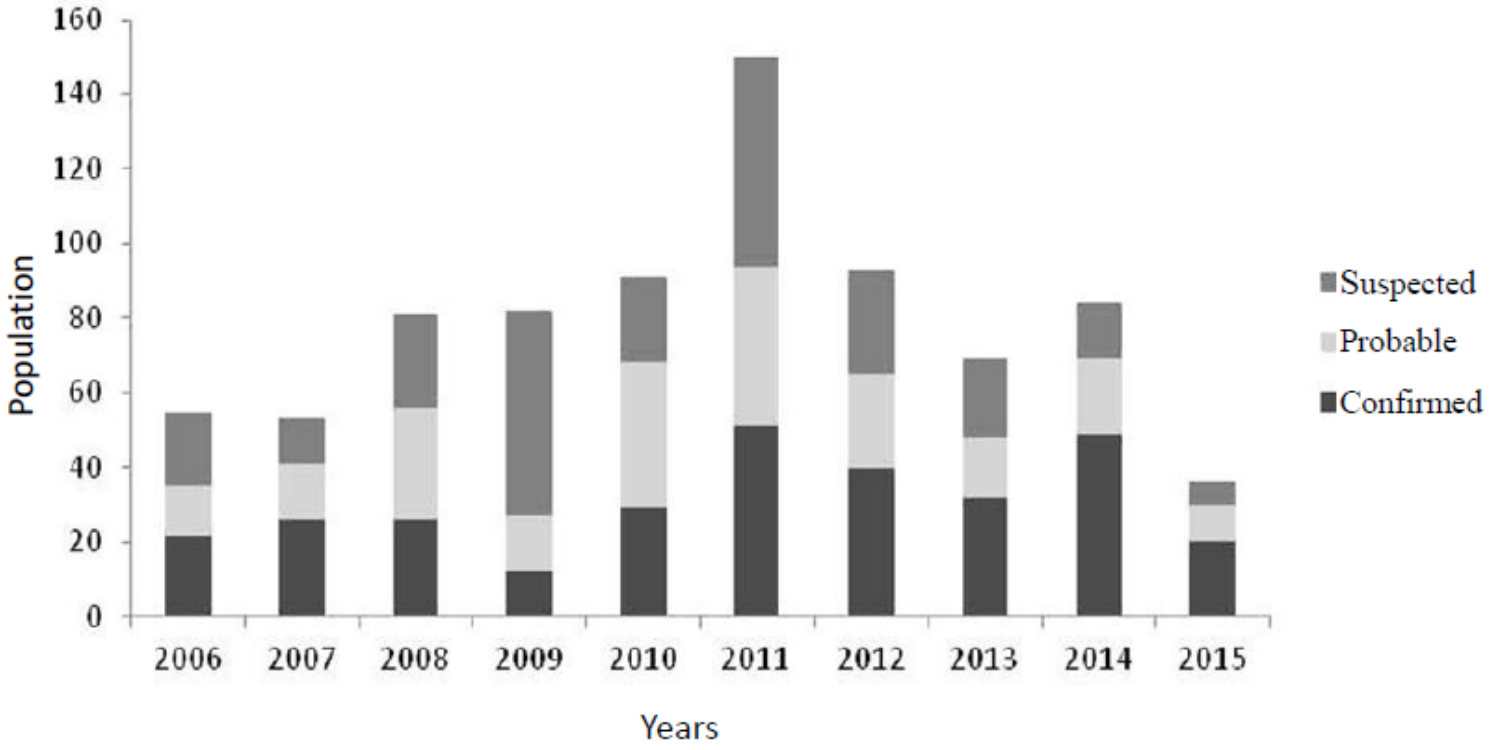

Figure 2

Suspected, probable and confirmed cases reported annually in the two districts from 2006 to 2015.

