Plague Manual

Epidemiology, Distribution, Surveillance and Control

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CONTENTS

List of Tables ........................................................................................................ 4
Figure Legends ........................................................................................................ 5
List of Maps ............................................................................................................ 5
Acknowledgements ................................................................................................ 7
Preface ..................................................................................................................... 9
References ............................................................................................................... 10

1 Epidemiology and Distribution of Plague ........................................................ 11
    Africa .................................................................................................................... 27
    Americas ............................................................................................................. 31
    Asia ..................................................................................................................... 34
    Summary of trends ............................................................................................ 37
    References ......................................................................................................... 39

2 Diagnosis and Clinical Manifestations ............................................................. 43
    Bubonic Plague .................................................................................................. 43
    Septicaemic Plague ......................................................................................... 44
    Pharyngeal Plague ............................................................................................ 46
    Meningeal Plague ............................................................................................. 46
    Laboratory Diagnosis ....................................................................................... 48
    References ......................................................................................................... 51

3 Treatment of Plague .......................................................................................... 55
    Case Management : Therapy and epidemic prevention .................................. 55
    Phylactic therapy .............................................................................................. 57
    Hospital precautions ......................................................................................... 57
    Vaccination ....................................................................................................... 58
    References ......................................................................................................... 61

4 Rodent Reservoirs & Flea Vectors of Natural Foci of Plague ......................... 63
    Rodent Reservoirs ............................................................................................ 63
    Flea Vectors .................................................................................................... 64
    References ......................................................................................................... 87
CONTENTS CONT.

5 Control of Plague Transmission............................... 97
Principles of Control ........................................................................................................... 98
Control of Flea Vectors ................................................................................................. 99
Control of Rodent Reservoirs.................................................................................... 104
References .................................................................................................................. 131

6 Plague Surveillance ..............................................135
Human Surveillance ........................................................................................................ 136
Surveillance of Rodent Populations.................................................................................... 140
References .................................................................................................................. 161

7 National Health Services in Prevention
and Control ...............................................................167
Phase 1: Case Recognition and Medical Intervention ................................................ 168
Phase 2: Epidemiological and Epizootical Investigation
and Emergency Control .................................................................................................. 168
Phase 3: Surveillance and Control .................................................................................. 169
Phase 4: Management ...................................................................................................... 169
References .................................................................................................................. 171

LIST OF TABLES

Table 1: Human plague, number of cases (and deaths)
reported in the world, 1954-1997 .................................................................................. 18
Table 2: Plague treatment guidelines ............................................................................... 59
Table 3: Plague prophylaxis guidelines .......................................................................... 60
Table 4: List of host–flea complexes found involved in epizootic plague amplification in western North America by
global regions ..................................................................................................................... 82
Table 5: Insecticide dusts commonly employed in flea control ........................................ 102
Table 6: Insecticide resistance reported in flea populations .......................................... 104
Table 7: Comparison of acute and chronic rodenticides ............................................... 109
Table 8: Relative potencies, recommended concentrations to
give a LD50 dose of several anticoagulant rodenticides to Norway rats ......................... 110
Table 9: Characteristics of acute and subacute rodenticides ......................................... 115
Table 10: Characteristics of rodent fumigants ............................................................... 127
FIGURE LEGENDS:
PHOTOGRAPHS BY L. CARTER

Figure 1: Rodent anaesthetized in jar containing Metofane.
The cotton in the lid is soaked with a small amount of the anaesthetic agent prior to placing the animal in the jar................................................................. 142

Figure 2: Typical wire mesh live trap designed to capture medium-sized mammals. The white material in the trap is upholstery cotton, added to prevent hypothermia during cold weather................................. 146

Figure 3: Aluminum live traps used to capture small mammals. The first two traps are collapsible (the trap on the left has been closed for storage). The trap on the far right is a non-collapsible style that is sturdier but less easy to transport and store................................................................. 146

Figure 4: A typical snap trap used to capture rodents. These traps are relatively inexpensive and can be used to collect a variety of animals. The trap in this picture has been baited with peanut butter................................. 147

Figure 5: Nobuto strips and a mailing envelope stamped with blanks for collection data. The long, narrow portion of the Nobuto strip at the bottom of the figure has been saturated with the proper amount of blood. This portion of the strip is removed in the laboratory for further processing................................................................. 149

Figure 6: Combing a rabbit for fleas. The animal and fleas have been anaesthetized prior to processing. As the comb passes through the hair it will dislodge fleas into the pan where they can be collected for identification and analysis................................................................. 153

Figure 7: Surveillance worker using a burrow swab to collect fleas from burrows................................................................. 154

LIST OF MAPS

Map 1 Natural plague foci (in rodent population)................................. 15
Map 2 Distribution of Rattus rattus.................................................. 85
Map 3 Distribution of Rattus norvegicus........................................... 86
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Preface

One of the oldest identifiable diseases known to man, plague remains endemic in many natural foci around the world. It is widely distributed in the tropics and subtropics and in warmer areas of temperate countries. Essentially a disease of wild rodents, plague is spread from one rodent to another by flea ectoparasites and to humans either by the bite of infected fleas or when handling infected hosts. Recent outbreaks have shown that plague may reoccur in areas that have long remained silent. Untreated, mortality from pneumonic plague may reach high levels. When rapidly diagnosed and promptly treated, plague may be successfully managed with antibiotics such as streptomycin and tetracycline, reducing mortality from 60% to less than 15%. However, the recent appearance in Madagascar of a strain of Yersinia pestis showing multiresistance to antibiotics is a matter of much concern and highlights the necessity for effective surveillance of the disease.

The World Health Organization (WHO) in 1976 issued its Plague Manual, covering the surveillance of plague, bacteriological and serological examination and rodent reservoirs and flea vectors of the infection. Since then there have been many developments, and an updated publication is needed for front line health personnel, especially for those at the primary health care level. This publication presents new information on the diagnosis and treatment of plague and a comprehensive review of the control of rodent reservoirs and flea vectors. Due to the considerable progress made in the laboratory diagnosis of plague, a publication dealing specifically with this subject will be published separately.
REFERENCES


1

Epidemiology and Distribution of Plague

Dr Eugene Tikhomirov

Plague is one of three epidemic diseases still subject to the International Health Regulations and notifiable to the World Health Organization (1). The pathogen causing the disease *Yersinia pestis* circulates in animal reservoirs, particularly in rodents, in the natural foci of infection found on all continents except Australia. The natural foci of plague are situated in a broad belt in the tropical and sub-tropical latitudes and the warmer parts of the temperate latitudes around the globe between the parallels 55 degrees North and 40 degrees South. However, within these limits many areas are free of natural foci of plague, such as desert areas with few or no rodents and large areas of continuous forest, particularly in the tropics and high glacier-covered mountain ranges.

Plague is transmitted between rodents and to other animals via wild rodent fleas, cannibalism or (possibly) contaminated soil. Wild plague exists in its natural foci independent of human populations and their activity (2). Domestic plague is intimately associated with rodents living with humans and can produce epidemics in both human and animal populations (2).

The plague microbe *Y. pestis* is a non-motile, non-acid fast, non-sporeforming, Gram-negative cocco-bacillus measuring 1.5 by 0.75 microns. When stained with aniline dyes the ends of the bacillus take stain more intensely; this is known as “bipolar staining”. *Y. pestis* belongs to the group of bacilli with low resistance to environmental factors. Sunlight, high temperatures and desiccation have a destructive effect, and ordinary disinfectants such as lysol and preparations containing chlorine kill it within 1 to 10 minutes.

Humans are extremely susceptible to plague and may be infected either directly or indirectly. Indirect transmission through the bite of a flea is the most common route of transmission between plague-infected rodents and humans. Human infection most frequently occurs when an epizootic develops among synanthropic rats in centres of human population, following contact with infected wild rodents. Commensal rat fleas, including plague-infected fleas, leave the bodies of rats killed by plague seeking a blood meal.
from another host and may bite human beings. Humans who contract the
disease may subsequently become infective to other people. Less common is
human infection following the death of rodents during an epizootic in a
natural focus. The fleas can accumulate at the entrance to and the ground
surface around burrows and B as the fleas are not strictly species-specific
parasites of their rodent hosts B bite and infect humans with plague. People
can be infected directly from a plague-infected rodent or other animal while
handling, skinning or cutting up the meat. The plague agent penetrates the
human organism through skin lesions or through the mucous membranes of
the mouth, nose or eyes.

Plague is only occasionally transmitted between humans, either
through the bites of human fleas (Pulex irritans) infected after biting patients
in the septicemic stage, or through direct contact between a healthy person
with an infected person (3). When primary bubonic plague develops into
secondary pneumonic plague, airborne transmission of the infective agent
may take place via the respiratory route, leading to primary pneumonic
plague among close contacts. Infection through direct contact with objects
contaminated with sputum from pneumonic plague patients can lead to the
development of bubonic plague.

Cases of human plague have been known from time immemorial (4).
Although it is difficult on the basis of the information that has survived
from the distant past to distinguish plague from other acute communicable
diseases, from what is known plague is an ancient disease which originated
in the cradle of human civilization in Central Asia. The first plague epidemic
on record was the outbreak among the Philistines in 1320 BC, described in
the Bible (I Samuel, V and VI) as characterized by the appearance of
"emerods in their secret parts".

In the last two millennia, plague has become widespread, affecting a
large number of countries on most continents during several pandemics. The
first certain pandemic, known as Justinian's plague, was recorded in the
sixth century AD. Between 542 and 546 AD epidemics in Asia, Africa and
Europe claimed nearly 100 000 000 victims.

The second plague pandemic is the well known "Black Death" of the
fourteenth century (1347–1350). It was the cause of some 50 000 000
deaths, half of them in Asia and Africa and the other half in Europe, where a
quarter of the population succumbed. This pandemic was the beginning of a
number of outbreaks of plague which ravaged Europe and Africa in
subsequent centuries.
The third pandemic began in Canton and Hong Kong in 1894 and spread rapidly throughout the world, carried by rats aboard the swifter steamships that replaced slow-moving sailing vessels in merchant fleets. Within 10 years (1894–1903) plague entered 77 ports on five continents: Asia (31 ports), Europe (12), Africa (8), North America (4), South America (15) and Australia (7).

Plague spread widely in India where it caused nearly 13,000,000 deaths and claimed many victims in a number of other countries. Early in the pandemic, important discoveries enabled plague prevention and control to be placed on a scientific basis. In 1894 the causal agent was discovered. It was also established that rats contract plague and that the rat flea *Xenopsylla cheopis* is the common vector.

Plague doubtlessly existed as a disease of wild rodents even before the appearance of humans. The commensal rats of the genus *Rattus* migrated throughout the world from their origins in Asia but became numerous only with the development of towns and transport and the rise of thickly-populated urban and rural areas. Plague penetrated urban rat colonies, as it often still does, from its wild foci. Consequently, foci of wild plague involving sylvatic rodents are primary and those of urban rat plague are secondary or temporary.

Many natural foci of plague have been identified and measures of prophylaxis and control developed which make it possible to prevent plague outbreaks. Effective treatment methods enable almost all plague patients to be cured if diagnosed in time. The use of these measures has led to a sharp reduction in the epidemicity of plague throughout the world. Today the distribution of plague coincides with the geographical distribution of its natural foci.

It is unlikely that all the primary foci of plague have been discovered. Accordingly, close examination should be given to any rural area in which repeated cases of human plague occur. The prolonged absence of human cases in the vicinity of a natural focus does not in itself mean that plague has disappeared. If there is no evidence that plague has come from outside sources, the disease must be sought among local wild rodents (4).

On every continent, primary natural foci of plague are connected with particular types of landscape in which climatic conditions are favourable for a high and stable number of rodent reservoirs and flea vectors of *Y. pestis*. Most natural foci of plague, including the mountains, are found where there
is low annual precipitation, or where dry seasons inhibit the growth of thick woody vegetation and lead to the formation of deserts, semi-deserts and steppes (savannas, prairies, pampas and so on).

Human cases of plague are relatively sparse in natural foci. Cases occur among people who come in contact with wild rodents in the course of their work, hunting, or camping. The risk of human infection increases significantly when plague penetrates populations of domestic rodents, particularly rats of the genus *Rattus*. Foci of "rat" plague still exist in Africa, Madagascar (5), Viet Nam (6) and possibly in several South American countries (7).

"Rat" plague presents a particular danger where, in addition to synanthropic rats in human settlements, there are also wild rats in the surrounding fields (such as in Madagascar and East Africa). In these areas, complex secondary foci of "rat" plague arise which are more stable than temporary foci in towns.

Plague foci are dynamic, changing in response to shifts in factors such as climate, landscape, and rodent population migration. Natural foci of plague persist at the present time in North and South America, Africa and Asia, and to some extent in South-East Europe (Map 1). These are described below.

Europe. Natural foci of plague in Europe still exist only in fringe areas of the Caspian depression and the eastern slopes of the Caucasus.

Eurasian land mass. The north western boundary of the natural plague foci extends slightly beyond the limits of the desert zone, continuing a short distance into the desert steppe; that is, the area between the Volga, the Don and the Ural rivers. The main focus of natural plague in the eastern part of the continent lies in the steppe region. The foci extend as far as the northern and eastern limits of the steppes and penetrate widely into the forest steppe zone.
Map 1  Natural plague foci (in rodent population)
Asia. Natural foci in Asia stretch in an uninterrupted chain across the desert and steppe regions in the foothills of the Caucasus, eastern Turkey and north east Iran in the west as far as Liao-Ho to north east China. The southern boundary of the plague area passes to the north of Shenyang and through Chileng to Kalgan. Nowhere do the Asian foci reach the Pacific coast. Endemic foci are found in Cambodia, China, India, Indonesia, Iran, Mongolia, Myanmar, Nepal, Viet Nam and the southern part of the Arabian peninsula, the Yemen-Saudi Arabian border, and in Saudi Arabia.

Africa. Natural foci of plague are known to exist in broad areas of Africa. These include areas in the Democratic Republic of the Congo, Kenya, Lesotho, Libya, Madagascar, Mauritania, Mozambique, Namibia, Senegal, South Africa, Tanzania, Uganda, and probably Egypt.

Americas. In North America, natural foci of plague occur in 15 western states of the United States, in south-western Canada on the border with the United States, and in northern Mexico. In South America foci have been recorded in Argentina, Bolivia, Brazil, Ecuador, Peru and Venezuela.

Table 1 shows the number of cases and deaths due to human plague notified to WHO over the past 44 years. It must be emphasized that these data do not adequately reflect the incidence of plague. They represent only a portion of the actual number of cases and in fact may not even represent all of the known, active enzootic foci in the world. Global statistics on plague are incomplete because of the reluctance to officially notify plague cases as well as inadequate surveillance and reporting. Systems of reporting differ considerably in countries, and under-reporting of plague due to lack of laboratory facilities for diagnostic confirmation is not uncommon. In most countries only bacteriologically or serologically confirmed cases are reported. It is estimated that laboratory confirmation of cases is obtained in only approximately one-third of suspected cases, making the actual epidemiological situation or disease incidence difficult to assess. However, a general idea of the distribution of plague and global trends can be obtained from WHO data.

According to notifications received by WHO during the period from 1954 to 1997, plague affected 38 countries, with 80,613 cases and 6,587 deaths. The maximum number of plague cases (6,004) occurred in 1967 and the minimum (200) occurred in 1981. Between 1967-1971 the annual number of cases exceeded 4,000. The total for the 5-year period was 22,335 cases and 975 deaths.
The decrease in the incidence of plague today is due primarily to the improvement of living standards and health services in many countries, to the extent that the possibility of outbreaks of anthroponotic bubonic and primary pneumonic plague, the most epidemic forms of the disease, has been reduced nearly to zero. During this period epidemics of human plague in India have ceased. The reasons for this have not been determined.

However, the extensive use of insecticides for malaria control in Indian towns and villages has probably played an important role.

Analysis of plague statistics over the 44-year period by continent shows that the largest proportion of reported cases (58.4%) was notified in Asia. For Africa and the Americas the percentages were 27.8 and 13.8 respectively. Mortality was 54.6% for Asia, 34.4% for Africa and 11.0% for the Americas. There were 47,091 cases and 3,595 deaths in 10 Asian countries. In 1967-1971, the period of the highest incidence of the disease in the world in the last 44 years, the plague situation in the world at large (not solely in Asia) was determined by plague outbreaks in Viet Nam. There were 21,716 human plague cases reported from Viet Nam, comprising 97.2% of cases in Asia and 89.2% of the global total.
### Table 1 Human plague, number of cases (and deaths) reported in the world, 1954-1997

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Table 1  Human plague, number of cases (and deaths) reported in the world, 1954-1997  cont.

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* Figures not available
* includes suspected cases
Increased plague morbidity in Viet Nam was due to disruption of the economy, ecosystem and infrastructure as a result of prolonged armed conflict. A considerable proportion of human plague cases occurred in southern Viet Nam where the defoliation of vast areas during military operations is thought to have been one cause of the high incidence (8).

For the last 44 years the mean perennial plague mortality for the world has been 7.4%, ranging from a high of 23.8% in 1961 to a low of 2.4% in 1970. While the impression given by these figures is that plague mortality is relatively low, analysis by continent and country shows that mortality remains high. In Asia the mean perennial mortality for the period 1954–1997 was 7.6%, varying from 0 in 1981 to 32.6% (1982). In the Americas, the mean perennial mortality for the same period was 6.5%. In Africa the mean perennial mortality was 10.1%, ranging from 45% (1971) to 2.8% (1964).

Despite the availability of a number of highly–effective therapeutic agents, mortality due to plague in many countries was high during the period 1954–1997. Again, it should be noted that these data are incomplete, due to the limitations mentioned above.

Despite the general decline in the incidence of plague worldwide, the number of countries affected by plague remains substantial. In 1954–1997 human plague was recorded in 38 countries, 7 of which (Brazil, Democratic Republic of the Congo, Madagascar, Myanmar, Peru, United States, Viet Nam) were affected virtually every year. In the remaining countries, outbreaks of human plague occurred during years when plague resurged globally. The reasons for this apparent worldwide cycle are not fully understood.

Over the past 44 years there have been three periods of increased plague activity. The first was during the mid–1960s, the second between 1973 and 1978, and the third was from the mid–1980s. The rise in reported plague morbidity continued worldwide in the 1990s. The number of cases reported during the 5–year period 1990–1994 was approximately 57% of all cases notified within the 15–year period 1980–1994. Long silences of 10 years or more, followed by sudden explosions of rodent or human plague have been confirmed in some natural foci. For example, in 1994 plague reappeared in Malawi, Mozambique and India, after a "calm" period of 15–30 years.
Although national plague reporting systems vary greatly, there has been an obvious change in the distribution of plague morbidity by continent. Whereas in the 1970s plague cases were reported predominately from Asia, in the 1980s and the 1990s a small number of African countries with well-known natural plague foci reported the highest number of cases.

Africa

In 1980–1997 human plague was reported from 13 countries (Angola, Botswana, Democratic Republic of Congo, Kenya, Libya, Madagascar, Malawi, Mozambique, South Africa, Uganda, United Republic of Tanzania, Zambia, Zimbabwe) with a total of 19,349 cases and 1,781 deaths (66.8% and 75.8% of the world’s total). This was a yearly average of 1,073 cases and 99 deaths (9.2% mean case-fatality rate).

Angola (9,10)

Human plague was recorded in 1980–1981 at Bocoio in Benguela Province (27 cases, 4 deaths). This was the first time that plague had been notified from Angola since 1975.

Botswana (11,12,13)

Prior to an outbreak in 1989–1990, there had been no official notification of human plague since 1951. An outbreak began in Boteti District and lasted 24 weeks (173 cases, 12 deaths). Plague affected six neighbouring villages located in the natural focus; the most affected were Rakops, Toromoja and Xhumo. Following the bumper harvest of 1989 which stimulated a high density of rodent population, a large epizootic of plague among wild rodents penetrated into human settlements and caused an epizootic among commensal rats, which then transmitted the disease to humans. Only bubonic plague was observed; 72% of patients were under 15 years old. At the beginning of the outbreak several patients died of septicaemic plague.

Democratic Republic of the Congo/former Zaire (10,17,18,20,21,26,38)

The total number of plague cases reported from the Democratic Republic of the Congo in the 18-year period 1980–1997 was 2,824 with 536 deaths (case-fatality rate 19.0%). Sporadic cases of plague were seen in 1982 and 1989 and significant outbreaks occurred in 1987–1988 and
1991–1995. The latest outbreaks occurred in the Ituri sub-region (Upper Zaire Province), the major foci in Logo, Rimba, Nyamibe, Rethy and Bunia Rural Health Zones. Plague occurred from January to October with peak incidence in February–May and September.

Kenya (9,12,14)

Plague has been known in Kenya since 1902. Large epidemics occurred primarily in urban areas in the first half of the century. Since 1942 the incidence has declined and the disease has appeared as sporadic cases. The last documented urban case was in Fort Hall in 1964 until its reappearance in 1990. Serological surveys have shown that rodent plague persists over wide areas, including Kisumu, Mombasa, M alindi, Kombei ni, Kitale, Kerio, Tavets, Rongai and Machakos.

An outbreak of human plague was reported to have started in the south (Kijiado district of the Rift Valley Province) in late August 1978. Further bubonic cases, mainly in women and children, were diagnosed in Kitui district of the Eastern Province, Kiambu district of the Central Province and Taita–Taveta district of the Coast Province. There were 393 cases with 10 deaths recorded from September 1978 to March 1979. There was an increased rodent population with unusual numbers of dead rats in many households in the months prior to the outbreak of human plague. Mastomys natalensis was the most common species (89%) of rodents trapped. Other small mammals were present in relatively small numbers: Tatera spp., Acomys spp., R. rattus and the elephant shrews Petrodromus spp. and Arvicanthis niloticus. In March 1980, 5 cases (2 deaths) were reported in Nairobi Region.

Another outbreak of human plague in Kenya occurred in 1990, when 44 cases (8 deaths) were reported. There were two foci of the disease: Machakos district of the Eastern Province (22 cases, 5 deaths; the majority of cases occurred in early February) and in Nairobi (22 cases, 3 deaths in late August).

Libyan Arab Jamahiriya (15,16)

Eight cases of bubonic plague occurred in September 1984 in two locations 25 km from Tobruk, where plague foci had been noted in 1976–1977. The foci of bubonic plague in Libyan Arab Jamahiriya are of great interest from an epidemiological point of view: the fact that the cases which occurred in 1972, 1976 and 1977 were from different parts of the country
scattered over a vast area is evidence that an extensive epizootic of plague had taken place. Reports of plague in 1976 in places where sick camels had been slaughtered draws attention to the role of these animals in the epidemiology of the disease in some areas.

**M adagascar (11,12,17,18,19,20,21,22,38,39)**

Plague appeared in ports of Madagascar for the first time in 1898. In 1921 it spread to the high plateau (above 700 metres), where it has persisted. Human plague cases occur throughout the year but most occur during the hot, wet season of October to March.

During the 18-year period 1980–1997, human plague cases were registered every year, totalling 5986 cases and 493 deaths (31.0% and 27.7% of corresponding figures for Africa). The mean case-fatality rate was 8.2%, varying from 2.3% in 1995 to 56.5% in 1979. There has been an upward trend in reporting since 1995. Natural foci of plague are widespread in the country’s six provinces. Major foci are located in the provinces of Antananarivo and Fianarantsoa where outbreaks have been continuously notified. Sporadic cases are periodically recorded in Mahajanga, Majumga, Tamative and Toamasina Provinces. Eighteen prefectures in the provinces of Antananarivo and Fianarantsoa have been affected, connected with an important epizootic among wild rodents over a large area of these two provinces. It should be emphasized that in the mid 1990s the first naturally occurring antibiotic-resistant strain of *Y. pestis* was isolated in Madagascar. This strain was isolated from a patient with bubonic plague, and was resistant to all first-line antibiotics as well as to the principal alternative drugs for treatment and prophylaxis. The resistance was mediated by a plasmid and was transferable.

**M alawi (21)**

In 1994, nine suspected cases of bubonic plague were reported, of which 4 were confirmed. All cases occurred in Manhokwe, Nsanje District among Mozambican refugees living in the Mankhowe refugee camp and surrounding villages. In 1997, an outbreak of human plague with a total of 582 cases (11 deaths) was notified in Chikwawa district, Nsanje district and Nchisi. This outbreak began in Nsanje district in September 1997 and was continuing in 1998.
Mozambique (21,23,38,39)

There were 12 cases of plague recorded in 1978, reflecting a continuation of plague activity registered in previous years. In 1976 plague was reported in the village of Culecha in northern Mutarara District, Tete Province. In 1977 it broke out in other villages in the same district. The peak was in August–September 1977 (97 cases, 14 deaths). Mutarara District is known as a plague–enzootic area. There was drought in the country in 1976 and it is possible that plague was spread to domestic Rattus by peridomestic rodents, in particular Mastomys natalensis. It is likely that there was an epidemiological significance associated with the local custom of catching wild rodents (mainly M. natalensis) for food. Women and children use sacks to collect rodents which are then killed, skinned and dressed. Out of 77 patients placed under medical supervision during the epidemic, 70 were women and children (under age 14). In such a complex epidemiological situation, one cannot exclude the possibility of development of human–to–human transmission of bubonic plague. In 1994 human plague reappeared for the first time for more than 15 years in Mutarara District of the Tete Province. The epidemic of plague continued from August to October (bubonic form, 216 cases, 3 deaths). Another outbreak of human plague (825 cases, 18 deaths) was reported in the same area in 1997.

South Africa (24)

Human plague was recorded in 1982 after a dormant period of 10 years: 19 cases (1 death) were registered in southern Cape of Good Hope Province in a village north of Port Elizabeth.

Uganda (20,24,25)

Cases of human plague have been recorded only three times in the last 38 years: 1982 (153 cases, 3 deaths), 1986 (340 cases, 27 deaths), and 1993 (167 cases, 18 deaths). Human plague was reported in Nebbi District, Western Region, one of the plague-endemic areas of the country, bordering on the Eastern Province of Democratic Republic of the Congo where human plague is frequent. The site of the outbreak is a densely-populated area (the average population density is 60–80 persons/km2), rats and gerbils of the genus Tatera are frequently found in human dwellings. The possibility that the appearance of human plague may have resulted from an epizootic among synanthropic rodents cannot be excluded.
United Republic of Tanzania (12,15,21,25,26,27,38,39)

During the 18-year period 1980–1997 human plague was reported every year totalling 7246 cases and 585 deaths (37.5% and 32.9% of the corresponding figures for Africa). The average case-fatality rate was 8.1% with a high of 66.6% in the early 1980s. Since 1983 outbreaks of human plague have occurred almost non-stop in this country, which had not been the case for the previous 30-year period. The increased incidence of human plague was due to continuous outbreaks in the Tanga Region (Lushoto District), which became widespread in 1983–1984, 1991 and 1994–1997. Cases of pneumonic plague traced to Lushoto were reported for the first time in Dar-es-Salaam in 1991. Most plague cases occur in January–March.

Zimbabwe (21,24,28,29)

Sporadic cases of human plague were recorded in 1982, 1983 and 1985 (5 cases, 3 deaths) and in 1997 (8 cases, 2 deaths). In 1994, 392 cases with 28 deaths were reported in Matabeleland North, Nkaye and Lupane Districts. The highest number of cases occurred in October–November; 80% of the patients were under 15 years old. The last local outbreak of human plague was reported in 1974–1975.

