Plague Risk and Prevention

8

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Plague is a severe infectious disease caused by *Yersinia pestis*. It is primarily a disease of wild rodents and humans get infection mainly by direct contact with the tissues of an infected animal or by bite of an infected flea. Three worldwide plague pandemics had occurred in history, causing hundreds of millions of death [1], which affected the progress of civilizations of human beings. The natural plague foci are widely distributed in many areas of the world [2]. Traced by lineage-specific single nucleotide polymorphisms (SNPs), phylogenetic analysis showed that *Y. pestis* evolved in East Asia, then spread to the rest of the world including Europe, Africa, South America, and Southeast Asia [3]. Most human cases of plague occurred in areas of natural plague foci [4]. At present, the known natural plague foci are distributed in more than 50 countries in Asia, Africa, and the Americas. Even in some countries, such as Madagascar and the Democratic Republic of Congo, plague epidemics are still serious [4]. Cost-effective management and sustainable preventive strategies should be adopted to deal with the re-emerging of plague, which is threatening the modern world [5].

8.1 Overview of the Plague Epidemic in the World

According to the data of the World Health Organization, there were 28 countries in the world that reported a total of 54,352 cases of human plague from 1990 to 2018 [6–8]. These countries, 13 were in Africa (Madagascar, Zambia, Uganda, Botswana, Kenya, Malawi, Zimbabwe, Mozambique, Libya Arab Jamahiriya, Namibia, United

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W. Yang (ed.), *Prevention and Control of Infectious Diseases in BRI Countries*,
https://doi.org/10.1007/978-981-33-6958-0_8

Republic of Tanzania, Democratic Republic of Congo, and Algeria), ten in Asia (China, India, Kazakhstan, Mongolia, Viet Nam, Myanmar, Laos, Russian Federation, Kyrgyzstan, and Indonesia), and five in the Americas (Brazil, Bolivia, Peru, Ecuador, and the United States).

Entering into the Twenty-first century, according to WHO statistics, human plague continued showing a high incidence worldwide. From 2000 to 2009, a total of 21,725 human plague cases with 1612 deaths were reported [6]. The countries that recently occurred plague outbreaks included Uganda, China, the Democratic Republic of Congo, the United States, and Madagascar, et al. In terms of geographical distribution of plague, Africa is the most serious epidemic region. From 2000 to 2009, there were a total of 21,064 cases in Africa with 1558 deaths, accounting for 96.96% and 96.65% of the total cases and deaths in the world, respectively [6]. From 2000 to 2009, a total of 234 cases of human plague with nine deaths were reported in the Americas, and 437 human cases of plague with 46 deaths were reported in Asia [6]. More than 90% of the plague cases occurred in Africa in the last two decades, particularly in Madagascar, democratic Congo [6–8]. The most recent plague outbreak occurred at the Uganda–Congo border on March 5, 2019 [9].

From August to November 2017, Madagascar experienced a large pneumonic plague outbreak [10]. The plague outbreak mainly occurred in two large cities, Antananarivo, the capital, and Toamasina, a western port city. A total of 2417 cases with 209 deaths (fatality rate 8.6%) were reported in Madagascar in 2017, including 1854 pneumonic plague patients (76.7% of the total confirmed cases), 355 bubonic plague cases (14.7%), 1 septic plague case, and 207 cases of undetermined infection type [11]. The comparative high fatality rate was attributed to the higher proportion of pneumonic plague in 2017.

Up to 2020, China had identified 12 natural plague foci with different ecological types, which are distributed in 321 counties (cities and banners) in 19 provinces (Autonomous Region). The area of plague natural foci includes about 1.58 million square kilometers [12].

