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Plague Manual: Epidemiology, Distribution, Surveillance and Control

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Plague Manual

Epidemiology, Distribution, Surveillance and Control

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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 **B**particularly from pneumonic plague **B**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 (*1*).

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 (*2*). 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.

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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 **B***Yersinia pestis* **B** 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 septicaemic 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*).

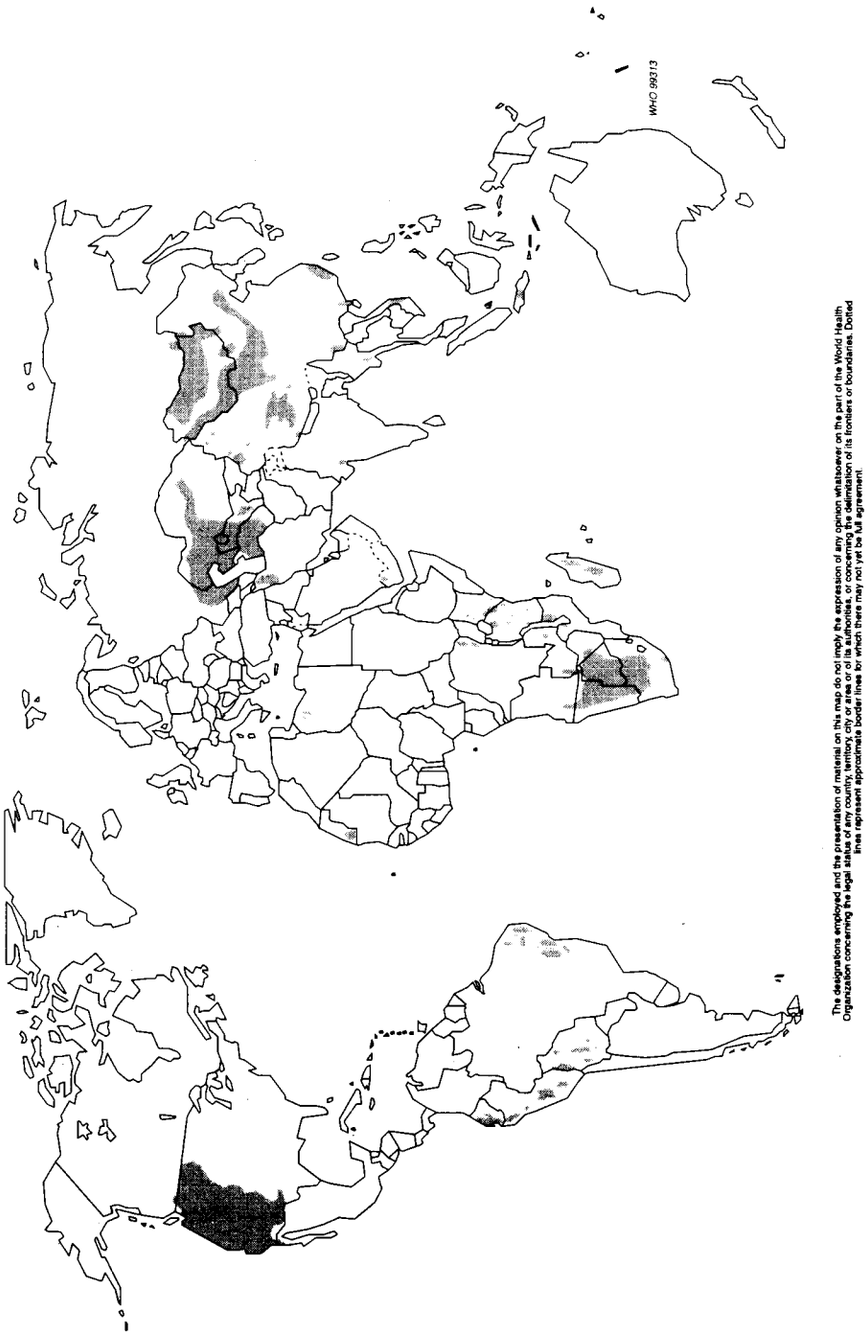
"Rat" plague presents a particular danger where, in addition to synanthropic rats in human settlements, there are also wild rats in the surrounding fields (such as in Madagascar and East Africa). In these areas, complex secondary foci of "rat" plague arise which are more stable than temporary foci in 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 6587 deaths. The maximum number of plague cases (6004) occurred in 1967 and the minimum (200) occurred in 1981. Between 1967–1971 the annual number of cases exceeded 4000. 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 **B**the most epidemic forms of the disease **B**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 (*8*).

