Interregional meeting on prevention and control of plague

Antananarivo, Madagascar
1 –11 April 2006

World Health Organization

Summary

The interregional meeting on prevention and control of plague, held 7–11 April 2006 in Antananarivo, Madagascar, gathered 70 participants from 24 countries. The meeting was held under the auspices of the World Health Organization (WHO), with the support of the Institut Pasteur of Madagascar and the Kazakh Scientific Centre for Quarantine and Zoonotic Diseases, Almaty, Kazakhstan, for the scientific organization. Since antibiotics became available in the mid-twentieth century, devastating plague epidemics have been considered to be a phenomenon of the past; however, the disease is far from being eradicated and is re-emerging in several countries and regions (e.g. Algeria and the Democratic Republic of the Congo).

The key features of the five plenary sessions are summarized below, and the abstracts of the oral presentations and the conclusions of three expert round tables are compiled in the main body of this document.

Session 1. Epidemiology

Plague remains an epidemiological threat and a disease of major public health importance in Africa. The occurrence of recent outbreaks shows that plague can re-emerge after a long period of silence. The most heavily affected African countries are the Democratic Republic of the Congo, Madagascar, Mozambique, Uganda and the United Republic of Tanzania.

In Madagascar, a computerized database has been set up at the Institut Pasteur for surveillance and standardized notification. This tool is valuable for analysing plague trends and for improving the reliability of notification.

Plague is endemic in the Democratic Republic of the Congo and represents a heavy public health burden. During the civil war (2002–2003), the number of human cases increased drastically. In 2005, an outbreak of pulmonary plague occurred outside the known focus of Ituri. Unfortunately, the current lack of specific resources and surveillance for plague increases the risk for extension of the existing foci.

In the United Republic of Tanzania, no human plague cases have been reported since 2003; however, surveillance of vectors and reservoirs shows that the disease has not disappeared.

In 2003, plague re-emerged in Algeria, in two villages south of Oran. Epidemiological and molecular investigations showed that the strains were unrelated to any other *Yersinia pestis* strain studied. The origin of this outbreak remains unclear.

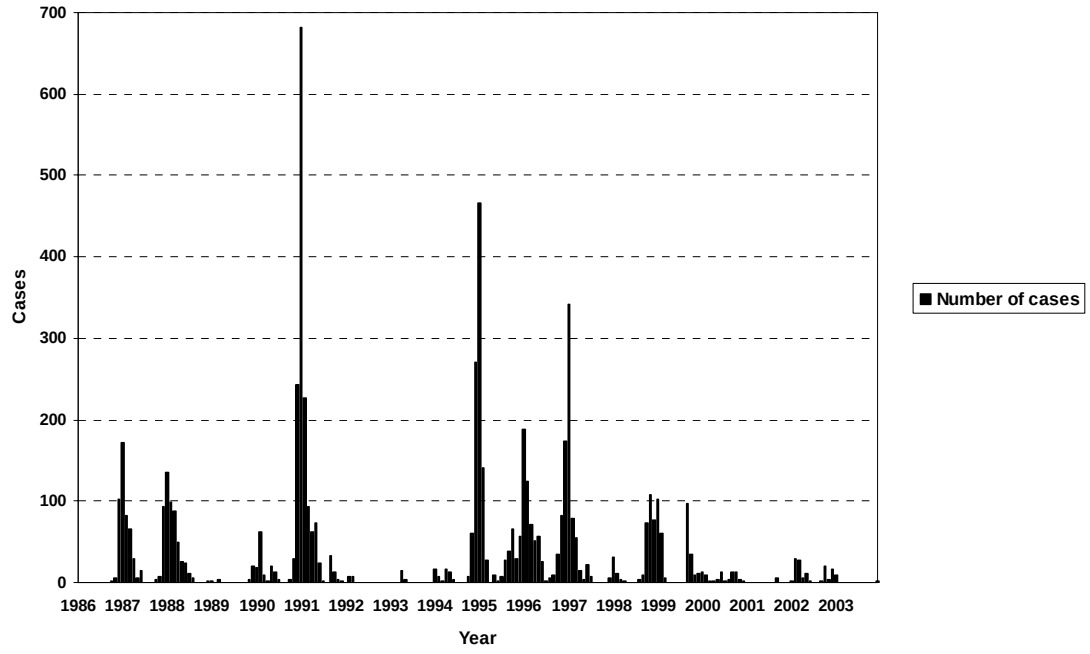
The Central Asian region has active plague foci in deserts, mountains and steppes. The most active focus is in the Central Asian desert, affecting Kazakhstan, Turkmenistan and Uzbekistan. The only country in Central Asia from which human plague cases are still reported to WHO is, however, Kazakhstan. The disease is transmitted through flea bites and direct contact with infected camels.

