

THE PLAGUE: MEDICAL AND HISTORICAL CHARACTERIZATION. REPRESENTATION IN LITERATURE (CASE STUDY: “A JOURNAL OF THE PLAGUE YEAR BY DANIEL DEFOE”)

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ABSTRACT

The article presents the medical and historical characterization of the pest from the perspective of current scientific knowledge, together with the descriptions outlined in Defoe's novel “A Journal of the Plague Year” regarding the medical aspects of this pathology.

Keywords: Plague, Yersinia Pestis, A Journal of the Plague Year, Daniel Defoe

Motto:

„It is possible in the future for people to believe that such horrors have happened? Even for us, who have seen and lived them, it is hard to believe they were possible.” (Francesco Petrarca)

THE PLAGUE OR PEST – MEDICAL LANDMARKS

Etymologically, the term “*pest*” derives from the Latin word “*pestis*” (pest, plague, curse) (1). Throughout the centuries, the plague was the most terrifying infectious contagious disease which generated a series of demographic crises. The plague epidemics influenced the evolution of society biologically and culturally speaking (2).

The Epidemiological focus

The etiological agent of plague, *Yersinia (Pasteurella) pestis sp.* was described by Alexandre Yersinin in 1894 (3). *Y. pestis* is an immobile Gram-negative bacillus, which is aerobian and encapsulated (4)

The permanent epidemiological reservoir is represented by rodents (5).

The transmission of the infectious agent from rodents to humans was discovered by Jean-Paul Simond in 1898 (6), and is being made through the Oriental rat flea (intermediary host-vector), *Xenopsylla Cheopis*.

There have been hypotheses according to which the human flea (*Pullex irritans*) or other ectoparasites (lice, ticks etc.) could be vectors (7). The transport of the vector by sea was essential for the intercontinental transmission, but port-towns didn't prove to be useful niches on the long term (8,9). The infection can be transmitted directly (from a sick person-touch, kiss, sexual intercourse) and indirectly by courier (meaning through any contaminated material or object) or by air. Reception is general (4).

Among the secondary epidemiological factors there could be mentioned: climatic-natural factors,

atmospheric humidity (10) and climatic fluctuations (11,12,13), telluric natural factors – earthquakes (a plague's center of contagion outburst can appear after months after an earthquake of high magnitude) (14), socio-economic factors – poor population (15).

The epidemiological supervision of possible cases tends to be done through the analyses of genomes (16) or detection with monoclonal antibodies (17).

Pathogenesis

The plague presents two main clinical forms: bubonic form and pulmonary one (18).

The bubonic form

Soon after a flea transmits *Y. pestis* to a mammal host, the bacteria are transported to a regional lymphatic nodule where they breed exponentially, spreading logarithmically afterwards. The bacillus interacts with the neutrophils that they infest, and through their circulation, the spread of the infection is ensured in distal regions (19). The inflammation of the lymphatic nodules is progressive, leading to suppuration and necrosis (20).

The pulmonary form

It is mainly done through the inhalation of infested aerosols (21). A bronchopneumonia or a lobule pneumonia occurs there, with a pre-inflammatory stage, where the bacteria breeds inside the lungs and an inflammatory stage, with the intensive migration of the neutrophils toward the lungs, a “storm” of inflammatory cytokines and the tissue necrosis (22). *Y. pestis* can coordinate the inflammatory response by regulating the cells of the immune system (23). IL-17A and IFN- γ could promote macrophage anti-infection immunity and provide protection against acute pneumonic plague (24).

There have been mentioned other clinical forms as well: tonsillar pest, inapparent pest, chronic pest (4).

The Clinical Picture

The bubonic form

Incubation lasts from one to six days. The outset is sudden, with fever, chills, nausea, vomiting and headaches. As the bacillus penetrates the tegument, there can be noticed inflamed lymphatic nodules, with regional adenopathy, which is very painful especially in the inguinal and axillary areas. After the

necrosis, the region turns black and through tegument fistulization a purulent liquid leaks out (Fig. 1, 2) (25).



FIGURE 1. Inguinal adenopathy in the bubonic form of Plague (Jochmann G. *Lehrbuch der Infektionskrankheiten für Ärzte und Studierende*. Berlin: Verlag von Julius Springer; 1916: Abb.108)



FIGURE 2. Higher latero-cervical adenopathy and to angle of the mandible; blisters of the skin fistulization (Jochmann G. *Lehrbuch der Infektionskrankheiten für Ärzte und Studierende*. Berlin: Verlag von Julius Springer; 1916: Abb.109).

The pulmonary form

Primary or secondary to the bubonic one, this form has an incubation of one, two days, accompanied by the sudden outset of the following symptoms (fever, dyspnea, cyanosis, cough, hemoptysis etc.) (26).

Diagnosis

The anamnesis, the clinical exam and the lab analyses (the isolation of *Y. pestis* requires minimum four days (27)) establish the diagnosis. Unfamiliarity of clinicians with plague and lack of sputum examination, blood culture or postmortem

examination delayed sometimes the diagnosis (28). The PCR tests were presented as instruments/tools of rapid diagnosis but, but until now none of these was validated for clinical use (29).

