

Correlates of environmental factors and human plague: an ecological study in Vietnam

Hau V Pham,^{1*} Dat T Dang,¹ Nguyen N Tran Minh,² Nguyen D Nguyen³ and Tuan V Nguyen^{3,4}

Accepted 4 June 2009

Background Human plague caused by *Yersinia pestis* remains a public health threat in endemic countries, because the disease is associated with increased risk of mortality and severe economic and social consequences. During the past 10 years, outbreaks of plague have occasionally occurred in Vietnam's Central Highlands region. The present study sought to describe and analyse the occurrence of plague and its association with ecological factors.

Methods The study included all 510 communes of the Central Highlands region (with a total population of ~4 million) where 95% of incidence of plague cases in Vietnam had been reported from 1997 through 2002. Plague was clinically ascertained by using a standard protocol by WHO. Data on domestic fleas and rodents were obtained by using traps and periodic surveillance in accordance with the WHO guidelines. Temperature, duration of sunshine, rainfall and humidity were recorded as monthly averages by local meteorological stations. The association between these ecological factors and plague was assessed by using the Poisson regression model.

Results From 1997 through 2002, 472 cases of plague were reported, of whom 24 (5.1%) died. The incidence of plague peaked during the dry season, with ~63% of cases occurring from February through April. The risk of plague occurrence was associated with an increased monthly flea index (RR and 95% CI: 1.93; 1.61–2.33 for months with the flea index >1) and increased rodent density (RR 1.23; 1.15–1.32 per each 3% increase in density). Moreover, the risk of plague increased during the dry season (RR 2.07; 1.64–2.62), when rainfall fell <10 mm (RR 1.44; 1.17–1.77).

Conclusions These data suggest that the flea index, rodent density and rainfall could be used as ecological indicators of plague risk in Vietnam. The data also suggest that the occurrence of plague in Vietnam's Central Highlands is likely resulted from multiple causes that remain to be delineated.

Keywords *Yersinia pestis*, *Xenopsylla cheopis*, *Rattus exulans*, plague, epidemiology, Vietnam

¹ Institute of Hygiene and Epidemiology of Tay Nguyen, Dak Lak, Vietnam.

² Vietnam Field Epidemiology Training Programme (FETP) Office, Hanoi, Vietnam.

³ Garvan Medical Research Institute, Sydney, Australia.

⁴ St Vincent's Clinical School University of New South Wales, Sydney, Australia.

* Corresponding author. Institute of Hygiene and Epidemiology of Tay Nguyen, 59 Hai Ba Trung, Buon Ma Thuot, Dak Lak Province, Vietnam. E-mail: pvhau@vnn.vn

Introduction

Human plague caused by *Yersinia pestis*¹ is commonly viewed as a problem of the past, but it remains a public health threat in endemic countries, including Vietnam. According to notifications received by the World Health Organization (WHO), from 1989 through 2003, there had been 38 310 cases of plague with 2845 deaths in the world. The majority of plague cases have been clustered in 25 countries in Africa and Asia.^{2,3} Because of the lack of systematic surveillance, poor diagnostic facility and reluctance to report outbreaks, these statistics are likely underestimates of the true magnitude of plague in the world.

Plague is transmitted primarily from rodents to other animals and humans by infected fleas.⁴ The risk of plague has been reported to be associated with seasonal changes in climate, rodent density and the prevalence of fleas.^{5–7} Studies in the late 1960s and early 1970s indicated that the monthly flea population was inversely correlated with rainfall^{8,9} and that the index of *Xenopsylla cheopis* on *Rattus rattus* increased 3-fold in the dry season.⁸ Furthermore, variations in temperature and relative humidity have also been shown to be associated with the outbreak of plague and its intensity.¹⁰

In Vietnam, like in other parts of Southeast Asia, plague has been historically significant because the disease has caused considerable adverse social and health consequences. The first plague outbreak was recorded in 1898 in the coastal city of Nha Trang, which is ~150 km from Tay Nguyen.¹¹ The disease was thought to have been introduced to Vietnam by a commercial ship from Hong Kong.¹¹ Later (1961–67), there have been a number of outbreaks with a high rate of case fatality in areas where the disease was not previously found.^{8–10,12–15} In recent years, the Central Highlands region has been identified as a major focus of plague. As a part of the national plague control programme, this study was undertaken to describe the epidemiological characteristics of plague and to analyse the ecological factors associated with the occurrence of plague in Vietnam.

