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Diseases of Human Plague in 1974 - 2003 in Kazakhstan

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Abstract

Plague is a natural focal zoonotic infection. The natural carriers of the plague bacteria are various animals (mostly rodents). A human becomes infected either by bite of an infected flea, or by direct contact with a sick animal (most often during cutting). From 1974 to 2003 on the territory of Kazakhstan 33 cases of people infected with plague (including 2 cases of bacteria carrier) were registered in 25 natural epidemic foci. Over the past 30 years bubonic, bubonic-septic, skin-septic, tonsillar-bubonic and tonsillar forms of the plague have been reported. The age range of people infected with plague ranged from 3 to 65 years. Among infected with plague the largest number were workers involved in various agricultural work and schoolchildren. By a sign of gender, the majority of cases are men. Sources of the disease were different: wild rodent fleas, camels, two cases of disease associated with cutting of plague-infected hare, one person became infected while cutting saiga carcass, one case of the disease was recorded as a result of a child bite by a wild rodent, an aerosol infection was registered in 9% of cases. During the years of observation the largest number of patients was recorded in July and in August. Modeling data on human plague disease using the K-function showed that there are clusters of outbreaks of human plague. Such clustering of outbreaks is observed at a distance of 1000 m, and from the distance between outbreaks of 4000 m there is a dispersed spatial arrangement of outbreaks. The proximity analysis showed that in outbreaks of plague from 1974 to 2003 there is a clustering of diseases of people with plague with a 99% confidence interval at a z-score value: - 2.03 and p values <0.01.

Keywords: human plague, natural plague foci, plague in Kazakhstan, infection disease, modeling, cluster

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INTRODUCTION

Plague is a natural focal zoonotic infection, man is not the main target of the plague bacterium. Various rodents, hares and foxes are can be infected too, and among domestic animals - camels. Rodents, unlike humans, have a certain immunity to the plague. The bacterium “allows” to survive part of sick animals, thereby maintaining their own habitat. But the human body is not such for the plague, so people have practically no immunity against this extremely dangerous infection (Voitsekhovsky, 2015, February 23). The causative agent of plague is the gram-negative bacterium Yersinia pestis. It was discovered in June 1894 by the French Alexander Yersen. It is a zoonotic bacterum usually found in small mammals and their fleas (Inglesby et al. 2000, Perry and Fetherston 1997).

As an animal disease, plague is found in all continents, except Oceania. There is a risk of human plague wherever the presence of plague natural foci (the bacteria, an animal reservoir and a vector) and human population co-exist. Plague epidemics have occurred in Africa, Asia, and South America; but since the 1990s, most human cases have occurred in Africa. The three most endemic countries are the Democratic Republic of Congo, Madagascar, and Peru. In Madagascar cases of bubonic plague are reported nearly every year, during the epidemic season (between September and April) (Nikolaev 1968, Plague 2017, October). The initial limits of geographical distribution were gradually narrowed. But with help of human plague spread around the world. In primary foci main vectors were local rodents. Instead in secondary foci (like towns near ports) it became rats. At first, the disease spread rapidly, but with the development of human society, its level and economic activity had a great influence on this, as well as changes in the natural conditions, occurring independently of humans, had an effect. Changed the type of buildings in the settlements. Wooden houses, that were favorable home for rats and fleas, gave way to stone. Slowly but systematically improved hygienic skills of people. Also as the vast virgin lands were developed, on which the steppe rodents had previously

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live, European natural foci of plague stopped exist (Daniel 1990, Ershova et al. 2018).

In the past, the plague caused three pandemics, which caused the death of millions of people, devastated cities, villages, destroyed states. Nowadays, epidemic outbreaks of plague pose a serious threat to public safety, which are characterized by a sudden onset, high mortality, and a significant level of costs for conducting anti-epidemic and anti-epizootic measures (Inglesby et al. 2000, Perry and Fetherston 1997). According to available data of the World Health Organization, from 1989 to 2004 there were about forty thousand cases of disease in 24 countries, and mortality was about 7% of the number of sick (David et al. 1999). And from January 2010 to December 2015 in the world 3248 people became sick with plague, 584 of them died (World Health Organization 2016). Every year the number of people infected with plague is about 2.5 thousand people, and without a downward trend. In a number of countries in Asia (China, Mongolia and Vietnam), Africa (Congo, Tanzania and Madagascar), the Western Hemisphere (USA, Peru) human infections are recorded almost annually (David et al. 1999).

The spread of plague has also been promoted by its use as a biological weapon in the past, and with the development of technology this is a serious potential danger to the modern world. In particular, in ancient China and medieval Europe, the corpses of infected animals and human bodies were used to infect water sources. There are also historical data on cases of ejection of infected material during the siege of some cities. During the Second World War the Japanese military developed samples of biological weapons intended for the mass dumping of a specially prepared plague carrier - infected fleas (Barenblatt 2004). Among pathogens that act as potential biological weapons or bioterrorist weapons, Y. Pestis (which is a category A of biological agent) ranks first in terms of the danger, importance, and potential transmission of the pneumonic form of this disease in humans (Gage and Kosoy 2005, Glynn et al. 2005, Özer 2018).