Almost 30% of the vast Mongolian territory consists of natural plague foci. Human infection occurs through flea bites and during skinning of marmots. Of the cases of plague, 90% are the bubonic form, and more than 40% of the cases of primary bubonic plague evolve into secondary pneumonic plague. The mortality rate can be up to 70% owing to lack of availability of treatment in remote areas and the low density of health structures.

Plague foci are distributed in 19 provinces and autonomous regions of China, and the incidence has been increasing rapidly since the 1990s. Two main type of foci exist. In the south, *Xenopsylla cheopis* bites cause bubonic plague, and the lethality rate is low. In the western and northern provinces, contamination occurs during skinning of infected animals, most cases evolve into septicaemic or primary pneumonic plague, and the case-fatality rate is over 50%.

Although no human plague cases were reported in the country in 2004–2006, there is no reason to conclude that the disease has disappeared, as surveillance of vectors and reservoirs shows an abundance comparable to that observed during plague outbreak years. Plague vectors and reservoirs in the plague foci are surveyed regularly, supported by the Ministry of Health and local district councils.

Figure 5 - Plague cases recorded in Tanzania, 1986–2004



1.6 Plague situation in Mongolia

Dashdawaa Otgonbaatar, Ministry of Health, Ulaanbaatar, Mongolia

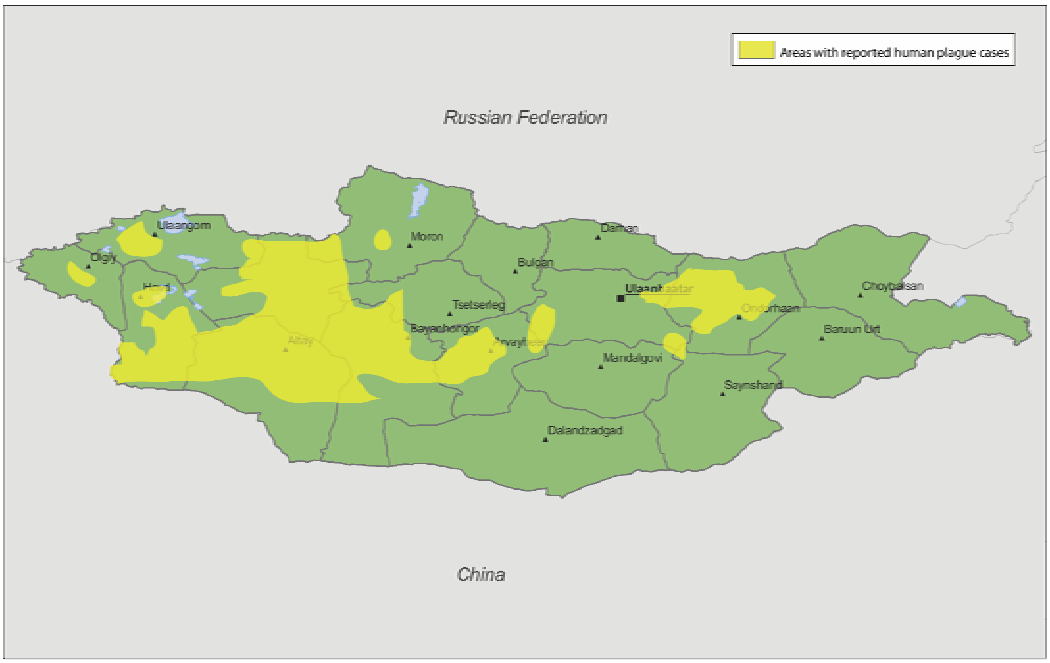
Plague has been known in Mongolia since 1897, and the natural foci have been studied since 1911. In 1924, the Government organized the first structure for plague control. Today, close to 30% of the vast Mongolian territory (1.6 million km^2) consists of natural foci.