Evolution and prognosis

Both forms of Plague can progress to septicemia, toxico-septic shock, coma and death.

The bubonic form

Without treatment, the rate of mortality is around 60%. The bubonic plague responds well to antibiotics treatment, and the mortality rate under antibiotic treatment is below 5% (21). The bubonic form can lead to septicemia or pulmonary form (30).

The pulmonary form

It has a rate of mortality of 100% in 1, 2 days. If the patient survives, the immunity after the disease is temporary and relative (4,7). IL-6 was the only elevated cytokine in the patients. IL-6 might be a prognostic marker for predicting the progression of plague (31).

Treatment

The treatment with antiserum was initiated in 1896, the therapy being supplanted by sulphonamides in 1930 and streptomycin in 1947 (6). Today, the treatment of plague must be based on gentamicin or doxy cycline (32). *Y. pestis* presents sensibility to streptomycin, ciprofloxacin, amoxicillin (33). There has been also studied the treatment with bacteriophages (34,35).

Prophylaxis

Vaccine development started in 1897 with whole dead bacterial cells and this was followed by a live attenuated bacterial vaccine. In 1981 the plasmid-mediated virulence was established, and by DNA methods have allowed detection of plague genes in skeletal specimens from European graves of the sixth to 17th centuries (6). Even today, the scientists work on the improvement of the anti-plague vaccine (36,37,38,39). It appears that the antiport pump Na^+/H^+ is indispensable for *Y. pestis*'s survival and could be considered a promising target (40). It seems that the prophylaxis with immune modulating cytosine-phosphate-guanidine oligodeoxynucleotide confers protection against *Y. pestis* for laboratory rats (41).

Based on the risk for human health, the biological warfare agents have been classified into three categories, the first one including micro-organisms or easily spread toxins, with high rates of death: anthrax, botulism, plague, chickenpox and viral hemorrhagic fever (42,43). Therefore, using of *Y. pestis* as a biological weapon in generating pest pneumonia could be extremely dangerous (44,45).

Currently there is no licensed vaccine available for prevention of plague in the USA or Western Europe (46).

PLAGUE – HISTORICAL LANDMARKS

In ancient historical sources, the term “*plague*” appears as referring to other serious infecto-contagious pathologies. In the Bible, Samuel 2 24:25 is mentioned: “*God sent plague to Israel...70,000 people died*”. Some researchers believe that there are sufficient archaeological arguments to sustain the idea that there is a bubonic plague (47,48), others believe it's a Bacillary Dysentery (49), and others consider that the etiology is not precise (50).

The first safe data belong to Dionysos of Kyrta (280-277 a. Chr.); he describes the disease with “*pestilentes bubones, maxime letales et acuti*”. Dioscorides and Poseidonius, doctors from Alexandria, describe plague as “*febram acutem, dolorem, perturbationem totius corporis et delirium et bubonum aparitionem, non solum in solitis locis, verum et in poplitibus et cubitis*” (51).

Throughout history, there have been three waves of maximum virulence and expansion of plague: the Plague of Justinian (540-590) (52) has a mortality between 5,000-10,000 people dead/day, when the bodies were not buried, but thrown in the sea (53,51). **The Black Death** (1346-1361) and **The Chinese Plague** (1855-1900) (54). Each pandemic was caused by a different biovar of *Y. pestis*, respectively Antiqua (still found in Africa and Central Asia), Medievalis (currently limited to Central Asia), and Orientalis (almost worldwide in its distribution) (55,56). All these three waves of plague were genetically classified through PCR strategies (by use of dental pulp) (59).

The hypothesis of lethal viruses, such as *Filoviridae*, has been circulated, these viruses causing the epidemic of plague in 1346-1361 (60). *Y. pestis* discovered in the genetic material of the dead people in this period support the idea of *Y. pestis* being the agent (62).

The first hospital for patients with plague (lazaretto) was opened in 1423 (63).

A common image of these epidemics is represented by grave diggers, who were wandering through the streets in order to gather the dead bodies to bury them. They did not interact or have any kind of contact with anybody during the epidemics. The grave diggers from Romanian Principalities even had an oath before the authorities. “I (the name) swear [...] I will bury the bodies with humanity, I will not rob them, I will dig good, deep graves, [...]”. More often than not, the bodies were sprinkled with quick lime and buried without funeral marks (64).

Due to the fact the Turks were against adopting measures to prevent plague (the Quran promised to the Sick of the plague “the pleasures of the after-life”), the Romanian Principalities could not fight against the disease, and were for a very long time chased by this pathology (65).

