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REVIEW ARTICLE

A forgotten fatal pathogen – *Yersinia pestis*

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Introduction

Yersinia pestis is a bacterium discovered by Alexandre E. J. Yersin in 1894 during an outbreak of plague in Hong Kong. The bacterium is famous for causing widespread pandemics with high mortality. During the fourteenth century it was known as "Black Death", and it was responsible for up to 75-200 million deaths in Eurasia and North Africa [1, 2]. *Y. pestis* causes three types of plague [2]:

- bubonic,
- pneumonic, and
- septicaemic.

Nowadays, it can usually be easily treated with antibiotics and prevented by precautions, such as: avoiding areas with high incidence of plague, preventing flea bites and avoiding contact with sick and/or dead animals.

Plague is categorized as a re-emerging disease. The numbers of human cases have risen since the beginning of 1990, and countries have been experiencing outbreaks after numerous years of dormancy [3]. There are several hundred cases reported to WHO every year. The current most endemic countries are the Democratic Republic of Congo, Madagascar (endemic season between September and April) and Peru [4, 5].

The bacteria are gram-negative non-motile rod-shaped facultatively anaerobic coccobacilli which do not form spores. Since it's a zoonotic bacterium, it is found in small mammals (often rodents) and their exoparasites, i.e. fleas. Please see Figures 1 and 2 for a graphic depiction of these bacteria.

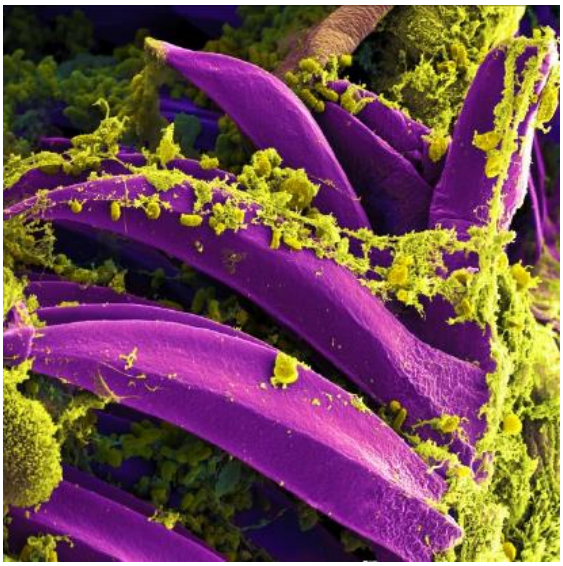

Figure 1. *Y. pestis* on proventricular spines of a *Xenopsylla cheopis* flea. Credit: *"Yersinia pestis* bacteria*"* by National Institute of Health (NIH), marked under CC PDM 1.0. To view the terms, visit: http://creativecommons.org/publicdomain/mark/1.0/

