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ScienceDirect
Acta Tropica 100 (2006) 133–141
ACTA TROPICA
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Demographic and spatio-temporal variation in human plague at a persistent focus in Tanzania

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Received 18 May 2006; received in revised form 9 October 2006; accepted 10 October 2006

Abstract

Human plague in the Western Usambara Mountains in Tanzania has been a public health problem since the first outbreak in 1980. The wildlife reservoir is unknown and eradication measures that have proved effective elsewhere in Tanzania appear to fail in this region. We use census data from 2002 and hospital records kept since 1986 to describe the temporal, spatial and demographic variation in human plague. A seasonal peak in cases occurs from December to February with the numbers of cases during this peak varying between 0 and 1150. Variation in incidence, calculated for each village as the mean number of cases per thousand inhabitants per year, indicates that human plague is concentrated around a group of three neighbouring, relatively isolated, high-altitude villages; Nywelo, Madala and Gologolo. However, there was no evidence that these villages were acting as a source of infection for the remainder of the focus. The likelihood of becoming infected with plague is highest between the ages of 5 and 19 and lowest for adult men. This was most clear in the ward encompassing the three high-incidence villages where the risk of plague among children aged 10–14 was 2.2 times higher than for adults aged 30–34, and among adults aged 30–34, the risk was 2.4 times higher for women than men.

Keywords: Rodent-borne disease; Plague focus; Yersinia pestis; Zoonotic disease; Vector-borne disease

1. Introduction

Plague is a rodent-associated, flea-borne zoonosis that persists throughout Asia, Africa and North and South America as a threat to public health. The causal agent of plague is the Gram-negative bacterium *Yersinia pestis*. Although plague can be treated with antibiotics, it is often fatal when treatment is delayed or otherwise inadequate. This is particularly true in Africa where plague is now endemic in many countries; 98.7% of all cases of plague reported to WHO for 2003 were from Africa (WHO, 2005). In the Western Usambara Mountains, north eastern Tanzania, plague has continued to be a serious problem despite numerous attempts to control the disease and to improve health education among the local population (Kilonzo et al., 1992, 1997; Kilonzo, 1994).

Plague was first reported in north eastern Tanzania in April 1980 when an outbreak of human plague occurred at Mkunki, a small village belonging to the ward of Shume, in the Lushoto District (Kilonzo and Mhina, 1982). By the year 2004 a total of 7603 cases had been recorded (records held at the Lushoto District Hospital).

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doi:10.1016/j.actatropica.2006.10.006

The majority of cases (∼90%, see Section 3) have been bubonic plague and are likely to have originated from flea bites and hence represent primary cases. The unusual persistence of human plague prompted a number of epidemiological and anthropological investigations (Kilonzo et al., 1992, 1993, 1997; Kilonzo and Mhina, 1983; Njunwa et al., 1989; Kilonzo, 1994), which have produced a large cumulative collection of rodent, human and dog sera. Apart from the clear result that plague was present and circulating in the rodent community the authors of these studies consistently reported; (i) that local beliefs in witchcraft and a tendency for infected people to turn to traditional healers for help leads to delays in treatment, (ii) that plague affects women and children more than men, and (iii) high-levels of sero-prevalence in the domestic dog population (indicating only that they are serological sentinels).

The sylvatic reservoir(s) for plague in Lushoto have not been clearly identified. While serological studies have confirmed infection in a number of species it is not known which are true reservoir species and which provide a route for the bacteria to spread from the wildlife reservoir to commensal rodents and humans. Small mammal species that have been implicated in maintenance and transmission of plague in the Lushoto district are *Rattus rattus*, *Mastomys natalensis*, *Arvicanthis nairobae*, *Lophuromys flavopunctatus* and *Otomys* spp. These species are commonly trapped in and around plague-affected villages (Kilonzo et al., 1992).

The first outbreak of human plague in the Lushoto district involved 49 cases and 11 deaths (indicating a lethality of 22.4%). Only two villages were affected. Recurring outbreaks prompted control measures, such as removal of rodents and flea control using insecticides during and immediately after each outbreak. Steps were also taken to improve health education and sanitary conditions. Beginning in 1983 spraying of houses with DDT was carried out in the affected villages irrespective of whether or not an outbreak had occurred. A special flea control operation, also using DDT, was carried out in April 1987. Human cases of plague continued to occur with alarming frequency and in July 1987 a Permanent Plague Control Team (PPCT) was formed in an attempt to ensure plague control measures were promptly and properly implemented. The PPCT remained functional until 1990 when plague control activities were delegated to the District Health Officer, whose responsibilities include control of potential reservoirs (rodents) and vectors (fleas) within houses and peri-domestic areas. Control operations consisted of baiting with rodenticides and use of different insecticides (permethrin and pirimephos-methyl, later changed to 5% carbamate).