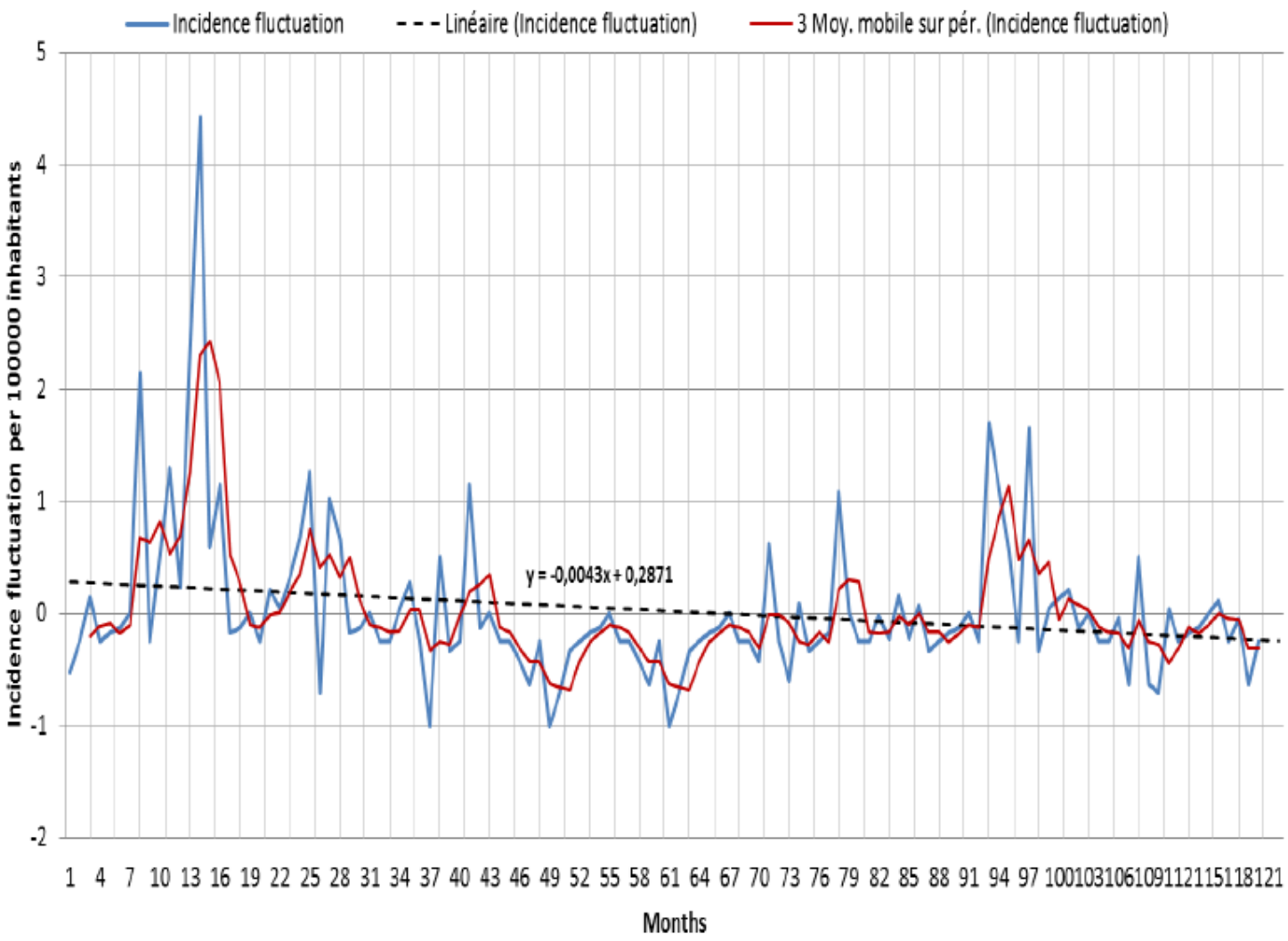

Figure 3

Time trend in incidence fluctuations of plague cases from month 1 to month 120 in the district of Ambositra - Legends. The blue curve represents the incidence fluctuations; the red curve represents the quarterly moving averages of the incidence fluctuations; the dashed line is a linear regression line showing the trend of the incidence fluctuations for the period under study.