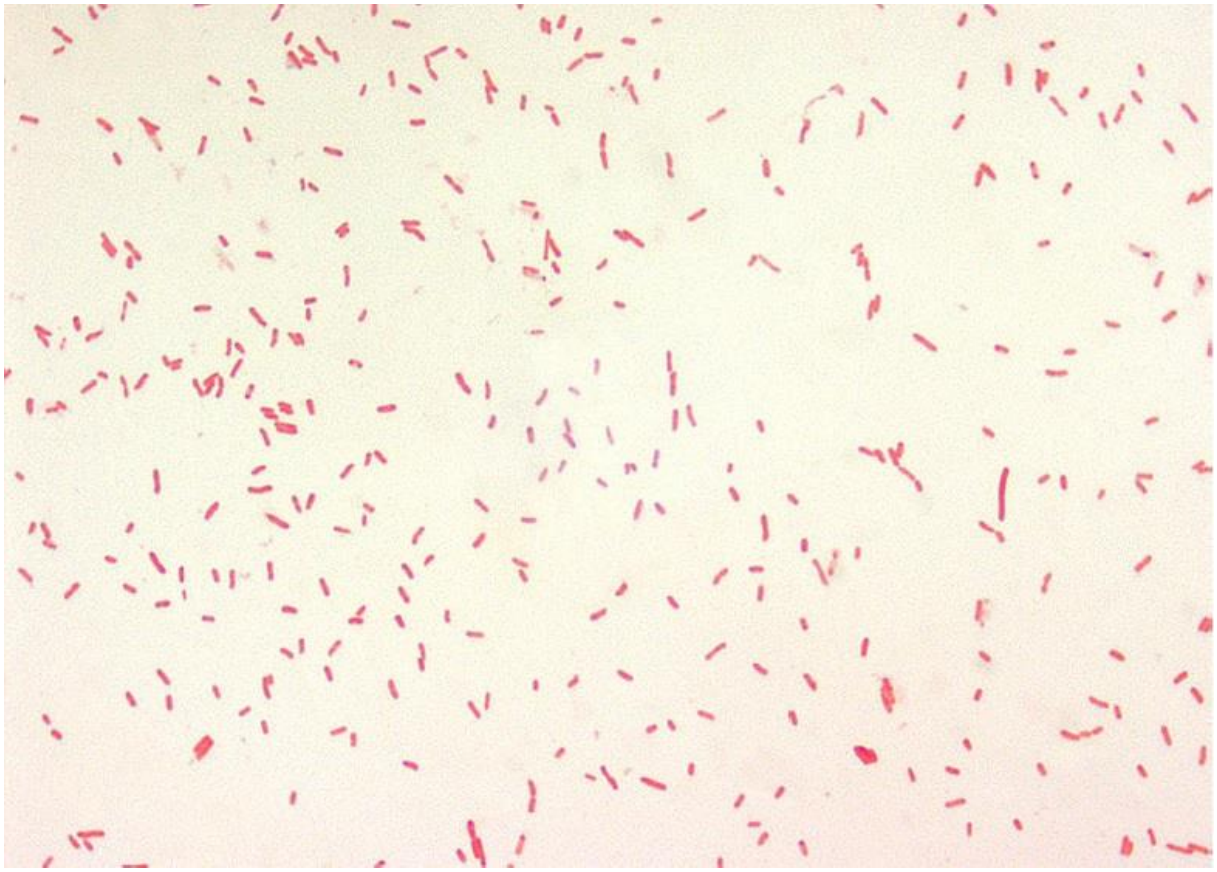

Figure 2. Photomicrograph of numerous, rod-shaped, gram-negative *Yersinia pestis* bacilli. Credit: Original image sourced from US Government department: Public Health Image Library, Centers for Disease Control and Prevention. It is marked under CC0 1.0. To view the terms, visit: http://creativecommons.org/licenses/cc0/1.0/

Typically, it has infected humans via the oriental rat flea (*Xenopsylla cheopis*), but it can also be transmitted through unprotected contact with infected body fluids or other contaminated materials, or through inhalation of respiratory droplets from a patient with pneumonic plague [2, 6, 7].

Y. pestis expresses virulence factors such as plasmin activator (important for pneumonic plague) that might degrade on blood clots to facilitate systemic invasion.

Many of the factors are antiphagocytic antigens (F1, V). *Y. pestis* survives and produces these antigens while residing in white blood cells (not in neutrophils) [2, 8].

Disease and pathogenesis

As mentioned previously, there are three types of plague, i.e. bubonic, pneumonic and septicaemic. The types are the result of the route of infection.

Bubonic plague is mainly spread by infected fleas from the disease reservoir (mainly small mammals), but it can also be contracted from exposure to body fluids of a dead plague-infected animal. Symptoms occur one to seven days post exposure. Flu-like symptoms develop first with fever, headaches and vomiting. In the area closest to where the bacteria entered the skin, swollen and painful lymph nodes occur. These swollen lymph nodes, known as "buboes", may break open. Diagnosis is based on finding the bacteria in serum, sputum or fluid drained from an infected lymph node [2, 4, 7, 9].

Infection of the lungs with the plague bacterium causes pneumonic form of plague, a severe respiratory illness. It is especially contagious and fatal unless treated early. The incubation can be as short as 24 hours. The disease can be transmitted via respiratory droplets to other humans, and this can trigger severe epidemics. Symptoms may be high fever, chills, cough, breathing difficulty, and the patient may expel bloody sputum (haemoptysis) [2, 4, 7, 9].

The last form of *Y. pestis* infection is the septicaemic type. When being exposed to the bacteria, there is a risk that it will enter the bloodstream, instead of the lungs or the lymph, and cause bacteraemia and sepsis (septicaemic plague). It does not have to happen initially. Both above mentioned types can lead to infection of the blood later on. Sepsis is a very severe condition, in which the endotoxins produced by the bacteria cause disseminated intravascular coagulation (DIC), with blood clots forming throughout the whole body causing ischemia ultimately leading to tissue necrosis. As the body no longer can provide more clotting resources, the patient will have uncontrolled bleeding internally. Symptoms of septicaemic plague are many: pain, haematemesis or haemoptysis (due to DIC), bleeding, a variety of GI symptoms, fever, chills, low blood pressure, organ failure, shock, gangrene and dyspnoea. In some cases, death will occur before any symptoms [2, 9, 10].