Here we present results from hospital records on human plague cases in the western Usambara Mountains kept between 1986 and 2003. Up until the time of writing, no cases have been reported since December 2003, and prior to 1986 a consistent protocol for recording case details was not followed. This is the first time that the hospital records have been computerised, analysed and combined with census data. Our purpose here is to (i) describe the spatio-temporal and demographic variation in incidence of human plague (cases per thousand inhabitants), and (ii) in doing so confirm or disagree with the principle findings that have been previously reported from anecdotal observations. In particular, there have been many claims that a disproportionate number of plague cases occur among women and children, but until now this has not been established using both hospital records and census data. Describing the spatio-temporal variation is a crucial first step towards identifying the environmental, ecological and anthropological factors that determine plague risk.

2. Methods

Data on human plague cases, reported between October 1986 and December 2003, were obtained from hospital records kept at the Lushoto District Hospital. The data are the month of onset of disease, the village where the patient lived, the patient's age and gender, the form of plague (bubonic, pneumonic or septicaemic) and whether the patient died. While most patients are diagnosed and treated at local health centres or dispensaries, the District Medical Officer at the Lushoto District Hospital is contacted when plague is suspected. The hospital then sends a health officer who follows up the case, confirms that it is genuine and adds the record to the database. Diagnosis is based on clinical manifestations including typical buboes, chest pains accompanied by coughing with blood in the sputum, headache, chills and malaise. A limited number of human cases have been presumptively diagnosed by microscopic observations of bipolar staining, Gram-negative cocobacilli. These procedures are not confirmatory by themselves. However, bacteriological culturing and isolation of *Yersinia pestis* was performed for a number of suspected cases during the plague outbreaks in 1980 and 1991 and plague was confirmed as the causative agent (Kilonzo and Mhina, 1982; Lyamuya et al., 1992). In more recent studies, during the 1998 outbreak of plague in the Lushoto district, PCR and ELISA techniques were used to confirm the presence of plague bacteria in samples of rodent and human sera (Kilonzo, 2000).

When bubonic plague is recorded as the form of plague, this indicates a primary case where the patient has been bitten by a plague-infected flea. Pneumonic and septicaemic forms of the disease occur when bacteria are present in the lungs and blood of the patient respectively. These forms of plague may develop from bubonic plague and are noteworthy because human-to-human transmission is possible from such patients. Human-to-human transmission occurs through airborne transmission in the case of pneumonic plague or possibly also through the bites of human fleas in the case of septicaemic plague. Direct contact with the sputum of pneumonic plague patients can also lead to development of bubonic plague although this is considered rare. Human consumption of rodents is not practiced in Lushoto (personal communication, Monica Janowski) and so may be ignored as a source of transmission. We note here that to understand the ecological or environmental factors that determine the plague risk posed by wildlife hosts, secondary cases arising from human-to-human transmission are not relevant. However human-to-human transmission, even in the case of pneumonic plague, is considered rare and cases diagnosed as pneumonic plague probably represent secondary pneumonic plague (Kool, 2005; Tikhomirov, 1999).

The latitude, longitude and altitude readings for villages were taken with a GPS at the village office. This was possible for 48 of the 49 villages having one or more recorded plague cases, and a further 57 villages located in the same region but with no recorded plague cases. For those villages recording at least one plague case, a mean incidence (number of cases per year per thousand inhabitants) and frequency (proportion of years in which there was at least one plague case) were calculated. Villages with no plague cases reported were assumed to have an incidence of 0.

As a georeference for plague cases, the GPS reading at the village office is considered to be a coarse representation of the data. This is because a village typically consists of many small hamlets and the incidence values should be associated with areas rather than points. At the time of writing, reliable information on village boundaries was not available. A further complication is that over the period 1986–2003, some hamlets became recognised as separate villages. For example, until 2001 the village of Mkunki (the locality of the first outbreak of human plague) was considered part of Nywelo and patients from this locality were recorded as residents of Nywelo. In such cases, numbers of plague cases and demographic information were pooled and the resulting statistics georeferenced to the village with the longest history of being recognised.