The main plague reservoirs are the marmot (*Marmota sibirica)*, the suslik or ground squirrel (*Citellus undulatus*), the pika (*Ochotono pallasi*) and the vole (*Lasiopodomys brandti*). The main vector is the flea *Oropsylla silantiewi*. Plague cases are registered every year; human transmission is seasonal, linked to the hunting period (May–October). As Mongolians traditionally hunt marmots for their fur and meat, the risk of human infection from aerosols released during skinning of marmots is very high. Flea bites also play a role in plague transmission from infected rodents to humans. Of the 160 human plague cases registered between 1971 and 2000 (Figure 6), 90% were the primary bubonic form, 4.2% the primary pneumonic form and 6% the septicaemic form. More than 40% of the cases of primary bubonic plague evolve into secondary pneumonic plague because of lack of treatment. The mortality rate is very high (up to 70%, five times the world average) because of the lack of treatment in remote areas and the low density of health structures in the huge territory of Mongolia.

Despite the severe logistic constraints to plague control in Mongolia, some measures have been implemented, including surveillance of active natural foci, data collection and processing, rat and insect eradication campaigns, public health education, immunization and genetic analysis of *Y. pestis* strains.

Collaboration has been established with plague control organizations in China and the Russian Federation, to share information above plague activity across national borders, such as the Altai Mountains, the Sailugem area, the Chitinsk foci next to the Russian border; Khangai, Khentii Mountain, the eastern steppe and Gobi Desert, and the Manjuur region close to China.

Figure 6 - Human plague distribution in Mongolia



Data Source: Ministry of Health, Ulaanbaatar, Mongolia. Map Production: Public Health Mapping & GIS; Communicable Diseases (CDS); World Health Organization

1.7 Plague situation in China

Rong Hai, Institute for Communicable Disease Control and Prevention, Beijing, China

Natural plague foci are widely distributed throughout China, and epizootics and human cases are described every year. The plague foci are distributed in 19 provinces and autonomous regions of China; new natural foci were identified in Sichuan and Guizhou provinces in 1999.

Since the 1990s, the incidence of plague in China has been increasing rapidly, with fewer than 10 human cases per year in the 1980s, nearly 100 cases in 1996 and 254 cases in 2000. A total of 631 human cases were reported between 1995 and 2004, with a fatality rate of 6.67%.

The surveillance network analyses host and vector populations and their spatial distribution and studies the genetic characteristics of the pathogen. Two main type of foci exist in China, corresponding to different geographical zones, reservoirs and infection mode. In the southern region, where more than half of the human cases are declared, *R. flavipectus* is the main reservoir, *X. cheopis* bites cause bubonic plague, and the lethality rate is low. In the western and northern provinces, the reservoirs are *Spermophilus dauricus* (north-east), *Meriones unguiculatus* (north) and *Marmota himalayana* (Qinghai–Tibet). Hunters are frequently

contaminated while skinning infected animals, and most cases are septicaemic or primary pneumonic plague. Because of the remoteness of the north-western foci, the fatality rate is greater than 50%.

