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Summary

Background Madagascar accounts for 75% of global plague cases reported to WHO, with an annual incidence of 200–700 suspected cases (mainly bubonic plague). In 2017, a pneumonic plague epidemic of unusual size occurred. The extent of this epidemic provides a unique opportunity to better understand the epidemiology of pneumonic plagues, particularly in urban settings.

Methods Clinically suspected plague cases were notified to the Central Laboratory for Plague at Institut Pasteur de Madagascar (Antananarivo, Madagascar), where biological samples were tested. Based on cases recorded between Aug 1, and Nov 26, 2017, we assessed the epidemiological characteristics of this epidemic. Cases were classified as suspected, probable, or confirmed based on the results of three types of diagnostic tests (rapid diagnostic test, molecular methods, and culture) according to 2006 WHO recommendations.

Findings 2414 clinically suspected plague cases were reported, including 1878 (78%) pneumonic plague cases, 395 (16%) bubonic plague cases, one (<1%) septicaemic case, and 140 (6%) cases with unspecified clinical form. 386 (21%) of 1878 notified pneumonic plague cases were probable and 32 (2%) were confirmed. 73 (18%) of 395 notified bubonic plague cases were probable and 66 (17%) were confirmed. The case fatality ratio was higher among confirmed cases (eight [25%] of 32 cases) than probable (27 [8%] of 360 cases) or suspected pneumonic plague cases (74 [5%] of 1358 cases) and a similar trend was seen for bubonic plague cases (16 [24%] of 66 confirmed cases, four [6%] of 68 probable cases, and six [2%] of 243 suspected cases). 351 (84%) of 418 confirmed or probable pneumonic plague cases were concentrated in Antananarivo, the capital city, and Toamasina, the main seaport. All 50 isolated *Yersinia pestis* strains were susceptible to the tested antibiotics.

Interpretation This predominantly urban plague epidemic was characterised by a large number of notifications in two major urban areas and an unusually high proportion of pneumonic forms, with only 23% having one or more positive laboratory tests. Lessons about clinical and biological diagnosis, case definition, surveillance, and the logistical management of the response identified in this epidemic are crucial to improve the response to future plague outbreaks.

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Introduction

Plague, a disease caused by a Gram-negative bacillus *Yersinia pestis*, has been linked to three major historical pandemics with devastating impacts on human populations.[1] Plague can manifest itself through different clinical presentations. Bubonic plague is the most common form and is acquired through bites from fleas that serve as vectors between reservoirs (wildlife or commensal rodents) and humans. A small number of bubonic plague cases might develop into secondary pneumonic plague through septicaemic spread. Although there is generally no onward transmission from bubonic plague cases, interhuman transmission from pneumonic plague cases to close contacts can occur through droplet spread.[2] Bubonic plague cases are characterised by fever and painful lymphadenitis in the area of the fleabite, whereas pneumonic plague cases are characterised by sudden fever, cough, and symptoms of lower respiratory tract infections, often with haemoptysis as the disease progresses. Prompt treatment with appropriate antibiotics is usually effective; however, case fatality rates (CFRs) have remained high, at about 10% and 40% in previous bubonic plague and pneumonic plague epidemics, respectively, as reported by WHO.[3]

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Research in context

Evidence before this study

Madagascar accounts for 75% of plague cases reported to WHO globally, with an annual incidence of 200–700 cases (mainly bubonic plague). In 2017, a pneumonic plague epidemic of unusual size, timing, and geographical location occurred. On July 13, 2018, we searched Web of Science for articles published in English between Jan 1, 2017, and July 13, 2018, with the terms "plague" and "Madagascar" in the title. We found 20 publications, including seven news items, five perspective articles discussing the response to the epidemic, and six articles presenting research unrelated to the 2017 plague epidemic in Madagascar. One article estimated the basic reproduction number of pneumonic plague in the 2017 epidemic from an analysis of preliminary data extracted from situation reports. Another article evaluated the risks of exportation. We identified no detailed descriptions of the 2017 epidemic.

Added value of this study

In this study, we present the epidemiology and transmission dynamics of the 2017 plague epidemic in Madagascar. This predominantly urban epidemic was characterised by many notified cases, with a quarter classified as confirmed or probable cases, and an unusually high proportion of pneumonic forms. The study provides a unique opportunity to better understand the epidemiological characteristics of pneumonic plague in a densely populated urban setting. The outbreak also illustrates the many challenges associated with the control of plague in Madagascar.

Implications of all the available evidence

This epidemic confirmed the significant public health risk of re-emergence of pneumonic plague in urban areas and its potential for rapid expansion. Lessons learned from this epidemic concerning clinical and biological diagnosis, case definition, surveillance, and logistical management of the response will form the basis for improved plague investigation and response efforts in Madagascar and beyond.