Americas

Human plague was reported from five countries (Bolivia, Brazil, Ecuador, Peru and the United States), three of which (Brazil, Peru and the United States) notified the disease in humans nearly every year in the 18-year period 1980–1997. Totals for this period were 3137 cases with 194 deaths (10.8% and 8.3% of the world total respectively), with an average of 175 cases, 11 deaths. The case-fatality rate was 6.2%, varying from 2.2% (1982) to 12.5% (1990). There were no deaths notified on the continent in 1989 and 1991.

Bolivia (9,10,12,24,25,26,28,30,38,39)

During the 18-year period 1980–1997, human plague was not recorded in 1985, 1989, 1991–1995. There were 216 cases with 31 deaths (case fatality rate 14.4%). Outbreaks occurred mainly in La Paz Department in Franz Tamayo and Nor Yungas Provinces, which are known plague-endemic areas. In 1977 plague was reported in the provinces of Tomina and Azurduy, in Chuquisaca Department. Plague was reported in September–
October 1987 in Santa Cruz Department in south–eastern Bolivia, where no outbreaks had occurred since 1965.

The seasonal distribution of human plague has been characterized by peaks in February–May and September–October. The role of anthroponotic bubonic plague in some outbreaks is probable, as investigations in the 1980s in two localities during the outbreak (Mohima and Culata) of Franz Tamayo Province demonstrated a high density of *Pulex irritans*.

**Brazil (9,10,11,12,15,18,19,21,24,25,26,28,29,30,31,38,39)**

The incidence of human plague has remained fairly constant during the 18–year period with some upsurge of the disease in the 1980s. There were 710 cases (22.6% of the total notified for the Americas) with 9 deaths (case fatality rate 1.3%). A typical feature of the plague epidemiology in Brazil is the appearance of multiple foci of human plague against a background of seasonal increase of plague epizootics among wild rodents. Many municipalities in the north–eastern States of Ceara and Bahia have been affected where the infection remains active in the endemic zones. Sporadic cases and local outbreaks have been periodically registered in the State of Minas Gerais (1983–1984), Paraiba (1987, 1989 and 1990) and Pernambuco (1980, 1982). The only case of bubonic plague in 15 years was noted in Rio do Norte State. Cases of human plague occur throughout the year with peaks in February–March and September–October.

**Ecuador (10,15,28,29,30)**

Prior to 1980, there was no year free of human plague. During 1980–1997 human plague cases were reported in this country only in 1981 and 1983–1985 (83 cases, 3 deaths). An important outbreak occurred in 1983 Alausi Canton, Chimborazo Province where the disease affected 64 people in May 1983 with further cases in October 1983 and February 1984. A small cluster of human plague cases also occurred in early 1985 (3 cases, 2 deaths) in Macara Canton, Loja Province.

**Peru (10,12,15,17,19,20,21,24,26,28,29,30,38,39)**

Plague cases reported from Peru during 1980–1997 totalled 1881 cases (60% of the total notified for the Americas) with 114 deaths (case fatality rate 6.1%). There was a downward trend in the incidence of human plague in Peru until 1984 when a large outbreak occurred, affecting large areas of the departments of Cajamarca and Piura. Human infections
occurred throughout the year and seem to have originated from an intensive epizootic of wild rodent plague. In some localities, sporadic cases of human plague may have resulted in limited outbreaks of anthroponotic bubonic plague; i.e., infection transmitted by the human flea *Pulex irritans*. There were 413 cases (31 deaths) in 1984 and 44 cases (3 deaths) in 1985 related to this outbreak—the dimensions of which may be compared with the epidemic spread of the disease in the mid-1960s. Another large outbreak of plague started in October 1992 in Bolivar District, San Miguel Province of Cajamarca Department and later spread to the areas of the Departments of Piura, Lambayeque and La Libertad with a total of 1310 cases (56 deaths) reported during 1992–97.

**United States of America** (9,10,11,12,17,18,19,20,21,24,25,26,28,29,32,33,34,38,39)

247 human plague cases were reported in the United States during 1980–1997, the highest of any 18-year period since the epidemic years in the early part of the century. Thirty-seven patients died, a case fatality rate of 15%. One case was imported from Bolivia to Washington, D.C. in 1990. The number of cases by year during this 18-year period ranged from one indigenous case in 1990 to highs of 40 in 1983 and 31 in 1984. Natural foci of plague infection among rodents and their fleas are widespread in the western United States, and plague epizootics among susceptible rodent species occur frequently throughout the West. Human cases occur with greatest frequency in two regions: the south-western region that includes northeastern Arizona, southern Colorado, southern Utah all of northern and part of southern New Mexico; and the Pacific region that includes much of California, southern Oregon and western Nevada. Human cases outside these two regions have been few and scattered, and have usually been acquired through direct contact with plague-infected animals rather than by flea-bite.

In the United States, rapid sub-urbanisation has resulted in increasing numbers of people living in or near active plague foci. During each successive decade from 1944 to 1993, the number of states reporting plague cases increased: from 3 in 1944–1953 to 13 in 1984–1993. Surveillance of plague in rodent and rodent-consuming carnivore populations indicates that plague spread eastward in the 1990s to areas believed to have been disease-free since extensive animal surveillance began in the 1930s. A recent Centers for Disease Control and Prevention report on human plague in the United States emphasizes the importance of two related trends in the epidemiology of human plague: (1) increased
peridomestic transmission and (2) the role of domestic cats as a source of human infection, including primary pneumonic plague.

**Asia**

In 1980–1997 human plague was reported from seven countries (China, India, Kazakhstan, Lao Peoples Democratic Republic, Mongolia, Myanmar, and Viet Nam) with a total of 6501 cases and 374 deaths (22.4 and 15.9 of corresponding world figures). Yearly averages were 361 cases and 21 deaths with a mean case-fatality rate of 5.8%.

**China** (9,10,11,12,17,18,19,20,21,25,26,28,29,35,38,39)

Between 1980–1997, 401 cases with 83 deaths (case-fatality rate 20.7%) were recorded in the provinces of Qinghai, Yunnan, Gansu as well as the autonomous regions of Tibet, Inner Mongolia and Xianjiang. Most of the cases were scattered. The majority were infected through hunting, skinning and eating marmots and other infected animals.

Plague foci are distributed in 197 districts of 17 provinces and autonomous regions in China. They are divided into 10 types according to their main reservoirs and their land forms. In the 1980s, epizootics were detected in 9 out of 10 types of natural foci. Active natural foci were detected in Inner Mongolia, Ningxia, Shanxi, Gansu, Qinghai, Tibet and Yunnan. In southern and south-eastern coastal provinces, epizootics have been controlled since the late 1950s, but serologically–positive cases have been occasionally recorded during surveillance, even after 30 years. In 1996, the number of active natural foci of plague in China was the highest in the past 40 years. Outbreaks of epizootic plague occurred in 49 counties in the following provinces and autonomous regions: Gansu, Inner Mongolia, Qinghai, Xinjiang, Xizang and Yunnan. Eighteen counties were considered to be newly recognized natural foci of plague.

**India** (8,21,36,37)

In India large plague outbreaks occurred during the first half of the 20th century. The last laboratory–confirmed human cases were reported in 1966 from Karnataka State. Since then, several suspected outbreaks have occurred, in the historic plague–endemic areas of south India and Himachal province in north India. An outbreak in Himachal in 1983 was similar to pneumonic plague (22 cases, 17 deaths) but was not confirmed as plague.
In August–October 1994 human plague was reported in India for the first time in 30 years. During this outbreak, 876 cases, 54 of which were fatal, were characterized as presumptive plague. Most cases (596) were reported from Maharashtra State: 151 in Gujarat State, 68 in Delhi, 50 cases in Karnataka, 10 in Uttar Pradesh, and 12 cases in Madhya Pradesh. Fifty-two of the 54 fatal cases occurred in Gujarat, 1 in Delhi and 1 in Karnataka.

Although the exact circumstances are unknown, factors contributing to the re-emergence of plague in India have been identified by the National Technical Advisory Committee on Plague constituted by the Government of India (37). Beed district (Maharashtra State) has had sylvatic plague in the past. Ecological changes created by the earthquake in September 1993 disturbed the equilibrium density of domestic rodents (R. rattus) and their fleas (X. cheopis), generating large energy supplies for domestic rodents in the form of stored foodgrains, this resulted in a gradual growth of R. rattus population in the subsequent 10 month period. On 5 August 1994 in Mamlia village in the Beed district, rat-fall was reported, followed by reports of flea nuisance. Three weeks later, suspected cases of bubonic plague were notified, followed by reports from other villages in Beed and other districts.

The resurgence of plague in Surat, Gujarat State, was related to a record high rainfall during the September monsoon. Feast of Topi river flood waters inundated localities in the north, south-west, central and eastern zones of Surat City. Many rodents and other animals were found dead when the water floods receded 5 days later. While cleaning up local residents have become infected after contact with dead animals. Shortly after the flood the Ganapati festival brought huge crowds of people together in the city which would facilitate the spread of acute respiratory illness. Based on the clinical picture and the plague outbreak in neighbouring Maharashtra State, the outbreak in Surat was declared as pneumonic plague on 21 September 1994.

Kazakhstan (11,12,18,20)

Human plague cases were notified to WHO for the first time in 1989 (Kazakh Republic of the former USSR). During 1989–1997 there were 11 cases (4 deaths) recorded, in areas well known as enzootic for wild rodent plague: the Guriev and Kzyl-Orda regions. Infection occurred following hunting and skinning wild rodents (marmots) or slaughtering a sick camel.
M. _ongolii_ (11,12,18,19,20,38,39)

Human plague was reported to WHO for the first time in 1989 and 68 cases (22 deaths) were reported to 1997. Plague cases were detected in 8 aimaks (districts): Arkhangai, Baganur, Bayankhongor, Bayanulgii, Govaltai, Uvs, Uvurhangai and Zavkhan. These aimaks are enzootic for plague. The cases were mostly associated with marmot hunting during July and August.

M. _yannar_ (9,10,11,12,15,17,18,19,20,21,24,25,26,28,29,35)

During 1980–1994, human plague cases were registered every year, totalling 1160 cases with 14 deaths (about 21% of plague incidence in Asia). The case-fatality rate was 1.2%.

Since official plague recording began in 1905, human plague cases have occurred in Myanmar (former Burma) every year. Since mid-century, plague has been found predominantly in Central and Upper Myanmar. There have been repeated outbreaks in Myingyan, M eiktila and M agway and the surrounding districts, Pakokku, Yamethiu and Sagaing on the periphery, suggestive of possible natural foci. In the 1980s and early 1990s most human plague cases were reported from M agway, M andalay and S againg D ivisions. The principal type of plague is bubonic plague with the highest incidence during the cold season November to M arch with a peak in January or February.

V iet N am (9,10,11,12,15,17,18,19,20,21,24,25,26,28,29,35,38,39)

In Viet Nam plague has been active since its introduction almost 90 years ago. Within the 18–year period (1980–1997), human plague cases were registered every year, with a total 3973 cases with 197 deaths (61.1% and 52.7% of the corresponding figures recorded in Asia). The yearly average was 221 cases and 11 deaths with a mean case-fatality rate of 5.0%. Human plague was most frequently observed in Central Viet Nam and the T ay–N guen Plateau. In 1985 the disease was again notified in H o Chi M inh City. Human plague cases usually occur during the dry season with a peak in April–June. Bubonic plague prevails, representing 95–97% of the cases. Primary septicemic and pulmonary plague are rare. Epizootic plague is spread primarily in domestic rat species, particularly in rural areas.
Summary of trends

In analysing plague distribution by continent, it is evident that some countries exert a decisive influence on the overall epidemiological situation. For example, only two countries, Madagascar and Tanzania, accounted for 62.5% of the total plague cases in Africa, Brazil and Peru accounted for 82.9% of the total cases in the Americas, and Myanmar and Viet Nam for 78.5% of the cases reported in Asia during the last 15 years.

Periodic epizootics have been observed in all natural foci studied to date. However, the periodicity of plague outbreaks is variable. Silent periods may last for 10 years or more, after which sudden explosions of rodent or human plague may occur. The reasons why this happens merit further study. Although the disease continues to be active mainly in wild natural foci, recent experience points to the possibility of sporadic outbreaks in humans: China, Ecuador and the United Republic of Tanzania (1983), Libyan Arab Jamahiriya (1984), in Peru (1992–94), Botswana (1989), Kenya (1990) and India, Mozambique and Zimbabwe and India (1994). This variability emphasizes the need to maintain close epidemiological surveillance, especially in endemic or enzootic countries. Efforts must be continued to improve community and health personnel awareness and the ability to detect sporadic cases, thus averting possible epidemics.
References


Diagnosis and Clinical Manifestations

Dr Jack D. Poland and Dr D. T. Dennis

Yersinia pestis infection in humans occurs in one of three primary clinical forms (1-3). Bubonic plague is characterized by regional lymphadenopathy resulting from cutaneous or mucous membrane exposure. Primary septicaemic plague is an overwhelming plague bacteriaemia usually following cutaneous exposure. Primary pneumonic plague follows inhalation of aerosolized droplets containing Yersinia pestis. Although uncommon, skin or mucous membrane lesions at the point of entry of Y. pestis in humans may be important manifestations, because a local cutaneous ulcer will mimic tularemia when associated with regional lymphadenitis, and plague pharyngitis may be confused with streptococcal or viral pharyngitis. Other clinical forms, such as secondary septicaemia plague, secondary pneumonic plague, meningal plague, plague endophthalmitis and multiple lymph node involvement result from bacteriaemic dissemination of the plague bacillus. These clinical forms are discussed in detail below.

Bubonic plague

The classic disease in humans, bubonic plague, results from flea bite or direct contamination of an open skin lesion by plague-infected material. Following inoculation a local cutaneous proliferation, not usually clinically evident, ensues. In some cases, a vesicle, pustule, or ulcer develops at the inoculation site (1,3). The infection spreads via the lymphatics to the regional lymph nodes causing inflammation and swelling in one or several nodes (buboes). Buboes may occur in any regional lymph node sites including inguinal, axillary, supravacular, cervical, post-auricular, epitrochlear, popliteal or pharyngeal. Deeper nodes (such as intrabdominal or intrathoracic nodes) may also be involved through lymphatic or haematogenous extension.

After an incubation period of 2 to 6 days, patients typically experience a sudden onset of illness characterized by headache, shaking chills, fever, malaise and pain in the affected regional lymph nodes. The nodes may not be clinically enlarged at this stage. Progression of
symptoms is usually rapid with the regional lymphadenitis becoming excruciatingly tender and painful. Small to moderately enlarged buboes may be masked by an extensive perinodal inflammation and oedema. Within 24 hours after specific therapy has been started, the surrounding erythema clears rapidly. The primary bubo is considerably slower to resolve.

With specific treatment in uncomplicated cases, fever and general clinical symptoms usually resolve over 3 to 5 days. The bubo may, however, remain enlarged and tender for weeks following an otherwise satisfactory clinical recovery. If the bubo becomes suppurative, surgical incision and drainage should be electively performed. Necrotic material from such buboes may contain viable \textit{Y. pestis}.

When a superficial bubo is not found in a patient suspected to be infected with \textit{Y. pestis}, the primary lymph node involvement may be present in deeper areas of the body including mediastinal and intra-abdominal lymph nodes. In this latter circumstance, abdominal pain suggestive of appendicitis, colitis, enteritis or cholecystitis may represent the patient's principal complaint (3-6). In such cases, abdominal tenderness to palpation, rebound tenderness, or localization of pain in the abdomen may be misleading and may result in hazardous exploratory surgery. Primary septicaemic plague is the most serious diagnostic consideration in a patient with suspected plague without evident lymphadenitis or pneumonia.

\textbf{Septicaemic Plague}

Primary septicaemic plague is a progressive, overwhelming bloodstream infection with \textit{Y. pestis} in the apparent absence of a primary lymphadenopathy (1-3). Without a bubo to prompt a suspicion of plague, the correct diagnosis may easily be overlooked. Septicaemic plague occurs in all age groups, but the elderly appear to be at greatest risk (4).

The presence of rapidly replicating Gram-negative bacilli in the bloodstream initiates a self-perpetuating immunological cascade typically linked to host response to severe injury, in this case the agent inciting injury is bacterial endotoxin (7,8). The host response may result in a wide spectrum of pathological events including disseminated intravascular coagulopathy (DIC), multiple organ failure (MOF), and adult respiratory distress syndrome (ARDS) (2-4, 9-12). Disseminated intravascular coagulation can lead to arteriolar thrombosis, haemorrhage in skin, serosal
surfaces, and organ parenchyma, and sometimes results in acral cyanosis and tissue necrosis (13). Plague septicaemia, whether primary or secondary to bubonic plague, may lead to metastatic infection of other organ systems. Complications include plague pneumonia, plague meningitis, plague endophthalmitis, hepatic or splenic abscesses, or generalized lymphadenopathy (1,3).

Pneumonic plague

Primary pneumonic plague is the most fulminating and fatal form of plague. The incubation period is usually 1-3 days (1,14,15). Disease onset typically manifests by the sudden onset of chills, fever, headache, body pains, weakness and chest discomfort. Cough, sputum production, increasing chest pain, difficulty in breathing, hypoxia and haemoptysis become prominent as the disease rapidly progresses. Death usually ensues if specific antibiotic therapy is not begun within 18-24 hours of disease onset (16). Segmental pneumonitis may progress to lobar pneumonia and then to bilateral lung involvement; pulmonary complications may include localized areas of necrosis and cavitation, pleurisy with effusion, and adult respiratory distress syndrome (14,15,17,18). Concurrent sepsis and endotoxemia may further complicate the patient’s management.

Plague pneumonia occurs in two distinct and epidemiologically significant forms. Secondary plague pneumonia results from haematogenous spread of _Y. pestis_ to the lungs. This invasive infection provokes a masked inflammatory response and results in bacterial multiplication in pulmonary tissue. This process then spills over into the alveolar spaces and provides a mechanism for _Y. pestis_ to be expelled during coughing episodes (13,14,15). Spread of _Y. pestis_ to contacts by the respiratory droplet route can initiate an epidemic of primary pneumonic plague (1,14,15,19,20).

A primary pneumonic plague patient usually has an infectious pneumonitis at the onset of symptoms, often within 24 to 48 hours after exposure. Consequently, physical vigour is largely intact when infection generates an intense cough reflex productive of thin sero-sanguineous expectorate. This is readily aerosolized into fine droplets (<5 µm diameter) which may be inhaled deep into the respiratory tract of close contacts. In contrast, a patient with secondary plague pneumonia has usually been acutely ill for several days prior to lung invasion. Many patients succumb to their infection before they develop a well-advanced pneumonia. Those who do not succumb may be so morbid that their
cough reflex lacks the vigour to produce finely aerosolized droplets. A purulent, thick or tenacious exudate may further limit the patient's ability to produce fine droplets.

Pneumonic plague must be considered highly contagious whenever it occurs, although person-to-person transmission is most likely in cold humid environments coupled with overcrowding (1,14,15,19,20). Since Y. pestis is not truly airborne, person-to-person transmission requires face-to-face exposure within 2 metres of a coughing patient (19,21,22). The organism does not permeate room air where the patient is housed and is not carried through air ducts or vents.

**Pharyngeal plague**

Plague pharyngitis results from contamination of the oropharynx with Y. pestis-infected material. Recognized sources of exposure include respiratory droplets expelled during coughing by a patient (or animal) with a respiratory plague infection (1,19,23), or ingestion of undercooked or raw tissues of an infected animal (24). It is conceivable that bacteria contaminating the hands or instruments used in skinning an infected animal could be transferred to the mouth.

Asymptomatic colonization of the pharynx has been reported in contacts of pneumonic plague patients (25). Symptomatic plague pharyngitis is clinically similar to streptococcal or viral pharyngitis although the cervical lymphadenopathy of plague is often more severe and painful. Without epidemiological or historical information to suggest plague pharyngitis, it is likely that the diagnosis will be missed until there is laboratory identification of Y. pestis in a throat culture (10).

**Meningeal plague**

Plague meningitis is characterized by fever, headache and stiff neck (nuchal rigidity/meningismus), delirium, confusion, obtundation or coma (1,26,27). Examination of spinal fluid will demonstrate pleocytosis, predominantly polymorphonuclear leukocytes, and often Gram-negative plague bacilli are seen. Meningeal plague may be a primary manifestation, but it usually occurs a week or more after the onset of bubonic or septicaemic plague. It is often associated with delayed, inappropriate or bacteriostatic antibiotic therapy and is more common in patients with axillary (as opposed to inguinal) buboes (27,28).
Plague meningitis has been associated with the use of antibiotics which suppress infection but are not bacteriocidal and which do not readily penetrate the meninges, e.g. the tetracyclines. These agents may not eradicate Y. pestis before meningeal invasion occurs, and once the meninges become infected, the organisms there may be protected by the blood-brain barrier. The clinical course is often subacute, and permanent neurological sequelae are rare (26,28).

Clinical presentations relative to the source of exposure

The location of the primary bubo suggests the source of infection. Inguinal buboes in adults and older children indicate that infection was transmitted by the bite of an infective flea on the lower extremities. Axillary buboes suggest upper extremity inoculation through handling of infected animal tissues, including cuts incurred while skinning an animal or contamination of open sores, abrasions, or other breaks in the skin.

In circumstances where patients are exposed to flea bites while sleeping, such as when plague-infected rats and rat fleas have invaded residences, localizing a bubo to the upper or lower torso does not serve to differentiate flea bite from exposure to contaminated material.

Differential diagnosis

Bubonic plague may be confused with streptococcal or staphylococcal lymphadenitis, infectious mononucleosis, cat-scratch fever, lymphatic filariasis, tick typhus, tularemia and other causes of acute lymphadenopathy. Involvement of intra-abdominal lymph nodes may mimic appendicitis, acute cholecystitis, enterocolitis or other intra-abdominal surgical emergencies (5,10). Inguinal buboes have been mistaken for an inguinal hernia. Involvement of intrathoracic lymph nodes and deep cervical lymph nodes also presents diagnostic dilemmas. In the case of severe deep cervical adenitis, displacement of the trachea threatening an airway obstruction may constitute a medical emergency.

Septicaemic plague also constitutes a medical emergency which, unless the clinician has good reason to suspect the specific etiology, the working diagnosis is often a non-specific sepsis syndrome, or a Gram-negative sepsis. Fortunately, some empiric antibiotic regimens for Gram-negative sepsis, e.g. aminoglycosides or fluoroquinolones are effective against Y. pestis, but increasing use of advanced generation cephalosporins is problematic. As in other sepsis syndromes, gastrointestinal complaints of abdominal pain, nausea, vomiting and diarrhoea may be prominent and
misleading (1,4,5). Perhaps the most serious point of confusion in the differential consideration of plague sepsis may come from the laboratory. For example, an improperly decolorized Gram's stain examination of a blood smear or lymph node aspirate may result in the interpretation of Y. pestis bipolarity as a Gram-positive diplococcus; also, automated bacterial identification devices may not code for Y. pestis and may result in misidentifications (29).

Pneumonic plague may be confused with other causes of acute, severe community-acquired pneumonia, such as pneumococcal, streptococcal, H. influenzae, anthrax, tularaemia, L. pneumophila, leptospiral, hantavirus pulmonary syndrome, and influenza virus pneumonia. Regional lymphadenitis may indicate plague or tularemia pneumonia arising secondary to a cutaneous infective exposure.

Laboratory diagnosis

When plague is suspected, clinical specimens should be collected immediately, and specific antimicrobial treatment begun. A definitive laboratory diagnosis of Y. pestis infection is based on the isolation and identification of the organism from clinical specimens or by demonstrating a diagnostic change in antibody titre in paired serum specimens. Routine diagnostic specimens for smear and culture include the following: whole blood; aspirates from suspected buboes; pharyngeal swabs, sputum samples or tracheal washes from those with suspected plague pharyngitis or pneumonia; and cerebrospinal fluid from those with suspected meningitis. Since early buboes are seldom fluctuant or necrotic, they usually require aspiration after an injection of 1-2 ml of saline through an 18-22 gauge needle. Suitable microbiological culture media (e.g. brain-heart infusion, broth, sheep blood agar, or MacConkey agar) should be inoculated with a portion of each specimen. Smears should be examined with Wayson or Giemsa stain and with Gram's stain; smears should also be submitted for direct fluorescent antibody testing (anti-F1 antibody). An acute-phase serum specimen should be tested for antibody to Y. pestis; for serological confirmation, a convalescent-phase serum specimen should be collected 4-6 weeks or more later. When a suspected plague patient dies, appropriate autopsy tissues for culture, immunohistochemical staining, and fluorescent antibody testing include lymph nodes, liver, spleen, lung and bone marrow. Materials for culture should be sent to the laboratory either fresh or frozen on dry ice. Cary-Blair or a similar holding medium can be used to transport Y. pestis-infected tissues.
Plague patients typically have white blood cell (WBC) counts of 12,000 to 25,000/µl blood, with a predominance of immature polymorphonuclear cells (PMNs) (7). Leukaemoid reactions sometimes occur. Chest roentgenograms of patients with pneumonic plague usually show patchy bronchopneumonic infiltrates as well as segmental or lobar consolidation with or without confluence; they occasionally show cavitation, or bilateral diffuse infiltrates of acute respiratory distress syndrome (17). Stained sputum specimens usually contain PMNs and may demonstrate bipolar staining Gram-negative bacilli. In Y. pestis septicaemia, the finding of characteristic organisms in a stained peripheral blood smear or a buffy-coat smear is a grave prognostic sign (27). In patients with plague meningitis, cerebrospinal fluid pleocytosis with a predominance of PMNs is typical. The characteristic bipolar appearance is not unique to Y. pestis, and is best seen in Wayson- or Giemsa-stained material.

The diagnosis of plague is confirmed in the laboratory by the isolation of Y. pestis from cultures of body fluids or tissues (30,31). Cultures of three blood samples taken over a 45-minute period before treatment will usually result in isolation of the bacterium. Y. pestis on solid media grows as grey-white, translucent colonies, usually too small to be seen as individual colonies at 24 hours. After incubation at 37°C for 48 hours, colonies are about 1-2 mm in diameter. After 48-72 hours of incubation colonies are raised and have an irregular, ahammered copper appearance (30,31). Cultures are definitely identified as Y. pestis by specific phage lysis. Automated bacteriological test systems can be used to assist in the identification of isolates as Y. pestis, but such isolates can be misidentified (e.g. as Y. pseudotuberculosis) or overlooked if these systems are improperly programmed (29).

When Y. pestis is not isolated, plague can be confirmed by seroconversion (a four-fold or greater titre change) to Y. pestis F1 antigen by passive haemagglutination testing of paired serum specimens (30,31). The specificity of a positive passive haemagglutination test requires confirmation with the F1 antigen haemagglutination-inhibition test (31). A few plague patients seroconvert as early as 5 days after onset of symptoms. Most seroconvert between 1 and 2 weeks after onset; a few seroconvert 3 weeks or more after onset; and a few (less than 5%) fail to seroconvert (32). Early, specific antibiotic treatment may delay seroconversion by several weeks. After seroconversion, positive serological titres usually diminish gradually over months to years. Enzyme-linked immunosorbent assays (ELISAs) for detecting IgM and IgG antibodies,
and for antigen capture, are especially useful in laboratory diagnosis in the early period of illness (31).