Symptoms and signs are not diagnostic of any form of plague. Due to this fact, it is vital that when it is suspected, further testing can be done to rule it out. Early and correct treatment is needed for the fatality to be low.

Reservoir

The main reservoirs for *Y. pestis* are several rodent species. In forested areas, the reservoir rodent is a wild animal, and in the urban setting the rodent is most often the brown rat (*Rattus norvegicus*). In the steppes, the reservoirs are thought to be primarily the marmot [2, 7, 9].

Broadening our knowledge about all the different species of rodents known, or thought to maintain *Y. pestis*, is important in order to prevent infections and outbreaks. These rodents are also recognized to have a variable resistance, which makes part of the reservoir asymptomatic carriers. In some regions of the world, the reservoirs are not clearly identified. This complicates prevention and early-warning programmes. To complicate it even more, new reports and case-studies also suggest that there could be more reservoirs and routes of infection than initially thought.

Figure 3 shows a global map of cases of plague reported to WHO in the years 2013-2018.

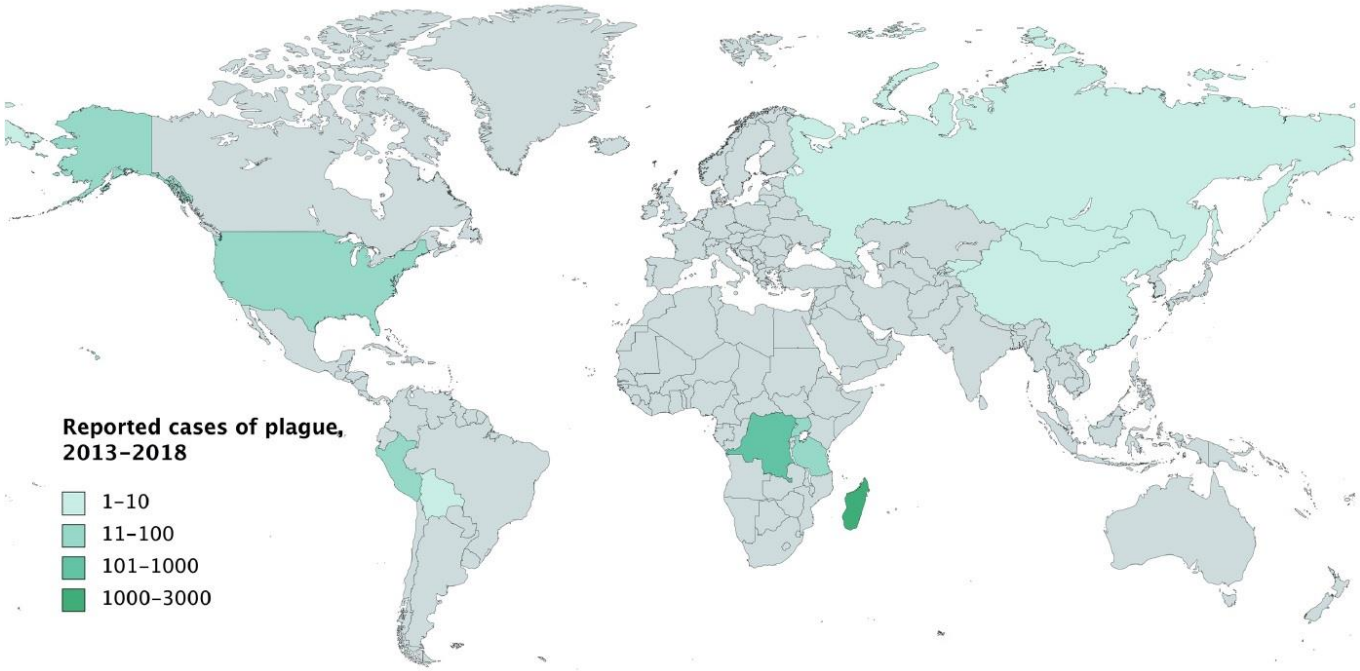

Figure 3. World map showing the number of plague cases reported to WHO in the years 2013-2018. In total there were 2886 cases reported. Madagascar alone reported 2323 cases, proving its status as one of the most endemic countries. Based on data from [11].

