

Epidemiological trends for human plague in Madagascar during the second half of the 20th century: a survey of 20 900 notified cases

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Summary

OBJECTIVES To describe the principal characteristics and epidemiological trends for human plague in modern times based on the largest reported series of cases from the highly active Malagasy focus. **METHODS** We used a file of 20 900 notified cases of suspected plague, 4473 of which were confirmed or probable, to carry out a statistical analysis of incidence and mortality rates and associated factors for 5-year periods from 1957 to 2001.

RESULTS Our analysis of trends showed (1) an increase in the incidence rate and the number of districts affected, (2) an increase in the proportion of bubonic forms (64.8–96.8%) at the expense of the pneumonic forms (35.2–3.2%) more frequent in elderly subjects and (3) a decrease in case fatality rate (CFR, 55.7–20.9%) associated with five factors: clinical form, season, province, urban/rural and period considered. The median age of patients was 14 years and more men than women were affected.

CONCLUSIONS Since the end of the 1980s, the incidence of plague in Madagascar has increased in both rural and urban areas, because of multiple socioeconomic and environmental factors. However, the plague mortality rate has tended to decrease, together with the frequency of pneumonic forms, because of the strengthening of control measures. Making dipstick tests for the rapid diagnosis of human cases and epizootics in rats available for health structures should make it possible to raise the alarm and to react rapidly, thereby further decreasing morbidity and CFR.

keywords human plague, Madagascar, surveillance, case fatality rate

Introduction

Plague is an infectious disease caused by a Gram-negative bacillus, *Yersinia pestis*. This ancient disease has marked human history by causing three deadly pandemics, the last of which began in China at the end of the 19th century and rapidly spread throughout the world via large ports (Pollitzer 1954). During the second half of the 20th century, the number of cases notified with large undernotification to the World Health Organization (WHO) showed two peaks – one in the 1970s, during the Vietnam War and the other in 1983, extending to the present day and affecting primarily African countries (WHO 1999, 2003). During this period of plague recrudescence or reemergence in the world, five countries have declared cases every year: Madagascar, Tanzania, Vietnam, China and the USA. In reality, Africa is the continent most

affected, particularly in the region of the great lakes, Mozambique and Madagascar. Between 1987 and 2001, more than 36 000 cases were notified to the WHO, with Tanzania and Madagascar, in particular, accounting for 60% of the African cases (Chanteau *et al.* 2000a). The recrudescence of plague on this large island has been attributed to multiple, complex factors (Duplantier *et al.* 2005).

Plague causes spectacular epizootics in rodents and may accidentally cause disease in humans. It manifests in two principal clinical forms: bubonic plague when contamination results from the patient being bitten by an infected flea from a rodent that has died of plague, and pneumonic plague that results from direct human-to-human transmission via the respiratory droplets. There is also a third, rare clinical form – septicæmic plague – in which neither buboes nor pulmonary signs are apparent. This third form

is frequently fatal within 24 h. The first reported cases of plague in Madagascar occurred in November 1898, in the port of Toamasina. The disease reached the capital, Antananarivo, in 1921. It then rapidly spread through the central highlands, remaining endemic to the present day (Chanteau *et al.* 2000a). The *Y. pestis* of the third pandemic is of the *orientalis* biotype and of ribotype B, but new biotypes have appeared over time throughout the world (Guiyoule *et al.* 1994). In Madagascar, the new Q, R and T ribotypes emerged at the beginning of the 1980s in highly active rural plague zones (Guiyoule *et al.* 1997). Two rodents – *Rattus rattus*, which is widespread throughout the island, and *Rattus norvegicus*, which is abundant in the large urban centres – and an insectivore, *Suncus murinus*, have been implicated in plague transmission cycles. Two fleas also play a role in plague transmission: *Xenopsylla cheopis*, a cosmopolitan flea found exclusively on rats within dwellings, and *Synopsyllus fonquerniei*, an endemic flea described in 1932 that lives as a parasite on outdoor rats in fields (Duplantier *et al.* 2005).

Madagascar has 16 million inhabitants and is divided into 6 administrative provinces and 111 health districts. It has three topological zones, conditioning climatic aspects: the central highlands (at an altitude of 800–2000 m), the narrow eastern coastal plain and the western part of the island dominated by a series of low- and medium-sized hills to the west.

As part of the national plague control programme, all suspected cases of plague should be declared to the Ministry of Health. The central plague laboratory then analyses the samples sent with the declaration forms and updates the national plague database. Bubonic plague is treated by a combination of injected streptomycin and oral sulfamethoxazole plus trimethoprim (cotrimoxazole). Pneumonic plague is treated with injected streptomycin only. Chemical prophylaxis is limited to subjects in contact with suspected plague cases. Sulfadoxine, cotrimoxazole and tetracycline are the recommended prophylactic drugs. Fleas are eliminated from a 200-m perimeter around the patient's home, including the patient's home itself, neighbouring homes and open spaces. In rural areas, deltamethrin powder is used for this purpose. In towns, carbamate insecticides are preferred because of pyrethroid resistance (Ratovonjato *et al.* 2000).