Since the 1990s, plague has been considered a re-emerging disease.[4–6] A few countries continue to report plague cases annually and, despite surveillance and response efforts, Madagascar accounts for 75% of plague cases reported to WHO.[3] Between 2010 and 2015, 200–700 suspected cases (about 55% of which were laboratory confirmed) were reported annually to the Central Laboratory for Plague (WHO collaborating centre) at the Institut Pasteur de Madagascar (Antananarivo, Madagascar), with a CFR of 20%. Most of these notifications (>75%) were bubonic plague cases from rural areas of the central highlands, where plague is endemic and seasonal, with cases typically occurring between October and April.[3] Small outbreaks of pneumonic plague were reported in 1997, 2011, and 2015 in rural areas of Madagascar (14–20 cases)[7–9] and in 2004 in Antananarivo (81 notified cases restricted mainly to one commune in the capital; Rajerison M, unpublished).

Between late August and November, 2017, Madagascar had an unprecedented plague epidemic with a large volume of notifications, a predominance of pneumonic forms, and multiple geographic foci, including two main urban areas—Antananarivo, the capital (with around 2·8 million inhabitants), and Toamasina, the main seaport (with around 290 000 inhabitants). The index case was a 31-year-old man who died from respiratory distress on Aug 28, 2017, while travelling in a bush taxi between the middle-west central highlands (Ankazobe) and the coastal town of Toamasina. Two fellow passengers from the taxi subsequently died on Sept 2, 2017, in Toamasina, and Sept 3, 2017, in Antananarivo, presumably contributing to further disease transmission in both cities. The first laboratory-confirmed pneumonic plague case was a 47-year-old woman from Antananarivo who was linked to the Toamasina cluster and died on Sept 11, 2017, confirming the suspicion of a pneumonic plague outbreak. WHO was notified by the Malagasy Ministry of Public Health on Sept 13, 2017, as per 2005 international health regulations, and the potential for a large-scale epidemic in an urban context prompted a large international response.[10,11]

The objective of this report is to describe the epidemiological characteristics of this epidemic. Before this report, our knowledge of pneumonic plague was largely based on a few small rural outbreaks or century-old information.[2,7–9,12–14] The extent of this epidemic therefore provides a unique opportunity to better understand the epidemiology of pneumonic plagues, particularly in urban settings. For completeness, we also describe bubonic plague over the same period, even though the trends were similar to those of previous years and represent the endemic background observed every year in Madagascar.

Methods

Data collection, biological analyses, and case classification

This is a retrospective observational study based on national surveillance data. The plague national surveillance system in Madagascar requires health-care professionals to notify suspected cases, on the basis of clinical presentation, to the Malagasy Ministry of Public Health and Institut Pasteur de Madagascar, where the Central Laboratory for Plague records the details on case notification forms and analyses biological samples for laboratory confirmation.

Case notification forms contained information on symptoms on admission, demographics (age, sex, occupation, and residence), the reporting health facility, key dates (symptom onset, clinical examination, and

sample collection), use of medication before admission, vital status, and type of laboratory samples collected. For cases without a notification form or with substantial missing information, the epidemiological team at Institut Pasteur de Madagascar followed up with the notifying health-care professionals.

Biological samples (bubo aspirates for bubonic plague, sputum for pneumonic plague, and liver or lung puncture from deceased patients) were collected by health-care workers or physicians from suspected plague cases. Biological diagnosis of plague was done at the Central Laboratory for Plague by rapid diagnostic tests,[15] molecular biology,[16,17] and culture[18] (appendix). At the beginning of the pneumonic plague epidemic, molecular biology, on the basis of conventional PCR targeting the *pla* gene, was used for *Y pestis* confirmation.[16,17] However, as the implemented protocol lacked specificity, this was replaced by real-time PCR (rtPCR) targeting the *pla* and *caf1* genes[19] on Nov 3, 2017. Furthermore, conventional PCR targeting the *pla*, *caf1*, and *inv* genes[20] was done on samples with inconclusive rtPCR results based on a new decision tree (appendix). All samples received before this date were retested using these new protocols over the months of November, and December, 2017. Cases were classified as suspected, probable, or confirmed based on the results of three types of diagnostic tests (rapid diagnostic test, molecular methods, and culture) according to 2006 WHO recommendations (table 1).[21] Point-of-care testing using rapid diagnostic tests was also done in public health-care centres as recommended by the Plague National Control Program. Because of insufficient experience of health-care staff operating in newly affected districts, the results of these tests were not considered, except when no other test could be done at the Central Laboratory for Plague.