From 2001 to 2020, a total of 252cases of human plague with 44 deaths were reported in China [13], in which four plague outbreaks, whose lessons and experiences are especially worth being remembered. In 2005, An outbreak of pneumonic plague occurred in Yulong County in Yunnan Province. A total of five cases with two deaths were reported. In 2006, the area of the county was identified as a new *Apodemus chevrieri* and *Eothenomys miletus* plague focus [14]. In 2009, an outbreak of pneumonic plague occurred in Qinghai Province. The index patient got infection from an infected dog. A total of 12 cases were involved in the outbreak and three deaths. The event let us profoundly realized the dogs could cause human being's plague infection [15]. In 2014, Three pneumonic plague cases were separately reported in Gansu Province, where belongs to *Marmota himalayana* plague focus in the northern edge of the Qinghai–Tibet plateau [13]. In 2019, there were two pneumonic plague cases and two bubonic plague cases were identified in Inner Mongolia *Meriones unguiculatus* plague focus. In which the two pneumonic plague cases sought treatment in Beijing. The event became the major public health event in China in 2019 for it was the first time that pneumonic plague cases were

transported into Beijing since the founding of the People's Republic of China [16]. In next 2020, still in the *M. unguiculatus* plague focus, three human plague cases occurred and two cases died in Inner Mongolia Autonomous Region [13, 17].

8.2 Plague Risk and Prevention and Control Principles

8.2.1 Risk Assessment

Plague is primarily a disease of rodents in corresponding natural plague foci. The disease is transmitted from rodent to rodent via wild rodent fleas, contaminated soil, or cannibalism. Infected fleas play important role in transmission to human plague. Human plague is more frequently occurred by the bite of an infected flea and occasionally by direct contact with the tissues of an infected animal or inhaling infectious aerosol, such as soil contaminated by *Y. pestis* [16]. Person-to-person transmission typically occurs only among pneumonic plague patients. Wild rodent plague exists in many natural foci, and these plague foci are widely distributed in Continents except Oceania in our earth. Today, there are more than 50 countries of Asia, South America, North America, Africa, and Europe existed natural plague foci [18]. It should be said that the risk of human plague would be persisting as long as the animal plague is active in natural plague foci.

According to the route of infection, plague presents three main clinical forms: bubonic, septicemic, and pneumonic plague. Bubonic plague can further spread to the lungs or blood and cause pneumonic plague, or septicemic plague. Pneumonic plague, the most dangerous form of plague, is highly contagious infectious disease and can spread *Y. pestis* from person to person by airborne droplets. Septicemic and pneumonic plague can lead to a 30–100% of mortality ratio if no timely treatment were admitted [18]. The incubation period of bubonic plague infection is 1–7 days, while the incubation period of pneumonic plague is 1–3 days [18]. So a superficial "healthy personal" who coincidently was being in an incubation period could cause a long-distance dissemination through transportation. In addition, goods, such as goods in container, if it starts shipment from a field located in certain natural plague foci, the infected fleas or rodents in a container could be disseminated from one province to another in a country, or from one country to another country by road, rail, river, and sea.

Modern transportation has greatly facilitated the communication of people and the circulation of materials around the world. However, such convenience also increased the risks of disease spreading. Most of the countries along with the "One Belt and One Road" are developing countries, meanwhile, majority of them have natural plague foci. Therefore, national health services in these countries should work together to better identify the risk of human plague and animal plague, establish communication channels to exchange information about the occurrence of human plague cases and rodent surveillance data, as well as issue early warning bilaterally or multilaterally, carry out joint animal plague investigation, and joint control epizootics in border areas when necessary.

8.2.2 Principles of Prevention and Control

As mentioned above, plague is primarily a disease of wild rodents, while human plague, especially the pneumonic plague, possesses characteristics with high infectivity and fatality. So, comprehensive prevention and control measures should be emphasized. These measures include human plague and animal plague surveillance, epidemiological survey, laboratory timely inspection, and public health education. These measures for prevention and control of plague should be stressed as follows:

1. Prompt reporting. Prompt reporting is especially necessary for human plague cases, especially for the pneumonic plague, because this form of the disease can transmit directly from person to person via infectious aerosols. In China, an information management and report network system for plague surveillance has been established.
2. Strengthen surveillance. Here mentioned surveillance includes human plague monitoring and reservoir surveillance in natural plague foci. Effective human plague monitoring programs include collecting and reporting plague corresponding clinical information from hospitals or clinics, analyses and interprets epidemiological data of plague. On the other hand, continuous and thorough reservoir plague surveillance should be organized within the territory having endemic plague foci. Where all carcasses of rodents should be collected and perform laboratory tests. Such animal plague surveillance aims at detecting plague activity in susceptible rodent populations, assessing potential risk to humans, and issuing an early warning.
3. Patients' quarantine and ensure proper treatment. Patient should be placed in an isolation ward for treatment. It is stressed that patients could obtain appropriate and combined antibiotics treatment, necessary antibiotics susceptibility monitoring of *Y. pestis* should also be performed, especially when treatment failure is suspected due to antibiotic resistance. The corpse of a plague victim should be buried in a safe way. Healthcare staff should be trained and take adequate protective measures when they contact patients or collect samples. According to different situations, the quarantine of close contacts or a *cordon sanitaire* establishing around the infected locality and the field hospital could be considered as soon as the first case of pneumonic plague is detected.
4. Epidemiological investigation. The purpose of this investigation is to obtain detailed exposure history from the patient and further make an initial assessment of likely sources of infection and potential risks to others in certain areas.
5. Control of plague transmission. The most important and effective measure to break the chain of plague transmission is by proper application of effective insecticides. It must be emphasized that immediate control of flea vectors should precede to any measures against rodent hosts, or simultaneously. Because killing rodent hosts may result in the release of large numbers of fleas carrying plague organisms seek new hosts. Such a campaign actually is an eco-

logical disturbance activity, and it increases corresponding risk that free fleas inhabited in focus to attack humans. In addition, insecticide susceptibility tests must be done to determine the status of resistance of the flea populations and for selecting insecticides used. Once flea indices have been reduced, control of rodent reservoirs can be undertaken. In fact, the control of rodents in rural areas is a more difficult undertaking. The way of using proper rodenticides is only one of selection for reducing the rodent population. The most effective methods of reducing the rodent population in human dwelling are comprehensive public health campaign, including improvement in sanitation, waste disposal, storage of grain, and foodstuffs. It must be emphasized that in order to guarantee the efficiency of controlling plague rodent reservoirs, it is necessary to evaluate the effect of rodenticides including actual endemic extinguishing effectiveness in an active plague foci.

6. Enhance the ability of laboratory diagnosis. This kind of ability is directed at guaranteeing the surveillance programs are fulfilled smoothly. The process includes timely reservoir specimens shipment, bacteriological examinations, appropriate molecular and serological detection, as well as necessary quality control.
7. Emergency management and response. The successful control and disposal of plague outbreaks, especially for a large-scale epidemic, depends on efficient emergency management and response. This kind of ability should permeate into every corresponding organization at the national, provincial, municipal, and county levels.
8. Public Health Education. Public health education is an important part of plague prevention and control measures. The focus of education should emphasize on "Three Avoid": Avoid hunting and handling rodents, Avoid skinning and eating sick or dead animals, Avoiding take the reservoirs out the endemic locus; "Three Report": Reporting dead reservoirs or its reductions, Reporting suspect plague case, Reporting patient with high fever or die-offs; "Three Preventing": Preventing fleas bites, Preventing cats and dogs getting infected, Preventing ecological disturbance; "Three Applying": Applying insect repellent, Applying insecticides to kill fleas, Applying prophylactic antibiotics [19].
9. Risk assessment and early warning. Up to now, there is no fully risk communication among countries threatened by plague, including lack of risk communication after occurrence of human plague cases and lack communication on animal plague surveillance. It is necessary to lay emphasis upon risk assessment based on animal plague surveillance. In addition, early warning should not stay only on documents, but should tell the public and corresponding health authorities. Such measures could allow prevention and control programs to be implemented before human plague cases occurred.
10. Scientific research and technology communication. There should be a consensus that bilateral or multilateral scientific cooperation and technical communication could promote the world professionals unite and co-deal with plague epidemics or international transmission, which will great benefits the plague surveillance, risk assessment, early warning, and outbreak control.