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 3595 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

AFRICA	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968
Angola	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Botswana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Burkino Faso	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(1)	(—)	(—)
Cameroon	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(1)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Democratic	42	25	22	35	8	12	26	6	1	4	4	16	8	7	104
Republic	(...)	(...)	(...)	(...)	(6)	(12)	(—)	(6)	(1)	(—)	(—)	(—)	(3)	(—)	(21)
of the Congo															
Guinea	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Kenya	9	27	8	6	19	14	36	3	2	3	1	—	—	1	—
	(...)	(...)	(...)	(...)	(5)	(1)	(1)	(—)	(—)	(—)	(—)	(—)	(—)	(1)	(—)
Lesotho	8	2	—	—	—	—	—	—	—	—	—	—	—	3	108
	(...)	(...)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(3)	(46)
Libyan Arab	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Jamahiriya	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Madagascar*	17	17	20	57	21	5	6	4	28	9	6	32	9	10	28
	(...)	(...)	(...)	(...)	(16)	(3)	(3)	(2)	(5)	(5)	(3)	(11)	(2)	(4)	(12)
Malawi	—	—	—	—	—	—	—	—	—	30	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(9)	(—)	(—)	(—)	(—)	(—)
Mozambique	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Namibia	—	—	—	—	—	—	—	9	80	3	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(4)	(6)	(—)	(—)	(—)	(—)	(—)	(—)
South Africa	4	8	3	5	—	10	1	1	7	4	17	—	—	1	2
	(...)	(...)	(...)	(...)	(—)	(...)	(—)	(1)	(4)	(1)	(—)	(—)	(—)	(—)	(—)
Uganda	18	—	—	—	2	2	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(...)	(...)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
United Republic	—	—	5	5	—	—	—	—	2	—	513	1	—	—	6
of Tanzania*	(—)	(—)	(...)	(...)	(—)	(—)	(—)	(—)	(2)	(—)	(11)	(1)	(—)	(—)	(5)
Zambia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Zimbabwe	12	—	49	—	—	—	—	—	—	—	—	—	1	—	—
	(...)	(—)	(...)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Total	110	79	107	108	50	43	69	24	120	53	541	49	19	22	248
	(...)	(...)	(...)	(...)	(27)	(16)	(4)	(14)	(18)	(15)	(14)	(12)	(6)	(8)	(84)