Isolated *Y pestis* strains were tested for susceptibility to streptomycin, co-trimoxazole, tetracycline, ciprofloxacin, gentamicin, and chloramphenicol following Clinical Laboratory Standards guidelines.[23,24]

We used the collated database (Institut Pasteur de Madagascar database) of epidemiological, clinical, and laboratory data describing cases with disease onset between Aug 1, and Nov 26, 2017, since the pneumonic plague epidemic was officially declared over on Nov 27, 2017. Patients with a missing onset date were included if the date of clinical examination, sample collection, or sample receipt was within the epidemic period.

The data reported here are part of the plague national surveillance system and no specific additional ethics approval was necessary. All information on individual patients has been anonymised for presentation.

Treatment of cases

Treatment of suspected cases and preventive measures were implemented without waiting for biological confirmation. Although intramuscular high-dose streptomycin is the recommended first-line treatment for plague, fluoroquinolones are sometimes used to avoid potential side-effects of streptomycin.[25] We describe the use of antibiotics with known effect on *Y pestis*, including tetracyclines (doxycycline), sulfamides (co-trimoxazole), aminoglycosides (streptomycin, amikacin, or gentamicin), and fluoroquinolones (ciprofloxacin or ofloxacin) as reported by the notification forms.

Several control measures were put in place to contain the outbreak. These included the set-up and strengthening of effective triage measures and treatment centres for patients with plague, post-exposure antibiotic prophylaxis for contacts of all suspected cases, follow-up of these contacts to ensure rapid isolation and treatment, strengthening of surveillance through a range of activities, such as active case finding, air, ground, and seaport screening, and the set-up of an alert phone line, and appropriate and wide-ranging health promotion, social mobilisation, and community communication activities to the population. In the context of a condition such as plague, which carries potential stigma, health education messages were particularly important to strengthen early warning and ensure that patients sought care early. Finally, the widespread use of antibiotics in the community might have also contributed to reduction of community transmission.

Statistical analysis

We produced epidemic curves, sociodemographic and clinical case characteristics, and CFR estimates of plague cases according to case classification and clinical form. We then focused analyses on confirmed or probable cases (ie, cases with at least one positive laboratory test).

We explored potential differences in the CFR over time. Geographical zones were classified as Antananarivo area (urban community of Antananarivo and the three neighbouring districts), Toamasina district, endemic zone (plague-endemic districts[26] apart from Antananarivo area), or other. To investigate risk factors of death among confirmed cases, we estimated CFRs and exact binomial

	Definition
Suspected cases	All clinically suspected plague cases that meet the clinical and epidemiological criteria as per WHO recommendations*
Probable cases†	Clinically suspected cases with positive rapid diagnostic test or positive molecular biology, and culture negative or not done
Confirmed cases	Clinically suspected cases with positive rapid diagnostic tests and positive molecular biology, or positive culture

Case definitions made on the basis of 2006 WHO recommendations,[21] using three diagnostic tests done at Institut Pasteur de Madagascar—rapid diagnostic tests, molecular biology (following the algorithm detailed in the appendix), and culture. Serologies (anti-F1 IgG detection) were not done during the epidemic period. *Compatible clinical presentation (fever, sepsis syndrome, lymphadenopathy, or acute pneumonitis) and epidemiological features (such as exposure to infected animals or humans, evidence of flea bites, or residence in or travel to a known endemic focus within the previous 10 days).[21,22] †For a single pneumonic plague case, none of the three diagnostic tests could be done at Institut Pasteur de Madagascar, but the rapid diagnostic test done at the health-care centre was positive and associated with clinical symptoms of plague; this case was classified as probable.