In the Middle Ages, the plague was practically not treated, the actions were mainly reduced to cutting out or burning the plague buboes. People didn't know the true cause of the disease, so there was no idea how to treat it. Starting from the 13th century, the plague was tried to be quarantined. For the first time, a vaccine that was effective against bubonic plague was created at the beginning of the 20th century by Vladimir Khavkin from the plague sticks killed by the temperature. More effective are the live vaccines that was created and tested on herself by Pokrovskaya Magdalina Petrovna in 1934. The turning point in the treatment of plague was reached in 1947, when Soviet doctors were the first in the world who use streptomycin to treat the plague in Manchuria. As a result, all patients who were treated with streptomycin, including the patient with pneumonic plague, who was considered hopeless, recovered. Treatment of patients with plague is currently carried out with the help of antibiotics, sulfonamides and therapeutic anti-plague serum.

WHO developed guidelines for the prevention of the spread of plague. Here is their summary World Health Organization. (2017, October):

1) Find and stop the source of infection. Identify the most likely source of infection in the area where the human case(s) was exposed, typically looking for clustered areas with large numbers of small animal deaths. Institute appropriate infection, prevention and control procedures. Institute vector control, then rodent control. Killing rodents before vectors will cause the fleas to jump to new hosts, this is to be avoided.

2) Protect health workers. Inform and train them on infection prevention and control. Workers in direct contact with pneumonic plague patients must wear standard precautions and receive a chemoprophylaxis with antibiotics for the duration of seven days or at least as long as they are exposed to infected patients.

3) Ensure correct treatment: Verify that patients are being given appropriate antibiotic treatment and that local supplies of antibiotics are adequate.

4) Isolate patients with pneumonic plague. Patients should be isolated so as not to infect others via air droplets. Providing masks for pneumonic patients can reduce spread.

5) Surveillance: identify and monitor close contacts of pneumonic plague patients and give them a seven-day chemoprophylaxis. Chemoprophylaxis should also be given to household members of bubonic plague patients.

6) Obtain specimens which should be carefully collected using appropriate infection, prevention and control procedures and sent to labs for testing.

7) Disinfection. Routine hand-washing is recommended with soap and water or use of alcohol hand rub. Larger areas can be disinfected using 10% of diluted household bleach (made fresh daily).

8) Ensure safe burial practices. Spraying of face/chest area of suspected pneumonic plague deaths should be discouraged. The area should be covered with a disinfectant-soaked cloth or absorbent material.

Preventive measures include informing people when zoonotic plague is present in their environment and advising them to take precautions against flea bites and not to handle animal carcasses. Generally people should be advised to avoid direct contact with infected body fluids and tissues. Prevention of possible foci of the disease consists in conducting special quarantine measures in port cities, deratization of all vessels that take international routes, creating special anti-plague institutions in the steppe areas where rodents are found, identifying plague epizootics among rodents and fighting them (Anisimov and Amoako 2006, Musagalieva 2013).

There are three main clinical forms of plague infection: bubonic, pneumonic and septic, as well as mixed types. The plague pathogen can enter the human body through blood, skin and mucous membranes. When an infected by a plague bacteria flea bite a human a papule (skin form) may occur at the site of the bite. Then the process spreads through the lymphatic vessels and the reproduction of bacteria in the lymph nodes leads to their sharp increase, merger and the formation of buboes. Further development of infection can lead to the development of a septic form, accompanied by the defeat of almost all internal organs. In rare cases, the disease develops in the pneumonic form. From the moment of the development of the plague pneumonia, the pneumonic form of the disease is already transmitted from person to person by airborne droplets - an extremely dangerous one, with a very rapid course. Anginal or tonsillary plague is rare. In 1999, in Kazakhstan, one case of tonsillar-bubonic plague and two cases of excretion of Y.pestis from the throat of people without clinical manifestations of the plague who had contact with a plague patient were reported (Pollitzer 1953).

Case-fatality ratio of 30% to 60% for the bubonic type, and is always fatal for the pneumonic and septic type when left untreated. In the modern therapy, mortality in the bubonic form does not exceed 5-10 %, but with other forms, the percentage of recovery is high enough if treatment is started early. Confirmation of plague requires lab testing. The best practice is to identify Y. pestis from a sample of pus from a bubo, blood or sputum. A specific Y. pestis antigen can be detected by different techniques. One of them is a laboratory validated rapid dipstick test now widely used in Africa and South America, with the support of WHO. Antibiotic treatment can save lives. In some cases, a transient septic form of the disease is poorly susceptible to in vivo diagnosis and treatment ("fulminant form of the plague") (Inglesby et al. 2000, Perry and Fetherston 1997, Ganin 2006). Anti-plague vaccine exists, but WHO does not recommend vaccination, except for high-risk groups (such as laboratory personnel who are constantly exposed to the risk of contamination, and health care workers). Domestic camels are vaccinated as well (World Health Organization. (2017, October).

At present, the circulation of the plague microbe has been established in populations of more than 200 species of wild rodents inhabiting the natural plague foci on all continents except Australia and the Antarctic (Sariyeva et al. 2018). According to the main carrier, natural plague foci are divided into inhabited by gophers, marmots, gerbils, voles and pikas. In addition to wild rodents, the epizootic process sometimes includes so-called synanthropic rodents (in particular rats and murids), as well as some wild animals (hares, foxes, saigas) that are the object of hunting. Among domestic animals camels suffer from plague. There are sporadic cases of the disease of predatory animals that feed on rodents (feline, wolves, coyotes) (David et al. 1999). There are some documented facts of human infected by plague around the world. For example, a boy fell ill with plague and died as a result of hunting for woodchucks in the Sarydzhazsky plague focus, Kyrgyzstan (Sariyeva, Abdel, Shabunin, Sagiyev, Abdikarimov, et al.) In China, a person became infected with plague and died as a result of contact with a dog that caught a groundhog infected with plague (Ge et al. 2015). In 1997 12 cases of plague were reported in Jordan by people associated with slaughter a sick camel (Arbal et al. 2005). In the United States, a case of human plague was reported associated with a meadow dog bite (Gunnison's prairie dog) (Melman et al. 2018). Another case of human plague occurred as a result of aerosol infection of a person, as was the case in 1999 in Kazakhstan. In 2007 a 37-year-old biologist found a mountain lion's corpse in Grand Canyon National Park, Arizona. Then he transported by his car the body to his garage, where he made an autopsy of the animal's