In this study, we aimed to describe the principal characteristics and epidemiological trends of this epidemic-prone disease and to analyse the factors associated with mortality in the largest series of cases recorded in a single country in the second half of the 20th century.

Methods

Monitoring of human plague

Since its introduction, the plague, a notifiable disease, has remained active in Madagascar. The national monitoring system was set up very early, in the 1950s, by the Pasteur Institute of Madagascar and is one of the oldest and best managed in any endemic country. In the absence of a diagnostic laboratory for case confirmation, several criteria can be used to identify cases of suspected plague: a favourable epidemiological context (occurrence of successive deaths in a single family or location, abnormally high levels of rat mortality and proliferation of fleas) and suggestive clinical signs (fever, painful adenopathy, haemoptysis and pneumopathy). In such situations, any patient identified by the health worker as requiring antiplague treatment is considered to be a suspected plague case.

Suspected cases are notified on a standardized form accompanied by Gram-stained blood smears and samples (pus from buboes, sputum or autopsy samples from the lungs and liver). These samples are used for the isolation of *Y. pestis* and are transported to Cary–Blair medium. This transport medium has only been used since 1995. Until then, samples were stored in saline (Brygoo & Rajenison 1969).

In Madagascar, patients are classified into three groups based on the results of biological tests: (1) confirmed cases (C) are defined as suspected cases for which a strain of *Y. pestis* was isolated in bacteriological tests, (2) probable cases (P) are defined as suspected cases with positive microscopy results (Gram-negative bacillus showing bipolar staining) without *Y. pestis* isolation and (3) suspected (S) clinical cases if the results of tests are negative or if no samples were taken from the patient.

National monitoring spreadsheet

We analysed data from the national archives compiled in a Microsoft Access file at the Central Plague Laboratory, covering the period 1957–2001. The information collected has varied over time, but the following data are available for the entire period: sex and age of the patient, geographical location, date of the examination, clinical form (bubonic or pneumonic), clinical progression and bacteriological results (positive direct examination, isolation of *Y. pestis*). For the period 1995–2001, the following data were also collected: the date on which the samples were taken, the date of arrival of the samples at the central laboratory, date of death, location of plague buboes and rodent mortality over the last 15 days. Finally, for the period 1998–2001, the following data were also collected: the painfulness and size of buboes, the general condition of

the patient, deaths among the patient's family and neighbours and the results of ELISA immunocapture tests for the detection of F1 antigen (not analysed here) (Chanteau *et al.* 2000b).

Data analysis

The denominators used to calculate the incidence rate of plague were obtained from the population census carried out in 1993 (Anonymous 1996). For each year in the period studied, the growth rates in the census document were applied in a retrospective manner to years before 1993 and in a prospective manner to years after 1993, as a means of estimating population size. The study period was subdivided into nine 5-year periods. We used bacteriological criteria (isolation of *Y. pestis* and/or positive microscopy results) to identify confirmed and probable (C + P) cases, because these were the only criteria for which data were available throughout the period studied.

We did a descriptive analysis of the principal characteristics of confirmed and probable cases of plague (sex, age and clinical form) and of mortality. Frequencies and proportions were compared by means of chi-square tests for trend. The significance threshold was fixed at 5%.

We studied the factors associated with death by means of logistic regression analysis. We calculated odds ratios (OR) with 95% confidence intervals from the β coefficients and their standard errors, using SPSS version 10.0 (SPSS, Inc., Chicago, IL, USA). The variables identified in univariate analysis as accounting for at least 20% of the variation in the variable to be explained were retained. A Hosmer–Lemeshow test was used to test the fit of the model, at the 5% level.

Results

Between 1 January 1957 and 31 December 2001 (45 years), 20 900 suspected cases of plague were declared, including 4473 confirmed or probable cases (21.4%). The progression of the disease over 5-year periods is described in Table 1, in terms of the numbers of suspected and C + P cases of the bubonic and pneumonic forms, the mortality rate and the number of districts declaring C + P cases. The incidence of suspected and C + P cases increased significantly over time ($P < 10^{-6}$ for both), as did the number of districts declaring plague cases ($P = 0.01$). Figure 1 shows the districts with human plague cases from 1957 to 2001. From 1995 to 2001, the median delay between sample collection and analysis was 8 days (range: 24 h to 110 days) for all districts, 1 day for the capital and 9 days for rural zones. These delays had not decreased over the study period (7–9 days depending on the year).

The seasonal variations in the number of C + P cases of bubonic and pneumonic plague are shown for the highlands only in Figure 2. Cases are reported throughout the year, with a marked epidemic season between October and March corresponding to the hot, rainy season. Incidence is the highest in January in the highest districts (above 1200 m) and in November in the other districts (Figure 3). The proportion of pneumonic forms was much higher in July ($P < 10^{-3}$), corresponding to the coldest period of the year (14 °C; Figure 2).