Table 1: **Case definitions**

See Online for appendix

	Pneumonic plague			Bubonic plague		
	Confirmed (n=32)	Probable (n=386)	Suspected (n=1460)	Confirmed (n=66)	Probable (n=73)	Suspected (n=256)
Sex						
Male	23 (72%)	195/381 (51%)	819/1443 (57%)	39 (59%)	41/72 (57%)	145/254 (57%)
Female	9 (28%)	186/381 (49%)	624/1443 (43%)	27 (41%)	31/72 (43%)	109/254 (43%)
Age (years)						
0–4	5/31 (16%)	89/377 (24%)	407/1444 (28%)	4 (6%)	12/70 (17%)	34/252 (13%)
5–14	3/31 (10%)	42/377 (11%)	152/1444 (11%)	26 (39%)	29/70 (41%)	99/252 (39%)
15–49	19/31 (61%)	206/377 (55%)	758/1444 (52%)	33 (50%)	26/70 (37%)	108/252 (43%)
≥50	4/31 (13%)	40/377 (11%)	127/1444 (9%)	3 (5%)	3/70 (4%)	11/252 (4%)
Use of antibiotics with effect on *Yersinia pestis* before clinical examination*	8 (25%)	70 (18%)	221 (15%)	14 (21%)	14 (19%)	62 (24%)
Time to clinical examination (days)	1·5 (0·0–3·0)	1·0 (0·0–3·0)	1·0 (1·0–3·0)	1·0 (1·0–2·0)	1·0 (1·0–3·0)	1·0 (0·0–2·3)
Fever (≥37·5°C)	21/28 (75%)	220/329 (67%)	771/1288 (60%)	52/53 (98%)	47/60 (78%)	182/231 (79%)
Pulmonary symptoms						
Cough	26 (81%)	268/354 (76%)	977/1370 (71%)	9/56 (16%)	10/54 (19%)	15/233 (6%)
Chest pain	16 (50%)	127/348 (36%)	429/1366 (31%)	3/53 (6%)	1/54 (2%)	8/233 (3%)
Haemoptysis	15/31 (48%)	118/349 (34%)	461/1361 (34%)	0	0	2/233 (1%)
Adenopathy	1/25 (4%)	12/338 (4%)	34/1338 (3%)	66 (100%)	70/70 (100%)	249/249 (100%)
Fatal outcome	8 (25%)	27/360 (8%)	74/1358 (5%)	16 (24%)	4/68 (6%)	6/243 (2%)

Data are n (%), n/N (%), or median (IQR). In addition to the cases in this table, there was one case of septicaemic plague and 140 cases whose clinical form was not specified (appendix). Characteristics of confirmed or probable cases are presented in the appendix. Some individuals had missing case characteristics; the total number of observations by characteristic might therefore not add up to the total number of cases. *Cases without any reported treatment probably include cases with missing information.

Table 2: **Characteristics of pneumonic plague and bubonic plague cases**

95% CIs by sociodemographic, clinical, and epidemiological factors. Because of the small number of confirmed cases, we described trends in the data but could not assess statistical evidence for differences. We explored if similar trends were present for the larger number of confirmed or probable cases, for which we estimated risk ratios (RR) of death and 95% CIs using a log-binomial regression model (appendix). We did a survival analysis to investigate the potential effects of censoring (eg, deaths that occurred after case reporting) and evaluated the effect of inclusion of cases with unspecified clinical forms on CFR estimates among confirmed or probable cases (appendix). We estimated survival probability by days since onset of illness on the basis of a generalisation of the Kaplan-Meier curve. We compared the time to death among confirmed or probable pneumonic plague and bubonic plague cases with a weighted log-rank test.

We used a simple exponential growth model to compute the doubling time (ie, the time it takes for the number of cases to double) of confirmed and confirmed or probable cases in the growing phase of the pneumonic plague epidemic, for the whole country and for the Antananarivo area.[27] We derived upper bound estimates for the reproduction number of pneumonic plague (ie, the average number of people infected by a pneumonic plague case; appendix).

We mapped the spatial distribution of confirmed or probable cases using districts of residence (n=114) as geographical scales, with an analysis of spatial clustering (appendix).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 1, and Nov 26, 2017, 2414 plague cases were reported, including 1878 (78%) pneumonic plague cases, 395 (16%) bubonic plague cases, one (<1%) septicaemic case, and 140 (6%) cases with unspecified clinical form (table 2; appendix). 66 additional cases with missing dates were not included in our study. Case notification forms were available for 2266 (94%) of 2414 cases and biological samples were available for 2405 (>99%) of 2414 cases. 32 (2%) of 1878 notified pneumonic plague cases were confirmed and 386 (21%) were probable. 66 (17%) of 395 notified bubonic plague cases were confirmed and 73 (18%) were probable.

After an initial phase with low numbers of notified cases, the weekly number of notified pneumonic plague cases increased markedly at the end of September, 2017, reaching its peak (423 cases) in the week beginning Oct 2, 2017 (figure 1). The number of bubonic plague cases peaked at

the same time as pneumonic plague cases, with 245 (62%) notifications occurring in October, 2017 (figure 1).

The median age of confirmed pneumonic plague cases was 26 years (IQR 15–28) and 23 (72%) of 32 patients were male (table 2). Most confirmed pneumonic plague cases reported cough (26 [81%] of 32 cases), and around half of cases had chest pain (16 [50%] of 32 cases) and haemoptysis (15 [48%] of 31 cases). Eight (25%) of 32 confirmed pneumonic plague cases reported use of antibiotics active on *Y pestis* before clinical examination (table 2). The frequency of symptoms in probable pneumonic plague cases often fell between the frequency in confirmed and suspected pneumonic plague cases (eg, prevalence of cough, 26 [81%] of 32 confirmed cases, 268 [76%] of 354 probable cases, and 977 [71%] of 1370 suspected cases; prevalence of fever, 21 [75%] of 28 confirmed cases, 220 [67%] of 329 probable cases, and 771 [60%] of 1288 suspected cases; table 2).