body without a protective suit. In two days, he felt bad: high temperature, fever, and coughing with blood. The next morning, the biologist went to the nearest clinic, where he was diagnosed with a viral infection and sent home with the necessary instructions in case of deterioration. About 6 days after contact with the lion's body, the biologist died. Plague cultures were isolated from the lungs and prepared. Isolates of Y. pestis, cultured from the tissues of a mountain lion, were studied by pulsed field electrophoresis (PFGE) and turned out to be identical with Y. pestis isolates isolated from a biologist. As a result of the epidemiological study, it was concluded that the infection by the primary pneumonic plague of the biologist occurred by aerosol during the autopsy of the dead animal (Wong et al. 2009).

There are several ways to transmit plague bacteria:

- transmissible (bite of infected fleas, rarely ticks);
- contact-wound (cutting animal, rarely animal bite);
- alimentary (with food through the mouth);
- air-dust (inhalation with dust).

The transmission of plague between animals and humans is carried out by at least 80 species of fleas. In a natural focus, infection usually occurs through the bite of an infected flea that previously fed on a sick rodent. Infection also occurs during the hunt for wild rodents, many of which have commercial value, and their further processing. Mass diseases of people occur during the slaughter of a sick camel, skinning, cutting, processing. An infected person, in turn, is a potential source of plague, the transmission of a pathogen from which to another person or animal, depending on the form of the disease, can be carried out by an airborne droplet, contact or transmission (The war with the "black death": from defense to attack 2006, Mead 2015, Suntsov and Suntsova 2006).

Outbreaks of plague in humans are preceded by an epizootic among rodents that are seasonal and periodic in nature. Acute epizootics, as a rule, occur in the spring, when rodents leave the burrows, and the young begin to move along new burrows, as well as during the mass migration of fleas in search of a new host. A person is involved in this process by chance during staying on the epizootic territory. The probability of infection increases significantly with the inclusion of synanthropic rodents in the epizooty. Diseases among people are caused by flea bites, direct contact with infected animal tissues, consumption of insufficiently cooked meat products, or inhalation of animal excreta or patients with pneumonic plague (Anisimov 2002, Anisimov et al. 2004, Musagalieva 2013).

Primary cases of human infection with plague occur as a result of flea bites or direct contact with sick animals. A person becomes a source of plague only in those cases when the primary bubonic form of infection is complicated by secondary pneumonia. Then the plague begins to spread in the form of airborne infections and becomes especially dangerous due to the high contagiousness. It was the pneumonic form of the plague that caused the epidemics and all three pandemics that led to the death of millions of people (Musagalieva 2013).

The considerable part of the territory of Kazakhstan is located on the range of one of the biggest plague foci in the world – Central Asian desert plague focus, occupying vast zone of a desert and semi-desert of the Central Asia and Kazakhstan. In Kazakhstan 39% of territory (1.4 million squares km) is the area of the plague natural foci. In Kazakhstan 113 strains of the plague microbe were isolated on the territory of the Aral-Karakum, Kyzylkum, Moiynkum and Pribalkhash natural foci. By immunological methods the circulation of the plague microbe was confirmed on the territory of the Taukum natural focus. The most complex epidemiological situation was noted in the southern and central parts of the desert zone within the borders of Almaty, Zhambyl and Kyzylorda regions of Kazakhstan. Epizootics with isolation of hundreds of virulent plague strains from the rodents and fleas are registered annually. The primary carrier of plague in this focus is Great gerbil. In this focus Yersinia pestis, besides Great gerbil, is detected at more than 20 species of rodents. Twenty seven species of wild rodent's fleas are plague vectors (Aikimbayev 1992, Aikimbayev et al. 2010, Burdelov 2010).

On the territory of the Republic of Kazakhstan, diseases of the plague of people have been officially documented since 1904 (Rivkus et al. 1992). The deadly plague outbreaks took place in Kazakhstan many times. At first there was an epidemic of 1905-1906. Then hundreds of people were killed by this dangerous disease in 1923-1924. After it shook the region in the 50s. But the most monstrous was the epidemic that hit the Ural steppe precisely at the beginning of the 20th century.

In the middle of the XIX century, the plague in the territory of present-day Kazakhstan, was a frequent occurrence. Basically, it was recorded among the

livestock. During the period from 1883 to 1888 in the Inner Horde about 800 heads of livestock died from the plague annually, which caused great losses to the population. At the same time in the XIX century it was only about the disease of animals, the human victims were silent. And only at the beginning of the 20th century, when people began to massively perish with animals, they paid more attention to the problem. But the doctors did not know how to fight the plague microbe. Taking measures, only the epidemic did not spread.