In the port of Mahajanga, where plague reappeared between 1991 and 1999, a different pattern was observed, with incidence beginning to increase in July, when mean temperatures are the lowest (24 °C) and reaching a maximum in October (Figure 3). No case of pneumonic plague was recorded in this coastal focus.

We analysed the distribution of C + P cases between different age groups, sexes, clinical forms and bubo sites (Table 2). Plague affected more men (57.1%) than women (42.9%). The proportion of men in the general population (49.5%) is significantly lower than the percentage of male plague patients ($P < 10^{-6}$). The mean age of the cases was 18.6 years and the median age was 14 years (range: <12 months to 98 years). The sex distribution of cases did not change with age ($P = 0.38$).

Bubonic forms accounted for more than 9 C + P cases in 10 (92.8%). Between 1957 and 2001 (Table 1), we observed a significant decrease in the proportion of pneumonic forms ($P < 10^{-6}$). This frequency (Table 2) varied with age ($P < 10^{-9}$), being around 5% until the age of 30 years and then gradually increasing to 25% after the age of 50 years. We compared the proportions of the clinical forms as a function of age with the distribution of the Malagasy population (Figure 4). Bubonic forms were overrepresented in children and adolescents between 5 and 19 years ($P < 10^{-6}$) of age, whereas pneumonic forms were overrepresented in adults over the age of 30 years ($P < 10^{-6}$).

The anatomical locations of plague buboes varied with age in C + P cases diagnosed between 1995 and 2001, the only period for which such information was available (Table 2). There was only one bubo in 98.1% of cases. Inguinal–femoral buboes were the most frequent (64.5%, for patients of all ages). The frequency of cervical buboes decreased with age ($P < 10^{-6}$), with this location most frequent in children under the age of 10 years (20.7%). This location was particularly frequent in children under the age of 2 years (27.3%, 9/33). The bubo was painful in 96% (818/852) of the C + P cases diagnosed between 1998 and 2001.

The case fatality rate (CFR) for C + P cases from 1957 to 2001 (Table 1) was 25.1%. We observed a significant

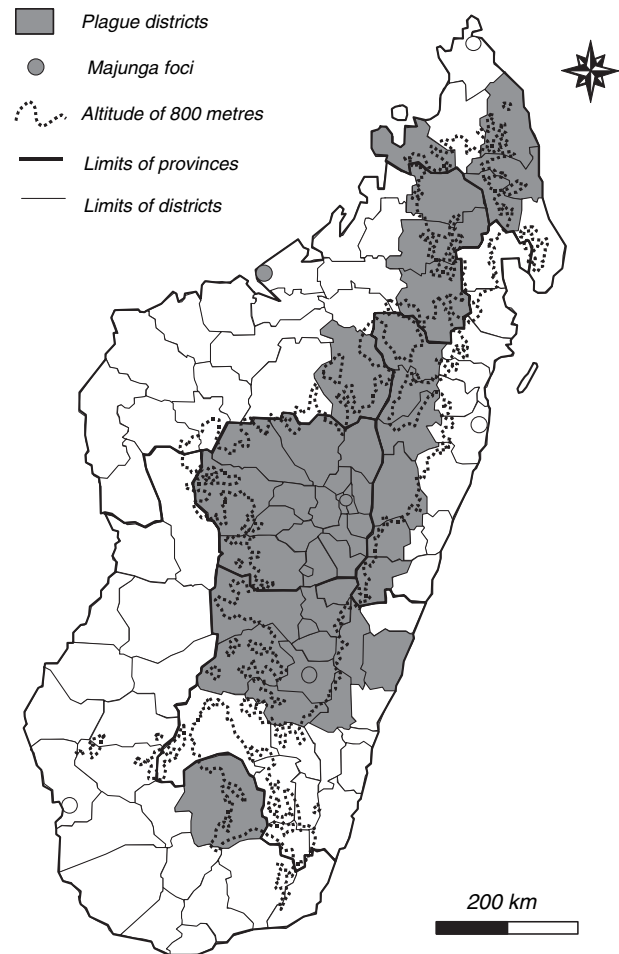
Table 1 Notified cases of plague in Madagascar from 1957 to 2001