Materials and methods

Study setting

The study was conducted in Dak Lak and Gia Lai provinces in the Central Highlands of Vietnam. The region is also commonly known as 'Tay Nguyen', a Southwestern part ~350 km from Ho Chi Minh City. The region shares borders with Laos and Cambodia (Figure 1). The region is primarily agricultural, with coffee plantation and production being the chief sector. The coffee production from this region accounts for most of coffee production of Vietnam—the world's second largest coffee exporter. The Central Highlands region is considered one of the most disadvantageous and remote regions in Vietnam.

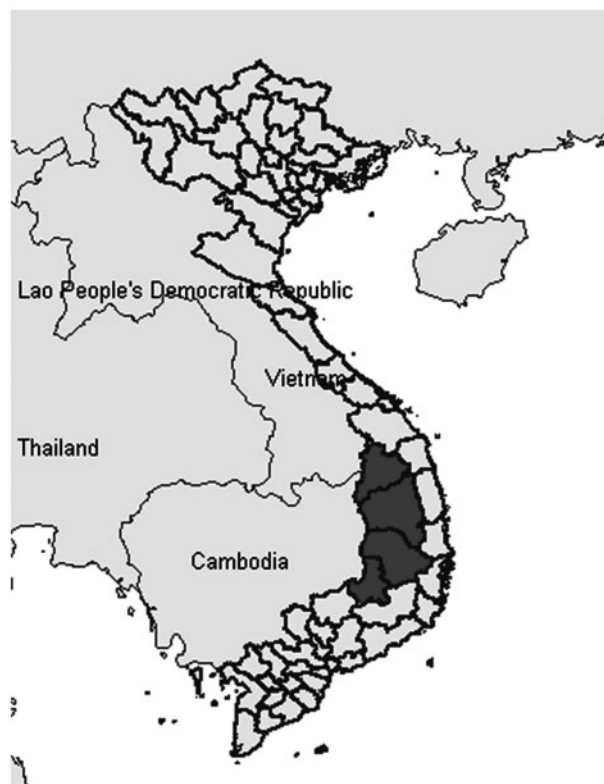


Figure 1 Map of Vietnam showing the location of the Central Highlands (dark grey area)

According to the Vietnam's General Statistics Office, the per capita income in 2004 was ~290 USD.

Dak Lak has a population of 1.74 million, among whom 30% are of ethnic minorities. The province is located from 11°30' to 13°25' North latitude and 107°30' to 109°30' East longitudes. The province has a relatively flat terrain with an average altitude being ~500 m above sea level lowering from the southeast to the northwest. Gia Lai is a province with a population of 1.17 million, of which 44% are ethnic minorities with the majority being Jarai and Bahnar ethnics. The province is located from 107°27'E to 108°55' East, latitude from 12°58'N to 14°36'N, with an elevation of 800–900 m above sea level. The two provinces, as in the entire Central Highlands region, have only two seasons: the rainy season is from May through October and the dry season is from November through April. The average rainfall is between 2200 and 2500 mm. The annual average temperature ranges between 22 and 25°C (Table 1).

In the last 15 years, ~95% of plague cases in Vietnam had occurred in these two provinces. Due to their relative isolation and a well-established system of public health surveillance, the provinces are ideal settings for investigation into plague and its ecological correlates.

Table 1 Geographical description of study settings (Central Highlands of Vietnam)

| Characteristics | Dak Lak province | Gia Lai province |
|----------------------------|------------------|------------------|
| Average elevation (m) | 500 | 850 |
| Temperature (°C) | 23.2 ± 1.8 | 22.1 ± 1.7 |
| Average sunshine/year (h) | 2305 ± 239 | 2369 ± 181 |
| Average rainfall/year (mm) | 1674 ± 171 | 2092 ± 290 |
| Relative humidity (%) | 83.1 ± 6.0 | 84.9 ± 6.7 |

Values are expressed as mean ± standard deviation (SD).