Y. pestis strains isolated from natural plague foci in China were analysed by ribotyping and showed clustering related to their geographical origin. Ribotype B covers a large area including most of the Qinghai–Tibet plateau and the western region of Yunnan. The pattern indicates that ribotype A and ribotype C are closely related.

Plague control measures include insecticide and rodenticide use and health personnel training to detect clinical manifestations and for diagnosis, treatment, control and reporting.

1.8 Plague situation in the Americas

Kenneth Gage, Centers for Diseases Control and Prevention, Fort Collins, Colorado, USA

Following the introduction of plague in the Americas in the early 1900s, permanent foci of infection became established among native rodent and flea populations in a number of countries, including Brazil, Bolivia, Ecuador, Peru and the USA. Large epidemics have occurred recently only in Peru (1248 cases reported between 1992 and 1994). Ecuador experienced a small outbreak of pneumonic plague in 1998: the index case had skinned and cooked sick guinea-pigs, and other family members were infected via airborne transmission.

Although human plague in native rodent foci in the Americas often appears as isolated cases or small clusters of cases (Figure 7), the potential for more widespread outbreaks exists, particularly when the disease passes from native rodent hosts and their fleas to peridomestic rats and fleas. There is a risk that plague will spread from the Andes to other regions through trade and travel, as regional markets attract villagers and rural inhabitants move to cities.

2.7 Human case management and prevention in China

Rong Hai, Institute for Communicable Disease Control and Prevention, Beijing, China

Epizootics occur every year in China, and 11 natural plague foci have been identified, which are distributed in 19 provinces. Plague surveillance at county, province and central levels has been enforced. The surveillance data indicate two main routes of human contamination. The southern focus harbours bubonic plague transmitted by the bites of *X. cheopis* infected after feeding on *R. flavipectus*. More than 50% of human cases derive from this focus. With adequate, early treatment, most of the cases recover. Marmot hunting and skinning are responsible for human transmission in the northern focus. Most of the cases are pneumonic or septicaemic plague, and, because of the remoteness of the northern areas, the fatality rate is more than 50%.

Streptomycin is the first-choice antibiotic treatment for human cases. Patient isolation, contact tracing and chemoprophylaxis are performed routinely. In some cases, emergency measures like road traffic quarantine are also enforced. Prevention measures include training in safety procedures in the laboratory, medical staff education, public health information with the participation of television, radio and newspapers, and reduction of rodent populations with chemical agents.

2.8 Vaccine development

Christian Demeure, Institut Pasteur, Paris, France

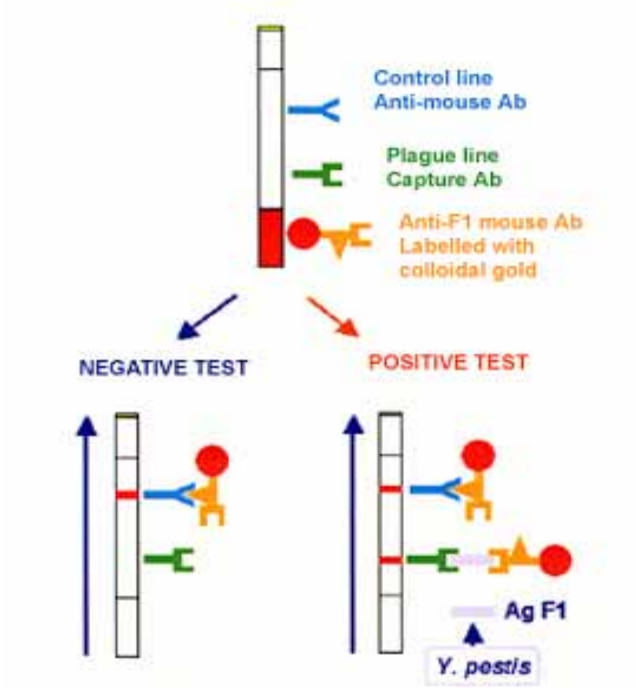
Despite the availability of effective antibiotic treatments, the vaccine option remains valid because the fatality rate from plague is significant and immunization is cheaper than treatment. Vaccination with the live attenuated vaccine EV76 was used successfully by G. Girard and J. Robic to control plague in Madagascar and several other countries during the first half of the twentieth century. Vaccines made from killed bacteria were then developed and used until recently. None, however, conferred long-lasting protection against bubonic plague, none protected against pneumonic plague, and all sometimes had severe side-effects. With the advent of antibiotics, mass immunization against plague was abandoned in most endemic foci worldwide. During the past decade, the number of notified human cases of plague has increased steadily, and plague has been categorized as a re-emerging disease. The isolation of antibiotic-resistant strains and the threat of use of plague bacteria in bioterrorism have renewed interest in plague immunization.