Census data taken in 2002 throughout Tanzania were used to scale the frequency of cases in each age- and sex-class by the frequency of that demographic group in the population to show how risk of infection varies with sex and age. These analyses assume that the sex and age distributions calculated using the 2002 census apply to the whole time period. Detailed demographic information (number of persons in each age-class) is only available at the administrative unit of ward (a group of several villages; several wards make a division; several divisions make a district). Annual incidence rates (cases per thousand inhabitants) for each plague year in the period of the data set were calculated by assuming a population growth rate of 1.022 (the intercensal growth rate reported for the district of Lushoto for 1988–2002) and using the village population sizes reported in the 2002 Population and Housing Census (published in 2003 by the Central Census Office and National Bureau of Statistics, Dar es Salaam, Tanzania). This takes into account the growth of the human population that has occurred throughout the district over the last three decades.

All statistics, such as autocorrelation coefficients and cross correlation coefficients for time series data, were performed in R which is a fast S-Plus clone freely available to the public (http://cran.r-project.org). Villages were identified as exceptional by making a scatter plot of incidence and frequency of human plague calculated for 49 plague-affected villages. Outliers (points representing villages with unusual frequency and incidence values) were identified on the basis of standardised robust residuals (Rousseeuw and Leroy, 1987). The risk of plague among different demographic groups was quantified by scaling the frequency of an age- and/or sex-class in the pooled hospital data (all years combined) by the frequency of the same age- and/or sex-class in the 2002 census data. Confidence intervals for the frequencies calculated from the hospital records were calculated as $\pm 1.96\sqrt{p(1-p)/N}$ where the frequencies were treated as estimates of a proportion p based on a sample of N plague cases. The ratios used to summarise differences in risk of plague between age groups and between males and females were calculated by dividing the relative frequency of plague cases for one group by the relative frequency for the other.

3. Results

3.1. Types of plague

The hospital records represent a total of 6168 cases reported as plague. These represent those that have been recorded since 1986 and are hence a subset (81%) of the total number for the Lushoto district since it was first observed in 1980. The majority of patients (87.6%) were diagnosed with bubonic plague. A further 6.1% of patients were recorded as septicaemic and the remaining 6.3% represent pneumonic plague cases. Mortality rates for bubonic, pneumonic and septicaemic patients were 0.05, 0.23 and 0.15, respectively.

3.2. Temporal variation

A plot of the numbers of bubonic, pneumonic and septicaemic plague cases each month (Fig. 1) reveals a seasonal peak in human plague in December, January and February. This is consistent for the three types of plague and on this basis a "plague year" was defined as the 12 month period beginning in July of one year