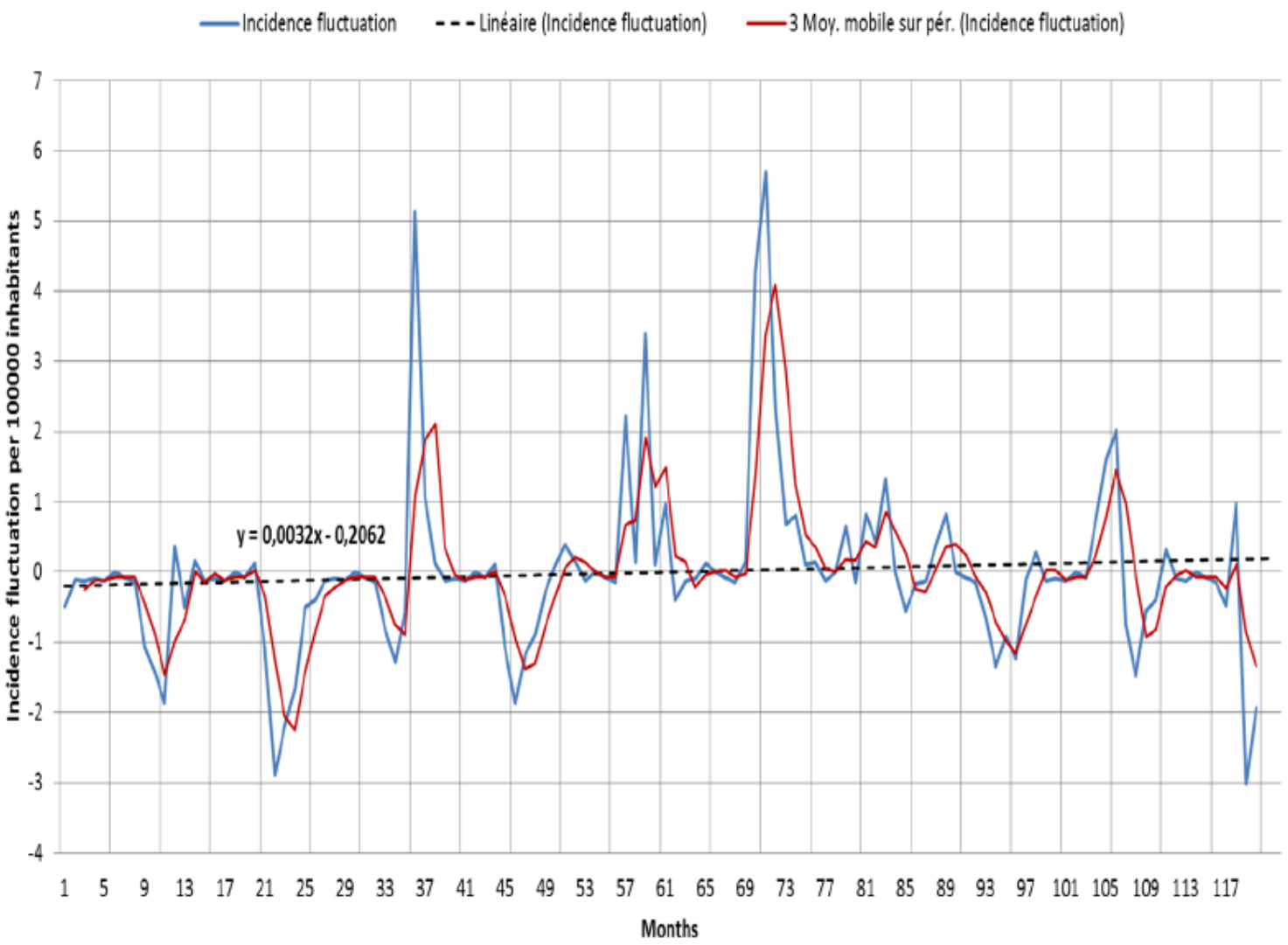

Figure 4

Time trend in incidence fluctuations of plague cases from month 1 to month 120 in the district of Tsiroanomandidy - Legends. The blue curve represents the incidence fluctuations; the red curve represents the quarterly moving averages of the incidence fluctuations; the dashed line is a linear regression line showing the trend of the incidence fluctuations for the period under study.