Detection of the F1 antigen in tissues or fluids by direct fluorescent antibody testing (or other standardized antigen detection procedures) provides presumptive evidence of plague, as does a diagnostically elevated F1 antibody titer in a single serum sample from a patient with a plague-compatible illness who has not received plague vaccine (30,31). Visualization of bipolar coccobacilli in a Wayson- or Giemsa-stained specimen supports a diagnosis of clinically suspect plague. A summary of laboratory diagnostic categories for human plague is as follows:

**Case definitions**

**Suspect plague:**
- compatible clinical and epidemiological features; and
- suspicious organisms seen or isolated from clinical specimens.

**Presumptive plague:**
- Y. pestis F1 antigen detected in clinical materials by direct fluorescent antibody testing, or by some other standardized antigen detection method; or
- isolate from a clinical specimen demonstrates biochemical reactions consistent with Y. pestis or PCR positivity; or
- a single serum specimen is found positive for diagnostic levels of antibodies to Y. pestis F1 antigen, not explainable on the basis of prior infection or immunization.

**Confirmed plague:**
- isolate identified as Y. pestis by phage lysis of cultures; or
- a significant ($\geq$4-fold) change in antibody titre to the F1 antigen in paired serum specimens.
References


3  
TREATMENT OF PLAGUE

Dr Jack D. Poland and Dr D. T. Dennis

Case management: therapy and prevention of spread

When a diagnosis of human plague is suspected on clinical and epidemiological grounds, appropriate specimens for diagnosis should be obtained immediately and the patient should be started on specific antimicrobial therapy without waiting for a definitive answer from the laboratory (Table 2). Suspect plague patients with evidence of pneumonia should be placed in isolation, and managed under respiratory droplet precautions (1).

Specific therapy

Aminoglycosides: streptomycin and gentamicin

Streptomycin is the most effective antibiotic against Y. pestis and the drug of choice for treatment of plague, particularly the pneumonic form (2-6). Therapeutic effect may be expected with 30 mg/kg/day (up to a total of 2 g/day) in divided doses given intramuscularly, to be continued for a full course of 10 days of therapy or until 3 days after the temperature has returned to normal. Gentamicin has been found to be effective in animal studies, and is used to treat human plague patients (7-10).

Chloramphenicol

Chloramphenicol is a suitable alternative to aminoglycosides in the treatment of bubonic or septicaemic plague and is the drug of choice for treatment of patients with Y. pestis invasion of tissue spaces into which other drugs pass poorly or not at all (such as plague meningitis, pleuritis, or endophthalmitis) (3,4,11,12). Dosage should be 50 mg/kg/day administered in divided doses either parenterally or, if tolerated, orally for 10 days. Chloramphenicol may be used adjunctively with aminoglycosides.
Tetracyclines

This group of antibiotics is bacteriostatic but effective in the primary treatment of patients with uncomplicated plague (3-5). An oral loading dose of 15 mg/kg tetracycline (not to exceed 1 g total) should be followed by 25-50 mg/kg/day (up to a total of 2 g/day) for 10 days. Tetracyclines may also be used adjunctively with other antibiotics.

Sulfonylamides

Sulfonylamides have been used extensively in plague treatment and prevention; however, some studies have shown higher mortality, increased complications, and longer duration of fever as compared with the use of streptomycin, chloramphenicol or tetracycline antibiotics (3-6,13). Sulfadiazine is given as a loading dose of 2-4 g followed by a dose of 1 g every 4-6 hours for a period of 10 days. In children, the oral loading dose is 75 mg/kg, followed by 150 mg/kg/day orally in six divided doses. The combination drug trimethoprim-sulfaemethoxazole has been used both in treatment and prevention of plague (6,14,15).

Fluoroquinolones

Fluoroquinolones, such as ciprofloxacin, have been shown to have good effect against Y. pestis in both in vitro and animal studies (16,17). Ciprofloxacin is bacteriocidal and has broad spectrum activity against most Gram-negative aerobic bacteria, including Enterobacteriaceae and Pseudomonas aeruginosa, as well as against many Gram-positive bacteria. Although it has been used successfully to treat humans with Francisella tularensis infection (18,19), no studies have been published on its use in treating human plague.

Other classes of antibiotics (penicillins, cephalosporins, macrolides)

These classes of antibiotics have been shown to be ineffective or of variable effect in treatment of plague and they should not be used for this purpose.

Supportive therapy

The clinician must prepare for intense supportive management of plague complications, utilizing the latest developments for dealing with Gram-negative sepsis (20). Aggressive monitoring and management of possible septic shock, multiple organ failure, adult respiratory distress
syndrome (ARDS) and disseminated intravascular coagulopathy should be instituted.

Treatment of plague during pregnancy and in children

With correct and early therapy, complications of plague in pregnancy can be prevented. The choice of antibiotics during pregnancy is confounded by the potential adverse effects of three of the most effective drugs. Streptomycin may be ototoxic and nephrotoxic to the foetus. Tetracycline has an adverse effect on developing teeth and bones of the foetus. Chloramphenicol carries a low risk of "grey baby" syndrome or bone-marrow suppression. Experience has shown that an aminoglycoside judiciously administered is effective and safe for both mother and foetus, and in children. Because of its safety, intravenous or intramuscular administration, and ability to have blood concentrations monitored (21), gentamicin is the preferred antibiotic for treating plague in pregnancy (22).

Prophylactic therapy

Persons in close contact with pneumonic plague patients, or persons likely to have been exposed to Y. pestis-infected fleas, to have had direct contact with body fluids or tissues of a Y. pestis-infected mammal, or exposed during a laboratory accident to known infectious materials should receive antibiotic preventive therapy, if the exposure was in the previous six days (23).

The preferred antimicrobials for preventive or abortive therapy are the tetracyclines, chloramphenicol, or one of the effective sulfonamides (Table 3).

True prophylaxis, i.e. the administration of an antibiotic prior to exposure, may be indicated when persons must be present for short periods in plague-active areas under circumstances in which exposure to plague sources (fleas, pneumonic cases) is difficult or impossible to prevent (23).

Hospital precautions

Standard patient-care precautions should be applied to management of all suspected plague patients. These include prescribed procedures for handwashing, wearing of latex gloves, gowns, and protective devices to protect mucous membranes of the eye, nose and mouth during those
procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, secretions and excretions (1). Additionally, a patient with suspected respiratory plague infection should be specifically managed under respiratory droplet precautions (1), including management in an individual room, restriction of movement of the patient outside the room, and masking of the patient as well as persons caring for the patient until the patient is no longer infectious.

**Vaccination**

Worldwide, live attenuated and formalin-killed *Y. pestis* vaccines are variously available for human use. The vaccines are variably immunogenic and moderately to highly reactogenic. They do not protect against primary pneumonic plague. In general, vaccinating communities against epizootic and enzootic exposures is not feasible; further, vaccination is of little use during human plague outbreaks, since a month or more is required to develop a protective immune response. The vaccine is indicated for persons whose work routinely brings them into close contact with *Y. pestis*, such as laboratory technicians in plague reference and research laboratories and persons studying infected rodent colonies (23).
## Table 2  Plague treatment guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Interval (hours)</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>2 g/day</td>
<td>12</td>
<td>IM</td>
</tr>
<tr>
<td>Children</td>
<td>30 mg/kg/day</td>
<td>12</td>
<td>IM</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>3 mg/kg/day</td>
<td>8</td>
<td>IM or IV</td>
</tr>
<tr>
<td>Children</td>
<td>6.0-7.5 mg/kg/day</td>
<td>8</td>
<td>IM or IV</td>
</tr>
<tr>
<td>Infants/neonates</td>
<td>7.5 mg/kg/day</td>
<td>8</td>
<td>IM or IV</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>2 g/day</td>
<td>6</td>
<td>PO</td>
</tr>
<tr>
<td>Children $\leq$ 9 years</td>
<td>25-50 mg/kg/day</td>
<td>6</td>
<td>PO</td>
</tr>
<tr>
<td>Chloramphenicol</td>
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<td></td>
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<tr>
<td>Adults</td>
<td>50 mg/kg/day</td>
<td>6</td>
<td>PO or IV</td>
</tr>
<tr>
<td>Children $\leq$ 1 year</td>
<td>50 mg/kg/day</td>
<td>6</td>
<td>PO or IV</td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>200 mg/day</td>
<td>12 or 24</td>
<td>PO</td>
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<tr>
<td>Children $\leq$ 9 years</td>
<td>200 mg/day</td>
<td>12 or 24</td>
<td>PO</td>
</tr>
<tr>
<td>Oxytetracycline</td>
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<tr>
<td>Adults</td>
<td>250-300 mg/day</td>
<td>8,12 or 24</td>
<td>PO or IM</td>
</tr>
<tr>
<td>Children $\leq$ 9 years</td>
<td>250 mg/day</td>
<td>8,12, or 24</td>
<td>PO or IM</td>
</tr>
</tbody>
</table>

IM = Intramuscular; IV = Intravascular; PO = Orally

### Table 3  Plague prophylaxis guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Interval (hours)</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
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<td></td>
</tr>
<tr>
<td>Adult</td>
<td>1-2 g/day</td>
<td>6 or 12</td>
<td>PO</td>
</tr>
<tr>
<td>Children &lt; 9 years</td>
<td>25-50 mg/kg/day</td>
<td>6 or 12</td>
<td>PO</td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>100-200 mg/day</td>
<td>12 or 24</td>
<td>PO</td>
</tr>
<tr>
<td>Children &lt; 9 years</td>
<td>100-200 mg/day</td>
<td>12 or 24</td>
<td>PO</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trimethoprim</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>1.6 g/day *</td>
<td>12</td>
<td>PO</td>
</tr>
<tr>
<td>Children &lt; 2 months</td>
<td>40 mg/kg/day *</td>
<td>12</td>
<td>PO</td>
</tr>
</tbody>
</table>

* Sulfamethoxazole component
PO=Orally

References


4

**RODENT RESERVOIRS & FLEA VECTORS OF NATURAL FOCI OF PLAGUE**

Dr Norman Gratz

Rodent reservoirs

Plague is primarily a disease of rodents. The infection is maintained in natural foci of the disease in wild rodent colonies through transmission between rodents by their flea ectoparasites. For the most part, the sylvatic rodent reservoirs are species that are susceptible to the infection but resistant to the disease. While upwards of 200 species of rodents and lagomorphs have been implicated in the epidemiological cycle of plague in one geographical area or another, the true number of rodent species important as more than accidental reservoirs of plague is uncertain.

Many species of rodents and other small mammals are susceptible to infection but are only occasionally infected and are not necessarily important reservoirs of infection. The animal hosts of plague are classified as enzootic (maintenance) hosts and epizootic (amplification) hosts (1). The first group includes rodents from genera that are relatively resistant to plague. In this group mortality from plague infection is low, although antibody surveys of field populations may show a positivity rate as high as 100%. Die-offs commonly seen among more susceptible rodent species are rare in this group. The plague organism is occasionally introduced into colonies or areas of more susceptible species. This occurs in nature by an overlap of individuals or populations of two species. When this happens in a species that is highly susceptible to plague, an epizootic – sometimes of considerable magnitude – may occur, and high mortality (rodents positive for plague) is seen in sylvatic and peridomestic areas or even in villages or cities.

It is difficult to group the many different species of rodents, lagomorphs and other small mammals involved as common or occasional reservoirs or hosts of plague to fit the above classification. The susceptibility to plague infection of a given species may vary even within
the geographical limits of a foci. Furthermore, susceptibility may vary temporally with variations in the density of the host populations or in the density of their flea ectoparasite vectors. The virulence of the particular strain of the plague bacterium involved in the epizootic may also vary over a period of time.

As most of the natural foci of plague have existed for long periods of time, it is clear that a portion of any reservoir population must survive infection. In some species the infection can continue to circulate with relatively little mortality (2).

**Flea vectors**

About a dozen cosmopolitan species are implicated in the transmission of domiciliary plague (3). However, many more species of the order Siphonaptera have been implicated in the transmission of sylvatic plague (4).

To understand the epidemiology and transmission of the infection from rodent reservoirs to human hosts, it is essential to determine the flea species involved in plague transmission in a given area. Information on the bionomics of the flea vectors is basic to their control and control of transmission of the infective agent. The following section provides information on the most important flea vectors of plague in the various endemic foci. If this information is not already available for an area in which plague is suspected or known to be endemic, surveys of flea ectoparasites should be done. Survey methods are described elsewhere in this publication.

Entomological expertise is needed for the design, implementation and (particularly) identification of the flea species taken and evaluation of their importance in relation to plague transmission.

**Cosmopolitan vectors of plague**

The majority of the flea species described below are ectoparasites of commensal or peridomestic rodents. Because of their close proximity to humans and their dwellings, these fleas are often found on livestock and household animals. Most of these species have a wide distribution, although their percentage in the flea population varies from place to place as does their role as vectors of plague. All, however, readily feed on humans. The commensal rodent fleas are classed as follows (5):
(1) Fleas specific to commensal rodents which show a wide distribution and are found in several plague-endemic areas. *Xenopsylla cheopis* (Oriental rat flea) has a wide distribution, while the distribution of *X. brasiliensis* and *Nosopsylla fasciatus* is more limited.

(2) Species specific to commensal rodents which show a limited or even restricted geographical distribution, such as *X. astia*.

(3) Wild rodent fleas which frequently infest commensal rodent species.

(4) Flea species which, because they are common in the environment of commensal rodents, are often found in limited numbers on these rodents although they are not specific for them. *Echidnophaga gallinacea* and *Pulex irritans*, both of which have a cosmopolitan distribution, and the cat flea, *Ctenocephalides felis*, are examples of this latter group.

To act as an efficient plague vector, the flea must be able to ingest the plague organism with its blood meal. Second, it must live long enough for the pathogen to multiply sufficiently. Third, it must be able to transfer the pathogen to an animal or human host in sufficient concentrations to cause an infection and last, it must be present in large enough numbers to maintain the infection in the local rodent hosts (6). There are a number of other characteristics but these are the most important.

When a flea sucks blood from an infected rodent or other host, some of the bacteria settle on the flea’s proventriculus. This spined structure shuts off the stomach while the flea is sucking but opens to allow ingested blood to enter the stomach. Plague bacteria that have settled on the spines of the proventriculus multiply and eventually block the passage of blood into the stomach. Although the flea continues to feed (with increasing avidity as time passes) blood cannot continue to enter its stomach and instead remains in the oesophagus. When the flea stops sucking, the oesophagus recoils and the accumulated blood is driven into the bite wound, bringing *Y. pestis* with it. A flea in this condition is known as a “blocked” flea. Those species of fleas most subject to blocking are the most efficient vectors of plague, providing that the other requirements of transmission are met and that the flea survives long enough to transmit the infection.

*Xenopsylla cheopis* is the most important vector of plague and the rickettsial infection murine typhus. The species is thought to have originated in Egypt but during the 19th century spread to all parts of the
world as parasites of rats infesting ships' cargos. A high incidence of plague-infected *X. cheopis* in a given focus, greatly increases the risk of transmission to humans. *X. cheopis* most commonly parasitizes *Rattus* species but is frequently found on other rodent species in and around houses.

*Xenopsylla astia* is a parasite of both gerbils and rats. It ranges from the Arabian peninsula through Iran to southeast Asia and to Korea (7) and has been found on the east coast of Africa. It is a less efficient vector than *X. cheopis*.

*Xenopsylla brasiliensis* is native to all Africa south of the Sahara where it is the most common vector in some areas (8), often more common than *X. cheopis*. It has spread to other parts of the world such as Brazil and India. It is an effective plague vector, especially in rural environments. It is less tolerant of high temperatures than *X. cheopis* but is more resistant to drought conditions.

*Nosopsyllus fasciatus*, the Northern rat flea, is one of the most prevalent fleas in Europe on commensal rats (9). Its distribution is virtually global and it is found from the United States to China (10) and Korea (11). Its numbers appear to be increasing in Japan (12). It is also found on mammals and rodents other than *Rattus* and feeds freely on humans. It is relatively unimportant as a vector of plague.

*Monopsyllus anisus* is the common rat flea of temperate east Asia, extending from China and Transbaikala Russia to Japan. It has been found in ports in San Francisco and Vancouver and in the United Kingdom.

*Leptopsylla segnis*, the mouse flea, probably originated in western Asia on *Mus* or *Apodemus*. It is generally abundant on rats than on mice. It is widely distributed, particularly in temperate areas, but is only a weak vector of plague and an uncertain vector of murine typhus (13).

*Pulex irritans*, the human flea, was considered to have originated as an Old World species (3) but a more recent review (14) observes that the species probably originated in South or Central America as an ectoparasite of the guinea pig or peccary. *P. irritans* is now worldwide in its distribution. Despite its common name it has a wide range of hosts: it is found in the wild on foxes, badgers, ground squirrels, guinea pigs and rats as well as domestically on pigs, goats, dogs, cats and humans. It is often found in high densities in habitations. *P. irritans* has been considered as a
possible or probable vector of plague in Angola (15), Brazil (16), Burundi (17), the Democratic Republic of the Congo (21), Iran (2), Iraq (18), Nepal (19), and Tanzania (20).

Ctenocephalides felis, the cat flea, has become completely cosmopolitan in its distribution. It is frequently found not only on cats but also on a large number of other hosts, including dogs, humans, other mammals and birds (22). There appears to be a gradual northern extension of this species (12). It may be a vector of murine typhus and is also an intermediate host of some cestodes. Both the cat flea and the dog flea (Ctenocephalides canis) are able to transmit plague to humans from pet animals.

The following section considers the main rodent reservoirs and flea vectors of plague in most of the better-known endemic foci. Some foci are large and contiguous—such as those in the western United States, the Russian Federation, China and Mongolia—and extend across borders to more than one country. In foci such as these, reservoir and flea vector species may differ considerably from one part of the focus to another.

**Plague reservoirs and vectors in Africa**

**Plague foci of southern Africa (23,24,25,26,27,28,29,30)**

This area includes foci in South Africa, Lesotho, Namibia and Zimbabwe. Although the number of plague outbreaks in this subregion have declined considerably in recent years, the infection persists in many areas where human plague has not been apparent for years. It is therefore important to understand the mechanism and the rodent species responsible for persistence in the natural foci.

The main reservoir in many parts of this geographical region was long thought to be the gerbil, *Tatera brantsi*. The passage of plague infection in Orange Free State, South Africa, has been traced from gerbils as the reservoir to other wild rodents, *Otomys irroatus* to *Mastomys natalensis* to *Rattus rattus* and to humans. *M. natalensis* is now understood to be a species complex: early studies have separated it into species A and B. The distribution of human plague in southern Africa is apparently linked to the distribution of species B of the *Mastomys* (*Praomys*) *natalensis* species complex.

Studies have been done to determine if the sibling species of *M. natalensis*, *Aethomys chrysophilus*, *Mastomys coucha*, *Tatera leucogaster* and
A. namaquensis differed in their potential as reservoirs of plague in southern Africa. M. natalensis with 32 diploid chromosomes was significantly more resistant to experimental plague infections with high level inoculations of Y. pestis than M. coucha with 36 diploid chromosomes. The geographic distribution of human plague in southern Africa corresponds closely with that of the plague-susceptible species, M. coucha, while the plague-resistant species M. natalensis predominates in areas where human plague has not been recorded. A. namaquensis is extremely plague-sensitive, much more so than A. chrysophilus, and they may play different roles in the plague cycle.

In an outbreak of plague in Coega in the Cape Province of South Africa in 1982 plague antibody was found in two rodent species: the four-striped mouse, Rhabdomys pumilo and the vlei rat, Otomys irroratus. Sera from 3012 rodents of 24 species captured in South Africa were tested for antibody to the Fraction 1 antigen of Y. pestis by passive haemagglutination. Of 24 species investigated, antibodies were found in seven (0.23%) rodents of three species, Desmodillus auricularis and Tatera brantsii in the northern Cape Province and in R. pumilo in the eastern Cape Province.

The gerbils Tatera brantsi, T. leucogaster and T. africana play an important role in southern African plague epidemiology. Rhabdomys pumilio and Otomys irroratus were found infected in Cape Province in studies carried out in 1982 (29).

The fleas most frequently found on the rodent reservoirs of plague are X. philoxera, X. brasilienensis and Dinopsyllus ellobius. However, in ports and coastal towns X. cheopis is the dominant flea species on Rattus species and is the dominant flea vector of plague.

In Zimbabwe, T. leucogaster and M. coucha are highly susceptible to plague and die soon after infection, making it unlikely that they act as reservoir hosts. Because they are relatively resistant to plague, Aethomys chrysophilus and M. natalensis are the more likely reservoirs. In Zimbabwe both M. coucha and M. natalensis are semi-domestic and probably act as a link between humans and the true sylvatic foci of plague (30).

**Plague foci of East Africa**

This area includes plague-endemic regions of Kenya, Tanzania, Mozambique and Madagascar. Plague is widely endemic in the four countries.
Kenya (31,32,33,34)

In an early survey of rodents for plague in a plague focus near Rongai, north of Nakaru, plague was isolated from five species of wild rodents: Otomys angoniensis, Arvicanthis abyssinicus, M. natalensis, Lemniscomys striatus and Rhabdomys pumilo. The reservoirs of plague have been extensively studied in Kenya. Sera from 8,860 rodents and other small mammals were examined for antibodies to Y. pestis in one survey, where it was noted that enzootic plague in Kenya is much more widely distributed than the human cases reported. A. niloticus, M. natalensis and R. rattus are probably the most important and widespread reservoirs of plague in Kenya. Ten percent of all R. rattus tested were found to be positive, as compared to 12% of the Arvicanthis. Tatera robustis has also been found positive at a low level. The high prevalence of plague antibodies in R. rattus is significant, in that the species readily lives both as a commensal and wild species and thus can serve to introduce plague from its sylvatic reservoirs into a commensal cycle. That plague in Kenya can be more widespread than previously thought was shown by a survey in the Tana River area prior to the construction of a dam at that site. Four of the seven species of rodents captured (T. robusta, A. niloticus, L. striatus and Pterodromus tetradactylus) were positive for plague.

Xenopsylla cheopis, X. braziliensis and Dinopsyllus lypusus are abundant on the most important rodent reservoirs of plague in Kenya and, as elsewhere in East Africa, are the main vectors of the infection.

Tanzania (35,36,37)

In Tanzania the most important commensal and peridomestic rodents involved in the transmission of plague are R. rattus and M. natalensis. Cricetomys gambianus, Lophuromys flavopunctatus, Tatera robusta, Otomys angoniensis, Arvicanthis niloticus and A. abyssinicus are also involved where human cases occur. In most of the plague-endemic areas of the country, the majority of the rodents are A. abyssinicus and M. natalensis. Lemniscomys striatus has been found positive for plague in the Mbulu focus. Lophuromys flavopunctus, L. sikapusi, Otomys angoniensis, Pelomys fallax, O. denti and Gramomys dolichurus are among other rodent species found positive for plague in a serological survey in the western Usunbara mountains. Once surveyed, plague will probably be found to be endemic in still other areas of the country and in other species of rodents. Reservoir species are widespread and human cases of plague occur in the country nearly every year.
Xenopsylla cheopis and X. brasiliensis are common on both Rattus and T. robusta. P. irritans has also been found frequently in the plague endemic area of Lushoto (38). X. brasiliensis and D. lyupus are more common than X. cheopis on rodents in the country (39). X. humilis and X. nilotica are found on Tatera and Gerbillus species (40).

Mozambique (41,42,43)

Mastomys natalensis is widespread in Mozambique as well as in neighbouring countries and is probably the main sylvatic reservoir of plague. In the cities, population densities of R. norvegicus and R. rattus are high and plague may have spread from M. natalensis to R. rattus in the 1976 outbreak.

Madagascar (41,44,45)

An estimated 15% of the island of Madagascar is endemic for plague and there is some evidence that strains of Y. pestis have become more virulent. The infection established itself on the high plateau of central Madagascar in 1921, remaining endemic and spreading over the years with the occurrence of sporadic cases. There are two large foci in the country: the first from the central province of Tananarive to the south in Fianarantsoa; the second in the north near the region of Balanana.

The only apparent reservoir of plague in Madagascar is R. rattus. The number of rodent species on the island is relatively small, with only three muroid rodents: R. norvegicus, the only species found in the ports and the most common species in the city of Antananarivo; Mus musculus, which is found everywhere but appears to have no role in the epidemiology of plague; and R. rattus, whose density is often high and is widely distributed in rural areas, rice fields, villages and urban areas. The flea vector is mainly X. cheopis but R. rattus is frequently parasitized by Synopsyllus fonquerniei.

In central and southwest Africa, plague is endemic in Angola, Equatorial Guinea and the Democratic Republic of the Congo. Little information is available on the reservoirs and vectors in Angola or Equatorial Guinea.

Democratic Republic of the Congo (46,47)

Extensive studies have been carried out on the rodent reservoirs of the two plague foci in the Democratic Republic of the Congo. The areas have a rich rodent fauna and the main species involved in the
The epidemiology of plague are *Arvicanthis abyssinicus*, *M. natalensis*, *Lemniscomys striatus*, *R. rattus* and *Leggada minutodies*, which continue to maintain plague transmission in the northeastern part of the country. *A. abyssinicus* is a peridomestic species which serves as an intermediary between the wild or sylvatic reservoirs and domestic species. *M. natalensis* is frequently found nesting in thatched roofs.

*P. irritans* is a possible vector of plague in the Democratic Republic of the Congo (46) and Angola, at least in domestic transmission (17).

The fleas *Dinopsyllus lypusus* and *Ctenophthalmus cabirus* and *C. phyris* are common on *Arvicanthis* and *Lophuromys* and have been found plague-positive, especially in the Blukwa plague focus. In the Lake Edward focus in the Democratic Republic of the Congo, *R. rattus* and *M. natalensis* are the principal commensal and peridomestic rodents and *Xenopsylla brasiliensis* the most important flea vector.

### The plague focus of northwest Africa

**Mauritania (48,49)**

A focus of plague exists in the northern part of western Mauritania. The rodent populations of the area, particularly the gerbils, *Gerbillus gerbillus* and *G. nanus*, the jerboa *Juculus jaculus* and *Psammomys obesus* are important desert or semi-desert rodent species. The gerbils are the principal reservoirs of plague in the area.

*Xenopsylla ramesis* is the vector among the *Psammomys* populations. *X. nubica* is common on gerboas *Juculus jaculus*. *Synosternus cleopatrae* is the most common flea on *Gerbillus* species and is the vector of plague among gerbil populations. *X. cheopis* is found only in seaside towns. All these species feed readily on humans and can transmit *Y. pestis* from rodent reservoirs to domestic animals and humans.

### The plague focus of North Africa

**Libya (50,51)**

Libya appears to be the only country in North Africa still endemic for plague. Though the focus was silent for some thirty years, cases appeared in the Nofila area in 1972. Surveys of rodents in the area indicate that *G. gerbillus* and *Meriones shawi* are the most common species of rodents in areas where human cases of plague have been reported. The former were captured inside the tents of nomads and may serve as maintenance host for the infection. *M. libycus* is an even more widespread...
species and is comparatively resistant to plague; it was also found to be seropositive for plague in Libya. Other animals, including camels, may also be involved in the epidemiology of plague. Further investigation is necessary for a better understanding of the reservoirs maintaining plague in this long-standing focus.

Flea densities are low in the Libyan plague foci. In the northern plague foci, *M. libycus*, *M. caudatus*, *M. shawi* and *P. obesus* are present. The flea ectoparasites are *X. ramesis*, *X. cheopis*, *X. taractes* and *Nosopsylla henleyi*.