In our country, vinegar, garlic and brandy have been considered basic preventive treatments against plague. Also were used tar, sulfur in fumigation, tarred water in wash, camphor, plants (as: mint, chamomile, yellow rattle) for tea, juices and balms. In the 18th century as prophylactic measures were used also gun powder, arsenic, pitch, money were washed in vinegar and brine; in the 19th century – fumes of vinegar, Cl₂, SO₂, quick lime, AgNO₃ and washing the nostrils with vinegar (66). Magic was used against plague in our country as there were insufficient medical strategies (67,68). An odd number of women were spun and wove a hemp shirt which was believed to possess supernatural therapeutic powers. The shirt was either burned in the middle of the yard (69,70) or the patients were wearing it (71), or it was stuffed with hay. Dolls were made and placed in the entrance and exits of village (72) hoping that plague could be stopped. Saint Haralambie was considered the protector of plague patients (73).

During the 18th century, plague mainly spread in Eastern Europe. During the epidemic from winter of 1709-1710 in Southern Transylvania, the authorities forced the people to have resin, pitch, phosphor to fumigate the houses, everyone had to stay away from the home of a sick person (which should be closed and marked with a cross, and those left inside should be provided with food and medicine). In this way they could keep count the infected homes, the dead bodies and the buried ones; the dead bodies should not be held more than six hours. If somebody died into a house, the house was burned to the ground and the servants were forced to go into the woods and stay there for forty days (74).

During the epidemic plague of 1770 in Iasi, mainly manifested in bubonic form, most of the dead people were buried inside their house while the infested one were quarantined to the nearby woods. “*Everywhere on the fields or in huts slow fire burn garbage piles of bones and various other debris. This unpleasant smoke fill the air day and night. The Sick people are helpless, nobody is caring about them, and uses no medications*”. “*Poorest Moldavians who had relatives suffering from the plague, to not be suspected, they went them secretly to the nearest woods, after which they (the Sicks ones) were seated on the grass and clothes, putting them in shady spots. Nearby they put a pot of water and some food, and thus leave the unfortunate on their own fate [...] when they rot are torn apart by dogs or worms or wild beasts*” (51).

In 19th century only few, relatively unimportant epidemics occurred in the Romanian Principalities. The last appearance of plague was in 1829 in Transylvania (51). The quarantines were useful to prevent the malady, together with the Carpathian sanitary cordon, and the Danubian sanitary cordon (75,76).

Today, human cases and foci are present in Bolivia, Brazil, Ecuador, and Peru (77). The Plague will persist in rodent reservoirs mostly in African countries burdened by poverty and civil unrest (78).

THE PLAGUE REPRESENTATION IN LITERATURE AND PLASTIC ART

Despite the medical research devoted to the etiopathogenesis, epidemiology and treatment, the Plague still remains a mysterious figure in literature. The Canon of plague literature includes “*The Decameron*” by Giovanni Boccaccio, “*The Fiances*” by Alessandro Manzoni, “*A Journal of the Plague Year*” and “*Due Preparations for the Plague as Well for Soul as Body*” by Daniel Defoe (54).

The functions of the plague literature can be seen from a triple angle: post-traumatic expression, historical landscape, and the source of an ailing metaphorical vocabulary (54). Until the end of the 14th century the plague is presented in literature from a theological perspective, as a divine punishment. Beginning with the 15th century, it is presented from a medical and scientific perspective (54). The literature of the Plague as an infection contagious disease presents “*no hero, no story [...] only a fabulous and killing force and the scheme of an action (the spread of evil), its raging and the men fighting*” (79).

In fine arts, the plague has themes like: the image of an infant next to his dead mother's breast (Fig. 3), people holding their breath not to inhale the smell of plague, the image of a doctor who holds his nose to protect himself from the miasma of plague while he consult a sick patient, but also pictures of saints that protect towns devastated by plague (80).



FIGURE 3. “The dreadful plague in London, 1665”, picture (http://sewerhistory.org/grfx/disease/plague_life/index.html accessed 20 march 2014)

“A JOURNAL OF THE PLAGUE YEAR” BY DANIEL DEFOE

By the richness of details and feelings expressed through the objectivity of data taken from geographical works, travel journals and diaries, biographies, Daniel Defoe (1660-1731) created an anti-fiction literature, and he is considered “the father of the English and European Novel” (82). If the prose of the beginning of 18th century (especially the writings of Steele and Addison) was characterized by harmonious writing with well-chosen vocabulary, Defoe’s writing is alive, in a spoken English of his times, very accessible to anyone (83,82). Defoe succeed creating characters with the necessary qualities to survive, specific his time.

“*A Journal of the Plague Year*” is considered a masterpiece, a realistic depiction, offering credibility through the circumstantial detail. The author used the research method (newspapers, testimonies of witnesses) making up a very convincing material; that is why it is very difficult to draw the line between reality and fiction (83). The novel presents the London pandemic of 1665 (when died between 75000 and 100000 people (84)) from a realistic point of view. The historical context of this work is the outbreak of French Plague of 1720 (54).

In what follows we will analyze the novel descriptions about the medical aspects of the disease.

