RAPID RISK ASSESSMENT

Plague outbreak, August–November 2014, Madagascar

4 December 2014

Main conclusions and recommendations

In Madagascar an outbreak of plague has been evolving since 31 August 2014; as of 16 November 2014, 40 people have died from the disease.

The ongoing plague outbreak in Madagascar with 119 cases reported to the World Health Organization (as of 16 November 2014) was not an unexpected event. However, the recent occurrence of two cases in Antananarivo, Madagascar's capital, poses a potential risk of a rapid spread of the disease due to the city's high population density, poor sanitation, deficient garbage collection, and the overall weakness of the healthcare system.

Despite the risk of further spread, the risk of contracting plague for EU travellers to the affected area in Madagascar is considered to be very low.

The local authorities are experienced in responding to plague outbreaks and have set up a control coordination committee with dedicated funding to support response measures. There is no restriction of movement in and out of Antananarivo, where the two urban cases occurred, which is consistent with the standard response to plague outbreaks in Madagascar.

Resistance of *Yersinia pestis* to antibiotics seems very limited. However, circulating strains are monitored to provide accurate public health information on *Y. pestis* antimicrobial susceptibility.

WHO does not recommend any travel or trade restrictions based on the current information available for this outbreak.

Source and date of request

ECDC internal decision, ECDC Round Table report, 24 November 2014.

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Public health issue

This rapid risk assessment of a plague outbreak in Madagascar addresses the following public health questions:

- Does the current outbreak of plague in Madagascar increase the overall risk for the spread of infection?
- What is the risk to EU citizens travelling to or visiting the affected areas?

Consulted experts

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Disease background information

Disease information

Plague is a bacterial zoonotic disease caused by the gram-negative bacillus *Yersinia pestis*. In several parts of the world (Africa, Asia and the Americas), the bacteria is maintained in an enzootic cycle involving animal reservoirs and fleas. Rodents are the most important animal reservoirs but other mammals, including domestic cats, dogs, rabbits and hares, can get infected [1,2].

Most frequently, human infections occur in households during an epizootic in synanthropic rats. The bacillus is often transmitted through the bite of infected fleas, but infected humans may also transmit disease to other people [3]. More rarely, humans get infected during an epizootic in a natural focus, when fleas are seeking a blood meal after the death of infected rodents.

There are three main transmission routes of plague to humans:

- The bite of an infected flea is the most common transmission route. It is usually involved in the transmission of the bacillus from plague–infected rodents to humans but the bacillus can occasionally be transmitted between humans, through the bites of human fleas (*Pulex irritans*).
- Direct contact when handling an infected animal can also result in human infection. The bacteria can penetrate the human organism through skin lesions or mucous membranes of the mouth, nose or eyes.
- Airborne transmission of the infective agent can occur in cases of pneumonic plague, when bacteria-containing droplets are breathed in by other person.

Plague occurs in three main clinical forms:

- The most common form, the bubonic plague, results from the infection of the lymph nodes that drain the inoculation site of the bacillus. After an incubation period of one to seven days, patients develop sudden onset of fever, headache, chills, and weakness and the infected lymph nodes develop into suppurative lymphadenitis (swollen, tender, and painful lymph nodes), called buboes. Bubonic plague has a fatality rate of 50–60%. It is not transmitted from one person to another unless there is direct contact with pus from the suppurative buboes.
- The second clinical form, the pneumonic plague, can result from direct infection of the airway system (primary pneumonic plague) or seeding in the lungs as a result of bloodstream infection (secondary pneumonic plague). The incubation period is very short, one to four days or even less than 24 hours. Patients develop fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, cough, and sometimes bloody or watery mucous. The pneumonia may cause respiratory failure and shock. Untreated pneumonic plague is invariably fatal. This form is highly transmissible between humans.
- The third form, the septicemic plague, is due to the dissemination of the infection in the bloodstream. Patients develop fever, chills, extreme weakness, abdominal pain, shock, and possibly bleeding into the skin and other organs. Skin and other tissues may turn black and die, especially on fingers, toes, and the nose. It can also result in meningitis, endotoxic shock or disseminated intravascular coagulation. Septicemic plague can occur as the first symptom of plague, or may develop from untreated bubonic plague.