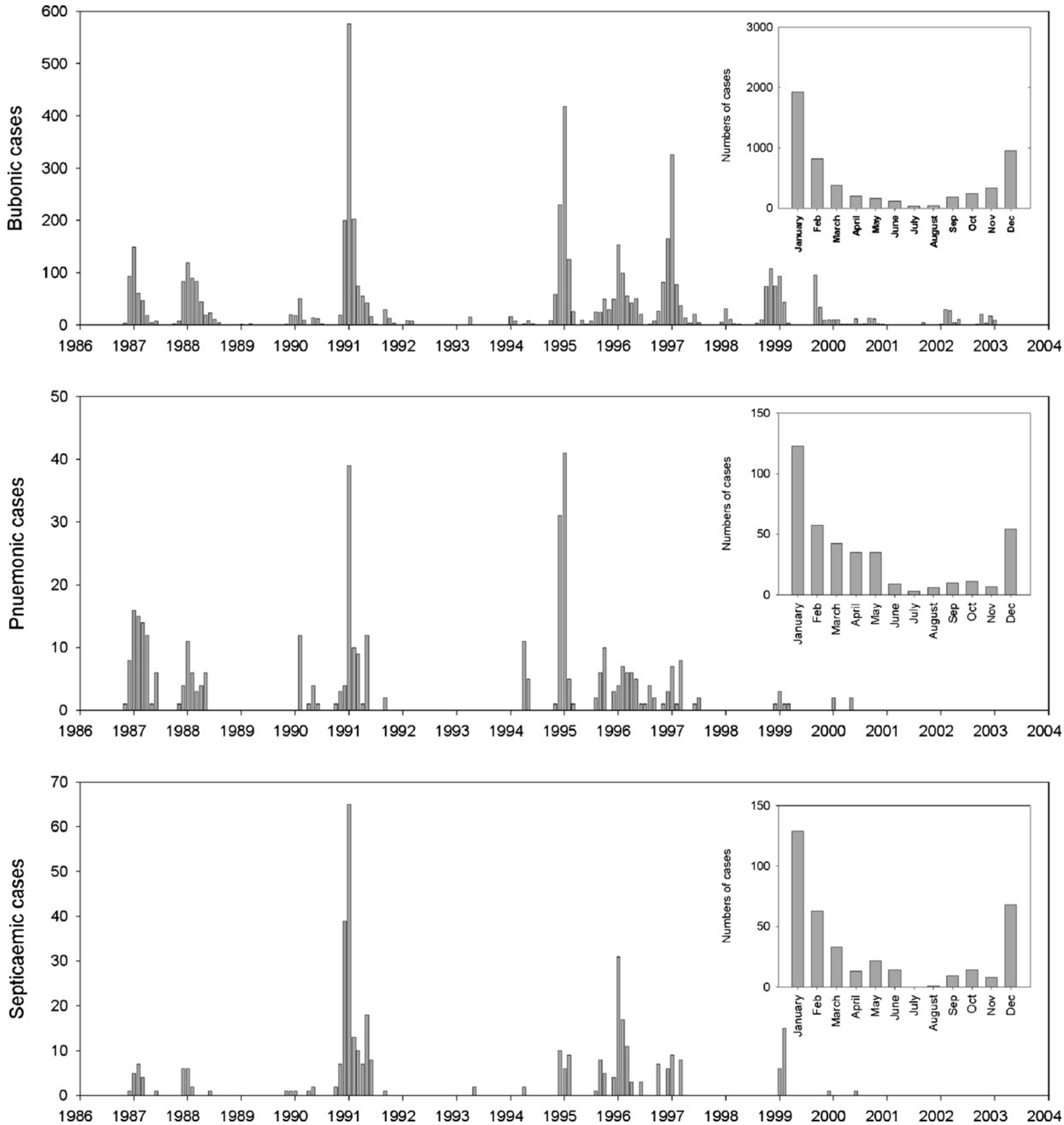

Fig. 1. Temporal variation in numbers of cases of bubonic, pneumonic and septicaemic plague (monthly totals) recorded between between October 1986 and December 2003. There is a strong seasonal peak (see insets) when the case data are pooled across years with the majority of cases occurring in the months December, January and February.

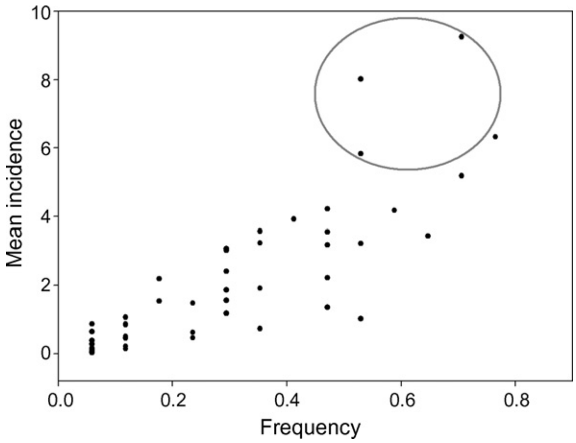

Fig. 2. Scatter plot of frequency (proportion of plague years in which at least one case was reported) and mean incidence of human plague for 49 plague-affected villages based on hospital records from 1986 to 2003. The three points circled represent three neighbouring villages with unusually high incidence (see Fig. 3).

and ending in June of the following year. While this seasonal pattern appears when plotting total or mean number of cases each month, for individual years and individual villages the seasonal variation can be quite different. For example, in Kwemakame village in the Division of Lushoto there was a high number of cases in 1995 with a peak in September/October. And in 1999 in a group of three neighbouring villages in Mlola (Lwandai, Mazashai and Ungo) there was a peak in cases in September. This being said, within the Mlalo division, seasonality in plague cases is consistent with all villages tending to be affected in the same months and same years.

The interannual variation in numbers of cases occurring in each plague year is high (variance in monthly totals is higher than the mean even in the quietest months of June, July and August). A time series plot of monthly cases (Fig. 1) identifies the 1990/1991 season and 1994–1997 as periods in which particularly high numbers of cases occurred. There are also years (e.g. 1992/1993 and 2001/2002) in which very few plague cases were reported. At the annual scale there was no discernible pattern in numbers of cases and no evidence of cyclicity (all autocorrelation coefficients were non-significant).