Most of the vaccines under development are composed of a combination of two antigens: the F1 antigen encoded by the plasmid pFra, which is *Y. pestis*-specific, produced in large amounts and not essential to strain virulence; and the type III secretion system component LcrV, which is encoded by the pYV plasmid and common to the three pathogenic *Yersinia* species. The latter component is necessary for virulence. Various forms and galenic formulations of these vaccines have been tested successfully in mice, but the results in primates vary depending on the species. Human trials have passed phase I (toxicity testing).

Other vaccine approaches include naked DNA vaccines, *Y. pestis* strains attenuated by a known gene deletion and vaccines with other antigenic targets, like Yscf, and other surface virulence factors.

Since 2001, several vaccine programmes to prepare for potential bioterrorist attacks have been funded by large grants from the governments of the United Kingdom and the USA. The possibility that aerosolized *Y. pestis* could be deployed as a biological weapon dictates that vaccines should protect against pneumonic plague. Antigens trapped inside biodegradable polylactide microspheres constitute a suitable form for mucosal vaccination. Adjuvants (recombinant *Salmonella* flagellin, *Neisseria meningitidis* outer membrane proteins and

Figure 12 - F1 detection principle of the Institute Pasteur Rapid Diagnostic Test



3.2 Immunological diagnosis

Philippe Thullier, Centre de recherche du service de santé des armées, La Tronche, France

The etiology of the outbreak of pneumonic plague in the Zobia region of the Democratic Republic of the Congo (see section 2.5) in December 2004 was first assessed from clinical and epidemiological data. The preliminary laboratory results, obtained on site, included direct microscopic observation of Gram-negative bacteria in sputum and blood smears and positive rapid diagnostic tests for F1 antigen in sputum. The cultures were negative, but transport difficulties and frequent self-medication with gentamycin might explain this finding. Confirmation of diagnosis was finally provided by laboratory-based serological evidence, with five cases of seroconversion among the six available pairs of sera, showing at least a fourfold increase in anti-F1 IgG titre. Anti-F1 IgM (presumptive cases) was found in 44 of 66 tested sera. Only two patients were shown to have anti-F1 IgA. The etiology of the outbreak was then proven, according to WHO criteria, by serodiagnosis.

The same diagnostic procedure was used to determine the nature of the outbreak in Uttar Kashi, India, in 2004, on the basis of three paired sera. These reports underline the importance of immunological diagnosis of infectious diseases, particularly plague, when the presence of pathogens is difficult to prove by strain isolation.

A rapid test based on protein A–gold conjugate has been developed for plague serodiagnosis by detection of anti-F1 IgG. It is compatible with human and rodent samples and perhaps those from the other animals that constitute the wild plague reservoir (marmots, gerbils, camels, carnivores). This test is designed for surveillance and control of plague foci; as it does not recognize IgM, it is not designed for diagnosis of human plague.

In the development of future rapid diagnosis tests, protein A might be replaced by antibodies directed against human IgG or human IgM, keeping F1 as the capture antigen. Such a test would allow on-site serodiagnosis of a human plague outbreak. More elaborate tests could be conceived, such as two capture lines and two colours of beads to test the presence of both human