Descriptions of the epidemiological focus

Regarding the etiological agent and mode of transmission, the narrator creates a symbiotic theory between the effluvius theory from Antiquity, and the modern contagious theory (54): “*the Calamity was spread by Infection [...], by some certain Steams, or Fumes, which the Physicians call Effluvia, by the Breath, or by the Sweat, or by the Stench of the Sores of the sick Persons [...]. Effluvia affected the Sound, who come within certain Distances of the Sick [...], and so those newly infected Persons communicated it in the same Manner to others*”, “*I say, I must be allowed to believe, that no one in this whole Nation ever recev’d the Sickness or Infection, but who recev’d it in the ordinary Way of Infection from some Body, or the Cloaths, or touch, or stench of some Body that was infected before*”. The family members became “*a walking Destroyer, perhaps for a Week or Fortnight before that, how he had ruin’d those, that he would hazarded his Life to save, and had been breathing Death upon them, even perhaps in his tender Kissing and Embracings of his own childrean*”. The Plague is described as a contagious disease which can be transmitted directly and indirectly.

From secondary epidemiological factors, there are mentioned the social-economic ones: “*the Infection kept chiefly in the Outparishes, which being very populous, and fuller also of Poor; the Distemper found more to pray upon than in the City*”. “*Many of those died calling for help, and even for Sustenance out of their Windows, in a most miserable and deplorable manner*”.

“*The acute penetrating Nature of the Disease it self was such [...] that the most exact Caution could not secure us*”, so contagiousness was high and receptivity general. The epidemic curve is described vaguely: “*So while the Plague went on raging from West to East, as it went forewards East, it abated in the West, by which means those parts of the Town which were not seiz’d, or who were left, and where it had spent its Fury, were (as it were) spar’d to help and assist the other*”.

Descriptions of the pathogenesis of plague

The progression of the inflamed lymphatic node towards necroses is described so: “*those Spots they call’d the Tokens were really gangreen Spots, or mortified Flesh in small Knobs as broad as a little silver Peny, and hard as a pice of Callous or Horn*”.

Descriptions of the clinical picture

“The Plague [...] operated in different manner [...] some were immediately overwhelm’d with it, and it came to violent Fevers, Vomiting, unsufferable Head-achs, Pains in the Back, and so up to Ravings and Ragings with those Pains (Pulmonary form followed by septicemia): Others with Swellings and Tumours in the neck or Groyn, or Arm-pits (Bubonic form) [...]; while others [...] were silently infected, the Fever preying upon their Spirits insensibly, and they seeing little of it, till they fell into swooning, and faintings, and Death without pain. (probably the asymptomatic form)”. “The Pain of the Swelling was in particular very violent”.

Descriptions of the applied treatment

The therapeutic measures mentioned in the novel refer to the opening techniques of the infectious-inflammatory processes secondary to adenopathies. *“The Swellings in some grew hard, and they (the Physiacins and Surgeons) apply’d violent drawing Plasters, or Pultices, to break them; and if these did not do, they cut and scarified them”. “Nay there was another Thing which made the mere catching of the Distemper frightful, and that was the terrible burning of the Causticks, which the Surgeons laid on the Swellings to bring them to brake, and to run; without which the Danger of Death was very great”.*



FIGURE 4. The attire worn by physicians (http://sewerhistory.org/grfx/disease/plague_life/index.html accessed 20 march 2014)

Descriptions of the epidemiological measures

Among the initial measures mentioned was the transformation the houses in quarantined environments and lazarettos – closing the house with least one patient and supervision by a watchman. Such methods were controversial as this strategy was raising political, ethical and social-economic issues, requiring a careful balance between public interest and individual rights (63). On front door of a closed house was painted with red a cross, and above wrote: *“Lord have mercy upon us”* (85,86).

“There was likewise Violence used with the Watchmen, as was reported in abundance of Places”, “the People broke out, whether by Force or by Stratagem, even almost as often as they pleas’d [...] those that did thus break out, were generally People infected, who in their Desperation, running about from one Place to another, valued not who they injur’d”. Then “People sicken’d so fast, and died so soon, that it was impossible and indeed to no purpose to go about to enquire who was sick and who was well, or to shut them up with such Exactness, ass the thing required”.

For the “sterilization” of the air, fires were set up on the streets of London as Hyppocrates saved Athens through fire. Substances as tar, gunpowder, smoke, sulfur, pitch, resin, spices and incense were used to fumigate the inside the houses as well.

Gathering and burying the bodies was done at night (Fig. 5): *“if any diseas’d Bodies were remov’d,*



FIGURE 5. Burying the dead during plague of 1665 (http://sewerhistory.org/grfx/disease/plague_life/index.html accessed 20 march 2014)

or dead Bodies buried, or infected Cloths burnt, it was done in the Night; and all the Bodies, which were thrown into the great Pits in the several Churchyards, or burying Grounds [...] were so remov'd in the Night". People were forbidden to stay in the proximity of the mass graves: "There was a strict Order to prevent People coming to those Pits, and that was only to prevent Infection". "But after some Time, that Order was more necessary, for People that were Infected, and near their End, and delirious also, would run to those Pits wrapt in Blankets, or Rugs, and throw themselves in, and as they said, bury themselves".