Among confirmed bubonic plague cases, the median age was 15 years (IQR 8–20) and 39 (59%) of 66 cases were male. Fever was reported in 52 (98%) of 53 confirmed cases, 47 (78%) of 60 probable cases, and 182 (79%) of 231 suspected bubonic plague cases (table 2).

Characteristics of confirmed or probable cases are presented in the appendix.

The CFR was higher among confirmed cases (eight [25%] of 32 cases) than probable (27 [8%] of 360 cases) or suspected pneumonic plague cases (74 [5%] of 1358 cases; table 2), and a similar trend was seen for bubonic plague cases (16 [24%] of 66 confirmed cases, four [6%] of 68 probable cases, and six [2%] of 243 suspected cases; table 2). CFR estimates for probable cases were similar regardless of which diagnostic test was positive (appendix). The CFR among confirmed, probable, and suspected pneumonic and bubonic plague cases was stable over time (figure 2). Cases with unspecified clinical form had a high CFR (78 [92%] of 85 cases; appendix).

The risk of death for confirmed pneumonic plague cases tended to be higher among cases with chest pain than others (seven [44%] of 16 cases *vs* one [6%] of 16 cases; appendix), among cases with haemoptysis than others (six [40%] of 15 cases *vs* two [13%] of 16 cases), and among cases in the endemic zone than in Antananarivo area (five [50%] of ten cases *vs* three [17%] of 18 cases). The risk of death for confirmed bubonic plague cases tended to increase with time to clinical examination (five [13%] of 38 cases with 0 to 1 days *vs* eight [40%] of 20 cases with 2 to 4 days; appendix). The analysis of risk factors of death among confirmed or probable cases showed similar trends, but did not support a higher risk of death among cases with chest pain or haemoptysis (appendix).

All deaths among confirmed or probable cases occurred within 8 days of symptom onset (figure 2), with a median delay from onset to death of 1 day for pneumonic plague cases and 2 days for bubonic plague cases (weighted log-rank test p=0·12).

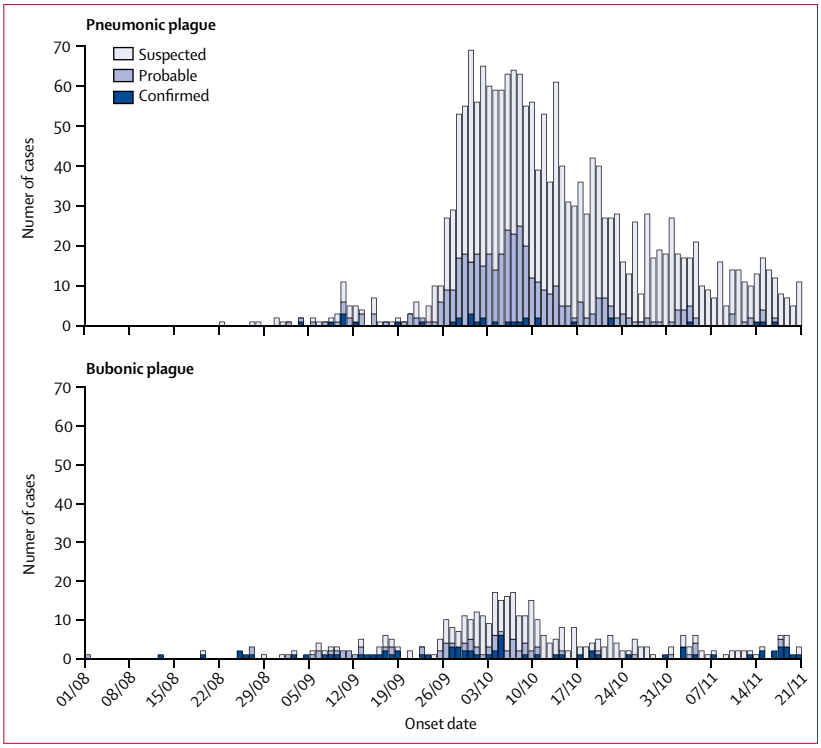

Figure 1: **Daily number of notified plague cases over time (onset date) by case classification**
Numbers of pneumonic plague (A) and bubonic plague (B) cases. Onset dates were imputed for 140 pneumonic plague and 22 bubonic plague cases. Seven pneumonic plague and two bubonic plague cases with missing onset, clinical examination, and sample collection dates are not shown.

Between Sept 13, and Oct 9, 2017, the number of confirmed or probable pneumonic plague cases doubled on average every 5 days (95% CI 4–6) in the whole country and in Antananarivo area (appendix). The reproduction number of pneumonic plague was estimated to be 1·6 or less (appendix).