3.3. Spatial variation

A scatter plot of frequency and mean incidence for the 49 plague-affected villages is shown in Fig. 2. The frequency of human plague (proportion of plague years in which at least one case was reported) and mean incidence are positively correlated ($p < 0.0001$). The three villages circled in Fig. 2 have high incidence and they surround the location of the first plague outbreak in Lushoto. The villages are Gologolo, Nywelo and Madala, all of which lie in the ward Shume in western Mlalo. Gologolo and Madala are clear vertical outliers (with standardised robust residuals >4 (Rousseeuw and Leroy, 1987)) and hence can be said to have exceptionally high incidence.

The three villages circled in Fig. 2 are geographically close to one another (see Fig. 3) and form a hot-spot for human plague in western Mlalo. The location of the first outbreak of human plague in the district, the village of Mkunki, lies just to the north of Nywelo and was only recently considered to be a separate village from Nywelo. Until 2001 patients living in Mkunki were recorded as coming from the village Nywelo and so Mkunki does not appear in Fig. 3. Villages that experienced significant numbers of plague cases also lie to the east of this hot-spot, but not to the north-east or far to the north. The area encompassing these villages is relatively small (approximately 15 km × 15 km) and village-level incidence is generally consistent with the incidence in neighbouring villages. However, there was no evidence that this hot-spot is a source of human plague. Comparing the time series of the monthly totals for the three villages with the time series of monthly totals for elsewhere indicated no lagged relationship between numbers of cases in the hotspot and numbers of cases elsewhere (the cross-correlation coefficient for the two time series with lag 0 was clearly the highest).

Finally, we emphasise that the map of mean incidence (Fig. 3) fails to communicate the dynamic nature of the spatial distribution of plague cases. In no village is human plague a regular event. Outbreaks occur irregularly and for every village there are many years in which no plague cases are recorded.

3.4. Demographic variation

The frequency of plague cases in each age- and sex-class (scaled by the frequency of that demographic group in the population) indicates that children (older than 4) are over-represented in the hospital cases and adult men are under-represented, particularly for the divisions of Mlalo and Mtae (see Table 1). The frequencies of the age- and sex-classes in the census data and in the hospital records for the ward Shume (including the villages Viti, Gologolo, Nywelo, Manolo, Madala, and Mkunki) are shown in Fig. 4 where these sex and age differences are most pronounced. The first age-class, children younger than 5, appears to be under-represented but risk among