"Wherefore, were we ordered to koll all the Dogs and Cats: But because as they were domestick Animals, and are apt to run from House to House, and from Street to Street; so they are capable of carrying the Effluvia or Infectious Steams of Bodies infected, even in their furs and Hair".

In all this period, medicine could not fight against plague (87) ("the Power of Man was baffled, and brought to an End"), the only method of prevention was avoiding contact with infected people and contaminated objects (88).

Psycho-sociological descriptions of the London plague epidemic

The narrator conceptualizes the disease from a Christian perspective "nothing attended us without Direction or Permission of Divine Power". The priest has an important role in the patient's life: "Some of the Ministers did Visit the Sick at first, and for a little while, but it was not to be done; it would have been present Death, to have gone into some Houses". The emotional state played an important role in healing process, the sick trusting in the interaction miracle-medicine (89).

People's emotional reaction to the outbreak is depicted impressively: "London might well be said

to be all in Tears; the Mourners did not go about the Streets indeed, for no Body put on black, or made a formal Dress of Mourning for their nearest Friends; but the Voice of Mourning was trully heard in the Streets; the shrieks of Women and Children at the Windows, and Doors of their Houses, where their dearest Relations were, perhaps dying, or just dead [...], that it was enough to pierce the stoutest Heart in the World". "It was observable then, that this Calamity of the People made them humble".

Then "(the People) were allarm'd, and unallarm'd again, and this several times, till it began to be familiar to them" (psychosocial adaptation responses). "The People harden'd by the Danger they had been in, like Sea-men after a Storm is over, were more wicked and more stupid, more bold and hardened in their Vices and Immoralities than they were before".

When dramatic social situations when everyone loses their jobs, work ceases, and wages are not paid, episodes of violence and violation even of the most basic moral rules occur in the community (90): "the Power of Avarice was so strong in some, that they would run any Hazard to steal and to plunder, and particularly in Houses where all Families, or Inhabitants have been dead, and carried out, they would break in at all Hazards, and without Regard to the Danger of Infection, take even the cloths off, of the dead Bodies, and the Bed-Cloths from others where they lay dead".

Although nowadays fewer cases are found only sporadically, this pathology has a special meaning in the history of epidemiology and humanity.

Note. Literary texts came from: Defoe Daniel. A Journal of the Plague Year. George Routledge & Sons. London; 1884: 101-102, 247, 257, 26, 115, 247, 270, 249, 255, 110, 287, 73, 96, 213, 207, 307, 237, 83, 160, 44, 21, 51, 28, 131, 30, 290-291, 112-113.

REFERENCES

1. Simici P. (editor). Dicționar medical vol II. Editura Medicală. București; 1970:360.
2. Signoli M. Reflections on crisis burials related to past plague epidemics. *Clin Microbiol Infect.* 2012; 18(3):218-223.
3. Kousoulis A.A., Karamanou M., Tsoucalas G., Dimitriou T., Androutsos G. Alexandre Yersin's explorations (1892-1894) in French Indochina before the discovery of the plague bacillus. *Acta Med Hist Adriat.* 2012; 10(2):303-310.
4. Voiculescu M. Boli infecțioase. București: Editura Medicală; 1968:717-720.
5. Wilschut L.I., Addink E.A., Heesterbeek H., Heier L., Laudisoit A., Begon M. et al. Potential corridors and barriers for plague spread in Central Asia. *Int J Health Geogr.* 2013; 12:49.
6. Butler T. Plague history: Yersin's discovery of the causative bacterium in 1894 enabled, in the subsequent century, scientific progress in understanding the disease and the development of treatments an vaccines. *Clin Microbiol Infect.* 2014; 20(3):202-209.
7. Walløe L. Medieval and modern bubonic plague: some clinical continuities. *Med Hist Suppl.* 2008; (27):59-73.
8. Vogler A.J., Chan F., Nottingham R., Andersen G., Drees K., Beckstrom-Sternberg S.M. et al. A decade of plague in Mahajanga, Madagascar: insights into the global maritime spread of pandemic plague. *MBio.* 2013; 4(1):e00623-12.
9. Tsiamis C., Poulakou-Rebelakou E., Tsakris A., Petridou E. Epidemic waves of the Black Death in the Byzantine Empire (1347-1453 AD). *Infez Med.* 2011; 19(3):194-201.