Surveillance and data collection

In Vietnam, there is a network of commune health stations located in each village in the entire country. Each station is in charge of public health surveillance and reporting to district and provincial health centres. Whenever there is a suspected case of plague, the standard protocol of management is immediately enacted. According to the protocol, individuals suspected to have plague were those who had lived in or recently exposed to plague-endemic areas and had clinical symptoms that were consistent with a presumptive diagnosis of plague, such as fever, bubo and lymphadenopathy in the inguinal region, axilla or neck.¹⁶ Once a patient was identified, he/she was treated with antibiotics; a triage system was applied and depending on the severity of the condition, the patient was transferred to the nearest district hospital or provincial hospital for further test and treatment. A confirmed case was defined as an individual who met the above clinical criteria and had a positive result for the indirect haemagglutinin antibody test for a plague F1 antibody. In this system, it was possible to systematically capture the number of plague patients. Therefore, we collected the incidence of plague cases through the surveillance system. Total numbers of human plague cases were recorded in each month during the surveillance period of 1997 and 2006.

Collection of fleas and rodents was conducted from 1997 through 2006. The collection was undertaken in accordance with the technique and method of the WHO guidelines.^{16,17} During the study period, each month, we conducted two surveys, one in the Dak Lak province and the other in the Gia Lai province. At each survey, we selected two communes for data collection. In each commune, we randomly sampled between 35 and 40 houses for trapping. The average number of traps per house was three. Therefore, the average number of traps per night was about 100. In each house, the traps were placed in three locations: the kitchen, rice store and in cages for hens and cows outside a house. The average duration of follow-up for each house was 3 days. The trap was of 20 cm height, 40 cm length and 30 cm width. Depending on the local condition, traps were baited with a sweet potato, dry fish and dry shrimps.

The duration of data collection was 3 consecutive nights for each surveillance. Total rodent density was estimated as the number of rodents captured per 100 traps, and the flea index was derived as the ratio of total of fleas collected over the number of rodents.¹⁶

Meteorological data (e.g. temperature, duration of sunshine, amount of rainfall and relative humidity) were obtained from the local bureau of meteorology. The data represent monthly averages for each year during the study period.

Data analysis

The primary aim of data analysis was to describe the incidence of plague and its association with potential ecological risk factors. The outcome considered in the analysis was the actual number of plague cases that was recorded monthly during the study period for each of the two provinces. Variables included in the analysis were the flea index, rodent density, temperature, duration of sunshine, amount of rainfall and relative humidity, which were also collected monthly during the study period. Based on preliminary analyses of the association between each risk factor and plague occurrence, we grouped the flea index into two groups: those months with the flea index >1 and those with the flea index ≤1. Moreover, based on previous studies,^{8,9} we dichotomized rainfall into two groups: <10 versus ≥10 mm. Because the number of plague cases was small relative to the provincial population, it is reasonable to assume that the distribution of plague cases followed the Poisson distribution. Accordingly, a zero-inflated Poisson regression model¹⁷ was used to model the relationships between the potential risk factors and plague cases. In this model, the log incidence of plague, log(*Y*), was assumed to be related to a risk factor *X* by an additive linear function as follows: log(*Y*) = *a* + *bX* + *e*, where *a* and *b* are regression parameters to be estimated from the observed data, and *e* represents the residual not explained by the variable *X*. Since the flea index and rodent density could be varied by season and locale, in subsequent analyses, several risk factors were simultaneously considered in a multivariable model. The estimation of regression parameters was based on the method of maximum likelihood with the R program package.¹⁸

Results

From 1997 through 2002, there were 472 cases of plague; of which 189 cases occurred in Gia Lai province and 283 in Dak Lak province. Among them, 24 patients died, making the case fatality rate of 5.1%. The number of cases fluctuated from year to year (Figure 2) without any apparent systematic trend. Since 2003, no cases of plague have been reported.