Time period (years)	1957–1961	1962–1966	1967–1971	1972–1976	1977–1981	1982–1986	1987–1991	1992–1996	1997–2001	1957–2001
Suspect cases	798	689	988	1085	656	1161	2592	5174	7757	20 900
Incidence per 100 000	2.74	2.14	2.70	2.65	1.43	2.25	4.42	7.87	10.48	4.08
C + P* cases (%)	122 (15.3)	154 (22.4)	370 (37.4)	223 (20.6)	155 (23.6)	233 (20.1)	666 (25.7)	1030 (19.9)	1520 (19.6)	4473 (21.4)
Incidence per 100 000	0.42	0.47	1.01	0.54	0.34	0.45	1.13	1.56	2.07	0.89
Bubonic	79 (64.8)	118 (77.6)	325 (88.1)	203 (92.3)	142 (91.6)	201 (86.3)	631 (95.0)	954 (94.2)	1432 (96.8)	4085 (92.7)
C + P cases (%)†	43 (35.2)	34 (22.4)	44 (11.9)	17 (7.7)	13 (8.4)	32 (13.7)	31 (5.0)	59 (5.8)	47 (3.2)	322 (7.3)
Pneumonic C + P cases (%)‡	68	52	120	76	52	80	159	199	317	1123
Decased C + P cases (%)	55.7	33.8	32.4	34.1	33.5	34.3	23.9	19.3	20.9	25.1
Case fatality rate (%)	21 (18.9)	24 (21.6)	23 (20.7)	23 (20.7)	23 (20.7)	18 (16.2)	27 (24.3)	30 (27.0)	37 (33.3)	47 (42.3)
Number of districts (C + P) (%)‡										

* Confirmed (isolation of *Yersinia pestis*) or probable (positive microscopy) cases.

† Lack of information for some cases.

‡ Percentage of a total of 111 districts.

**Figure 1** Districts with confirmed or probable plague cases in Madagascar from 1957 to 2001.

decrease in CFR over time ($P < 10^{-9}$). We identified a number of associated factors, after adjustment for death (Table 3). The Hosmer–Lemeshow test was not significant ($P = 0.07$). Five factors were associated with death from plague: clinical form, season, province, urban/rural environment and the period considered. CFR was higher for the pneumonic than for the bubonic forms [adjusted OR (OR_a) = 6.04], in May ($OR_a = 1.85$) and in June ($OR_a = 2.06$) than in January and in the province of Antananarivo than elsewhere. The other provinces all had significantly lower OR_a values than Antananarivo, with the exception of Toliara, where few plague cases were declared. CFR was lower for patients treated in urban than in rural environments ($OR_a = 0.77$) and has been lower since the 1980s than before, with patients three times more likely to die of the disease between 1957 and 1961 than between 1992

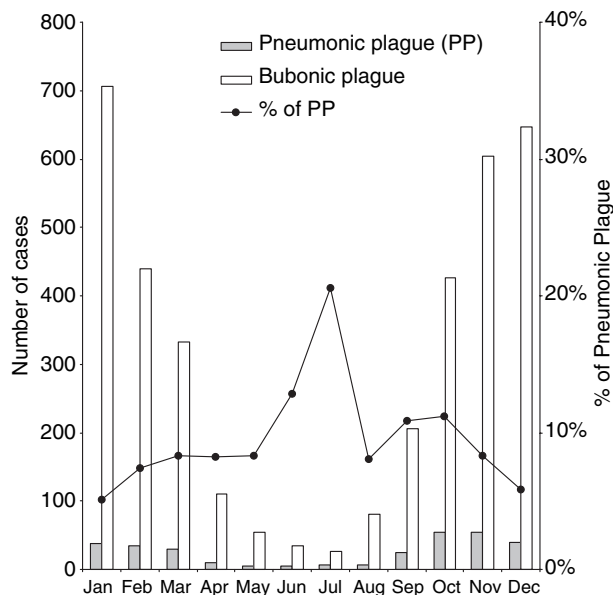


Figure 2 Seasonal variation in C + P human plague according to clinical form in the Malagasy highlands.

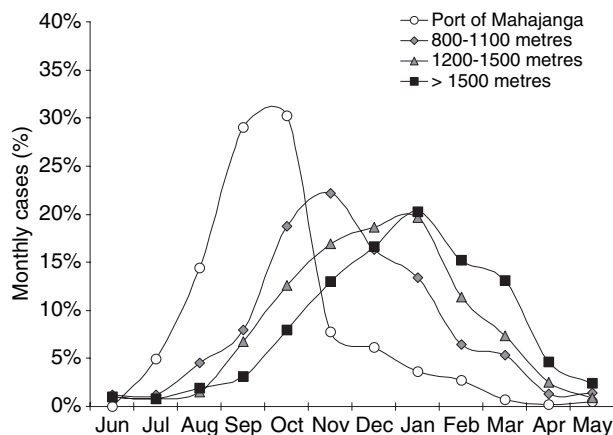


Figure 3 Shift in seasonality according to altitude in Madagascar (1957–2001).

and 2001 ($OR_a = 0.31$ in 1992–1996 and $OR_a = 0.32$ in 1997–2001).

