Review

YERSINIA PESTIS - OLD AND NEW CHALLENGES IN HUMANS AND IN ANIMALS

I. Mladenova-Hristova*, I. Tsachev

1 Department of Hygiene, Epidemiology and Infectious Diseases, Medical Faculty, Trakia University, Stara Zagora, Bulgaria
2 Department of Microbiology, Infectious and Parasitic Diseases, Faculty of Veterinary Medicine, Trakia University Stara Zagora, Bulgaria

ABSTRACT
The influence of environmental, dynamics in the evolution of the vectors and the susceptibility of the human organism are the most important factors for the infectious and epidemic process of Y. pestis. Travel, tourism, business etc. play a significant role in the emergence and spread of communicable, especially in the so-called “emerging” diseases, incl. plague. Persistence of the plague epizootic process is a function of dynamic interactions between flea vectors of disease and infected animals - reservoirs. The plague epidemic has followed climatic changes over the years. Increased humidity and temperature, associated with the global warming, could lead to an increase in the population of the reservoirs by increasing food supplies and flea population and could activate the epidemic process of plague, over the coming decades.

Key words: Plague, epidemiology, global warming, Yersinia pestis

INTRODUCTION
After the terrorist attacks of September 11, 2001, the epidemiology departments in ministries of health and medical universities, all over the world, have initiated many activities to improve the surveillance of emerging infections, especially the biological agents, used as bioweapons. Activities in bioterrorism preparedness and emerging infections include measures against plague like the infectious disease with the highest mortality rate in the human history!

IN HUMANS
The first known pandemic of plague in people is called „Justinian plague” which raged between 540 and 750 AD in the Roman Empire. It is assumed that it is estimated to have killed 50-60% of Europe’s population and has made the decline of the empire. After 800 AD plague disappeared for more than 500 years, until a second, so-called pandemic "Black Death", which has killed 25-30 million people in Europe. On the occasion of this pandemic, the Italian poet Petrarch has written: „Oh, Lucky you come after us and not experienced such endless troubles, you will think that our experience is fiction” (1, 2).

While the geographic origin of the "Justinian plague" is not known, the second and third pandemic (at the end of XIX century and early XX century) spread from the interior of Central Asia, where there are endemic areas of Yersinia pestis infectious process. The first cases of human infection is the result of contact with infected wild animals - through flea, by consuming or processing of products from these animals (3, 4).

The etiology of "Black Death" remains controversial for many years and vague, raising doubts that another cause, not Y. pestis, is the basis of this pandemic. Technological developments in DNA sequencing dramatically extend the application of genetic analysis and with respect to samples of the old material.
Kirsten et al. described decoding the "ancient" Y. *pestis* genome in samples of the remains of victims of the "Black Death" (1348-1350) in London. The comparison with the genome of modern strains *Y. pestis* demonstrates that differences in "medieval" *Y. pestis* are insignificant. The high virulence of *Y. pestis* during this plague pandemic apparently not due to the bacterial phenotype. Possibly other factors such as the influence of environmental, dynamics in the evolution of the vector and the susceptibility of the human organism should be at the forefront of epidemiological discussions regarding *Y. pestis* infectious and epidemic process (5, 6).

Subject of discussion is whether the same etiology in Northern and Southern Europe. Haensch et al. reported for identification by genetic methods of bacterial DNA and specific proteins *Y. pestis* in human skeletons from mass graves in Northern, Central and Southern Europe, which could be associated with the "Black Death". Based on the 17 nucleotide polymorphism, and the absence of the deletion in the gene glpD- DNA these data demonstrate two previously unknown type *Y. pestis*, associated with various medieval mass graves. These two types *Y. pestis* are "ancestors" of modern biovars Orientalis and Medievalis. The results of this study clarify the etiology of the "Black Death" and show that plague was introduced into Europe at least two different routes and establishes an appropriate paradigm for the reconstruction of the ways of spreading the plague during this period (2).