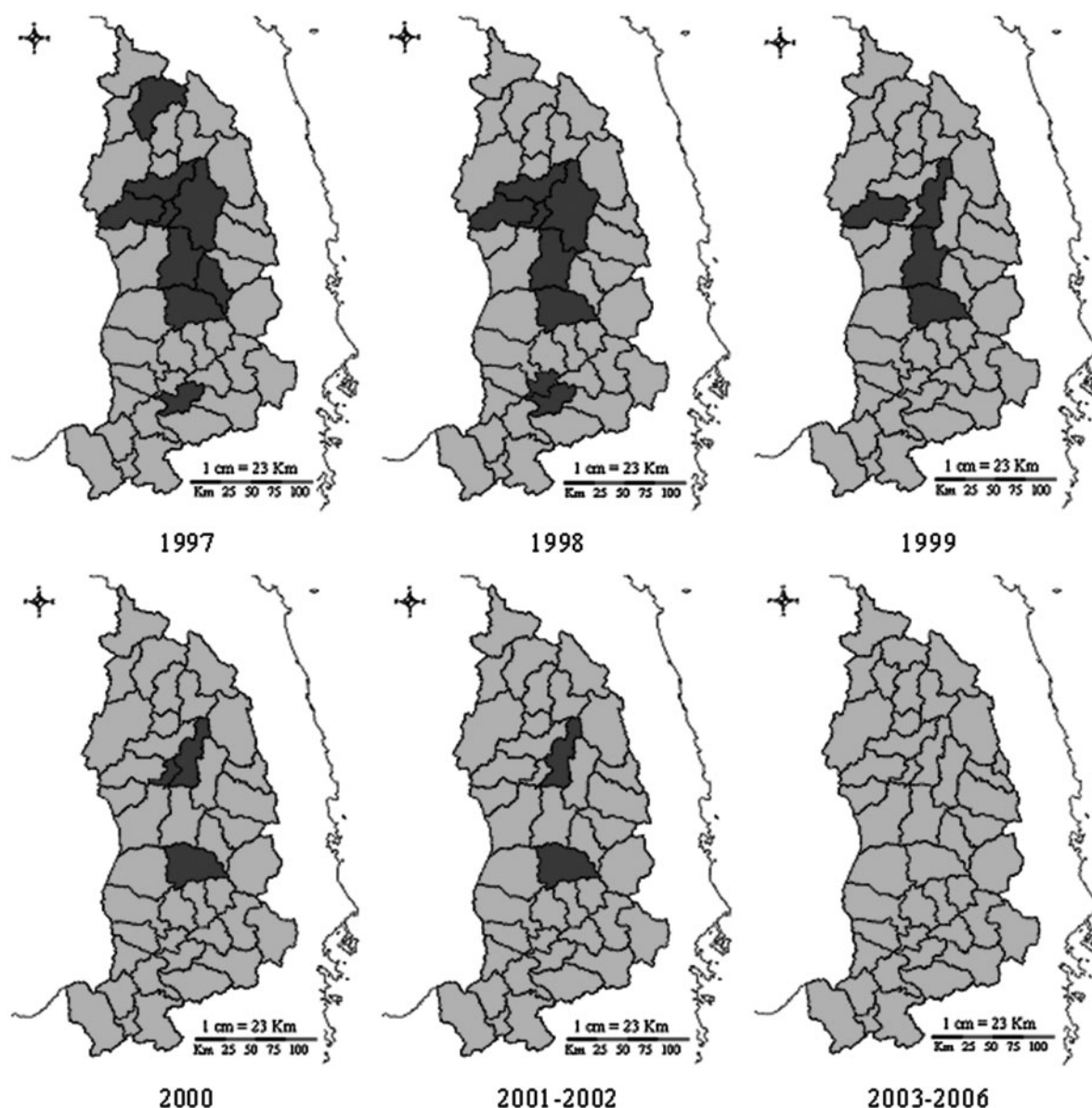


Figure 2 Distribution of plague cases in Vietnam's Central Highlands from 1997 through 2006. The dark grey spots show the presence of plague. There were no cases reported after 2002

The number of plague cases by month during the 1997–2002 period is shown in Table 2. The number of cases occurred more often during the dry season (from December to April) with a peak in the February–April period; from 1997 through 2002, the total number of plague cases recorded during the February–April period accounted for 62.5% of total cases. Univariate analysis revealed that the risk of plague during the dry season was 2.8-fold (95% CI 2.3–3.4) higher than the wet season. On the other hand, the risk of plague was increased by 2-fold (RR 2.0; 95% CI 1.7–2.5) when monthly rainfall fell <10 cm.