Discussion

Analysis of the surveillance data for human plague in Madagascar from 1957 to 2001 shows a significant increase in the incidence of the disease since the end of the 1980s. This recrudescence follows a global trend, most marked in Africa. Madagascar accounted for about

half the suspected cases in Africa declared in the last 10 years (WHO 2003). At least some of the increase is real and is linked to multiple factors (socioeconomic, behavioural, bacteriological, rodentological and entomological) (Handschrumer *et al.* 2000; Duplantier *et al.* 2005). The rest may be artificial, linked to the intensification of monitoring and control activities in this country since 1995. This recrudescence concerns not only the rural environment traditionally affected by endemic plague but also the large urban centres, including the capital Antananarivo in the highlands and the port of Mahajanga (Boisier *et al.* 1997; Chanteau *et al.* 2000a; Boisier *et al.* 2002). Outside Mahajanga, the plague remains confined to altitudes of 800 m and above in the high central plateaus. This altitude threshold was discovered very early (Brygoo 1966) and is not specific to Madagascar. Following its introduction via the large ports of the world at the beginning of the 20th century, in most countries, plague took refuge at medium altitude, where the climatic conditions are optimal for the proliferation of rodents and plague-carrying fleas (particularly at the free pre-adult stage), maintenance of the bacillus and the heat-dependent expression of plague genes involved in blocking the flea's proventriculus (Cavanaugh 1971; Jarrett *et al.* 2004). In Madagascar, the endemic plague-carrying flea, *S. fonquerniei*, is not found below this altitude (Duplantier *et al.* 2005).

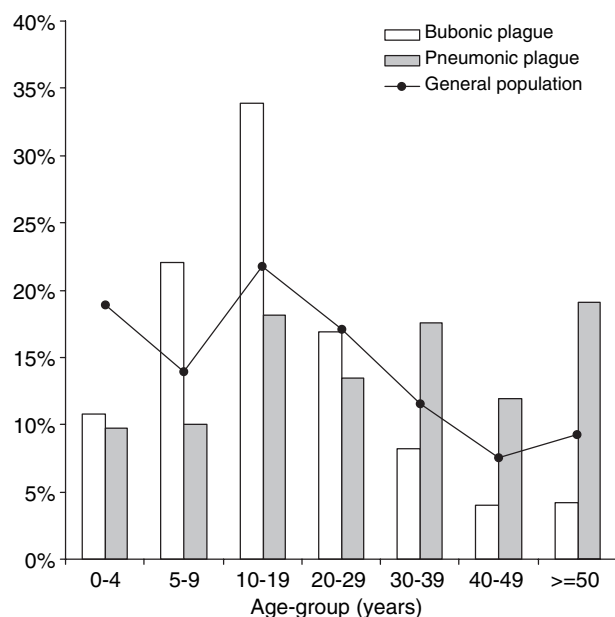
Plague is a seasonal disease. At the start of the rainy season, in rural areas in the highlands, fleas reach their maximum abundance at a time when *R. rattus* numbers are minimal. Human contamination occurs from September, by contact with endemic plague-carrying fleas from *R. rattus*. The rains bring rats from crops into close contact with rats from human dwellings, with *X. cheopis* taking over the role of endemic plague-carrying flea (Robic 1952). Recent studies have demonstrated that climatic factors affect the incidence of plague in humans. Plague incidence is positively correlated with spring rainfall (Parmenter *et al.* 1999) and negatively correlated with temperature, decreasing as the temperature increases up to a maximum of 32.2–35 °C (Enscore *et al.* 2002). Temperature has a direct effect on the blocking of the proventriculus of the flea (Cavanaugh 1971): at temperatures exceeding 27.5 °C, this process is no longer possible. *Yersinia pestis* can multiply over a large range of temperatures but grows optimally at temperatures of 26–28 °C. All these findings are consistent with observed altitude-dependent shifts in the timing of the plague season (Figure 3).

Plague more frequently affects men than women, regardless of the age of the individual, the clinical form of the disease and the geographical zone. This remarkable feature of plague was reported in early studies (Brygoo

Table 2 Human plague in Madagascar from 1957 to 2001: sex, clinical form and bubo location, by age group

Age group (years)	0–4	5–9	10–19	20–29	30–39	40–49	≥50	All ages
Confirmed and probable cases from 1957 to 2001								
Male (%)	271 (10.8)	527 (21.1)	845 (33.9)	408 (16.3)	215 (8.6)	112 (4.5)	120 (4.8)	2498 (57.1)
Female (%)	200 (10.7)	400 (21.3)	581 (31.0)	312 (16.6)	173 (9.2)	91 (4.9)	118 (6.3)	1875 (42.9)
Bubonic plague cases (%)	430 (93.2)	882 (96.5)	1352 (95.6)	673 (94.0)	328 (85.4)	160 (80.8)	169 (73.5)	3994 (92.6)
Pneumonic plague cases (%)	31 (6.8)	32 (5.7)	58 (4.1)	43 (6.0)	56 (14.6)	38 (19.2)	61 (26.5)	319 (7.4)
Confirmed and probable cases from 1995 to 2001								
Localization of buboes								
Cervical–maxillary (%)	41 (20.8)	74 (20.7)	69 (12.8)	25 (7.8)	14 (9.3)	7 (8.5)	5 (7.5)	235 (13.7)
Axillary (%)	43 (21.8)	79 (22.1)	108 (20.0)	50 (15.6)	30 (20.0)	16 (19.5)	14 (20.9)	340 (19.8)
Inguinal–femoral (%)	108 (54.8)	200 (55.9)	352 (65.2)	236 (73.5)	106 (70.7)	58 (70.7)	47 (70.1)	1107 (64.5)
Others* (%)	5 (2.5)	5 (1.4)	11 (2.0)	10 (3.1)	0 (0.0)	1 (3.0)	1 (1.5)	33 (1.9)

* Epitroclear, subclavicular, multiple.