... Figures not available
* includes suspected cases

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

AFRICA	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983
Angola	—	—	—	—	—	—	49	—	—	—	—	21	6	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(4)	(—)	(—)	(—)
Botswana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Burkino Faso	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Cameroon	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Democratic	68	16	6	8	36	20	1	12	4	—	1	—	—	1	—
Republic	(17)	(—)	(2)	(2)	(1)	(2)	(—)	(10)	(3)	(—)	(1)	(—)	(—)	(—)	(—)
of the Congo															
Guinea	49	3	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Kenya	—	—	—	—	—	—	—	—	—	166	227	5	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(9)	(1)	(2)	(—)	(—)	(—)
Lesotho	2	—	—	8	—	—	8	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(2)	(—)	(—)	(8)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Libyan Arab	—	—	—	16	—	—	—	19	11	—	—	—	—	—	—
Jamahiriya	(—)	(—)	(—)	(2)	(—)	(—)	(—)	(6)	(6)	(—)	(—)	(—)	(—)	(—)	(—)
Madagascar*	26	13	31	63	20	38	55	47	58	25	23	11	44	38	24
	(15)	(5)	(7)	(26)	(7)	(10)	(21)	(13)	(16)	(6)	(13)	(5)	(13)	(19)	(10)
Malawi	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Mozambique	—	—	—	—	—	—	—	15	97	12	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(6)	(14)	(—)	(—)	(—)	(—)	(—)	(—)
Namibia	—	—	—	—	—	102	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(5)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
South Africa	—	—	—	1	—	—	—	—	—	—	—	—	—	19	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(1)	(—)
Uganda	—	—	—	—	—	—	—	—	—	—	—	—	—	153	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(3)	(—)
United Republic	2	—	—	32	—	—	—	—	2	—	—	49	9	76	569
of Tanzania*	(—)	(—)	(—)	(9)	(—)	(—)	(—)	(—)	(2)	(—)	(—)	(11)	(6)	(18)	(49)
Zambia	—	—	—	—	—	—	—	—	—	—	—	—	—	...	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Zimbabwe	—	—	—	—	—	23	34	—	—	—	—	—	—	3	1
	(—)	(—)	(—)	(—)	(—)	(8)	(12)	(—)	(—)	(—)	(—)	(—)	(—)	(2)	(—)
Total	147	32	37	128	50	183	147	93	172	203	251	86	59	290	594
	(32)	(5)	(9)	(41)	(8)	(25)	(41)	(35)	(41)	(15)	(15)	(22)	(19)	(43)	(59)

... Figures not available
* includes suspected cases

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

AFRICA	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Angola	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Botswana	—	—	—	—	—	103	70	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(9)	(3)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Burkino Faso	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Cameroon	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Democratic	—	—	—	474	369	1	—	289	390	636	82	582	—	—
Republic	(—)	(—)	(—)	(160)	(86)	(—)	(—)	(28)	(140)	(89)	(10)	(23)	(—)	(—)
of the Congo														
Guinea	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Kenya	—	—	—	—	—	—	44	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(8)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Lesotho	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Libyan Arab	8	—	—	—	—	—	—	—	—	—	—	—	—	—
Jamahiriya	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Madagascar*	39	85	29	23	93	170	226	137	198	147	126	1147	1629	1820
	(18)	(18)	(6)	(4)	(19)	(41)	(55)	(30)	(26)	(23)	(15)	(26)	(109)	(56)
Malawi	—	—	—	—	—	—	—	—	—	—	9	—	—	582
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(11)
Mozambique	—	—	—	—	—	—	—	—	—	—	216	—	—	825
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(3)	(—)	(—)	(18)
Namibia	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
South Africa	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Uganda	—	—	340	—	—	—	—	—	—	167	—	—	—	—
	(—)	(—)	(27)	(—)	(—)	(—)	(—)	(—)	(—)	(18)	(—)	(—)	(—)	(—)
United Republic	603	129	360	356	647	31	364	1293	16	18	444	831	947	504
of Tanzania*	(41)	(22)	(57)	(34)	(33)	(4)	(32)	(60)	(2)	(—)	(50)	(74)	(64)	(28)
Zambia	—	—	—	1	—	—	—	—	—	—	—	—	—	319
	(—)	(—)	(—)	(1)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(26)
Zimbabwe	—	1	—	—	—	—	—	—	—	—	392	—	—	8
	(—)	(1)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(28)	(—)	(—)	(2)
Total	650	215	729	854	1109	305	704	1719	604	968	1269	2560	2576	4058
	(59)	(41)	(90)	(198)	(138)	(54)	(98)	(118)	(168)	(130)	(106)	(123)	(173)	(141)