In 2007 there was an outbreak of gastroenteritis in Afghanistan. This proved later to be caused by *Y. pestis* originating from an ill camel the town slaughtered earlier on [12]. Other rare cases like this have also been reported. These are sporadic infections or outbreaks resulting from exposure to infected carcasses of camels and other animals.

The fact that the reservoir of the bacteria is based on a variety of mammals living in different environments, is also making it unlikely that the disease will disappear in the future [2].

Prevention, management and treatment

Public health measures are the best way to prevent the disease today, since vaccination is not yet effective enough.

Preventative measures include informing people when plague is present in their environment and what to do if it is. People should be precautious about flea bites, not handle dead animal carcasses, and avoid contact with bodily fluids [2, 4, 6].

Furthermore, managing plague outbreaks along with surveillance is important. Considering the differences in type of reservoir, risk of transmission and types of plague, it is troublesome to make one universal guideline. Accordingly, the most affected regions of the world have specific guidelines created by WHO [6]. To manage a plague outbreak, WHO highlights the need to investigate and stop the source of infection, protect those working with the diseased (e.g. protective clothing when in direct contact), administer correct treatment and isolate pneumonic plague

patients, identify and monitor contacts, give antibiotic chemoprophylaxis for seven days to contacts (all contacts of pneumonic plague and household members of patients with bubonic type), carefully collect specimens, disinfect, disinsect if needed, and lastly, bury the infected deceased according to a safety protocol [2, 6].

Several antibiotics are used as treatment: streptomycin, gentamicin and doxycycline have proven to be very effective [2, 4, 8]. However, there were resistant strains of *Y. pestis* (among others) discovered during the outbreaks on Madagascar [3]. This could potentially become a risk to global public health. Without treatment, plague is deadly in 30-90% of cases. Death usually occurs within 10 days [2, 4, 8].

Vaccination

Nowadays there are two types of vaccines available in the world: a live attenuated one and a killed vaccine.

The killed vaccine was developed in the US and given to military personnel in the 1940s. Currently, the vaccine is only given to people at high risk of exposure. It has shown adverse effects in a large percentile of vaccinated subjects, and it requires a booster dose every 1-2 years. There is also reason to believe that it does not provide protection against the pneumonic form [2, 8, 13].

Due to this information, research and experiments are ongoing to find a new and better vaccine against *Y. pestis*. The hope is that genetic engineering will result in a new vaccine based on F1 and V antigens of the bacteria [2, 8].

Recent outbreaks

As previously mentioned, WHO receives reports of several hundred cases of plague yearly. Considerable outbreaks have been, and still are, being reported around the world. From August to November 2017, there was an outbreak of plague reported in Madagascar. 2348 cases were confirmed, probable or suspected, and most of them were due to pneumonic plague. The Analamanga region of Madagascar was most affected, but 55 out of 114 districts had detected cases [5]. 202 deaths (case fatality rate 8.6 %) were reported by the Ministry of Health of Madagascar to WHO [14].

In 2019 in Bayan-Olgii, Mongolia, it was reported that a couple had died of bubonic plague after eating raw marmot meat. In early July 2020, two people in the province Khovd tested positive for the disease, and in mid-July in Govi-Altai, another province of Mongolia, a 15-year-old boy died of bubonic plague after eating marmot meat. Aforementioned outbreaks were reported by The National Center for Zoonotic Diseases (NCZD) [15].

In October 2020, a new report from Congo disclosed a new outbreak of bubonic plague in the Ituri province, which is the most active plague focus in Africa. It reported seven cases of the disease where two boys and two girls aged 10-14 had died. Inhabitants had reported of murine epizootic deaths (rat falls) in the week before the first human cases of disease [16]. This may of course lead us to think about rats as the bacterial reservoir.

Public health responses in the three different countries are important to review. In the outbreak in Madagascar, it was a cooperation

between the country's own ministry of health, WHO and others agencies. The goal was to rapidly investigate and trace new cases, monitor contacts and give free prophylactic antibiotics, and also to perform disinsection. A total of 7289 contacts were identified. After the outbreak in 2017, raising public awareness on the prevention of plague was highly valued. Over 1800 community health workers were trained for contact tracing and a rapid response team was established. Exit screenings were introduced at the airports as a measure to avoid international spread and 9 countries/overseas territories were identified as a priority for plague preparedness due to travel and trade links to Madagascar [5].