**Figure 4** Frequency of clinical forms by age group in Madagascar from 1957 to 2001 (C + P cases).

1966). The preference for men has been attributed, in the highlands, to the agricultural activities of men, which bring them into greater contact with the rat/flea plague reservoir. Boisier *et al.* (1997, 2002) showed that this hypothesis was unlikely to apply to the coastal town of Mahajanga, taking into account the non-agricultural occupations of its population. Pollitzer (1954) reported a higher frequency of plague in men than in women in Manchuria, but a higher frequency in women than in men in India. Specific studies taking into account exposure and intrinsic factors are required to determine why men are more frequently affected in Madagascar.

Plague affects subjects of all ages but is more frequent in children and adolescents between 5 and 19 years of age. Several hypotheses have been put forward to account for this higher frequency in young subjects: (1) the behaviour of young people may expose them to a greater risk of contamination, (2) the immune system becomes stronger with age and young children may be less able to defend themselves against the plague bacterium. The observations made at Mahajanga are not consistent with the immune hypothesis, because the population had essentially no immunity when plague reappeared in 1991 after an absence from the area of 62 years (Boisier *et al.* 1997).

The bubonic form, which is transmitted by flea bites, accounted for more than 90% of the cases reported during the 45 years of monitoring. In almost all cases (98%), patients had a single bubo, mostly around the inguinal and femoral ganglia (64.5%). Cervical locations were rare overall (13.7%) but were more frequent in children under the age of 2 years (27.3%). This observation confirms long-standing reports on Madagascar (Brygoo 1966). Children, especially those sleeping or playing on the ground, may have a much higher level of exposure to flea bites, which may account for the higher frequency of these bubal locations (Chanteau *et al.* 2000a).

Another remarkable element is the decreasing frequency of pneumonic forms over time, indicating the efficacy of plague control programmes. The intensification of control measures, including rapid recourse to health structures and chemoprophylaxis for contacts of pneumonic cases, has undoubtedly contributed to this improvement. Pneumonic forms are more frequent in adults than in children, probably because adults are more likely to come into contact with more seriously ill patients during their care and transport and in the performance of funeral rites. These were the reasons given to account for the plague

Table 3 Risk factors for dying from plague in Madagascar 1957–2001 (C + P cases, logistic regression)