... Figures not available
* includes suspected cases

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

AMERICAS	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968
Argentina	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Bolivia	9	45	3	—	—	—	12	20	—	53	49	149	3	3	30
	(...)	(...)	(...)	(—)	(—)	(—)	(...)	(8)	(—)	(7)	(18)	(...)	(—)	(—)	(14)
Brazil	6	27	4	37	25	16	28	106	36	39	285	115	48	157	285
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(11)	(1)	(12)	(...)	(...)	(...)	(...)	(...)
Ecuador	81	85	80	79	22	40	77	140	326	258	194	369	171	19	24
	(...)	(85)	(...)	(...)	(...)	(...)	(...)	(1)	(21)	(12)	(11)	(...)	(7)	(1)	(1)
El Salvador	—	6	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(6)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Peru	75	8	24	37	50	33	139	68	164	72	125	200	662	41	45
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(17)	(22)	(22)	(13)	(25)	(44)	(12)	(17)
United States	—	—	1	1	—	4	2	3	1	1	—	8	5	3	3
of America	(—)	(—)	(...)	(...)	(—)	(...)	(...)	(3)	(—)	(1)	(—)	(1)	(3)	(1)	(1)
Venezuela	—	—	3	—	—	—	—	6	—	1	—	—	—	—	—
	(—)	(—)	(...)	(—)	(—)	(—)	(—)	(...)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Total	171	171	115	154	98	93	258	343	527	424	653	841	889	223	387
	(...)	(91)	(...)	(...)	(...)	(...)	(...)	(40)	(44)	(54)	(42)	(26)	(54)	(14)	(33)

AMERICAS	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983
Argentina	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Bolivia	95	54	19	—	—	14	2	24	29	68	10	26	21	1	21
	(28)	(—)	(3)	(—)	(—)	(5)	(—)	(5)	(9)	(2)	(—)	(2)	(1)	(—)	(4)
Brazil	293	101	146	169	152	291	496	97	1	11	—	98	59	151	82
	(...)	(4)	(2)	(13)	(...)	(...)	(5)	(. . .)	(. . .)	(. . .)	(—)	(—)	(—)	(1)	(—)
Ecuador	23	30	27	9	1	—	—	8	—	—	—	—	8	—	65
	(—)	(1)	(—)	(—)	(1)	(—)	(—)	(1)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
El Salvador	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Peru	8	128	22	118	30	8	3	1	—	6	—	—	27	11	17
	(2)	(13)	(5)	(15)	(2)	(2)	(—)	(—)	(—)	(1)	(—)	(—)	(7)	(—)	(2)
United States	5	13	2	1	2	8	20	16	18	12	13	18	13	19	40
of America	(—)	(1)	(—)	(—)	(—)	(1)	(4)	(3)	(2)	(2)	(2)	(5)	(4)	(3)	(6)
Venezuela	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Total	424	326	216	297	185	321	521	146	48	97	23	142	128	182	225
	(30)	(19)	(10)	(28)	(3)	(8)	(9)	(9)	(11)	(5)	(2)	(7)	(12)	(4)	(12)

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

AMERICAS	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Argentina	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Bolivia	12	—	94	2	2	—	10	—	—	—	—	—	26	1
	(2)	(—)	(15)	(1)	(—)	(—)	(2)	(—)	(—)	(—)	(—)	(—)	(4)	(—)
Brazil	37	64	58	43	25	26	18	10	25	—	4	9	1	—
	(2)	(2)	(4)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Ecuador	7	3	—	—	—	—	—	—	—	—	—	—	—	—
	(1)	(2)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
El Salvador	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Peru	413	44	—	31	10	—	18	—	120	611	420	97	23	39
	(31)	(3)	(—)	(6)	(5)	(—)	(4)	(—)	(4)	(31)	(19)	(2)	(—)	(—)
United States	31	17	10	12	15	4	2	11	13	10	14	9	5	4
of America	(6)	(2)	(—)	(2)	(—)	(—)	(—)	(—)	(2)	(1)	(2)	(1)	(2)	(1)
Venezuela	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Total	500	128	162	88	52	30	48	21	158	621	438	115	55	44
	(42)	(9)	(19)	(9)	(5)	(—)	(6)	(—)	(6)	(32)	(21)	(3)	(6)	(1)