The third plague pandemic began in the middle of the XIX century in China and India, where her victims are approximately 12 million. Much lower they are outside this region, due to the discovery of the causative microorganism in 1894, as well as vectors of plague, which helps to limit the plague epidemic process. Plague is in one of the first places in the arsenal of biological weapons. In Manchuria, where even now there are endemic foci, Japan developed a secret biological weapons program in 1934 lasted until 1945. It has been suggested that in the former USSR and the USA was founded biological weapons on the basis of *Y. pestis*, during the Cold War. In 1970 it was reported that if 50 kg *Y. pestis* aerosol spread over a city of 5 million people, pneumonic plague can develop at 150 000 people , while in 36 000 will be fatal outcome (7-10).

At present endemic foci of plague are primarily in Central and Southeast Asia, Africa, South America and western North America. Each year in the world register 1000-6000 cases (8, 9). In 1997, the World Health Organization reported 5419, of which 274 were fatal (11). Persistence of the plague epizootic process is a function of dynamic interactions between flea vectors of disease and follow-infected hosts (12). Foley et al. develop a mathematical model of endemic in the western parts of the United States for tracking the dynamics of plague (13). She enters for the first time in the New World during the third pandemic in the late 19th century and early 20th century, through infected rats Rattus rattus and infected rat fleas Xenopsylla cheopis. Door plague in U.S. is the port of San Francisco, California. The first case was in San Francisco in 1900, followed by outbreaks in California in 1907, 1919 and 1924. The last outbreak of pneumonic plague in the United States is in 1924/1925 in Los Angeles.

At least 18 species of rodents and 27 species of fleas are involved in *Y. pestis* epizootic process in the Western U.S. (14, 15, 16). Recently created a mathematical model of pneumonic plague, is focused on people without considering the zoonotic endemic, animals - sources and arthropods - vectors (17). A group of researchers tracked the effects of climate change on the dynamics of plague in the western regions of the United States using data from 56 years (1950-2005) (18). The final models of the activity of *Y. pestis* infectious process in California, based on the recent changes in climatic conditions, predict six future climate scenarios. These patterns suggest the idea that by 2050 climate change will reduce the risk of plague outbreaks in Southern California, but will increase the risk in the north. Modelling of endemic areas (ecological niches) could be a useful tool for studying and mapping of potential response to plague according to the climatic conditions (19).

Demographic and social factors also play an important role in the morbidity and unlikely occurrence of cases of plague in the United States would lead to major epidemics in the current and evolving public health infrastructure (20). Travel, tourism, business etc play a significant role in the emergence and spread of
communicable, especially in the so-called "emerging" diseases. Migration of people provides different routes of transmission in the special case of zoonoses (eg, yellow fever, plague, smallpox, monkeypox, SARS, etc.). Passengers in the international transport services increased by more than 1300 % in the last 50 years! More than 80 million people are legal and illegal immigrants! Primary prevention, epidemiological surveillance and health education remains the cornerstone for the control of zoonoses in the context of tourism and immigration phenomena (21, 22).

Neerinckx et al. examine the prevalence of plague in humans, using data from the sub-Saharan Africa for the period 1970-2007, they created a model to study the potential geographic distribution of plague and environmental characteristics of this natural - focal infection in Africa. This approach could be the basis for the testing of hypotheses concerning focal distribution of plague and its relation to historical factors, and environmental factors (23). In Madagascar plague was transmitted in 1898 and continues to be a significant health problem. It exists mainly in the central highlands of the island, but in 1990 he was brought again in the port city of Mahajanga, where it causes outbreaks. Using the methods of molecular epidemiology, SNP (single-nucleotide polymorphism), genotyping etc Vogler et al. examine the genetic diversity of Y. pestis to determine the reason for maintaining the continuity and spread the plague epidemic process. They have studied 262 isolates Y. pestis. The authors conclude that the prevalence of the plague is a dynamic and highly active process that depends on the lifecycle and relationships in natural focus, between the primary reservoir - black rat and its fleas as vectors, as well as by human activity (24).