10. Xu L., Stige L.C., Kausrud K.L., Ben Ari T., Wang S., Fang X. et al. Wet climate and transportation routes accelerate spread of human plague. *Proc Biol Sci.* 2014; 281(1780):20133159.
11. McMichael A.J. Paleoclimate and bubonic plague: a forewarning of future risk? *BMC Biol.* 2010; 8(1):108.
12. World Health Organization. *Plague.* Wkly Epidemiol Rec. 2003; 78:253–260.
13. Stapp P., Antolin M.F., Ball M. Patterns of extinction in prairie dog metapopulations: plague outbreaks follow El Niño events. *Front Ecol Environ.* 2004; 2:235–240.
14. Tsiamis C., Poulakou-Rebelakou E., Marketos S. Earthquakes and plague during Byzantine times: can lessons from the past improve epidemic preparedness. *Acta Med Hist Adriat.* 2013; 11(1):55-64.
15. Carmichael A.G. Universal and particular: the language of plague, 1348-1500. *Med Hist Suppl.* 2008; (27):17-52.
16. Yan Y., Wang H., Li D., Yang X., Wang Z., Qi Z. et al. Two-step source tracing strategy of *Yersinia pestis* and its historical epidemiology in a specific region. *PLoS One.* 2014; 9(1):e85374.
17. Simon S., Demeure C., Lamourette P., Filali S., Plaisance M., Créminon C. et al. Fast and simple detection of *Yersinia pestis* applicable to field investigation of plague foci. *PLoS One.* 2013; 8(1):e54947.
18. Williamson E.D., Oyston P.C. The natural history and incidence of *Yersinia pestis* and prospects for vaccination. *J Med Microbiol.* 2012; 61(Pt 7):911-918.
19. Bland D.M., Anderson D.M. Imaging early pathogenesis of bubonic plague: are neutrophils commandeered for lymphatic transport of bacteria? *MBio.* 2013; 4(6):e00837-13.
20. Flexner S. *The pathology of bubonic plague.* *Am J Med Sci.* 1901; 122:396-416.
21. Dennis D.T. Plague as a biological weapon. In: Fong IW, Alibek K. (editors). *Bioterrorism and infectious agents: a new dilemma for the 21st century.* Springer Science; 2005:37–64.
22. Pechous R.D., Sivaraman V., Price P.A., Stasulli N.M., Goldman W.E. Early host cell targets of *Yersinia pestis* during primary pneumonic plague. *PLoS Pathog.* 2013; 9(10):e1003679.
23. Peters K.N., Dhariwala M.O., Hughes Hanks J.M., Brown C.R., Anderson D.M. Early apoptosis of macrophages modulated by injection of *Yersinia pestis* YopK promotes progression of primary pneumonic plague. *PLoS Pathog.* 2013; 9(4):e1003324.
24. Bi Y., Zhou J., Yang H., Wang X., Zhang X., Wang Q. et al. IL-17A produced by neutrophils protects against pneumonic plague through orchestrating IFN- γ -activated macrophage programming. *J Immunol.* 2014; 192(2):704-713.
25. Pollitzer R. Plague studies – 8 Clinical aspects. *Bull World Health Organ.* 1953; 9(1):59–129.
26. Butler T. *Plague and Other Yersinia Infections.* New York: Plenum Medical Book Company, 1983.
27. Stenseth N.C., Atshabar B.B., Begon M., Belmain S.R., Bertherat E., et al. Plague: Past, Present, and Future. *PLoS Med.* 2008; 5(1):e3.
28. Luo H., Dong X., Li F., Xie X., Song Z., Shao Z. et al. A cluster of primary pneumonic plague transmitted in a truck cab in a new enzootic focus in China. *Am J Trop Med Hyg.* 2013; 88(5):923-928.
29. Riehm J.M., Rahalison L., Scholz H.C., Thoma B., Pfeiffer M., Razanakoto LM et al. Detection of *Yersinia pestis* using real-time PCR in patients with suspected bubonic plague. *Mol Cell Probes.* 2011; 25(1):8-12.
30. Lawrenz M.B. Model systems to study plague pathogenesis and develop new therapeutics. *Front Microbiol.* 2010; 1:119.
31. Wang X., Wang Z., Guo Z., Wei B., Tian F., Yu S. et al. Serum cytokine responses in primary pneumonic plague patients. *Clin Vaccine Immunol.* 2011; 18(1):184-186.
32. Raoult D., Mouffok N., Bitam I., Piarroux R., Drancourt M. Plague: history and contemporary analysis. *J Infect.* 2013; 66(1):18-26.
33. Wendte J.M., Ponnusamy D., Reiber D., Blair J.L., Clinkenbeard K.D. In vitro efficacy of antibiotics commonly used to treat human plague against intracellular *Yersinia pestis*. *Antimicrob Agents Chemother.* 2011; (8):3752-3757.
34. Filippov A.A., Sergueev K.V., Nikolich M.P. Can phage effectively treat multidrug-resistant plague? *Bacteriophage.* 2012; 2(3):186-189.
35. Filippov A.A., Sergueev K.V., He Y., Huang X.Z., Gnade B.T., Mueller A.J. et al. Bacteriophage therapy of experimental bubonic plague in mice. *Adv Exp Med Biol.* 2012; 954:337-348.