Definitive diagnosis for plague is made through the isolation and identification of *Y. pestis* bacteria in clinical specimens or a diagnostic change in antibody titres in paired serum samples. Smears are coloured with Giemsa or Wayson stain and checked for the presence of bipolar staining gram-negative bacteria. Culture of tissue samples (lymph nodes, liver, spleen, lung, bone marrow) can be done. Acute-phase serum can be investigated in ELISA or (less common) direct immunofluorescence tests for the presence of antibodies against the specific *Y. pestis* F1-capsular antigen. The ELISA can also be used for antigen detection. Small quantities of *Y. pestis* can be detected in PCR assays. New optical fibre biosensor techniques for plague antigen and antibody detection are under development and have promising sensitivity and specificity characteristics but are not yet routinely available.

Transmission of plague through transfusion and transplantation is theoretical whereas the absence of reported cases and the virulence of the pathogen make asymptomatic bacteraemia unlikely.

Plague can be avoided by reducing contact with wild rodents and their fleas, either through personal protection or by environmental sanitation including rodent and flea control. In natural foci, monitoring programmes should be set up so that control can be promptly initiated. Medical staff should wear gloves and masks when nursing plague patients. There is no approved vaccine but antibiotics can be used as prophylaxis.

Plague can be successfully treated with antibiotics. Antibiotic treatment should begin as soon as possible after laboratory specimens are taken. The mortality rate depends on how soon treatment is started, but without treatment the mortality is high. Control measures during outbreaks include isolation procedures for suspected cases, targeted chemoprophylaxis, sanitation and vector control [4]. Overcrowding and cool temperatures facilitate transmission.

Yersinia 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 the bacteria within 1 to 10 minutes [5].

Plague in Madagascar

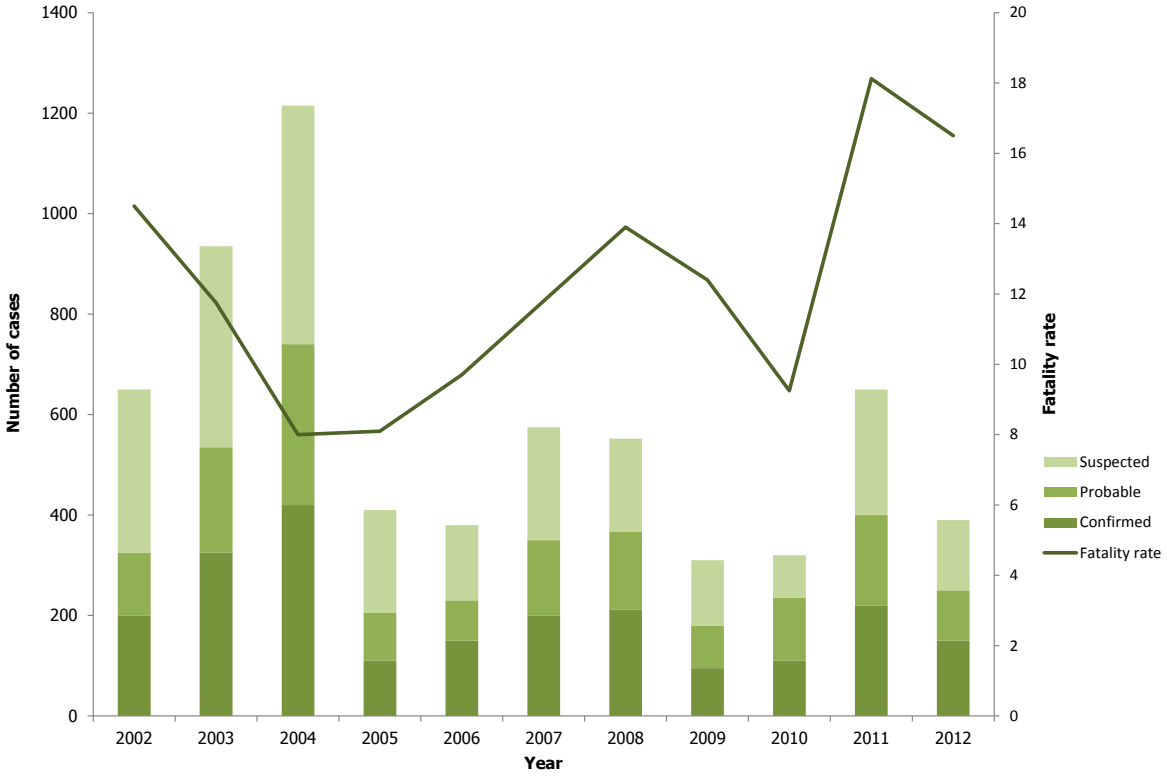
There are natural foci of plague infection in rodents in many parts of the world. Plague in wild rodents has been detected in central, eastern and southern Africa, South and North America and in large areas of Asia. In some areas, contact between wild and domestic rats is common, resulting in sporadic cases of human plague and occasional outbreaks [6]. According to WHO, 21 725 persons were infected with plague worldwide in the first decade of the 21st century, accounting for 1 612 deaths and a case fatality rate of 7.4 percent [7]. Plague is endemic in Madagascar, where 45% of all African cases have been notified in the past 15 years.