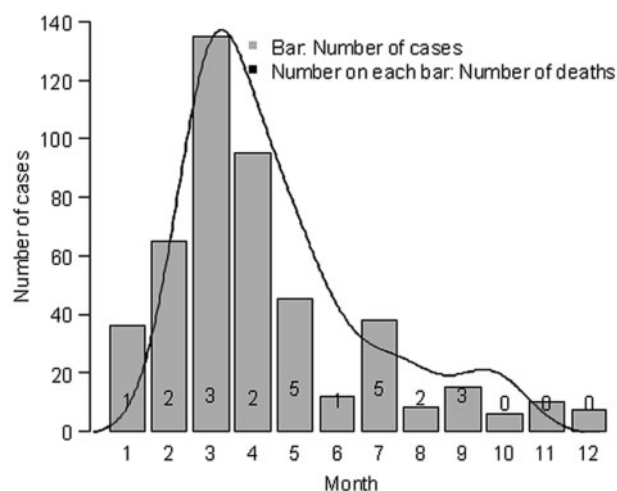
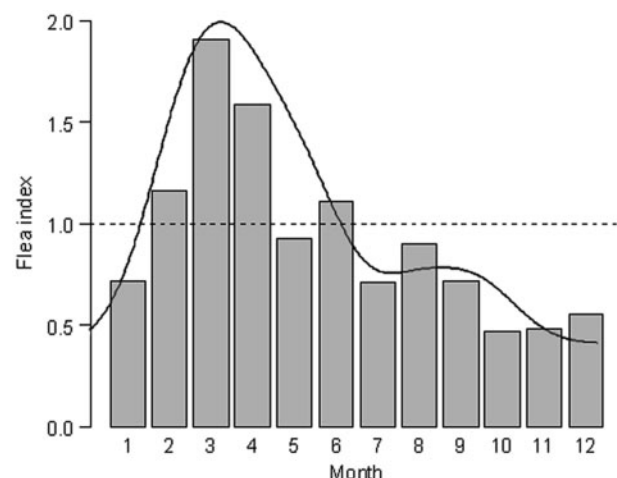
Moreover, the February–April period was characterized by a relatively high flea index and high

rodent density (Figures 3 and 4). During the period 1998–2005, 7097 rodents had been trapped and examined for plague infection. The majority of rodents captured belonged to three species: *Rattus exulans* (83%), *Suncus murinus* (13.6%) and *Rattus nitidus* (2.8%). The other species were *R. rattus*, *Bandicota bengalensis*, *Rattus hoxaensis* and *Rattus argentiventer*. The sera of these rodents were tested for specific *Y. pestis*, and the results showed that from 1998 through 2001, 1.4–2.2% of the rodents were infected with *Y. pestis*; however, virtually no infection was observed after 2001.

During the same period, we captured 1141 fleas, which were grouped into four main flea species as follows: *X. cheopis* (97%), *Pulex irritans* (1.5%),

Table 2 Climate change and occurrence of plague cases stratified by month

| Month | Rodent density ^a | Flea index ^a | Temperature (°C) ^a | Sunshine (h) ^a | Rainfall ^a (mm) | Relative humidity ^a | No. of cases ^b | No. of deaths ^b |
|-----------|-----------------------------|-------------------------|-------------------------------|---------------------------|----------------------------|--------------------------------|---------------------------|----------------------------|
| January | 7.50 | 0.72 | 20.1 | 250 | 5 | 81 | 36 | 1 |
| February | 9.40 | 1.16 | 21.4 | 245 | 12 | 77 | 65 | 2 |
| March | 7.40 | 1.91 | 23.3 | 265 | 29 | 75 | 135 | 3 |
| April | 5.81 | 1.58 | 25.0 | 235 | 84 | 77 | 95 | 2 |
| May | 5.30 | 0.93 | 24.5 | 202 | 229 | 83 | 45 | 5 |
| June | 5.95 | 1.10 | 23.8 | 174 | 251 | 88 | 12 | 1 |
| July | 7.22 | 0.70 | 23.2 | 152 | 298 | 90 | 38 | 5 |
| August | 5.30 | 0.90 | 22.9 | 134 | 384 | 91 | 8 | 2 |
| September | 7.03 | 0.72 | 22.9 | 138 | 318 | 90 | 15 | 3 |
| October | 5.66 | 0.47 | 22.5 | 177 | 159 | 88 | 6 | 0 |
| November | 4.91 | 0.47 | 21.6 | 184 | 88 | 85 | 10 | 0 |
| December | 7.00 | 0.55 | 20.3 | 180 | 26 | 84 | 7 | 0 |