From the cities of the Russian Empire, to Kazakhstan were sent detachments of doctors, who tried to find out the reason for the mass death of people. Among these heroic people, who subjected themselves to mortal danger, were the famous Astrakhan physician Hippolytus Deminsky, professor Daniil Babel, professor of the Kharkov Veterinary School Edward Ostrovskii, and the local doctor Mazhit Chumbalov, who became a state first plague specialist of Kazakhstan

In January 1901, the causative agent of plague from a deceased person was isolated for the first time in Kazakhstan. At that time in the village of Tekebay-Tubek, which is in the territory of the West Kazakhstan region, the entire population died in a month and a half - 151 persons. And in 1905, the largest plague outbreak in the history of the region, known as the "Beketaev outbreak", appeared in Western Kazakhstan and Astrakhan province. According to official dates, from November 1905 to February 1906, the plague struck 177 families in this sparsely populated area, 659 people died. An epidemic affected 55 tracts. Along with the people, also in great numbers died animals.

To study the impending plague epidemic it was necessary to organize special anti-plague laboratories, warehouses with medical equipment in the field. Through the efforts of Professor Daniil Zabolotny, in the villages of New Kazanka, Jambeit, Krasny Kut, Kalmykovo, in 1912-1913, special laboratories were opened. And in 1914 in Uralsk receive the central anti-plague laboratory, which marked the beginning of the official history of the anti-plague service of Kazakhstan. At the same time, the primary task was set not only to deal with outbreaks, but also to prevent them.

However, the measures taken were not enough, and in 1923–1924, an epidemic of plague again broke out in the Ural region, which killed about 350 people. Akbasty-Avan outbreak in 1945 claimed 127 lives. In 1947, in the area of Bakanas, in the village of Kok-Uzek, there was an outbreak of plague that killed about 40 people. Nearly 500 people died from the plague in the Atyrau region (Kenzhegalieva 2015, April 3).

The restoration of the chronological data of the diseases of the people by the plague is painstaking work, requiring the retrieval of historical data, which are often almost lost. The study of retrospective data from human plague diseases has both scientific and practical value in the study of plague, which makes it possible to build an epidemiological link between the relationships between natural foci of plague and man. Currently we have collected historical data on plague outbreaks from 1974 to 2003. Work on the collection of retrospective data on the disease of people with plague in Kazakhstan continues. The last case of the plague of people was registered in 2003. But the epizootics are detected in different regions almost every year.

Above the study of the problems of the spread, prevention and control of the plague in Kazakhstan works the Kazakh Scientific Center for Quarantine and Zoonotic Infections named after M. Aikimbaev. Also in the republic there is a developed anti-plague system, consisting of many stations. This is a fairly powerful, organized and structured service for the control of especially dangerous infections throughout the country. Since 2003, no cases have been recorded in Kazakhstan. This is the main result of the efforts of the anti-plague services. And their constant task is that those terrible outbreaks of the plague never be repeated.

MATERIALS AND METHODS

For this study archival materials were collected on plague diseases in Kazakhstan from 1974 to 2003, obtained from the archives of the Kazakh Scientific Center for Quarantine and Zoonotic Infections named after M. Aikimbaev, anti-plague stations of Kazakhstan. Anti-plague station specialists have helped in the collection of geographic data of disease registration sites. The geographic coordinates of the sites for the registration of human diseases by the plague were determined using paper archival geographical maps. The coordinates were then transferred from paper to a spatial database created in ArcGIS.

In a cluster analysis of the nature of outbreaks of plague among humans and the refutation of the null hypothesis, we applied 2 types of statistical data processing. To determine the degree of clustering and dispersion of cases of human plague cases, we used a K-function (second-order analysis) simulation in PPA Statistics. For the proximity analysis the QGIS program was used (QGIS Tutorials and Tips). Interpretation of

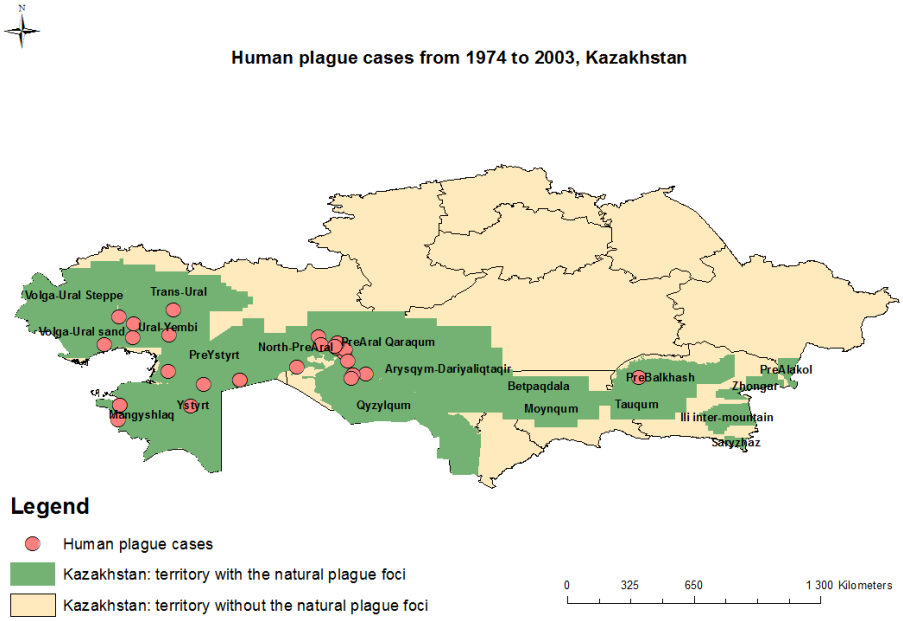


Fig. 1. Registration of human cases of plague from 1974 to 2003 in Kazakhstan

Table 1. The number of patients with plague people in the Republic of Kazakhstan for the years 1974-2003