... Figures not available
* includes suspected cases

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

ASIA	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968
China	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)
Dem. Kampuchea	1	12	2	1	...	...	...	...	...	...	...	...	...	...	...
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)
India	1031	542	262	162	206	214	122	402	697	205	109	14	11	6	—
	(663)	(220)	(209)	(162)	(206)	(180)	(25)	(55)	(88)	(24)	(15)	(—)	(8)	(—)	(—)
Indonesia	348	354	113	17	—	18	5	—	—	—	—	—	—	—	102
	(...)	(...)	(...)	(...)	(—)	(...)	(...)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(43)
Iran	—	—	—	—	12	—	—	7	—	26	—	—	—	—	—
	(—)	(—)	(—)	(—)	(6)	(—)	(—)	(—)	(—)	(14)	(—)	(—)	(—)	(—)	(—)
Kazakhstan	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)
Lao People's Democratic Republic	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)
Mongolia	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)
Myanmar	265	203	273	227	76	21	22	39	68	34	—	36	48	120	86
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(—)	(...)	(7)	(8)	(3)
Nepal	...	...	...	...	...	...	...	...	...	...	...	...	...	24	13
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(17)	(12)
Philippines	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Viet Nam*	...	1	34	4	15	—	14	8	29	115	297	368	2844	5619	4193
	(...)	(—)	(...)	(...)	(2)	(—)	(1)	(5)	(9)	(17)	(49)	(50)	(141)	(269)	(215)
Total	1645	1112	686	411	309	253	163	456	794	380	406	418	2903	5769	4394
	(663)	(220)	(209)	(162)	(214)	(180)	(26)	(60)	(97)	(55)	(64)	(50)	(156)	(294)	(273)
WORLD TOTAL	1926	1362	908	673	457	389	490	823	1441	857	1600	1308	3811	6014	5029
	(663)	(311)	(209)	(162)	(241)	(196)	(30)	(114)	(159)	(124)	(120)	(88)	(216)	(316)	(390)

... Figures not available
* includes suspected cases

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

ASIA	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983
China	...	...	...	...	...	...	...	...	...	...	8	30	1	—	25
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(6)	(20)	(—)	(—)	(15)
Dem. Kampuchea	...	...	...	5	1	—	—	...	...	...	—	—	—	—	—
	(...)	(...)	(...)	(...)	(1)	(—)	(—)	(...)	(...)	(...)	(...)	(...)	(...)	(—)	(—)
India	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Indonesia	4	10	—	—	—	—	—	—	—	—	—	—	—	—	—
	(1)	(2)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Iran	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Kazakhstan	...	...	...	...	...	...	...	...	...	...	...	...	...	. . .	. . .
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)
Lao People's Democratic Republic	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)
Mongolia	...	...	...	...	...	...	...	—	—	...	...	2	...	...	...
	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(—)	(—)	(...)	(...)	(—)	(...)	(...)	(...)
Myanmar	32	43	189	63	17	700	275	673	591	171	73	73	1	165	96
	(1)	(2)	(16)	(3)	(3)	(22)	(20)	(55)	(26)	(6)	(2)	(4)	(—)	(1)	(3)
Nepal	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Philippines	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Viet Nam*	3850	4056	3997	1340	425	1552	536	593	667	314	306	180	11	116	127
	(159)	(78)	(149)	(63)	(35)	(108)	(32)	(5)	(...)	(8)	(8)	(5)	(—)	(—)	(3)
Total	3886	4109	4186	1408	443	2252	811	1266	1258	485	387	285	13	281	248
	(161)	(82)	(165)	(66)	(39)	(130)	(52)	(60)	(26)	(14)	(16)	(29)	(—)	(1)	(21)
WORLD TOTAL	4457	4467	4439	1833	678	2756	1479	1505	1478	785	661	511	200	753	1067
	(223)	(106)	(184)	(135)	(50)	(163)	(102)	(104)	(78)	(34)	(33)	(58)	(31)	(48)	(92)