^aData are averages of 10 years (1997–2006).^bData are total number of cases tallied from 1997 through 2006.**Figure 3** Total number of plague cases (the number on each bar is the number of deaths) and month in Vietnam's Central Highlands region from 1997 through 2006**Figure 4** Average flea index by month in Vietnam's Central Highlands region from 1997 through 2006

Ctenocephalides felis felis (1.3%) and *C. felis orientalis* (0.1%). Because of high clustering of species, all species were combined into a single group for subsequent analyses. The proportion of fleas infected with *Y. pestis* varied from 1.7% in 1999 to 2.7% in 1998. However, there was no evidence of *Y. pestis* among the fleas that were captured after 2001.

Rainfall was inversely associated with the flea index (Figure 5). The monthly flea index increased exponentially when monthly rainfall fell <10 cm. In the multivariable Poisson regression model (Table 3), an increased risk of plague was independently associated with higher flea index [risk ratio (RR) 1.9; 95% confidence interval (CI) 1.6–2.3 for months with

the flea index >1] and greater rodent density (RR 1.2; 95% CI 1.1–1.3 per 3% increase). The effects of the flea index and rodent density were independent of rainfall (RR 1.4; 95% CI 1.2–1.8 for months with rainfall <10 mm) and the dry season (RR 2.1; 95% CI 1.6–2.6 for months from December through April).

Discussion

Plague is one of the most ancient and feared diseases, having caused severe epidemics in human history. Since the Black Death epidemic that struck Europe,⁴

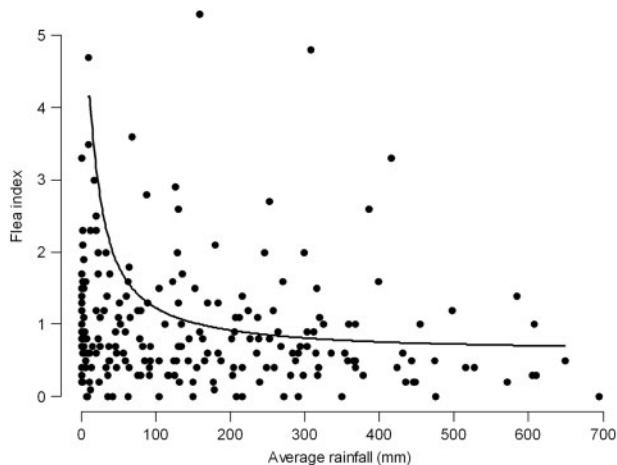


Figure 5 Relationship between monthly rainfall and the monthly flea index in Vietnam's Central Highlands region from 1997 through 2006

Table 3 Risk factors of human plague: RR (95% CI)

| Risk factor | Unit of comparison | RR (95% CI) | P-value |
|---------------------|--------------------|-------------------|---------|
| Flea index | >1 vs ≤1 | 1.93 (1.61, 2.33) | <0.0001 |
| Rodent density | Per 3% increase | 1.23 (1.15, 1.32) | <0.0001 |
| Rainfall | <10 vs ≥10 mm | 1.44 (1.17, 1.77) | <0.0001 |
| Months ^a | Dry vs wet months | 2.07 (1.64, 2.62) | <0.0001 |

^aDry season was from December through April.

the disease still occurs frequently around the world, and the world is still at a risk of the next pandemic as *Y. pestis* occasionally re-emerges from wild rodents.¹⁹

The present study data suggested that the pattern of human plagues in Vietnam's Central Highlands region varied by season, with the highest number of cases occurring in the hot and dry months. Our result is consistent with previous studies showing that the majority of plague cases were found in months with reduced rainfall^{8,10} or rainy tropical summer season.²⁰ In this Central Highlands region, we found that the dry season is characterized by a high flea index and high rodent density, which is also consistent with a previous observation that fleas tended to blossom during the hot and dry months.¹¹