The spatial distribution of confirmed or probable cases is shown in figure 3. Pneumonic plague mainly affected the urban centres of Antananarivo (288 [69%] of 418 cases) and Toamasina (63 [15%] of 418 cases), and showed substantial spatial clustering (appendix). 131 (94%) of 139 confirmed or probable bubonic plague cases were observed in plague-endemic districts (31 in Antananarivo area and 100 outside).

50 *Y pestis* strains were isolated (41 bubonic plague, eight pneumonic plague, and one unspecified form). All isolated strains were susceptible to the tested antibiotics.

Discussion

In this study, we described the epidemiology of the 2017 plague epidemic in Madagascar. This predominantly urban epidemic was characterised by many notified cases, with a quarter of cases classified as confirmed or probable, and an unusually high proportion of pneumonic forms. This study provides a unique opportunity to better understand the epidemiological characteristics

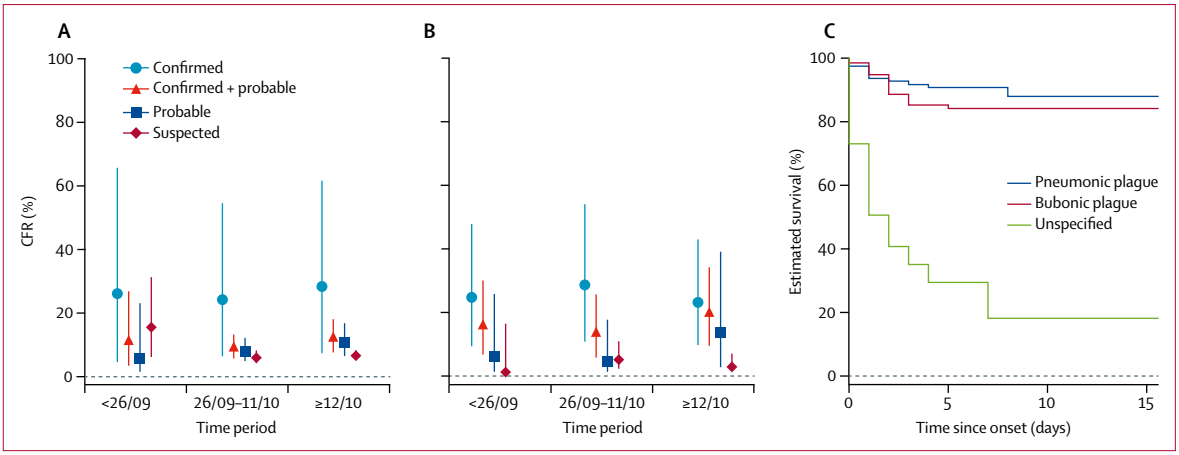

Figure 2: **CFRs by time period among confirmed, probable, and suspected pneumonic plague (A) and bubonic plague (B) cases, and probability of survival by days since symptom onset for confirmed or probable cases (C)**
Plots represent CFR and 95% CIs for confirmed, probable, and suspected cases by time period of the epidemic (initial, rapid growth, and control phase). CFR=case fatality ratio.