Years	Regions of Kazakhstan					Total	Confirm	
	Aktobe	Almaty	Atyrau	Kyzylorda	Mangystau		Bacterio-logically	Serolo-gically
1974	0	0	0	0	2	2	2	
1975	0	0	0	0	2	2	2	
1979	0	0	0	1	0	1	1	
1988	0	0	1	0	0	1	1	
1989	0	1	1	0	0	2	2	
1990	0	0	1	2	0	3	2	1
1991	0	0	0	1	0	1	1	
1992	0	0	1	0	0	1	1	
1993	1	0	1	1	0	3	3	
1997	0	0	1	0	0	1	1	
1999	6*	0	0	3	0	9*	9	
2001	0	0	0	2	0	2	1	1
2002	0	0	0	1	0	1		1
2003	0	0		1	3	4	3	1
Total	7* (21%)	1 (3%)	6 (18%)	12 (37%)	7 (21%)	33*	29*	4

* Includes 2 cases of bacteria carriers

the results was performed using reference data from ArcGIS Pro (ArcGIS Pro. Tool References). Statistics on the population of Kazakhstan from 1974 to 2003 were obtained from the site about population of the country (Population of Kazakhstan).

Clinical forms of plague were classified according to the G.P. Rudnev's plague classification (1936) (Aikimbayev 1992). To calculate morbidity, mortality, mortality, methods from the methodological manual were used (Dicker et al. 2012).

RESULTS AND DISCUSSION

From 1974 to 2003 in Kazakhstan 33 cases of human plague were reported (including 2 carrier cases) in 25 epidemic plague foci. Of the 33 patients recovered 21 people (64%).

The outbreaks of plague were recorded in the following natural foci: Balkhash (1); Volga-Ural sandy (1); Volga-Ural steppe (1); Ural-Embenski (4); Preustyurt (2); Ustyurt (2); Mangyshlak (2); North Aral (4); Priaral-Karakum (7), Kyzylkum (1). The geographical location of the disease registration sites, as well as the natural foci of the plague in Kazakhstan, are shown in **Fig. 1**.

As can be seen from the figure, the foci of infection are confined to deserts and semi-deserts, where the main carriers of the plague - marmots, ground squirrels and pikas live.

All collected data on confirmed infected people in Kazakhstan were sorted by regions and years and described in **Table 1**.