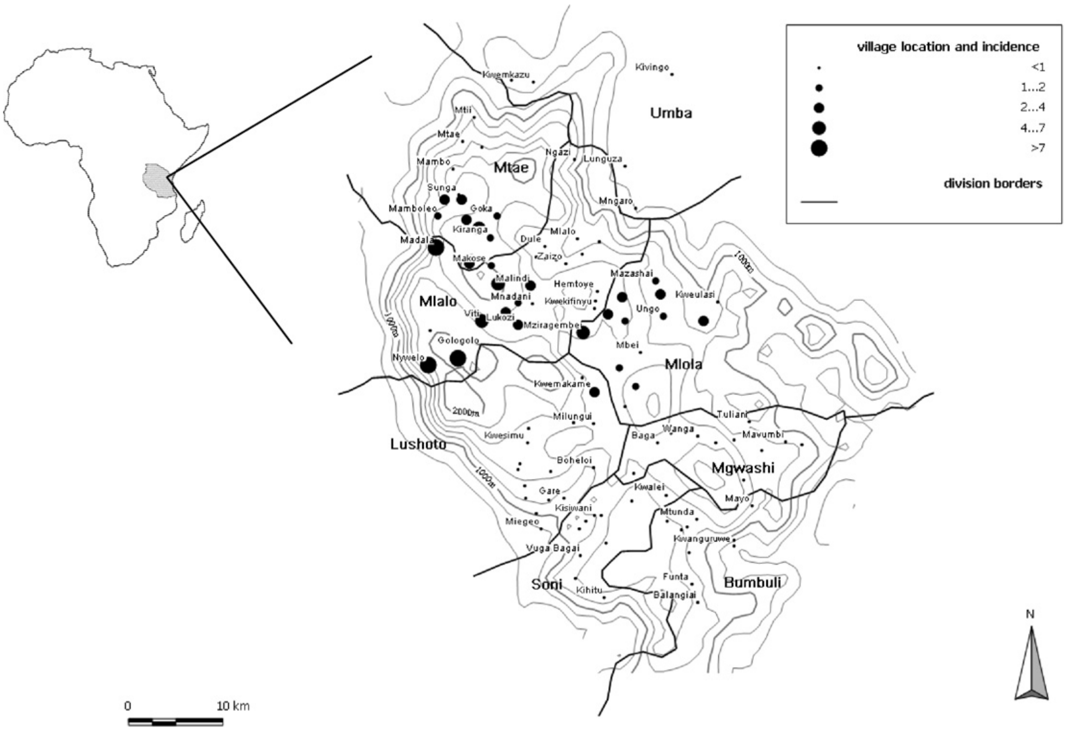

Fig. 3. A map of the Lushoto district. Villages with known locations (GPS readings taken at the village office) are plotted together with the boundaries for the eight divisions and 200 m elevation lines. A sharp escarpment demarcates the western edge of the Lushoto district—the escarpment and the plains below are not inhabited. The size of the dots for each village indicates the mean incidence of plague (cases per thousand per year) at that village for the period 1986–2003.

Table 1
The age- and sex-class frequency in the hospital records scaled by the frequency of the same age- and sex-class in the 2002 population census

Age	Lushoto		Mlalo		Mlola		Mtae		Shume	
	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males
0–4	**0.637**	**0.567**	**0.716**	**0.689**	**0.598**	0.886	**0.634**	**0.746**	**0.692**	**0.685**
5–9	0.817	1.037	**1.116**	**1.407**	1.069	1.210	**1.431**	**1.440**	1.116	**1.452**
10–14	1.092	**1.454**	**1.413**	**1.463**	**1.513**	**1.749**	**1.700**	**1.647**	**1.496**	**1.509**
15–19	1.190	1.180	**1.391**	1.158	**1.560**	**1.630**	**1.474**	**1.363**	**1.352**	1.124
20–24	1.630	0.888	**1.207**	1.089	0.820	1.163	0.930	1.244	1.145	0.881
25–29	1.077	0.560	0.953	0.928	0.826	**0.434**	0.841	**0.608**	0.881	**0.780**
30–34	0.856	1.181	0.876	**0.505**	1.158	0.658	**0.632**	**0.484**	0.874	**0.375**
35–39	1.088	0.850	**0.687**	**0.583**	**0.644**	0.703	0.775	**0.355**	**0.702**	**0.331**
40–44	1.148	0.849	**0.725**	**0.308**	0.782	0.620	0.708	**0.398**	0.761	**0.208**
45–49	1.005	1.381	0.915	**0.331**	0.723	**0.550**	0.796	**0.432**	0.820	**0.268**
50–54	0.918	**0.242**	0.793	**0.361**	**0.541**	1.134	0.923	**0.279**	0.888	**0.227**
55–59	1.239	0.349	0.756	**0.536**	0.543	**0.405**	0.844	**0.292**	0.784	**0.408**
60–64	2.385	1.741	1.013	0.700	0.879	**0.499**	0.815	**0.507**	1.073	0.674
65–69	0.799	0.451	**0.566**	**0.436**	**0.253**	**0.158**	0.692	**0.407**	0.692	**0.547**
70–74	0.377	1.115	**0.362**	**0.457**	0.000	**0.198**	0.650	0.603	**0.346**	0.511
75–79	1.819	0.000	**0.398**	**0.172**	0.000	0.000	**0.227**	0.000	0.806	**0.159**
80+	0.000	0.000	**0.276**	**0.210**	0.000	0.000	0.608	**0.382**	**0.424**	**0.138**

A value of 1 indicates that the frequencies are equal. Values greater than 1 indicate that the age/sex-class is over-represented in the hospital records, i.e. there are more patients in this age/sex-class than you would expect if the hospital records were a random sample from the population. Similarly values less than 1 indicate that the age/sex-class is under-represented in the hospital records. The tabulated values in boldface indicate that the 95% confidence interval for the frequency ratio does not include 1. The locations of the 4 divisions (Lushoto, Mlalo, Mlola and Mtae) are shown in Fig. 3. The Shume Ward represents a subset of the villages in the Mlalo division where human plague was particularly common.