Consistent with previous observation,⁸ we also found that the flea index decreases exponentially when monthly rainfall exceeds 10 cm and it increases when monthly rainfall is <10 cm. It has been hypothesized that rainfall reduces the abundance of fleas because they are more susceptible to fungal, bacterial or viral infection, or they are trapped in the rat burrows and feeding areas.⁸ The inter-relationship between rainfall, flea index, rodent density and

plague appears to support the 'tropic cascade' hypothesis,^{21,22} in which it is hypothesized that high precipitation leads to plant growth and food availability, which in turn increases the rodent population and density.²¹

In this study, *R. exulans* and *S. murinus* together accounted for ~97% rodents captured. Thus it appears that *R. exulans* and *S. murinus* are the primary reservoirs of plague in the Central Highlands. This is somewhat different from previous studies in Vietnam's urban regions, where among 13 121 rodents captured, 29% was *R. exulans* and 16% *S. murinus*.¹¹ Thus, it appears that the reservoir of plague in the Central Highlands is different from urban regions. Moreover, our data also suggest that *X. cheopis* (found in 97% of fleas captured) was the major classical vector of bubonic plague in the region, and this finding was consistent with the previous study,¹¹ in which 99% of the fleas was *X. cheopis*.

It is interesting to observe that there was no plague case during the period of 2003–2007. During the same period, the number of rodents and fleas trapped was lower than that during 2000–2001, and there was absence of *Y. pestis* from rodents and fleas. The absence of new plague cases could also be a sign of a 'silent period', which may last as long as 10 years or even longer, after which sudden explosions of rodent or human plague may occur. Such a silent period has been observed in India in 1994.²³

Plague can be successfully treated with inexpensive antibiotics. In this study, the case fatality rate was 5%, which is substantially lower than that reported in Madagascar (20%).^{20,24} It is difficult to compare the fatality rates between countries because of differences in local conditions and health care systems. In the Central Highlands, there is a well-organized network of commune health stations that are ready to deal with any outbreak by identifying suspected cases early and administering appropriate treatment. This system could contribute to the lowering of mortality from plague over the years, although we have no scientific evidence to make a conclusive inference.

The present finding should be interpreted within the context of some strengths and potential weaknesses. The strength of this study is that it could ascertain most (if not all) cases of plague. The two provinces were the main foci of plague, which provided ideal settings for studying risk factors of plague. However, other animal carriers or fleas were not sampled, and the confirmed rodent cases that we collected might not be the same rodents that caused the outbreak. The present study was an ecological investigation; therefore, it is not possible to make inference concerning the causative relationship between the flea index and plague at the individual patient level. The number of deaths was small and therefore not suitable for a thorough analysis of risk factors for mortality from plague.

In summary, these data indicate that in Vietnam's Central Highlands the risk of plague was increased during dry and hot months when monthly rainfall decreased and the monthly flea index and rodent density increased. The data also suggest that the incidence of plague is likely resulting from multiple ecological factors that are linked to the classical reservoir and vector of bubonic plague.

Acknowledgements

We acknowledge the technical and financial support of Institute of Hygiene and Epidemiology of Tay Nguyen, the Centers for Preventive Health of Dak Lak and Gia Lai provinces, Vietnam.

Conflict of interest: None declared.

KEY MESSAGES

- Human plague is an ancient disease that repeatedly appears in endemic regions around the world, with more than 38 000 cases reported to the WHO between 1989 and 2003.
- In Vietnam, there have been some recently reported cases of plague, with 95% having occurred in the Central Highlands plateau.
- Reduced rainfall was inversely associated with the proliferation of fleas, increased rodent density and increased risk of plague.
- There were four main flea species identified in the study: *X. cheopis* (97%), *P. irritans* (1.5%), *C. felis felis* (1.3%) and *C. felis orientalis* (0.1%); and three main rodent species: *R. exulans* (83%), *S. murinus* (13.6%) and *R. nitidus* (2.8%).