Factor	Cases C + P*	Deaths (mortality %)	P value	OR (95% CI)†	Adjusted OR (95% CI)
Sex					
Female	1848	452 (24.5)	0.83	1.00	–
Male	2461	595 (24.2)		0.98 (0.86–1.13)	
Age group (years)					
0–9	1373	321 (23.4)	<10 ^{−9}	1.00	1.00
10–19	1408	298 (21.2)		0.88 (0.74–1.05)	0.88 (0.73–1.07)
20–29	716	155 (21.6)		0.91 (0.73–1.13)	0.88 (0.70–1.12)
30–39	384	123 (32.0)		1.54 (1.21–1.98)	1.27 (0.97–1.67)
40–49	198	64 (32.3)		1.57 (1.13–2.16)	1.18 (0.82–1.70)
50+	230	86 (37.4)		1.96 (1.46–2.63)	1.23 (0.87–1.72)
Time period (years)					
1957–1961	120	67 (55.8)	<10 ^{−9}	1.00	1.00
1962–1966	150	51 (34.0)		0.41 (0.25–0.67)	0.63 (0.36–1.10)
1967–1971	367	120 (32.7)		0.38 (0.25–0.59)	0.59 (0.37–0.94)
1972–1976	217	72 (33.2)		0.39 (0.25–0.62)	0.77 (0.46–1.28)
1977–1981	153	52 (34.0)		0.41 (0.25–0.67)	0.58 (0.33–0.99)
1982–1986	233	80 (34.3)		0.41 (0.26–0.65)	0.78 (0.47–1.30)
1987–1991	663	157 (23.7)		0.25 (0.16–0.37)	0.55 (0.34–0.87)
1992–1996	977	180 (18.4)		0.18 (0.12–0.27)	0.31 (0.20–0.49)
1997–2001	1429	268 (18.8)		0.18 (0.12–0.27)	0.32 (0.21–0.50)
Months					
January	752	172 (22.9)	<10 ^{−2}	1.00	1.00
February	479	116 (24.2)		1.08 (0.82–1.41)	0.95 (0.71–1.27)
March	359	83 (23.1)		1.01 (0.75–1.37)	0.86 (0.62–1.19)
April	120	32 (26.7)		1.23 (0.79–1.90)	1.15 (0.71–1.85)
May	61	23 (37.7)		2.04 (1.18–3.52)	1.85 (1.03–3.31)
June	39	18 (46.2)		2.89 (1.51–5.55)	2.06 (1.01–4.19)
July	52	19 (36.5)		1.94 (1.08–3.50)	1.70 (0.89–3.24)
August	144	28 (19.4)		0.81 (0.52–1.27)	0.74 (0.45–1.20)
September	330	74 (22.4)		0.97 (0.72–1.33)	1.03 (0.73–1.44)
October	592	152 (25.7)		1.16 (0.91–1.50)	1.18 (0.90–1.55)
November	676	171 (25.3)		1.14 (0.90–1.46)	1.12 (0.86–1.46)
December	705	159 (22.6)		0.98 (0.77–1.25)	1.01 (0.78–1.32)
Region					
Antananarivo	2000	649 (32.5)	<10 ^{−9}	1.00	1.00
Fianarantsoa	1597	274 (17.2)		0.43 (0.37–0.51)	0.45 (0.37–0.54)
Toamasina	127	32 (25.2)		0.70 (0.46–1.06)	0.49 (0.30–0.79)
Mahajanga	564	83 (14.7)		0.36 (0.28–0.46)	0.38 (0.28–0.51)
Toliara	3	2 (66.7)		4.16 (0.38–46.00)	2.71 (0.23–31.33)
Antsiranana	18	7 (38.9)		1.32 (0.51–3.43)	0.29 (0.09–0.92)
Environment					
Rural	3619	896 (24.8)	0.11	1.00	1.00
Urban	690	151 (21.9)		0.85 (0.70–1.04)	0.77 (0.60–0.99)
Clinical form					
Bubonic plague	3992	830 (20.8)	<10 ^{−9}	1.00	1.00
Pneumonic plague	317	217 (60.5)		8.27 (6.45–10.60)	6.04 (4.61–7.93)

* Confirmed or probable.

† Odds ratio (95% confidence interval).

epidemics at Doany in 1957 (Brygoo & Gonon 1958) and Ambatolampy in 1997 (Ratsitorahina *et al.* 2000).

The higher risk of dying from pneumonic plague simply confirms the greater severity of this clinical form. Before

the advent of antibiotics, pneumonic plague was fatal in less than 3 days in all cases and often in less than 24 h (Robic 1952). For this form of plague, treatment must be administered as rapidly as possible (within a few hours) to

be effective (WHO 1999). This highlights the importance of early diagnosis and chemoprophylaxis in subjects who have been in contact with a pneumonic case.

Plague occurs throughout the year in the highlands but displays a markedly seasonal pattern. The risk of dying from plague is higher from May to July – a period when plague transmission rates are low. However, the proportion of pneumonic forms is the highest in this cool period of the year (Figure 2) and health workers may be less likely to diagnose plague at this time of year, thereby retarding treatment. The lower risk of death in urban environments demonstrates disparities in medical care, because access to health care infrastructures is generally better in urban than in rural areas.

Plague can be cured with inexpensive antibiotics, provided it is diagnosed and treated early. CFR because of plague decreased between 1957 and 2001. The marked decrease in CFR towards the end of the 1950s was due to the generalization of streptomycin treatment, which led to a decrease in the frequency of pneumonic forms (Table 1). Another major decrease in lethality towards the end of the 1980s (Table 1) also corresponded to a decrease in pneumonic forms. The CFR has stabilized at about 20% since the beginning of the 1990s. Rural areas face problems of access to health care structures, particularly during the rainy season. In addition, current treatment protocols for plague, involving streptomycin injections over several days, may not be appropriate and applicable in these areas, particularly for disponibility of health workers. The use of traditional medicine and certain popular beliefs in these zones may also delay diagnosis (Ratsitorahina *et al.* 2000). Population-based studies of the knowledge, attitudes and practices of health care professionals with respect to plague are clearly required. Such studies would make it possible to identify the sociocultural and technical factors responsible for the persistence of such a high CFR, despite the existence of a long-standing, established control programme. The development of more appropriate treatment protocols for rural areas in Madagascar should also be considered.