**Yemen (52)**

A small outbreak of plague occurred in Yemen in 1969 in a focus in which earlier outbreaks had occurred at the beginning of the century and in 1951 and 1952. Epidemiological investigation following the 1969 outbreak showed *R. rattus* present in houses, and *Meriones rex* and gerbils (*Gerbillus* species) in the fields surrounding the infected village, although none were found infected with *Y. pestis*. No information is available on the flea vectors in this focus nor on its current status.

**Islamic Republic of Iran (2,53)**

Though no human cases have been reported for many years, there are three active areas of endemic plague still known to exist. These are Kordestan (Kurdistan) and Hamadan in the west, and a focus in East Azerbaijan (including the Sarab desert) in the northwest. Prior to its discovery in 1980 plague had never been reported from this area. The other foci have been known for a long time and are well studied. The most important rodent reservoirs in the area are the gerbils *M. libycus* and *M. persicus*, both of which are highly resistant to plague infection, and *M. tristrami* and *M. vinogradovi* which are highly susceptible to both infection and the disease. *Tatera indica* has also been associated with transmission of *Y. pestis* in the country.

The flea vectors among the gerbils are *Xenopsylla buxtoni* and *Stenoponia tripectinata*. Flea densities are often high on *M. persicus*. Past epidemics of bubonic plague may have been due to human-to-human transmission by *P. irritans*. 


Plague foci of the Russian Federation and the CIS Republics (54, 55, 56, 57, 58, 59, 60)

The endemic foci of plague cover vast areas and their ecology, reservoirs and vectors differ considerably from one another. They will therefore be considered separately based on a report by B.K. Fenjuk and V.P. Kozakevic to WHO, 1968 (unpublished report). An extensive review of the plague literature in the former USSR was made by Pollitzer in 1966 (54). The classification of these foci are taken from that report.

A large natural focus of plague remains active in the Asian part of the Russian Federation and in the Asian republics. In the pre-Caspian region, the main rodent reservoir of plague is the suslik, Citellus pygmaeus. In sandy areas, Meriones meridiana (a species rather resistant to plague infection) and M. tamariscinus may also be reservoirs. In the central Asian plague focus, the main rodent reservoirs in the desert lowlands are Rhombomys opimus and Meriones erythrous and in the high mountain areas of this large focus, the marmots Marmota baibacina and M. caudata. In the transcaucasian area, gerbils (M. libycus and others) are important reservoirs, while Marmota siberica and Citellus dauricus are involved in the epidemiology of plague in the Transbaikalian focus. Commensal rodent species have rarely been involved in plague transmission in these foci.

The northwest Caspian focus

The focus covers an area lying to the west of the lower source of the Volga and the northern shores of the Caspian Sea. The western boundary of the focus is the River Don. Enzootic plague is reported to have disappeared from a large portion of this focus. The main reservoir of plague is the small or lesser suslik, Citellus pygmaeus. Two species of voles, Microtus arvalis and laagers may have been involved as reservoirs in the focus (61).

The most important flea vectors are Ceratophyllus tesquorum and Neopsylla setosa.

The focus between the Rivers Volga and the Ural Mountains

Two types of landscape are found in this area: rocky steppes in the north, west and east; and sandy semidesert (the Volga-Ural sands). The main reservoir of plague in the steppes is the small suslik, C. pygmaeus. In the sandy areas it is the gerbil Meriones meridianus and to a lesser extent M. tamariscinus.
The most important flea vectors in the steppe regions are *Ceratophyllus tesquorum* and *Neopsylla setosa* and in the sandy semi-deserts, *Xenopsylla conformis*, *Ceratophyllus laeviceps* and *Rhadinopsylla cedestis*.

**The focus on the left bank of the Ural River**

The reservoirs in this area are also *C. pygmaeus* and *M. tamariscinus*. The flea vectors are the same as those mentioned above.

**The focus in the Transcaucasian lowlands**

This focus in Azerbaijan may be linked with the natural focus in Iranian Kurdistan. The main plague reservoir in this area is the gerbil, *Meriones libycus erythrourous*. The flea vectors are *X. conformis* and *C. laeviceps*.

**The focus in the high mountain areas of Transcaucasia**

This focus of plague is located at an altitude of 2000 to 3000m and covers areas in Armenia and Azerbaijan. The main reservoir species is the vole *Microtus arvalis*; infected vole fleas *Ctenophthalmus teres*, *C. vladimiri* and *Ceratophyllus caspius* have been found in nature. The identity of the main rodent reservoir in the lower altitudes and plains of this focus remains uncertain.

**The central Asian desert focus**

This focus covers a large area of central Asia and southern Kazakhstan Republic to the borders with China in the east and with Afghanistan and Iran in the south. The most important reservoir is the gerbil, *Rhombomys opimus*.

The flea vectors are *Xenopsylla skrjabini*, *X. hirtipes*, *X. gerbilli gerbilli*, *X. gerbilli minax*, *X. gerbilli caspica*, *X. nutalli* and *X. conformis*.

**The Tien-Shan focus**

This focus is situated in a mountainous area of Kazakhstan and Kirgsia. The main reservoir is *Marmota baibacina* and the flea vectors are *Oropsylla silantiewi* and *Rhadinopsylla ventricosa*.

**The Pamir-Alai focus**

This is a focus of limited size in the Alai valley. The reservoir is the Altai marmot, *Marmota caudata*. The flea vectors are *R. ventricosa* and possibly *O. sillantiewi* and *Ceratophyllus lebedwi*. 
The Transbaikalian focus

This is a focus on the north–east edge of the extensive Mongolian focus of plague. The rodent reservoirs are Marmota sibirica and Citellus dauricus. The main vector flea is Oropsylla silantiewi. Isolations of Y. pestis have also been made from the flea Frontopsylla luculenta.

The High Altai and Tuva Autonomous Region focus

In this area, also adjacent to Mongolia, the weasel Putorius eversmannii and the suslik Citellus undulatus have been found plague–positive. The fleas on the suslik species are Ceratophyllus tesquorum.

India (62,63,64,65,66,67)

A large number of rodent species are known from the Indian subcontinent, including some 46 genera, 135 species and many subspecies. The diverse ecological conditions in different parts of this large country has also resulted in a diverse rodent and flea ectoparasite fauna. Rodents cause serious agricultural and stored food losses and are important reservoirs of a number of diseases including plague, leptospirosis and murine typhus. Many species of rodents have been reported as actual or potential reservoirs of plague. Depending on the region, the more important species are Bandicota bengalensis, Tatera indica, Rattus norvegicus, R. rattus and R. rattus diardii, among others.

The species shown to be important as reservoirs of plague at one time or another include the urban rats, R. rattus, R. norvegicus and B. bengalensis; the latter is also an important agricultural pest. The gerbil Tatera indica, the Indian field mouse Mus budoga, and the squirrels Funambulus pennanti and F. palmarum have all been found positive for plague in various foci.

Until the recent outbreak of plague in Maharashtra and Gujurat States of India in 1994, no human cases of the disease had been reported since the cases in Karnataka State in 1966. However, there have been a number of suspected outbreaks reported including in Himachal Pradesh in 1983, similar to pneumonic plague (22 cases, 17 deaths).

From the 1960s to 1989, a total of 188,025 rodent sera were examined in India. Only 12 sera from Tatera indica were found positive for Y. pestis antibody in 1979 and three from the same species found positive in 1989. Only two R. rattus were reported as serologically positive for
Y. pestis in 1988 despite many reports of rat falls from the country. Population densities of rats including *B. bengalensis*, *R. norvegicus* and *R. rattus* in most urban areas are generally high. In rural areas agricultural development, including large irrigation projects, is changing ecological patterns and the composition of rodent populations.

As of 1973, 76 species of fleas have been recorded in India (68). The most important rat flea vector of *Y. pestis* in urban or domestic situations (found on wild rodents) is *X. cheopis*, while *X. astia* predominates on wild rodents. *X. brasiliensis* is also frequently found on rodents. *Nosopsyllus fasciatus* has also been found infected by *Y. pestis*.

**Nepal (69)**

Only a few cases of plague have been reported from Nepal and little information is available on the reservoirs. During a small outbreak in 1971, *P. irritans* was reported to be the vector in the affected village.

**Myanmar (4,70,71,72,73,74,75,76)**

Zoonotic plague is endemic over large areas of the country. The rat species with the highest plague antibody rates in Yangon (Rangoon) among 1,620 animals tested in 1976 was the bandicoot *B. bengalensis*, the most common rodent species in the city. Its rate of positivity was 15.4%. *R. norvegicus* showed 11.1% positivity, *R. rattus* 7.6%, and the insectivore *Suncus murinus* 3.35%. Plague antibody in *B. bengalensis* is transient in nature and when found indicates recent infection. Little is known, however, about the epidemiology, maintenance cycle or reservoirs of plague in the rural or sylvatic areas of the country.

*Xenopsylla cheopis* and *X. astia* have been recovered from the three species of *Rattus* as well as from *B. bengalensis* and the shrew *S. murinus* in Yangon (Rangoon). *X. astia* is most abundant on the bandicoot and Norway rat while *X. cheopis* is more common on *R. exulans* and *S. murinus*. Both species of *Xenopsylla* are found in almost equal numbers on *R. rattus*. The two species of *Xenopsylla* are probably the most important vectors of both plague and murine typhus (75). *R. rattus* has been considered the most important reservoir of plague in the foci in the country and *X. cheopis* the most important vector with *X. astia* also a vector (76).

**Indonesia (77,78,79,80)**

A focus of plague was active until recently in the Boyolali area of central Java. There have been no recent reports of plague activity in this focus despite an active surveillance programme. The two rodent species
from which \textit{Y. pestis} was detected in this area are \textit{R. rattus diardii} and \textit{R. exulans ephippium}. \textit{R. r. diardii} is the predominant species inside houses and \textit{R. exulans} is the most common species in the fields.

The most common flea species and vectors of plague in the Boyolali focus are \textit{X. cheopis} and \textit{Stivalis cognatus}. \textit{R. rattus} and \textit{X. cheopis} have been collected most often from buildings, where contact with humans occurs readily. \textit{R. exulans} and \textit{S. cognatus} have generally been taken in field and forest habitats.

\textit{Viet Nam} (81,82,83,84,85,86,87,88,89,90,91,92)

In urban areas, the reservoirs of plague are the domestic rats \textit{R. norvegicus} and \textit{R. rattus} and the insectivore \textit{S. murinus}. Sylvatic plague was first found in Viet Nam in 1968 when specimens of the large bandicoot \textit{B. indica} and the fleas (\textit{X. cheopis}) infesting it collected near a plague focus were found positive for plague. Recent studies indicate that plague is probably maintained by these species in a domestic or peridomestic cycle and it is doubtful that there is a true sylvatic cycle in the country (90).

Only \textit{X. cheopis} was collected on all four species of small mammals trapped in the Pleiku plague-endemic area: \textit{R. rattus}, \textit{R. norvegicus}, \textit{B. bengalensis} and \textit{S. murinus}. The species \textit{R. rattus}, \textit{R. norvegicus} and \textit{S. murinus} are most closely associated with plague transmission. Of the fleas collected on four small mammal species in Pleiku, 94\% were on \textit{R. rattus} (91). \textit{X. cheopis} was the most common flea species collected on small mammals in a plague focus; \textit{X. vesiculosis} was found in much smaller numbers (92). It thus seems likely that the most important flea vector of plague in the country is the Oriental rat flea, \textit{X. chopis}. \textit{B. indica} has also been found plague-positive in Viet Nam, infested with \textit{X. cheopis} (85).

\textit{China} (74,93,94,95)

China is the only country of the western Pacific region aside from Viet Nam where plague remains endemic. There are ten geographical foci of plague in China. The following review of the status of plague in these foci is taken from a report provided by Xu Rongman (94). Foci are classified according to rodent reservoir species.

(1) The plague focus of the commensal rat \textit{Rattus flavipectus}. This species is found in southern Yunnan and the coastal areas of Zenjiang, Fujian, Taiwan, Guangdong and Guangxi in southern China, an area of over 20 000 sq. km which includes
56 counties. Other hosts infected with Y. pestis in these regions have been R. norvegicus, M. musculus and Suncus murinus. The only part of this area where human plague cases have been reported since 1953 is southern Yunnan.

(2) The plague focus characterized by Eothenomys miletus is located in the mountains of northwestern Yunnan over an area of 600 sq. km. The main vectors are Ctenophthalmus quadratus and, to a lesser degree, Neopsylla specialis. The main reservoir host is Eothenomys miletus. Apodemus chevrieri, Apodemus speciosus and Rattus nitidus have also been found infected in the focus. While enzootic plague has been reported on many occasions, no human cases have been reported.

(3) The Marmota himalayana plague focus. This large focus is found mainly in Tibet and Qinghai, south to the Himalaya Mountains, north to the Qilian mountains in Xinjiang and east to southern Gansu, covering nearly 1 000 000 sq. km of land and 54 counties. The principal flea vectors are Callopsylla dolabris and Oropsylla silantevi. Other fleas and hosts found infected are Rhadinopsylla li and Pulex irritans, Ochotona dau Rica annectens, O. curzoniae, Lepus oiostolus, Vulpes ferrilata, Procarpra picticauda, Mus musculus, Clethrionomys glareolus and Pitymys leucurus. This stable enzootic focus is active from April to September. It is the most important focus of plague in China and the majority of human cases in the country arise from this focus.

(4) The Marmota caudata plague focus is in southwestern Xinjiang. It is part of the Pamir Plateau plague focus in Middle Asia and covers 600 sq. km in two counties. The main vectors are Oropsylla silantevi and Rhadinopsylla li. Citellophilus lebedewi priceps has also been found infected, as has the rodent Pitymys juldaschi. There have been no human cases of plague recorded in this zoonotic focus.

(5) The Marmota baibacina and Spermophilus undulatus focus. Located in the Tianshan Mountains of Xinjiang Province, the focus covers an area of 7,000 sq. km over 10 counties, extending into Kazakhstan and Kyrgyzstan. The main flea vector is Oropsylla silantevi. Callopsylla dolabris, Citellophilus tesquorum altaicus and the widespread Clethrionomys glareolus are other rodents that have been reported as infected in the focus. Epizootic plague occurs from May to September. No human cases have been reported in this focus since 1973.

(6) The Spermophilus alaschanicus plague focus in Gansu-Ningxia covers eastern Gansu and southern Ningxia in northern China,
an area of 3,000 sq km over five counties. The main flea vector is *Citellophilus tesquorum mongolicus*. *Neopsylla abagatui*, *Frontopsylla elata* and *Ophtalmopsylla praefecta* are also found infected with *Y. pestis*. Other mammal species infected are *Myospalax fontanieri*, *Meriones meridianus*, *Cricetulus triton*, *Allactaga siberica* and *Ochotona daurica*. Epizootic plague occurs from April to October. No human cases have been reported since 1978.

(7) The *Meriones unguiculatus* plague focus in the Inner Mongolian plateau covers the Inner Mongolian plateau and the three nearby Provinces of Ningxia, Shaanxi and Hebei, an area of 100 000 sq km. The principal flea vectors are *Nosopsyllus laeviceps* and *Xenopsylla conformis*. *Neopsylla pleskei*, *Citellophilus tesquorum mongolicus*, *Paradoxopsyllus kalabukovi*, *Rhadinopsylla insolita* and *Rhadinopsylla tenella* have also been found infected. Other mammals found infected in the focus are *Spermophilus dauricus*, *Spermophilus erythrogenys*, *Meriones meridianus*, *Dipus sagitta* and *Mus musculus*. Epizootic plague occurs from April to November; there have been no human cases reported since 1973.

(8) The *Spermophilus dauricus* plague focus in the plains of the Songhuajiang-Liaohe Rivers includes parts of Inner Mongolia, Liaoning, Jilin and Heilongjiang provinces over an area of 120 000 sq. km. The main vector is *Citellophilus sungaris*; *Neopsylla bidentaformis* and *Xenopsylla cheopis* are also involved. Rodent reservoirs are *R. norvegicus* and *M. musculus*. No human cases have been reported since 1959.

(9) The *Microtus brandti* focus on the Xilin Gol Plateau covers 60,000 sq. km. in northern Inner Mongolia. The main vectors in this purely zoonotic focus are *Amphipsylla primaris* and *Neopsylla pleskei* along with *Frontopsylla luculenta*, *Neopsylla bidentaformis*, *Citellophilus tesquorum mongolicus* and *Nosopyllus laeviceps*. *Meriones unguiculatus*, *Spermophilus dauricus*, *Ochotona daurica*, *Allactga siberica* and *Mus musculus* are rodent species found infected.

(10) The *Marmota bobac siberica* focus in the Hulum Buir Plateau. This epizootic focus covers 40 000 sq. km. in northeastern Inner Mongolia and is part of a focus with the same reservoir in the Russian Federation and Mongolia. No isolation of plague has been made from marmots or their fleas for many decades.
Plague reservoirs of North America

United States of America (96,97,98,99,100,101,102,103,104,105,106,107,108,109)

Plague infection has been found in many different animal species in North America. During a period of active surveillance in 1970–1980, evidence of plague infection was found in 76 species of five mammalian orders. Most of the wild-rodent-associated plague cases in the United States are reported in the south west, including most of New Mexico, northeastern Arizona, southern Colorado and southern Utah. The major hosts of Y. pestis in this area are the prairie dog *Cynomys gunnisoni* and the rock squirrel *Spermophilus variegatus*. Devastating plague epizootics are common among prairie dog populations in the large colonies formed by these species. Epizootics among *C. gunnisoni* may kill 99% of the colony and it may take four to five years for the affected colony to recover. Despite the heavy mortality, survivors are found with antibody to plague. Human cases acquired from prairie dog sources are relatively few.

Similar epizootics have been observed among *C. ludovicianus*, *C. leucurus*, and *C. parvidens*. More than 80% of the cases of wild rodent-associated human plague in the United States occur in this area and are associated with these host-flea complexes. Despite the size of epizootics, human cases are relatively few and generally result from contact with an infected animal rather than from the bite of the *Opisocrostis* species, which do not readily bite humans.

On the Pacific coast the reservoirs are *Spermophilus beecheyi* (the most important rodent species in the epidemiology of plague on the Pacific coast), and the chipmunks *Eutamias* species, *Microtus californicus* and *S. lateralis*. There has been a single report of an epizootic in the domestic fox squirrel, *Sciurus niger*, in Colorado state. In the northern foci of plague ground squirrels, including *S. beldingi*, are important reservoirs. Other rodent species are frequently infected and there has been a report of the black footed ferret *Mustela nigripes* found infected with plague in Wyoming which endangers the only known colony of this species. Cats have frequently been a source of commensal infection in the southwestern United States. Several cases of plague have been contracted directly from domestic cats, *Felis catus*, infected after contact with plague-infected rodents. The flea vectors of plague in the southeast are *Opisocrostis hirsutus* and *O. tuberculatus* on the prairie dog *C. gunnisoni*, and *Diamanus montanus* and *Hoplopsyllus anomalus* on the rock squirrel *S. variegatus*. 
Rapid human population growth and rural development have increased the densities of *Spermophilus variegatus* populations by providing additional habitats. Plague cases in California generally originate from two primary epizootic complexes: *S. beecheyi* and its fleas *D. montanus* and *H. anomalous*, and a less well-defined complex involving several species of chipmunks, *Eutamias* species and the golden-manteled squirrel *S. lateralis*.

The host-flea complexes involved in the transmission of *Y. pestis* both in zoonotic and reservoir-to-human transmission are summarized in Table 4.

**Plague foci of South America**

**Bolivia (3,110)**

Since the first reports of plague in Bolivia in the early 1920s, plague has spread widely throughout the country. Today there are two widely-separated foci, one in the north-west near La Paz, the other in south central Bolivia. When plague outbreaks occur in settled areas the rodent involved is usually *R. rattus* and the vector flea *X. cheopis*. In sylvatic areas in Vallegande Province, *Graomys griseoflavus* and *Galea musteloides* have both been found infected with plague. *G. griseoflavus* is particularly important, as it frequently infests domestic areas and transmits plague to purely sylvatic rodent populations. Other rodents found infected with plague in Bolivia are *Dasyprocta variegata boliviana*, *Hesperomys fecundus*, *H. venustus*, *Oryzomys flavescens*, *Oxymycterus paramensis*, *Phyllotis wolhsohni*, *Rhipidomys leucodatylus* and *Sylvilagus brasiliensis gibsoni*. More research is needed to clarify the relative importance of each of these species in the sylvatic foci.

**Brazil (3,111,112,113)**

Plague apparently entered Brazil by sea route in 1899, infecting first Santos and then Sao Paulo. Plague has spread to other ports and to rural areas of Brazil; while the infection has disappeared from Sao Paulo several natural foci have become established in the country. Of the commensal reservoirs of plague, *R. rattus* is the most important. In the plague foci which persist in northeastern Brazil, the most important wild rodent reservoir is *Zygodontomys lasiurus pixuna*. The cavia species *Galea spixii*, *Ceromys inermis*, *Holochilus sciureus*, *Kerodon rupestris* and *Cavia aperea* are among the species that have been found naturally infected with plague. Plague-infected fleas have been found on *Calomys callosus* and *Oryzomys subflavus*.
Table 4  List of host–flea complexes found involved in epizootic plague amplification in western North America by geographic regions

<table>
<thead>
<tr>
<th>States &amp; regions</th>
<th>Rodent species</th>
<th>Flea vectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona, New Mexico so. Colorado, so. Utah</td>
<td>Spermophilus variegatus</td>
<td>Diamanus montanus</td>
</tr>
<tr>
<td>Arizona, New Mexico Colorado, Utah, Rocky Mts and west</td>
<td>Cynomys gunnisoni</td>
<td>Opisocrostis hirsutus O. tuberculatus</td>
</tr>
<tr>
<td>Colorado (east of Rocky Mts) western Texas, Oklahoma, Kansas</td>
<td>C. ludovicianus</td>
<td>O. hirsutus O. tuberculatus</td>
</tr>
<tr>
<td>Wyoming, northwestern Colorado, northeastern Utah (high plains grasslands)</td>
<td>S. richardsoni</td>
<td>O. lahis Orlopsylla idahoensis (Rocky mts) O. t. tuberculatus, Thrassis bacchi</td>
</tr>
<tr>
<td>California, Oregon, northern Nevada, Northwestern Idaho (montane meadows, great Basin sagebrush-grasslands)</td>
<td>S. beldingi</td>
<td>Thrassis francisi, T. pandorae, T. petiolatus Opisocrostis t. tuberculatus</td>
</tr>
<tr>
<td>Southern Idaho, eastern Oregon, Nevada, Utah, (Great Basin, sagebrush)</td>
<td>S. townsendi</td>
<td>T. francisi</td>
</tr>
<tr>
<td>Idaho, Utah, Wyoming (Great Basin &amp; mountain 4000-8000 elevation)</td>
<td>S. armatus</td>
<td>T. pandorae T. francisi</td>
</tr>
<tr>
<td>California, Oregon, western Nevada (valleys, foothill savanna, open pine forest to temperate rain forest edge)</td>
<td>S. beechyi</td>
<td>D. montanus H. anomalus</td>
</tr>
<tr>
<td>Arizona, California, Colorado Idaho, Montana Nevada, New Mexico, Oregon (mountain areas, open pine forest)</td>
<td>S. lateralis</td>
<td>Orlopsylla, idahoensis D. montanus (Sierra-Cascade, O. labis (Rocky mountains)</td>
</tr>
<tr>
<td>Western United States from Rocky mts westward M.eutamias, M.eutamiadis,</td>
<td>Eutamias spp¹ 16 species</td>
<td>Monopsyllum eumolpi, M. ciliatus, M. fornacis (last 3 from Pacific states only)</td>
</tr>
<tr>
<td>Western USA from Texas to the Pacific States (desert to high Montana shrubby habitats)</td>
<td>Neotoma spp² 8 species</td>
<td>Orchopeas sexdentatus O. neotomae Anomiopsyllus spp</td>
</tr>
<tr>
<td>Colorado, Wyoming California (urban residential and rural environments) States.</td>
<td>Sciurus niger³</td>
<td>Orchopeas howardii</td>
</tr>
</tbody>
</table>

a Individuals of nine species found plague infected or carrying plague-infected fleas
b Individuals of five species were found to have plague-infected or carried plague-positive fleas
c This peridomestic species introduced in western cities as a park squirrel with O. howardi

Several species of fleas found on wild hosts in northeastern Brazil and the State of Bahia may be involved in the maintenance and transmission of plague, particularly fleas of the genus *Polygenis*. Of these *P. bohlsi jordani* has perhaps the widest distribution, highest density and greatest contact with domestic rats followed by *P. tripus*.

Further to the south in the plague-endemic area of Goias 14% of the *O. elurus* and *Calomys callosus* have been found infested with *P. bohlsi*. The infestation rate for *Zygodontomys* sp. has been reported at 42%. Still further south in the focus of Minas Gerais, the infestation rates of *P. tripus* were 50% on *O. subflavus*, 47% on *Z. lasiurus* and 30% on *R. norvegicus*.

**Ecuador** (115,116)

*Rattus norvegicus*, *R. rattus* and their common flea ectoparasite *X. cheopis* are found in most of the towns of the coast of Ecuador. However, the *Rattus* species appear to have little role in the transmission of plague in the country. Domesticated guinea pigs are frequently infected and pass the infection on to humans. The specific flea of the guinea pig, *Tiamastus caviola*, has been found naturally infected with plague (116). Guinea pigs are often infested with *P. irritans* though their vectorial role is uncertain. The most common wild rodents in some areas of plague outbreaks are *Akodon mollis* and *Oryzomys xanthaeolus*. These species have been found infected with plague inside houses. *Sigmodon peranus* and *S. puna* have also been found naturally infected with plague. The squirrel *Sciurus stramineus nebulos* is considered a reservoir in Loja province as it is comparatively resistant to plague and is responsible for acute epizootics in the highly plague-susceptible *A. mollis* and *O. xanthaeolus*. *Polygenis litargus* is one of the most important flea vectors of plague on wild rodents in Ecuador. The fleas *P. litargus*, *P. bohlsi bohlsi*, and *P. brachimus* infest the important reservoirs *Oryzomys xanthaeolus* and *Akodon mollis* in Loja province where *Sciurus stramineus* may be one of the wild-rodent plague reservoirs in this province. There is little information on the principal rodent reservoirs or flea vectors of plague in Tungurahua and Canar provinces, which also have foci of plague.

**Peru** (110,115,116,117)

At the beginning of the century *X. cheopis*-transmitted plague was introduced into populations of *R. rattus* and *R. norvegicus* and subsequently wild rodent foci and epizootics developed on the Peru-Ecuador border and in the Andean district of Huancabamba. The principal reservoir in the Peru-Ecuador border focus is the tree squirrel *Sciurus stramineus*, parasitized by the flea *Polygenis litargus*. In the Huancabamba district, the infection is carried mainly by
the mountain field mouse *Akodon mollis* and a oricetine rat, *Oryzomys andinus*. Other species of *Oryzomys* are associated with plague in the area as are the cavy *Cavia tshudii* and the cottontail rabbits *Sylvilagus andinus* and *S. ecaudatus*. The progenitor of the guinea-pig, *Cavia porcellus*, is frequently kept in houses in the area and is often infected by plague. *C. porcellus* and *C. tshudii* are parasitized by *Hectopsylla* species and *Tiamastus cavicola*, all of which have been found infected by plague in nature. In urban areas and the coastal cities, *R. norvegicus* and *R. rattus* are common and are parasitized by *X. cheopis*; this is the only important vector species when *Rattus* species are involved in plague transmission in settlements. While it appears that *A. mollis* and *Oryzomys xanthaeolus* are the most common sylvatic rodents and most frequently found infected with plague, many aspects remain to be clarified regarding the epidemiology of plague transmission in Peru, particularly those related to the wild rodent reservoirs.
Map 3  Distribution of Rattus norvegicus
References


60. Fenyuk BK. Influence of human activities, fluctuation in carrier numbers and limit lines of their distribution areas upon the boundaries of natural foci of plague. *Czechoslovak Academy of Science: Symposium, Theoretical questions of natural foci of disease.* 1965, 235-265.