8.3 Plague Control Cases

Case 1: Treatment of Plague in Yunnan, China, in 2016

1. **Overview**

In 2016, a human case of plague was reported in Yunnan Province [20]. The patient (female, 68 years old) was a retired worker from a farm in Puwen Town, Jinghong City. The initial symptoms of the patient included fever, fatigue, poor appetite, and malaise for several days. Thereafter, on June 1, she was admitted to the local hospital with a high fever (39.5 °C), accompanied by chills, sweating, nausea, vomiting, and coughing occasionally. No expectoration and hemoptysis were complained by the patient, and her pulse rate was 87 times/min, breath rate was 19 times/min, blood pressure was 130/50 mmHg; in addition, no swelling of superficial lymph node was detected and there was no obvious rale in the lungs; the X-ray chest film presented a common image of chronic bronchitis; WBC was 13.13×10^9/L, the absolute value of neutrophils was 12.2×10^9/L, the percentage of neutrophils was 92.91%; The bacterial culture of throat swab was reported as *Candida albicans*; but the vein blood culture was reported as *Yersinia pestis*. The patient recalled that she once collected dead commensal rats (local reservoirs, *R. flavipectus*) from a chicken house without any protection about 15 days ago [21]. The patient was finally diagnosed with primary septicemic plague and she was cured on June 18, 2016 [20].

According to the epidemiological investigation, a total of 58 close contacts of the patient, including four medical staff in the village clinic, 16 relatives or immediate family members, 11 neighbors, and 27 medical staff in Jinghong People's Hospital [21], were put in quarantine and medical observation. No abnormality was found in these contacts. According to reports from the residents in same community, the phenomenon of dead rats had appeared in the community since mid-May. During June 11–13, the field survey team in local CDC collected four dead rats (*Rattus flavipectus*) in the community. The reverse indirect hemagglutination tests for these rat's organs specimens were positive, and two *Y. pestis* strains were isolated from these carcass specimens. So the area outbreak that occurred was determined as a re-active *R. flavipectus* plague focus, for there once occurred human plague epidemics in Jinghong County in Yunnan Province in the 1980s and 2008 [21].

2. **Prevention and Control Measures**

The local government and relevant departments performed a comprehensive prevention and control measures to cope with the public health event, as follows:

First, the local government strengthened the organizational leadership. Corresponding plans associated with prevention and control were formulated. The local government established an epidemic prevention and control headquarters with the government leaders as commander, and ten professional and technical groups were organized, such as epidemiological investigation, inspection, public health campaign, rodenticide and insecticide, information notification, laboratory testing, and media publicity group. On one hand, the headquarter assigned concrete assignments to corresponding groups, on the other hand, the headquarters guided and inspected implementation of these measures.

Second, laboratory testing and patient treatment were strengthened. National, provincial, and municipal microbiological laboratories joined together to guarantee specimens from animals or patients were tested timely. A professional medical treatment team in the local hospital was organized for patient treatment.

Third, professional personnel were deployed to carry out epidemiological surveys. All close contacts were identified through such investigation. In this event, a total of 58 close contacts were quickly identified, and a 9-day home quarantine and medical observation were conducted. In order to strengthen the ability of information notification, an active fever patient searching campaign was performed, and a zero-reporting system of patients with fever with unknown causes was also initiated.

Fourth, a comprehensive public health campaign including rodenticide and insecticide measures were implemented to control plague epizootics. In order to guarantee the best effectiveness for breaking the chain of plague transmission, four concrete steps of public health measures were performed, as follows: performing public health and environmental cleaning campaign; conducting effective insecticides; killing rodent hosts by rodenticides; and application insecticides again. Next, the assessment of endemic extinguishing effectiveness was carried out to inspect the effect of above prevention and control measures.

In addition, an enhanced rodents surveillance, as well as health promotion and education was also carried out to consolidate these measures.

3. **Prevention and Control Experience**

The situation that the human plague epidemics had been successfully controlled in China benefitted from the efficient emergency management in China. In which, the first and most important experience in successful control of plague outbreaks lies in dealing with the plague epidemics according to corresponding infectious disease prevention and control laws and technical standards. Corresponding national regulations associated with public health emergency disposal provided a legal basis for plague emergency management when plague epidemic occurred. In such a situation, the local government burdens the responsibility to prevent and control plague outbreaks. In addition, local government coordinates all related departments, such as traffic units, public security agents, CDC, and hospital to respond quickly and more effectively. Through above-mentioned plague emergency management system, governments at all levels could ensure corresponding comprehensive prevention and control measures be carried out efficiently.