36. Huang S.S., Li I.H., Hong P.D., Yeh M.K. Development of *Yersinia pestis* F1 antigen-loaded microspheres vaccine against plague. *Int J Nanomedicine.* 2014 ;9:813-822.
37. Zhang X., Wang Q., Bi Y., Kou Z., Zhou J., Cui Y. et al. Kinetics of memory B cell and plasma cell responses in the mice immunized with plague vaccines. *Scand J Immunol.* 2014; 79(3):157-162.
38. Zhang Q., Wang Q., Tian G., Qi Z., Zhang X., Wu X. et al. *Yersinia pestis* biovar *Microtus* strain 201, an avirulent strain to humans, provides protection against bubonic plague in rhesus macaques. *Hum Vaccin Immunother.* 2013; 10(2).
39. Price J.L., Manetz T.S., Shearer J.D., House R.V. Preclinical safety assessment of a recombinant plague vaccine (rF1V). *Int J Toxicol.* 2013; 32(5):327-335.
40. Minato Y., Ghosh A., Faulkner W.J., Lind E.J., Schesser Bartra S., Plano GV et al. Na⁺/H⁺ antiporter is essential for *Yersinia pestis* virulence. *Infect Immun.* 2013; 81(9):3163-3172.
41. Hickey A.J., Lin J.S., Kummer L.W., Szaba F.M., Duso D.K., Tighe M. et al. Intranasal prophylaxis with CpG oligodeoxynucleotide can protect against *Yersinia pestis* infection. *Infect Immun.* 2013; 81(6):2123-2132.
42. Balali-Mood M., Moshiri M., Etemad L. Medical aspects of bio-terrorism. *Toxicon.* 2013; 69:131-142.
43. Ligon B.L. Plague: a review of its history and potential as a biological weapon. *Semin Pediatr Infect Dis.* 2006; 17(3):161-170.
44. Papagrigrakis M.J., Synodinos P.N., Stathi A., Skevaki C.L., Zachariadou L. The plague of Athens: an ancient act of bioterrorism? *Biosecur Bioterror.* 2013; 11(3):228-229.
45. Bossi P., Garin D., Guihot A., Gay F., Crance J.M., Debord T. et al. Bioterrorism: management of major biological agents. *Cell Mol Life Sci.* 2006; 63(19-20):2196-2212.
46. Oyston P.C., Williamson E.D. Prophylaxis and therapy of plague. *Expert Rev Anti Infect Ther.* 2013; 11(8):817-829.
47. Griffin J.P. Plague, rats and the Bible again. *J R Soc Med.* 2006; 99(8):387.
48. Freeman F.R. Bubonic plague in the Book of Samuel. *J R Soc Med.* 2005; 98(9):436.
49. Russell W.M.S. Plague, rats and the Bible again. *J R Soc Med* 2005; 98:169.
50. Sabbatani S., Fiorino S. The plague of the Philistines and other pestilences in the Ancient World: exploring relations between the religious-literary tradition, artistic evidence and scientific proof. *Infez Med.* 2010; 18(3):199-207.
51. Preliceanu I. Ciurma dela lasi din 1770 după descrierea lui Orraeus. Teză pentru doctorat în medicină și chirurgie, Universitatea din Cluj, Tipografia cultura, 1927:7.
52. Tsiamis C., Poulakou-Rebelakou E., Petridou E. The Red Sea and the port of Clysma. A possible gate of Justinian's plague. *Gesnerus.* 2009; 66(2):209-217.
53. Vătămanu N. Câteva epidemii antice. In: Brătescu G (editor). *Din istoria luptei antiepidemice din România, București: Editura Medicală; 1972:31-34.*
54. Vidrutiu C. Imaginarul epidemic. Reprezentări istorice și metaforice ale ciumei în literatură. Cluj-Napoca: Editura Casa Cărții de Știință; 2012:76, 83, 78-79, 133, 158.
55. Devignat R. Variétés de l'espèce *Pasteurella pestis*. Nouvelle hypothèse. *Bulletin de l'Organisation Mondiale de la Santé.* 1951; 4:247–263.
56. Guiyoule A., Grimont F., Iteanu I., Grimont P.A.D., Lefevre M., et al. Plague pandemics investigated by ribotyping of *Yersinia pestis* strains. *J Clin Microbiol.* 1994; 32:634–641.
57. Wagner D.M., Klunk J., Harbeck M., Devault A., Waglegner N., Sahl J.W. et al. *Yersinia pestis* and the Plague of Justinian 541-543 AD: a genomic analysis. *Lancet Infect Dis.* 2014. pii: S1473-3099(13)70323-2.
58. Bos K.I., Stevens P., Nieselt K., Poinar H.N., Dewitte S.N., Krause J. *Yersinia pestis*: new evidence for an old infection. *PLoS One.* 2012; 7(11):e49803.
59. Malou N., Tran T.N., Nappes C., Signoli M., Le Forestier C., Castex D. et al. Immuno-PCR – a new tool for paleomicrobiology: the plague paradigm. *PLoS One.* 2012; 7(2):e31744.
60. Scott S., Duncan C.J. *Biology of plagues: Evidence from historical populations.* Cambridge: Cambridge University Press; 2001.
61. Antoine D. The archaeology of "plague". *Med Hist Suppl.* 2008; (27):101-114.