... Figures not available
* includes suspected cases

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

	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
China	—	6	8	7	6	10	75	29	35	13	7	8	98	43
	(—)	(2)	(3)	(2)	(4)	(6)	(2)	(11)	(6)	(1)	(4)	(—)	(7)	(—)
Dem. Kampuchea	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
India	—	—	—	—	—	—	—	—	—	—	876	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(54)	(—)	(—)	(—)
Indonesia	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Iran	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Kazakhstan	. . .	. . .	. . .	. . .	...	2	4	1	—	3	—	—	—	1
	(...)	(...)	(...)	(...)	(...)	(1)	(2)	(—)	(—)	(1)	(—)	(—)	(—)	(—)
Lao People's	...	...	...	...	...	...	...	...	...	...	...	7	3	—
Democratic	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(—)	(—)	(—)
Republic														
Mongolia	...	1	...	...	...	5	15	3	12	21	—	1	6	4
	(...)	(...)	(...)	(...)	(...)	(3)	(5)	(—)	(4)	(7)	(—)	(1)	(—)	(2)
Myanmar	10	35	6	5	8	34	6	100	528	87	6	—	—	—
	(—)	(—)	(—)	(—)	(—)	(2)	(—)	(1)	(3)	(. . .)	(—)	(—)	(—)	(—)
Nepal	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Philippines	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)	(—)
Viet Nam*	196	137	104	107	196	374	405	94	437	481	339	170	279	220
	(6)	(6)	(3)	(6)	(6)	(37)	(20)	(3)	(17)	(19)	(27)	(10)	(19)	(10)
Total	206	179	118	119	210	425	505	227	1012	605	1228	186	386	268
	(6)	(8)	(6)	(8)	(10)	(49)	(29)	(15)	(30)	(28)	(85)	(11)	(26)	(12)
WORLD TOTAL	1356	522	1009	1061	1371	760	1257	1967	1774	2194	2935	2861	3017	4370
	(107)	(58)	(115)	(215)	(153)	(103)	(133)	(133)	(204)	(190)	(212)	(137)	(205)	(154)

... 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 1781 deaths (66.8% and 75.8% of the world's total). This was a yearly average of 1073 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 2824 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, Nyarambe, 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, Malindi, Kombieni, 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.

Madagascar (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.

Malawi (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 Ntchisi. This outbreak began in Nsaanje 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 People's 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 Xianjang. 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, Xinjing, 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, 17deaths) 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 **B** 54 of which were fatal **B** 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 Mamla 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.

Mongolia (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.

Myanmar (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, Meiktila and Magway 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 Magway, Mandalay and Sagaing Divisions. The principal type of plague is bubonic plague with the highest incidence during the cold season November to March with a peak in January or February.

Viet Nam (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 Tay-Nguen Plateau. In 1985 the disease was again notified in Ho Chi Minh 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 septicaemic 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 **B** Madagascar and Tanzania **B** 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.

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2
DIAGNOSIS AND CLINICAL MANIFESTATIONS

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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 pharangitis may be confused with streptococcal or viral pharyngitis. Other clinical forms, such as secondary septicaemia plague, secondary pneumonic plague, meningeal 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, supraclavicular, 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 *Y. pestis.*

When a superficial bubo is not found in a patient suspected to be infected with *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.

Septicaemic plague

Primary septicaemic plague is a progressive, overwhelming bloodstream infection with *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 ($< 5\,\mu m$ 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. aminoglycocides 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, *Haemophilus influenzae*, anthrax, tularaemia, *Legionella 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, "hammered 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 ($4-fold) change in antibody titre to the F1 antigen in paired serum specimens.

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