CONTROL OF PLAGUE TRANSMISSION

Dr Norman G. Gratz

Plague is primarily a disease of wild rodents, transmitted from one wild rodent to another or from wild rodents to commensal rodents and to humans through fleas. Control of transmission is directed at controlling the rodent reservoirs and flea vectors of the disease. As will be discussed below, during outbreaks immediate control of flea vectors should precede any measures against rodent hosts. As a first step in ensuring preparedness for plague outbreaks, known endemic foci should be identified and essential information accumulated on the epidemiology and epizoology of the infection. Such information should include the seasonality of past outbreaks and the identity of rodent reservoirs and flea vectors. If it is anticipated that plague control measures may have to be carried out at some time in the focus, baseline data should be gathered on factors likely to affect control. These include the insecticide susceptibility status of the most important flea vectors to insecticides likely to be used, seasonal variations in flea population densities and indices on their most important hosts. Information on normal seasonal variations in population density of rodent reservoirs is essential for detecting any abnormal changes such as a sudden decline or increase in the populations, which may indicate an epizootic.

In addition to the above measures, plague's endemic cycle in the focus must be understood, by gathering information on the species and degree of immunity of small mammal reservoirs, and the species and vectorial capacity of the flea vectors. The most important measure thereafter will be to establish a surveillance system adequate to detect unusual plague activity in a focus (see Surveillance). A natural focus of plague may be dormant for many years, during which time no human cases are reported. Subsequently, for reasons which may include ecological changes, human population movements into the focus, occurrence of an epizootic and others, the focus may flare up and cases of human plague occur.

Thus, from the viewpoint of anticipating the appearance of plague, knowledge of the location of existing natural foci is as important as
knowing where cases have appeared in a given period. The known, and in some cases, the suspected foci are shown on the map compiled from published literature and government reports. The foci have been described in the first section of this manual.

**Principles of control**

Control of plague transmission, from one reservoir animal to another or from animals to humans, can be most rapidly effected by control of the flea vector. The question of whether to give priority to control of the rodent reservoir or the flea vector was considered by Gordon and Knies, who concluded that the flea is the primary objective, the rat (diseased or harboring fleas) is secondary, and that the principle of focal disinfection applies (1). Certain principles they recommended remain valid, although their insecticide of choice B DDT B would not probably be the one now selected:

The first consideration in control of human plague is direct attack on reported foci of infection. This involves diagnosis and recognition of the disease, which is essential to establish firmly the existence of plague, isolation of the patient and of the immediate contacts, focal attack on the area invaded by plague through disinestation of premises and persons with insecticide DDT (1).

This approach was first developed by Simond in 1898 (2) and is still followed in the sense that plague control measures should start with the control of the vector flea rather than the reservoir rodent. Although it might be feasible to achieve a high level of rodent control in a plague focus (whether rural or urban), the death of a large number of plague-infected rodents is likely to introduce large numbers of flea ectoparasites of the killed rodents, (many of which might be infected with plague) into the environment. These fleas, particularly blocked@fleas, will avidly seek another host, thus spreading the disease to a greater extent than would have been likely had the rodent hosts not been killed. Thus the first step in controlling an outbreak of plague and interrupting its transmission remains that of control of the vector flea.

**Control of flea vectors**

The literature on control of the flea vectors through the use of insecticides is extensive (3). Every large-scale rodent control action, especially in an urban area or in a rural area in or close to human
habitations, should be preceded by or (at the very least) accompanied by flea control, the objective of which is to reduce the density of the rodent-flea vectors as quickly and as completely as possible. Although residual sprays as applied for the control of malaria vectors may effectively reduce indoor flea populations, they will have relatively little effect on fleas on rodents or in rodent burrows, and would thus have little or no effect on interrupting plague transmission occurring outside dwellings (4).

Dusts applied to rodent runways and burrows (commensal rodents) or into rodent burrows (wild rodents) is effective in controlling flea vectors. Rodents crossing dust patches on runways or when exiting burrows pick up the insecticidal dust on their fur and spread it over themselves when grooming, killing the flea ectoparasites. Dusts are the formulation of choice but may not be readily available. When flea control is urgent a liquid insecticide spray can be used to control flea ectoparasites on indoor rodent populations. If a residual spray formulation is applied, greater attention will have to be placed on spraying floors and rodent holes than would normally be done when carrying out a residual spray application for malaria vector control.

Flea control on commensal rodents

In most towns or urban areas endemic for plague the flea vector is likely to be *X. cheopis*, *X. astia* or *X. brasiliensis*. Their rodent hosts, often *R. rattus* or *R. exulans*, usually nest in dwellings or buildings. *R. norvegicus* and *B. bengalensis* usually nest in burrows around houses, warehouses and other structures. No matter what the species of rodent host, control staff must learn to recognize and seek out rodent runways and burrows which must be treated. The insecticidal dust should be blown into the mouth of a burrow and a patch of dust approximately 1cm thick left around it. Indoors, patches of dust should be applied to rat runways, which are usually found along walls. Patches 15–30cm wide should be placed at several points along each runway. A shaker can attached to a long pole can be used to reach runways along rafters or the wall–roof junction. As much as possible, the dust patches should be left where they will not be swept away or disturbed by human activity. Care must be taken not to contaminate foodstuffs or cooking utensils.

Special care should be taken when dusting food warehouses or storage rooms, which are often heavily infested by rodents. An alternative is to use bait boxes, which contain both a slow-acting rodenticide in an attractive bait and insecticidal dust at the openings. In tropical countries
bait boxes can be rapidly and cheaply constructed of sections of bamboo tubes approximately 40cm long and 7–10cm in diameter. Some 30gm of bait B with or without a rodenticide B is placed in the centre of the tube and 5–6gm of the insecticide dust placed at each opening. The tube is fastened to the earth or floor by a long nail (5). This method is labour-intensive but has several advantages, including the protection of dust by placement inside the tubes. The use of bait boxes for rural areas is described below. The use of dust patches is advantageous in that application can be carried out rapidly with a minimum of training and the patches can easily be checked for rodent tracks, indicating that they have been crossed.

The extent of an area to be dusted in a city or town where plague has appeared is determined by the location of plague cases, whether human or rodents were found bacteriologically positive, and the size of the area to be protected. The risk can probably best be judged by the extent of rodent activity in and around the focus. In any event, insecticidal dusting should begin as soon as possible after the verification of human cases or rodents positive for plague. The dusting operations should be announced in schools, on the radio and in the local press to ensure that teams carrying out the work are allowed free access to all structures and that dust deposits are not swept up but left undisturbed as long as possible. Actions to be taken in towns or villages are similar but great attention must be given to avoid contaminating stored foodstuffs in houses and farm areas.

In areas at high risk for plague periodic surveys should be made of flea densities, their seasonal variation and their susceptibility to insecticides in stock or to those which may be procured should a dusting programme be required.

**Flea control on wild rodents**

Wild rodents and their flea ectoparasites are more difficult to control than commensal species, due to difficulties in locating burrows and runways, wide population dispersion and the difficulties of deciding on the limits of the area to be treated. Before the appearance of DDT and in some areas of the world to this day, flea and rodent control were carried out in conjunction by fumigating burrows with cyanide gas through insufflation of HCN dusts or granules. While the results of fumigation are often dramatic, this method has several shortcomings. First, in large burrow systems the fumigant is often too light to reach all parts of the burrow system and rodents can often escape its effect. Second, there is no
persistence of action and rodents or fleas which have not been controlled by the fumigation will not be affected when the gas has dissipated. Last, toxic fumigants carry considerable risk to applicators and to people living in houses where fumigants are applied.

In as much as fumigants are easily and rapidly applied and results are seen to be immediate (dead rodents free of living fleas in their burrows) directly after the application, their use was and is still popular. However, fumigants—whether cyanide or others—have little persistence of action and the appearance of DDT and other organochlorine insecticides created immediate interest in their use for plague flea vector control. Indeed, some of the earliest uses of DDT on a large scale in the mid-1940s were in large-scale dusting programmes to halt plague epidemics (6,7,8).

Wild rodent fleas have since been controlled by a variety of different methods of insecticide application, including broadcast from aircraft and application in and around burrows with power and hand dusters. With the growing concern about the introduction of insecticides into the environment, increasing use has been made in the United States of bait boxes (referred to above). Such boxes, whatever their shape and construction, include a food bait attractive to rodents in the interior and insecticidal dusts at the box entrances. Rodents entering the boxes cross the dust, picking up insecticide onto their fur and carrying it back to their nests, killing the fleas on their bodies and those in the nests (9,10,11). Bait boxes have been found to be quite effective, reducing flea populations over a considerable radius from the boxes as the rodents bring the insecticide back to their nests. As has been observed above, the method is labour-intensive and the stations require rebaiting and replenishment of the dusts until the threat of plague abates. Because of these limitations most countries will probably use insufflation of dusts in and around rodent burrows as the approach of choice. If this is assiduously carried out little else need be done except to evaluate periodically the effect of the dusting and repeat, if necessary, when the effect of the insecticide begins to wane.

**Insecticides used in rodent flea control**

Prior to selecting an insecticide for use in a plague-flea vector control programme, susceptibility tests must be done to determine the status of resistance of the flea populations to the insecticides which may be used (discussed under Flea resistance to insecticides). If possible, field trials should be done to determine the efficacy of candidate insecticides against flea vector populations under local conditions.
In the past, 10% DDT dust was one of the most common and effective compounds used in rodent–flea control programmes. However, due to the widespread development of insecticide–resistant populations among several important vector species, including X. cheopis, and the increased concern over environmental contamination, alternative compounds are now used. Most of these compounds, are effective against both adult and larval fleas. Use should be made of alternative insecticides among the organo–phosphorus, carbamate, pyrethroid and insect–growth–regulator compounds shown to be effective in field trials. Table 5 lists those compounds readily available and commonly employed in flea control.

Table 5  Insecticide dusts commonly employed in flea control

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Class</th>
<th>Concentration (%)</th>
<th>Oral LD50 to rats (mg/kg oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bendiocarb</td>
<td>carbamate</td>
<td>1.00</td>
<td>55.00</td>
</tr>
<tr>
<td>carbaryl</td>
<td>carbamate</td>
<td>2.0 - 5.0</td>
<td>3,000.00</td>
</tr>
<tr>
<td>deltamethrin</td>
<td>pyrethroid</td>
<td>0.005</td>
<td>135.00</td>
</tr>
<tr>
<td>diazinon</td>
<td>OP</td>
<td>2.00</td>
<td>300.00</td>
</tr>
<tr>
<td>diflubenzuron</td>
<td>IGR</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>fenitrothion</td>
<td>OP</td>
<td>2.00</td>
<td>503.00</td>
</tr>
<tr>
<td>jofenphos</td>
<td>OP</td>
<td>5.00</td>
<td>2,100.00</td>
</tr>
<tr>
<td>lambdacyhalothin</td>
<td>pyrethroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lindane</td>
<td>Org.chl</td>
<td>3.00</td>
<td>100.00</td>
</tr>
<tr>
<td>malathion</td>
<td>OP</td>
<td>5.00</td>
<td>2,100.00</td>
</tr>
<tr>
<td>methoprene</td>
<td>IGR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>permethrin</td>
<td>pyrethroid</td>
<td>0.50</td>
<td>430.00</td>
</tr>
<tr>
<td>propetamphos</td>
<td>OP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pirimiphos-methyl</td>
<td>OP</td>
<td>2.00</td>
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<tr>
<td>propoxur</td>
<td>carbamate</td>
<td>1.00</td>
<td>95.00</td>
</tr>
</tbody>
</table>

Source: Gratz, N.G. & Brown, A.W.A.: 1983
Other insecticides now available, among them fipronil, imidacloprid, lufenuron and pyriproxyfen, are very effective in the control of fleas. They should undergo field trials against populations of flea vectors of plague to determine their efficacy and best manner of application under local, field conditions.

Field trials have demonstrated the potential of systemic insecticides, including phoxim, chlorphoxim and dimethoate incorporated in rodent baits for controlling flea ectoparasites (11, 13, 14). Little use appears to have been made of these compounds.

It is unlikely that insect growth regulators would be applicable under plague epidemic conditions. They are considered here inasmuch as they are highly effective (though not rapid) in their action. Field trials carried out with the insect growth regulator methoprene for flea control in domestic situations as well as against the flea ectoparasite of ground-squirrel wild reservoirs of plague in Texas (15) have shown good results. Application to rodent burrows in the fall at a rate of 0.05g of a.i./ burrow resulted in a complete disappearance of adult fleas from mid-June to late fall. Field trials have also been carried out with Bacillus thuringiensis preparations; while some of these containing beta-endotoxin were larvicidal against X. cheopis, they were more effective against first-instar larvae than later instars which required a 15-fold greater dose for effective control (16).

Vector flea resistance to insecticides

As noted above, flea resistance to insecticides can be a serious impediment to control. Therefore the susceptibility of target flea populations to locally-used insecticides should be determined periodically. DDT resistance was first confirmed in X. cheopis in the Poona District of India (17). Insecticide resistance has since spread widely in other flea vectors of plague (Table 6).

Where flea control programmes are planned or there is a threat of flea-borne diseases which may make the application of insecticides necessary, surveys of the prevalent flea species and their seasonal variations in population densities should be accompanied by tests to determine their susceptibility status. This is especially important in areas where extensive applications of residual insecticides have been made to houses, as in malaria or Chagas disease vector control programmes.
The test for the determination of insecticide susceptibility or resistance in fleas can be carried out on adult fleas using a WHO Susceptibility test kit. The test kit, along with instructions for use (18), may be ordered from the WHO Regional Offices or from the Division of Control of Tropical Diseases, WHO (Address: 20 avenue Appia, CH-1211 Geneva 27, Switzerland).

**Table 6  Insecticide resistance reported in flea populations**

<table>
<thead>
<tr>
<th>Species</th>
<th>Insecticides</th>
<th>OP compounds</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceratophyllus fasciatus</td>
<td>USSR</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Ctenocephalides felis</td>
<td>Colombia, Guyana,</td>
<td>USA, USA, Tanzania</td>
<td>USA</td>
</tr>
<tr>
<td>Pulex irritans</td>
<td>Brazil, Czechoslovakia,</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Ecuador, Egypt, Greece, Peru, Turkey</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stivalius cognatus</td>
<td>Indonesia</td>
<td>Indonesia</td>
<td></td>
</tr>
<tr>
<td>Synopsyllus fonquerniei</td>
<td>Madagascar</td>
<td>Madagascar</td>
<td></td>
</tr>
<tr>
<td>Xenopsylla astia</td>
<td>Burma, India</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Xenopsylla brasiliensis</td>
<td>Tanzania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xenopsylla cheopis</td>
<td>Brazil, Burma, China, Ecuador, Egypt, India, Indonesia, Israel, Madagascar, Philippines, Tanzania, Thailand, Vietnam</td>
<td>India, Tanzania, Madagascar</td>
<td>Madagascar</td>
</tr>
</tbody>
</table>


**Control of rodent reservoirs**

As emphasized above, during an outbreak of plague in a human population or an epizootic among either commensal or sylvatic rodent populations, the first step is to control flea vectors on the rodents. In areas where flea populations are high and plague infections intense, killing rodent hosts may result in the release of large numbers of avid fleas carrying plague organisms seeking new hosts. If the rodent population has been decimated by an epizootic, many flea species, including efficient vectors of plague, will seek an alternative host which in the absence of rodent hosts might well be humans, resulting in spread of infection to humans.
Once flea indices have been reduced, control of rodent reservoirs can be undertaken. In areas where plague is not endemic or during periods when plague is not circulating in a sylvatic or commensal rodent population, rodent control measures can be carried out independently of flea control.

Knowledge of the species present in a plague focus or an area into which plague has been introduced as well as of the bionomics of the reservoir or potential reservoir rodent species is essential as a base for rodent control. For target control areas, the extent of infestations, population densities, seasonal fluctuations, rodent movements and the status of susceptibility to the anticoagulant rodenticides must be known.

Effective rodent control is a complex undertaking and the following provides only basic information on methods and materials used to control reservoir populations of plague. Readily available publications are listed at the end of the section.

**Target commensal species: bionomics and reservoir importance**

The material in this section is based on the WHO Vector Biology and Control Training and Information Guide, Rodents, 1987 (unpublished document No.VBC/87.949). Copies can be requested from the Control of Tropical Diseases Programme, WHO (Address: 20 Avenue Appia, CH-1211 Geneva 27, Switzerland).

Three species of commensal rodents with a global distribution are the Norway rat *R. norvegicus*, the roof rat *R. rattus* and the house mouse *M. musculus* (Table 7). Although it is a reservoir and vector of other diseases of humans, the house mouse has little role in plague epidemiology.

**The Norway rat**

Norway rats are stocky, medium-to-large-sized rodents; the tail is shorter than the head and body. Under favorable conditions colonies of several hundred Norway rats may develop. It is primarily a burrowing species and is commonly found living near sources of food and water, such as refuse and drainage ditches, streams or sewers. While mainly a temperate climate species with a patchy distribution in the tropics, its range appears to be continually expanding. The Norway rat is more
abundant in the northern than the southern hemisphere and is the predominant species of commensal rat in Europe, North America and parts of the Mediterranean basin (Map 2).

In temperate areas it is commonly found in both urban and rural areas. The Norway rat is omnivorous, consuming food waste, stored food such as cereal grains and seeds and growing crops. Poor disposal of garbage and other types of organic refuse offers a ready supply of foodstuffs to this species. Warehouses or other areas with stored foodstuffs can be readily infested if not rodent-proofed.

Reproduction is rapid with a gestation period of 22–24 days with large litters. In warmer areas, reproduction may continue throughout the year. In temperate areas, there are litters in the spring and autumn. There is generally a high mortality among the young and few rats live longer than a year in the wild. An abundance of food and harbourage will result in better survival rates.

*R. norvegicus* is often heavily infested by *X. cheopis* and is readily susceptible to plague, though some individuals in a population may survive the infection. Because of its proximity to human populations, an epizootic of plague in *R. norvegicus* populations represents an immediate danger to humans.

**The roof rat**

The roof rat is a moderate-sized, slender agile rat. The snout is slender, ears are large and thin and the eyes are prominent. The tail is generally longer than the head and body. The species has been displaced to some extent by *R. norvegicus* in many urban areas but still finds ecological niches adequate in most areas to maintains its presence. In Asia a number of rat species are closely related to *R. rattus*, including *R. jalloensis*, *R. argentiventer*, *R. diardii* and *R. exulans*.

The roof rat exists in small family groups in smaller colonies than the Norway rat. It is found both indoors and outdoors depending on the climate. It is a semi-arboreal species, climbing shrubs, vines and trees, and nests outdoors in warmer areas. In temperate areas it inhabits a wide range of buildings, from dwellings to food stores and warehouses. It is the most frequent rat found on vessels and is also known as the "ship rat". It is a more skilful climber than the heavier Norway rat, and more extensively distributed (Map 3) in both the northern and southern hemispheres.
In general the roof rat prefers grains, seeds, nuts and fruits but will readily change to insects and herbivorous foods if necessary. They can live on cereals for relatively long periods without access to free water. Reproduction is slightly faster than the Norway rat with a gestation period of 20–22 days but with fewer embryos and young per year.

The roof rat appears to be as susceptible to infection by *Y. pestis* as the Norway rat and suffers considerable mortality when exposed to infection. Its flea load is often lighter than that of the Norway rat but their propensity for living inside dwellings makes them an effective reservoir and source of infection to fleas and humans.

**The Polynesian rat**

*R. exulans* is a small species of rat rarely weighing more than 110g in the wild. It usually lives in close association with humans throughout its range in southeast Asia and Indonesia but can be found in fields and ricefields as well. It has been found infected with plague in several endemic countries.

**The lesser bandicoot rat**

The lesser bandicoot *B. bengalensis* is a medium- to large-sized rat. It is a burrowing species, creating large burrow systems in urban areas and in fields in rural areas. It does not readily climb. It has become the main urban species of rat in many cities of southeast Asia including Bombay, Calcutta, Madras, Dhaka, Yangon (Rangoon) and Bangkok. It has been frequently found infected with plague in India, Myanmar (Burma) and Viet Nam and can serve as an important reservoir, as in some areas it is susceptible to infection but relatively resistant to the disease.

**The multimammate rat**

*M. natalensis*, or the multimammate rat, occurs over large areas of Africa south of the Sahara and can reach high population densities. Though frequently found in fields and forest clearings, it is a peri-domestic species living in close association with humans and readily inhabiting houses or granaries. It is mainly granivorous, eating wild grasses, millet, maize and rice as well as stored foodstuffs in houses and stores. This rat is the most economically important of all rodent species in Africa, although it is being replaced in some areas by the roof rat.
The species reproduces rapidly: females breed at approximately 3 months with a gestation period of 23 days. Litter size is from 9.5 to 12.1.

*M. natalensis* is highly susceptible to plague infection. It is the main link in many parts of Africa between peridomestic and wild rodents and is the main reservoir of plague in many parts of the continent.

**Commensal rodent control**

There are different approaches to control utilizing chemical rodenticides, traps or environmental measures, including rodent exclusion. Environmental measures, while more effective in reducing rodent population densities, are slow to take effect and it may be more important in a plague-threatened area to immediately reduce the rodent reservoir populations.

**Rodenticides**

Most measures to control commensal rodents depend on the application of rodenticides incorporated in either bait, dust or water formulations (1). Rodenticides are classified as chronic (multiple dose, slow-acting) or acute (single dose, quick-acting) compounds. The most widely used are the anticoagulants: these slow-acting compounds are now regarded as first-choice rodenticides against commensal rodents in most control operations. Acute rodenticides are principally and most effectively employed in situations demanding a rapid reduction of high-density populations. As will be seen, some of the most recently developed anticoagulants are effective in a single feeding and the distinction between the two groups is somewhat blurred. A comparison is given in Table 7.

**Anticoagulants**

The anticoagulant rodenticides disrupt the mechanism that controls blood-clotting and cause fatal internal haemorrhages (2). Their action is cumulative and most must be ingested over a period of several days to be effective. Anticoagulants have two main advantages over acute rodenticides. First, they are readily accepted by commensal rodents when they are included in bait at low concentration so that sublethal dosing and bait-shyness problems do not normally arise. Second, primary and secondary poisoning hazards to non-target species are generally low and, if accidental poisoning of humans or animals does occur, an effective
antidote (phytomenadione—vitamin K) is available. Even so, their use can present a danger to non-target species and the utmost care should be taken in their application.

Table 7  Comparison of acute and chronic rodenticides

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages in use</strong></td>
<td><strong>Disadvantages in use</strong></td>
</tr>
<tr>
<td>1. Fast kill</td>
<td>1. Bodies generally not seen (die under cover)</td>
</tr>
<tr>
<td>2. Bodies seen by user</td>
<td>2. Tend to be non-selective</td>
</tr>
<tr>
<td>3. Effective where anticoagulant resistance is a problem</td>
<td>3. Slow to act; dominant rodents may eat several lethal doses; wasteful and may increase secondary poisoning hazard</td>
</tr>
<tr>
<td>4. Relatively small amounts of bait rodent kill</td>
<td>4. Relatively large quantities of bait required per rodent kill can lead to underbaiting</td>
</tr>
<tr>
<td>5. Very low concentration means active ingredient cost per kg of formulation is low</td>
<td>5. Anticoagulant resistance</td>
</tr>
<tr>
<td>6. Antidote very effective and practical (except bromethalin and calciferol)</td>
<td></td>
</tr>
</tbody>
</table>

The anticoagulants have been particularly successful in controlling Norway rats. The roof rat is less susceptible and house mice can be highly variable in their response. Recommended dosage levels for anticoagulant rodenticides are given in Table 8. In the non-target species, pigs are about as susceptible to anticoagulants as are rats; cats and dogs are moderately susceptible; and chickens, rabbits and horses are the least susceptible to poisoning.
Table 8  Relative potencies, recommended concentrations to give a LD50 dose of several anticoagulant rodenticides to Norway rats

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>LD50 mg/kg Norway rat</th>
<th>Bait conc. ppm.</th>
<th>LD50 dose g bait/250g rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodifacoum</td>
<td>0.3</td>
<td>50</td>
<td>1.5</td>
</tr>
<tr>
<td>Flocoumafen</td>
<td>0.4</td>
<td>50</td>
<td>2.0</td>
</tr>
<tr>
<td>Bromadiolone</td>
<td>1.3</td>
<td>50</td>
<td>6.5</td>
</tr>
<tr>
<td>Difenacoum</td>
<td>1.6</td>
<td>50</td>
<td>9.03</td>
</tr>
<tr>
<td>Coumatetralyl</td>
<td>16.5</td>
<td>375</td>
<td>11.0</td>
</tr>
<tr>
<td>Diphacinone</td>
<td>3.0</td>
<td>50</td>
<td>15.0</td>
</tr>
<tr>
<td>Warfarin</td>
<td>58.0</td>
<td>250</td>
<td>58.0</td>
</tr>
<tr>
<td>Pival</td>
<td>50.0</td>
<td>250</td>
<td>50.00</td>
</tr>
<tr>
<td>Chlorphacinone</td>
<td>20.5</td>
<td>50</td>
<td>102.5</td>
</tr>
</tbody>
</table>

All anticoagulant compounds are virtually insoluble in water, although the sodium or calcium salts of most are water-soluble and available for the preparation of liquid baits. Chlorphacinone and bromadiolone are available as mineral oil-soluble concentrates. All are chemically stable either in concentrate or in prepared bait form.

There are 12 anticoagulants in use throughout the world. Most of these are considered here, including the so-called "second-generation" anticoagulants, difenacoum, brodifacoum bromadiolone and, most recently, flocoumafen, which appears from preliminary data to be almost as toxic as brodifacoum (3). As the availability of different anticoagulant rodenticides varies considerably from country to country, the following section reviews the characteristics of those used to any extent. Some are no longer readily available, though stocks may still be found.

**First-generation anticoagulants**

**Warfarin.** Warfarin [3-a-acetonylphenyl]-4-hydroxycoumarin] was the first major anticoagulant to be developed in 1950 as a rodenticide. It has had widespread use. Warfarin was the most effective of the early anticoagulants against Norway rats. In many countries warfarin use has been declining, since the introduction of the newer, more potent anticoagulants, the development of physiological resistance (4).

The sodium salt is available as a 0.5% concentrate; this is dissolved in water to make a final concentration of 0.05%mg/ml. In contrast to highly-purified warfarin incorporated in bait, sodium warfarin solution can be detected by rats and sugar is usually added to mask the taste. There appears to be some unacceptability in baits at the 0.05% level or higher.
Fumarin. Fumarin, or coumafuryl [3-(a-cetonylfurfuryl)-4-hydroxycoumarin], is a whitish or cream-coloured compound supplied as a 0.5% concentrate in cornstarch. It has been shown to be equally as effective and palatable as warfarin and a water-soluble salt is used in preparing liquid baits.