The frequency of biological confirmation of cases over the period as a whole was low (21.4%). The need to send samples to the capital, sometimes waiting for chance and after a delay of several weeks or even months, is a constraint to most of the African countries in which plague remains rife. Since 1999, the WHO has considered the detection of the F1 antigen in samples to be a presumptive criterion for plague in international definitions (WHO 1999). According to the National Plague Control Programme, a patient with suspected plague should be considered a confirmed case if the F1 antigen is detected, regardless of the culture results obtained, even if culture remains the gold standard technique for diagnosis. Indeed, the heat-stable F1 capsule

antigen is secreted universally by *Y. pestis* at 37 °C and is found at high concentration in the culture medium and in human and mouse samples. Furthermore, ELISA and dipstick (immunochromatographic) tests for the detection of this antigen are highly sensitive and specific (Chanteau *et al.* 2000b, 2003a). The dipstick test is rapid and easy to perform. It gives a reliable diagnosis of plague and can accelerate treatment and responses. In 2002, the Malagasy Health Ministry made this test available to all health structures, where there was a risk of plague, for the diagnosis of plague in human patients and dead rats. This test has since become indispensable for raising the alarm early and for screening for the rat epizootics that precede human epidemics (Migliani *et al.* 2001; Chanteau *et al.* 2003b).

Madagascar has undoubtedly been the most active and most investigated focus of plague in the last 10 years. This study, covering the largest possible number of years and of patients, provides precise epidemiological details concerning human plague in modern times. Combined with a greater overall understanding of the factors responsible for the recrudescence of plague (Duplantier *et al.* 2005), this study should help the most recent foci of plague reemergence, such as Democratic Republic of Congo, to define more effective programmes for monitoring, controlling and preventing plague.

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Tendances épidémiologiques de la peste à Madagascar durant la seconde moitié du 20^{ème} siècle: étude sur 20900 cas notifiés

OBJECTIFS Décrire les caractéristiques principales et les tendances épidémiologiques de la peste humaine des temps modernes sur base des séries de cas les plus élevées rapportées dans le foyer très actif de Malagasy.

MÉTHODES Nous avons utilisé des fiches de 20900 cas suspects de peste notifiés dont 4473 confirmés ou probables, pour effectuer des analyses statistiques sur les taux d'incidence et de mortalité ainsi que les facteurs associés pour 5 périodes entre 1957 et 2001.

RÉSULTATS L'analyse de tendance a démontré: 1) une augmentation des taux d'incidence et des districts affectés, 2) une augmentation des formes buboniques (de 64,8% à 96,8%) à l'inverse des formes pneumoniques (35,2% à 3,2%), plus fréquemment chez les sujets âgés et 3) une diminution du taux de cas mortels (de 55,7% à 20,9%) associée avec 5 facteurs identifiés: forme clinique, saison, province, zone rurale/urbaine et période considérée. L'âge médian des patients était de 14 ans avec plus d'hommes que de femmes affectés.

CONCLUSIONS Depuis la fin des années 80, l'incidence de la peste à Madagascar a augmenté autant en zone rurale qu'urbaine à cause de multiples facteurs socioéconomiques et environnementaux. Cependant, la tendance de la mortalité due à la peste est en régression ainsi que les formes pneumoniques à cause de l'intensification des mesures de contrôle. La disponibilité de tests sur bandelettes dans les structures de santé pour le diagnostic rapide des cas humains et épidémiologiques chez les souris, devrait permettre de tirer l'alarme et de réagir rapidement, ce qui alors réduira encore plus la morbidité et le taux de cas mortels.

mots clés peste humaine, Madagascar, surveillance, taux de cas mortels

Tendencias epidemiológicas de la peste humana en Madagascar durante la segunda mitad del siglo 20: estudio de 20,900 casos notificados

OBJETIVOS Describir las principales características y las tendencias epidemiológicas de la peste humana en tiempos modernos, basándose en la más grande serie de casos reportados en un foco altamente activo de Madagascar.

MÉTODOS Utilizamos los reportes de 20,900 casos notificados de sospecha de peste, de los cuales 4473 eran confirmados o probables, con el fin de realizar un análisis estadístico de tasas de incidencia y mortalidad y factores asociados para un período de 5 años entre 1957 y 2001.

RESULTADOS Nuestro análisis de tendencias mostró: 1) un aumento en la tasa de incidencia y el número de distritos afectados; 2) un aumento en la proporción de formas bubónicas (64.8% a 96.8%) a expensas de las formas neumónicas (35.2% a 3.2%) más frecuentes en personas mayores; y 3) una disminución en la tasa de letalidad (55.7% a 20.9%) asociada con cinco factores identificados: presentación clínica, estación, provincia, urbano/rural y período considerado. La edad media de los pacientes era 14 años y había más hombres que mujeres afectados.

CONCLUSIONES Desde finales de los años 80, la incidencia de la peste ha aumentado en Madagascar, tanto en áreas urbanas como rurales, debido a una multiplicidad de factores socio-económicos y ambientales. Sin embargo, la tasa de mortalidad de la peste ha tendido a la baja, junto con la frecuencia de formas neumónicas, debido al fortalecimiento de las medidas de control. El que los tests tipo *dipstick* para el diagnóstico de casos humanos y epizooticos en ratones estuviesen disponibles dentro de las estructuras sanitarias, debería facilitar el activar la alarma y reaccionar más rápidamente, de forma que se disminuiría la morbilidad y la tasa de letalidad.

palabras clave peste humana, Madagascar, vigilancia, tasa de letalidad