Case 2: Plague Epidemic in Madagascar in 2017

1. **Overview**

In 2017, Madagascar suffered an urban pneumonic plague epidemic in the capital city Antananarivo and major western city Toamasina [10]. From August 1 to November 26, a total of 2414 cases, contained confirmed, probable, and suspected cases of plague, were reported in Madagascar, including 202 deaths, with a case fatality rate of 8.6% [10]. The weekly number of reported pneumonic plague cases increased significantly at the end of September 2017, reaching a peak of 423 cases in the week beginning on October 2, 2017. On November 27, 2017, the Health

Ministry of Madagascar announced the urban pneumonic plague outbreak was controlled.

Among these plague cases, there were 1878 cases of pneumonic plague, 395 cases of bubonic plague, 140 cases of no clinical types plague, and 1 septicemic case. Of the 1878 pneumonic plague cases, 32 were confirmed (2%) and 386 (21%) were probable plague cases. Of the 395 bubonic plague cases, 66 were confirmed cases (17%) and 73 (18%) were probable cases [10]. Only about 50 strains of *Y. pestis* were isolated totally. All strains were sensitive to the antibiotics following Clinical Laboratory Standards guidelines. Pneumonic plague occurs mainly in the cities of Antananarivo (288 / 418, 69%) and Toamasina (63 /418, 15%), with significant spatial clustering. The bubonic plague cases increased and peaked in the same period as pneumonic plague [10]. Of the 139 confirmed or probable cases of bubonic plague, 131 (94%) occurred in plague endemic areas that contained 31 districts in Antananarivo [10].

2. **Prevention and Control Measures**

The Madagascar's Public Health Ministry cooperated in response, with the aid of WHO, the Pasteur Institute of Madagascar, and other international agencies (China also organized and dispatched two expert teams to Madagascar). The Madagascar's Public Health Ministry launched emergency response field teams in Antananarivo and Toamasina to deal with the outbreak. The public health response measures are as follows [10, 11]:

1. All patients were placed in the isolation wards for treatment with sufficient doses of antibiotics, and all patients and contacts received treatment or prophylactic antibiotics.
2. Quick investigation of new cases was undertaken, strengthened epidemiological surveillance in all epidemic areas, including strengthening case detection, actively sought, tracked, monitored contacts, and provided free prophylactic antibiotics.
3. Vector and animal control was performed, including proper pesticides and public sanitation.
4. Collected, transferred, and tested samples. Applying rapid detection technology to improve diagnostic accuracy.
5. Improved public awareness of the prevention of plague; provided suggestions about infection control about funeral; improved awareness of medical staff and provide suggestions to promote case detection and protective measures.
6. Import and export port screening measures were implemented at Antananarivo and Nocibe International airports to prevent the international spread of pneumonic plague cases.

3. **Prevention and Control Experience**

The Madagascar plague in 2017 was a typical urban pneumonic plague epidemic. The epidemic had a huge impact on the economy and society in Madagascar in 2017. The plague epidemic in Madagascar came earlier in 2017. In previous years,

the plague usually happened from October to April of next year, but in 2017, it began in August. Patients were mostly concentrated in large central cities, with plague outbreaks occurred in some epidemic and non-epidemic regions. The intensity of the bubonic plague cases was basically the same as in previous years, but the intensity of pneumonic plague cases far exceeded that in previous plague epidemics in Madagascar. Because urban pneumonic plague and human-to-human transmission presented multipoint outbreaks in Madagascar and the pneumonic plague has a high fatality rate, so rapid and comprehensive measures were the key for controlling the urban pneumonic plague epidemic in Madagascar in 2017.

In this plague epidemics, WHO was invited to support corresponding breakout control. WHO sent more than 100 experts for assistance. Many countries or organizations also participated in the epidemic treatment. According to the published literature [10], lack of laboratory testing capabilities in the field should be the reason that too many untyped cases were reported in this epidemic. In addition, there lacks continually and systematic reservoirs plague surveillance in Madagascar.

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