Coumachlor. Coumachlor [3-(l-p-chlorophenyl–2-acettylethyl)-4-hydroxycoumarin], also known as Tomorin, was one of the first anticoagulants. While it is similar to warfarin it is the least toxic of the first generation anticoagulants and is somewhat less useful against R. norvegicus. It has been applied successfully in dust formulations.

Coumatetralyl. Coumatetralyl [3-(a-tetralyl–4-hydroxycoumarin], also known as Racumin, has been widely used against all three commensal species. It has been reported that coumatetralyl at 0.03% and 0.05% is extremely well-accepted by Norway rats, better than warfarin at 0.025%. At 0.05% it is about as toxic to warfarin-resistant Norway rats as 0.005% warfarin is to normally-susceptible individuals (5). Coumatetralyl was not effective against warfarin-resistant rats in the field in Denmark (6), but in other field trials it was found to be more toxic than warfarin against the house mouse. A high degree of resistance to coumatetralyl and many other anticoagulants has been reported in Germany (7). Coumatetralyl is still widely used throughout the world and, next to the second-generation anticoagulants, remains one of the most important of the earlier anticoagulant rodenticides.

Pival. Pival [2-pivalyl–1, 3-indandione], also known as pindone, is a fluffy yellow powder with a slightly acrid odour. The sodium salt (Pivalyn) is a grainy powder with only a trace of odour. Pival is only slightly soluble in water; the sodium derivative is soluble up to 0.1 mg/ml, but nevertheless it precipitates unless a suitable agent is added when it is used with many natural waters.

Pival is available as a 2.0% concentrate and a 0.5% concentrate in cornstarch. The sodium salt is available in sachets, dosed for a litre of water. Pival has a good record of performance against all three species of commensal rodents. It was found to be as effective as warfarin against roof rats and house mice, but less so against Norway rats (8).

Diphasicnone. Diphasicnone [2-diphenylacetyl–1, 3-indandionel] is a pale yellow, odourless crystalline material, nearly insoluble in water (the sodium salt is soluble). Diphasicnone is supplied as a 0.1% concentrate in
cornstarch and the sodium salt as a 0.106% concentrate mixed with sugar for use in either cereal or water bait. The concentrate is added to bait (1:19) to give a final concentration of 0.005% of diphacinone.

Diphacinone is reported to be considerably more toxic to rats, mice, dogs and cats than warfarin. Diphacinone at a concentration of 0.0125%, was reported as the most effective of the anticoagulants against roof rats. Resistance has been reported from Denmark where the compound had no effect on bromadiolone-resistant Norway rats (9).

Chlorphacinone. Chlorophacinone, \( [2(2-p\text{-chlorophenyl}-a\text{-phenylacetyl})-l, 3\text{-indandionel}] \), also known as Kozol, has been found to be more toxic to Norwegian rats and house mice than warfarin. It is available as a 0.28'4 concentrate in mineral oil, for dilution in bait to give a 0.005% concentration. A 0.2% formulated dust for use against Norway rats and house mice is also marketed. Resistance to chlorphacinone has been reported in \( R.\text{ rattus diardii} \) in Malaysia (10) and Germany (8).

Second-generation anticoagulants

Difenacoum. Difenacoum \( [3-(3-p\text{-diphenyl-1,2,3,4-tetrahydronaph-1-y1}-4\text{-hydroxycoumarin}] \) is a close relative of coumatetralyl. It was discovered as a result of the search for alternative rodenticides to overcome anticoagulant-resistant rat problems in the United Kingdom. Probably because of the novel structure of the molecule, difenacoum was toxic to Norway rats resistant to warfarin or other anticoagulants.

Laboratory and field reports on the efficacy of difenacoum showed it to be an excellent rodenticide against Norway rats, including warfarin-resistant populations (11). It is also highly toxic to \( R. \text{ rattus} \) and \( M. \text{ musculus} \). In trials against confined colonies of warfarin-resistant wild mice, difenacoum resulted in 88.9% and 97.0% mortality when offered in bait at 0.005% and 0.01% respectively for 21 days in the presence of unpoisoned food (12).

Initial field trials of difenacoum (3) on farms in England and Wales gave excellent control of warfarin-resistant Norway rat populations when used at 0.005-0.01%. No difference in effectiveness was evident and the lower concentration was recommended for field use. The first reports of resistance to difenacoum came in 1976 and by 1980 resistant Norway rat populations were established in Hampshire, England. Other reports
indicate the occasional occurrence of difenacoum–resistance in the roof rat in France and England and in house mice in the United Kingdom (13).

Brodifacoum. Brodifacoum 3–(3–[4'–bromobiphenyl–4–yl]–1,2,3,4–tetrahydronaphth–1–yl)–4 hydroxycoumarin is closely related to but more toxic to rodents than difenacoum (14). Brodifacoum even in small doses is highly toxic, more so than most acute rodenticides. Thus it is more hazardous to non–target species than the previously–described anticoagulants. Its extreme toxicity has suggested that brodifacoum be used as a "one shot" poison; that is, used in the same way as acute rodenticides. Its use in conventional anticoagulant treatments (baiting until feeding ceased) resulted in complete control when it was included at either 0.002, 0.001 or 0.005% (15). Brodifacoum is recommended at a field concentration of 0.005% against Norway rats.

Brodifacoum gave complete kills of both warfarin–resistant and nonresistant Norway rats in the laboratory at a concentration of 0.0005% in bait for two days, or at 0.001% for one day. At 0.005% complete kills of warfarin–resistant R. rattus were obtained in two–day feeding tests and resistant house mice were found to be similarly susceptible. In pen trials, using warfarin–resistant mice given alternative food, brodifacoum at 0.002, 0.005 and 0.01% in cereal bait gave kills of 98.6, 98.4 and 100% respectively and it performed slightly better than difenacoum. It has now been widely tested against different species in many countries and is generally effective against most rodent pest and reservoir species (16).

Bromadiolone. Bromadiolone, 3-[3–(4'–bromo[1,1biphenyl]–4–yl)–3–hydroxy–l–phenylpropyl]–4–hydroxy–2H–l–benzopyran–2–one], is another potent hydroxycoumarin derivative. It is a white powder, insoluble in water but soluble in acetone, ethanol and dimethylsulfoxide. Bromadiolone is highly toxic to rats and mice. It is well accepted by Norway rats at a concentration of 0.005% in bait and extremely effective against this species (LD50 less than 1.2 mg/kg). House mice are also susceptible to bromadiolone.

Bromadiolone at 0.005% in bait for one night only gave 100% mortality in test groups of wild Norway rats and house mice. Its potency, and that of brodifacoum and flocoumafen, has led to the experimental use of each of these anticoagulant poisons in restricted amounts of bait, minimal or Apulsed@baitings at intervals of five to seven days over a several–week period. In numerous field trials indoors and outdoors in the United States and Europe, it has given 70–100% control of Norway rats,
85–100% control of roof rats and 75% to near 100% reduction of house mouse populations (17).

In 1982, Norway rat populations in the United Kingdom were reported to be slightly resistant to this compound in spite of its being effective against difenacoum-resistant strains. Field tests resulted in only 51% mortality after 14 days of baiting and 83% after 35 days, values that compare unfavourably with the results obtained in trials on susceptible populations (3). Laboratory tests on mice surviving brodifacoum treatment in farm buildings showed that some individuals were resistant to bromadiolone. Similar evidence of increased tolerance to bromadiolone has been found in house mice in Canada. Bromadiolone and difenacoum resistance in Norway rats has been detected in Denmark and in house mice in Sweden.

Flocoumafen. Flocoumafen is chemically related to brodifacoum; it is 3 = (4′-trifluoromethylbenzyl-oxyphenyl-4-yl)-1,2,3,4-tetrahydro-L-naphthyl-4-hydroxycoumarin, an off-white powder, almost insoluble in water, slightly soluble in alcohols and soluble in acetone. It is recommended for use at 0.005% in loose grain baits and wax-bound cereal blocks.

The acute oral LD50 values have been determined to be 0.4 mg/kg for male laboratory R. norvegicus and 0.8 mg/kg for male laboratory M. musculus. The LD50 for male rats compares favourably with that for brodifacoum of 0.3 mg/kg, making flocoumafen the second most toxic anticoagulant to R. norvegicus. "No-choice" tests on a homozygous Welsh strain of warfarin-resistant R. norvegicus and resistant house mice killed all animals after only one day of feeding at 50 ppm active ingredient. Field trials in England using flocoumafen at 0.005% against M. musculus showed no further bait consumption 16 days after the bait was first laid and no further activity at the end of 24 days. Resistance has already been reported to flocoumafen in a Norway rat population in the United Kingdom (18).
Acute rodenticides

Acute-acting rodenticides used in commensal rodent control are grouped in three hazard-in-use categories:

1. Compounds that are highly toxic and extremely hazardous to humans and non-target animals;
2. Compounds that are both moderately toxic and hazardous to humans and non-target animals, requiring considerable care in use; and
3. Compounds of relatively lower toxicity that are the least hazardous to humans and animals.

The main characteristics of the compounds reviewed are outlined in Table 9. Apart from zinc phosphide and Calciferol, few are now used to any marked extent in rodent control. All of the compounds described have some disadvantage or another, either in relation to toxicity, acceptability, safe usage or secondary poisoning hazards. Regulations governing their use vary among countries and it is mainly for this reason and for historical reference purposes that some of the better-known compounds which are not now recommended as rodenticides are described. Some of these are still stocked in certain countries and every effort should be made to safely dispose of those likely to be toxic to humans and non-target animals.

Table 9 Characteristics of acute and subacute rodenticides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Lethal dose (mg/kg in baits)</th>
<th>% used in baits</th>
<th>Species efficacy</th>
<th>Hazard to man</th>
<th>Recommended?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>13–25</td>
<td>1.5</td>
<td>x x x</td>
<td>extreme</td>
<td>no</td>
</tr>
<tr>
<td>Bromethalin</td>
<td>2.5</td>
<td>0.005</td>
<td>x x x</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Cimidin</td>
<td>1–5</td>
<td>0.5</td>
<td>x x</td>
<td>extreme</td>
<td></td>
</tr>
<tr>
<td>Flouroacetamide</td>
<td>13–16</td>
<td>2.0</td>
<td>x x x</td>
<td>extreme</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>5–10</td>
<td>0.25</td>
<td>x x x</td>
<td>extreme</td>
<td></td>
</tr>
<tr>
<td>Strychnine</td>
<td>6–8</td>
<td>0.6</td>
<td>x</td>
<td>extreme</td>
<td></td>
</tr>
<tr>
<td>Thallium sulfate</td>
<td>25</td>
<td>1.5</td>
<td>x x x</td>
<td>extreme</td>
<td>no</td>
</tr>
<tr>
<td>Alpha-chloralose</td>
<td>300</td>
<td>4.0</td>
<td>x</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Alpha-chlorohydrin</td>
<td>165</td>
<td>1.0</td>
<td>x</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>ANTU</td>
<td>6–8</td>
<td>1.5</td>
<td>x</td>
<td>extreme</td>
<td>no</td>
</tr>
<tr>
<td>Calciferol</td>
<td>40</td>
<td>0.1</td>
<td>x x x</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Zinc phosphide</td>
<td>40</td>
<td>1.0</td>
<td>x x x</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Red squill</td>
<td>500</td>
<td>10.0</td>
<td>x</td>
<td>low</td>
<td></td>
</tr>
</tbody>
</table>

a. LD50 for R. norvegicus
b. Rn=R. norvegicus Rr=R. rattus Mm=M. musculus
c. Recommendation of WHO Expert Committee (19)
Extremely hazardous rodenticides

Arsenic trioxide. Arsenic trioxide, AS203, when chemically pure, is a fine, white powder, practically insoluble in water and chemically stable in air. The impure compound has a bitter acid taste. Early field trial reports indicated that 85–100% kills of Norway rats could be expected in poison treatments carried out after adequate prebaiting. Arsenic-treated bait is also relatively effective against roof rats but not against house mice.

Arsenic trioxide is a slow-acting poison. Death occurs in rats from a few hours to several days after poisoning when corrosion of the gastrointestinal lining results in haemorrhage and shock. Arsenic trioxide is also toxic to humans, domestic animals and birds. There is a slight degree of safety, particularly in cats and dogs, because arsenic poisoning can cause vomiting. Since arsenic can be absorbed through cuts or breaks in the skin, gloves must be worn in preparing or handling baits.

The use of arsenic trioxide as a rodenticide is not recommended by a 1973 WHO Expert Committee (19) nor is there any advantage in its use. It should not be used in plague reservoir control programme.

Bromethalin. Bromethalin [N-methyl-2, 4-dinitro-N-(2,4,6-tribromo-phenyl)-6-(trifluoromethyl) benzenamine] is one of a class of toxic diphenylamines developed as a possible replacement for anticoagulant rodenticides. Bromethalin is a highly-toxic, single- or multi-dose rodenticide. Death follows a lethal dose (at initial feeding) by two to five days. It has been shown to be effective against all three species of commensal rodents.

Technical bromethalin is a pale yellow, odourless, crystalline solid. It is soluble in many organic solvents but insoluble in water. Bromethalin is supplied as a 0.5% concentrate to be mixed as a final concentration of 0.005% in ready-to-use bait.

Bromethalin in levels as low as 10 ppm has given 100% kills of laboratory Norway rats after feeding for one night. Bromethalin apparently does not cause bait shyness in rodents. The LD50 for male and female Norway rats is 2.46 and 2.01 mg/kg, respectively. House mice require between 5.25 to 8.13 mg/kg and roof rats 6.6 mg/kg to give an LD50 dose. On free-choice feeding tests, bromethalin was well accepted by Norway rats, house mice and roof rats at 50 ppm. Bromethalin has
been found to be effective against anticoagulant–resistant Norway rats and house mice (20).

Field trial data indicate that bromethalin is exceptionally effective against Norway rats and house mice in a variety of habitats. Bromethalin treatments ranged from 7 to 30 days = duration and averaged 14 and 16 days for Norway rats and house mice, respectively. The long treatment duration is due in part to the delay in time of death after feeding. A greater–than–90% reduction in rodent numbers was obtained in most field trials.

Crimidin. Crimidin (2, chloro–4, dimethylamino–6, methylpyrimidine), also called Castrix, was developed in Germany in the 1940s and further evaluated in the United States. Partly due to its extreme toxicity (oral LD50 of 1–5 mg/kg for Norway rats), but more importantly because of the availability of sodium fluoroacetate and warfarin, it was never accepted commercially. It has had rather limited use outside the Federal Republic of Germany and Denmark (21).

Crimidin is a fast–acting poison. The symptoms shown are typical of central nervous stimulation. Following oral ingestion and a latent period of 15–45 minutes, seizures occur intermittently, terminating in death—–or in complete recovery in the case of sublethal dosing. This rodenticide is toxic to dogs and cats as well as to rodents. It has been reported to be acceptable to rats at concentrations of 0.25–1.0% in bait. The 1% concentration killed all Norway rats in two hours and the lower concentrations were lethal in less than 12 hours.

Vitamin B6 is an effective antidote against crimidin poisoning in rats and dogs, even when given after convulsions have started. The availability of this antidote places crimidin, along with phosacetim, in a unique class among the highly–toxic rodenticides.

Fluoroacetamide. Fluoroacetamide was first proposed as a rodenticide on the grounds that it was safer to manufacture and handle than sodium fluoroacetate. The onset of effect was also found to be slower than sodium fluoroacetate, resulting in ingestion of many times the lethal dose before poisoning symptoms appear. In field trials against Norway rats in sewers, fluoracetamide at 2% in bait proved to be more successful than sodium fluoroacetate at 0.25%.
Fluoroacetamide is effective against all three commensal rodent species. However, its use has been largely confined to treating rats living in sewers (22). Fluoroacetamidem at 1% in bait gave excellent control (99% and 100%) in two trials against R. rattus in sewers. The poison was incorporated in paraffin wax blocks containing rolled oats and 5% sucrose. It was reported that the application of fluoroacetamide-treated bait on several farms in the Netherlands resulted in the eradication of anticoagulant-resistant Norway rat populations.

Although fluoroacetamide is slightly less toxic than sodium fluoroacetate, it is used at a higher concentration in bait; hence, it is just as hazardous to domestic animals and humans, and subject to the same restrictions in use. Where still available, it should only be used by well-trained licensed personnel under conditions where there is no access to the baits by non-target animals. It should not be made available for general use.

Sodium fluoroacetate. This compound is also known as 1080. Early work on the monofluoroacetate compounds was done in Poland and one of the compounds discovered, sodium fluoracetate, was assigned the laboratory code number 1080 in the United States. Sodium fluoroacetate is a white odourless powdery salt which is essentially tasteless and highly soluble in water. It is chemically stable in air but has some instability in water with solutions becoming less toxic in time.

Sodium fluoroacetate is highly toxic to rats, mice, domestic animals, birds and primates. It is fast-acting, producing symptoms in rats in 30 minutes or less and causing death in one to eight hours. Rats do not detect sodium fluoroacetate in bait and by the time poisoning symptoms occur, a lethal dose has usually been consumed. In surface treatments sodium fluoroacetate is preferably used in water, since cereal or other highly-toxic baits may be displaced by rats and prove difficult to recover. It has been mainly used at a concentration of 0.025% in water or solid bait.

The use of sodium fluoroacetate should be restricted to sewers, ships and other structures where the operator can completely control the rodenticide and the environment (23). It has been used, for example, in feed mills during weekends, where the treated premises were locked, patrolled, and all bait stations accounted for. Excess poison bait, bait containers and rat carcasses should be disposed of by incineration or deep burial.
It should be applied only by well-trained personnel under conditions where there is no access to the baits by non-target animals, and should not be made available for general use.

Strychnine. Strychnine, an alkaloid, is a white, crystalline compound insoluble in water. The sulfate is slightly soluble in water. Both the alkaloid and the sulfate have a bitter taste. Strychnine and its salts are highly toxic to all mammals. An LD50 of 6-8 mg/kg is given for wild R. norvegicus. Strychnine produces violent muscular spasms, symptoms often appearing within a few minutes. Death due to paralysis of the central nervous system generally occurs in half an hour or less. Strychnine is not effective against Norway rats which find its bitter taste objectionable, but it has been used for the control of house mice (applied to oats or canary seed).

Its use is not recommended owing to its high toxicity (rapid and violent death it causes) and its stability, which can cause secondary poisoning problems in other animals. Even available, it should not be used in any plague reservoir control programme.

Thallium sulfate. Thallium sulfate, T12SO4, is a white crystalline material, stable in air and baits and soluble in water. It is odourless and tasteless when chemically pure and rodents readily accept it in bait. Thallium sulfate has both advantages and disadvantages as a rodenticide. Its ready acceptance in bait and its slow action are distinctly advantageous attributes. However, treated bait, being odourless and tasteless, can easily be eaten accidentally by birds and mammals, including humans. Other disadvantages concern its solubility, cumulative effect and hazards associated with secondary poisoning. It is readily absorbed through cuts and wounds on the skin and rubber gloves should be worn during handling and mixing in bait or water.

Thallium sulfate is highly toxic to Norway rats and most other mammals. It is slow-acting in relation to the other rodenticides and although death can occur in 36 hours it may be delayed up to six days. Thallium sulfate has been used at a 0.5-2% concentration in food or water bait.

Despite its proven efficacy and acceptability to rodents the use of thallium sulfate is prohibited on safety grounds, in many countries. A WHO Expert Committee has recommended against its use: it should not be used in any plague reservoir control programme (19).
Moderately hazardous rodenticides

Alpha-chloralose. Alpha-chloralose is a narcotic drug used for mice control. It acts by retarding metabolic processes, causing death from hypothermia. It is most effectively employed when outside temperatures are below 16°C. Poisoning symptoms occur in mice within 5–10 minutes, and feeding usually ceases after 20 minutes, sometimes leading to inadequate intake of bait and sublethal poisoning. It is most effective in cool conditions against small rodents, such as mice, which have a high surface-to-volume ratio (24). Alpha-chloralose is not recommended for use against rats. It is recommended for use in indoor environments only against house mice at 2–4% in baits. It has no role in plague reservoir control programmes.

Alpha-chlorohydrin. Alpha-chlorohydrin (3-chloro-1,2-propanediol), also known as U-5897 and EPIBLOC, is a single-dose toxicant/chemosterilant. The technical material is a light straw-coloured liquid, miscible with water and most organic solvents. It is supplied as a 1% concentration in a ground cereal grain bait mixture.

Alpha-chlorohydrin is generally effective against Norway rats, less so against roof rats and with no permanent effect against house mice and Polynesian rats. In the Norway rat, the margin between the sterilizing dose and the lethal dose is small and only the sexually-mature male rat is sterilized. It is poorly accepted by both laboratory and wild Norway rats when given a choice of baits.

Field trials of alpha-chlorohydrin have given conflicting results. Several trials reported moderate-to-high kills (70–90%), with a high percentage of the adult males made sterile and a continued population decline. In other studies, even a high level of sterility among adult male rats did not decrease female pregnancies significantly and population growth was unaffected. It is difficult to see a role for this chemosterilant in a plague control programme.

ANTU. Alpha-naphthyl-thiourea (ANTU) is a greyish-white fine powder; its bitter taste is not discernible to all people. Insoluble in water, it is highly toxic to adult wild Norway rats, dogs and pigs. ANTU is a slow-acting compound, rats dying up to 48 hours after ingestion. Death results from drowning or pulmonary oedema.
ANTU is effective against adult Norway rats; young R. norvegicus, roof rats and house mice are much less affected. Rats ingesting a sublethal dose can develop tolerance to subsequent doses as high as 50 times the normal lethal dose. This tolerance can persist for up to six months. For this reason ANTU should not be used against the same rat population more than once every 6 months. ANTU has been used at a 1–2% concentration in cereal, fish or ground meat baits and incorporated in dust (20% ANTU and 80% pyrophyllite). Field trials have been done using directly laid poison bait; in other tests the dust has been placed in burrow openings and on runways with good results.

WHO Expert Committee, noting the potential induction of bladder tumours in humans by 2-naphthylamine (a 2% impurity in ANTU), has recommended against the use of ANTU (19). Where it is still available it should not be used in plague rodent reservoir control.

Calciferol. Calciferol (Vitamin D2, activated ergosterol) has been used to control both susceptible and anticoagulant-resistant house mice and Norway rats. It is a white crystalline material, slightly soluble in vegetable oils and soluble in organic solvents such as acetone, chloroform and ether. Calciferol is unstable and degrades into less toxic products in the presence of sunlight, air or moisture. Calciferol is a common dietary supplement in homogenized milk, infants' diets, animal feed and vitamins. When taken in toxic amounts it promotes the absorption of calcium from the gut and from bone tissue. This results in a high level of calcium in the blood which is deposited in the lungs, cardiovascular system and kidneys. Death occurs in rats four to eight days following feeding on calciferol baits.

The acute oral toxicity of calciferol for M. musculus 15.7 mg/kg and for R. norvegicus about 40 mg/kg. The chronic oral toxicity over three days for each species is 8 mg/kg and 11.5 mg/kg, respectively. Calciferol is palatable to both rats and mice at a 0.1% concentration in bait. Treated bait is generally well-accepted only for the first two or three days, as poisoning symptoms then occur and feeding and drinking virtually stop.

Calciferol treatments are similar to anticoagulant treatments. Field trials with 0.1% calciferol bait against Norway rats on farms in a warfarin-resistant area in Denmark were reported successful in most cases, even though alternative foods were abundant. In a control trial against R. norvegicus on farms in Hampshire, 20–50% of the rats survived despite repeated access to the poison (25). In six field trials against house mice infesting farm buildings up to 97–100% mortality was obtained (12).
Calciferol is toxic to many mammals, including humans, but its slow action allows adequate time for antidotal measures (with cortisone and procaine calcitonin). There may be a primary poisoning hazard to birds. Calciferol can be used against single anticoagulant-resistant Norway rat or house mouse populations, but its high cost tends to preclude its use in large-scale rat poisoning operations. Because of its subacute action, there is a possibility that sublethal dosing and consequent bait shyness may develop; prebairting is recommended in situations where alternative foods are abundant.

This rodenticide is not recommended for use in rodent reservoir control.

Zinc phosphide. Zinc phosphide is a fine-greyish black powder with a definite garlic-like odour and strong taste. It is a good general rodenticide that has been widely used for several decades to control a number of rodent species. Although fairly stable in air and water, it degrades in the presence of dilute acids, liberating highly toxic phosphine gas. Zinc phosphide is moderately fast-acting: death may occur in less than an hour, most rats dying from heart failure accompanied by liver and kidney damage. It is generally used at 1–2.5% in cereal, fish, meat, vegetable or fruit baits; sometimes a fat or oil is used as a binder. The characteristics that make zinc phosphide attractive to domestic rodents (odour, taste and colour) apparently make it unattractive to other mammalian species. It has a good record of safety in use, although it is toxic to humans and domestic animals, especially chickens (26). Primary and secondary poisoning of domestic animals and wildlife has been reported. A dust mask should be worn when mixing bait to avoid inhalation of the technical powder; gloves should also be worn when applying fresh baits.

The shelf life of ready-made zinc phosphide baits in the tropics may be greatly reduced due to extreme heat and humidity, so baits should be used as fresh as possible.

Zinc phosphide may still be considered for large-scale use as an acute poison against commensal rodents (23).

Red squill. Red squill is derived from the bulb of the onion-like plant, Urginea maritima, which grows near the Mediterranean. The bulbs of the squill plant are sliced, dried and ground to a fine reddish powder.
Squill keeps well if stored in a tightly–capped can or bottle, but slowly loses its toxicity when exposed to air. A method of stabilizing the powder has been developed whereby squill is formulated to give a minimum LD50 of 500 mg/kg for Norway rats. Squill has been used as a rat poison since the Middle Ages, its toxicity depending on the presence of a glycoside (scilliroside). It kills by a digitalis–like action which causes heart paralysis and is moderately slow–acting, death occurring within 24 hours (23).

Red squill powder has a bitter taste and severe vomiting occurs after ingestion. Despite its taste, squill is fairly well accepted in bait by Norway rats, at least initially, but should not be used at concentrations exceeding 10%. Red squill is not effective against roof rats but has been incorporated in dust for house mouse control. It exhibits a differential toxicity to male and female Norway rats, with females twice as susceptible. Rats consuming a sublethal dose of the poison become bait–shy, which lasts for a long period. Field trials showed that only about 75% of rat populations were killed when squill was used in damp bait. Laboratory and field trials showed that stabilized scilliroside is a highly–effective rodenticide against Norway rats when used at a concentration of 0.015% in cereal bait (27).

While considered generally safe for use because it acts as its own emetic in animals capable of vomiting, it is extremely irritating to the skin and must be handled with rubber gloves. Its use has been banned in some countries as a cruel poison and, due to the problems associated with its use, it is not recommended as a rodenticide for use in plague rodent reservoir control.

The use of anticoagulants

When anticoagulants are used against rats or mice there is no need to prebait. It is essential to survey the infested area and record the sites to be baited. Baits should be set out under cover and protected from the weather and other animals. Adequate protection can usually be devised from materials at hand, such as bricks and planks, but bait containers are sometimes required or preferred. If it is necessary to use bait containers, they should be put down for 4–10 days before baiting begins, thereby allowing their thorough investigation by rodents.