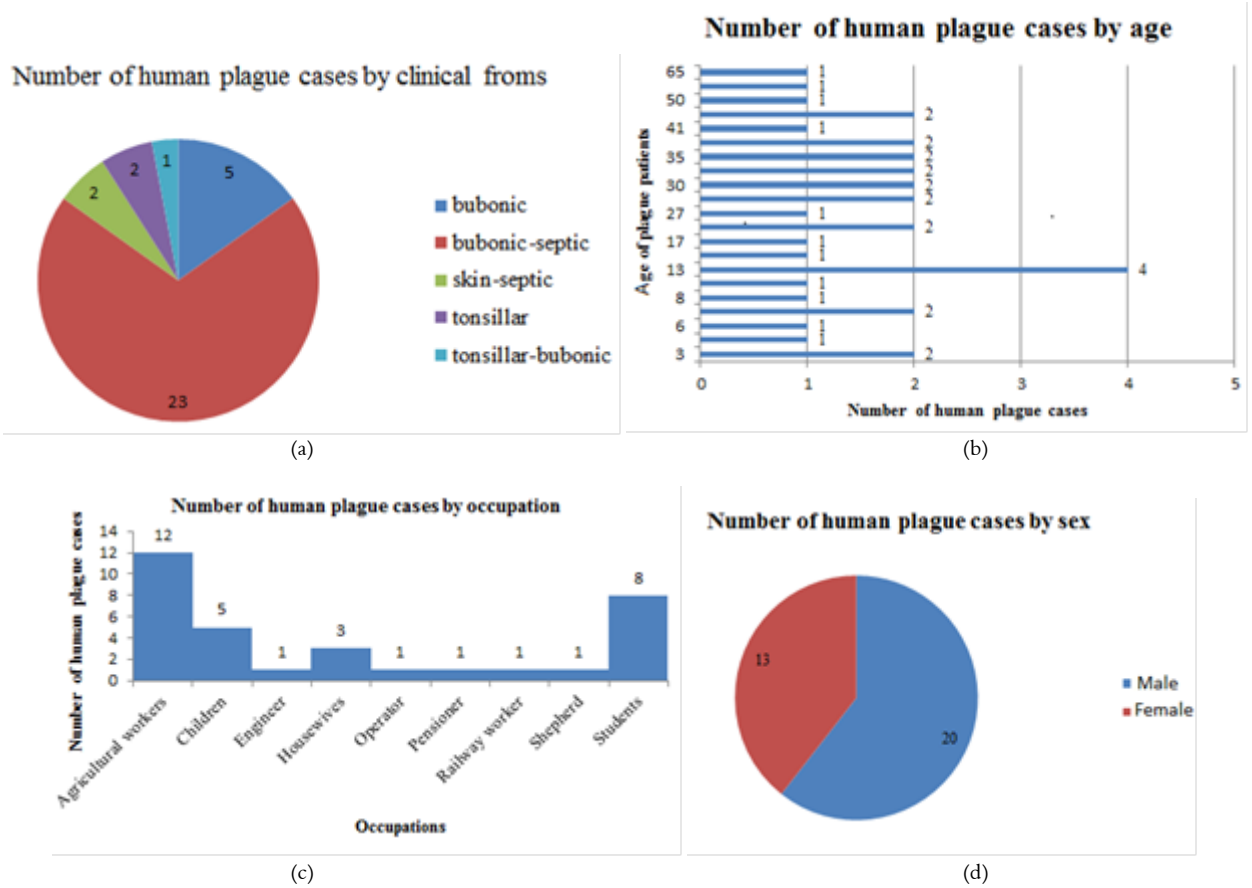


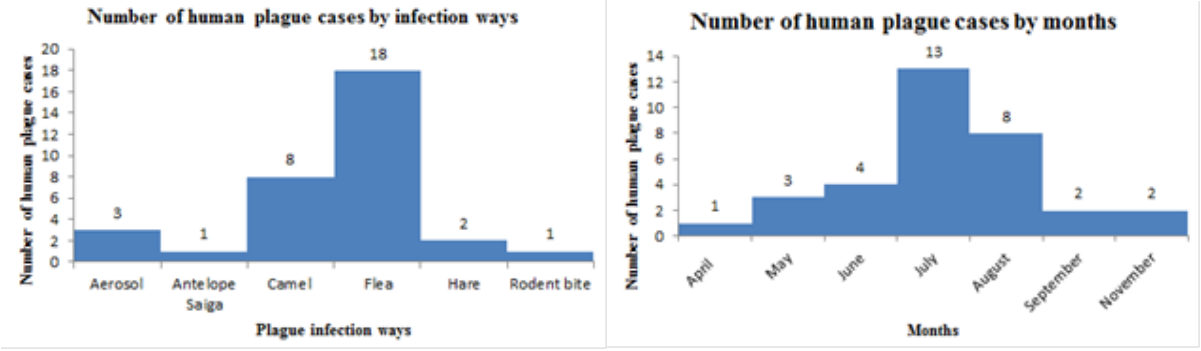
Fig. 2. Represent of people infected with plague by clinical form (a), by age (b), by profession (c), by gender (d)

The largest number of diseases is in the Atyrau, Mangystau and Kyzylorda regions, which is presumably due to the fact that they are completely in the desert zone, which means that the risk of infection among the population is higher. The increase in the number of cases in 1999 is due to the decline and reorganization of the anti-plague organizations.

All cases of the disease in Kazakhstan during the years of our study can be divided into certain categories:

- on the clinical form of the plague: bubonic, bubonic-septic, bubonic-tonsillar, tonsillar, and skin-septic (**Fig. 2a**);
- the age range of sick people ranged from 3 to 65 years; in 57% of cases adults suffered from plague, while the average age of the diseased was 25 years; the age range of children was from 3 to 17 years, among infected, children under 17 years old made up 43%, the average age of sick children is 9 years old (children tend to get sick with plague during games on the territory where plague epizootic occurs, with the participation of farm animals in grazing, catching sick wild animals for feeding their birds of prey) (**Fig. 2b**);
- by a professional occupation the largest number of patients were workers involved in various agricultural work (36%) and schoolchildren (24%) (**Fig. 2c**);
- by a gender the division was next: men - 61% (they fell ill by contact in the natural foci of the plague when grazing farm animals, hunting, when slaughter a camel); women - 39% (they fell ill when cutting meat and as a result of bites infected with fleas) (**Fig. 2d**).

During the study period, in most cases (18 people) source of plague infection were flea - people became ill as a result of its bites. 8 people became ill with plague as a result of slaughter of an ill with plague camel. Wild animals were also sources of infection for humans: 2 people were infected plague as a result of cutting the carcass of a hare, that was sick with plague. In one case, a 13-year-old child fell ill as a result of contact with the corpse of a hare, which he used to feed his eagle in the natural focus of the plague. During this period, a case of human plague was registered, associated with cutting a sick saiga. The plague microbe was isolated from the body of the saiga and from a sick person. In one case,



(a) (b)

Fig. 3. Characteristics of patients with plague by source of plague disease (a), by month of illness (b)