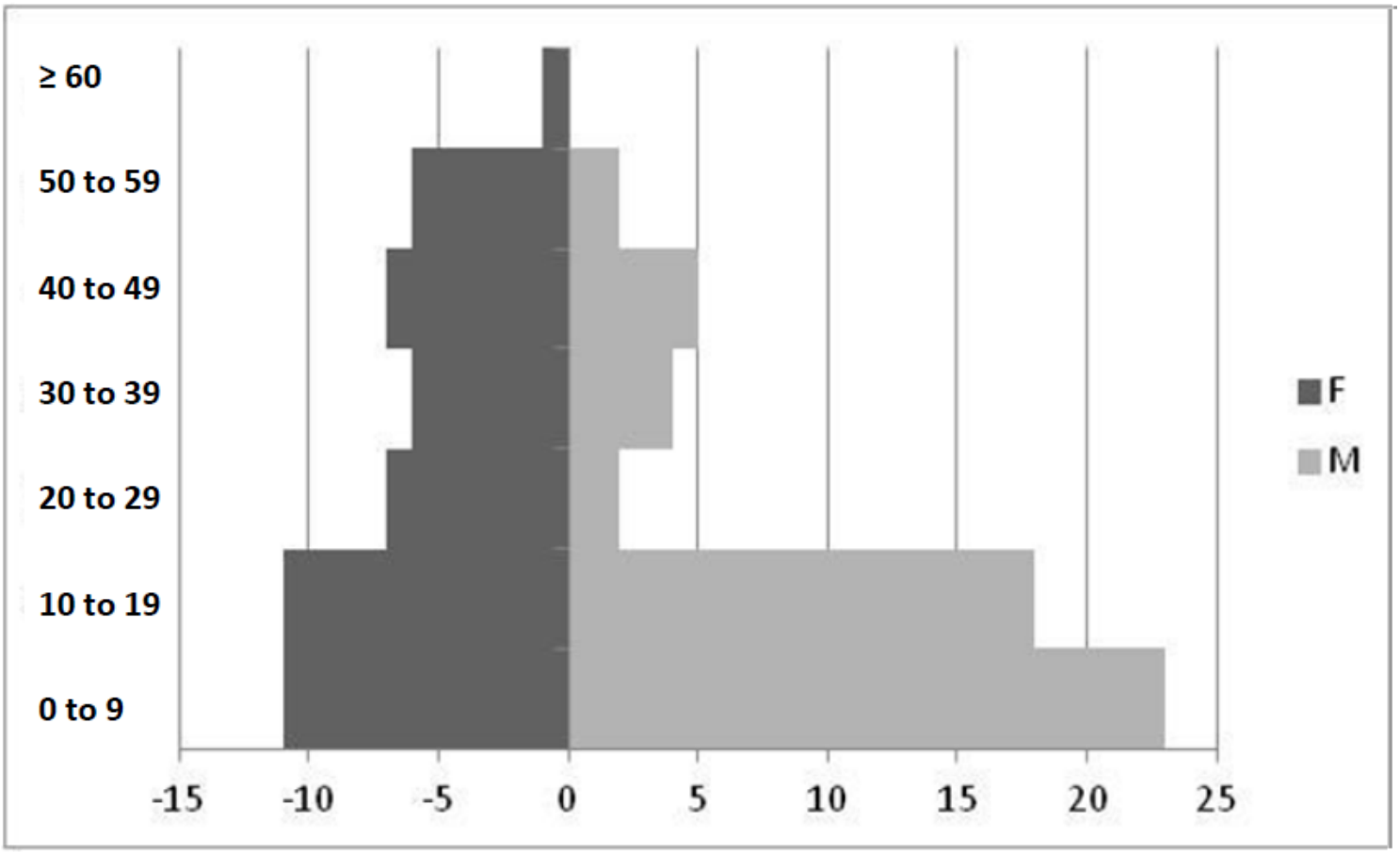

Figure 5

Confirmed and probable cases of plague, by sex and 10-year age group in Ambositra district, Madagascar, 2006-2015