It is extremely important to maintain surplus anticoagulant bait throughout the entire operation. When a large enough amount is used initially (25–50g for mice and 200g or more for rats at each baiting point) and quantities are replenished as necessary, the intervals between visits
can be lengthened. If the infestation is large, the baits should be checked every one to two days, at least during the early stages of a treatment, and more bait added as necessary. When no more bait is being consumed, generally after about two or three weeks, the excess bait should be removed. Dead rats or mice recovered are burned or buried. All obvious rodent traces should be removed and a survey made for fresh traces a few days later. If new traces are found, a different palatable bait should be tried. With rats it is not normally necessary to change the anticoagulant at the same time, although this can be done if another one is at hand. In the case of surviving mice, it is best to adopt another control method, either an acute rodenticide in a different bait or traps.

Typically, a treatment against rats involves surveying the infested areas and leaving about 200g of anticoagulant bait at or near sites where rat traces are found. Each site is then revisited on the second, fourth and seventh days of each seven-day cycle. The baiting sites where feeding is active are recorded on work sheets and the schedule of visits is continued until no more bait is consumed.

The second generation anticoagulants have proved so lethal to susceptible rats and mice on one feeding that an alternative baiting strategy has been developed, known as a pulsed or minimal baiting. The strategy is to use a large number of small baits (5–15g) in a once every 5–7 days baiting schedule, placing the small baits at all sites where large quantities of first-generation anticoagulants normally would have been laid. The purpose is to minimize the possibility of excessive bait consumption by any one rodent. This also exploits the extreme toxicity of the newer rodenticides by using minimum amounts of bait to achieve a satisfactory kill, instead of the saturation amounts (200 to 500g) laid when using first generation anticoagulants. The effect of this baiting strategy is that after one baiting up to 75% of the initial population should be dead or dying after one week: a second "pulse" or baiting reduces the surviving population again by 75% and a third "pulse" after 14 days gives a final mortality leading to near-extinction (98.5–100% mortality). Field trials using "pulsed" baiting methods have shown its effectiveness in a variety of habitats. Its advantages are that there is a considerable saving in both labour and bait costs to achieve the same level of control as saturation baiting. The safety for primary and secondary non-target species in laying much less bait per unit area is another consideration.
The application of acute rodenticides

When using an acute rodenticide it is essential to first survey the infested area and number the baiting points to be used. Poison bait is generally better accepted and an improved kill obtained by laying prebait for a few days beforehand. The prebait should be the same as that used later in the poison treatment. Small amounts of prebait, about 50–100g for rats and 10g for mice, should be placed wherever traces of rodents are found—close to burrows, nests and runways—to encourage feeding on the bait before other food sources are reached. Baits should be set out under cover, using containers where necessary, in a manner similar to that employed with anticoagulants. While prebaiting may not be practical in a plague reservoir control programme, if an effective flea vector control has been carried out then time may be available for prebaiting.

Prebaiting usually achieves its purpose in four to eight days; at the appropriate time all uneaten prebait should be removed and the acute poison bait laid. Generally, only one-fourth to half as much poison bait is needed at each site as was eaten on the last day of prebaiting. The poison baits should be maintained for one or two nights. During the poison treatment, particularly during the first night, the area should be disturbed as little as possible. At the end of the treatment period, the uneaten poison baits and any dead rodents should be collected and disposed of by incineration or deep burial. Burrows should be filled in, all obvious traces of rodents removed and, a few days later, the area re-inspected for fresh traces. Where rodents still appear to be active a different prebait should be laid down and if any is eaten in a day or two a second poison treatment should be applied, using a different poison.

The use of rodenticidal dusts, gels and grease

The use of rodenticides in dusts or other contact formulations in rodent control is an alternative approach to toxic baits. Their main use is in cases where poison acceptance or other baiting problems arise. This control method relies upon rodents coming (inadvertently) into contact with the poison in the form of a dust, as a liquid on a wick or in a gel or grease formulation. The poison sticks to the rodents' fur and feet and is ingested during normal grooming. Advantages of this method of control are that affected rodents do not suspect the source of illness resulting from ingestion of the poison, nor do they avoid normal travel routes or change their feeding habits.
Rodenticidal dusts usually contain a considerably higher concentration of the toxicant than that used in food baits because contaminated rats or mice consume considerably less poison during grooming than eating. This makes the use of dusts uneconomical since excess dust must be laid although only a small amount will be consumed. Dusts must be used with great care to avoid contaminating food supplies and killing other non-target species.

Dusts can be applied as patches on runways or other areas frequented by rodents, around the openings and on the floors of bait containers, or blown into burrows, between walls or into other spaces occupied by rodents. They can also be applied inside plastic or cardboard tubes, placed on runways or along walls. It is usual to lay poisonous dust in isolated patches about 5cm wide, 0.5m long and 3mm thick inside buildings, along walls, in corners and in areas well away from food. Further applications should be made as necessary during the course of a treatment. The patches should be examined and smoothed every few days to determine whether they are still being crossed by rodents. Although DDT dust was extensively used at one time for the control of mice its use in most countries is now banned. In Europe anticoagulant dusts have been used extensively, even against rats in refuse dumps. Dusts surrounding poisoned water bait have been used successfully against mice.

Fumigants

Fumigants can be used to kill rodents and their ectoparasites living in inaccessible areas in buildings, ships and in burrows in the soil. They are generally fast-acting but their use can be quite dangerous both to the person applying them and to other persons and animals in the immediate area. They should only be applied by persons well-trained and experienced in their use. Fumigants with a molecular weight of less than 29 tend to rise to the top of the burrow systems when used in soil. Factors which can be important in burrow fumigation are the moisture content of the soil and its particle size. Table 10 gives characteristics of some commonly used and available fumigants.
Table 10 Characteristics of rodent fumigants

<table>
<thead>
<tr>
<th>Fumigant</th>
<th>Molecular weight</th>
<th>Action mg/litre</th>
<th>LD50 (rat)</th>
<th>Flammable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen cyanide**</td>
<td>27</td>
<td>C. A.</td>
<td>0.4</td>
<td>yes</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>28</td>
<td>C. A.</td>
<td>(0.35% conc)</td>
<td>no</td>
</tr>
<tr>
<td>Hydrogen phosphide</td>
<td>34</td>
<td>I.</td>
<td>0.8</td>
<td>yes</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>44</td>
<td>S. A.</td>
<td>(20-30% conc)</td>
<td>no</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>64</td>
<td>I.</td>
<td>1.6</td>
<td>no</td>
</tr>
<tr>
<td>Methyl bromide</td>
<td>95</td>
<td>I.</td>
<td>3.6</td>
<td>no</td>
</tr>
<tr>
<td>Chloropicrin</td>
<td>164</td>
<td>I.</td>
<td>2.0</td>
<td>no</td>
</tr>
</tbody>
</table>

* C.A.=chemical asphyxiant; S.A.=simple asphyxiant; I=irritant
** Produced from Calcium cyanide

Calcium cyanide. Ca(CN)₂ is available in granular and powdered form and when blown or placed into a burrow, releases hydrogen cyanide gas (HCN). It should only be used outdoors. As the gas is lighter than air, it gathers in the upper part of the burrow system and thus all burrows into which the calcium cyanide has been placed must be sealed quickly. It has frequently been used at quarantine stations for the deratization of vessels. It should only be applied by specially-trained personnel who are aware of the precautions that must be taken in its use. Due to its very high toxicity to humans and all other non-target animals it should not be made available to untrained personnel.

Fumigation with cyanide should always be done by more than one operator, as a person working alone could be exposed and die without assistance. Ampoules of amyl-nitrate should be carried during use, in case of accidental poisoning. Cyanide fumigation should not be used in plague reservoir control programmes.

Hydrogen phosphide. This fumigant, also known as phosphine, is sometimes used to fumigate burrows of R. norvegicus, B. bengalensis and N. indica in parts of Asia and elsewhere. One or two tablets are placed into each burrow entrance and the openings are then closed with soil. The speed of liberation of the gas in burrow systems depends upon both soil moisture and temperature levels but it normally takes several hours to fumigate a burrow. Tablets containing this rodenticide must be handled with gloves.

Carbon monoxide (CO) from petrol engine exhaust fumes can be used to kill rats in outdoor burrows. A hose is attached to the exhaust pipe and the other end is inserted inside the burrow. All of the burrow openings are then sealed and the engine run for about five minutes. Precautions must
be taken to ensure good ventilation of the vehicle since carbon monoxide might be forced back along the exhaust system and leak into it.

Control by CO is usually not very efficient and should not be encouraged as a rodent control method in general, nor in plague reservoir control programmes.

Sulfur dioxide (SO2) is a colourless, non-flammable gas with a strong suffocating odour. It is intensely irritating to the eyes and to the respiratory tract. Sulfur dioxide was formerly used to fumigate rat-infested ships but now it is mainly used in the preservation of fruits and vegetables. Sulfur mixed with potassium nitrate (saltpetre) and a small amount of tallow constitutes the so-called smoke ferrets; the smoke produced on burning has been used to bolt rats from their burrows when they can be killed by force.

The use of SO2 as a general burrow fumigant is not recommended for use in plague reservoir control programmes.

**Village rodent control**

Control of rodent populations in villages is complicated by the constant infestation by native or commensal rodents from surrounding fields or adjacent vegetable gardens. Large-scale reduction of the rodents living in and around the village structures frequently leads to invasion of the village habitat by field rodents. Invasion may also occur on a seasonal basis when crops are harvested. Thus, control methods in villages must consider potential immigrant rodents and may have to be scheduled according to a community’s cropping and harvesting practices. For plague reservoir control, a high degree of control of rodent populations in and around structures is required. Once this has been accomplished villagers should be encouraged to carry out rodent-proofing to prevent or reduce re-entry.

There is no effective way to rodent-proof the open houses common to many areas in the tropics, so it is virtually impossible to keep rats and mice from seeking harbourage in residences and shops. In Africa, southern Asia and the Pacific, village structures are infested by one or more species of commensal rodent. Under these conditions it important to at least provide rodent-proof containers for stored foods.
In carrying out treatments to eliminate rodents, it is essential to survey the entire village area for signs of rodents. Plots of vacant land, outhouses, latrines and refuse heaps as well as houses and stores must be checked. Records of the survey and of each treatment (amount of poison bait used, length of treatment, labour and transport costs and so on) should be kept to evaluate the success and cost.

In addition to poisoning, traps can be used to deal with small infestations, especially in areas subject to repeated invasion. Traps should be used in adequate numbers and maintained in good operating condition. All buildings and places frequented by rodents should be trapped, paying particular attention to latrines, cooking houses, food stores, nearby undergrowth and rubbish piles.

Conclusions

It must be emphasized that the efficient and safe control of plague rodent reservoirs requires well-trained personnel and an efficient organization. Most countries have rodent control organizations. Their personnel should receive additional training in the control of rodent reservoirs of plague before they must take the responsibility of carrying out reservoir and vector control measures. They should receive specific training in methods to protect against exposure to infection, and in the safe disposal of the bodies of rats poisoned in plague-endemic areas. Professional supervision of plague reservoir control is essential. The control of rodents in rural areas is a more difficult undertaking. In areas where plague is endemic, surveys should be carried out to ascertain the most important rodent species, their importance as reservoirs and the best methods to control them well before it becomes necessary because of an outbreak of the disease.
References


Plague pandemics of past centuries illustrate how quickly plague can spread through human populations when medical services and control measures are inadequate. Although no one expects to again see the massive deaths observed during past pandemics, plague continues to pose a threat to human health in certain regions of the world where natural foci still exist. Effective plague prevention and control programmes require up-to-date information on the incidence and distribution of the disease. The best means of gathering this information is through a surveillance programme that collects, analyses, and interprets clinical, epidemiological, and epizootiological data on plague. Surveillance should identify cases and epizootics as quickly as possible so that steps can be taken to control disease spread. Systematic collection of surveillance information over many years will provide information that can be used to:

1. predict areas where future human cases and rodent epizootics may occur;
2. identify the most common zoonotic sources of human infection;
3. identify the most important rodent and flea species maintaining a given focus of *Y. pestis*;
4. indicate the hosts and flea species that should be targets for control measures;
5. assess the effectiveness of plague prevention and control measures;
6. identify local ecological factors or human activities that may result in increased plague exposure risks for humans; and
7. detect trends in the epidemiology and epizootology of plague in a given region.

Many years may elapse between the occurrence of isolated cases or epidemics. Continuous surveillance of rodent and vector populations is therefore important even during periods when no human cases are reported. This chapter describes a comprehensive plague surveillance...
programme including human, rodent and vector surveillance. The unique needs and resources of each country will determine the actual organization of national surveillance programmes.

**Human surveillance**

**Reporting human cases**

At present, plague is one of only three infectious diseases subject to the International Health Regulations, which stipulate that all confirmed cases of human plague be investigated and reported through appropriate authorities to the World Health Organization. Whenever clinical symptoms or laboratory results suggest that a patient is infected with *Y. pestis*, the suspect case should be reported immediately. This will allow public health authorities to:

1. advise on treatment and management of human plague cases;
2. initiate efforts to identify the source of infection;
3. determine the extent of any epizootic activity;
4. assess the potential for additional human cases;
5. disseminate information on plague to health care personnel; and
6. implement emergency prevention and control measures.

Prompt reporting is especially important for cases of pneumonic plague because this form of the disease can be transmitted directly from person to person via infectious aerosols. Emergency procedures as described below must be implemented immediately to prevent further human infections.

Local physicians and other health care workers must be familiar with the symptoms of plague and consider it in the differential diagnosis. If a patient's symptoms suggest human plague, samples should be collected for diagnostic confirmation at a microbiological laboratory. If local laboratory facilities are inadequate, health care workers should know where to send samples for bacteriological or serological confirmation. The plague surveillance programme should be prepared to provide this information along with medical and epidemiological assistance.
Increasing plague awareness and knowledge in the health care community

Because of personnel turnover or lack of prior training, it cannot be assumed that health care workers, laboratory personnel and other public health authorities in plague-endemic areas are familiar with plague diagnosis and treatment. It is therefore important that a plague surveillance programme ensure that members of the local health care community are aware of the possibility of cases of plague occurring. This can be accomplished through brief training courses, plague surveillance newsletters, brief notes in other health-related newsletters or periodic contact with other health personnel.

Active surveillance

Following identification of a suspect case of human plague, surveillance personnel should immediately determine whether other cases exist or have occurred recently in the same vicinity. Hospital and clinical records from areas near where the case occurred should be reviewed and local health care providers should be interviewed to identify other potential cases. If possible, blood and other appropriate samples should be obtained from survivors who are considered to be potential cases to determine whether these persons are infected with or have antibody against Y. pestis. If possible, blood samples should be obtained from other family members or likely contacts. Record reviews and interviews with health care personnel should also be done when plague is identified for the first time in a region's animal or flea populations. In such situations, human cases might have occurred recently but may have been misdiagnosed or gone unreported (1). While performing the above activities, surveillance personnel should brief local health workers on plague diagnosis, treatment, prevention and control and explain the activities of the plague surveillance programme (1).

Standardized reports

Human case reports should be standardized so that whenever possible the same information is recorded for each case. This will result in a database that can be combined with rodent and vector surveillance data to design better plague prevention and control strategies. The reporting form should include core patient information, clinical observations and treatment, laboratory results and results from epidemiological and environmental investigations.
Core information

The following core information should be collected for each patient: age; sex; occupation; residence, including country; place of exposure if known; source of exposure if known; date of onset; clinical presentation (bubonic, septicaemic, pneumonic); treatment; recovered or fatal; possible exposure of others in contact with the patient; and preliminary classification of the case as suspected, presumptive or confirmed.

Case definition

Suspect cases are those cases that lack laboratory confirmation but where the patient has symptoms consistent with plague. Plague should also be suspected when patient specimens contain Gram-negative bacteria that exhibit bipolar staining with Wayson or Wright's Giemsa stains. Cases may be considered presumptive when immunofluorescence assays on patient samples are positive, or when a single serum sample is positive. Cases are classified as confirmed when Y. pestis has been isolated and identified by cultural characteristics, biochemical characterization and specific bacteriophage typing, or when there is a four-fold rise in antibody titres against Y. pestis for paired acute phase and convalescent phase serum samples. The upgrade of a case from suspect or presumptive to confirmed should be noted on the report form along with the date of confirmation.

Clinical observations and treatment

Whenever possible, additional information on the clinical course and treatment of the disease should be recorded, including: antibiotics administered; dosage given; duration of treatment; elapsed time between the onset of symptoms and initiation of antibiotic therapy; unusual observations or complications (such as the occurrence of skin ulcers, insect bites, disseminated intravascular coagulation, meningitis, other); presence of cough; productivity of cough; intensity and duration of fever; and location and size of buboes.

The last sign (location of buboes) can provide useful information on the likely modes of transmission. For example, the presence of an inguinal bubo is strong evidence that the patient was infected by flea bite.

Laboratory analyses

The report should document all relevant laboratory work including: types of samples analysed (blood, sputum, bubo aspirate, serum, other); dates of sample collection; light and fluorescence microscopy results; chest X-ray results; haematological findings; bacteriological results; results of serological tests; and autopsy results for fatal cases.
Additional epidemiological and environmental information

An epidemiological investigation should be performed for each human case to determine the source of infection and the risk of additional human cases. Reports of these investigations should include: 1) a complete history of the patients' activities and travel during the incubation period of the infection; 2) results of field studies to determine which animal and flea species are likely sources of infection or pose a continuing threat to humans (surveillance techniques for rodents and fleas can be found in later sections of this chapter); 3) proximity of infected rodents and fleas to human dwellings or workplaces; 4) estimated number of people involved in activities that place them at high risk of plague infection; and 5) information on possible exposure to *Y. pestis* infection of patient contacts (especially important for pneumonic plague cases).

Epidemiologic follow-up of pneumonic plague cases

When there is clinical evidence of plague pneumonia, it is important to document the efforts that were made to isolate pneumonic plague patients and protect health care personnel (2). The length of time a patient remained in isolation should be recorded, along with the results of periodic sputum tests. These tests are done to determine whether *Y. pestis* is present in the patient's sputum (patients should remain in isolation until test results are negative). Attempts should be made to identify and treat prophylactically individuals who had contact with the patient during the incubation period of the infection. If possible, throat swabs or serum samples should be collected from known patient contacts. Probable contacts can be ascertained from interviews with the patient, family and friends. A history of the patient's travel and activities will suggest possible contacts. Even in the absence of plague pneumonia, it should be determined whether other persons with similar exposure histories have contracted plague. The results of tests performed on samples from patient contacts should be recorded.

Ecological and environmental observations

A basic understanding of the area's landscape ecology is useful for predicting the future course of epizootics and identifying areas of high risk for humans. Information should be collected on predominant vegetation types and the amount of local land surface covered by each vegetation type, roads, railways, airports, and seaports, land use patterns (agricultural, residential, industrial, other), types of dwellings present and whether these dwellings and associated food storage areas or other man-made sites provide food and harbourage for rodents.
Flea and rodent control programmes implemented as a result of human plague case investigations should be described with an evaluation of their success.

**Surveillance of rodent populations**

Rodents are the primary vertebrate reservoirs of plague, and nearly all human cases are associated with rodent epizootics. Surveillance programmes that monitor plague activity in susceptible rodent populations alert public health authorities to increased human plague risks, thus allowing prevention and control programmes to be implemented before human plague cases occur. Identification of plague in rodent populations also serves as a warning that human cases may appear and require treatment and follow-up.

**Rodent sampling techniques**

The most common techniques for monitoring plague in rodent populations (discussed in detail under vector control) include:

1. collecting and examining dead rodents;
2. monitoring activity among plague-susceptible rodents;
3. trapping rodents for population data, serum, tissue samples and ectoparasite collections; and
4. conducting serosurveys of carnivore populations that consume rodents.

**Recruitment and training of personnel**

The techniques of rodent surveillance are relatively simple, but the quality of samples and data obtained using these methods is likely to be higher if the persons performing them receive adequate training. If there is a shortage of trained personnel, it may be possible to enlist the help of other local health authorities, biologists, game managers, veterinarians, animal damage control personnel, agricultural officials, nature park employees, or other individuals working outdoors in plague-endemic areas. These persons often have some appropriate background training and are likely to be familiar with the area where sampling is to take place (3). If local surveillance personnel and volunteer assistants have not received prior training, they should be taught:

1. rodent and ectoparasite collection techniques;
2. methods for collecting, preserving and shipping blood, tissues, carcasses and ectoparasite samples;
(3) measures for safely handling rodents and collecting specimens;
(4) how to identify local rodent species; and
(5) methods of preparing voucher specimens to verify field identification of rodents.

Each of these issues is discussed below or in the flea surveillance section of this chapter.

Safety concerns and animal handling techniques

Some collection techniques require surveillance personnel to handle live rodents or rodent carcasses. Personnel must be taught how to protect themselves from infection with plague or other rodent-borne zoonoses. Collectors should always wear gloves when handling animals. Before handling, animals should be anaesthetized, firmly restrained or humanely killed to reduce the danger of pathogen transmission via scratches or bites. Animals can be anaesthetized by placing them in a jar containing an absorbent cotton pad soaked with a suitable anaesthetic, such as halothane or metofane (Fig. 1). Ether should not be used for field work because of the danger of accidental explosions. Chloroform also is not recommended because of its presumed carcinogenicity and the possibility that it might interfere with attempts to isolate plague bacteria from sample materials (4). Animals also can be anaesthetized by intramuscular injection of a 1:10 mixture of Ketamine and Xylazine, respectively. Dosage will vary with the size and species of animal, but the above Ketamine-to-Xylazine ratio used at a dosage of between 10-150 mg of Ketamine per kilogram of body weight should adequately anaesthetize most small animals (5).

Animals can also be restrained in a thick cloth bag for bleeding by cardiac puncture; the heart can be located by palpation. The latter technique does not require anaesthesia, but care must be taken to maintain control of the animal. Following bleeding, the animal can be killed by cervical dislocation or other humane means.

It may be appropriate for rodent collectors and animal processors to apply insect repellents or insecticides to clothing as a means of reducing the risk of flea bites. The most commonly used repellents are those containing N,N-diethyl-m-toluamide (DEET) as the active ingredient. Insecticial sprays, such as those containing permethrin, can also be applied directly to clothing and are effective against fleas.
Whenever hantaviruses or other rodent-borne haemorrhagic fever viruses are likely to be encountered, workers might be required to take precautions against infection via direct contact and aerosols. Recommendations for plague surveillance workers and others removing rodents from traps in such a situation include wearing rubber or plastic gloves and respirators fitted with filters to prevent aerosol transmission of hantaviral agents. Individuals collecting traps likely to be contaminated with such viruses should wear gloves, but are not required to wear respirators. All traps and processing equipment should be disinfected after use.

Supervisors of collecting teams might also consider recommending vaccination for their employees as an additional protection against plague; however, any protection is likely to be short-lived and frequent booster injections may be necessary to maintain presumably protective titres. Surveillance personnel can also carry a supply of prophylactic antibiotics which should be taken if the worker is bitten by fleas, exposed to potentially infectious aerosols, or scratched or bitten by potentially plague-infected animals.
Collection of dead animals after die-offs and ratfalls

One of the simplest techniques for monitoring plague in rodent populations is to collect dead rodents and examine the carcasses for evidence of plague infection. Carcasses of other plague-susceptible animals, such as lagomorphs (hares and rabbits) and domestic cats should also be collected for analysis. Plague surveillance personnel always should be alert for signs of a rodent die-off or ratfall and the public should be encouraged to report sick or dead rodents observed near their homes or work places. Where poisoning can be ruled out, authorities should report rodent die-offs as soon as possible to verify local reports and collect any dead rodents for laboratory analysis.

Identification of Y. pestis in tissues of dead animals

Y. pestis can be detected in tissues of dead animals by direct immunofluorescence assay, agglutination, enzyme-linked immunosorbent assays, or by isolating the organism in pure culture. Direct immunofluorescence assays have many advantages over other methods for routine plague surveillance. When performed by an experienced technician using appropriate controls and plague-specific conjugates, the test has high specificity and sensitivity as well as specimen handling times that are often less than two hours (6,7). The rapid specimen handling times of direct immunofluorescence assays make them especially useful for emergency situations because local officials can be notified of positive test results on the same day the specimens are received and use the results to make timely decisions on plague control strategies. Another advantage of immunofluorescence assay is that Y. pestis can be detected in carcasses long after an animal has died. Even when animals have been dead for many days to weeks, it is possible to detect plague antigen in moist marrow samples taken from long bones such as the femur. Fraction I-specific fluorescent antibody conjugates can be prepared by hyperimmunizing rabbits with purified Fraction I antigen of Y. pestis. The resulting high titre antibody preparation is then conjugated to a fluorescent label by standard methods (8).

A definitive diagnosis of plague infection of rodents relies on culturing Y. pestis from tissues, but isolation is more time-consuming than direct immunofluorescence and may not be necessary in situations where reliable immunofluorescence assay is available. Samples should be processed for isolation of Y. pestis when they are collected from poorly-characterized foci or areas where plague has not been previously identified. Samples from well-characterized areas should also be processed periodically for isolation in order to verify the accuracy of direct
immunofluorescence results and to monitor the variability of plague strains within the foci. Direct isolation of Y. pestis from the tissues of decaying carcasses can be complicated by the presence of other microorganisms. For this reason, it is often advisable to first inoculate laboratory mice or guinea pigs subcutaneously with a suspension of tissues from the dead animal. If the sample suspension contains viable Y. pestis the animals will become infected and provide a source of Y. pestis-infected tissues free from most of the original contaminants. Suspensions for inoculation can be prepared in a mortar and pestle using physiological saline (0.85%) and a small amount of sterile sand to aid the grinding process. Tissue samples (such as liver or spleen) can be aseptically removed from infected laboratory animals and streaked on culture plates for isolation of Y. pestis.

§ shipping and labelling specimens

Depending on the materials available and the time required to ship specimens to the laboratory, rodent carcasses or tissues can be shipped on wet ice, dry ice (frozen CO), freezer packs or in special shipping containers filled with liquid nitrogen. If these are not available samples (such as liver or spleen) can be taken from carcasses and sent at ambient temperature in Cary-Blair transport medium (9,10). All specimens should be clearly labelled with waterproof labels and indelible inks. Each specimen should be accompanied by a data sheet stating: 1) specimen type; 2) where it was collected; 3) who collected it; 4) what laboratory tests are being requested; and 5) to whom the results should be reported. If an animal has died only recently, it may also be possible to collect fleas from the carcass as described below.

§ observations of rodent colonies and signs of rodent activity

Another useful rodent surveillance technique is to map and periodically check the area for visible signs of activity among plague-susceptible rodents, especially in areas where colonies of diurnal burrowing rodents are abundant. If these animals are normally visible during fair weather, their disappearance following a plague epizootic is usually obvious. The number of animals observed at each site over a set interval of time should be recorded. If it is suspected that a plague epizootic has occurred recently or is still underway in one of these colonies, the area should be inspected for dead animals. Other telltale signs of a rodent die-off include carrion-feeding flies at burrow entrances, bad odours near burrows and poorly-maintained burrows. Potentially infected fleas can also be collected from dead animals or abandoned burrows using techniques described in the vector surveillance section of
this chapter. Other types of rodents also produce visible signs of activity, including droppings, runways, nests, burrows, gnawed objects, or partially-eaten food. Persons familiar with these signs or structures often are able to estimate the age of these signs or structures with reasonable accuracy. This information can be used to determine the level of current rodent activity in an area.