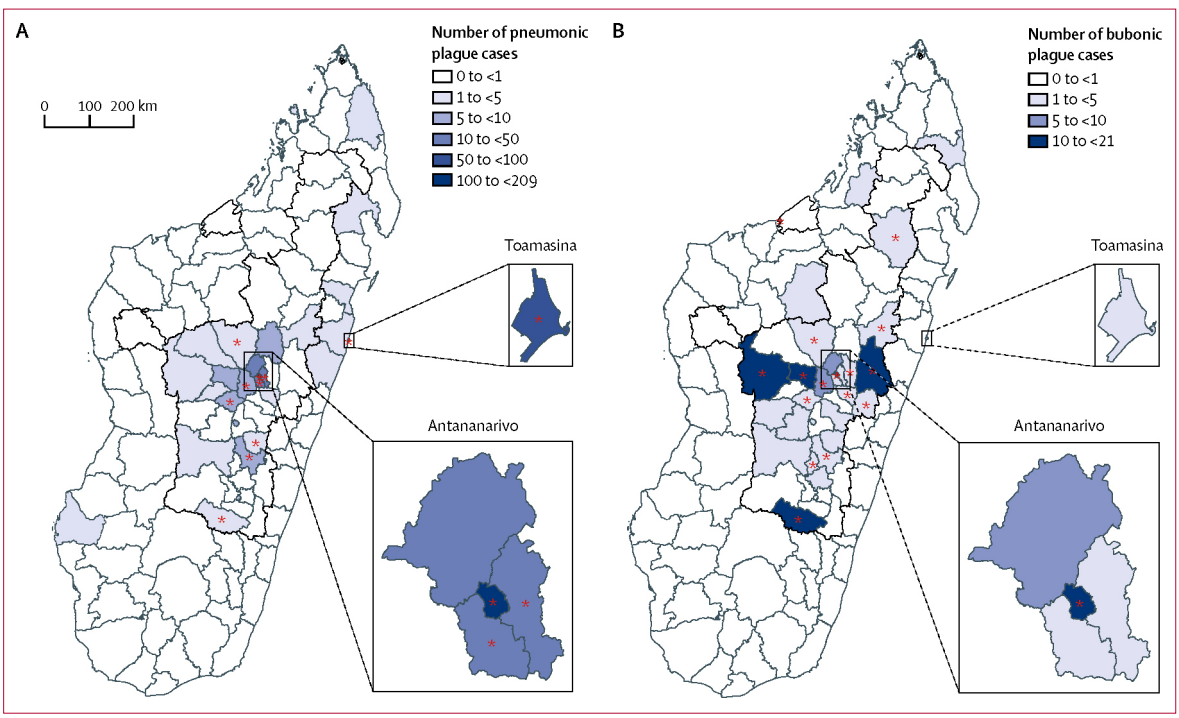

Figure 3: **Spatial distribution of confirmed or probable plague cases**
Number of pneumonic plague cases per district (A). Number of bubonic plague cases per district (B). Red stars indicate districts with at least one confirmed case. The solid black line delimits the endemic districts.

of pneumonic plague in a densely populated urban setting. The outbreak also illustrates the many challenges associated with control of plague in Madagascar.

The epidemic was characterised by exceptionally large numbers of pneumonic plague case notifications (1878 in 2017 *vs* 83 per year on average in 2010–15), although the number of notified bubonic plague cases remained similar to that of recent years.[3] The rapid increase in notified cases, particularly of pneumonic form, at the end of September, 2017, prompted a large national and international multisectoral response, the creation of a national emergency task force, and a joint response plan to curtail the epidemic.[10] The urban nature of the epidemic, its multiple foci, and the potential for international human-to-human spread, as well as the potentially high lethality, required rapid and sustained multipronged efforts. The outbreak also had a substantial impact on society (eg, school closure) and travel and

trade for Madagascar (eg, implementation of airport screening measures—some airlines cancelled flights). The large number of suspected cases was a major hurdle for logistical management of the different aspects of the response.

This outbreak was the first time that the Central Laboratory for Plague had received such a large number of pneumonic plague samples, which raised several challenges for laboratory confirmation of cases. The tests initially used by the Central Laboratory for Plague had mainly been done on bubonic plague samples and their performance on primary pneumonic plague samples had not been evaluated. Testing the presence of *Y pestis* is much more challenging for pneumonic plague because of the quality of sputum samples and the contamination of samples by the commensal flora of the upper respiratory tract. For example, the insufficient specificity of conventional *pla* PCR on pneumonic plague samples led to rapid implementation of improved molecular diagnostics. Samples collected before Nov 3, 2017, were retrospectively retested in November, and December, 2017, with the upgraded molecular biology techniques. The higher specificity of these techniques led to a decrease in the final number of confirmed or probable cases compared with previous reports during the outbreak, particularly for pneumonic plague cases.[10]

Therefore, the magnitude of the pneumonic plague epidemic is likely to have been smaller than suggested by notifications, since only 23% of notified pneumonic plague cases had more than one positive laboratory test, with laboratory results available for more than 99% of cases. The spatial extent of the pneumonic plague epidemic appears to have been relatively restricted, with 84% of the confirmed or probable pneumonic plague cases observed in the initial two main urban transmission sites (Antananarivo area and Toamasina). With a doubling time of 5 days, the growth in confirmed or probable pneumonic plague cases was fast, but part of that growth might have been due to increased reporting thanks to enhanced contact tracing and a rise in public awareness. Factors that might explain over-reporting of pneumonic plague cases include little clinical experience in newly affected areas (pneumonic plague is rare and few clinicians in Madagascar had had first-hand experience of it), and difficulty of clinical diagnosis in a context in which respiratory signs can be caused by other circulating pathogens (eg, a concomitant outbreak of bronchiolitis among children). Indeed, patients with pneumonic plague initially present with mostly non-specific upper respiratory symptoms, such as cough, fever, and headache, and differential diagnosis is therefore difficult on clinical grounds, particularly in the early stages of disease. Some similarities to this outbreak can be seen in an outbreak of pneumonic plague in India in 1994 that resulted in more than 6000 notifications for less than 300 confirmed or probable cases.[28] In this Indian epidemic, experts recommended that suspected cases with negative biological test results should remain classified as suspected.[22] Overall, more than 99% of suspected cases tested negative on both rapid diagnostic tests and PCR (with a culture that was either negative or not done). Investigating these negative cases more thoroughly in future outbreaks, and revising guidelines accordingly, might help better characterise the true magnitude of plague outbreaks.