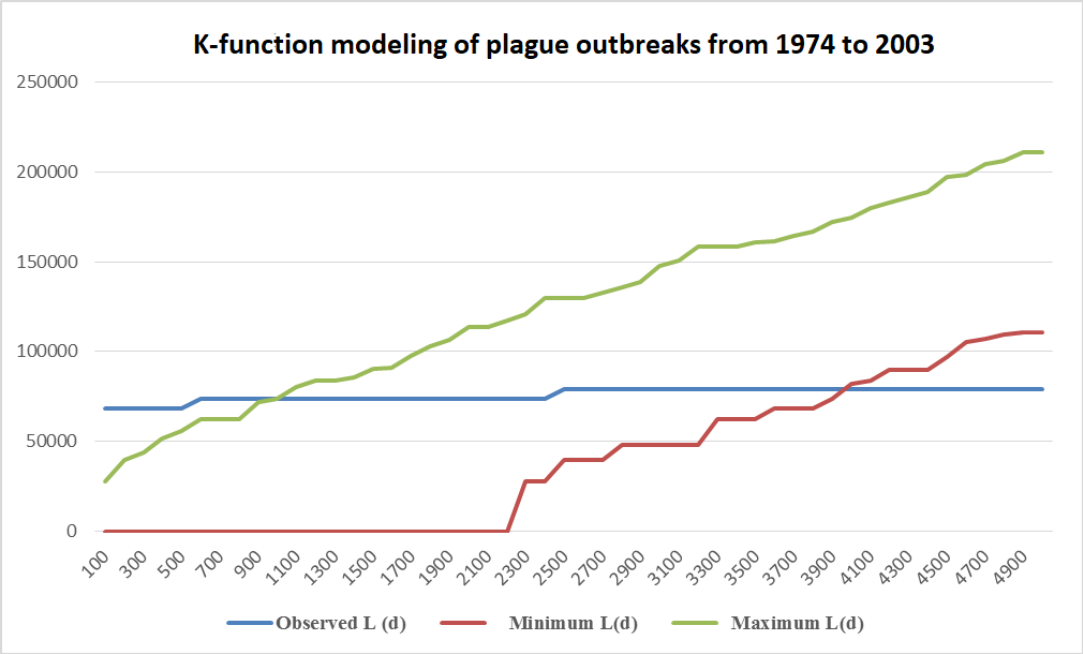


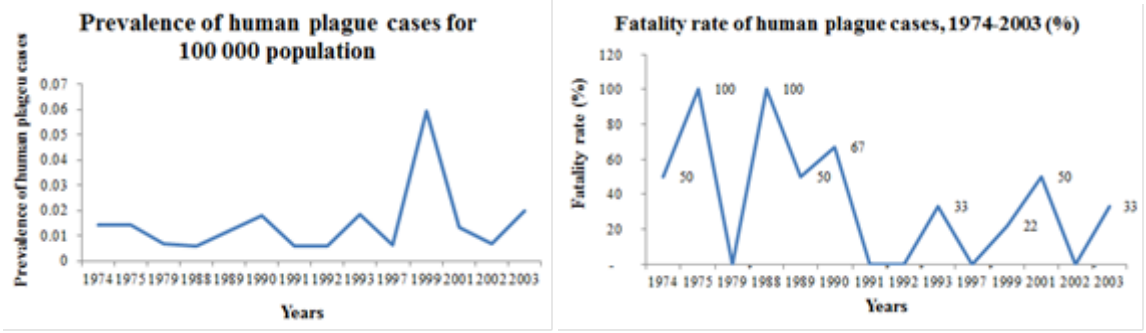
Fig. 4. Clustering and dispersion of cases of plague among people in Kazakhstan for the period from 1974 to 2003

the child's illness was associated with a rodent bite: a 12-year-old girl caught a wild rodent on a country outing, which bit her finger, and the girl became sick with plague. Despite the specific treatment, the girl died of bubonic plague complicated by plague meningitis (Mead, 2015). Represent of sources of plague is shown in **Fig. 3a**. During the years of observation the largest number of patients were recorded in July (39%) and in August (24%) (**Fig. 3b**).

The overwhelming majority of epidemic foci were located in places of persistent plague epizootic. Modeling data on human plague disease using the K-function showed that there are clusters of outbreaks of human plague. Such clustering of outbreaks is observed at a distance of 1000 m, and from the distance between outbreaks of 4000 m there is a dispersed spatial arrangement of outbreaks. The maximum distance of the study was 5000 km. The size of the step is 100 km. The number of data processing 999 times (**Fig. 4**).

The proximity analysis showed that in the outbreaks of plague, during this period, a clustering of diseases of people with plague with a 99% confidence interval with a z-score value of -2.03 and a p value <0.01 is observed. The average distance between the sites of human diseases is 95824.6 meters. The number of treated points - 31 (cases of plague). For 30 years, the mortality rate from the plague was 31%. The incidence and mortality rates for plague by year are presented in **Fig. 5**.

As can be seen from the graphs, the incidence of plague among people per 100,000 population was high (0.06) in 1999, which was associated with the period of infrastructure restoration that was destroyed after the collapse of the USSR. After the restoration of



(a) (b)

Fig. 5. Morbidity rates (a) and mortality rates (b) of the plague of people, 1974-2003, Kazakhstan

infrastructure, the incidence of plague decreases, and the last case of plague was registered in 2003. Mortality among people with plague decreased over the years and was observed in the range from 0 to 100%. The highest mortality rates were observed in 1974, 1975, 1988, 1989, 2001. The high mortality rate was associated with late treatment of patients for medical care, incorrect and late diagnosis of plague, and the presence of concomitant chronic diseases.

CONCLUSION

Thus, from 1974 to 2003 in Kazakhstan, 33 cases of human plague were reported. K-function modeling and proximity analysis revealed the clustering of plague outbreaks. All cases of infection were reported in the territory of the natural plague foci of Kazakhstan. This study is very important in terms of studying the spread and ways to prevent plague, both in Kazakhstan and for the global practice of fighting this dangerous infectious disease.

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REFERENCES

Aikimbayev AM (1992) Guidelines for practical use “Plague”. Almaty. 106.

Aikimbayev AM, Bekenov JY, Meka-Mechenko TV, Temiraliyeva GA (2010) The epidemiological surveillance of highly pathogenic diseases in Kazakhstan. Emerging and Endemic Pathogens. Springer. https://doi.org/10.1007/978-90-481-9637-1_2

Anisimov AP (2002) Yersinia pestis factors, assuring circulation and maintenance of the plague pathogen in natural foci ecosystems. Mol. Gen. Mikrobiol. Virusol, 3-23.