**Trapping rodents**

Systematically trapping and examining rodents is important to determine: 1) the potential plague hosts in an area; 2) the number and kinds of fleas infesting these animals; 3) whether new rodent species have entered an area; and 4) whether the abundance of resident rodent species has changed significantly since the previous trapping period.

Trapping is also a source of basic population ecology data, including: 1) population densities (relative or absolute); 2) age structures and reproductive status of rodent populations; 3) rodent habitat preferences; and 4) local distribution. Estimates of absolute densities of rodent populations (number of animals present per unit area) can be made using mark-recapture techniques but these are not practical for most plague surveillance programmes. Percent trap success, a relative density estimate is more easily obtained. This quantity refers to the number of animals caught per unit effort, and equals the number of rodents caught divided by the number of trapping periods, divided by the number of traps set per period, multiplied by 100. 

\[
\text{percent trap success} = \frac{\text{no. animals caught}}{\text{no. trapping periods} \times \text{no. trap sets per period}} \times 100
\]

**Trap selection and trapping techniques**

Many types of traps are available for capturing small mammals, but some designs are more suitable than others for collecting certain kinds of samples. Although more expensive, live traps are preferable to snap or dead fall traps for capturing hosts for flea collection because fleas tend to leave a dead host’s body as it cools. Live traps can also be used to capture animals for tissue and blood samples. Live traps are typically rectangular box-shaped devices with hinged doors with spring mechanisms for shutting the door once an animal has entered the trap. Most models have walls made of either wire mesh or sheets of aluminum or light-gauge (usually galvanized) steel. If large numbers of simple traps are required, they can be constructed locally. Traps can be baited with grains, peanut butter, canned pet food, fish or other bait attractive to a particular rodent species.
Figure 2: Typical wire mesh live trap designed to capture medium-sized mammals. The white material in the trap is upholstery cotton, added to prevent hypothermia during cold weather.

Figure 3: Aluminum live traps used to capture small mammals. The first two traps are collapsible (the trap on the left has been closed for storage). The trap on the far right is a noncollapsible style that is sturdier but less easy to transport and store.
Snap traps are less expensive than live traps and are often used to capture animals for collection of tissues and fleas. When these traps are used for flea collection, however, they should be checked every couple of hours or so to reduce the likelihood that fleas will leave the dead host’s body as it cools. A common snap trap (Fig. 4) usually kills captured animals, but occasionally larger rodents are not killed immediately or are only slightly injured. Such animals can drag snap traps a considerable distance, making them difficult to find. For this reason, snap traps should be attached to a wire staked to the ground. Bait preparations similar to those described above for live traps are acceptable; the actual bait selected depends on the species of rodent being trapped.

Figure 4: A typical snap trap used to capture rodents. These traps are relatively inexpensive and can be used to collect a variety of animals. The trap in this picture has been baited with peanut butter.

Placement of traps

Traps may be set at specific sites where there are burrows, nests, runways, or other evidence of rodent activity, or they can be set along transects with 10-20 traps (or more) spaced at approximately 20m. intervals along each transect. This method allows a variety of habitats to be sampled and gives a good indication of the area’s rodent diversity. Trapping grids also can be established, with the intervals for trap spacing based on local conditions.
Rodent serosurveys

Serosurveys have at least two important advantages over attempts to isolate Y. pestis from tissues of captured rodents. First, the likelihood of detecting plague antibodies in rodent sera is many times higher than recovering an isolate of Y. pestis from tissues taken from captured animals (12). Second, the results of rodent serosurveys are much less likely to be affected by seasonal factors than are attempts to isolate Y. pestis from rodent tissues. Rodent serosurveys are most useful when a significant percentage of the affected rodent population survives plague infection and later seroconverts. For example, the percentage of seropositive individuals among resistant populations of California voles (Microtus californicus) can exceed 90% during the months following an epizootic (13,14). Other rodent species are poor candidates for serosurveys because few individuals survive epizootics and later seroconvert. This is true for the North American sciurid species, Cynomys gunnisoni, which may experience greater than 99% mortality during epizootics (3).

Collecting and shipping blood samples for serology and isolation attempts

Blood for serology can be collected from rodents by a variety of techniques, including cardiac puncture and retro-orbital bleeding from the eye. Blood for isolation attempts can be collected aseptically from animals by cardiac puncture. Blood samples collected for isolation of Y. pestis can be shipped directly in sterile, sealed tubes without the addition of transport media or freezing, provided the temperature and time required for shipping do not become excessive. All tubes should be clearly labelled and accompanied by a data sheet containing information similar to that listed in the above section on shipping dead animals.

Rodent sera can be analysed by various techniques, including complement fixation, passive haemagglutination, latex agglutination and enzyme immunoassays (13,15,16,17,18,19,20,21,22,23,24,25,26,27,28). Samples for serological analysis can consist of either whole sera or blood spread onto filter papers or Nobuto strips (Fig. 5) (29). The latter are especially useful for field studies because there is no need for refrigeration, centrifuges, removal of sera from cell fractions, nor for other special equipment or handling. After the blood-soaked strip has dried it is placed in an envelope with the appropriate data and mailed to a laboratory for testing (Fig. 5). The antibodies can then be eluted from the strip into a buffer solution and titrated by passive haemagglutination or other serologic techniques (29).
Analysis of tissues and ectoparasites of trapped animals

If animals are to be killed it is possible to take tissue samples for immunofluorescence assay and/or attempts to isolate Y. pestis. In most instances, however, analyzing tissues from apparently healthy animals is time-consuming and unlikely to yield a significant number of infected individuals. Greater effort should be placed on obtaining serum and fleas from the trapped animals (see below for flea collection techniques).

Recording data from trapping studies

Standardized forms should be used to record data from trapping studies. The most important data for each animal are: 1) place of capture; 2) species type; 3) type of samples taken (tissues, serum, ectoparasites, other); 4) age, sex and reproductive status; 5) standard measurements of the animal's weight, total length, hindfoot length, ear and tail length; and 6) a description of the trap site and surrounding habitat. It should be noted whether or not some specimens were kept for confirmation.
Carnivore serosurveys

One of the most powerful techniques for detecting evidence of plague activity is to collect serum samples from carnivores that consume rodent prey or are likely to scavenge fresh rodent carcasses (3, 20, 22, 31, 32, 33, 34, 35, 36, 37). This technique is much more sensitive than rodent serosurveys or attempts to isolate *Y. pestis* from rodents. Whenever plague-susceptible rodents constitute a major portion of a carnivore's diet, sampling sera from a few of these carnivores is roughly equivalent to sampling hundreds of rodents for plague infection. Carnivore serosurveys are especially recommended when vast areas must be sampled, plague has not previously been detected in local rodent populations, and epizootics have not occurred in local rodent populations for many years and it is suspected that plague may have disappeared from the area.

Although some carnivore species, such as those belonging to the cat family (*Felidae*), often die from *Y. pestis* infection, others apparently suffer little, if any, illness. Wild and domestic dogs and their relatives (family *Canidae*) typically survive plague infection and develop antibodies that can be detected for as long as six months (3). Seropositivity has also been reported for members of other carnivore families, including *Mustelidae*, *Procyonidae*, *Ursidae* and *Viverridae* (3, 17, 37).

Typically a small percentage of carnivores will be seropositive in plague-enzootic areas at any given time. A sudden increase in the percentage of seropositive animals indicates that there is ongoing or recent epizootic activity in the area's rodent populations. Such a sudden rise in antibody serves as an early warning of increased human risk of plague infection. For example, canine serosurveys conducted on the Navajo Indian Reservation in the southwestern United States demonstrated that when the percentage of seropositive dogs increased significantly there was heightened epizootic plague activity among local rodent populations and a corresponding increase in the number of human cases reported (3). Another advantage of carnivore serosurveys conducted in temperate climates is that sera can be collected early in the year before rodent epizootic activity reaches its peak. A greater-than-normal number of positive carnivore serum titres indicates that the risk of epizootic rodent plague will probably be higher than usual in the months to come and should serve as a warning of potentially-higher plague risk for humans during the upcoming plague season.
Follow-up investigations for carnivore serosurveys

Whenever carnivore serosurvey results suggest the presence of plague in a particular area, surveillance personnel should perform site investigations within the suspected home range of these carnivores to determine the location of infected rodent populations and whether the epizootic poses a threat to local human populations. These surveys should include collection of rodent and flea samples for laboratory analysis and visual inspection for dead animals and signs of rodent activity.

Sources and collectors of carnivore serum samples

Wild carnivores can be collected by trapping or shooting. Once these animals have been collected, blood samples can be obtained by cardiac puncture of recently killed or anesthetized animals, bleeding from large veins, or opening the body cavity to gain access to blood in this cavity or the heart. Less than 0.2ml of blood are required to coat a Nobuto strip with sufficient blood for serologic testing (Fig.5). Valuable samples can also be obtained from domestic dogs that roam freely and consume live rodents or fresh rodent carcasses. Live domestic dogs can be bled from veins in the forelegs or hindlegs without adverse effect. Dogs should be properly restrained and muzzled, or anesthetized prior to bleeding to prevent them from biting handlers.

Serosurveys using animals other than rodents or carnivores

Large- to-medium-sized mammals other than carnivores can be used as sentinel hosts under some circumstances (36,38). For example, feral swine have proved to be useful sentinel hosts in some areas of California in the United States (36).

Surveillance of vector populations

Fleas are the primary vectors of plague and knowledge of local flea species and their hosts is essential for estimating risks of human plague infection and designing specific control measures appropriate for local situations. The relative importance of local flea species as plague vectors can usually be determined by analysing relevant surveillance data, including the numbers of fleas per host, host preferences and Y. pestis infection rates for the species of fleas collected. Future surveillance efforts can then concentrate on important vectors and their hosts, thereby reducing costs while providing the most relevant information for control efforts. Host/flea data also provide indirect clues about which mammalian hosts are involved in local epizootics. For example, mortality among rock squirrels (Spermophilus variegatus) is high during plague epizootics, and it is
not unusual at these times to find their usual flea parasite *Oropsylla montana* (*Diamanus montanus*) on other hosts such as other sciurids, rabbits, mice or woodrats. The number of fleas per host also is important. An increase in the average number of fleas per host may be of little concern when the flea species is a poor vector of plague. However, when the numbers of *Xenopylla cheopis* on *Rattus* species increase above a certain level, it may be necessary to initiate control measures to decrease the risk of human cases and plague epizootics (39).

**Importance of proper taxonomic identification of fleas**

More than 1500 species of fleas have been described but less than 15% of them have been found to be infected naturally with plague (40). Distinguishing important vector species from those of little epizootiological or epidemiological significance often requires the skills of a trained entomologist. However, nonspecialists can learn to recognize common fleas present in their area. The importance of proper taxonomic identification of fleas was demonstrated by studies of the Plague Commission in India during the early 1900s. Initially *X. cheopis* was thought to be the only member of its genus infesting the local *Rattus* examined by the commission. It was eventually discovered, however, that these rats also were infested with *X. astia*, which is a relatively poor vector of plague and presents far less risk to humans than *X. cheopis*. Once it became apparent that two species of flea were present and that these fleas differed in seasonal abundance and in their ability to transmit plague, investigators were able to explain the observed seasonal fluctuations in human cases (39,41).

Often, trained entomologists can identify flea species directly from saline or alcohol without having to prepare permanent slide mounts in Canada balsam or other mounting media. Unfortunately, processing fleas for permanent slide mounts destroys any plague bacteria present and thus precludes determination of infection with *Y. pestis*. Nevertheless, at least a few fleas from each surveillance district should be mounted as permanent specimens for future taxonomic reference. Standard techniques for mounting fleas on slides can be found in a number of references (42,43).

**Removing fleas from captured animals**

Techniques for collecting fleas are relatively simple and can be carried out simultaneously with existing rodent surveillance programmes. The most common method for collecting fleas is to remove them from captured host animals. If hosts are captured alive, they should be anaesthetized as described in the rodent surveillance section before further processing
(Fig. 1). The anaesthetized animals are then placed in a white enamel pan (a depth of 20cm or more is recommended) and brushed vigorously from the tail end forwards with a toothbrush, pocket comb or other similar instrument (Fig. 6). This will dislodge fleas from the host; the fleas will fall to the bottom of the pan where they can be removed with forceps or a wetted applicator stick and placed in labelled vials containing either 2% saline or alcohol. Fleas stored in saline can be held for identification, bacterial isolation or other analyses (15,44,45,46). Those held in alcohol can be mounted for identification using standard methods (43) or analysed for Y. pestis infection by polymerase chain reaction (PCR) techniques (43,46). Hosts killed by capture in snap traps or other means can be examined directly for fleas, but insecticides or anaesthetic agents should be used to prevent live fleas from escaping onto the investigator or into the laboratory. Any bedding material placed in traps to provide warmth for the host should also be examined for fleas.

Figure 6: Combing a rabbit for fleas. The animal and fleas have been anaesthetized prior to processing. As the comb passes through the hair it will dislodge fleas into the pan where they can be collected for identification and analysis.

Collection of fleas from burrows

Fleas can be collected from rodent burrows by burrow swabbing or flagging. When fleas are periodically sampled by this method, it is often noted that burrow indices are low during interepizootic periods but
increase dramatically when plague epizootics cause high host mortality. A typical burrow swab consists of a flexible steel cable or hard rubber hose with a piece of white flannel cloth attached to the end (Fig. 7) (47,48). The cable is used to force the cloth down the burrow entrance; fleas mistake it for their normal hosts and cling to the cloth. The cloth is then removed from the burrow and inspected for fleas or placed in a plastic bag and held for later examination. Fleas in the bags can be killed by freezing, anaesthetization or insecticides.

Figure 7: Surveillance worker using a burrow swab to collect fleas from burrows

Collection of fleas from nesting material

Many fleas spend more time in the nests of their hosts than on the host itself. Nest material can be examined for fleas by sorting the contents in an enamel pan such as was described above for brushing fleas from hosts. It may be necessary to kill fleas before sorting to prevent them escaping from the pan. Nest material also can be loaded into a Berlese funnel, a device that uses heat from a lightbulb located at the top of the funnel to drive fleas and other arthropods to the bottom of the funnel. Once the fleas reach the bottom, they fall into a jar containing a saline solution or alcohol (49).
Flea indices

The most basic information obtained from flea and rodent surveys is the number of fleas of different species found on various species of hosts. This raw data can be used to calculate various indices, including:

- **Specific flea index** = number of fleas of species \( A \) collected from host species \( Y \), divided by the number of individuals of host species \( Y \) examined (multiplication of this index by 100 gives the percentage index);

- **Total flea index** = Total number of fleas collected (regardless of species), divided by the total number of hosts of species \( Y \) examined;

- **Percentage of hosts infested** = number of hosts of species \( Y \) infested with flea species \( A \), divided by the total number of hosts of species \( Y \) examined, multiplied by 100.

Similar indices can be calculated for flea collections taken from burrows, nests or houses:

- **Burrow (or nest or house) index** = number of fleas of species \( A \) collected from burrows (or nest or house) of host species \( Y \), divided by the total number of burrows (or nest or house) of host species \( Y \) examined.

The specific flea index is the most widely used of the above indices. It can be used in conjunction with other rodent and vector surveillance data to estimate human and epizootic risks. For example, it has been reported that a specific flea index of greater than 1 for \( X. \) *cheopis* on rats represents a potentially dangerous situation with respect to increased plague risk for humans (39). Many factors affect the reliability of flea indices, including host species, host age, trapping techniques, areas selected for sampling and the natural tendency of fleas to heavily infest several hosts within a population, while many animals have few or no fleas (high variance to mean ratios for sample data). To obtain reliable indices for comparison between different survey sites, all trapping and ectoparasite collection procedures should be standardized as much as possible.

A sequential sampling method for determining how many host animals must be sampled to derive a reliable flea index for a given host/flea relationship has been described by Schwan (50). He found that examination of as few as 20 Nile grass rats (Arvicanthis niloticus) was sufficient to establish a reliable specific flea index for either Dinopsyllus lypusus or Xenopsylla cheopis bantorum infestations. Schwan's method uses sequential calculation of the specific flea index to determine how the
inclusion of additional animals and their fleas changes the values for this index. As more and more animals and their fleas are included in the index calculations, the values begin to approach a particular value of the index that remains relatively stable with additional sampling. This can be shown graphically by plotting the number of host animals examined on the X axis and the specific flea index (calculated for X animals and their fleas) on the Y axis. Schwan proposed that the point at which the slope of this graph approaches zero represents the appropriate minimum number of animals that must be sampled to obtain a reliable specific flea index using standardized sampling techniques.

**Identification of Y. pestis in fleas**

Determining which flea species are infected with *Y. pestis* is critical for separating locally-important vectors from those which play only a minor role. Probably the most common method for determining whether fleas are infected with plague is to inoculate susceptible laboratory animals with ground fleas suspended in physiological saline (0.85%) (44). Material for flea suspensions may consist of either individual fleas or pools of fleas; fleas should be pooled by species, type of host, and area where collected. At the United States Centers for Disease Control and Prevention, Atlanta, the standard procedure to prepare fleas for inoculation is to grind flea pools (as many as 25 fleas per pool) in a mortar and pestle and then suspend the ground material in approximately 2 ml of physiological saline (0.85%). This suspension is then inoculated subcutaneously into mice (0.5ml suspension per mouse). The mice are monitored over the next 21 days, and those that die are necropsied to obtain tissues for bacterial isolation. Surviving mice can be sacrificed on day 21 postinoculation for sera and tissues. *Y. pestis* has also been detected in fleas using immunologic techniques, and PCR, but these procedures have yet to be widely tested under field conditions (15, 45, 46). Recently, PCR has been demonstrated to be more sensitive and reliable in some situations than mouse inoculation (45). As with all PCR assays, however, care must be taken to avoid false positives due to contamination with amplicons generated during previous reactions or as a result of contamination from other sources.

**Insecticide sensitivity surveys**

After locally-important flea vectors have been identified, their sensitivity to various insecticides should be determined. Data on insecticide susceptibility for flea populations in plague-endemic areas should be retained in the plague surveillance database and periodically updated. Prior knowledge of insecticide resistance among local flea
populations will enable plague control workers to select an appropriate insecticide and save valuable time in the event of a plague epizootic. Kits for testing fleas for insecticide sensitivity are available through the World Health Organization.

**Evaluation of surveillance data**

After each collection period, all data from dead animal collections, colony observations and rodent or carnivore serosurveys should be analysed and mapped to determine the distribution of plague-infected animals in the area under study. Information from human and flea surveillance should be included as well. Mapping this information during epizootics can help determine the extent of the epizootic and whether control efforts have succeeded in preventing its spread to areas where humans would be at high risk of infection. Such mapping helps clarify the risk that plague-infected rodents and their fleas pose to human populations in the surrounding area. The proximity of infected animals to other populations of the same species or those of other susceptible rodent species, as well as habitat availability, should also be noted. This information is useful for estimating the likelihood that plague will spread to new areas and other rodent populations.

Whenever possible surveillance personnel should be aware of human activities that are likely to affect local rodent populations, such as development of new agricultural areas, villages or other development projects. Rodents respond quickly to habitat changes that provide them with new sources of food and harbourage, and existing plague problems will be exacerbated by human activities that create new rodent habitats.

**Surveillance by health services**

National, regional and local health services should work together to develop a plague surveillance programme with clearly-defined responsibilities for routine surveillance tasks and emergency investigations. Responsibilities should be distributed among the different health services so that human cases and epizootics can be identified and investigated as quickly as possible by individuals trained to assess human plague risks and determine appropriate control measures. Such predictive surveillance and emergency response capabilities require certain personnel, equipment and facilities. The following section describes these basic requirements and suggests how responsibilities for various surveillance tasks can be allocated to local, regional or national services.

Country programmes must have a variety of personnel with training in such diverse fields as medicine, epidemiology, bacteriology, serology,
entomology, mammalogy, health education and environmental sanitation. There should be personnel at the local level trained to inspect areas for evidence of rodent die-offs, collect samples for routine rodent and vector surveillance, and conduct educational programmes to promote plague awareness, prevention and control. If local health services lack adequately-trained staff, experts from the regional or national health services should provide this training. At the local level, health services are also expected to maintain close contacts with the medical community so that human cases are recognized and reported as soon as possible.

Because of time and travel constraints, local agencies are normally responsible for at least the initial stages of human case investigations, including coordinating the collection and shipping of diagnostic specimens, obtaining exposure histories from patients and performing preliminary investigations of likely exposure sites.

Following these initial steps, more extensive epidemiological and environmental investigations (described earlier) should be instigated. Although local workers might be sufficiently trained to perform these investigations, the national (or regional) health services should be prepared to provide additional expert assistance if necessary. For this reason, national health services maintain at least one plague team composed of experts whose combined training includes the disciplines listed above, as well as knowledge of plague prevention and control techniques (12,51,52). A minimum, but adequate, plague team is comprised of an epidemiologist, bacteriologist/serologist and entomologist/zoologist.

At least one of these individuals (usually the epidemiologist) should have medical qualifications (12). These experts can participate directly in human case investigations and surveillance activities or serve as consultants for local or regional health officials. They can also train local workers in techniques of plague diagnosis, treatment, surveillance, prevention and control. If a country lacks the resources and personnel to form such a plague team, or if plague has just recently entered a country and a team has yet to be formed, it may be necessary to request the assistance of international consultants working under the direction of the World Health Organization. The national plague team should have sufficient field equipment and supplies to conduct emergency epidemic or epizootic investigations, as well as adequate transportation to move equipment and plague team members to the affected area (52). Surveillance programmes should be prepared, if necessary, to hire and
train temporary workers during emergency situations or seasonal peaks in plague activity.

Surveillance programmes must have adequate laboratory facilities for performing bacteriological and serological analyses on plague-suspect specimens. While it is preferable to have several laboratories located near plague foci, at a minimum a central (or national) laboratory that can analyse surveillance and diagnostic samples is essential (12). The central laboratory should be able to confirm the presence of Y. pestis in samples by culture, biochemical characterization and bacteriophage typing. The laboratory should also be proficient in using standard serological techniques to detect plague antibodies in serum samples. Whenever possible the laboratory should be able to analyse samples by direct immunofluorescence. Personnel at the central laboratory should keep abreast of recent developments in molecular biology and be prepared to adopt new techniques that are cost-effective and useful for surveillance purposes.
References


50. Schwan TG. Sequential sampling to determine the minimum number of host examinations required to provide a reliable flea (Siphonaptera) index. Journal of Medical Entomology, 1984, 21:670-674.


52. Plague surveillance and control. WHO Chronicle, 1980, 34:139-143.
Although local or regional health departments might have considerable expertise and do an excellent job of managing plague within their districts, the potential for the rapid spread of plague from one region of a country to another requires national prevention and control programmes capable of coordinating and assisting local and regional efforts. Plague's lack of respect for international boundaries also requires that national health services of neighbouring countries cooperate with one another to successfully control this disease. International control activities are best administered by national health services rather than by local or regional agencies. Surveillance and control of plague in port facilities and international airports should also fall under the supervision of the national health services. As was described under plague surveillance, the organization of national, local and regional plague prevention and control programmes may vary considerably from one country to another, but several important features are common to all.

The World Health Organization (3) has recommended a four-phased system of plague prevention and control that can be adapted to the requirements and resources of different countries. This section summarizes this system and describes how its implementation will result in a national plague prevention and control programme that is effectively integrated with local and regional programmes.

The first two phases of the WHO system address emergency measures to be implemented whenever a human plague case occurs. Plague prevention and control programmes in each country should have adequate personnel, equipment and laboratory facilities to undertake the phase 1 and phase 2 activities described below. Phases 3 and 4 outline the establishment of a surveillance system and development of long-term prevention and control measures. These activities require a greater commitment of personnel and resources than in phases 1 and 2, but their successful completion will significantly reduce the risk of human plague. It is recommended, therefore, that each country implement phases 3 and 4 to the fullest extent possible.
Phase 1: Case recognition and medical intervention

National health service officials should verify that local and regional officials are trained and prepared to undertake emergency measures whenever a human case is suspected. After identifying a suspect plague case, local health services should:

(1) notify national and/or regional authorities;
(2) ensure that appropriate specimens are shipped to a qualified laboratory for diagnostic confirmation of \(Y.\) \(p\)estis infection;
(3) verify that patients have been placed on appropriate antibiotic treatment and that local supplies of antibiotics are adequate to handle further cases; and
(4) isolate pneumonic plague patients and cooperate with other health services to identify, monitor and, if necessary, arrange prophylactic treatment for individuals in contact with cases.

In addition to the above measures, a preliminary epidemiological investigation should be initiated. The purpose of this investigation is to obtain an exposure history from the patient in order to make an initial assessment of likely sources of infection and potential risks to others in the area. National and regional health services, including the national plague team described earlier in this manual, may be dispatched to the area if local skills or resources are inadequate. Plague experts with the national health services can also help local and regional authorities determine whether to recommend vaccination for individuals in high-risk areas or occupations. If a vaccination programme is approved and vaccine stocks are not locally available, the national health services should be prepared to provide local and regional authorities with information on where supplies of vaccine can be obtained.

Phase 2: Epidemiological and epizootical investigation and emergency control

The second phase of the programme should be initiated immediately following phase 1. Phase 2 activities include an intensive environmental investigation of potential exposure sites for the human case(s) and initiation of emergency control measures to prevent additional cases. These investigations require both epidemiologists and persons trained in techniques for surveillance and control of rodents and fleas. The national plague team, whose services may have already been requested during phase 1, can provide this expertise when local or regional personnel lack adequate training. The plague team's central laboratory resources should be made available for the investigation.
The goals of the phase 2 environmental investigation are to:

1. identify the rodent and flea species most likely to be sources of infection in the area where the human case(s) was exposed;
2. determine the extent of epidemics and/or epizootics associated with the initial human case; and
3. identify areas of potential risk to humans.

This information is used to determine emergency control measures to be taken to prevent additional human cases.

**Phase 3: Surveillance and control**

The goal of phase 3 is to establish a surveillance and control programme. Because of ecological differences between plague foci in different geographic regions, preliminary research is needed to identify which local rodent and flea species should be targeted for extensive surveillance and control.

The research data can also be used in conjunction with information on local landscape, human activity and host/vector ecology to design prevention and control strategies appropriate for a particular plague focus. Any rodenticidal, insecticidal or environmental control measures developed during this phase should be tested locally to evaluate their effectiveness in reducing the human risk of plague.

Where local or regional health services lack the expertise to perform this research they must be assisted by personnel at the national level. The national health services should also work with local and regional authorities to develop and administer educational programmes to increase awareness and knowledge among health care personnel and the general public.

**Phase 4: Management**

The final phase of the plague prevention and control programme stresses long-term management of plague foci. Such management calls for continuous surveillance of the important host and vector species identified during phase 3. Once the surveillance programme identifies a plague epizootic, control measures developed in phase 3 should be implemented as soon as possible. Long-term environmental management of plague foci should also be promoted. Environmental management stresses the elimination or reduction of areas, near homes or workplaces, that are attractive to plague-susceptible rodents. Plague
staff should work with other government officials to regulate and modify activities and practices such as agricultural projects, construction, placement of garbage disposal facilities and so on that are likely to lead to increased food and harbourage for locally-important rodent hosts. Health services should continue the educational programmes developed during phase 3. Finally, research to improve existing surveillance and control techniques should continue, following the procedures outlined for phase 3.
References