In a context such as this, in which confirmatory diagnostics are challenging, it remains difficult to precisely quantify the prevalence of plague among notified cases. For example, newly implemented rtPCR targeting two genes is expected to be highly specific but could have insufficient sensitivity. Therefore, the true prevalence of plague in notified pneumonic plague cases is likely to lie somewhere between that of confirmed and probable cases, and also justifies why we did our analyses on confirmed cases and on confirmed or probable cases as a joint group. This theory was corroborated by the fact that numbers for demographic, clinical, and epidemiological characteristics of probable cases often fell between those for confirmed and suspected cases.

The CFRs of suspected (5%), probable (8%), and confirmed (25%) pneumonic plague cases differed markedly. These differences might be due to various reasons, including a proportion of false positives among probable cases, a lower probability of being diagnosed as a confirmed case among non-deaths, since sputum samples have a lower yield than do lung or liver samples, which are only taken from dead individuals (appendix), and early and frequent antibiotic use (because of frequent self-medication facilitated by the availability of antibiotics without a prescription) and better clinical care, which might both reduce the probability of confirmation (ie, hence cases are probable) and increase the likelihood of survival (hence lower CFR). These factors might also partly explain why the CFR did not substantially change with the response. Better access to health care and more intensive use of antibiotics in cities (that were predominantly affected by pneumonic plague) might partly explain why the CFR of pneumonic plague cases was lower in cities than in the endemic zone, and why pneumonic plague cases were not more severe than bubonic plague cases, as is typically observed. The CFR was particularly high in cases with unspecified clinical form, most of whom died before the history of symptoms could be accurately reported. No nosocomial cases were identified using the notification forms; assessment of the post-epidemic serological status of exposed health-care workers is ongoing.

Serology was not done because the collection of blood samples was restricted by logistical constraints and was not recommended by the Plague National Control Program in this epidemic context. Serological examination of recovered patients with pneumonic plague is ongoing during post-epidemic investigations.

We can only speculate about the factors that led to such an unprecedented outbreak. The early start might have been induced by changes in the demography or behaviour of the reservoir (potentially due to climatic or ecological variations), which could have increased the risk of contact with humans. Detection of pneumonic plague cases can be more challenging in the middle of the austral winter because of the concomitant circulation of other respiratory diseases with similar symptoms. Once plague reaches multiple locations, including urban centres with high population densities, management and control of the epidemic becomes much more challenging. The lower median age for bubonic plague cases might be explained by behavioural factors—young adults are more involved in agricultural activities, exposing them to contact with rodents and fleas, and children spend more time close to the floor than do adults, leading to greater exposure to flea bites.

There are several limitations to this study. The samples and data used were collected during the response to a major epidemic and should be interpreted in this context. For example, information on pre-examination treatment was collected as free text and absence of treatment could not be distinguished from missing information. Acquiring information from severely ill cases is difficult and the quality of collected data might be affected by outcome, potentially leading to some reporting biases.

Despite these challenges, our study provides invaluable information about the characteristics, epidemiology, and transmission dynamics of pneumonic plague. This epidemic illustrates the difficulty in adapting medical and public health responses during an epidemic of unusual magnitude and clinical form, in predominantly urban areas. In such an emergency context, national and international multidisciplinary mobilisation is important to support real-time surveillance capacity, improved microbiological testing, community sensitisation, and protection of health-care workers. Structures and strengthened surveillance mechanisms put in place during the epidemic now need to be optimised to strengthen national and international response capacities in case of another urban outbreak. Additionally, multidisciplinary research programmes to improve diagnostic algorithms, alternatives to aminoglycoside-based treatment, immune response mechanisms in humans, and studies disentangling causes for re-emergence[29] are required.

Overall, this epidemic confirmed the significant public health risk of re-emergence of pneumonic plague in urban areas and its potential for rapid expansion. Lessons learned from this epidemic will form the basis for improved plague investigation and response efforts in Madagascar and beyond.

Contributors

VA, BR, SRaha, SRahe, GM, A-SLG, and MRaj did the laboratory tests. RR, VA, SRaha, FR, FMR, LBR, VRaz, LB, and MRaj contributed to the data collection and management (including the geographical information system). MJDDR and MRab contributed to patient clinical management and expertise. BN, JP, JMR, QAtB, and SC analysed the data. BN, JP, SC, LB, and MRaj wrote the first draft of the manuscript. RR, VA, LAR, CFN, EB, VRas, LB, AS, and MRaj coordinated the response. All authors critically commented on the manuscript and approved the final version.

Declaration of interests

We declare no competing interests.

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