Plague was introduced into Madagascar in 1898 from India by rat-infested steamships [8]. Human cases of plague had never disappeared in Madagascar but the incidence dropped dramatically after the 1930s, but increased again in 1990, with more than 200 confirmed or presumptive cases reported each year since [9]. With the exception of the west coast port of Mahajanga, plague is mainly endemic in areas more than 800 m high. In these highlands, the human plague season is September to April, while in the Mahajanga area it is July to November [8]. *Xenopsylla cheopis* (Siphonaptera: Pulicidae) fleas have been known as the primary plague vector in urban areas, whereas *Synopsyllus fonquerniei* fleas have been usually involved in plague transmission in rural areas.

Despite surveillance and control measures to prevent the spread of cases, the elimination of plague has been difficult because the host and reservoir of the bacillus, *Rattus rattus*, is both a domestic and a sylvatic rat. *R. rattus*, as a documented source of *Y. pestis* infections in Madagascar, progressively acquired resistance to the infection so the mortality linked to bacteria transmission within the rodent population might be unnoticed [10,11]. Furthermore, the isolation of the first multidrug-resistant strain of *Y. pestis* in 1995 [12] and the increasing resistance of fleas to insecticides [13] have caused much concern. The national plague control programme, implemented in Madagascar for several decades, has been hampered by operational and managerial difficulties.

During January 2008–December 2012, the number of human plague cases reported in Madagascar ranged from 312 to 648 per year. Of these, 61.8%–75.5% were laboratory confirmed. Most of the confirmed cases were bubonic plague (>83%), which commonly results from flea bites, suggesting that these bites were the most common mode of *Y. pestis* transmission [14] (Figure 1). The case fatality rate (CFR) sharply increased in 2011 and 2012 [15]. In 2013, 346 probable and confirmed cases were reported from 34 affected districts, with a CFR of 20% (M. Rajerison, personal communication).

Figure 1. Case frequency and fatality rate of plague, Madagascar 2002–2012 [15]



Source: Graph based on data from the Institut Pasteur, Madagascar [15]

Event background information

The current outbreak of plague has been evolving since 31 August 2014 when the first case was notified by the Ministry of Health in a male child from Soamahatamana village in the district of Tsiroanomandidy. The child died on 3 September. In September 2014, 25 cases were reported, including 14 fatalities (56%) in four districts in three regions [16]. According to WHO, as of 16 November 2014, Madagascar reported 119 cases and 40 deaths (CFR 34%). Only 2% of reported cases were of the pneumonic form. Sixteen districts in seven regions were affected. Two cases, including one death, have been reported in the capital, Antananarivo, from two densely populated neighbourhoods [6]. According to media quoting the Institute Pasteur in Madagascar, as of 24 November, 138 cases, including 47 deaths (CFR 34%), have been reported since January 2014 [17].

High mortality is related to late detection of cases and poor healthcare systems, particularly in remote places with limited availability for care. Furthermore, a shortage of antibiotics, especially of streptomycin, from April to September 2014, could have significantly impacted the number of fatalities.