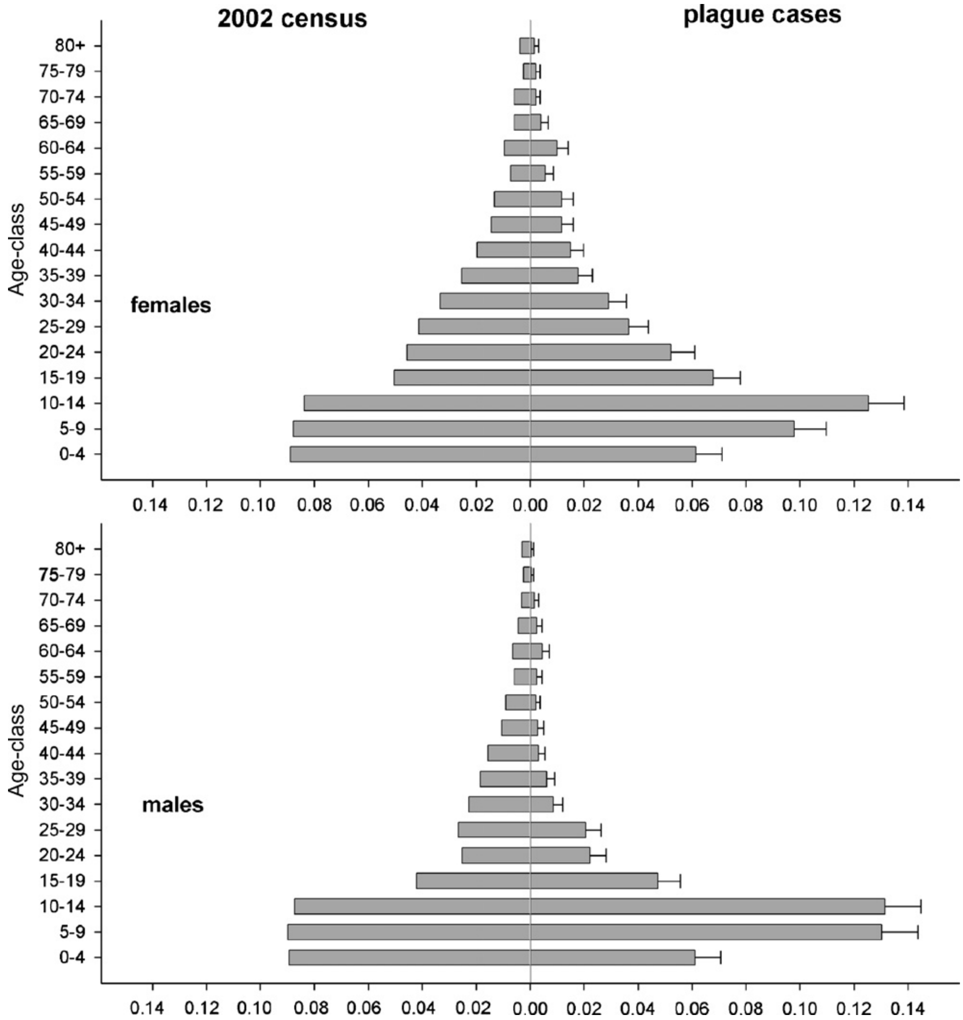

Fig. 4. Age-class frequencies from the 2002 Tanzania census (left) and in the hospital records of plague cases (right) for female and male residents of Shume Ward (western Malalo where the majority of plague cases occur). Shume includes the villages Viti, Gologolo, Nywelo, Manolo, Madala, and Mkunki.

children between 5 and 14 is clearly high. The relative frequency of plague among children aged 10–14 was 1.503 compared to 0.672 for adults aged 30–34 implying risk of plague for the first age group was 2.2 times higher than for the second. Until age 25–29 there is no difference in risk between males and females but among villagers older than 30, men are at less risk than women (see Table 1; the confidence intervals for the scaled frequencies for men and women do not overlap for most of these age-classes and the frequencies for men are always lower than for women). For adults aged 30–34, the relative frequencies of plague cases were 0.874 and 0.375 implying that while both groups are under represented in the hospital records the risk for women was 2.4 times higher than for men.

4. Discussion

Our analyses of the hospital records and census data from Lushoto has properly established that at least in some parts of Lushoto women and children are indeed more at risk of plague infection than men. The higher incidence among females certainly is not an inherent characteristic of plague. Tikhomirov (1999) mentions similar biases for plague epidemics in Kenya and Mozambique, but in Madagascar plague occurs more frequently in males than in females, although there is also a higher incidence among children there (Migliani et al., 2006). This suggests the involvement of sociological or behavioural factors. It has been argued by several authors (Kilonzo et al., 1992, 1993, 1997; Kilonzo and

Mhina, 1983; Njunwa et al., 1989; Kilonzo, 1994) that in Lushoto these differences are due to the sleeping arrangements in local households where it is often the case that the women and children sleep on the floor and the men sleep in beds. An alternative hypothesis is that differences in the outdoor activities of men, women and children explain the demographic variation in plague risk. Our results suggest anthropological studies that compare outdoor activities and household sleeping arrangements in villages belonging to the ward Shume (where there is a sex difference in plague risk) and villages in, for example, the nearby division Mlola (where there is not) will provide a test of the two hypotheses.