62. **Raoult D., Aboudharam G., Crubézy E., Larrouy G., Ludes B., et al.** Molecular identification by "suicide PCR" of *Yersinia pestis* as the agent of Medieval Black Death. *Proc Natl Acad Sci USA*. 2000; 97:12800–12803.
63. **Tognotti E.** Lessons from the History of Quarantine, from Plague to Influenza A. *Emerg Infect Dis*. 2013; 19(2):254–259.
64. **Lenghel A.** Istorical ciumei în Cluj la 1738-1739. Cluj: Tipografia Corvin; 1930:32-33.
65. **Barbu G.** Note despre organizarea carantinelor în țările Române. In: Brătescu G (editor) Din istoria luptei antiepidemice din România. București: Editura Medicală; 1972:223-238.
66. **Iugulescu C.** Contributie la studiul medicatiei în epidemiile de ciumă și holeră din țara noastră. In: Brătescu G (editor) Din istoria luptei antiepidemice din România. București: Editura Medicală; 1972:205-210.
67. **Mironescu N.A., Pastior-Capesius R.** „Cămasa ciumei”, o practică etnoiatrică astăzi dispărută. In: Brătescu G (editor) Din istoria luptei antiepidemice din România. București: Editura Medicală; 1972:55-62.
68. **Cordun V.** Tipuri și funcțiuni ale „chimesii ciumii”. In: Brătescu G (editor) Din istoria luptei antiepidemice din România. București: Editura Medicală; 1972:63-70.
69. **del Chiaro A.M.** Istoria delle moderne rivoluzioni della Valachia. Veneția; 1718:19.
70. **Sulzer F.J.** Geschichte des Transalpinischen Daziens vol II. Viena; 1781-82: 388.
71. **Novacovici E.** Colectiunea folclorică română din Răcsădie și jur. Oravița; 1902:32.
72. **Cristian V.** Mitteilungen der Anthropologischen Gesellschaft. Sitzungsberichte der Anthropologischen Gesellschaft. 1916; 46:25-29.
73. **Brătulescu-Trestioreanu O.** Despre unele reprezentări populare ale ciumei. In: Brătescu G (editor) Din istoria luptei antiepidemice din România. București: Editura Medicală; 1972:167-170.
74. **Jiga C.T.** Măsuri carantinale în epidemia de ciumă de la 1709-1710 din sudul Transilvaniei. In: Brătescu G (editor) Din istoria luptei antiepidemice din România. București: Editura Medicală; 1972:71-73.
75. **Nistor I.** Ravagiile epidemiilor de ciumă și holeră și instituirea cordonului carantină pe Dunăre. București: Imprimeria Națională; 1945:26, 30, 43.
76. **Chiș F.I.** Epidemiile și eradicarea lor în Nord-Vestul României (secolele XVIII-XIX). Cluj-Napoca: Editura Mega; 2012:163.
77. **Schneider M.C., Najera P., Aldighieri S., Galan D.I., Bertherat E., Ruiz A.** et al. Where does human plague still persist in latin america? *PLoS Negl Trop Dis*. 2014; 8(2):e2680.
78. **Butler T.** Plague gives surprises in the first decade of the 21st century in the United States and worldwide. *Am J Trop Med Hyg*. 2013; 89(4):788-793.
79. **Crochet M.** Les mythes dans l'oeuvre de Camus. Paris: Éditions universitaires; 1973:32.
80. **Mollaret H., Brossollet J.** La peste, source méconnue d'inspiration artistique. *Jaarboek Koninklijk Museum voor schone Kunsten Antwerpen*. 1965:14-20.
81. **Drimba O.** Istoria literaturii universale vol II. București: Saeculum I.O; 2008:47.
82. **Anixt A.A.** Istoria literaturii engleze. București: Editura Științifică; 1961:143.
83. **Levițchi L.D., Trifu S., Focșeneanu V.** Istoria literaturii engleze și americane vol II. București: Editura Dacia; 1998:29.
84. **The Great Plague of London, 1665**, in *Harvard University Library Open Collections Program: Contagion*, <http://ocp.hul.harvard.edu/contagion/plague.html>, accessed 16 March 2014.
85. **Chardwright F., Biddiss M.** Bolile și istoria. București: Editura All; 2008:39.
86. **Miller K.** Illustrations from the Wellcome Library William Winstanley's pestilential poesies in "The Christians refuge: or heavenly antidotes against the plague in this time of generall contagion to which is added the charitable physician (1665)". *Med Hist*. 2011; 55(2):241-250.
87. **McNeill W.** Plagues and peoples. New York: Anchor Books; 1998.
88. **Ziegler P., Platt C.** The Black Death. 2nd ed. London: Penguin; 1998.
89. **Archambeau N.** Healing options during the plague: survivor stories from a fourteenth-century canonization inquest. *Bull Hist Med*. 2011; 85(4):531-559.
90. **Priel B.** Thinking extreme social violence: the model of the literary plague. *Int J Psychoanal*. 2007; 88(Pt 6):1457-1472.