After the outbreak in Mongolia in 2019, there was a lockdown and in July 2020 a quarantine was placed on 5 districts in the province. Russia increased patrols to try to stop marmot hunting near the Mongolian border and China issued a warning after the case was discovered [15].

In 2020, after the outbreak in Congo, an investigation team searched for other cases in the area and contacts were treated preventively with antibiotics. The two houses that had the fatal cases were dusted with deltamethrin to control potentially infected fleas [16].

In all countries, Madagascar, Mongolia and Congo, plague was endemic in some areas at the time the mentioned cases occurred. It was endemic in areas of Madagascar at least until the end of the plague season in April 2018. After this period, WHO estimated the risk of plague to be moderate at national level and low at regional and global levels. Therefore, no restrictions on travel and trade were introduced. Travelers arriving in Madagascar were informed that plague was a seasonal endemic in Madagascar and they were introduced to the preventive measures (e.g. protecting themselves from flea bites and avoiding contact with dead animals). They were also told to contact medical service in case of symptoms of plague [5]. In Mongolia, plague is also endemic in some areas and vaccination programs are reported to be under way. NCZD is organizing a nationwide immunization program to stop the spread of the disease [15]. The outbreak mentioned in Congo is the 8th reported in less than a year in the endemic focus [16]. The fact that plague is still endemic in these different countries, despite preventive measures, surveillance and control, proves the importance of not losing awareness and vigilance about the disease.

These recent reports from 2017-2020 represent some of the diversity of outbreaks. The reservoirs of infection were most likely different. The report from Mongolia described cases of plague after eating marmot meat (probable route of transmission being vector fleas or the infected meat itself), and in Congo, the outbreak happened right after a murine epizootic deaths (probable route of transmission being fleas associated with the murine epizootics) [15, 16]. The report from Madagascar did not disclose the information about the reservoir [5]. There were also different public health responses as previously mentioned. It is worth noticing the management measures implemented in all three countries: investigation and restrictions of the source of infection and new cases; surveillance, prophylaxis and restrictions for contacts (quarantine, isolation) as well as correct treatment of the diseased [5, 15, 16].

Raising public awareness (community education) and assessing measures to prevent spread were also common in all outbreaks, but to a different extent.

In addition, Congo and Madagascar reports mention implementing disinsection as a measure of prevention and restriction of the spread [5, 16]. The reports do not say anything about the effectiveness of disinsection in the respective country, however other case-studies have shown that it is effective to control rodent-associated fleas within homes. In the West Nile Region of Uganda, rat fall surveillance was used (as a warning sign of transmission) together with vector control (disinsection) and community education as a plague prevention strategy and yielded very good results [17].

Concluding Remarks

It is now around 700 years since the Black Death ravaged Europe. Fortunately, we have come a long way since then. Plague is still an endemic disease in several countries. However, plague is now easily treated and our knowledge is by far better. By effectively preventing and managing outbreaks, countries like these three above-mentioned are able to ensure that the infection does not spread to become a pandemic. Still, this is highly dependent on rapid suspicion and confirmation of the disease pathogen, strictly following guidelines for management and efficient cooperation between the government of the given country, the health services, WHO and other public health agencies.

Resistant bacterial strains have been discovered, and similarly as for any other pathogen with resistance, this is a reason for concern.

Furthermore, it is, and will be, important that medical professionals and others learn from countries reporting outbreaks, like these in Madagascar, Mongolia and Congo.

We have to keep in mind that these are only some examples, and that there are several outbreaks reported every year in the world.

Moreover, whereas the cause is the same pathogen, the reports show variations with regards to the route of infection, symptoms and mortality.

For the future, it is vital that we continue the valuable work with prevention, reporting of outbreaks, research and sharing of information. Globally, the connotation of the disease and its pathogen varies greatly. With an increasing number of people travelling world-wide, expanding the general knowledge of the disease and its prevention is essential.

An unwary tourist might pose a risk for further spread. Due to the broad diversities of reservoirs it is very unlikely that the disease will disappear, and it’s reasonable to assume that outbreaks might arise in areas left dormant for many years. Outbreaks in new areas cannot be ruled out either. Plague might not be one of the biggest hazards of the global public health, but nevertheless, it is a severe infection with potential of rapid distribution and high case-fatality ratio if untreated. Granted, that we do not neglect it, act with precautions according to our knowledge and continue our research, it is highly possible that the world will have good control of the disease also in the future!

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