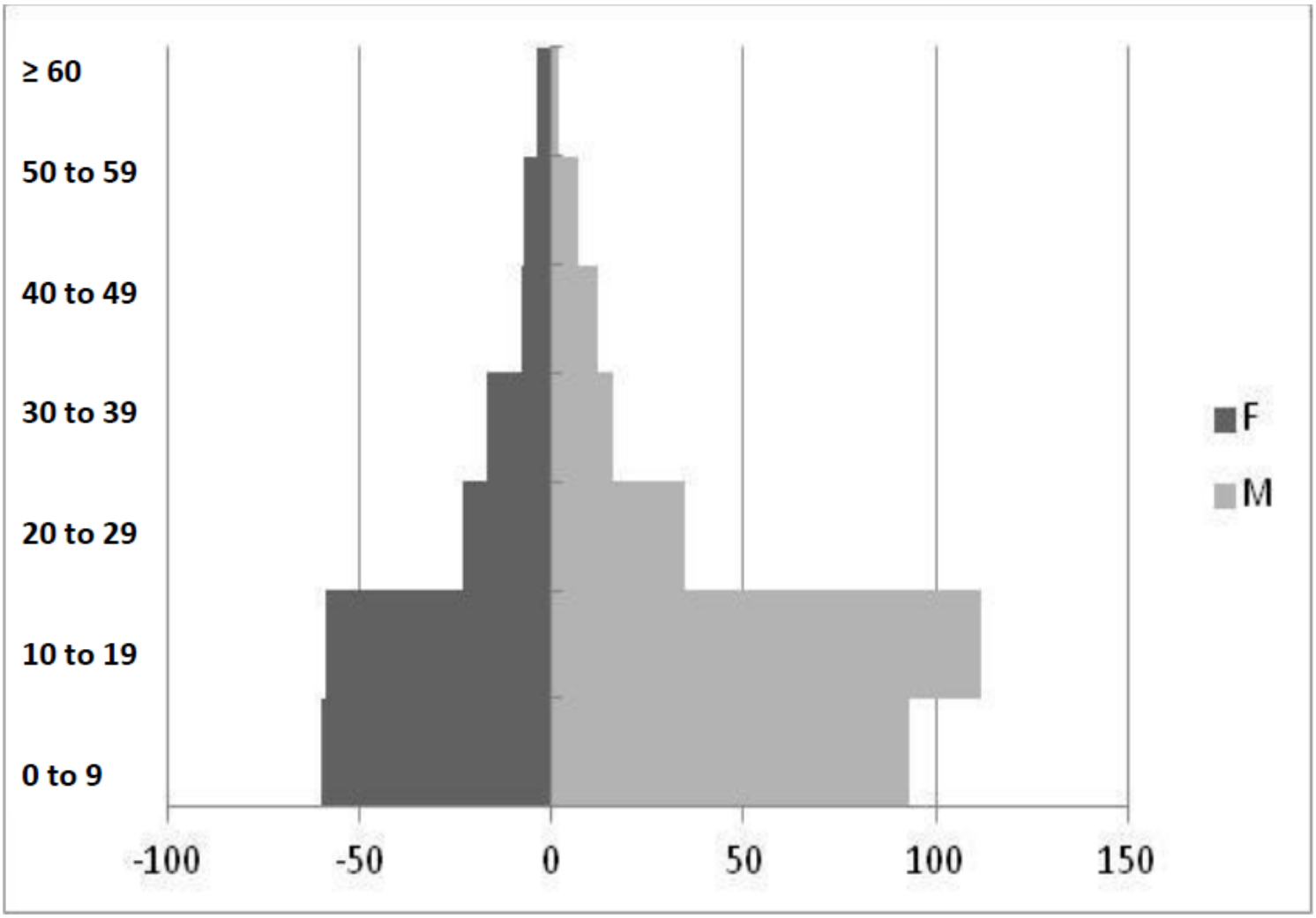

Figure 6

Confirmed and probable cases of plague, by sex and 10-year age group in Tsiroanomandidy district, Madagascar, 2006-2015