The relative proportion of the different clinical forms of plague in Lushoto is similar to what is found in Madagascar (Migliani et al., 2006), but the case fatality rate was lower in Lushoto than in Madagascar (Migliani et al., 2006), for bubonic (5% versus 21% in Madagascar) as well as pneumonic plague (23% versus 61%). This is a surprising difference, although earlier reviews report a large variation in global mortality rates between years (3–27%) and in perennial mortality rates between countries, with an average of about 10% for Africa. Whether the low mortality in Lushoto is due to differences in case definition or diagnostic specificity, differences in health care access or treatment, or differences in the pathogenicity of the strains of *Y. pestis*, remains to be investigated.

As in nearly all endemic foci (e.g. Begon et al., 2006; Tikhomirov, 1999; Boisier et al., 2002; Cavanaugh and Marshall, 1972; Davis et al., 2002), plague is clearly a seasonal disease in Lushoto, with a peak around the turn of the year. Rainfall in the Lushoto area is bimodal with a short peak in November–December and a longer one in March–May, indicating that the plague season coincides with the wet season. A similar relation was observed in the foci in the north-eastern part of the D.R. Congo (Misonne, 1959). In contrast, in Madagascar most plague cases occur in the dry cool period (Boisier et al., 2002). Nothing is known about the dynamics of plague in either the wildlife or peri-domestic small mammal communities in Lushoto. It is known that irregular epizootics are a common feature of sylvatic plague (Gage and Kosoy, 2004) and such dynamics in the wildlife host populations in the Usambara Mountains provide the most likely explanation for the high degree of temporal variation in human plague cases. That is, years in which there are outbreaks of human plague are years that plague epizootics occur in the wildlife and peridomestic rodent communities. There are alternative explanations, for example that plague is a constant presence in one or more reservoir populations in Lushoto but years with no or very few human cases are those in which one of the host or vector species crucial to the transmission route to humans is absent or at very low abundance.

The spatial concentration of plague in such a small area of less than 20 km × 20 km, persistent over many years, is remarkable. Plague has a focal distribution in many places, but such foci usually have much larger dimensions of hundreds or thousands of km (Chanteau, 2006; Tikhomirov, 1999; Gratz, 1999; Collinge et al., 2005). The sharp borders of the Lushoto plague focus are also unusual and the ecological conditions underlying this focality are unknown. The spatial description that we have provided allows for comparative ecological and anthropological studies to discover why plague persists in some villages and not in others despite the short distance between them.

The different types of variation observed in the data (spatial versus temporal and seasonal versus interannual) are likely to have different underlying causes. For example, the activities of people will vary seasonally by following regular crop cycles and school vacation periods, and their activities in the hottest months of the year may expose them to flea bites differently from the colder months. Such seasonal shifts in human behaviour might explain the observed peak in cases between December and February. The history of plague and plague control in the Lushoto area – especially that outbreaks have occurred irrespective of control initiatives – suggests that an explanation for the between year variation does not lie in the history of when intervention by health authorities occurred, nor do the time series suggest a gradual fall in human cases.

Discovering the underlying factors that are creating the spatial and temporal variation in human plague is an obvious next step. Soil type, climate, habitat type, habitat composition, composition of the rodent and flea communities, socio-economic indices, human population movements, changes in farming practices are all potential explanatory variables. Data are currently being collected for the purpose of finding explanations for the variability in human plague cases such that health workers will be able to reduce the impact of plague in Tanzania.

Acknowledgements

We wish to thank the Lushoto District Medical Officer, Dr. Mjema, making available all the files with records of plague cases and the assistance of the Assistant District Health Officer, Mr. Salehe Msingwa, in collecting coordinates (by GPS) of all the plague affected and unaffected villages. We also wish to thank Katrien Tersago and Anne Laudisoit for their encouragement and comments on the manuscript. This work was supported by the European Union (project RATZOOMAN, ICA4-CT-2002-10056), the SUA-VLIR Programme, and the Fund for Scientific Research-Flanders.

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