Kaurrud et al. based on paleoclimate data create a model covering the period from 542 to 2000, in which data is entered for temperature, precipitation, the population of great gerbils (Rhombomys opimus, the most common rodent in Central Asia) condition of vegetation in Central Asia and the morbidity of the population from the plague. The conclusion of the researchers is that the climate fluctuations in Central Asia have a significant impact on the growth of the incidence of plague in humans in the region in the early 20th century and probably the last activity in 1500 years. The plague epidemic have followed climatic changes over the years, according to this first attempt at eco-epidemiological its reconstruction. (4, 25) Increased humidity could lead to an increase in the population of the reservoirs by increasing food supplies and flea population. During such changes in the late 18th century and mid-19th century about 2.5 million people in 18 provinces of China are suffering from plague. Unusually intense outbreaks of primary pneumonic plague are recorded in Manchuria in 1910-1911 and 1920-1921 (26, 27).

IN ANIMALS
Yersinia pestis infection is acknowledged in wild rodents, lagomorphs, camels, and less frequently, in dogs and cats.

Epizootology. Plague is a disease of a chronic stationary type, with very well expressed endemicity. The infection occurs via air route, is transmitted by bites of infected insects, as well as consumption of food and water contaminated by affected rodents in natural plague foci. The primary sources of infection are the different rodent species, and fleas serving as transmission vectors. In different regions of the world, 235 rodent species are identified as permanent reservoirs of infection. Infected rodents undergo a long bacteriaemia period during which blood sucking ectoparasites ingest yersinia as well. Chronically infected rodents could sustain and shed the infection over up to one year. In fleas, yersinia persist for up to 396 days, in bed bugs – up to 147 days, in flies – up to 18 days, in lice – up to 14 days and in ticks – 100-170 days.

Clinical signs. The incubation period of naturally occurring infection is 2 to 8 days. Three clinical forms of plague are known – bubonic, septicaemic and pneumonic. Bubonic form – affects and external and internal lymph nodes (enlarged and painful). The body temperature is elevated (39-40°C), dyspnea and tachypnea, accelerated and arrhythmic heart rate is, lethargy and difficult locomotion, sometimes lameness is observed. This form could last for a few days to 2-3 weeks and end with a fatal outcome, recovery or could spread into septicaemic or pneumonic forms. The differences between them are mainly in the extent of lung affection (less or more). In septicaemic plague, the body temperature elevation is substantial – up to 41.5°C. The
general condition of animals is significantly worsened. Abortions are observed in pregnant animals. Cough and lung oedema appear. Nasal discharge, mixed with blood, is also observed (28).

**Gross anatomy findings.** The septicaemic course is characterized with multiple haemorrhages in all organs and tissues, sometimes with swelling of parenchymal organs, fatty degeneration of the liver, kidneys and the myocardium. Lymph nodes exhibit non-purulent lymphadenitis or hyperplasia. The spleen is often enlarged, and lungs – pneumatic. The specific lesions in bubonic plague are predominantly in the lymph nodes. They are enlarged (the size of a goose egg at least), flocculent and spattered with haemorrhages. In a prolonged course, the lymph nodes become necrotic. The pneumatic form is characterised with hyperaemia and lung oedema.

**Diagnostics.** *Y. pestis* is most commonly isolated on blood and MacConkey agars, and for detection, IF, ELISA and PCR tests are performed. The bio-sample on guinea pigs and albino mice with visceral organs homogenate is also applied in laboratory practice. From serological methods, the agglutination (F1 antigen) and passive haemagglutination tests are used.

**Differential diagnosis.** From differential diagnostic points of view, plague should be distinguished from diseases with signs of sepsis, pneumonia and lymph node lesions such as anthrax, tularaemia, pasteurellosis, trypanosomiases, and lymphadenitis of other origin.

**Treatment.** Early treatment with antibiotics can be successful. The most stringent measures are needed before antibiotics are begun and during the initial stages of treatment. In the USA, there are however sporadic reports for healing of cats and dogs by treatment with aminoglycosides (28).

**CONCLUSION**
Climate change impact on the three components of the scheme which is transmitted plague - cause, vectors and reservoirs, and could explain some variations in its distribution - regional or larger scale.

We could expect that global warming over the coming decades will affect the epidemiology of plague by increasing the activity of endemics, increasing numbers of rodents and "harvest" of steppe vegetation.

**REFERENCES**