References

- Perry RD, Fetherston JD. Yersinia pestis—etiologic agent of plague. *Clin Microbiol Rev* 1997;**10**:35–66.
- World Health Organization. Plague surveillance and outbreak response. *Report of an Informal Intercountry Consultation*. Bangalore, India: WHO, 2002.
- WHO. Human plague in 2002 and 2003. *Wkly Epidemiol Rec* 2004;**79**:301–6.
- Gage KL, Kosoy MY. Natural history of plague: perspectives from more than a century of research. *Annu Rev Entomol* 2005;**50**:505–28.
- Stark HE, Miles VI. Ecological studies of wild rodent plague in the San Francisco Bay area of California. VI. The relative abundance of certain flea species and their host relationships on coexisting wild and domestic rodents. *Am J Trop Med Hyg* 1962;**11**:525–34.
- Stenseth NC, Samia NI, Viljugrein H *et al.* Plague dynamics are driven by climate variation. *Proc Natl Acad Sci USA* 2006;**103**:13110–5.
- Velimirovic B. Plague in South-East Asia. A brief historical summary and present geographical distribution. *Trans R Soc Trop Med Hyg* 1972;**66**:479–504.
- Olson WP. Rat-flea indices, rainfall, and plague outbreaks in Vietnam, with emphasis on the Pleiku area. *Am J Trop Med Hyg* 1969;**18**:621–28.
- Olson WP. Rainfall and plague in Vietnam. *Int J Biometeorol* 1970;**14**:357–60.
- Cavanaugh DC, Marshall JD, Jr. The influence of climate on the seasonal prevalence of plague in the Republic of Vietnam. *J Wildl Dis* 1972;**8**:85–94.
- Cavanaugh DC, Dangerfield HG, Hunter DH *et al.* Some observations on the current plague outbreak in the Republic of Vietnam. *Am J Public Health Nations Health* 1968;**58**:742–52.
- Cavanaugh DC, Hunter DH, Nguyen van B, Tran cong D, Ryan PF, Marshall JD, Jr. Ecology of plagues in Vietnam: 3. Sylvatic plague; *Bandicota indica*, a transitional species. *Trans R Soc Trop Med Hyg* 1968;**62**:456.
- Conrad FG, LeCocq FR, Krain R. A recent epidemic of plague in Vietnam. *Arch Intern Med* 1968;**122**:193–98.
- Legters LJ, Cottingham AJ, Jr, Hunter DH. Clinical and epidemiologic notes on a defined outbreak of plague in Vietnam. *Am J Trop Med Hyg* 1970;**19**:639–52.
- Suntsov VV, Huong LT, Suntsova NI, Gratz NG. Plague foci in Viet Nam: zoological and parasitological aspects. *Bull World Health Organ* 1997;**75**:117–23.
- Dennis D, Gratz N, Poland J, Tikhomirov E. *Plague Manual: Epidemiology, Distribution, Surveillance and Control*. WHO/CDS/CSR/EDC/99.2. Geneva, Switzerland: World Health Organization, 1999.
- Yang Y, Kang J, Mao K, Zhang J. Regression models for mixed Poisson and continuous longitudinal data. *Stat Med* 2007;**26**:3782–800.
- R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2005.
- Thullier P, Guglielmo V, Rajerison M, Chanteau S. Short report: serodiagnosis of plague in humans and rats using a rapid test. *Am J Trop Med Hyg* 2003;**69**:450–51.
- Chanteau S, Ratsitorahina M, Rahalison L *et al.* Current epidemiology of human plague in Madagascar. *Microbes Infect* 2000;**2**:25–31.
- Parmenter RR, Yadav EP, Parmenter CA, Ettestad P, Gage KL. Incidence of plague associated with increased winter-spring precipitation in New Mexico. *Am J Trop Med Hyg* 1999;**61**:814–21.
- Ensore RE, Biggerstaff BJ, Brown TL *et al.* Modeling relationships between climate and the frequency of

human plague cases in the southwestern United States, 1960–1997. *Am J Trop Med Hyg* 2002;**66**:186–96.

- ²³ WHO. International meeting on preventing and control plague: the old calamity still has a future. *Wkly Epidemiol Rec* 2006;**28**:278–84.
- ²⁴ Migliani R, Chanteau S, Rahalison L *et al.* Epidemiological trends for human plague in Madagascar during the second half of the 20th century: a survey of 20,900 notified cases. *Trop Med Int Health* 2006;**11**: 1228–37.