Anisimov AP, Amoako KK (2006) Treatment of plague: promising alternatives to antibiotics. J Med Microbiol, Nov, 55(Pt 11): 1461-1475.

Anisimov AP, Lindler LE, Pier GB (2004) Intraspecific diversity of Yersinia pestis. Clin. Microbiol. Rev., 17(3): 434–464.

Arbal A, Kharabsheh S, Al-Azab S, Al-Kayed M, Amr ZS, et al. (2005) A 12-case outbreak of pharyngeal plague following the consumption of camel meat, in north–eastern Jordan. Annals of Tropical Medicine & Parasitology, 99(8): 789–793.

ArcGIS Pro. Tool References. Retrieved from http://pro.arcgis.com

Barenblatt D (2004) A plague upon Humanity. Harper Collns: 220–221.

Burdelov LA (2010) Atlas of the prevalence of bacterial and viral zoonotic infections in Kazakhstan. Almaty. 122.

Daniel M (1990) The Secret Paths of Death Carriers. 416.

David T, Kenneth D, Gage L, Gratz N, Jack D, Tikhomirov E (1999) Plague manual: epidemiology, distribution, surveillance and control. World Health Organization. 53. Retrieved from http://www.who.int/csr/resources/publications/plague/WHO_CDS_CSR_EDC_99_2_EN/en/

Dicker RC, Coronado F, Koo D, Parrish RG, et al. (2012) Principles of Epidemiology in Public Health Practice. An Introduction to Applied Epidemiology and Biostatistics. 511.

Ershova, R. V., Yarmotz, E. V., Koryagina, T. M., Semeniak, I. V., Shlyakhta, D. A., Tarnow, E (2018) A psychometric evaluation of the highly sensitive person scale: the components of sensory-processing sensitivity. Electronic Journal of General Medicine, 15(6), em96. https://doi.org/10.29333/ejgm/100634

Gage KL, Kosoy MY (2005) Natural history of plague: perspectives from more than a century of research. Annu. Rev. Entomol. (50): 505–528.

Ganin V (2006) The war with the "black death": from defense to attack. Science and Life, no 7.

Ge P, Xi J, Ding J, Jin F, Zhang H, et al. (2015) Primary case of human pneumonic plague occurring in a Himalayan marmot natural focus area Gansu Province, China. International Journal of Infectious Disease. no 33 (2015): 67-70.

Glynn A, Freytag LC, Clements JD (2005) Effect of homologous and heterologous prime-boost on the immune response to recombinant plague antigens. Vaccine, 23(16): 1957-1965.

Inglesby TV, Dennis DT, Henderson DA, et al. (2000) Plague as a biological weapon: medical and public health management. JAMA, 283(17): 2281–2290.

Kenzhegalieva G (2015, April 3) Plague in the Ural steppe. How it was. The newspaper "Caravan". Retrieved from https://www.caravan.kz/gazeta/chuma-v-uralskojj-stepi-kak-ehto-bylo-83832/

Mead PS (2015) Yersinia species (including plague). Philadelphia: Elsevier: 2607–2618.

Melman SD, Ettestad PE, VinHatton ES, Ragsdale JM, Takacs N, et al. (2018) Petersen Human case of bubonic plague resulting from the bite of a wild Gunnison's prairie dog during translocation from a plague endemic area. Zoonoses Public Health. (65): 254–258. Retrieved from https://onlinelibrary.wiley.com

Musagalieva RS (2013) In the fight against the invisible enemy. Academy of health .kz, 3-4(15): 26-27.

Nikolaev NI (1968) Plague. Pbl. Medicine. 239.

Özer G (2018) The impact of serum vitamin D concentration on median nerve conduction. J Clin Exp Invest, 9(2):63-6. https://doi.org/10.5799/jcei.433800

Perry RD, Fetherston JD (1997) Yersinia pestis—etiologic agent of plague. Clin Microbiol Rev.: 35–66.

Pollitzer R (1953) Plague studies. World Health Organization, Bull 9: 59-129. Retrieved from http://apps.who.int/iris/bitstream/handle

Population of Kazakhstan. Retrieved from https://countrymeters.info/ru/Kazakhstan

QGIS Tutorials and Tips. Retrieved from https://www.qgistutorials.com

Rivkus YuZ, Naumov AV, Hotko NI, Geldyev A (1992) Epidemiology and prevention of plague. Ashgabat. Pbl. Magaryf. 239.

Sariyeva G, Abdel Z, Shabunin A, Sagiyev Z, Abdikarimov S, et al. (2018) Current Status of the Sari-Dzhas Natural Focus of Plague. Retrieved from https://www.liebertpub.com

Suntsov VV, Suntsova NI (2006) Plague: The origin and evolution of the epizootic system (environmental, geographical and social aspects). Moscow: KMK Publishing House. 248.

Voitsekhovsky I (2015, February 23) Scientists do not know how the plague "deceives" the human immunity. Retrieved from https://forbes.kz/process/science/uchenyie_ne_znayut_kak_chuma_obmanyivaet_immunitet_cheloveka/

Wong D, Wild MA, Walburger MA, Higgins CL, Callahan M, et al. (2009) Primary pneumonic plague contracted from a mountain lion carcass. Clinical Infectious Diseases, 49(3): 33-38. https://doi.org/10.1086/600818

World Health Organization (2016) Plague around the world 2010-2015. Weekly epidemiological report, (8): 89-104. Retrieved from http://www.who.int/wer

World Health Organization (2017, October) Plague. Retrieved from https://www.cdc.gov/plague/symptoms/index.html