The situation is further complicated by the increasing level of resistance to deltamethrin (insecticide used to control fleas) that has been observed in the country [13]. The sensitivity of fleas to insecticides is systematically surveyed in Madagascar. A recent study on the susceptibility of *X. cheopis* fleas to deltamethrin showed that only two out of 32 different populations were susceptible to deltamethrin, four populations were tolerant, and 26 populations were resistant [18]. Combined with the number of bubonic plague cases, the results of Pasteur Institute of Madagascar have suggested a switch to an insecticide other than deltamethrin like fenitrothion for plague vector control in Madagascar.

Although one case of multiple-drug resistant *Y. pestis* has been documented in Madagascar in 1995, there is no further evidence of resistance to antibiotics [12,19]. Monitoring is important for providing accurate public health information regarding *Y. pestis* antimicrobial susceptibility.

According to WHO, Madagascar authorities activated their national task force to manage the outbreak. With support from partners including WHO, the Pasteur Institute of Madagascar, the 'Commune urbaine d'Antananarivo' and the Red Cross, the government of Madagascar has implemented effective strategies to control the outbreak. Personal protective equipment, insecticides, spray materials and antibiotics have been made available in affected areas [6].

A human plague case could signal increased transmission among rodents, but there are no reports of an ongoing epizootic in the area.

ECDC threat assessment for the EU

Assessment of the risk of increased transmission and spread of the plague in Madagascar:

- The occurrence of plague in Madagascar is not unusual. It seems, however, that the first cases occurred earlier in the season than usual, with cases reported as early as August. The number of cases could rise due to the 'seasonal increase' generally observed between October and March.
- Madagascar is endemic for plague, with the number of reported human cases ranging from 312 to 648 per year in the last five years. Zoonotic transmissions are expected, and Madagascar regularly reports human plague cases to WHO [20]. Madagascar's vast expanses of remote rural areas with limited access to medical care make containment difficult. The occurrence of cases in the capital, a city with an estimated 1.9 million inhabitants, is not unprecedented nor is it unexpected.
- There is a risk of rapid spread of the pneumonic form of the disease (if it emerges) due to the city's high population density and the weakness of the healthcare system. The present situation is further complicated by the high level of resistance of rats and fleas to most of the pesticides formerly used, along with a lack of medication, poverty, and poor hygiene. The substantial increase in fatality rate (34 %), compared with previous years, is an additional reason for concern, although the proportion of pneumonic cases is low (2%). Flooding expected during the rainy season may increase the risk of contact with rats.
- Additional efforts should be taken to contain the spread of the disease in urban settings. For example, the surveillance of rodents and fleas should be strengthened in order to detect critical situations before the emergence of clinical cases. This should be combined with better garbage and waste collection, and increasing awareness among the population. It is understood that the preventive and control strategies introduced by the government of Madagascar with support from partners – including WHO, the Pasteur Institute of Madagascar, the 'Commune urbaine d'Antananarivo', and the Red Cross – are being thoroughly implemented in the affected districts. Personal protective equipment, insecticides, spray materials and antibiotics have been made available in those areas.
- There is no evidence that close contacts of the last pneumonic cases have developed symptoms; most of them received prophylactic antibiotic treatment. There is also no evidence of additional human cases in the community surrounding the two last cases in Antananarivo. Pulmonary forms should be detected early in order to avoid further dissemination of the disease.

Risk to EU citizens travelling to or visiting the affected areas in Madagascar:

- At this point, the risk of contracting plague in the affected areas in Madagascar is considered to be very low for EU travellers unless there is direct contact with a new case of pneumonic plague, which is unlikely. The risk of importation to the EU through an incubating traveller arriving from Madagascar is considered very low. Around 225 000 non-resident visitors per year were reported between 2011 and 2013 and 105 000 were reported for the first six months of 2014. They originated mostly from France (47%), Italy (14%) and La Reunion (9%) [21]. The neighbourhood where the urban cases were reported does not usually attract foreign tourists. However, the multiple foci of transmission to humans within the country indicate a large spread of the bacteria within the rat population and potential occurrence in other places.
- WHO does not recommend any travel or trade restrictions based on the current information available.
- In urban areas, such as Antananarivo, the surveillance of epidemic risk indicators is highly recommended for the implementation of preventive vector control activities.

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